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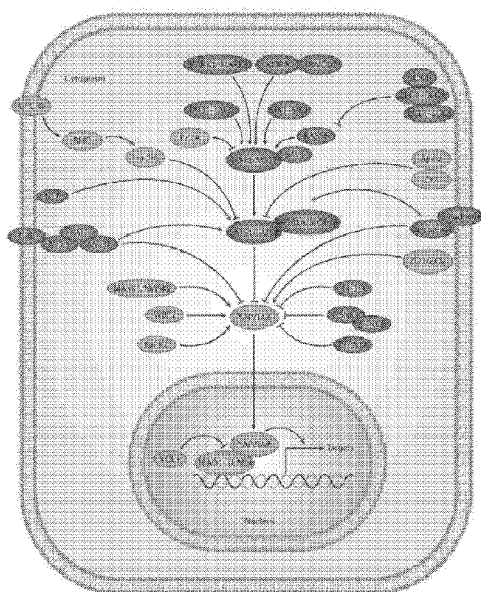
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KM, ML, MR, NE, SN, TD, TG).

(54) Title: OXADIAZOLE COMPOUNDS

(57) Abstract: Provided herein are compounds and pharmaceutical
compositions comprising said compounds that are useful for treating
cancers. Specific cancers include those that are mediated by YAP/TAZ
or those that are modulated by the interaction between YAP/TAZ and
TEAD.

FIG.1



Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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OXADIAZOLE COMPOUNDS

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 62/672,370 filed on May 16, 2018, which is incorporated herein by reference in its entirety.

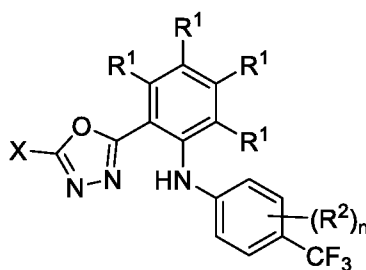
BACKGROUND OF THE DISCLOSURE

[0002] YAP and TAZ are transcriptional co-activators of the Hippo pathway network and regulate cell proliferation, migration, and apoptosis. Inhibition of the Hippo pathway promotes YAP/TAZ translocation to the nucleus, wherein YAP/TAZ interact with transcriptional enhancer associate domain (TEAD) transcription factors and coactivate the expression of target genes and promote cell proliferation. Hyperactivation of YAP and TAZ and/or mutations in one or more members of the Hippo pathway network have been implicated in numerous cancers. Described herein are inhibitors associated with one or more members of the Hippo pathway network, such as inhibitors of YAP/TAZ or inhibitors that modulate the interaction between YAP/TAZ and TEAD.

SUMMARY OF THE DISCLOSURE

[0003] Provided herein are substituted oxadiazole compounds and pharmaceutical compositions comprising said compounds. In some embodiments, the subject compounds are useful for the treatment of cancer.

[0004] Provided in one aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

X is H, -CN, halogen, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, -L²-L³-Y², -L²-L³-L⁴-Y², -L⁵-L⁶-L³-Y², or -L⁶-L⁵-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y^1 is N_3 , substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^2 is absent, substituted or unsubstituted C_1 - C_6 alkylene, substituted or unsubstituted C_3 - C_{10} cycloalkylene, or substituted or unsubstituted C_2 - C_{10} heterocycloalkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-, -O(C=O)-NR³(SO₂)-NR³-, -NR³(SO₂)NR³-(C=O)O-, -O-(SO₂)-, or -(SO₂)-O-;

each R³ is independently H, -CN, -S(=O)₂(C₁-C₄alkyl), or substituted or unsubstituted C_1 - C_6 alkyl;

L^4 is substituted or unsubstituted C_1 - C_6 alkylene;

L^5 is substituted or unsubstituted C_1 - C_6 alkylene;

L^6 is substituted or unsubstituted C_3 - C_{10} cycloalkylene;

Y^2 is H, -CN, -N₃, halogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂;

or R³ and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R⁶ is independently H or substituted or unsubstituted C_1 - C_6 alkyl;

or two R⁶ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or -L⁷-Y³;

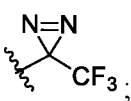
L^7 is substituted or unsubstituted C_1 - C_6 alkylene;

Y^3 is -Si(R⁷)₂;

each R⁷ is independently substituted or unsubstituted C_1 - C_6 alkyl;

n is 0, 1, 2, 3, or 4;

each R^2 is independently H, halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R^4 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^4 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

each R^5 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[0005] In some embodiments, if X, L^1 , L^2 , L^4 , L^5 , L^6 , L^7 , Y^1 , Y^2 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , or R^7 is substituted, then X, L^1 , L^2 , L^4 , L^5 , L^6 , L^7 , Y^1 , Y^2 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , or R^7 is substituted with 1-5 R^8 groups; each R^8 is independently selected from halogen, $-N_3$, $-CN$, $-NO_2$, $-OR^9$, $-SR^9$, $-S(=O)R^{10}$, $-S(=O)_2R^{10}$, $-S(=O)_2N(R^9)_2$, $-NR^9S(=O)_2R^{10}$, $-C(=O)R^{10}$, $-OC(=O)R^{10}$, $-CO_2R^9$, $-OCO_2R^{10}$, $-N(R^9)_2$, $-C(=O)N(R^9)_2$, $-OC(=O)N(R^9)_2$, $-NHC(=O)R^{10}$, $-NHC(=O)OR^{10}$, $-(CH_2)_r-R^9$, $-(CH_2)_r$ -halogen, unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or substituted C_1 - C_6 fluoroalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, unsubstituted or substituted C_1 - C_6 heteroalkyl, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_{10} heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; each R^9 is independently selected from H, substituted or unsubstituted C_1 - C_6 alkyl, unsubstituted or substituted C_1 - C_6 fluoroalkyl, unsubstituted or substituted C_1 - C_6 heteroalkyl, unsubstituted or substituted C_3 - C_{10} cycloalkyl,

unsubstituted or substituted C₂-C₁₀heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; or two R⁹ on the same N atom are taken together with the N atom to which they are attached to form a N-containing heterocycle; each R¹⁰ is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, unsubstituted or substituted C₁-C₆fluoroalkyl, unsubstituted or substituted C₁-C₆heteroalkyl, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₁₀heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; and r is 1, 2, 3, or 4.

[0006] In some embodiments, X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0007] In some embodiments, X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0008] In some embodiments, X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[0009] In some embodiments, X is substituted or unsubstituted C₁-C₄alkyl. In some embodiments, X is -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃.

[0010] In some embodiments, X is substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, X is -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.

[0011] In some embodiments, X is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, X is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl.

[0012] In some embodiments, X is substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, X is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-

dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl.

[0013] In some embodiments, X is substituted or unsubstituted heteroaryl. In some embodiments, X is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, X is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[0014] In some embodiments, X is $-L^1-Y^1$. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, Y^1 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, Y^1 is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted phenyl. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted heteroaryl. In some embodiments, Y^1 is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, Y^1 is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or

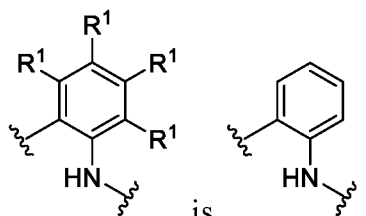
unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[0015] In some embodiments, X is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1 - C_4 alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-; Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂. In some embodiments, L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-; Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C_1 - C_4 alkyl.

[0016] In some embodiments, L^2 is absent; L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-; Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂. In some embodiments, L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-; Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl,

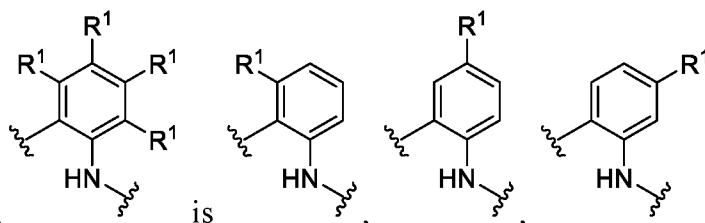
substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$; and each R^6 is independently H or substituted or unsubstituted C_1 - C_4 alkyl.

[0017] In some embodiments, X is $-\text{L}^2-\text{L}^3-\text{L}^4-\text{Y}^2$. In some embodiments, L^2 is substituted or unsubstituted C_1 - C_4 alkylene; L^3 is $-\text{O}-$, $-\text{S}-$, $-(\text{S}=\text{O})-$, $-(\text{SO}_2)-$, $-\text{NR}^3-$, $-(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{O}-$, $-\text{O}(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{NR}^3-$, $-(\text{C}=\text{O})\text{NR}^3-\text{O}-$, $-\text{NR}^3(\text{C}=\text{O})-$, $-\text{NR}^3(\text{C}=\text{O})\text{NR}^3-$, $-\text{O}(\text{C}=\text{O})\text{NR}^3-$, $-\text{NR}^3(\text{C}=\text{O})\text{O}-$, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-$, $-\text{NR}^3(\text{SO}_2)-$, $-(\text{SO}_2)\text{NR}^3-$, $-(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})-$, $-(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})-$, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$, or $-\text{O}-(\text{SO}_2)-$; L^4 is substituted or unsubstituted C_1 - C_4 alkylene; Y^2 is independently H, $-\text{CN}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$. In some embodiments, L^3 is $-\text{O}-$, $-\text{S}-$, $-(\text{S}=\text{O})-$, $-(\text{SO}_2)-$, $-\text{NR}^3-$, $-(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{O}-$, $-\text{O}(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{NR}^3-$, $-(\text{C}=\text{O})\text{NR}^3-\text{O}-$, $-\text{NR}^3(\text{C}=\text{O})-$, $-\text{NR}^3(\text{C}=\text{O})\text{NR}^3-$, $-\text{NR}^3(\text{C}=\text{O})\text{O}-$, $-\text{NR}^3(\text{SO}_2)-$, $-(\text{SO}_2)\text{NR}^3-$, or $-\text{O}-(\text{SO}_2)-$; Y^2 is independently H, $-\text{CN}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$; and each R^6 is independently H or substituted or unsubstituted C_1 - C_4 alkyl.



[0018] In some embodiments,

is



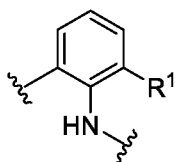
[0019] In some embodiments,

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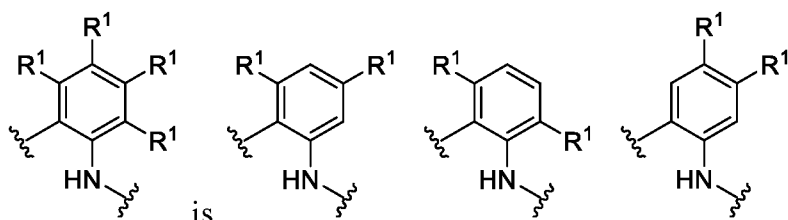
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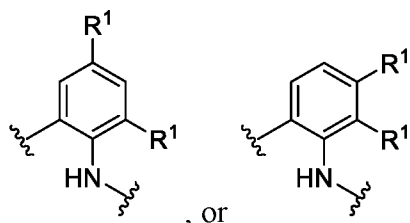
and R^1 is halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl,

substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0020] In some embodiments, R¹ is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R¹ is halogen, substituted or unsubstituted C₁-C₄alkyl, or substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, R¹ is F, Cl, Br, I, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -C(CH₃)₃, -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.

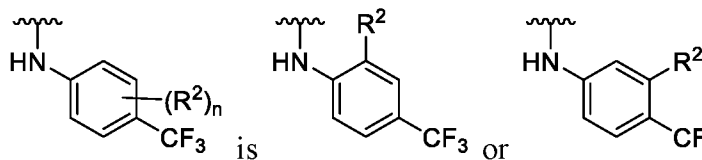


[0021] In some embodiments,



; and each R¹ is independently halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0022] In some embodiments, each R¹ is independently halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R¹ is independently halogen, substituted or unsubstituted C₁-C₄alkyl, or substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R¹ is independently F, Cl, Br, I, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -C(CH₃)₃, -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.



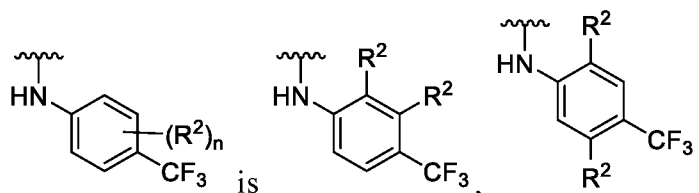
[0023] In some embodiments, is $\text{HN}-\text{C}_6\text{H}_4-\text{CF}_3$ or $\text{HN}-\text{C}_6\text{H}_3(\text{R}^2)-\text{CF}_3$ or $\text{HN}-\text{C}_6\text{H}_3(\text{R}^2)_2-\text{CF}_3$; and R^2 is halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl, or

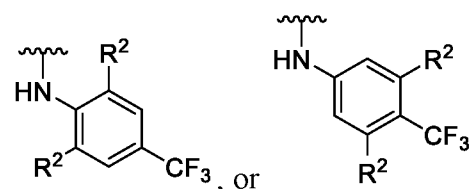
[0024] In some embodiments, R^2 is halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted

phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and each R^5 is independently H, or substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, R^2 is halogen, $-\text{N}_3$, $-\text{OR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted

C_1 - C_4 haloalkyl, or



[0025] In some embodiments, wherein:

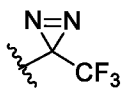


; and each R^2 is independently halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted aralkyl,

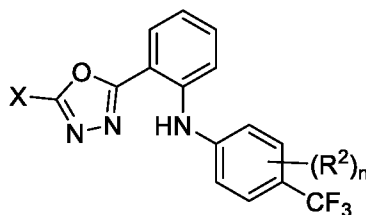
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or In some embodiments, each R^2 is independently halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted

phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and each R^5 is

independently H, or substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R² is independently halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl,

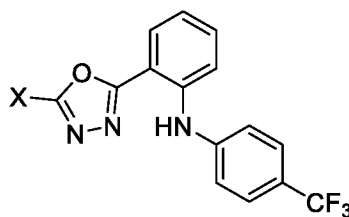
substituted or unsubstituted C₁-C₄haloalkyl, or .

[0026] In some embodiments, the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



Formula (Ia).

[0027] In some embodiments, the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:



Formula (Ib).

[0028] In some embodiments, the compound exhibits an IC₅₀ of no more than about 5.000 μM.

[0029] Provided in another aspect is a compound, or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1, or a pharmaceutically acceptable salt thereof.

[0030] Provided in another aspect is a pharmaceutical composition comprising a pharmaceutically acceptable excipient and any one of the compounds disclosed herein or a pharmaceutically acceptable salt thereof.

[0031] Provided herein is a method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound of any one of the compounds disclosed herein or a pharmaceutically acceptable salt thereof.

INCORPORATION BY REFERENCE

[0032] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0034] **FIG. 1** illustrates a schematic representation of the Hippo signaling network. Hippo pathway components shaded in dark gray indicate components that inhibit YAP/TAZ activity. Hippo pathway components shaded in light gray indicate components that promote YAP/TAZ activity. Pointed and blunt arrowheads indicate activating and inhibitory interactions, respectively. Abbreviations: α -CAT (α -Catenin), AJUB (Ajuba), AMOT (Angiomotin), β -TRCP (β -transducing repeat containing protein), CK1 (Casein Kinase 1), CRB (Crumbs), E-CAD (E-cadherin), EX (Expanded), GPCR (G-protein coupled receptor), HIPK (Homeodomain interacting protein kinase), KIBRA (Kidney brain), LATS (Large tumor suppressor), LGL (Lethal giant larvae), MASK (Multiple ankyrin single KH), MER (Merlin), MOB (Mps one binder), MST (Mammalian sterile 20 like), PALS (Protein Associated with Lin-7), PATJ (Pals1-associated tight junction protein), PP2A (Protein phosphatase 2A), PTPN14 (Protein tyrosine phosphatase non-receptor type 14), RASSF (Ras associated factor), SAV (Salvador), SCRIB (Scribble), SIK (Salt inducible kinase), TAO (Thousand and one amino acid protein), TAZ (transcriptional coactivator with PDZ-binding motif), TEAD (TEA domain protein), VGL4 (Vestigial-like 4), WBP2 (WW domain binding protein 2), YAP (Yes associated protein), ZO (Zonula occludens), ZYX (Zyxin).

[0035] **FIG. 2** illustrates a schematic representation of the Hippo signaling pathway regulated by G alpha proteins.

DETAILED DESCRIPTION OF THE DISCLOSURE

Certain Terminology

[0036] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

[0037] As used herein, in some embodiments, ranges and amounts are expressed as “about” a particular value or range. About also includes the exact amount. Hence “about 5 μL ” means “about 5 μL ” and also “5 μL .” Generally, the term “about” includes an amount that is expected to be within experimental error.

[0038] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0039] As used herein, the terms “individual(s)”, “subject(s)” and “patient(s)” mean any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g. constant or intermittent) of a health care worker (e.g. a doctor, a registered nurse, a nurse practitioner, a physician’s assistant, an orderly, or a hospice worker).

[0040] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0041] "Amino" refers to the $-\text{NH}_2$ radical.

[0042] "Cyano" refers to the $-\text{CN}$ radical.

[0043] "Nitro" refers to the $-\text{NO}_2$ radical.

[0044] "Oxa" refers to the $-\text{O}-$ radical.

[0045] "Oxo" refers to the $=\text{O}$ radical.

[0046] "Thioxo" refers to the $=\text{S}$ radical.

[0047] "Imino" refers to the $=\text{N}-\text{H}$ radical.

[0048] "Oximo" refers to the $=\text{N}-\text{OH}$ radical.

[0049] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to fifteen carbon atoms (e.g., $\text{C}_1\text{-C}_{15}$ alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (e.g., $\text{C}_1\text{-C}_{13}$ alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (e.g., $\text{C}_1\text{-C}_8$ alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (e.g., $\text{C}_1\text{-C}_5$ alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (e.g., $\text{C}_1\text{-C}_4$ alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (e.g., $\text{C}_1\text{-C}_3$ alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (e.g., $\text{C}_1\text{-C}_2$ alkyl). In other embodiments, an alkyl comprises one carbon atom (e.g., C_1 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (e.g., $\text{C}_5\text{-C}_{15}$ alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (e.g., $\text{C}_5\text{-C}_8$ alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (e.g., $\text{C}_2\text{-C}_5$ alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (e.g., $\text{C}_3\text{-C}_5$ alkyl). In other embodiments, the alkyl group is selected from methyl,

ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where *t* is 1 or 2), $-S(O)_tOR^a$ (where *t* is 1 or 2), $-S(O)_tR^f$ (where *t* is 1 or 2) and $-S(O)_tN(R^a)_2$ (where *t* is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl. In some embodiments, an alkyl chain is optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-CN$, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where *t* is 1 or 2), $-R^b-S(O)_tOR^a$ (where *t* is 1 or 2), $-R^b-S(O)_tR^a$ (where *t* is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where *t* is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0050] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula $-O$ -alkyl, where alkyl is an alkyl chain as defined above.

[0051] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to six carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification,

an alkenyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl.

[0052] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl comprises two to six carbon atoms. In other embodiments, an alkynyl has two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl.

[0053] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In some embodiments, the points of attachment of the alkylene chain to the rest of the molecule and to the radical group are through one carbon in the alkylene chain or through any two carbons within the chain. In certain embodiments, an alkylene comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C_1-C_2

alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C₁ alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C₅-C₈ alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C₂-C₅ alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C₃-C₅ alkylene). Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -C(O)N(R^a)₂, -N(R^a)C(O)OR^f, -OC(O)-NR^aR^f, -N(R^a)C(O)R^f, -N(R^a)S(O)_tR^f (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tR^f (where t is 1 or 2), and -S(O)_tN(R^a)₂ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl. In some embodiments, an alkylene chain is optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a, -R^b-N(R^a)S(O)_tR^a (where t is 1 or 2), -R^b-S(O)_tOR^a (where t is 1 or 2), -R^b-S(O)_tR^a (where t is 1 or 2), and -R^b-S(O)_tN(R^a)₂ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0054] "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from five to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π-electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl

radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-CN$, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0055] "Aryloxy" refers to a radical bonded through an oxygen atom of the formula $-O$ -aryl, where aryl is as defined above.

[0056] "Aralkyl" refers to a radical of the formula $-R^c$ -aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0057] "Aralkenyl" refers to a radical of the formula $-R^d$ -aryl where R^d is an alkenylene chain as defined above. The aryl part of the aralkenyl radical is optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical is optionally substituted as defined above for an alkenylene group.

[0058] "Aralkynyl" refers to a radical of the formula $-R^e$ -aryl, where R^e is an alkynylene chain as defined above. The aryl part of the aralkynyl radical is optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical is optionally substituted as defined above for an alkynylene chain.

[0059] "Carbocyclyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, and in some embodiments, include fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. In some embodiments, the carbocyclyl is saturated, (*i.e.*, containing single C-C bonds only)

or unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) A fully saturated carbocyclyl radical is also referred to as "cycloalkyl." Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In certain embodiments, a cycloalkyl comprises three to eight carbon atoms (*e.g.*, C₃-C₈ cycloalkyl). In other embodiments, a cycloalkyl comprises three to seven carbon atoms (*e.g.*, C₃-C₇ cycloalkyl). In other embodiments, a cycloalkyl comprises three to six carbon atoms (*e.g.*, C₃-C₆ cycloalkyl). In other embodiments, a cycloalkyl comprises three to five carbon atoms (*e.g.*, C₃-C₅ cycloalkyl). In other embodiments, a cycloalkyl comprises three to four carbon atoms (*e.g.*, C₃-C₄ cycloalkyl). An unsaturated carbocyclyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "carbocyclyl" is meant to include carbocyclyl radicals that are optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a, -R^b-N(R^a)S(O)_tR^a (where t is 1 or 2), -R^b-S(O)_tOR^a (where t is 1 or 2), -R^b-S(O)_tR^a (where t is 1 or 2), and -R^b-S(O)_tN(R^a)₂ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0060] The term "cycloalkylene" refers to a divalent cycloalkyl group and is optionally substituted as indicated for the term "cycloalkyl" or "carbocyclyl".

[0061] "Carbocyclylalkyl" refers to a radical of the formula -R^c-carbocyclyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0062] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo substituents.

[0063] The term “haloalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro-, or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2,2-difluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl. Other examples of haloalkyl include, but not limited to, chloromethyl, trichloromethyl, 2-chloroethyl, bromomethyl, and 2-bromoethyl. The term “perhaloalkyl” denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms. In some embodiments, the alkyl part of the haloalkyl radical is optionally substituted as defined above for an alkyl group.

[0064] “Heterocyclyl” or “heterocycle” refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which include fused or bridged ring systems in some embodiments. The heteroatoms in the heterocyclyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. In some embodiments, the heterocyclyl is attached to the rest of the molecule through any atom of the ring(s). In some embodiments, the heterocyclyl is saturated, (*i.e.*, containing single bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) A fully saturated heterocyclyl radical is also referred to as “heterocycloalkyl.” Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidiny, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl, tetrahydropyranlyl, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, and 1,1-dioxo-thiomorpholiny. Unless stated otherwise specifically in the specification, the term “heterocyclyl” is meant to include heterocyclyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, -R^b-CN, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a,

$-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0065] “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.* $-NH-$, $-N(alkyl)-$, sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1 - C_6 heteroalkyl. In some embodiments, the alkyl part of the heteroalkyl radical is optionally substituted as defined for an alkyl group.

[0066] A “heterocycloalkyl” or “heteroalicyclic” group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. In some embodiments, the heterocycloalkyl is dioxolanyl, oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidin-2-onyl, pyrrolidine-2,5-dithionyl, pyrrolidine-2,5-dionyl, pyrrolidinonyl, imidazolidinyl, imidazolidin-2-onyl, or thiazolidin-2-onyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C_2 - C_{10} heterocycloalkyl. In one aspect, a heterocycloalkyl is a C_2 - C_6 heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4 - C_{10} heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

[0067] The term “heterocycloalkylene” refers to a divalent heterocycloalkyl group and is optionally substituted as indicated for the term “heterocycloalkyl”.

[0068] “Heterocyclylalkyl” refers to a radical of the formula $-R^c$ -heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocyclyl group.

[0069] “Heterocyclylalkoxy” refers to a radical bonded through an oxygen atom of the formula $-O-R^c$ -heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a

nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkoxy radical is optionally substituted as defined above for a heterocyclyl group.

[0070] "Heteroaryl" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, in some embodiments, the heteroaryl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolyl, 5,6-dihydrobenzo[h]cinnolyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indolizyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolyl, quinoxalinyl, quinolyl, isoquinolyl, tetrahydroquinolyl, 5,6,7,8-tetrahydroquinazolyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl,

thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (*i.e.* thienyl). In some embodiments, the heteroaryl groups include monocyclic heteroaryls and bicyclic heteroaryls. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, haloalkenyl, haloalkynyl, oxo, thio, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0071] "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0072] "*C*-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A *C*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

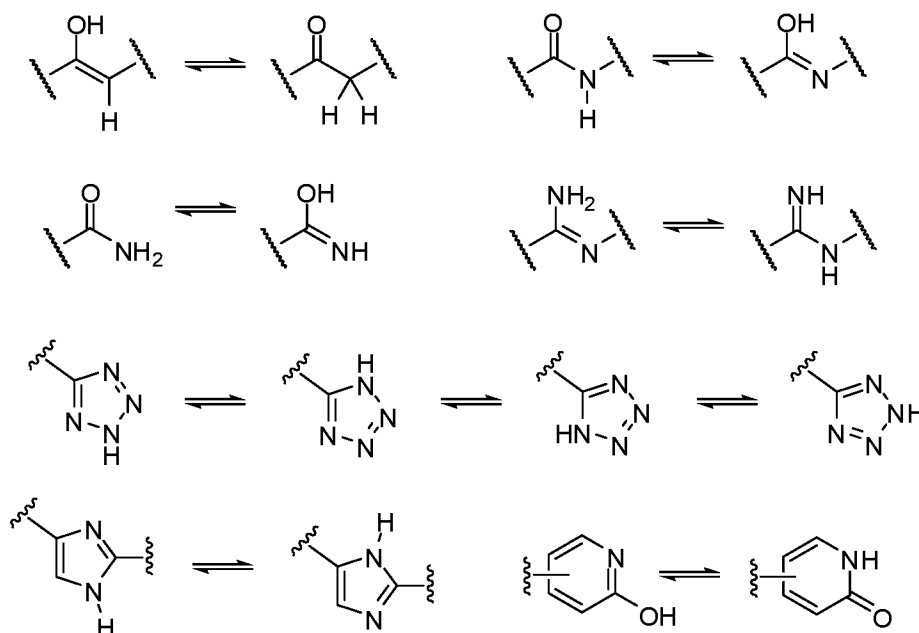
[0073] "Heteroaryloxy" refers to a radical bonded through an oxygen atom of the formula --O--heteroaryl , where heteroaryl is as defined above.

[0074] "Heteroarylalkyl" refers to a radical of the formula $\text{--R}^c\text{--heteroaryl}$, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

[0075] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula $\text{--O--R}^c\text{--heteroaryl}$, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical is optionally substituted as defined above for a heteroaryl group.

[0076] In some embodiments, the compounds disclosed herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless stated otherwise, it is intended that all stereoisomeric forms of the compounds disclosed herein are contemplated by this disclosure. When the compounds described herein contain alkene double bonds, and unless specified otherwise, it is intended that this disclosure includes both *E* and *Z* geometric isomers (*e.g.*, *cis* or *trans*.) Likewise, all possible isomers, as well as their racemic and optically pure forms, and all tautomeric forms are also intended to be included. The term "geometric isomer" refers to *E* or *Z* geometric isomers (*e.g.*, *cis* or *trans*) of an alkene double bond. The term "positional isomer" refers to structural isomers around a central ring, such as *ortho*-, *meta*-, and *para*- isomers around a benzene ring.

[0077] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0078] "Optional" or "optionally" means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0079] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s). In some other embodiments, optional substituents are individually and independently selected from D, halogen, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, -OH, -C(=O)OH, -C(=O)Oalkyl, -OC(=O)alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -NHC(=O)alkyl, -N(alkyl)C(=O)alkyl, -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, -CH₂CO₂H, -CH₂CO₂alkyl, -CH₂C(=O)NH₂, -CH₂C(=O)NH(alkyl), -CH₂C(=O)N(alkyl)₂, -CH₂S(=O)₂NH₂, -CH₂S(=O)₂NH(alkyl), -CH₂S(=O)₂N(alkyl)₂, alkyl, alkenyl, alkynyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, optional substituents are individually and independently selected from D, halogen, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, -OH, -CO₂H, -CO₂alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄alkyl), -C(=O)NH₂, -C(=O)NH(C₁-C₄alkyl), -C(=O)N(C₁-C₄alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(C₁-C₄alkyl), -S(=O)₂N(C₁-C₄alkyl)₂, C₁-C₄alkyl,

C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄heteroalkyl, C₁-C₄alkoxy, C₁-C₄fluoroalkoxy, -SC₁-C₄alkyl, -S(=O)C₁-C₄alkyl, and -S(=O)₂C₁-C₄alkyl. In some embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -OH, -NH(CH₃), -N(CH₃)₂, -CH₃, -CH₂CH₃, -CF₃, -OCH₃, and -OCF₃. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, substituted groups are substituted with one of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O). In some embodiments, an optional substituent on a sulfur atom includes one or two oxo (=O) groups.

[0080] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Pharmaceutically acceptable salts of the compounds described herein are optionally pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[0081] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrate, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66:1-19 (1997), which is hereby incorporated by reference in its entirety). In some embodiments, acid addition salts of basic compounds are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[0082] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. In some embodiments, pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts, and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chlorprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins, and the like. See Berge et al., *supra*.

[0083] As used herein, "treatment" or "treating" or "palliating" or "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is afflicted with the underlying disorder in some embodiments. For prophylactic benefit, in some embodiments, the compositions are administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

[0084] "Prodrug" is meant to indicate a compound that is converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some embodiments, a prodrug is inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam)).

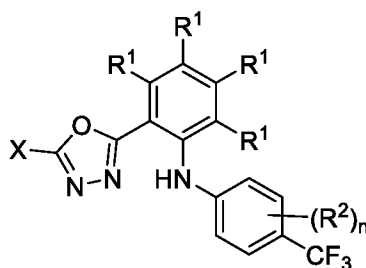
[0085] A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

[0086] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. In some embodiments, prodrugs of an active compound, as described herein, are prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino, or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol or amine functional groups in the active compounds and the like.

Compounds

[0087] In some embodiments, the compounds disclosed herein are oxadiazole compounds.

[0088] Provided in one aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

X is H, -CN, halogen, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, -L²-L³-Y², -L²-L³-L⁴-Y², -L⁵-L⁶-L³-Y², or -L⁶-L⁵-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y¹ is -N₃, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^2 is absent, substituted or unsubstituted C_1 - C_6 alkylene, substituted or unsubstituted C_3 -

C_{10} cycloalkylene, or substituted or unsubstituted C_2 - C_{10} heterocycloalkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-

O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -

NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -

(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-,

-O(C=O)-NR³(SO₂)-NR³-, -NR³(SO₂)NR³-(C=O)O-, -O-(SO₂)-, or -(SO₂)-O-;

each R³ is independently H, -CN, -S(=O)₂(C₁-C₄alkyl), or substituted or unsubstituted C_1 - C_6 alkyl;

L^4 is substituted or unsubstituted C_1 - C_6 alkylene;

L^5 is substituted or unsubstituted C_1 - C_6 alkylene;

L^6 is substituted or unsubstituted C_3 - C_{10} cycloalkylene;

Y^2 is H, -CN, -N₃, halogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 -

C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 -

C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 -

C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or

unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂;

or R³ and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R⁶ is independently H or substituted or unsubstituted C_1 - C_6 alkyl;

or two R⁶ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted

C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 -

C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 -

C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted

C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted

aryl, substituted or unsubstituted heteroaryl, or -L⁷-Y³;

L^7 is substituted or unsubstituted C_1 - C_6 alkylene;

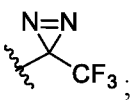
Y^3 is -Si(R⁷)₂;

each R⁷ is independently substituted or unsubstituted C_1 - C_6 alkyl;

n is 0, 1, 2, 3, or 4;

each R² is independently H, halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵,

substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R⁴ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R⁴ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

each R⁵ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R⁵ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[0089] In some embodiments, if X, L¹, L², L⁴, L⁵, L⁶, L⁷, Y¹, Y², R¹, R², R³, R⁴, R⁵, R⁶, or R⁷ is substituted, then X, L¹, L², L⁴, L⁵, L⁶, L⁷, Y¹, Y², R¹, R², R³, R⁴, R⁵, R⁶, or R⁷ is substituted with 1-5 R⁸ groups; each R⁸ is independently selected from halogen, -N₃, -CN, -NO₂, -OR⁹, -SR⁹, -S(=O)R¹⁰, -S(=O)₂R¹⁰, -S(=O)₂N(R⁹)₂, -NR⁹S(=O)₂R¹⁰, -C(=O)R¹⁰, -OC(=O)R¹⁰, -CO₂R⁹, -OCO₂R¹⁰, -N(R⁹)₂, -C(=O)N(R⁹)₂, -OC(=O)N(R⁹)₂, -NHC(=O)R¹⁰, -NHC(=O)OR¹⁰, -(CH₂)_r-R⁹, -(CH₂)_r-halogen, unsubstituted or substituted C₁-C₆alkyl, unsubstituted or substituted C₁-C₆fluoroalkyl, unsubstituted or substituted C₂-C₆alkenyl, unsubstituted or substituted C₂-C₆alkynyl, unsubstituted or substituted C₁-C₆heteroalkyl, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₁₀heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; each R⁹ is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, unsubstituted or substituted C₁-C₆fluoroalkyl, unsubstituted or substituted C₁-C₆heteroalkyl, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₁₀heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; or two R⁹ on the same N atom are

taken together with the N atom to which they are attached to form a N-containing heterocycle; each R^{10} is independently selected from H, substituted or unsubstituted C_1 - C_6 alkyl, unsubstituted or substituted C_1 - C_6 fluoroalkyl, unsubstituted or substituted C_1 - C_6 heteroalkyl, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_{10} heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; and r is 1, 2, 3, or 4.

[0090] In some embodiments, X is H. In some embodiments, X is $-CN$. In some embodiments, X is halogen. In some embodiments, X is substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, X is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, X is substituted or unsubstituted C_2 - C_6 alkenyl. In some embodiments, X is substituted or unsubstituted C_2 - C_6 alkynyl. In some embodiments, X is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, X is substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, X is substituted or unsubstituted aryl. In some embodiments, X is substituted or unsubstituted heteroaryl. In some embodiments, X is $-L^1-Y^1$. In some embodiments, X is $-L^2-L^3-Y^2$. In some embodiments, X is $-L^2-L^3-L^4-Y^2$. In some embodiments, X is $-L^5-L^6-L^3-Y^2$. In some embodiments, X is $-L^6-L^5-L^3-Y^2$.

[0091] In some embodiments, X is substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0092] In some embodiments, X is substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0093] In some embodiments, X is substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[0094] In some embodiments, X is substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, X is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$.

[0095] In some embodiments, X is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, X is $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$.

[0096] In some embodiments, X is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, X is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl.

[0097] In some embodiments, X is substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, X is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl.

[0098] In some embodiments, X is substituted or unsubstituted heteroaryl. In some embodiments, X is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, X is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[0099] In some embodiments, X is -L¹-Y¹. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene. In some embodiments, L¹ is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-. In some embodiments, Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted C₂-C₁₀ heterocycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted C₂-C₆ heterocycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted aryl. In some embodiments, Y¹ is or substituted or unsubstituted heteroaryl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is

substituted or unsubstituted C₂-C₆ heterocycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted phenyl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted heteroaryl. In some embodiments, Y¹ is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, Y¹ is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00100] In some embodiments, L² is absent. In some embodiments, L² is substituted or unsubstituted C₁-C₆alkylene. In some embodiments, L² is substituted or unsubstituted C₁-C₄alkylene. In some embodiments, L² is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-. In some embodiments, L² is substituted or unsubstituted C₃-C₁₀cycloalkylene. In some embodiments, L² is substituted or unsubstituted C₃-C₆cycloalkylene. In some embodiments, L² is substituted or unsubstituted cyclopropylene, substituted or unsubstituted cyclobutylene, substituted or unsubstituted cyclopentylene, or substituted or unsubstituted cyclohexylene. In some embodiments, L² is substituted or unsubstituted C₂-C₁₀heterocycloalkylene. In some embodiments, L² is substituted or unsubstituted C₂-C₆heterocycloalkylene. In some embodiments, L² is substituted or unsubstituted aziridinylene, substituted or unsubstituted azetidinylene, substituted or unsubstituted pyrrolidinylene, substituted or unsubstituted piperidinylene, substituted or unsubstituted oxetanylene, substituted or unsubstituted tetrahydrofuranylene, or substituted or unsubstituted tetrahydropyranylene. In some embodiments, L³ is -O-. In some embodiments, L³ is

-S-. In some embodiments, L^3 is $-(S=O)-$. In some embodiments, L^3 is $-(SO_2)-$. In some embodiments, L^3 is $-NR^3-$. In some embodiments, L^3 is $-(C=O)-$. In some embodiments, L^3 is $-(C=O)O-$. In some embodiments, L^3 is $-O(C=O)-$. In some embodiments, L^3 is $-(C=O)NR^3-$. In some embodiments, L^3 is $-(C=O)NR^3-O-$. In some embodiments, L^3 is $-O-NR^3(C=O)-$. In some embodiments, L^3 is $-NR^3(C=O)-$. In some embodiments, L^3 is $-NR^3(C=O)NR^3-$. In some embodiments, L^3 is $-O(C=O)NR^3-$. In some embodiments, L^3 is $-NR^3(C=O)O-$. In some embodiments, L^3 is $-NR^3(SO_2)NR^3-$. In some embodiments, L^3 is $-NR^3(SO_2)-$. In some embodiments, L^3 is $-(SO_2)NR^3-$. In some embodiments, L^3 is $-(SO_2)NR^3-(C=O)-$. In some embodiments, L^3 is $-(C=O)-NR^3(SO_2)-$. In some embodiments, L^3 is $-(SO_2)NR^3-(C=O)O-$. In some embodiments, L^3 is $-O(C=O)-NR^3(SO_2)-$. In some embodiments, L^3 is $-NR^3(SO_2)NR^3-(C=O)-$. In some embodiments, L^3 is $-(C=O)-NR^3(SO_2)NR^3-$. In some embodiments, L^3 is $-O(C=O)-NR^3(SO_2)-NR^3-$. In some embodiments, L^3 is $-NR^3(SO_2)NR^3-(C=O)O-$. In some embodiments, L^3 is $-O-(SO_2)-$. In some embodiments, L^3 is $-(SO_2)-O-$. In some embodiments, R^3 is H. In some embodiments, R^3 is substituted or unsubstituted C_1 - C_6 alkylene. In some embodiments, R^3 is substituted or unsubstituted C_1 - C_4 alkylene. In some embodiments, R^3 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$. In some embodiments, L^4 is substituted or unsubstituted C_1 - C_6 alkylene. In some embodiments, L^4 is substituted or unsubstituted C_1 - C_4 alkylene. In some embodiments, L^4 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

[00101] In some embodiments, Y^2 is H. In some embodiments, Y^2 is $-CN$. In some embodiments, Y^2 is $-N_3$. In some embodiments, Y^2 is halogen. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, Y^2 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, Y^2 is $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_6 alkenyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_4 alkenyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_6 alkynyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_4 alkynyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, Y^2 is substituted or

unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, Y² is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, Y² is substituted or unsubstituted aralkyl. In some embodiments, Y² is substituted or unsubstituted benzyl. In some embodiments, Y² is substituted or unsubstituted aryl. In some embodiments, Y² is substituted or unsubstituted phenyl. In some embodiments, Y² is substituted or unsubstituted heteroaryl. In some embodiments, Y² is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, Y² is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In some embodiments, Y² is -OR⁶. In some embodiments, Y² is -(C=O)OR⁶. In some embodiments, Y² is -N(R⁶)₂. In some embodiments, Y² is -(C=O)N(R⁶)₂. In some embodiments, R³ and Y² on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00102] In some embodiments, each R⁶ is independently H. In some embodiments, each R⁶ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁶ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁶ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, two R⁶ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

[00103] In some embodiments, X is -L²-L³-Y². In some embodiments, L² is substituted or unsubstituted C₁-C₄alkylene; L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -

NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-; Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂. In some embodiments, L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-; Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

[00104] In some embodiments, L² is absent; L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-; Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂. In some embodiments, L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-; Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

[00105] In some embodiments, X is -L²-L³-L⁴-Y². In some embodiments, L² is substituted or unsubstituted C₁-C₄alkylene; L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -

$\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})-$, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$, or $-\text{O}-(\text{SO}_2)-$; L^4 is substituted or unsubstituted C_1 - C_4 alkylene; Y^2 is independently H, $-\text{CN}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$. In some embodiments, L^3 is $-\text{O}-$, $-\text{S}-$, $-(\text{S}=\text{O})-$, $-(\text{SO}_2)-$, $-\text{NR}^3-$, $-(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{O}-$, $-\text{O}(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{NR}^3-$, $-(\text{C}=\text{O})\text{NR}^3-\text{O}-$, $-\text{NR}^3(\text{C}=\text{O})-$, $-\text{NR}^3(\text{C}=\text{O})\text{NR}^3-$, $-\text{NR}^3(\text{C}=\text{O})\text{O}-$, $-\text{NR}^3(\text{SO}_2)-$, $-(\text{SO}_2)\text{NR}^3-$, or $-\text{O}-(\text{SO}_2)-$; Y^2 is independently H, $-\text{CN}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$; and each R^6 is independently H or substituted or unsubstituted C_1 - C_4 alkyl.

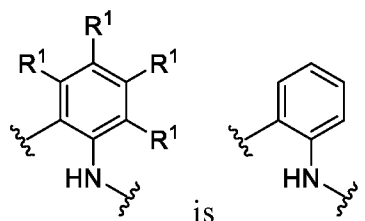
[00106] In some embodiments, X is $-\text{L}^5-\text{L}^6-\text{L}^3-\text{Y}^2$. In some embodiments, X is $-\text{L}^6-\text{L}^5-\text{L}^3-\text{Y}^2$. In some embodiments, L^5 is substituted or unsubstituted C_1 - C_4 alkylene. In some embodiments, L^5 is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. In some embodiments, L^6 is substituted or unsubstituted C_3 - C_6 cycloalkylene. In some embodiments, L^6 is substituted or unsubstituted cyclopropylene, substituted or unsubstituted cyclobutylene, substituted or unsubstituted cyclopentylene, or substituted or unsubstituted cyclohexylene.

[00107] In some embodiments, each R^1 is independently H. In some embodiments, each R^1 is independently halogen. In some embodiments, each R^1 is independently $-\text{CN}$. In some embodiments, each R^1 is independently $-\text{OR}^4$. In some embodiments, each R^1 is independently $-\text{SR}^4$. In some embodiments, each R^1 is independently $-\text{N}(\text{R}^4)_2$. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^1 is independently $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, or $-\text{C}(\text{CH}_3)_3$. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^1 is independently $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_6 alkenyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_4 alkenyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_6 alkynyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_4 alkynyl. In some

embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, each R^1 is independently substituted or unsubstituted aralkyl. In some embodiments, each R^1 is independently substituted or unsubstituted benzyl. In some embodiments, each R^1 is independently substituted or unsubstituted aryl. In some embodiments, each R^1 is independently substituted or unsubstituted phenyl. In some embodiments, each R^1 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^1 is independently substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R^1 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In some embodiments, each R^1 is independently $-L^7-Y^3$.

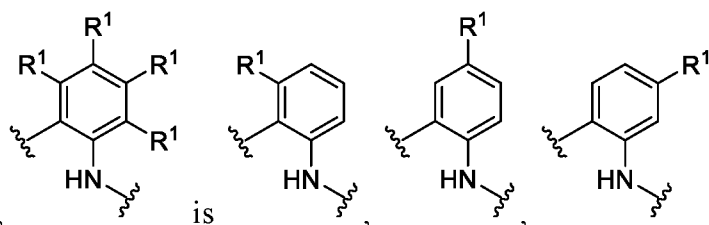
[00108] In some embodiments, L^7 is substituted or unsubstituted C_1 - C_6 alkylene. In some embodiments, L^7 is substituted or unsubstituted C_1 - C_4 alkylene. In some embodiments, L^7 is $-CH_2-$,

-CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-. In some embodiments, Y³ is -Si(R⁷)₂. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁷ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃.



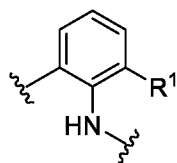
[00109] In some embodiments,

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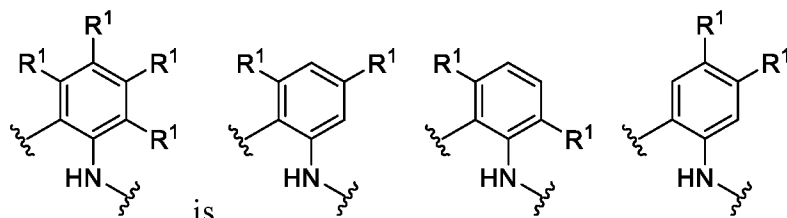
[00110] In some embodiments,

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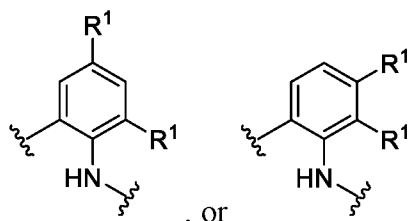
and R¹ is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00111] In some embodiments, R¹ is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R¹ is halogen, substituted or unsubstituted C₁-C₄alkyl, or substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, R¹ is F, Cl, Br, I, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -C(CH₃)₃, -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.



[00112] In some embodiments,

is



; and each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

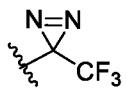
[00113] In some embodiments, each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R^1 is independently halogen, substituted or unsubstituted C_1 - C_4 alkyl, or substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^1 is independently F, Cl, Br, I, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$.

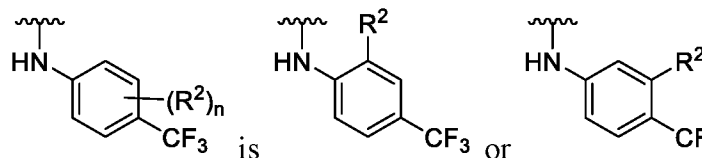
[00114] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[00115] In some embodiments, each R^2 is independently H. In some embodiments, each R^2 is independently halogen. In some embodiments, each R^2 is independently $-\text{N}_3$. In some embodiments, each R^2 is independently $-\text{CN}$. In some embodiments, each R^2 is independently $-\text{OR}^5$. In some embodiments, each R^2 is independently $-\text{SR}^5$. In some embodiments, each R^2 is independently $-(\text{SO}_2)\text{R}^5$. In some embodiments, each R^2 is independently $-\text{N}(\text{R}^5)_2$. In some embodiments, each R^2 is independently $-\text{CO}_2\text{R}^5$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^2 is independently $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, or $-\text{C}(\text{CH}_3)_3$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^2 is independently $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$. In some embodiments, each R^2 is independently substituted or unsubstituted C_2 - C_6 alkenyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_2 - C_4 alkenyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_2 - C_6 alkynyl. In some embodiments, each R^2 is

independently substituted or unsubstituted C₂-C₄alkynyl. In some embodiments, each R² is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R² is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R² is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R² is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, each R² is independently substituted or unsubstituted aralkyl. In some embodiments, each R² is independently substituted or unsubstituted benzyl. In some embodiments, each R² is independently substituted or unsubstituted aryl. In some embodiments, each R² is independently substituted or unsubstituted phenyl. In some embodiments, each R² is independently substituted or unsubstituted heteroaryl. In some embodiments, each R² is independently substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R² is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In

some embodiments, each R² is independently





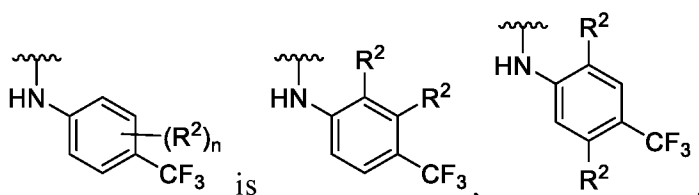
[00116] In some embodiments, halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl, or .

[00117] In some embodiments, R² is halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted

phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and each R⁵ is independently H, or substituted or unsubstituted C₁-C₄alkyl. In some embodiments, R² is halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted

C₁-C₄haloalkyl, or .



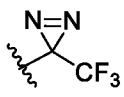
[00118] In some embodiments, wherein:

or ; and each R² is independently halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted aralkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or . In some embodiments, each R² is independently halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted

phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and each R⁵ is

independently H, or substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R² is independently halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl,

substituted or unsubstituted C₁-C₄haloalkyl, or .

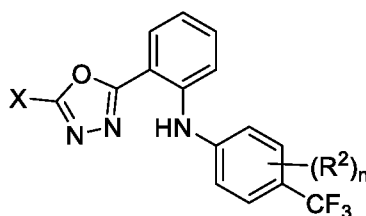
[00119] In some embodiments, each R⁴ is independently H. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁴ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R⁴ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aralkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted benzyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aryl. In some embodiments, each R⁴ is independently substituted or unsubstituted phenyl. In some embodiments, each R⁴ is independently substituted or unsubstituted heteroaryl. In some embodiments, each R⁴ is independently substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R⁴ is independently substituted or

unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In some embodiments, two R⁴ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00120] In some embodiments, each R⁵ is independently H. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁵ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R⁵ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, each R⁵

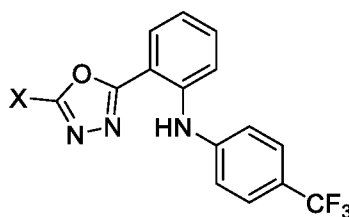
is independently substituted or unsubstituted aralkyl. In some embodiments, each R^5 is independently substituted or unsubstituted benzyl. In some embodiments, each R^5 is independently substituted or unsubstituted aryl. In some embodiments, each R^5 is independently substituted or unsubstituted phenyl. In some embodiments, each R^5 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^5 is independently substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R^5 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanlyl. In some embodiments, two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00121] In some embodiments, the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



Formula (Ia).

[00122] In some embodiments, the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:

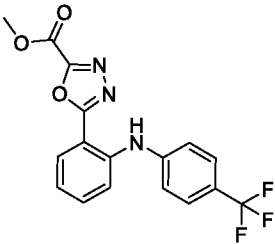
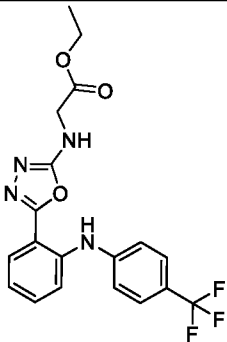
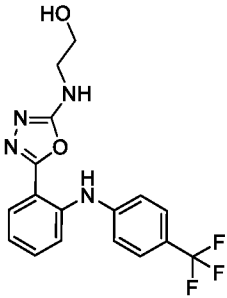
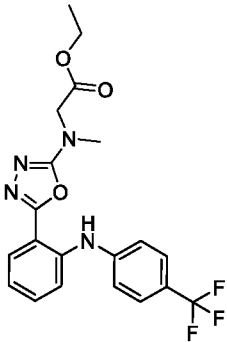
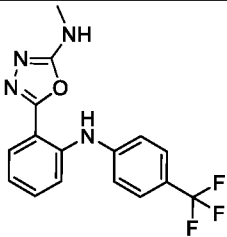


Formula (Ib).

[00123] In some embodiments, the compound disclosed herein has the structure provided in Table 1.

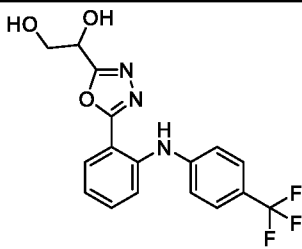
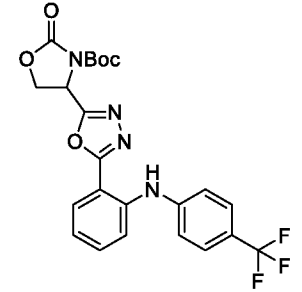
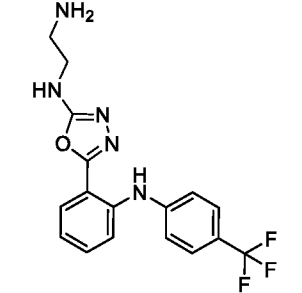
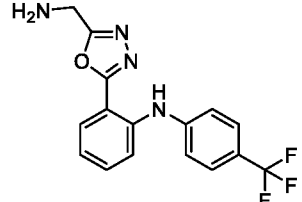
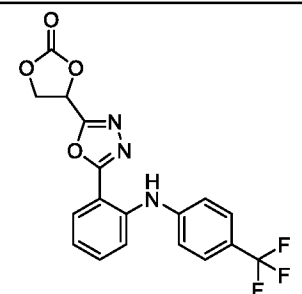
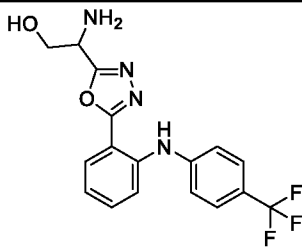
TABLE 1

Compound No.	Structure	Name
1		ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate
2		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol
3		ethyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate
4		5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine
5		(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol
6		N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine

Compound No.	Structure	Name
8		methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate
9		ethyl (5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate
10		2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol
11		ethyl N-methyl-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate
12		N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine

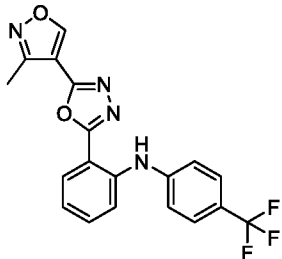
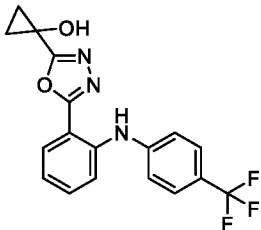
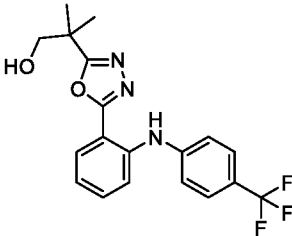
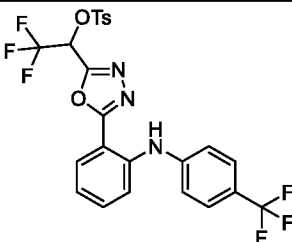
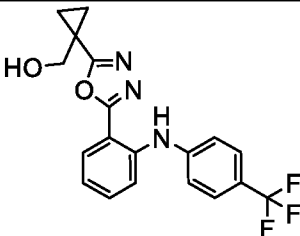
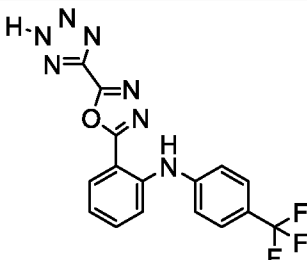
Compound No.	Structure	Name
13		5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
14		N-hydroxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
15		5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
16		3-tosyl-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
17		4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
18		(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycine

Compound No.	Structure	Name
19		2-(methyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol
20		2-(1,3,4-oxadiazol-2-yl)-N-[4-(trifluoromethyl)phenyl]aniline
21		2-[5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline
22		5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carbonitrile
23		1-(4-methoxybenzyl)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)urea
24		2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide

Compound No.	Structure	Name
25		1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethane-1,2-diol
26		2-oxo-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidine-3-carboxylate
27		N1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethane-1,2-diamine
28		2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline
29		4-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-1,3-dioxolan-2-one
30		2-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

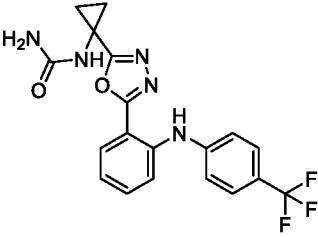
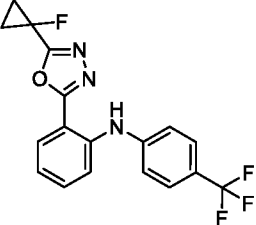
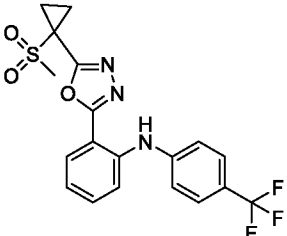
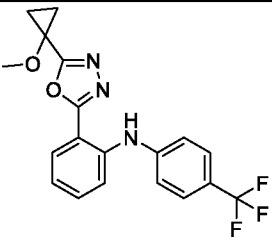
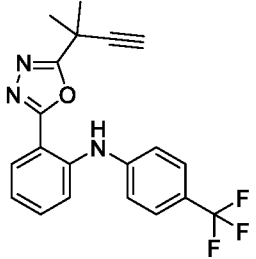
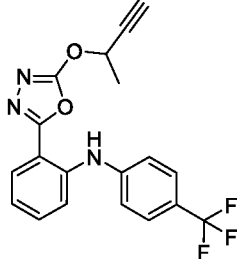
Compound No.	Structure	Name
31		2-[5-(azidomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline
32		N-(2-hydroxyethyl)-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide
33		N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)benzenesulfonamide
34		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)imidazolidin-2-one
35		2-(5-(5-methyloxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
36		2-(5-(oxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
37		2-(5-(oxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
38		N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide
39		2-(5-(4-methyloxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
40		2-(5-(5-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
41		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol
42		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol

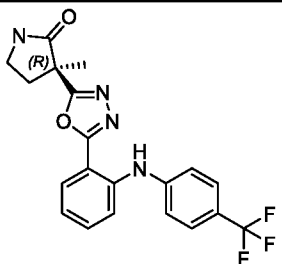
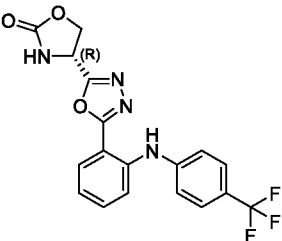
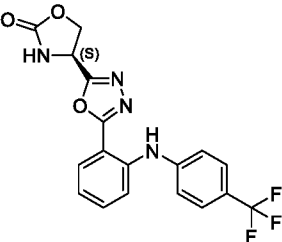
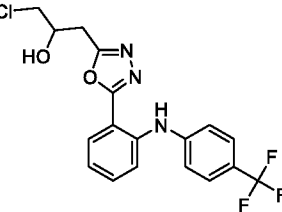
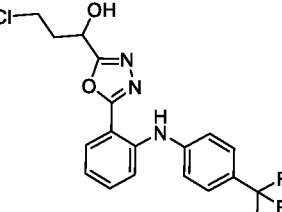
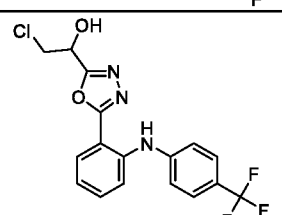
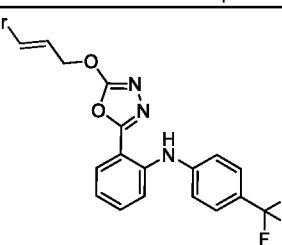
Compound No.	Structure	Name
43		2-(5-(3-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
44		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropanol
45		2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol
46		2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl 4-methylbenzenesulfonate
47		(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methanol
48		2-[5-(2H-tetrazol-5-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

Compound No.	Structure	Name
49		cyclopropyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol
50		3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-5-one
51		2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol
52		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopentanol
53		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl 4-methylbenzenesulfonate
54		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclobutanol

Compound No.	Structure	Name
55		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxetan-3-ol
56		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3-ol
57		(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate
58		2-(5-(1-aminocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
59		N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)acetamide
60		2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol
61		4-bromo-2-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
62		1-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)urea
63		2-(5-(1-fluorocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
66		2-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline
67		2-(5-(1-methoxycyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
68		2-(5-(2-methylbut-3-yn-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
69		2-(5-(but-3-yn-2-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

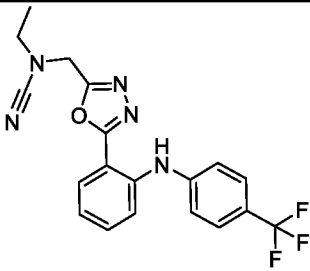
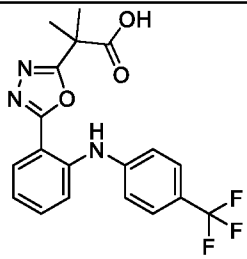
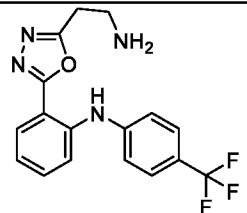
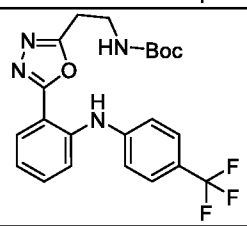
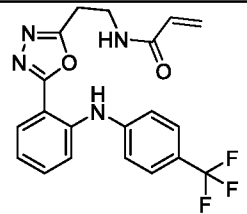
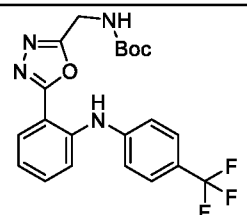
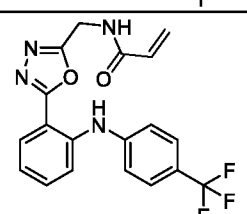
Compound No.	Structure	Name
70		2-(5-(but-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
71		2-(5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
72		2-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
73		2-(5-methoxy-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
74		(S)-4-(5-(4,5-difluoro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
75		(S)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one

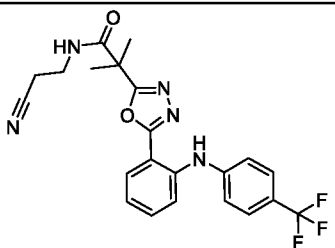
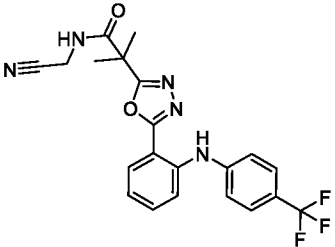
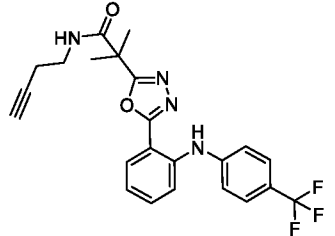
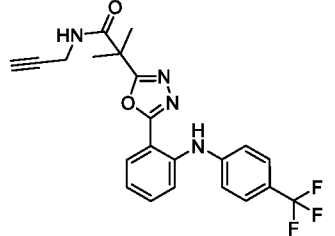
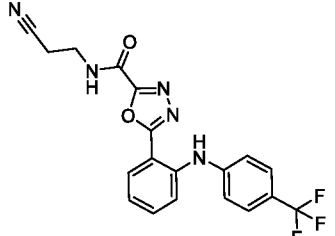
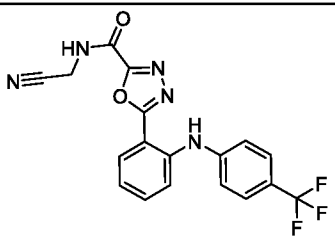
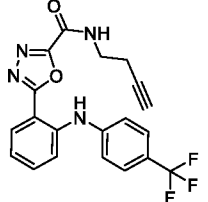
Compound No.	Structure	Name
76		(R)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one
77		(R)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
78		(S)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
79		1-chloro-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol
80		3-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol
81		2-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol
82		(E)-2-(5-((3-bromoallyl)oxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
83		2-(5-(prop-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
84		2-(5-(allyloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
85		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-one
86		2-(5-(2-methyl-1,3-dioxolan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
87		N-methoxy-N,2-dimethyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
88		1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyclopropane-1-carbonitrile

Compound No.	Structure	Name
89		2,2-dimethyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile
90		2-(5-ethyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
91		2-(5-(2-(isopropylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
92		tert-butyl isopropyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate
93		N-isopropyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide
94		2-(5-(2-(ethylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
95		tert-butyl ethyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

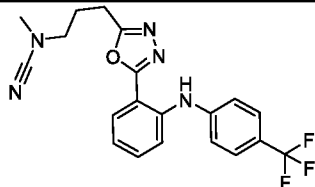
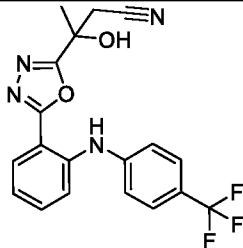
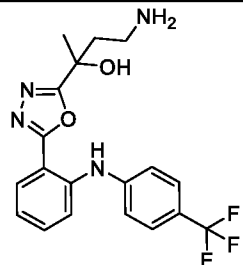
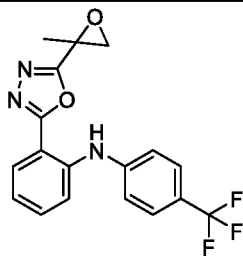
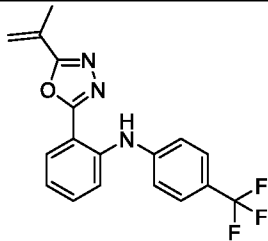
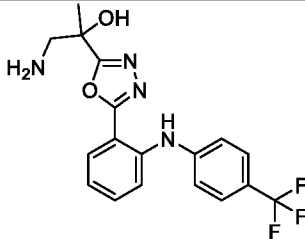
Compound No.	Structure	Name
96		N-ethyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide
97		2-(5-((isopropylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
98		tert-butyl isopropyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate
99		N-isopropyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide
100		2-(5-((ethylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
101		tert-butyl ethyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate

Compound No.	Structure	Name
102		N-ethyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide
103		2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoic acid
104		2-(5-(2-aminoethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
105		tert-butyl (2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate
106		N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)acrylamide
107		tert-butyl ((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate
108		N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)acrylamide

Compound No.	Structure	Name
109		N-(2-cyanoethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
110		N-(cyanomethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
111		N-(but-3-yn-1-yl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
112		2-methyl-N-(prop-2-yn-1-yl)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
113		N-(2-cyanoethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
114		N-(cyanomethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
115		N-(but-3-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide

Compound No.	Structure	Name
116		N-(prop-2-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
117		(E)-2-(5-(prop-1-en-1-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
118		2-(5-(2,2-diethoxyethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
119		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetic acid
120		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-2-ol
121		2-bromo-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol

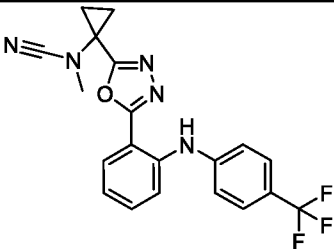
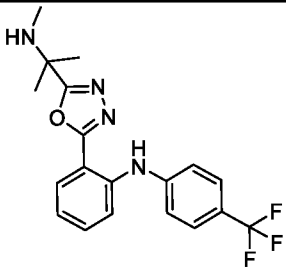
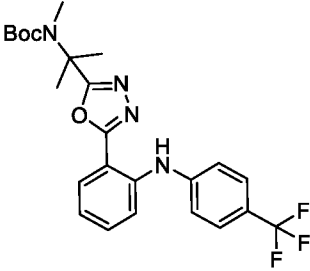
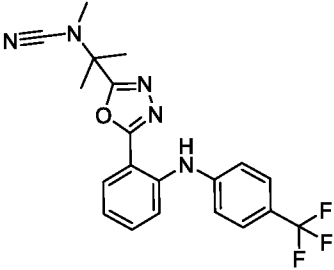
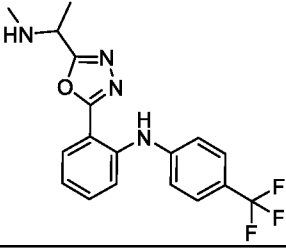
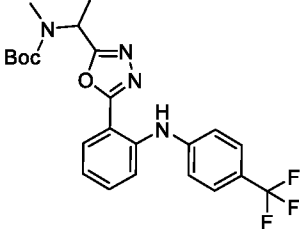
Compound No.	Structure	Name
122		2-(5-(oxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
123		N-(4-(trifluoromethyl)phenyl)-2-(5-vinyl-1,3,4-oxadiazol-2-yl)aniline
124		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-1-ol
125		4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile
126		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile
127		2-(5-(3-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
128		tert-butyl methyl(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate

Compound No.	Structure	Name
129		N-methyl-N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide
130		3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile
131		4-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol
132		2-(5-(2-methyloxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
133		2-(5-(prop-1-en-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
134		1-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol

Compound No.	Structure	Name
135		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol
136		2-(5-((1-aminocyclopropyl)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
137		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetonitrile
138		2-(5-(1-((methylamino)methyl)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
139		tert-butyl methyl((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)carbamate
140		N-methyl-N-((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)cyanamide

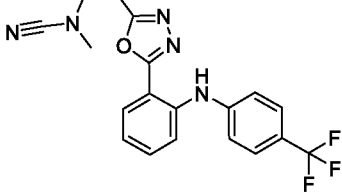
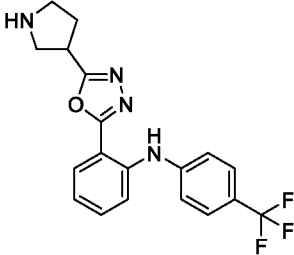
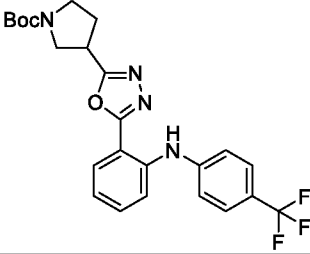
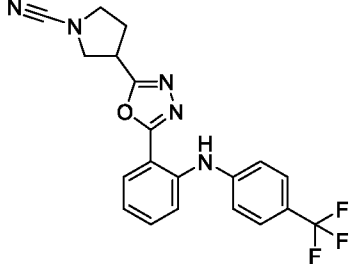
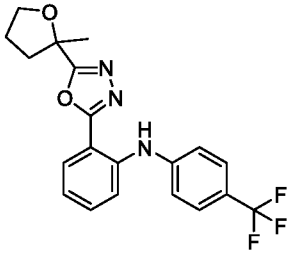
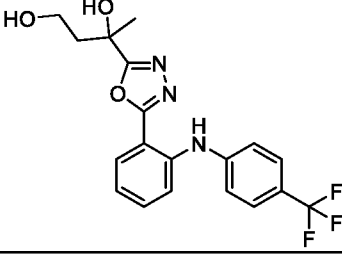
Compound No.	Structure	Name
141		2-(5-(2-methyl-2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
142		tert-butyl methyl(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate
143		N-methyl-N-(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide
144		2-(5-(2-methyl-1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
145		tert-butyl methyl(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate
146		N-methyl-N-(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide
147		2-(5-(2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
148		tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate
149		N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide
150		2-(5-(1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
151		tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate
152		N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide
153		2-(5-(1-(methylamino)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
154		tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate

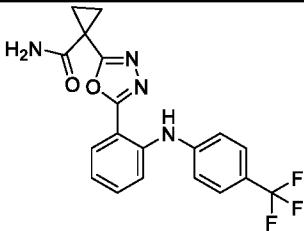
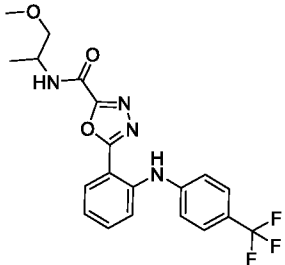
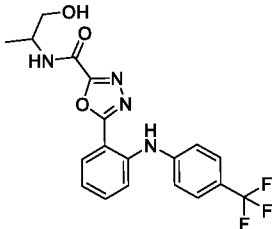
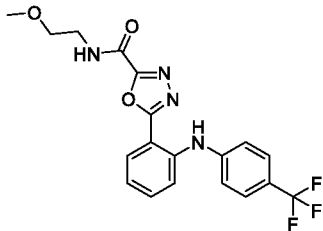
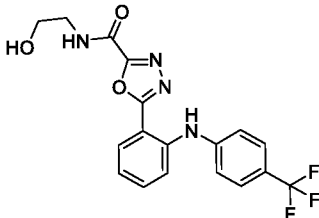
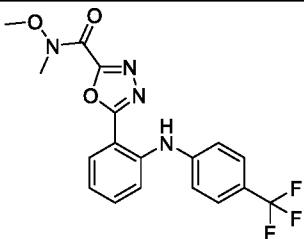
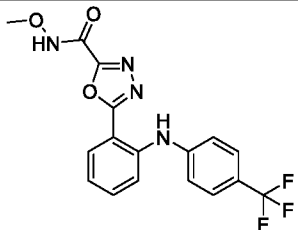
Compound No.	Structure	Name
155		N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)cyanamide
156		2-(5-(2-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
157		tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate
158		N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide
159		2-(5-(1-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
160		tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

Compound No.	Structure	Name
161		N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide
162		2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
163		2-(5-(2-(methylsulfonyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
164		2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile
165		tert-butyl 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylate
166		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylic acid

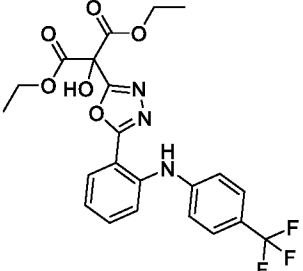
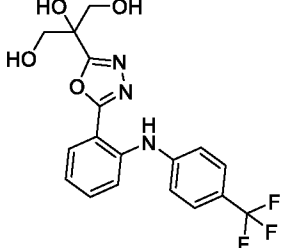
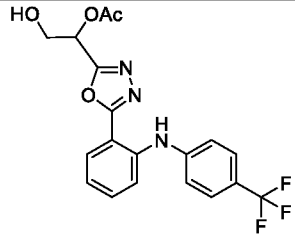
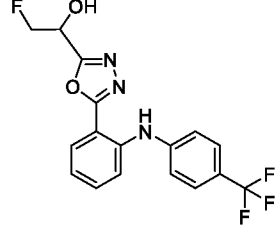
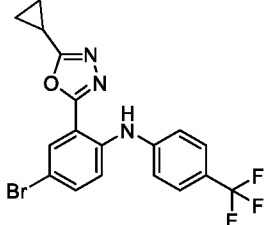
Compound No.	Structure	Name
167		tert-butyl methyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate
168		N-methyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide
169		2-(5-(pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
170		tert-butyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate
171		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile
172		2-(5-(2-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
173		tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

Compound No.	Structure	Name
174		N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide
175		2-(5-(pyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
176		tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate
177		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile
178		2-(5-(2-methyltetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
179		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butane-1,3-diol

Compound No.	Structure	Name
180		2-(5-(2-methyloxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
181		2-(5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
182		2-(5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
183		2-(5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
184		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carbonitrile
185		N,N-dimethyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide
186		N-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide

Compound No.	Structure	Name
187		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide
188		N-(1-methoxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
189		N-(1-hydroxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
190		N-(2-methoxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
191		N-(2-hydroxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
192		N-methoxy-N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
193		N-methoxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide

Compound No.	Structure	Name
194		N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
195		N-cyclopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
196		N-isopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
197		N-ethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
198		N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
199		2,2-dimethyl-5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)-1,3-dioxan-5-ol

Compound No.	Structure	Name
200		diethyl 2-hydroxy-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)malonate
201		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propane-1,2,3-triol
202		2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl acetate
203		2-fluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol
204		4-bromo-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Preparation of the Compounds

[00124] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH Inc. (Toronto, Canada), Bionet

(Cornwall, U.K.), Chemservice Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

[00125] Methods known to one of ordinary skill in the art are identified through various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[00126] In some instances, specific and analogous reactants are identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., is contacted for more details). Chemicals that are known but not commercially available in catalogs are prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

[00127] In some embodiments, the compounds disclosed herein are prepared as described in the Examples section.

Further Forms of Compounds Disclosed Herein

Isomers

[00128] Furthermore, in some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all *cis*, *trans*, *syn*, *anti*, *entgegen* (*E*), and *zusammen* (*Z*) isomers as well as the corresponding mixtures thereof. In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the *R* configuration, or *S* configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred (*e.g.*, crystalline diastereomeric salts). In some embodiments, the diastereomers have distinct physical properties (*e.g.*, melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Labeled compounds

[00129] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. In some embodiments, examples of isotopes that are incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, and the metabolites, pharmaceutically acceptable salts, esters, prodrugs, solvates, hydrates or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this disclosure. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^3H and carbon-14, i. e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, i. e., ^2H , produces certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof is prepared by any suitable method.

[00130] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00131] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00132] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ*

during the final isolation and purification of the compounds of the disclosure, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

Solvates

[00133] In some embodiments, the compounds described herein exist as solvates. The disclosure provides for methods of treating diseases by administering such solvates. The disclosure further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00134] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In some embodiments, solvates of the compounds described herein are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In some embodiments, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Prodrugs

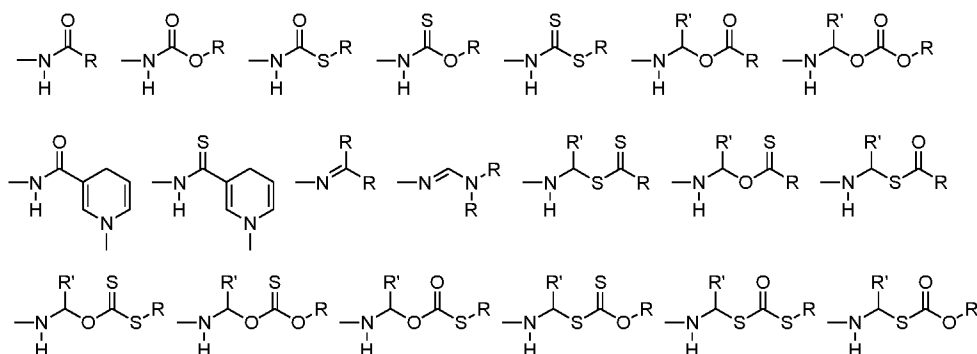
[00135] In some embodiments, the compounds described herein exist in prodrug form. The disclosure provides for methods of treating diseases by administering such prodrugs. The disclosure further provides for methods of treating diseases by administering such prodrugs as pharmaceutical compositions.

[00136] In some embodiments, prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e. g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy, or carboxylic acid group of compounds of the present disclosure. The amino acid residues include but are not limited to the 20 naturally occurring amino acids and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, cirtulline, homocysteine, homoserine, ornithine and methionine sulfone. In other embodiments, prodrugs include compounds wherein a nucleic acid residue, or an oligonucleotide of two or more (e. g., two, three or four) nucleic acid residues is covalently joined to a compound of the present disclosure.

[00137] Pharmaceutically acceptable prodrugs of the compounds described herein also include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, metal salts and sulfonate esters. In some embodiments, compounds having free amino, amido, hydroxy, or carboxylic groups are converted into prodrugs. For instance, free carboxyl groups are derivatized as amides or alkyl esters. In certain instances, all of these prodrug moieties incorporate groups including but not limited to ether, amine, and carboxylic acid functionalities.

[00138] Hydroxy prodrugs include esters, such as though not limited to, acyloxyalkyl (e.g. acyloxymethyl, acyloxyethyl) esters, alkoxycarbonyloxyalkyl esters, alkyl esters, aryl esters, sulfonate esters, sulfate esters and disulfide containing esters; ethers, amides, carbamates, hemisuccinates, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews* **1996**, 19, 115.

[00139] Amine derived prodrugs include, but are not limited to, the following groups and combinations of groups:



as well as sulfonamides and phosphonamides.

[00140] In certain instances, sites on any aromatic ring portions are susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, reduce, minimize, or eliminate this metabolic pathway.

Metabolites

[00141] In some embodiments, compounds described herein are susceptible to various metabolic reactions. Therefore, in some embodiments, incorporation of appropriate substituents into the structure will reduce, minimize, or eliminate a metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of an aromatic ring to metabolic reactions is, by way of example only, a halogen, or an alkyl group.

[00142] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

Pharmaceutical Compositions

[00143] In certain embodiments, the compound as described herein is administered as a pure chemical. In other embodiments, the compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)), the disclosure of which is hereby incorporated herein by reference in its entirety.

[00144] Accordingly, provided herein is a pharmaceutical composition comprising at least one compound described herein, or a stereoisomer, pharmaceutically acceptable salt, hydrate, solvate, or N-oxide thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.*, the subject) of the composition.

[00145] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[00146] Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[00147] In certain embodiments, the compound as described herein is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as contaminating intermediates or by-products that are created, for example, in one or more of the steps of a synthesis method.

[00148] These formulations include those suitable for oral, rectal, topical, buccal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, or intravenous), rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions are formulated as a unit dose, and/or are formulated for oral or subcutaneous administration.

[00149] In some instances, exemplary pharmaceutical compositions are used in the form of a pharmaceutical preparation, for example, in solid, semisolid, or liquid form, which includes one or more of a disclosed compound, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral applications. In some embodiments, the active ingredient is compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions,

and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[00150] For preparing solid compositions such as tablets in some instances, the principal active ingredient is mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a disclosed compound or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition is readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[00151] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions also comprise buffering agents in some embodiments. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[00152] In some instances, a tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets are prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets are made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, are optionally be scored or prepared with coatings and

shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[00153] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms contain optionally inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[00154] Suspensions, in addition to the subject composition, optionally contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00155] In some embodiments, formulations for rectal or vaginal administration are presented as a suppository, which are prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[00156] Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component is optionally mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which are required in some embodiments.

[00157] In some embodiments, the ointments, pastes, creams and gels contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[00158] In some embodiments, powders and sprays contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00159] Compositions and compounds disclosed herein are alternatively administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (*e.g.*, fluorocarbon propellant) suspension could be used. Sonic nebulizers are used because they minimize exposing the agent to shear, which result in degradation of the compounds contained in the subject compositions in some embodiments. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronic, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[00160] Pharmaceutical compositions suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which are reconstituted into sterile injectable solutions or dispersions just prior to use, which optionally contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[00161] Examples of suitable aqueous and non-aqueous carriers employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. In some embodiments, proper fluidity is maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00162] Also contemplated are enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about

8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (*e.g.*, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present disclosure.

[00163] In some embodiments, the dose of the composition comprising at least one compound as described herein differ, depending upon the patient's (*e.g.*, human) condition, that is, stage of the disease, general health status, age, and other factors that a person skilled in the medical art will use to determine dose.

[00164] In some instances, pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented) as determined by persons skilled in the medical arts. An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity). Optimal doses are generally determined using experimental models and/or clinical trials. In some embodiments, the optimal dose depends upon the body mass, weight, or blood volume of the patient.

[00165] In some embodiments, oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

The Hippo Signaling Network

[00166] The Hippo signaling network (also known as the Salvador/Warts/Hippo (SWH) pathway) is a master regulator of cell proliferation, death, and differentiation. In some embodiments, the main function of the Hippo signaling pathway is to regulate negatively the transcriptional co-activators Yes-associated protein (YAP) and its paralogue, the transcriptional co-activator with PDZ-binding motif (TAZ; also known as WWTR1) (**FIG. 1**). The Hippo kinase cascade phosphorylates and inhibits YAP/TAZ by promoting its cytoplasmic retention and degradation, thereby inhibiting the growth promoting function regulated under the YAP/TAZ control. In an un-phosphorylated/de-phosphorylated state, YAP, also known as YAP1 or YAP65, together with TAZ, are transported into the nucleus where they interact with TEAD family of transcription factors to upregulate genes that promote proliferation and migration, and inhibit apoptosis. In some instances, unregulated upregulation of these genes involved in proliferation, migration, and anti-apoptosis leads to development of cancer. In some instances, overexpression of YAP/TAZ is associated with cancer.

[00167] Additional core members of the Hippo signaling pathway comprise the serine/threonine kinases MST1/2 (homologues of *Hippo/Hpo* in *Drosophila*), Lats1/2 (homologues of *Warts/Wts*), and their adaptor proteins Sav1 (homologue of *Salvador/Sav*) and Mob (MOBKL1A and MOBKL1B; homologues of *Mats*), respectively (**FIG. 1**). In general, MST1/2 kinase complexes with the scaffold protein Sav1, which in turn phosphorylates and activates Lats1/2 kinase. Lats1/2 is also activated by the scaffold protein Mob. The activated Lats1/2 then phosphorylates and inactivates YAP or its paralog TAZ. The phosphorylation of YAP/TAZ leads to their nuclear export, retention within the cytoplasm, and degradation by the ubiquitin proteasome system.

[00168] In some instances, Lats1/2 phosphorylates YAP at the [HXRXXS] consensus motifs. YAP comprises five [HXRXXS] consensus motifs, wherein X denotes any amino acid residue. In some instances, Lats1/2 phosphorylates YAP at one or more of the consensus motifs. In some instances, Lats1/2 phosphorylates YAP at all five of the consensus motifs. In some instances, Lats1/2 phosphorylate at the S127 amino acid position. The phosphorylation of YAP S127 promotes 14-3-3 protein binding and results in cytoplasmic sequestration of YAP. Mutation of YAP at the S127 position thereby disrupts its interaction with 14-3-3 and subsequently promotes nuclear translocation.

[00169] Additional phosphorylation occurs at the S381 amino acid position in YAP. Phosphorylation of YAP at the S381 position and on the corresponding site in TAZ primes both proteins for further phosphorylation events by CK1 δ/ϵ in the degradation motif, which then signals

for interaction with the β -TRCP E3 ubiquitin ligase, leading to polyubiquitination and degradation of YAP.

[00170] In some instances, Lats1/2 phosphorylates TAZ at the [HXRXXS] consensus motifs. TAZ comprises four [HXRXXS] consensus motifs, wherein X denotes any amino acid residues. In some instances, Lats1/2 phosphorylates TAZ at one or more of the consensus motifs. In some instances, Lats1/2 phosphorylates TAZ at all four of the consensus motifs. In some instances, Lats1/2 phosphorylate at the S89 amino acid position. The phosphorylation of TAZ S89 promotes 14-3-3 protein binding and results in cytoplasmic sequestration of TAZ. Mutation of TAZ at the S89 position thereby disrupts its interaction with 14-3-3 and subsequently promotes nuclear translocation.

[00171] In some embodiments, phosphorylated YAP/TAZ accumulates in the cytoplasm, and undergoes SCF ^{β -TRCP}-mediated ubiquitination and subsequent proteasomal degradation. In some instances, the Skp, Cullin, F-box containing complex (SCF complex) is a multi-protein E3 ubiquitin ligase complex that comprises a F-box family member protein (e.g. Cdc4), Skp1, a bridging protein, and RBX1 which contains a small RING Finger domain which interacts with E2-ubiquitin conjugating enzyme. In some cases, the F-box family comprises more than 40 members, in which exemplary members include F-box/WD repeat-containing protein 1A (FBXW1A, β TrCP1, Fbxw1, hsSlimb, plkappaBalpha-E3 receptor subunit) and S-phase kinase-associated proteins 2 (SKP2). In some embodiments, the SCF complex (e.g. SCF ^{β TrCP1}) interacts with an E1 ubiquitin-activating enzyme and an E2 ubiquitin-conjugating enzyme to catalyze the transfer of ubiquitin to the YAP/TAZ substrate. Exemplary E1 ubiquitin-activating enzymes include those encoded by the following genes: *UBA1*, *UBA2*, *UBA3*, *UBA5*, *UBA5*, *UBA7*, *ATG7*, *NAE1*, and *SAE1*. Exemplary E2 ubiquitin-conjugating enzymes include those encoded by the following genes: *UBE2A*, *UBE2B*, *UBE2C*, *UBE2D1*, *UBE2D2*, *UBE2D3*, *UBE2E1*, *UBE2E2*, *UBE2E3*, *UBE2F*, *UBE2G1*, *UBE2G2*, *UBE2H*, *UBE2I*, *UBE2J1*, *UBE2J2*, *UBE2K*, *UBE2L3*, *UBE2L6*, *UBE2M*, *UBE2N*, *UBE2O*, *UBE2Q1*, *UBE2Q2*, *UBE2R1*, *UBE2R2*, *UBE2S*, *UBE2T*, *UBE2U*, *UBE2V1*, *UBE2V2*, *UBE2Z*, *ATG2*, *BIRC5*, and *UFC1*. In some embodiments, the ubiquitinated YAP/TAZ further undergoes the degradation process through the 26S proteasome.

[00172] In some embodiments, the Hippo pathway is regulated upstream by several different families of regulators (**FIG. 1**). In some instances, the Hippo pathway is regulated by the G-protein and its coupled receptors, the Crumbs complex, regulators upstream of the MST kinases, and the adherens junction.

YAP/TAZ Interaction with TEAD

[00173] In some embodiments, un-phosphorylated and/or dephosphorylated YAP/TAZ accumulates in the nucleus. Within the nucleus, YAP/TAZ interacts with the TEAD family of transcription factors (e.g. TEAD1, TEAD2, TEAD3, or TEAD4) to activate genes involved in anti-apoptosis and proliferation, such as for example *CTFG*, *Cyr61*, and *FGF1*.

[00174] In some embodiments, the compounds disclosed herein modulate the interaction between YAP/TAZ and TEAD. In some embodiments, the compounds disclosed herein bind to TEAD, YAP, or TAZ and prevent the interaction between YAP/TAZ and TEAD.

YAP/TAZ regulation mediated by G-proteins/GPCRs

[00175] In some embodiments, the Hippo pathway is regulated by the G protein-coupled receptor (GPCR) and G protein (also known as guanine nucleotide-binding proteins) family of proteins (**FIG. 2**). G proteins are molecular switches that transmit extracellular stimuli into the cell through GPCRs. In some instances, there are two classes of G proteins: monomeric small GTPases; and heterotrimeric G protein complexes. In some instances, the latter class of complexes comprise of alpha (G_α), beta (G_β), and gamma (G_γ) subunits. In some cases, there are several classes of G_α subunits: $G_{q/11}\alpha$, $G_{12/13}\alpha$, $G_{i/o}\alpha$ (G inhibitory, G other), and $G_s\alpha$ (G stimulatory).

[00176] In some instances, $G_i\alpha$ (G inhibitory), $G_o\alpha$ (G other), $G_{q/11}\alpha$, and $G_{12/13}\alpha$ coupled GPCRs activate YAP/TAZ and promote nuclear translocation. In other instances, $G_s\alpha$ (G stimulatory) coupled GPCRs suppress YAP/TAZ activity, leading to YAP/TAZ degradation.

[00177] In some cases, $G_i\alpha$ (G inhibitory), $G_o\alpha$ (G other), $G_{q/11}\alpha$, and $G_{12/13}\alpha$ coupled GPCRs activate YAP/TAZ through repression of Lats1/2 activities. In contrast, $G_s\alpha$, in some embodiments, induces Lats1/2 activity, thereby promoting YAP/TAZ degradation.

G_q Family

[00178] $G_q\alpha$ (also known as $G_{q/11}$ protein), participates in the inositol trisphosphate (IP_3) signal transduction pathway and calcium (Ca^{2+}) release from intracellular storage through the activation of phospholipase C (PLC). The activated PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacyl glycerol (DAG) and IP_3 . In some instances, IP_3 then diffuses through the cytoplasm into the ER or the sarcoplasmic reticulum (SR) in the case of muscle cells, and then binds to inositol trisphosphate receptor ($InsP3R$), which is a Ca^{2+} channel. In some cases, the binding triggers the opening of the Ca^{2+} channel, and thereby increases the release of Ca^{2+} into the cytoplasm.

[00179] In some embodiments, the GPCRs that interact with $G_q\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT₂ and 5-HT₃; alpha-1 adrenergic receptor; vasopressin type 1 receptors 1A and 1B; angiotensin II receptor type 1; calcitonin receptor;

histamine H1 receptor; metabotropic glutamate receptor, group I; muscarinic receptors M₁, M₃, and M₅; and trace amine-associated receptor 1.

[00180] In some instances, there are several types of G_qα: G_q, G_{q/11}, G_{q/14}, and G_{q/15}. The G_q protein is encoded by *GNAQ*. G_{q/11} is encoded by *GNAI1*. G_{q/14} is encoded by *GNAI4*. G_{q/15} is encoded by *GNAI5*.

[00181] In some instances, mutations or modifications of the G_qα genes have been associated with cancer. Indeed, studies have shown that mutations in G_qα promote uveal melanoma (UM) tumorigenesis. In some instances, about 80% of UM cases have been detected to contain a mutation in *GNAQ* and/or *GNAI1*.

[00182] In some instances, mutations or modifications of the G_qα genes have been associated with congenital diseases. In some instances, mutations of G_qα have been observed in congenital diseases such as Port-Wine Stain and/or Sturge-Weber Syndrome. In some instances, about 92% of Port-Wine stain cases harbors a mutation in *GNAQ*. In some instances, about 88% of Sturge-Weber Syndrome harbors a mutation in *GNAQ*.

G_{12/13} Family

[00183] G_{12/13}α modulates actin cytoskeletal remodeling in cells and regulates cell processes through guanine nucleotide exchange factors (GEFs). GEFs participate in the activation of small GTPases which acts as molecular switches in a variety of intracellular signaling pathways. Examples of small GTPases include the Ras-related GTPase superfamily (e.g. Rho family such as Cdc42), which is involved in cell differentiation, proliferation, cytoskeletal organization, vesicle trafficking, and nuclear transport.

[00184] In some embodiments, the GPCRs that interact with G_{12/13}α include, but are not limited to, purinergic receptors (e.g. P2Y₁, P2Y₂, P2Y₄, P2Y₆); muscarinic acetylcholine receptors M1 and M3; receptors for thrombin [protease-activated receptor (PAR)-1, PAR-2]; thromboxane (TXA₂); sphingosine 1-phosphate (e.g. S1P₂, S1P₃, S1P₄ and S1P₅); lysophosphatidic acid (e.g. LPA₁, LPA₂, LPA₃); angiotensin II (AT1); serotonin (5-HT_{2c} and 5-HT₄); somatostatin (sst₅); endothelin (ET_A and ET_B); cholecystikinin (CCK₁); V_{1a} vasopressin receptors; D₅ dopamine receptors; fMLP formyl peptide receptors; GAL₂ galanin receptors; EP₃ prostanoid receptors; A₁ adenosine receptors; α₁ adrenergic receptors; BB₂ bombesin receptors; B₂ bradykinin receptors; calcium-sensing receptors; KSHV-ORF74 chemokine receptors; NK₁ tachykinin receptors; and thyroid-stimulating hormone (TSH) receptors.

[00185] In some instances, G_{12/13}α is further subdivided into G₁₂ and G₁₃ types which are encoded by *GNA12* and *GNA13*, respectively.

G_{i/o} Family

[00186] $G_{i/o}\alpha$ (G inhibitory, G other) (also known as G_i/G_o or G_i protein) that suppresses the production of 3',5'-cyclic AMP (cAMP) from adenosine triphosphate (ATP) through an inhibition of adenylate cyclase activity, which converts ATP to cAMP.

[00187] In some embodiments, the GPCRs that interact with $G_i\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT₁ and 5-HT₅; muscarinic acetylcholine receptors such as M₂ and M₄; adenosine receptors such as A₁ and A₃; adrenergic receptors such as α_{2A} , α_{2B} , and α_{2C} ; apelin receptors; calcium-sensing receptor; cannabinoid receptors CB1 and CB2; chemokine CXCR4 receptor; dopamines D₂, D₃, and D₄; GABA_B receptor; glutamate receptors such as metabotropic glutamate receptor 2 (mGluR2), metabotropic glutamate receptor 3 (mGluR3), metabotropic glutamate receptor 4 (mGluR4), metabotropic glutamate receptor 6 (mGluR6), metabotropic glutamate receptor 7 (mGluR7), and metabotropic glutamate receptor 8 (mGluR8); histamine receptors such as H₃ and H₄ receptors; melatonin receptors such as melatonin receptor type 1 (MT1), melatonin receptor type 2 (MT2), and melatonin receptor type 3 (MT3); niacin receptors such as NIACR1 and NIACR2; opioid receptors such as δ , κ , μ , and nociceptin receptors; prostaglandin receptors such as prostaglandin E receptor 1 (EP₁), prostaglandin E receptor 3 (EP₃), prostaglandin F receptor (FP), and thromboxane receptor (TP); somatostatin receptors sst1, sst2, sst3, sst4, and sst5; and trace amine-associated receptor 8.

[00188] In some instances, there are several types of $G_i\alpha$: $G_{i\alpha 1}$, $G_{i\alpha 2}$, $G_{i\alpha 3}$, $G_{i\alpha 4}$, $G_{o\alpha}$, G_t , G_{gust} , and G_z . $G_{i\alpha 1}$ is encoded by *GNAI1*. $G_{i\alpha 2}$ is encoded by *GNAI2*. $G_{i\alpha 3}$ is encoded by *GNAI3*. $G_{o\alpha}$, the a_o subunit, is encoded by *GNAO1*. G_t is encoded by *GNAT1* and *GNAT2*. G_{gust} is encoded by *GNAT3*. G_z is encoded by *GNAZ*.

G_s Family

[00189] $G_s\alpha$ (also known as G stimulatory, G_s alpha subunit, or G_s protein) activates the cAMP-dependent pathway through the activation of adenylate cyclase, which converts adenosine triphosphate (ATP) to 3',5'-cyclic AMP (cAMP) and pyrophosphate. In some embodiments, the GPCRs that interact with $G_s\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT₄, 5-HT₆, and 5-HT₇; adrenocorticotrophic hormone receptor (ACTH receptor) (also known as melanocortin receptor 2 or MC2R); adenosine receptor types A_{2a} and A_{2b}; arginine vasopressin receptor 2 (AVPR2); β -adrenergic receptors β_1 , β_2 , and β_3 ; calcitonin receptor; calcitonin gene-related peptide receptor; corticotropin-releasing hormone receptor; dopamine receptor D₁-like family receptors such as D₁ and D₅; follicle-stimulating hormone receptor (FSH-receptor); gastric inhibitory polypeptide receptor; glucagon receptor; histamine H₂ receptor; luteinizing hormone/choriogonadotropin receptor; melanocortin receptors such as MC1R, MC2R, MC3R, MC4R, and MC5R; parathyroid hormone receptor 1; prostaglandin receptor types D₂ and

I₂; secretin receptor; thyrotropin receptor; trace amine-associated receptor 1; and box jellyfish opsin.

[00190] In some instances, there are two types of G_sα: G_s and G_{olf}. G_s is encoded by *GNAS*. G_{olf} is encoded by *GNAL*.

Additional Regulators of the Hippo signaling network

[00191] In some embodiments, the additional regulator of the Hippo signaling pathway is the Crumbs (Crb) complex. The Crumbs complex is a key regulator of cell polarity and cell shape. In some instances, the Crumbs complex comprises transmembrane CRB proteins which assemble multi-protein complexes that function in cell polarity. In some instances, CRB complexes recruit members of the Angiomotin (AMOT) family of adaptor proteins that interact with the Hippo pathway components. In some instances, studies have shown that AMOT directly binds to YAP, promotes YAP phosphorylation, and inhibits its nuclear localization.

[00192] In some instances, the additional regulator of the Hippo signaling pathway comprises regulators of the MST kinase family. MST kinases monitor actin cytoskeletal integrity. In some instances, the regulators include TAO kinases and cell polarity kinase PAR-1.

[00193] In some instances, the additional regulator of the Hippo signaling pathway comprises molecules of the adherens junction. In some instances, E-Cadherin (E-cad) suppresses YAP nuclear localization and activity through regulating MST activity. In some embodiments, E-cad-associated protein α-catenin regulates YAP through sequestering YAP/14-3-3 complexes in the cytoplasm. In other instances, Ajuba protein family members interact with Lats1/2 kinase activity, thereby preventing inactivation of YAP/TAZ.

[00194] In some embodiments, additional proteins that interact with YAP/TAZ either directly or indirectly include, but are not limited to, Merlin, protocadherin Fat 1, MASK1/2, HIPK2, PTPN14, RASSF, PP2A, Salt-inducible kinases (SIKs), Scribble (SCRIB), the Scribble associated proteins Discs large (Dlg), KIBRA, PTPN14, NPHP3, LKB1, Ajuba, and ZO1/2.

[00195] In some embodiments, the compounds described herein are inhibitors of transcriptional coactivator with PDZ binding motif/Yes- associated protein transcriptional coactivator (TAZ/YAP). In some embodiments, the compounds described herein increase the phosphorylation of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP) or decrease the dephosphorylation of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP). In some embodiments, the compounds increase the ubiquitination of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP) or decrease the

deubiquitination of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP).

[00196] In some embodiments, the compounds disclosed herein are inhibitors of one or more of the proteins encompassed by, or related to, the Hippo pathway. In some instances, the one or more proteins comprise a protein shown in Figs. 1 and/or 2. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein and/or its coupled GPCR. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of the $G_q\alpha$ family proteins such as G_q , $G_{q/11}$, $G_{q/14}$, and $G_{q/15}$; the $G_{12/13}\alpha$ family of proteins such as G_{12} and G_{13} ; or the $G_i\alpha$ family of proteins such as $G_{i\alpha1}$, $G_{i\alpha2}$, $G_{i\alpha3}$, $G_{i\alpha4}$, $G_{o\alpha}$, G_t , G_{gust} , and G_z . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_q . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/11}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/14}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/15}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{12} . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{13} . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha1}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha2}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha3}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha4}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{o\alpha}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_t . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{gust} . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_z .

[00197] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a core protein of the Hippo pathway. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Sav1. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Mob. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of YAP. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of TAZ. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of TEAD.

[00198] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a protein associated with the ubiquitination and proteasomal degradation pathway. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a proteasomal degradation pathway protein (e.g. 26S proteasome).

[00199] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a protein of the Ras superfamily of proteins. In some embodiments, an inhibitor of the Hippo pathway is an

inhibitor of a protein of the Rho family of proteins. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Cdc42.

[00200] Cdc42 is a member of the Ras superfamily of small GTPases. Specifically, Cdc42 belongs to the Rho family of GTPases, in which the family members participate in diverse and critical cellular processes such as gene transcription, cell-cell adhesion, and cell cycle progression. Cdc42 is involved in cell growth and polarity, and in some instances, Cdc42 is activated by guanine nucleotide exchange factors (GEFs). In some cases, an inhibitor of Cdc42 is a compound disclosed herein.

[00201] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a deubiquitinating enzyme. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a cysteine protease or a metalloprotease. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of an ubiquitin-specific protease. USP47 is a member of the ubiquitin-specific protease (USP/UBP) superfamily of cysteine proteases. In some embodiments, the compounds disclosed herein are inhibitors of USP47.

[00202] Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

Diseases

Cancer

[00203] In some embodiments, the compounds disclosed herein are useful for treating cancer. In some embodiments, the cancer is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes-associated protein transcription coactivator (TAZ/YAP). In some embodiments, the cancer is mediated by modulation of the interaction of YAP/TAZ with TEAD. In some embodiments, the cancer is characterized by a mutant $G\alpha$ -protein. In some embodiments, the mutant $G\alpha$ -protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant $G\alpha$ -protein is G12. In some embodiments, the mutant $G\alpha$ -protein is G13. In some embodiments, the mutant $G\alpha$ -protein is Gq. In some embodiments, the mutant $G\alpha$ -protein is G11. In some embodiments, the mutant $G\alpha$ -protein is Gi. In some embodiments, the mutant $G\alpha$ -protein is Go. In some embodiments, the mutant $G\alpha$ -protein is Gs.

[00204] In some embodiments, the cancer is a solid tumor. In some instances, the cancer is a hematologic malignancy. In some instances, the solid tumor is a sarcoma or carcinoma. In some instances, the solid tumor is a sarcoma. In some instances, the solid tumor is a carcinoma.

[00205] Exemplary sarcoma includes, but is not limited to, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastoma, angiosarcoma, chondrosarcoma, chordoma, clear cell sarcoma of soft tissue, dedifferentiated liposarcoma, desmoid, desmoplastic small round cell tumor, embryonal

rhabdomyosarcoma, epithelioid fibrosarcoma, epithelioid hemangioendothelioma, epithelioid sarcoma, esthesioneuroblastoma, Ewing sarcoma, extrarenal rhabdoid tumor, extraskeletal myxoid chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, giant cell tumor, hemangiopericytoma, infantile fibrosarcoma, inflammatory myofibroblastic tumor, Kaposi sarcoma, leiomyosarcoma of bone, liposarcoma, liposarcoma of bone, malignant fibrous histiocytoma (MFH), malignant fibrous histiocytoma (MFH) of bone, malignant mesenchymoma, malignant peripheral nerve sheath tumor, mesenchymal chondrosarcoma, myxofibrosarcoma, myxoid liposarcoma, myxoinflammatory fibroblastic sarcoma, neoplasms with perivascular epithelioid cell differentiation, osteosarcoma, parosteal osteosarcoma, neoplasm with perivascular epithelioid cell differentiation, periosteal osteosarcoma, pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, PNET/extraskeletal Ewing tumor, rhabdomyosarcoma, round cell liposarcoma, small cell osteosarcoma, solitary fibrous tumor, synovial sarcoma, and telangiectatic osteosarcoma.

[00206] Exemplary carcinoma includes, but is not limited to, adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer. In some instances, the liver cancer is primary liver cancer.

[00207] In some instances, the cancer is selected from uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the cancer is uveal melanoma. In some cases, the cancer is mesothelioma. In some cases, the cancer is esophageal cancer. In some cases, the cancer is liver cancer. In some cases, the cancer is primary liver cancer.

[00208] In some instances, the cancer is a hematologic malignancy. In some embodiments, a hematologic malignancy is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, a T-cell malignancy, or a B-cell malignancy. In some instances, a hematologic malignancy is a T-cell malignancy. Exemplary T-cell malignancy includes, but is not limited to, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma, angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), blastic NK-cell lymphoma, enteropathy-type T-cell lymphoma, hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma, nasal NK/T-cell lymphomas, and treatment-related T-cell lymphomas.

[00209] In some instances, a hematologic malignancy is a B-cell malignancy. Exemplary B-cell malignancy includes, but is not limited to, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, and a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

[00210] In some instances, the cancer is a relapsed or refractory cancer. In some embodiments, the relapsed or refractory cancer is a relapsed or refractory solid tumor. In some embodiments, the relapsed or refractory solid tumor is a relapsed or refractory sarcoma or a relapsed or refractory carcinoma. In some embodiments, the relapsed or refractory carcinoma includes adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer.

[00211] In some instances, the relapsed or refractory cancer is selected from relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular

carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma. In some cases, the relapsed or refractory cancer is relapsed or refractory mesothelioma. In some cases, the relapsed or refractory cancer is relapsed or refractory esophageal cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory liver cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory primary liver cancer.

[00212] In some instances, the relapsed or refractory cancer is a relapsed or refractory hematologic malignancy. In some embodiments, a relapsed or refractory hematologic malignancy is a relapsed or refractory leukemia, a relapsed or refractory lymphoma, a relapsed or refractory myeloma, a relapsed or refractory non-Hodgkin's lymphoma, a relapsed or refractory Hodgkin's lymphoma, a relapsed or refractory T-cell malignancy, or a relapsed or refractory B-cell malignancy. In some instances, a relapsed or refractory hematologic malignancy is a relapsed or refractory T-cell malignancy. In some instances, a relapsed or refractory hematologic malignancy is a relapsed or refractory B-cell malignancy, such as for example, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

[00213] In some instances, the cancer is a metastasized cancer. In some instances, the metastasized cancer is a metastasized solid tumor. In some instances, the metastasized solid tumor is a metastasized sarcoma or a metastasized carcinoma. In some embodiments, the metastasized

carcinoma includes adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer.

[00214] In some instances, the metastasized cancer is selected from metastasized uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the metastasized cancer is metastasized uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the metastasized cancer is metastasized uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the metastasized cancer is metastasized uveal melanoma. In some cases, the metastasized cancer is metastasized mesothelioma. In some cases, the metastasized cancer is metastasized esophageal cancer. In some cases, the metastasized cancer is metastasized liver cancer. In some cases, the metastasized cancer is metastasized primary liver cancer.

[00215] In some instances, the metastasized cancer is a metastasized hematologic malignancy. In some embodiments, the metastasized hematologic malignancy is a metastasized leukemia, a metastasized lymphoma, a metastasized myeloma, a metastasized non-Hodgkin's lymphoma, a metastasized Hodgkin's lymphoma, a metastasized T-cell malignancy, or a metastasized B-cell malignancy. In some instances, a metastasized hematologic malignancy is a metastasized T-cell malignancy. In some instances, a metastasized hematologic malignancy is a metastasized B-cell malignancy, such as for example, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell

lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

Congenital Diseases

[00216] In some embodiments, the compounds disclosed herein are useful for treating a congenital disease. In some embodiments, the congenital disease is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes- associated protein transcription coactivator (TAZ/YAP). In some embodiments, the congenital disease is characterized by a mutant G α -protein. In some embodiments, the mutant G α -protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant G α -protein is G12. In some embodiments, the mutant G α -protein is G13. In some embodiments, the mutant G α -protein is Gq. In some embodiments, the mutant G α -protein is G11. In some embodiments, the mutant G α -protein is Gi. In some embodiments, the mutant G α -protein is Go. In some embodiments, the mutant G α -protein is Gs.

[00217] In some embodiments, the congenital disease is the result of a genetic abnormality, an intrauterine environment, errors related to morphogenesis, infection, epigenetic modifications on a parental germline, or a chromosomal abnormality. Exemplary congenital diseases include, but are not limited to, Sturge-Weber Syndrome, Port-Wine stain, Holt-Oram syndrome, abdominal wall defects, Becker muscular dystrophy (BMD), biotinidase deficiency, Charcot-Marie-Tooth (CMT), cleft lip, cleft palate, congenital adrenal hyperplasia, congenital heart defects, congenital hypothyroidism, congenital muscular dystrophy, cystic fibrosis, Down syndrome, Duchenne muscular dystrophy, Fragile X syndrome, Friedreich's ataxia, galactosemia, hemoglobinopathies, Krabbe disease, limb-girdle muscular dystrophy, medium chain acyl-CoA dehydrogenase deficiency, myasthenia gravis, neural tube defects, phenylketonuria, Pompe disease, severe combined immunodeficiency (SCID), Stickler syndrome (or hereditary progressive arthro-ophthalmopathy), spinal muscular atrophy, and trisomy 18. In some embodiments, the congenital disease is Sturge-Weber Syndrome or Port-Wine stain. In some embodiments, the congenital disease is Sturge-Weber Syndrome. In some embodiments, the congenital disease is Port-Wine stain.

EXAMPLES

[00218] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

List of abbreviations

[00219] As used above, and throughout the disclosure, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN or MeCN	acetonitrile
Bn	benzyl
BOC or Boc	<i>tert</i> -butyl carbamate
t-Bu	tert-butyl
Cy	cyclohexyl
DBA	dibenzylideneacetone
DCE	dichloroethane (ClCH ₂ CH ₂ Cl)
DCM	dichloromethane (CH ₂ Cl ₂)
DIPEA or DIEA	diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	dimethylformamide
DMA	<i>N,N</i> -dimethylacetamide
DMSO	dimethylsulfoxide
Dppf or dppf	1,1'-bis(diphenylphosphino)ferrocene
eq	equivalent(s)
Et	ethyl
Et ₂ O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
HPLC	high performance liquid chromatography
LAH	lithium aluminum anhydride
LCMS	liquid chromatography mass spectrometry
Me	methyl
MeOH	methanol
MS	mass spectroscopy
NMM	<i>N</i> -methyl-morpholine
NMP	<i>N</i> -methyl-pyrrolidin-2-one
NMR	nuclear magnetic resonance
RP-HPLC	reverse phase-high pressure liquid chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran

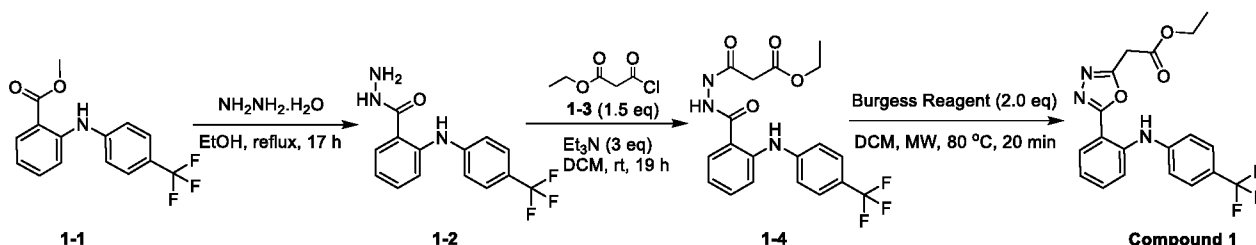
TLC

thin layer chromatography

I. Chemical Synthesis

[00220] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times were approximate and were not optimized. Column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted. Same reagents might have different assigned numbers throughout Examples.

Example 1: ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate (Compound 1)



Step 1: 2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00221] To a mixture of **1-1** (2.0 g, 6.8 mmol, 1 *eq*) in EtOH (20 mL) was added $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (4.1 g, 70.0 mmol, 4 mL, 85% purity, 10.33 *eq*). The resulted mixture was stirred at 80 °C for 17 h. LCMS and TLC showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography. **1-2** (1.8 g, 6.0 mmol, 89.1% yield) was obtained.

Step 2: ethyl 3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propanoate

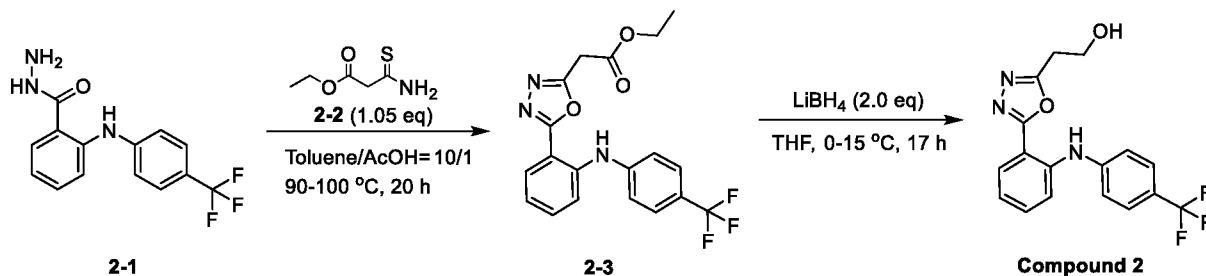
[00222] To a mixture of **1-2** (500 mg, 1.7 mmol, 1 *eq*) and TEA (514.1 mg, 5.1 mmol, 0.7 mL, 3 *eq*) in DCM (6 mL) was added **1-3** (382.4 mg, 2.5 mmol, 0.3 mL, 1.5 *eq*) dropwise. The resulting mixture was stirred at 15 °C for 19 h. LCMS showed the reaction was complete. The mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The organic layer was dried over anhydrous Na_2SO_4 , concentrated in vacuum. The residue was purified by silica gel chromatography. **1-4** (0.6 g, 1.2 mmol, 70.1% yield) was obtained.

Step 3: ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate

[00223] To a mixture of **1-4** (50 mg, 0.12 mmol, 1 *eq*) in DCM (3 mL) was added Burgess reagent (58.2 mg, 0.24 mmol, 2 *eq*). The resulted mixture was stirred at 80 °C under microwave condition for 20 min. LCMS and HPLC showed about 34% desired compound was detected, and 42% starting material was remained. The mixture was concentrated in vacuum. The residue was purified

by prep-HPLC. **Compound 1** (4.33 mg, 11.1 μmol , 9.1% yield) was obtained. LCMS (ESI): RT = 0.876 min, mass calcd. for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_3$ 391.11, m/z found 392.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.48 (s, 1H), 7.90 (dd, J = 1.1, 7.9 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.3 Hz, 1H), 7.43 - 7.35 (m, 3H), 6.97 (t, J = 7.5 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 4.06 (s, 2H), 1.32 (t, J = 7.2 Hz, 3H).

Example 2: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 2)



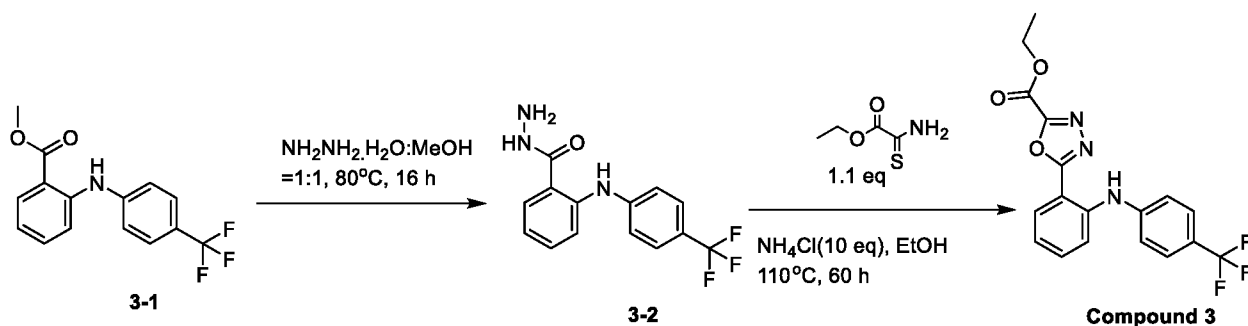
Step 1: ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate

[00224] To a mixture of **2-1** (50 mg, 0.17 mmol, 1 *eq*) in toluene (3 mL) and AcOH (0.3 mL) was added **2-2** (26.2 mg, 0.18 mmol, 1.05 *eq*). The resulted mixture was stirred at 90 °C for 17 h. LCMS showed the starting material was consumed completely, and 9% desired compound was detected. The mixture was stirred at 100 °C for 3 h. LCMS showed there's no obvious change. The mixture was concentrated in vacuum. The residue was checked by HPLC. The residue was purified by prep-HPLC. **2-3** (10 mg, 25.6 μmol , 15.1% yield) was obtained.

Step 2: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

[00225] To a mixture of **2-3** (10 mg, 25.6 μmol , 1 *eq*) in THF (2 mL) was added LiBH_4 (1.1 mg, 51.1 μmol , 2 *eq*) at 0 °C. The resulted mixture was stirred at 15 °C for 17 h. LCMS showed there's about 42% desired compound. The mixture was diluted with MeOH (3 mL), concentrated in vacuum. The residue was purified by prep-HPLC. **Compound 2** (3.9 mg, 11.2 μmol , 43.7% yield) was obtained. LCMS (ESI): RT = 0.788 min, mass calcd. for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$ 349.10, m/z found 349.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.48 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.5 Hz, 1H), 7.43 - 7.35 (m, 3H), 6.98 (t, J = 7.5 Hz, 1H), 4.17 (t, J = 5.8 Hz, 2H), 3.21 (t, J = 5.8 Hz, 2H).

Example 3: ethyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (Compound 3)



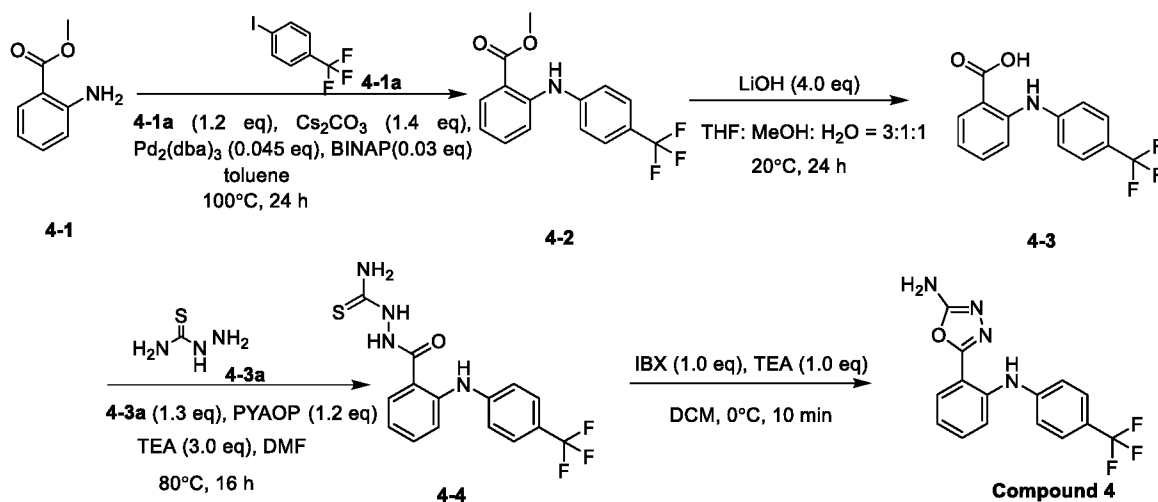
Step 1: 2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00226] To a solution of **3-1** (2.2 g, 7.45 mmol, 1 *eq*) in MeOH (5.5 mL) were added hydrazine-hydrate (5.7 g, 96.87 mmol, 5.5 mL, 13 *eq*) at 25 °C. The resulting solution was stirred at 80 °C for 16 h and cooled to 25 °C, along with lots of solid formed. LCMS showed no starting material was remained and 90% of desired product was detected. TLC (PE:EA = 2:1 UV) showed the reaction was complete. The mixture was filtered. The filter cake was washed with water (20 mL) and dried to give 1.9 g of residue. The filtrate was concentrated to remove most of methanol and extracted with EA (30 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was combined with 1.9 g of filter cake to give **3-2** (2.1 g, 7.11 mmol, 95.4% yield), which was used directly without purification. ¹H NMR (400MHz, CDCl₃) δ 9.25 (s, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.49 - 7.34 (m, 4H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.94 - 6.86 (m, 1H), 4.38 - 3.78 (m, 2H).

Step 2: ethyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate

[00227] A flask containing **3-2** (2.1 g, 7.11 mmol, 1 *eq*), NH₄Cl (3.8 g, 71.12 mmol, 2.5 mL, 10 *eq*) and ethyl 2-amino-2-thioxo-acetate (1.04 g, 7.82 mmol, 1.1 *eq*) in EtOH (60 mL) was heated at 110 °C for 60 h. (Note: ethyl 2-amino-2-thioxo-acetate was forgotten to add at the beginning, it was added after heating for about 1 h.) LCMS showed 34% of starting material was remained and 16% of desired product was formed. TLC (PE:EA = 2:1 UV) showed starting material was remained and new spots were formed. The mixture was filtered and the filter cake was washed with EA (30 mL). The filtrate was concentrated to give a residue. The residue was purified by column chromatography to give **Compound 3** (0.2 g) and recovery compound **3-2** (0.64 g, 2.17 mmol, 30.5% yield). **Compound 3** (0.2 g) was purified by prep-HPLC to give the title compound (112.8 mg, 0.30 mmol, 4.2% yield). LCMS (ESI): RT = 2.054 min, mass calc. for C₁₈H₁₄F₃N₃O₃ 377.10, *m/z* found 377.9[M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 10.27 (s, 1H), 9.44 (s, 1H), 8.07 - 7.97 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.52 - 7.31 (m, 4H), 6.99 (t, *J* = 7.5 Hz, 1H), 4.61 - 4.52 (m, 2H), 1.50 (t, *J* = 7.3 Hz, 3H).

Example 4: 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine (Compound 4)



Step 1: methyl 2-[4-(trifluoromethyl)anilino]benzoate

[00228] A mixture of **4-1** (2.32 g, 15.3 mmol, 2 mL, 1.0 eq), **4-1a** (5.0 g, 18.4 mmol, 2.7 mL, 1.2 eq), Cs_2CO_3 (7.0 g, 21.4 mmol, 1.4 eq), $\text{Pd}_2(\text{dba})_3$ (631.1 mg, 0.7 mmol, 0.1 eq) and BINAP (286.1 mg, 0.5 mmol, 0.03 eq) in toluene (80 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 24 hr under N_2 atmosphere. TLC (Petroleum ether:Ethyl acetate = 10: 1) indicated that **4-1** remained and three major new spots were detected. LCMS showed **4-1** was consumed completely and desired MS (m/z = 295.9; RT = 0.888 min) was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to give **4-2** (1.3 g, 4.3 mmol, 28.1% yield). LCMS showed the desired MS (m/z = 295.9; RT = 0.888 min) was detected. LCMS (ESI): RT = 0.888 min, mass calc. for: $\text{C}_{15}\text{H}_{12}\text{F}_3\text{NO}_2$ 295.08, m/z found 295.8 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 3.90-3.96 (m, 3H), 6.86 (ddd, J = 8.09, 5.58, 2.64 Hz, 1H), 7.26-7.33 (m, 2H), 7.36-7.43 (m, 2H), 7.56 (d, J = 8.53 Hz, 2H), 7.94-8.14 (m, 1H), 9.58-9.81 (m, 1H).

Step 2: 2-[4-(trifluoromethyl)anilino]benzoic acid

[00229] To a solution of **4-2** (1.1 g, 3.73 mmol, 1.0 eq) in THF (10 mL) and methanol (1 mL) was added LiOH (356.9 mg, 14.9 mmol, 4.0 eq) dissolved in H_2O (1 mL). The mixture was stirred at 20°C for 16 hr. TLC (Petroleum ether:Ethyl acetate = 1:1, UV) indicated compound **4-2** was remained, and one major new spot was detected. The mixture was concentrated to give a residue. The residue was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL). The aqueous phase was adjusted to pH~2 from 8 with HCl (2 M), along with lots of solid formed. **4-3** (0.7 g, crude) was obtained. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 6.96 (t, J = 7.40 Hz, 1 H), 7.39 (d, J = 8.28 Hz, 2 H), 7.43 - 7.53 (m, 2 H), 7.63 (d, J = 8.78 Hz, 2 H), 7.95 (dd, J = 7.91, 1.38 Hz, 1 H), 9.72-9.82 (s, 1 H), 13.23-13.32 (s, 1 H).

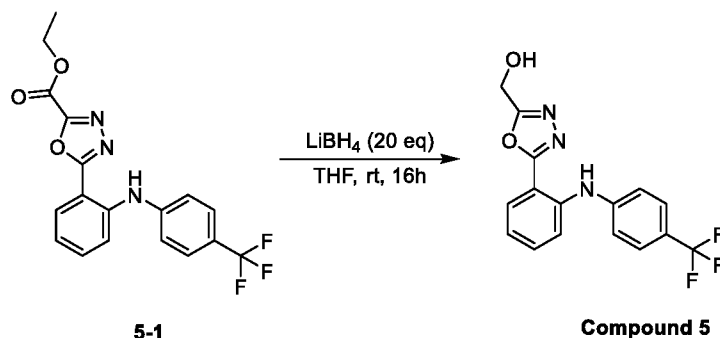
Step 3: [[2-[4-(trifluoromethyl)anilino]benzoyl]amino]thiourea

[00230] To a solution of **4-3** (30 mg, 0.1 mmol, 1.0 *eq*) in DMF (2 mL) was added PYAOP (66.7 mg, 0.1 mmol, 1.2 *eq*) and TEA (32.4 mg, 0.3 mmol, 0.1 mL, 3.0 *eq*). Then **4-3a** (12.6 mg, 0.1 mmol, 1.3 *eq*) was added to the mixture. The mixture was stirred at 80 °C for 16 hr. TLC (Petroleum ether:Ethyl acetate = 5:1, UV) indicated **4-3** was consumed and one new spot formed. LCMS showed **4-3** was consumed and 47% of desired MS ($m/z = 354.9$; RT = 0.720 min). The reaction mixture was concentrated under reduced pressure. The residue was diluted with H₂O (15 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂) to give **4-4**. LCMS (ESI): RT = 0.724 min, mass calc. for: C₁₅H₁₂F₃NO₂ 354.08, m/z found 354.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.33 (s, 1H), 6.94-7.03 (t, $J = 7.28$ Hz, 1H), 7.22-7.31 (d, $J = 8.53$ Hz, 2H), 7.38-7.50 (m, 3H), 7.59 (d, $J = 8.53$ Hz, 3H), 7.62-7.73 (m, 1H), 7.78-7.85 (d, $J = 7.53$ Hz, 1H), 9.24-9.34 (s, 1H), 9.44-9.53 (s, 1H), 10.41-10.51 (s, 1H).

Step 4: 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-amine

[00231] To a solution of **4-4** (40 mg, 0.1 mmol, 1.0 *eq*) in DCM (2 mL) was added IBX (31.6 mg, 0.1 mmol, 1.0 *eq*) and TEA (11.4 mg, 0.1 mmol, 1.0 *eq*). The mixture was stirred at 0 °C for 10 min. TLC (Petroleum ether:Ethyl acetate = 3:1, UV) indicated **4-4** remained and one major new spot was detected. LCMS showed **4-4** was consumed and desired product ($m/z = 320.9$; RT = 0.783 min) was detected. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **Compound 4** (6.5 mg, 19.7 μ mol, 17.4% yield). LCMS (ESI): RT = 0.769 min, mass calc. for: C₁₅H₁₁F₃N₄O 320.09, m/z found 320.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.08 (t, $J = 7.53$ Hz, 1H), 7.35-7.41 (m, 4H), 7.41-7.46 (m, 1H), 7.54 (d, $J = 8.03$ Hz, 1H), 7.64 (d, $J = 8.53$ Hz, 2H), 7.70 (d, $J = 8.03$ Hz, 1H), 9.34 (s, 1H).

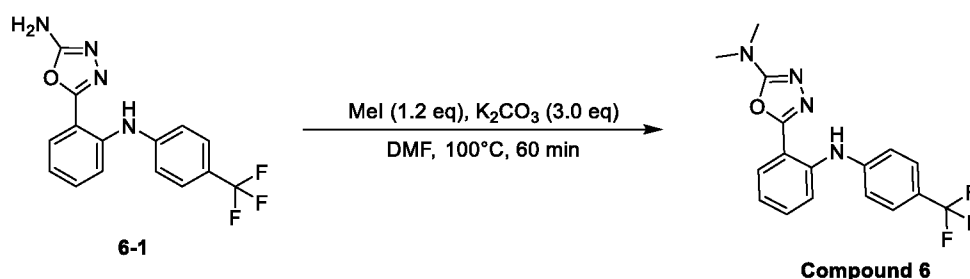
Example 5: (5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol (Compound 5)



[00232] To a solution of **5-1** (64 mg, 0.17 mmol, 1 *eq*) in THF (4 mL) was added LiBH₄ (73.9 mg, 3.4 mmol, 20 *eq*) at 0 °C. Then the mixture was stirred at 25 °C for 16 hr. TLC indicated that **5-1**

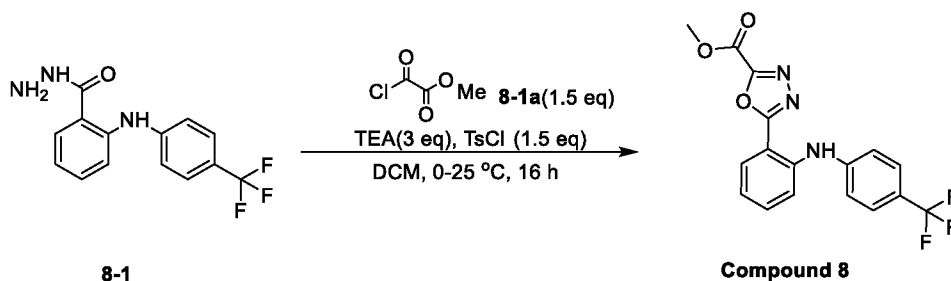
was consumed completely and four new spots formed. The reaction mixture was quenched by addition water 5 mL at 25 °C and the aqueous phase was extracted with ethyl acetate 40 mL (10 mL * 4). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 64 mg crude product. The crude product was purified by prep-TLC to give **Compound 5** (8 mg, 23.9 umol, 14.1% yield). LCMS (ESI): RT = 0.773 min, mass calcd. for C₁₆H₁₂N₃F₃O₂, 335.09 m/z found 335.9[M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 7.92 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.36 - 7.44 (m, 3H), 6.98 (t, *J* = 7.2 Hz, 1H), 4.99 (s, 2H), 2.51 (brs, 1H).

Example 6: N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine (Compound 6)



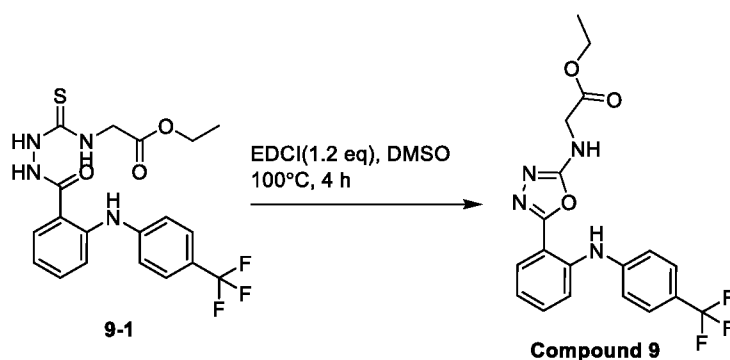
[00233] To a solution of **6-1** (40 mg, 0.1 mmol, 1.0 *eq*) in DMF (2 mL) were added K₂CO₃ (51.8 mg, 0.4 mmol, 3.0 *eq*) and MeI (35.5 mg, 0.3 mmol, 0.01 mL, 2.0 *eq*). The mixture was stirred under microwave tube at 100 °C for 60 min. LCMS showed **6-1** was consumed completely and two main peaks with desired mass was detected. TLC (Petroleum ether:Ethyl acetate = 1: 1, UV) indicated **6-1** was consumed, and two major new spots were detected. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 6** (3.5 mg, 0.01 mmol, 7.9% yield). LCMS (ESI): RT = 0.844 min, mass calc. for: C₁₇H₁₅F₃N₄O 348.12, m/z found 348.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.08-3.15 (m, 1H), 3.11 (s, 5H), 6.87 (t, *J* = 7.28 Hz, 1H), 7.22-7.30 (m, 3H), 7.43 (d, *J* = 8.28 Hz, 1H), 7.48 (d, *J* = 8.53 Hz, 2H), 7.58-7.75 (m, 1H), 9.44 (s, 1H).

Example 7: methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (Compound 8)



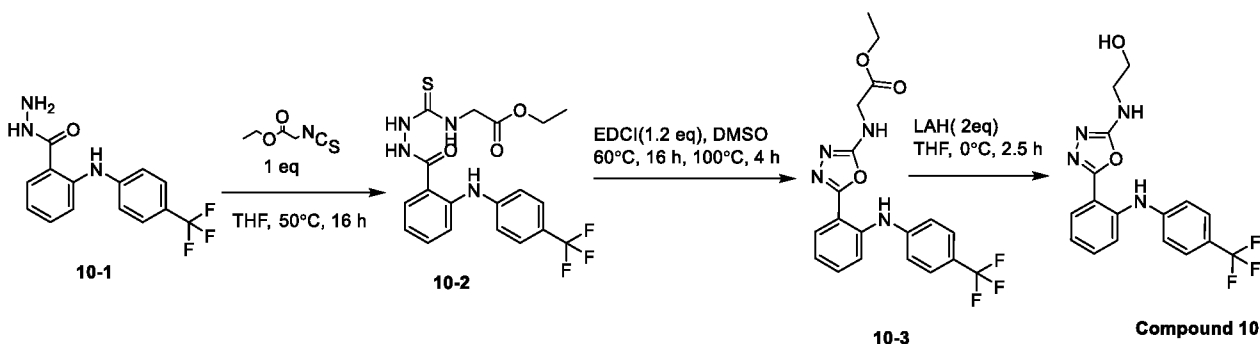
[00234] To a solution of **8-1a** (207.4 mg, 1.7 mmol, 0.2 mL, 1.0 eq) and TEA (514.1 mg, 5.1 mmol, 0.7 mL, 3.0 eq) in DCM (6.0 mL) was added **8-1** (0.5 g, 1.7 mmol, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 16 h. Then TsCl (322.8 mg, 1.7 mmol, 1.0 eq) was added and the mixture was stirred at 25 °C for 5 h. Several new peaks were shown and 47% of desired compound was detected on LC-MS. The reaction mixture was quenched by addition of saturated NaHCO₃ (30 mL), and then diluted with EtOAc (100 mL). The organic layers were washed with brine (50 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 8** (0.4 g, 1.1 mmol, 65.0% yield). 20 mg crude product was purified by prep-HPLC to give **Compound 8** (2.40 mg). LCMS (ESI): RT = 1.018 min, mass calc. for C₁₇H₁₂F₃N₃O₃ 363.08, m/z found 364.2 [M+H]⁺; ¹H NMR (400MHz, DMSO-*d*₆) δ 9.12 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 3.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.21-7.12 (m, 1H), 3.99 (s, 3H).

Example 8: ethyl (5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate (Compound 9)



[00235] A mixture of **9-1** (1.2 g, 2.72 mmol, 1 eq), EDCI (626.7 mg, 3.27 mmol, 1.2 eq) in DMSO (15 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 4 hr under N₂ atmosphere. LCMS showed the reaction was complete and 52% of desired product was formed. The mixture was combined with the another batch and diluted with EA (250 mL) and washed with brine (30 mL*5), dried by anhydrous Na₂SO₄, filtered and concentrated to give crude **Compound 9** (0.9 g, 2.21 mmol, 81.1% yield), which was used directly for next step. 50 mg of crude **Compound 9** was purified by prep-HPLC to give the title compound (21.07 mg, 51.8 umol, 1.9% yield). LCMS (ESI): RT = 0.821 min, mass calc. for C₁₉H₁₇F₃N₄O₃ 406.13, m/z found 406.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.27 (s, 1H), 8.42 (t, *J* = 6.4 Hz, 1H), 7.75 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 4.19 - 4.04 (m, 4H), 1.21 (t, *J* = 7.2 Hz, 3H).

Example 9: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol (Compound 10)



Step 1: 2-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbothioamido)acetate

[00236] To a solution of **10-1** (813.5 mg, 2.76 mmol, 1 eq) in THF (3.5 mL) was added ethyl 2-isothiocyanatoacetate (400 mg, 2.76 mmol, 0.4 mL, 1 eq). The mixture was stirred at 50 °C for 16 hr. LCMS showed **10-1** was consumed and 65% of desired mass was detected. The residue was concentrated under reduced pressure to give **10-2** (1.4 g, crude), which was used directly. LCMS (ESI): RT = 0.769 min, mass calc. for C₁₉H₁₉F₃N₄O₃S 440.11, m/z found 441.0 [M+1]⁺.

Step 2: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetate

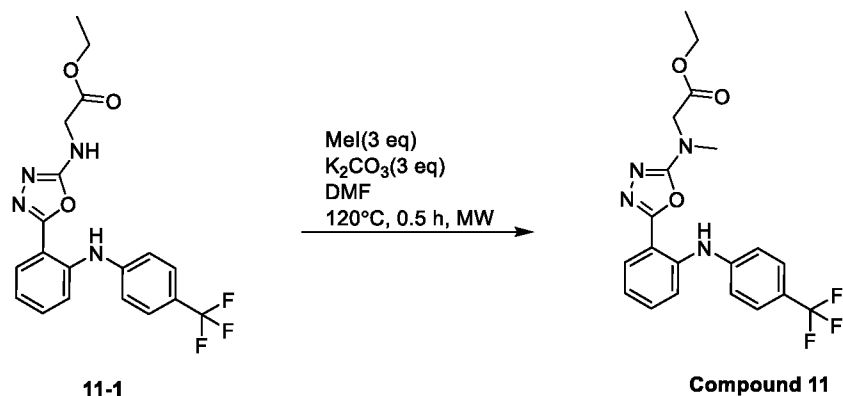
[00237] A mixture of **10-2** (1.2 g, 2.72 mmol, 1 eq), EDCI (626.7 mg, 3.27 mmol, 1.2 eq) in DMSO (15 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 4 hr under N₂ atmosphere. LCMS showed the reaction was complete and 52% of desired product was formed. The mixture was combined with another batch and diluted with EA (250 mL) and washed with brine (30 mL*5), dried by anhydrous Na₂SO₄, filtered and concentrated to give crude **10-3** (0.9 g, 2.21 mmol, 81.1% yield), which was used directly for next step. 50 mg of crude **10-3** was purified by prep-HPLC to give **10-3** (21.07 mg, 51.85 umol, 1.90% yield). LCMS (ESI): RT = 0.821 min, mass calc. for C₁₉H₁₇F₃N₄O₃ 406.13, m/z found 406.9 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.27 (s, 1H), 8.42 (t, *J* = 6.4 Hz, 1H), 7.75 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 4.19 - 4.04 (m, 4H), 1.21 (t, *J* = 7.2 Hz, 3H).

Step 3: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethanol

[00238] A solution of **10-3** (0.04 g, 98 umol, 1 eq) in THF (3 mL) was cooled to 0 °C. Then LiAlH₄ (7.5 mg, 0.20 mmol, 2 eq) was added, along with gas evolved. Then the mixture was stirred at 0 °C for 2.5 h. LCMS showed the reaction was complete and 93% of desired product was formed. The reaction was quenched with water (5 mL) and diluted with EA (50 mL) and separated. The separated organic layer was washed with brine (10 mL) and dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 10** (5.21 mg, 14 umol, 14.4% yield). LCMS (ESI): RT = 0.747 min, mass calc. for C₁₇H₁₅F₃N₄O₂ 364.11, m/z found 364.9 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.32 (s, 1H),

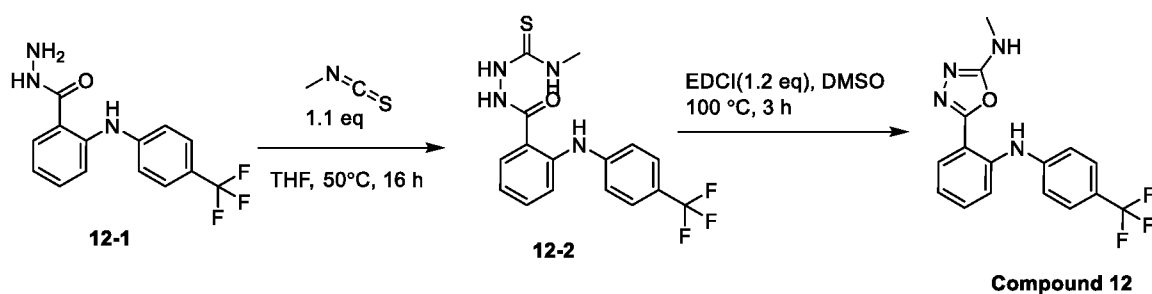
7.92 (br t, $J = 5.6$ Hz, 1H), 7.72 (d, $J = 7.5$ Hz, 1H), 7.64 (br d, $J = 8.5$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 1H), 7.46 - 7.32 (m, 3H), 7.08 (t, $J = 7.5$ Hz, 1H), 4.82 (t, $J = 5.4$ Hz, 1H), 3.62 - 3.51 (m, 2H), 3.32 (br d, $J = 5.8$ Hz, 2H).

Example 10: ethyl N-methyl-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate (Compound 11)



[00239] A mixture of **11-1** (200 mg, 0.49 mmol, 1 *eq*), MeI (209.58 mg, 1.48 mmol, 91.92 μL , 3 *eq*) and K_2CO_3 (204.07 mg, 1.48 mmol, 3 *eq*) in DMF (15 mL) was heated at 120 $^\circ\text{C}$ for 0.5 h under microwave. TLC (Petroleum ether:Ethyl acetate= 3:1, UV) indicated that **11-1** remained and one main spot was detected. LCMS showed **11-1** was consumed and desired mass (420.9) was detected. The mixture was combined with another batch, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2) to give **Compound 11** (66.17 mg, 0.15 mmol, 31.5% yield). LCMS (ESI): RT = 0.848 min, mass calc. for $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_3$ 420.14 m/z found 421.0 $[\text{M}+1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.18 (s, 1H), 7.86 (d, $J = 6.8$ Hz, 1H), 7.63 (d, $J = 8.5$ Hz, 2H), 7.56 - 7.50 (m, 1H), 7.48 - 7.41 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 2H), 7.11 (t, $J = 7.5$ Hz, 1H), 4.32 (s, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.15 (s, 3H), 1.20 (t, $J = 7.0$ Hz, 3H).

Example 11: N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine (Compound 12)



Step 1: N-methyl-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbothioamide

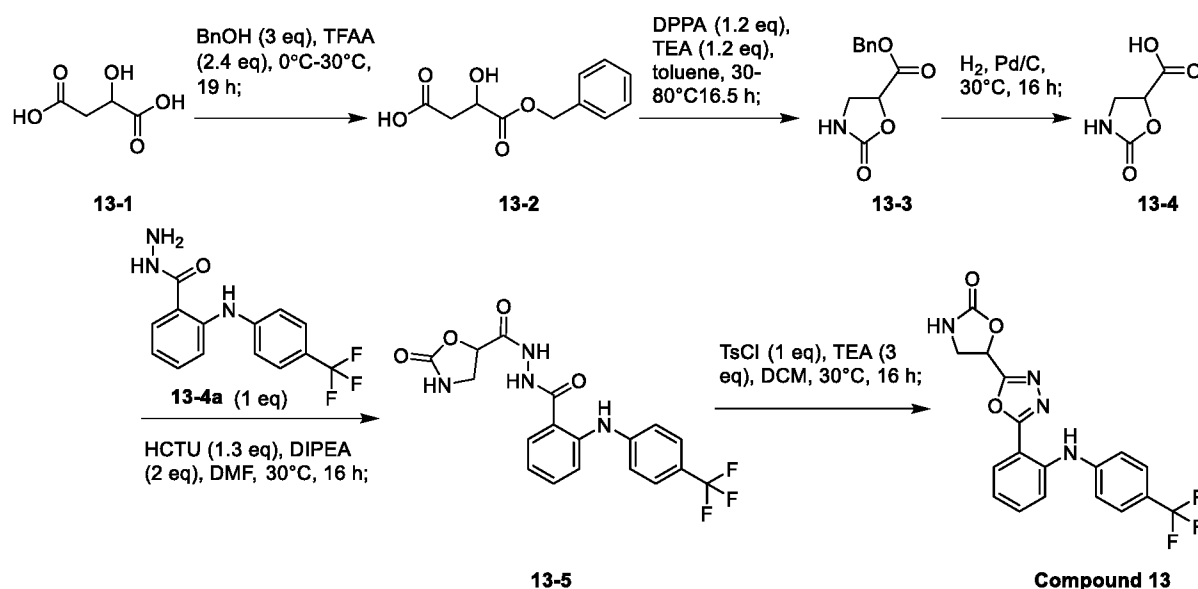
[00240] A tube containing **12-1** (0.2 g, 0.68 mmol, 1 *eq*) and methylimino(thioxo)methane (54.5 mg, 0.75 mmol, 51 μL , 1.1 *eq*) in THF (2.5 mL) was heated at 50 $^\circ\text{C}$ for 16 hr. LCMS showed the reaction was complete and 82% of desired product was formed. The mixture was concentrated to

give crude **12-2** (0.2 g, 0.54 mmol, 80.2% yield). LCMS (ESI): RT = 0.742 min, mass calc. for $C_{16}H_{15}F_3N_4OS$ 368.09, m/z found 368.9 $[M+1]^+$.

Step 2: N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine

[00241] A tube containing **12-2** (0.15 g, 0.41 mmol, 1 *eq*) and EDCI (93.67 mg, 0.49 mmol, 1.2 *eq*) in DMSO (1.5 mL) was heated at 100 °C for 3 hr. LCMS showed the reaction was complete and 64% of desired product was formed. The mixture was combined with another batch and filtered. The filtrate was purified by prep-HPLC to give **Compound 12** (6.54 mg, 19 umol, 4.8% yield). LCMS (ESI): RT = 1.366 min, mass calc. for C₁₆H₁₃F₃N₄O 334.10, m/z found 334.9 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.31 (s, 1H), 7.79 - 7.70 (m, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.56 - 7.51 (m, 1H), 7.46 - 7.40 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 2.87 (d, *J* = 5.0 Hz, 3H).

Example 12: 5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 13)



Step 1: 4-(benzyloxy)-3-hydroxy-4-oxobutanoic acid

[00242] To a solution of TFAA (18.80 g, 89.49 mmol, 12.5 mL, 2.4 *eq*) at 0 °C was added **13-1** (5.0 g, 37.29 mmol, 1 *eq*). The mixture was stirred at 30 °C until the mixture was a clear solution (about 2 h). And then the mixture was concentrated to remove TFAA and the residue was dissolved in phenylmethanol (12.90 g, 119.33 mmol, 12.4 mL, 3.2 *eq*). The resulting mixture was stirred at 30 °C for 16 h. TLC (DCM:MeOH = 10:1, I₂) showed starting material was consumed completely and one new spot was formed. The mixture was diluted with EA (20 mL) and extracted with saturated Na₂CO₃ solution (100 mL). The aqueous layer was separated, then acidified with conc. HCl to pH = 1-2 and then extracted with EA (100 mL *3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced

pressure to give **13-2** (5.0 g, 22.30 mmol, 59.80% yield). ^1H NMR (400MHz, CDCl_3) δ 7.44 - 7.29 (m, 5H), 5.23 (s, 2H), 4.58 - 4.50 (m, 1H), 2.99 - 2.79 (m, 2H).

Step 2: benzyl 2-oxooxazolidine-5-carboxylate

[00243] To a solution of **13-2** (5.0 g, 22.30 mmol, 1 *eq*) and TEA (2.71 g, 26.76 mmol, 3.7 mL, 1.2 *eq*) in toluene (100 mL) at 30 °C was added DPPA (7.36 g, 26.76 mmol, 5.8 mL, 1.2 *eq*) dropwise. After stirred at 30 °C for 30 min, the mixture was stirred at 80 °C for 16 h. TLC (PE:EA = 1:1, I_2 , plate 1) showed most of starting material still remained but no new spot was formed. TLC (PE:EA = 1:1, KMnO_4 , plate 2) showed most of starting material still remained and two new spots were formed. The mixture was concentrated to remove solvent. And the residue was diluted with saturated Na_2CO_3 solution (100 mL), and then extracted with EA (100 mL *3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to give **13-3** (890 mg, 4.02 mmol, 18.04% yield), which was confirmed by ^1H NMR. ^1H NMR (400MHz, CDCl_3) δ 7.39 (s, 5H), 5.28 (s, 2H), 5.07 (dd, J = 5.6, 9.4 Hz, 1H), 3.90 (t, J = 9.4 Hz, 1H), 3.70 (dd, J = 5.5, 9.0 Hz, 1H).

Step 3: 2-oxooxazolidine-5-carboxylic acid

[00244] To a solution of benzyl 2-oxooxazolidine-5-carboxylate **13-3** (0.89 g, 4.02 mmol, 1 *eq*) in EtOH (10 mL) was added Pd/C (0.3 g, 0.282 μmol , 10% purity, $7.01\text{e-}2$ *eq*) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 30 °C for 16 h. TLC (Petroleum ether/Ethyl acetate = 1:1 stained by iodine) showed the starting material was consumed completely and new spot was formed. The reaction mixture was filtered and the filtrate was concentrated to give **13-4** (0.47 g, 3.59 mmol, 89.12% yield), which was used directly without purification. ^1H NMR (400MHz, CD_3OD) δ 5.13 - 5.08 (m, 1H), 3.91 (t, J = 9.4 Hz, 1H), 3.68 - 3.55 (m, 1H).

Step 4: 2-oxo-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazolidine-5-carbohydrazide

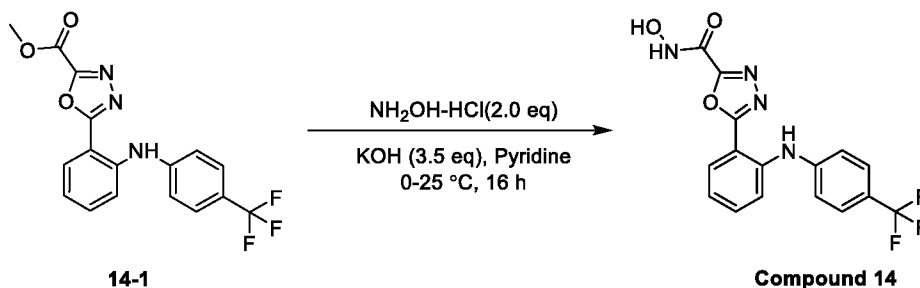
[00245] To a solution of **13-4** (20 mg, 0.153 mmol, 1.2 *eq*) in DMF (1 mL) at 30 °C was added HCTU (68.4 mg, 0.165 mmol, 1.3 *eq*), and the mixture was stirred at 30 °C for 20 min. And then **13-4a** (37.5 mg, 0.127 mmol, 1 *eq*) and DIPEA (32.9 mg, 0.254 mmol, 44.3 μL , 2 *eq*) was successively added at 30 °C into the above mixture. The resulting mixture was stirred at 30 °C for 16 h. TLC (DCM:MeOH = 10:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed starting material and desired product was included in one peak. The mixture was combined with another batch. The combined sample was purified by prep-HPLC to give **13-5** (18.46 mg, 45.2 μmol , 35.56% yield). LCMS (ESI): RT = 0.687 min, mass calc. for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_4$ 408.10, m/z found 431.0 $[\text{M}+23]^+$. ^1H NMR (400MHz, $\text{DMSO-}d_6$) δ 10.56 (s, 1H),

10.45 (s, 1H), 9.36 (s, 1H), 7.84 (s, 1H), 7.70 (d, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.48 (s, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 7.04 (s, 1H), 5.11 (d, $J = 3.5$ Hz, 1H), 3.79 (t, $J = 9.3$ Hz, 1H), 3.53 - 3.45 (m, 1H).

Step 5: 5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one

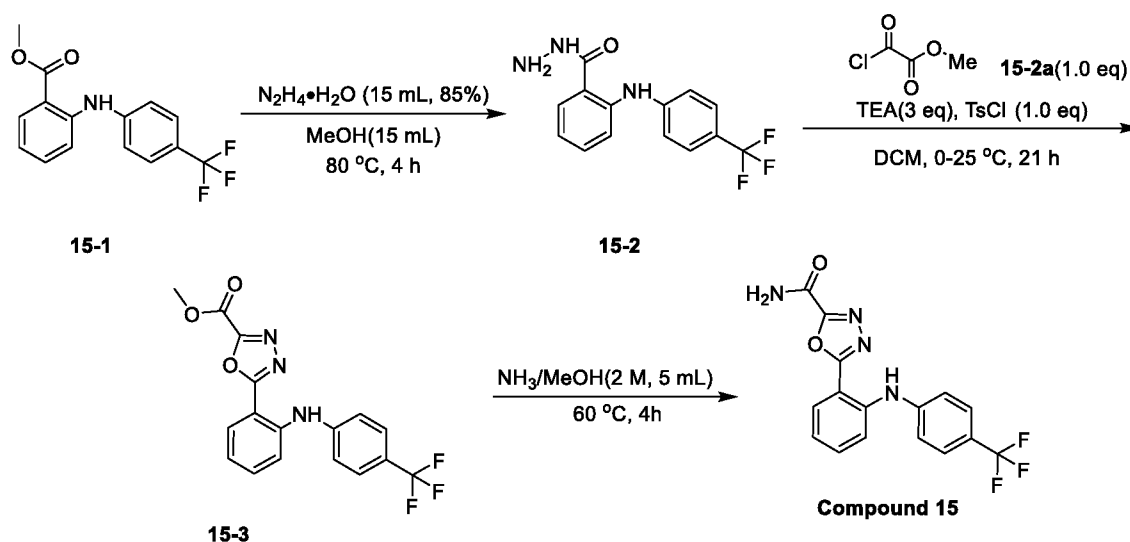
[00246] To a solution of **13-5** (80 mg, 0.20 mmol, 1 *eq*) and TEA (59.5 mg, 0.59 mmol, 81.8 μ L, 3 *eq*) in DCM (2 mL) at 30 °C was added TsCl (37.4 mg, 0.20 mmol, 1 *eq*), and the mixture was stirred at 30 °C for 16 h. TLC (DCM:MeOH = 10:1, UV) showed starting material was consumed completely and one new spot was formed. LCMS showed starting material was consumed completely and 54% of desired product was formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 13** (13.71 mg, 34.07 μ mol, 17.39% yield). LCMS (ESI): RT = 0.768 min, mass calc. for $C_{18}H_{13}F_3N_4O_3$ 390.09, m/z found 390.9[M+1]⁺. ¹H NMR (400MHz, DMSO- d_6) δ 9.13 (s, 1H), 8.09 (s, 1H), 7.93 (d, $J = 8.0$ Hz, 1H), 7.63 (d, $J = 8.5$ Hz, 2H), 7.59 - 7.52 (m, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.22 - 7.11 (m, 1H), 6.01 (dd, $J = 5.5, 9.0$ Hz, 1H), 3.99 - 3.92 (m, 1H), 3.90 - 3.84 (m, 1H).

Example 13: N-hydroxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 14)



[00247] To a solution of $NH_2OH \cdot HCl$ (58.3 mg, 0.6 mmol, 2.0 *eq*, HCl) in pyridine (2 mL) were added KOH (54.1 mg, 1.0 mmol, 3.5 *eq*) and **14-1** (0.1 g, 0.28 mmol, 1 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 h. LC-MS showed 16% of **14-1** remained and 39% of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 14** (13.06 mg, 36 μ mol, 13.0% yield). LCMS (ESI): RT = 0.743 min, mass calc. for $C_{16}H_{11}F_3N_4O_3$ 364.08, m/z found 364.9 [M+H]⁺; ¹H NMR (400 MHz, $CDCl_3$) δ 12.20 (s, 1H), 9.79 (s, 1H), 9.12 (s, 1H), 8.01 (d, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.59-7.54 (m, 2H), 7.37 (d, $J = 8.5$ Hz, 2H), 7.18-7.14 (m, $J = 3.0, 5.1, 7.9$ Hz, 1H).

Example 14: 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 15)



Step 1: 2-[4-(trifluoromethyl)anilino]benzohydrazide

[00248] To a solution of **15-1** (2.0 g, 6.7 mmol, 1.0 eq) in MeOH (15.0 mL) was added $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (15.4 g, 262.3 mmol, 15 mL, 38.7 eq). The mixture was stirred at 80 °C for 4 h. TLC (PE:EA = 2:1 UV) showed that **15-1** was consumed completely and one new spot formed. The solution was concentrated (lots of solid formed) and then filtered. The filter cake was washed with water (20 mL), triturated with PE (50 mL), filtered and dried under vacuum to give **15-2** (1.9 g, 6.44 mmol, 95.0% yield).

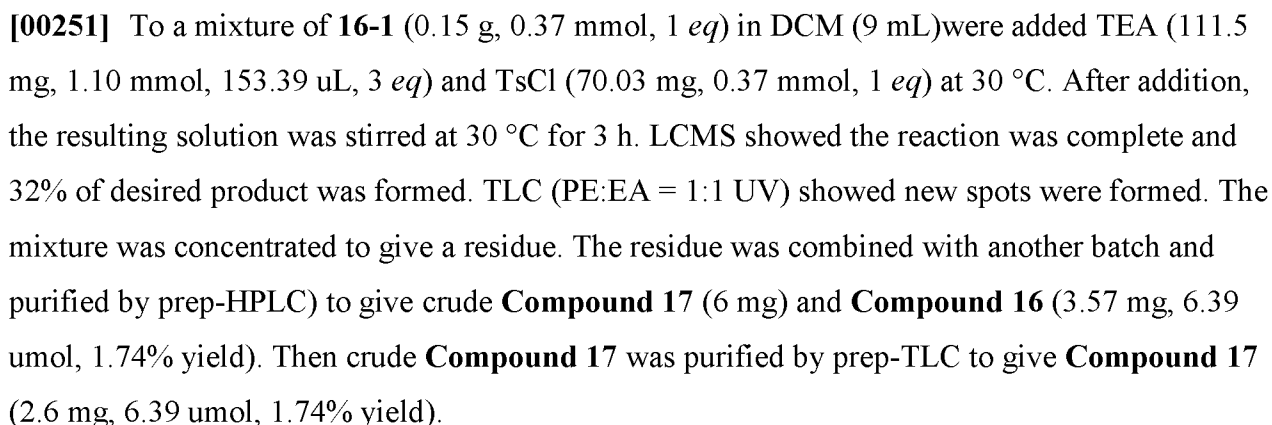
Step 2: methyl 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carboxylate

[00249] To a solution of **15-2a** (207.4 mg, 1.7 mmol, 0.2 mL, 1.0 eq) and TEA (514.1 mg, 5.1 mmol, 0.7 mL, 3.0 eq) in DCM (6.0 mL) was added **15-2** (0.5 g, 1.7 mmol, 1.0 eq) at 0 °C. The mixture was stirred at 25 °C for 16 h. Then TsCl (322.8 mg, 1.7 mmol, 1.0 eq) was added and the mixture was stirred at 25 °C for 5 h. Several new peaks were shown and 47% of desired compound was detected on LC-MS. The reaction mixture was quenched by addition of saturated NaHCO_3 (30 mL), and then diluted with EtOAc (100 mL). The organic layer was separated and washed with brine (50 mL * 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give **15-3** (0.4 g, 1.1 mmol, 65.0% yield). 20 mg crude product was purified by prep-HPLC to give to give desired compound (2.40 mg). LCMS (ESI): RT = 1.018 min, mass calc. for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_3\text{O}_3$ 363.08, m/z found 364.2 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.12 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 3.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.21-7.12 (m, 1H), 3.99 (s, 3H).

Step 3: methyl 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carboxylate

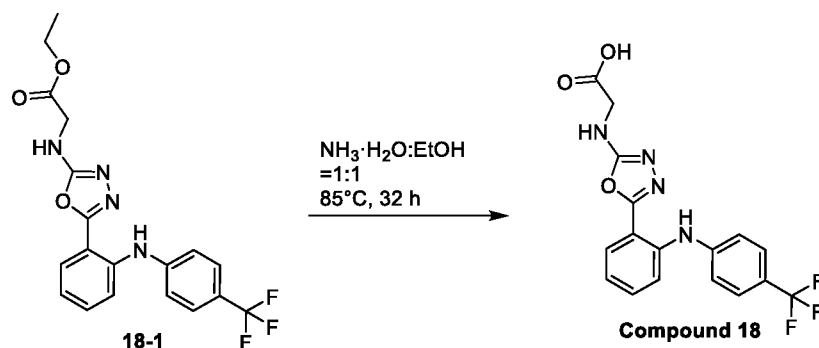
[00250] To a solution of NH_3 (46.9 mg, 2.75 mmol, 10 eq) in MeOH (5 mL) was added **15-3** (100.0 mg, 0.3 mmol, 1.0 eq) at 0 °C in seal pot. The mixture was stirred at 60 °C for 4 hr. Several new peaks were shown and 63% of desired compound was detected on LC-MS. The reaction

Example 15: 3-tosyl-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 16) and 4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 17)



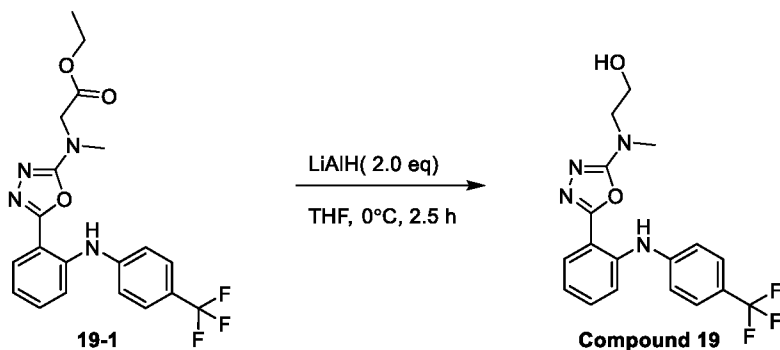
[00253] Compound 17: LCMS (ESI): RT = 0.760 min, mass calc. for C₁₈H₁₃F₃N₄O₃ 390.09, m/z found 391.3 [M+1]⁺. ¹H NMR (400MHz, DMSO-d₆) δ 9.16 (s, 1H), 8.57 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.70 - 7.53 (m, 4H), 7.36 (br d, *J* = 8.3 Hz, 2H), 7.17 (br t, *J* = 6.4 Hz, 1H), 5.37 (dd, *J* = 4.5, 8.5 Hz, 1H), 4.73 - 4.66 (m, 1H), 4.59 (dd, *J* = 4.4, 8.9 Hz, 1H).

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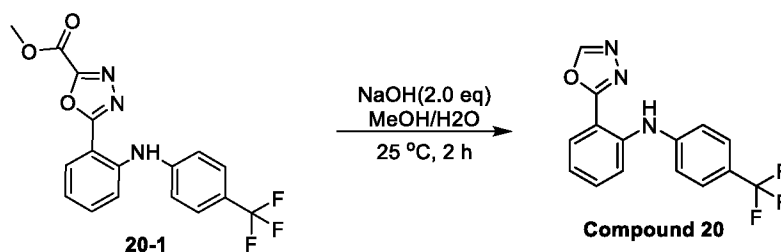


[00254] A solution of **18-1** (0.04 g, 98.44 μmol , 1 *eq*) in $\text{NH}_3\cdot\text{H}_2\text{O}$ (3.45 g, 24.61 mmol, 3.79 mL, 250 *eq*) was heated at 85 °C for 4 h. TLC (PE:EA = 1:1 UV) showed most of starting material remained. Then EtOH (4 mL) was added the mixture was heated at 85 °C for another 4 h. LCMS showed the reaction was complete and 52% of desired product was formed. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 18** (6.84 mg, 17.72 μmol , 18% yield). LCMS (ESI): RT = 0.747 min, mass calc. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_3$ 379.0, m/z found 378.09 $[\text{M}+23]^+$. ^1H NMR (400MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.09 (br s, 1H), 7.74 (br d, $J=7.8$ Hz, 1H), 7.64 (br d, $J=8.5$ Hz, 2H), 7.54 (br d, $J=8.3$ Hz, 1H), 7.47 - 7.35 (m, 3H), 7.08 (t, $J=7.5$ Hz, 1H), 3.88 (br s, 2H).

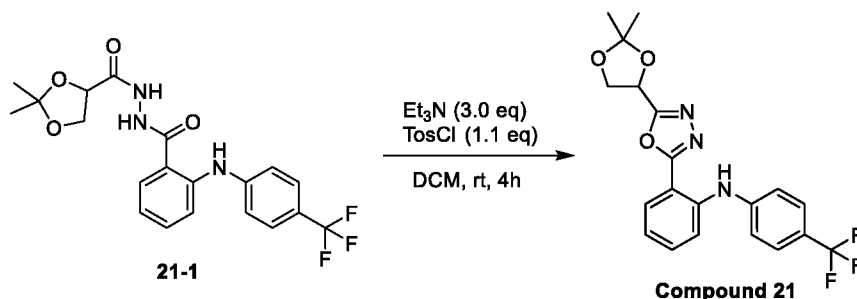
Example 17: 2-(methyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol (Compound 19)



[00255] A solution of **19-1** (50 mg, 0.1 mmol, 1.0 *eq*) in THF (4 mL) was cooled in ice-water bath. Then LiAlH_4 (9.0 mg, 0.2 mmol, 2.0 *eq*) was added, along with gas evolved. Then the mixture was stirred in ice-water bath for 2.5 hr. LCMS showed **19-1** was consumed and 67% of desired product was detected. Then the mixture was quenched with water (10 mL). The combined mixture was extracted with EA (20 mL*3), dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 19** (40.5 mg, 0.1 mmol, 89.1% yield). LCMS (ESI): RT = 0.766 min, mass calc. for: $\text{C}_{18}\text{H}_{17}\text{F}_3\text{N}_4\text{O}_2$ 378.13, m/z found 378.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 3.27 (s, 3H), 3.69 (t, $J=5.27$ Hz, 2H), 3.96 (t, $J=5.14$ Hz, 2H), 6.94 (t, $J=7.65$ Hz, 1H), 7.30-7.38 (m, 3H), 7.50 (d, $J=8.53$ Hz, 1H), 7.55 (d, $J=8.53$ Hz, 2H), 7.73 (d, $J=8.03$ Hz, 1H), 9.44 (s, 1H).

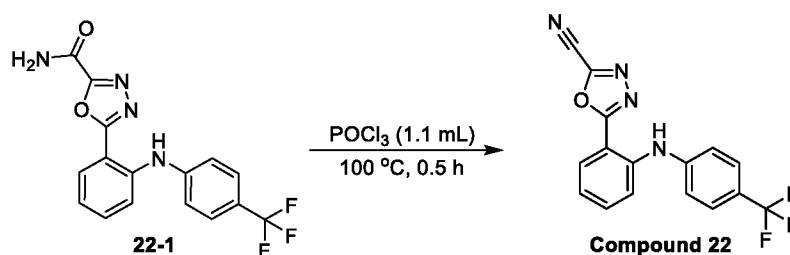
Example 18: 2-(1,3,4-oxadiazol-2-yl)-N-[4-(trifluoromethyl)phenyl]aniline (Compound 20)

[00256] To a solution of **20-1** (0.4 g, 1.1 mmol, 1.0 eq) in MeOH (0.8 mL) was added a solution of NaOH (88.1 mg, 2.2 mmol, 2.0 eq) in H₂O (0.5 mL). The mixture was stirred at 25 °C for 2 h. LC-MS showed **20-1** was consumed completely and 59% of desired mass was detected. The pH of the mixture was adjusted with HCl (1M) to 4-5, and then the mixture was filtered to give a residue. The residue was purified by prep-HPLC to give **Compound 20** (7.15 mg, 23.42 umol, 2.13% yield). LCMS (ESI): RT = 0.824 min, mass calc. for C₁₅H₁₀F₃N₃O 305.08, m/z found 305.9 [M+H]⁺; ¹H NMR (400MHz, CDCl₃) δ 9.39 (s, 1H), 9.23 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.59-7.51 (m, 1H), 7.59-7.51 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.18-7.12 (m, 1H).

Example 19: 2-[5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 21)

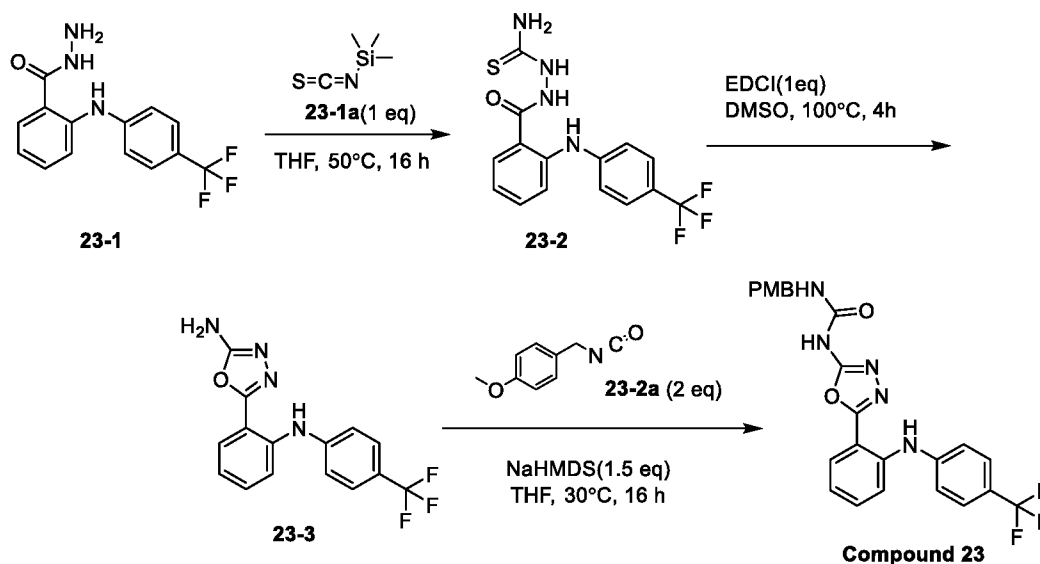
[00257] To a solution of **21-1** (62 mg, 0.15 mmol, 1 eq) and TEA (44.4 mg, 0.44 mmol, 61.15 uL, 3 eq) in DCM (2 mL) was added TsCl (29.3 mg, 0.16 mmol, 1.05 eq). The reaction was stirred at 25 °C for 3hr. LCMS showed that 78% of desired product was detected. HPLC showed that 89% of desired product was detected. The reaction was concentrated. The residue was purified by prep-HPLC to give **Compound 21** (18 mg, 44.40 umol, 30.32% yield). LCMS (ESI): RT = 0.873 min, mass calcd. for C₂₀H₁₈F₃N₃O₃, 405.15 m/z found 406.0[M+H]⁺. ¹H NMR (400MHz, DMSO) δ 9.16 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.71 - 7.49 (m, 4H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.25 - 7.17 (m, 1H), 5.45 (t, *J* = 5.2 Hz, 1H), 4.50 - 4.25 (m, 1H), 1.43 (d, *J* = 4.0 Hz, 3H).

Example 20: 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carbonitrile (Compound 22)



[00258] A solution of **22-1** (50 mg, 0.1 mmol, 1.0 eq) in POCl₃ (1.76 g, 11.5 mmol, 1.1 mL, 80.0 eq) was stirred at 100 °C for 0.5 h. LC-MS showed **22-1** was consumed completely and 70% of desired compound was detected. The reaction mixture was quenched by addition of H₂O (10 mL) at 0 °C. The mixture was extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 22** (7.61 mg, 21.66 μmol, 15.1% yield). LCMS (ESI): RT = 1.582 min, mass calc. for C₁₆H₉F₃N₄O 330.07, m/z found 331.0 [M+H]⁺; ¹H NMR (400MHz, CDCl₃) δ 9.24 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.51-7.47 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.03-6.99 (m, 1H).

Example 21: 1-(4-methoxybenzyl)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)urea (Compound 23)



Step 1: 2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbothioamide

[00259] To a solution of **23-1** (1.5 g, 5.08 mmol, 1 eq) in THF (25 mL) was added **23-1a** (666.9 mg, 5.08 mmol, 63 μL, 1 eq). The mixture was stirred at 50 °C for 16 hr. LCMS showed reactant **23-1** was consumed completely and 69% of desired mass was detected. The solution was concentrated to give compound **23-2** (1.9 g, crude), which was used directly. LCMS (ESI): RT = 0.721 min, mass calc. for C₁₅H₁₃F₃N₄OS 354.08, m/z found 354.9 [M+1]⁺.

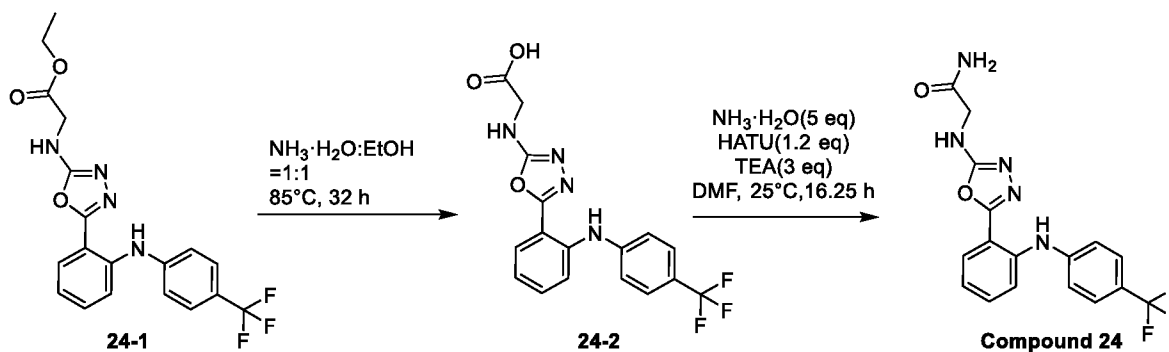
Step 2: 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine

[00260] To a solution of compound **23-2** (1.5 g, 4.23 mmol, 1 *eq*) in DMSO (10 mL) was added EDCI (811.5 mg, 4.23 mmol, 1 *eq*). The mixture was stirred at 100 °C for 4 hr. LCMS showed the reaction was complete and 52% of desired product was formed. TLC (PE:EA = 1:2 UV) showed the reaction was complete. The mixture was diluted with EA (250 mL) and washed with brine (30 mL*3), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂) to give **23-3** (0.7 g, 2.19 mmol, 51.6% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.28 (s, 1H), 7.76 - 7.67 (m, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.55 - 7.47 (m, 1H), 7.44 - 7.28 (m, 5H), 7.06 (t, *J* = 7.4 Hz, 1H).

Step 3: 1-(4-methoxybenzyl)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)urea

[00261] To a solution of **23-3** (0.1 g, 0.31 mmol, 1 *eq*) in THF (3 mL) were added NaHMDS (1 M, 0.5 mL, 1.5 *eq*) and **23-2a** (101.9 mg, 0.62 mmol, 89 uL, 2 *eq*) at 30 °C. The mixture was stirred at 30 °C for 16 h. LCMS showed no **23-3** was remained and 58% of desired compound was detected. The residue was purified by prep-HPLC to give **Compound 23** (105.84 mg, 0.22 mmol, 70.1% yield). LCMS (ESI): RT = 0.862 min, mass calc. for C₂₄H₂₀F₃N₅O₃ 483.15, *m/z* found 506.1 [M+23]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.10 (s, 1H), 9.11 (s, 1H), 7.96 (br t, *J* = 5.5 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.54 (m, 1H), 7.53 - 7.46 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.35 (d, *J* = 5.8 Hz, 2H), 3.74 (s, 3H), 3.31 (s, 1H).

Example 22: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide (Compound 24)



Step 1: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetic acid

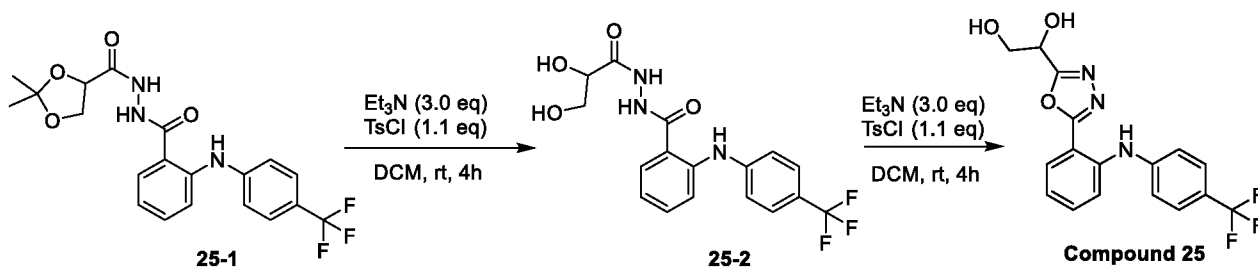
[00262] A solution of **24-1** (300 mg, 738.27 umol, 1 *eq*) in NH₃·H₂O (2.59 g, 73.83 mmol, 2.84 mL, 100 *eq*) was added EtOH (3 mL). The mixture was heated at 85 °C for 16 hr. TLC (PE:EA = 1:1 UV) showed most of material was remained. Then EtOH (3 mL) was added and the mixture was heated at 85 °C for another 16 h. LCMS showed **24-1** was consumed, 22% of **Compound 24** and 55% of **24-2** were formed. The reaction mixture was concentrated under reduced pressure to

give a mixture of **Compound 24** and **24-2** (300 mg), which was used into the next step without further purification. ^1H NMR (400MHz, DMSO- d_6) δ 9.37 (s, 1H), 9.27 (s, 1H), 7.76 - 7.69 (m, 3H), 7.64 (br d, J = 8.3 Hz, 4H), 7.54 (br dd, J = 3.8, 8.3 Hz, 3H), 7.48 - 7.43 (m, 2H), 7.42 - 7.35 (m, 5H), 7.08 (q, J = 7.9 Hz, 2H), 4.08 (s, 2H), 3.83 (s, 1H), 3.57 (s, 2H).

Step 2: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide

[00263] To a solution of **24-2** (0.3 g, 0.79 mmol, 1 *eq*) in DMF (10 mL) were added HATU (301.53 mg, 0.79 mmol, 1 *eq*) and TEA (240.73 mg, 2.38 mmol, 331.13 μL , 3 *eq*) at 25 °C. After stirring for 15 min, $\text{NH}_3 \cdot \text{H}_2\text{O}$ (555.8 mg, 3.97 mmol, 610.80 μL , 5 *eq*) was added and the resulting solution was stirred at 25 °C for 16 h. LCMS showed the reaction was complete and 78% of desired product was formed. TLC (PE:EA = 1:1 UV) showed the reaction was complete and new spot was formed. The reaction was diluted with EA (150 mL), washed with brine (20 mL*2) and saturated NaHCO_3 (20 mL*2) in turns, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2) and was lyophilized to give **Compound 24** (0.025 g, 63.14 μmol , 7.96% yield). LCMS (ESI): RT = 0.732 min, mass calc. for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_5\text{O}_2$ 377.11, m/z found 399.9 $[\text{M}+23]^+$. ^1H NMR (400MHz, DMSO- d_6) δ 9.32 (s, 1H), 8.15 (br s, 1H), 7.77 - 7.68 (m, 1H), 7.65 (br d, J = 8.3 Hz, 2H), 7.59 - 7.48 (m, 2H), 7.44 (br t, J = 7.2 Hz, 1H), 7.39 (br d, J = 8.3 Hz, 2H), 7.20 - 7.04 (m, 2H), 4.05 - 3.98 (m, 1H), 3.82 (br s, 2H), 1.19 - 1.14 (m, 1H).

Example 23: 1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethane-1,2-diol (Compound 25)



Step 1: N'-(2,3-dihydroxypropanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00264] To a solution of **25-1** (0.35 g, 0.83 mmol, 1 *eq*) and TEA (250.9 mg, 2.48 mmol, 0.34 mL, 3 *eq*) in DCM (10 mL) was added TsCl (165.4 mg, 0.86 mmol, 1.05 *eq*). The reaction was stirred at 25 °C for 16hr. LCMS showed that starting material was remained and 50% of desired product was detected. The reaction was concentrated. Compound **25-2** (300 mg, crude) was used for next step directly.

Step 2: 1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethane-1,2-diol

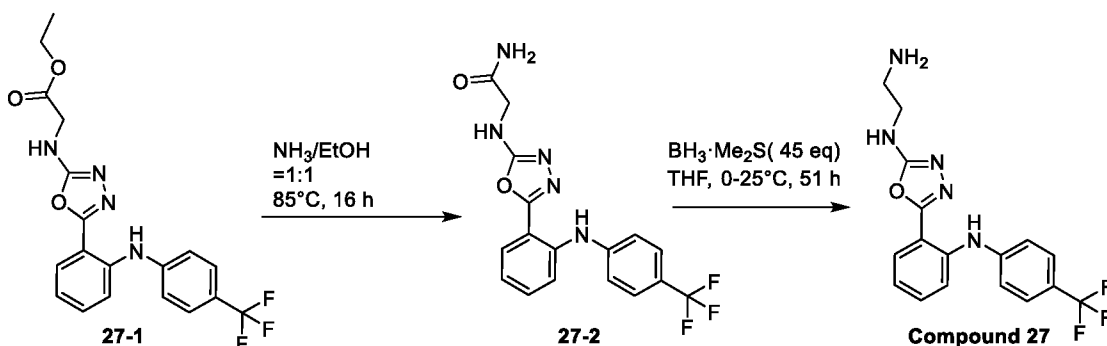
[00265] To a solution of compound **25-2** (250 mg, 0.65 mmol, 1 *eq*) and TEA (197.9 mg, 1.96 mmol, .27 mL, 3 *eq*) in DCM (10 mL) was added TsCl (136.7 mg, 0.72 mmol, 1.1 *eq*). The reaction was stirred at 25 °C for 16hr. LCMS showed that 38% of desired product was detected. HPLC showed that 30% of desired product was detected. The reaction was washed with water (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by prep-HPLC to give **Compound 25** (45 mg, 115.79 umol, 17.75% yield). LCMS and HNMR confirmed that desired product was obtained. LCMS (ESI): RT = 0.733 min, mass calcd. for C₁₇H₁₄F₃N₃O₃, 365.10 m/z found 365.9[M+H]⁺. ¹H NMR (400MHz, DMSO) δ 9.26 (s, 1H), 7.93 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.65 - 7.50 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 6.8 Hz, 1H), 6.19 (br, 1H), 5.05 (br, 1H), 4.95 - 4.80 (m, 1H), 3.85 - 3.70 (m, 2H).

Example 24: 2-oxo-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidine-3-carboxylate (Compound 26)



[00266] To a solution of **26-1** (0.25 g, 0.64 mmol, 1 *eq*), TEA (194.4 mg, 1.92 mmol, 0.3 mL, 3 *eq*) and DMAP (15.6 mg, 0.13 mmol, 0.2 *eq*) in DCM (5 mL) at 0 °C was added Boc₂O (139.8 mg, 0.64 mmol, 0.1 mL, 1 *eq*). Then the solution was stirred at 25 °C for 16 h. LCMS showed **26-1** was consumed completely and desired product was detected. TLC (Petroleum ether:Ethyl acetate = 2:1, UV) indicated **26-1** was consumed and two major new spots were detected. The reaction mixture was quenched with 10 mL of water and concentrated under reduced pressure to remove DCM. The resulting aqueous layer was extracted with ethyl acetate (20 mL*3). The combined organic layer was washed with brine (15 mL), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂) to give **Compound 26** (15.0 mg, 28.0 umol, 4.36% yield). LCMS (ESI): RT = 0.858 min, mass calc. for C₂₃H₂₁F₃N₄O₅ 490.15, m/z found 513.0 [M+23]⁺. ¹H NMR (400MHz, CDCl₃) δ 9.36 (s, 1H), 7.85 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.48 (m, 1H), 7.46 - 7.34 (m, 3H), 7.04 - 6.92 (m, 1H), 5.72 (dd, *J* = 4.1, 8.9 Hz, 1H), 4.73 (t, *J* = 9.2 Hz, 1H), 4.53 (dd, *J* = 4.0, 9.3 Hz, 1H), 1.52 - 1.45 (m, 9H).

Example 25: N1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethane-1,2-diamine (Compound 27)



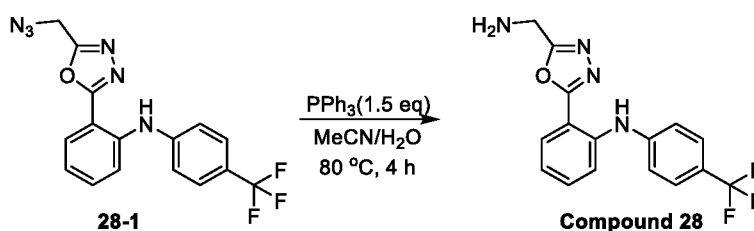
Step 1: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide

[00267] A solution of **27-1** (0.3 g, 0.74 mmol, 1 eq) in EtOH (15 mL) saturated with NH_3 (62.87 mg, 3.69 mmol) was stirred at 85°C for 16 h. LCMS showed 11% of **27-1** was remained and 77% of desired compound was detected. Then the solution was concentrated to give crude **27-2** (180 mg, 0.45 mmol, 61.58% yield), which was used directly without purification.

Step 2: N1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethane-1,2-diamine

[00268] To a solution of **27-2** (0.12 g, 0.32 mmol, 1 eq) in THF (5 mL) was added $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (10 M, 0.48 mL, 15 eq) at 0°C . The mixture was stirred at 25°C for 16 hr under N_2 atmosphere. LCMS showed 17% of **27-2** was remained and 57% of desired compound was detected. The mixture was quenched with 5 mL of methanol, stirred at 10 min at 25°C and concentrated to a residue. The residue was diluted with water (10 mL) and acidified to pH~2 with 1 M HCl and extracted with EA (15 mL*3). The combined organic layers dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue which was purified by prep-HPLC to give **Compound 27** (1.32 mg, 3.55 μmol , 1.12% yield). LCMS (ESI): RT = 0.639 min, mass calc. for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{N}_5\text{O}$ 363.13, m/z found 364.0 $[\text{M}+1]^+$. ^1H NMR (400MHz, METHANOL- d_4) δ 7.80 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.56 - 7.48 (m, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.05 - 6.99 (m, 1H), 3.82 (s, 4H).

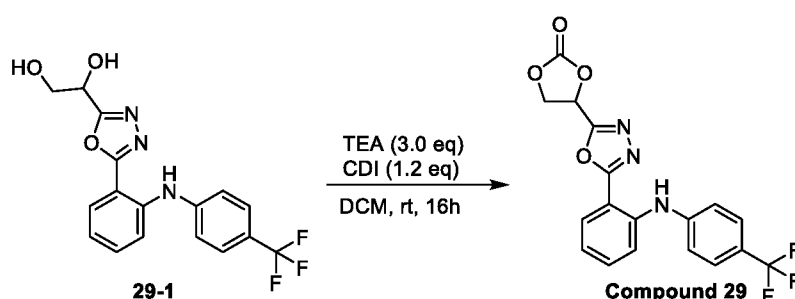
Example 26: 2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 28)



[00269] A solvent of **28-1** (50 mg, 0.1 mmol, 1.0 eq) and PPh_3 (54.6 mg, 0.2 mmol, 1.5 eq) in MeCN (1 mL) was stirred at 80°C for 1 h. After H_2O (0.2 mL) was added and the mixture was stirred at 80°C for 3 h. LC-MS showed reactant **28-1** was consumed completely and no desired

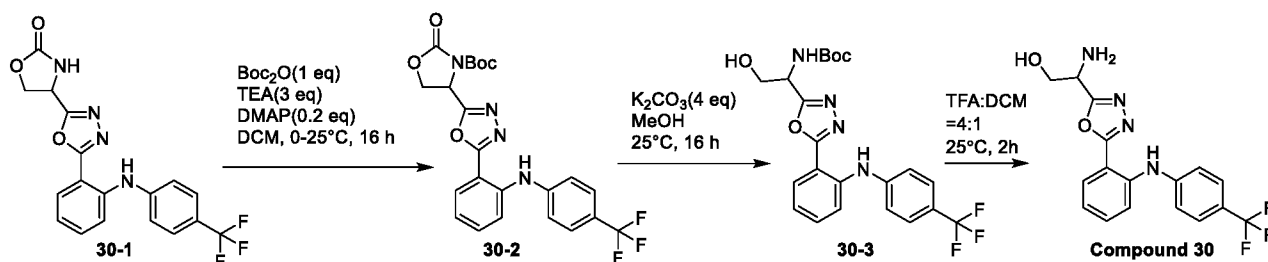
compound was detected. TLC (Petroleum ether:Ethyl acetate=0:1) indicated reactant **28-1** was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to give crude **Compound 28** (10 mg), which was purified by prep-HPLC to give **Compound 28** (2.13 mg, 6 μmol, 4.3% yield). LCMS (ESI): RT = 0.718 min, mass calcd. for C₁₆H₁₃F₃N₄O 334.10 m/z found 335.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.50 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44-7.33 (m, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 4.23-4.02 (m, 2H).

Example 27: 4-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-1,3-dioxolan-2-one (Compound 29)



[00270] To a solution of **29-1** (20 mg, 54.75 μmol, 1 eq) and Et₃N (16.6 mg, 0.16 mmol, 22.86 μL, 3 eq) in DCM (1 mL) was added triphosgene (24.3 mg, 82.12 μmol, 1.5 eq). The reaction was stirred at 25 °C for 16hr. LCMS showed that 85% of desired product was detected. The reaction was diluted with DCM (10 mL) and washed with water (2*5 mL). The organic was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 29** (15 mg, 33.35 μmol, 60.92% yield). LCMS (ESI): RT = 0.812 min, mass calcd. for C₁₈H₁₂F₃N₃O₄, 391.08 m/z found 392.0 [M+H]⁺. ¹H NMR (400MHz, CDCl₃) δ 9.32 (s, 1H), 7.92 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.50 - 7.40 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.05 - 6.00 (m, 1H), 5.10 - 5.00 (m, 1H), 5.00 - 4.85 (m, 1H).

Example 28: 2-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol (Compound 30)



Step 1: tert-butyl 2-oxo-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidine-3-carboxylate

[00271] To a solution of **30-1** (0.25 g, 0.64 mmol, 1 *eq*), TEA (194.4 mg, 1.92 mmol, 0.3 mL, 3 *eq*) and DMAP (15.6 mg, 0.13 mmol, 0.2 *eq*) in DCM (5 mL) at 0 °C was added Boc₂O (139.8 mg, 0.64 mmol, 0.2 mL, 1 *eq*). Then the solution was stirred at 25 °C for 16 h. LCMS showed **30-1** was consumed completely and desired product was detected. TLC (Petroleum ether:Ethyl acetate = 2:1, UV) indicated **30-1** was consumed and two major new spots were detected. The reaction mixture was quenched with 10 mL of water and concentrated under reduced pressure to remove DCM. The resulting aqueous layer was extracted with ethyl acetate (20 mL*3). The combined organic layer was washed with brine (15 mL), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂) to give **30-2** (15.0 mg, 28 umol, 4.4% yield). LCMS (ESI): RT = 0.858 min, mass calc. for C₂₃H₂₁F₃N₄O₅ 490.15, m/z found 513.0 [M+23]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.36 (s, 1H), 7.85 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.48 (m, 1H), 7.46 - 7.34 (m, 3H), 7.04 - 6.92 (m, 1H), 5.72 (dd, *J* = 4.1, 8.9 Hz, 1H), 4.73 (t, *J* = 9.2 Hz, 1H), 4.53 (dd, *J* = 4.0, 9.3 Hz, 1H), 1.52 - 1.45 (m, 9H).

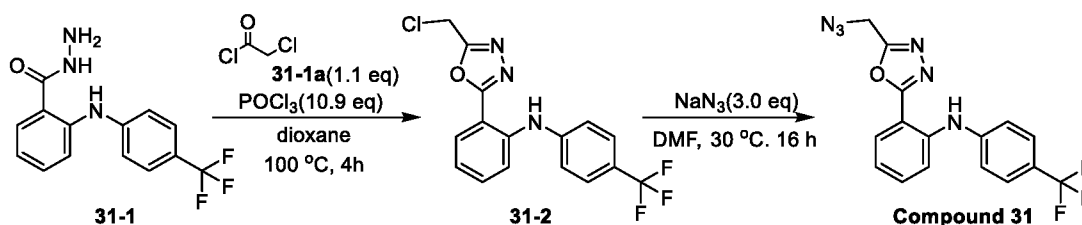
Step 2: tert-butyl (2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

[00272] A mixture of **30-2** (0.01 g, 20.4 umol, 1 *eq*) and K₂CO₃ (11.3 mg, 81.6 umol, 4 *eq*) in MeOH (1.5 mL) was stirred at 25 °C for 20 h. LCMS showed **30-2** was consumed and 58% of desired product was detected. The mixture was diluted with EA (50 mL), washed with water (10 mL*2), dried by anhydrous Na₂SO₄, filtered and concentrated to give compound **30-3** (0.01 g, crude), which was used directly.

Step 3: 2-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

[00273] To a solution of compound **30-3** (10.0 mg, 21.5 umol, 1 *eq*) in CH₂Cl₂ (1.6 mL) was added TFA (613.8 mg, 5.38 mmol, 0.4 mL, 250 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed compound **30-3** was consumed completely and 30% of desired product was formed. The mixture was concentrated at 25 °C to give a crude product and was diluted with water (10 mL), acidified to pH~2 with 1 M HCl and extracted with EA (5 mL*3). The combined organic layer was concentrated to crude product (15 mg), which was purified by prep-HPLC to give **Compound 30** (2.13 mg, 5.5 umol, 25.6% yield). LCMS (ESI): RT = 0.692 min, mass calc. for C₁₇H₁₅F₃N₄O₂ 364.11, m/z found 364.9 [M+1]⁺; ¹H NMR (400 MHz, CD₃OD) δ 8.03 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.68 - 7.57 (m, 3H), 7.50 (dt, *J* = 1.5, 7.9 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 4.43 - 4.32 (m, 1H), 4.02 - 3.92 (m, 2H).

Example 29: 2-[5-(azidomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 31)



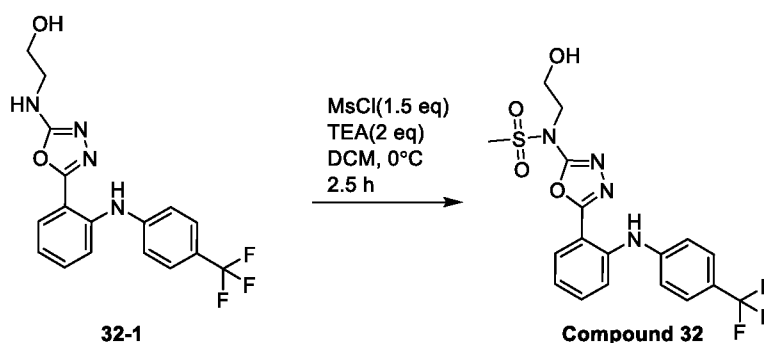
Step 1: 2-[5-(chloromethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00274] **31-1a** (84.1 mg, 0.7 mmol, 59 μ L, 1.1 eq) was added dropwise to the solution of **31-1** in dioxane (3 mL). The reaction mixture was refluxed 2 hours. POCl_3 (18 g, 117.2 mmol, 10.9 mL, 173.2 eq) was added to the reaction mixture, and the reaction was stirred at 100 $^{\circ}\text{C}$ for 2 h. LC-MS showed **31-1** was consumed completely and 43% of desired compound was detected. The mixture was poured into ice water, neutralized with saturated NaHCO_3 , extracted with EtOAc (20 mL * 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to give **31-2** (100 mg, 0.28 mmol, 41.7% yield). LCMS (ESI): RT = 0.853 min, mass calc. for $\text{C}_{16}\text{H}_{11}\text{ClF}_3\text{N}_3\text{O}$ 353.05 m/z found 353.9 $[\text{M}+\text{H}]^+$.

Step 2: 2-[5-(azidomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

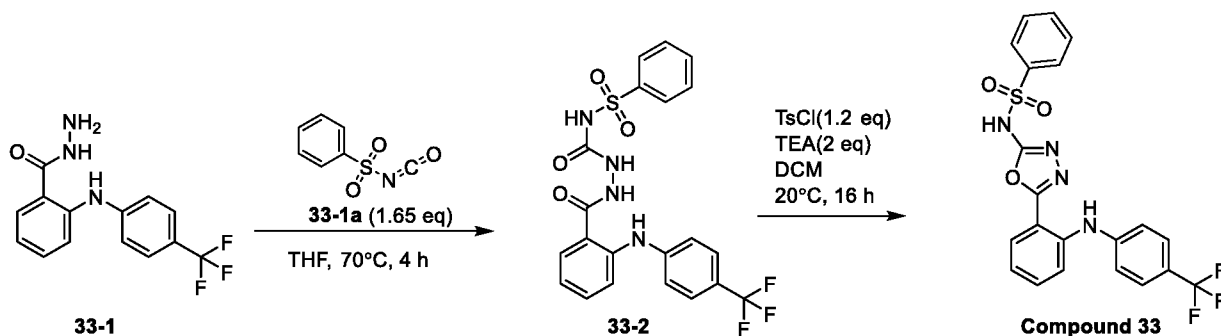
[00275] To a solution of **31-2** (100 mg, 0.3 mmol, 1 eq) in DMF (3 mL) was added NaN_3 (55.1 mg, 0.8 mmol, 3.0 eq). The mixture was stirred at 30 $^{\circ}\text{C}$ for 16 h. TLC indicated **31-2** was consumed completely and one new spot formed. The mixture was quenched by addition of H_2O (5 mL), and then extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give **Compound 31** (100 mg, crude). 20 mg of the crude product was purified by prep-HPLC to give **Compound 31** (3.41 mg). LCMS (ESI): RT = 0.921 min, mass calc. for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{N}_6\text{O}$ 360.09 m/z found 361.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1H), 7.91 (dd, J = 1.4, 7.9 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.55-7.49 (m, 1H), 7.46-7.34 (m, 3H), 7.03-6.96 (m, 1H), 4.67 (s, 2H).

Example 30: N-(2-hydroxyethyl)-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide (Compound 32)



[00276] To a stirred solution of **32-1** (0.03 g, 82 μ mol, 1 *eq*) and TEA (16.7 mg, 0.16 mmol, 23 μ L, 2 *eq*) in DCM (1 mL) was added MsCl (14.2 mg, 0.12 mmol, 10 μ L, 1.5 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2.5 h. LCMS showed the reaction was complete, 38% of **Compound 32** was detected. TLC (Petroleum ether:Ethyl acetate = 1:1 UV) showed new spots were formed. The mixture was concentrated to give a residue. The residue was purified by prep-TLC to give **Compound 32** (2.56 mg, 6 μ mol, 7.0% yield). LCMS (ESI): RT = 0.218 min, mass calc. for $C_{18}H_{17}F_3N_4O_4S$ 442.09, m/z found 443.0 $[M+1]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.65 (d, J = 6.8 Hz, 1H), 7.49 (br d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.3 Hz, 1H), 7.31 - 7.23 (m, 3H), 6.87 (t, J = 7.5 Hz, 1H), 5.27 (br d, J = 5.8 Hz, 1H), 4.45 (t, J = 4.9 Hz, 2H), 3.76 (q, J = 5.3 Hz, 2H), 3.15 - 2.84 (m, 3H).

Example 31: N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (Compound 33)



Step 1: N-(phenylsulfonyl)-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazine carboxamide

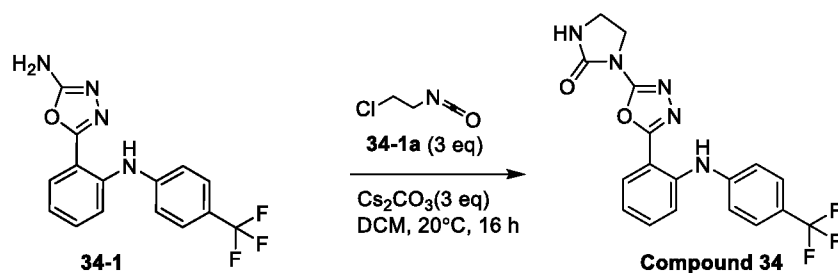
[00277] A mixture of 2-[4-(trifluoromethyl)anilino]benzohydrazide **33-1** (0.20 g, 0.68 mmol, 1 *eq*) and N-(oxomethylene)benzenesulfonamide **33-1a** (136.5 mg, 0.75 mmol, 99 μ L, 1.1 *eq*) in THF (3 mL) was stirred at 70 °C for 2 hr. LCMS showed 19% of starting material was remained and 40% of desired product was formed. Then N-(oxomethylene)benzenesulfonamide **33-1a** (68.3 mg, 0.37 mmol, 50 μ L, 0.55 *eq*) was added and the mixture was continuously stirred at 70 °C for another 2 h. LCMS showed starting material was consumed and 11% of desired product was formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give compound **33-2** (0.15 g, 0.16 mmol, 23.6% yield). LCMS (ESI): RT = 0.811 min, mass calc. for $C_{21}H_{17}F_3N_4O_4S$ 478.09, m/z found 501.0 $[M+23]^+$.

Step 2: N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)benzene sulfonamide

[00278] To a mixture of compound **33-2** (0.13 g, 0.27 mmol, 1 *eq*) and TEA (55.0 mg, 0.54 mmol, 76 μ L, 2 *eq*) in DCM (5 mL) was added TsCl (62.2 mg, 0.33 mmol, 1.2 *eq*) at 20 °C. The resulting mixture was stirred at 20 °C for 16 hr. LCMS showed no starting material was remained and 30%

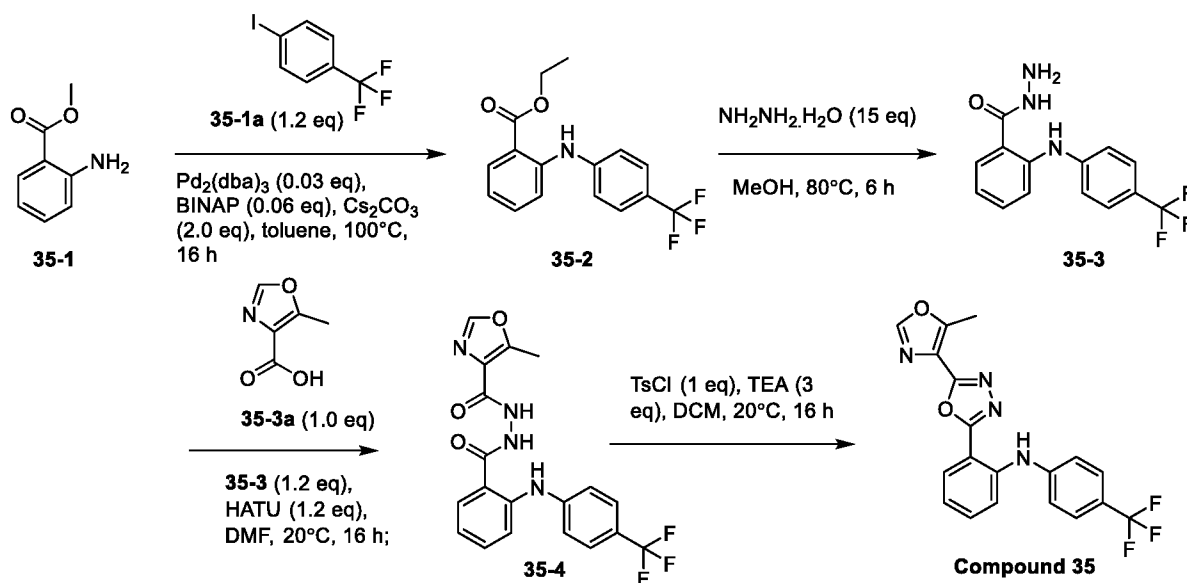
of desired product was formed. The mixture was concentrated at 25 °C to give a residue. The residue was purified by prep-HPLC to give **Compound 33** (2.48 mg, 6 μ mol, 2.0% yield). LCMS (ESI): RT = 0.867 min, mass calc. for C₂₁H₁₅F₃N₄O₃S 460.08, m/z found 461.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 11.13 - 10.59 (m, 1H), 8.22 (s, 1H), 8.03 - 7.97 (m, 2H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.63 - 7.56 (m, 3H), 7.55 - 7.48 (m, 2H), 7.45 - 7.38 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.97 (ddd, *J* = 2.1, 6.1, 8.1 Hz, 1H).

Example 32: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)imidazolidin-2-one (Compound 34)



[00279] To a stirred solution of 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-amine **34-1** (40.0 mg, 0.13 mmol, 1 *eq*) and Cs₂CO₃ (122.1 mg, 0.37 mmol, 3 *eq*) in DCM (3 mL) was added **34-1a** (39.5 mg, 0.37 mmol, 3 *eq*) at 20 °C. The mixture was stirred at 20 °C for 16 h. LCMS showed 48% of starting material was remained and 27% of **Compound 34** was detected. The mixture was concentrated at 20 °C to give a residue. The residue was purified by prep-HPLC to give **Compound 34** (8.65 mg, 21.6 μ mol, 17.3% yield). LCMS (ESI): RT = 0.803 min, mass calc. for C₁₈H₁₄F₃N₅O₂ 389.11, m/z found 390.0 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.27 (br s, 1H), 7.89 (br d, *J* = 7.5 Hz, 1H), 7.50 (br d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.33 - 7.25 (m, 3H), 6.90 (t, *J* = 7.3 Hz, 1H), 4.95 (br s, 1H), 4.16 (br s, 2H), 3.68 (br s, 2H).

Example 33: 2-(5-(5-methyloxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 35)



Step 1: ethyl 2-((4-(trifluoromethyl)phenyl)amino)benzoate

[00280] The mixture of compound **35-1** (15.00 g, 99.23 mmol, 12.8 mL, 1 eq), compound **35-1a** (32.39 g, 119.08 mmol, 17.5 mL, 1.2 eq), $\text{Pd}_2(\text{dba})_3$ (2.73 g, 2.98 mmol, 0.03 eq), BINAP (3.71 g, 5.95 mmol, 0.06 eq) and Cs_2CO_3 (64.66 g, 198.46 mmol, 2 eq) in toluene (250 mL) at 30 °C was purged and degassed with N_2 for 3 times, and the resulting mixture was stirred at 100 °C under N_2 for 16 h. TLC (PE:EA = 10:1, UV) showed starting material was consumed completely and one new spot was formed. The mixture was concentrated to remove the solvent. The residue was diluted with EA (300 mL), and then filtered to remove the solid. The filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2) to give compound **35-2** (21.0 g, 66.54 mmol, 67.1% yield). LCMS (ESI): RT = 0.978 min, mass calc. for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{NO}_2$ 309.10, m/z found 309.9 $[\text{M}+1]^+$. ^1H NMR (400MHz, CDCl_3) δ 9.69 (s, 1H), 8.05 - 8.00 (m, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.44 - 7.36 (m, 2H), 7.30 (d, J = 8.5 Hz, 2H), 6.86 (ddd, J = 2.5, 5.9, 8.2 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H).

Step 2: 2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00281] To a solution of compound **35-2** (21.00 g, 67.90 mmol, 1 eq) in MeOH (60 mL) at 20 °C was added $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (59.98 g, 1.02 mol, 58.2 mL, 15 eq), and the resulting mixture was stirred at 80 °C for 6 h. TLC (PE:EA = 10:1, UV) showed starting material was consumed completely and one new spot was formed. LCMS showed starting material was consumed completely and 94% of desired product was formed. The mixture was concentrated to remove the solvent. The residue was diluted with water (100 mL), and then filtered to collect the solid. The filtrate was extracted with EA (100 mL *3) and the combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was combined with the filtered solid. The combined solid was purified by washed with

PE/EA (200 mL, PE: EA = 5:1), filtered and dried in vacuum to give compound **35-3** (19.00 g, 64.35 mmol, 94.8% yield). ^1H NMR (400MHz, CDCl_3) δ 9.28 (brs, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.51 - 7.35 (m, 4H), 7.24 (d, J = 8.5 Hz, 2H), 6.96 - 6.88 (m, 1H), 4.08 (brs, 2H).

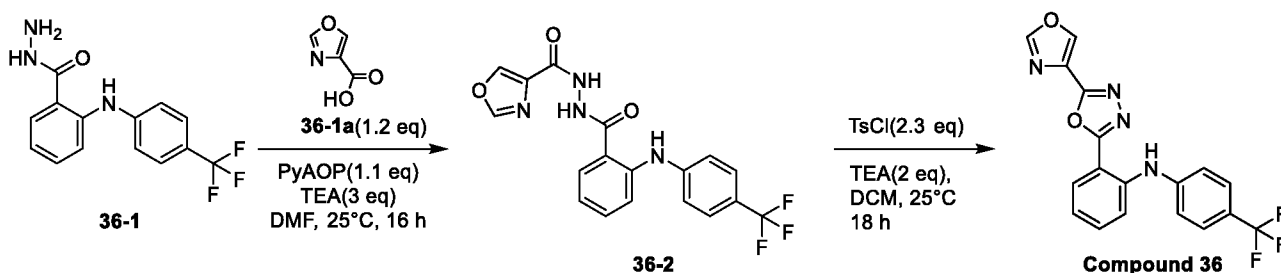
Step 3: 5-methyl-N'-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazole-4-carbohydrazide

[00282] To a solution of compound **35-3a** (200 mg, 1.57 mmol, 1 *eq*), compound **35-3** (557 mg, 1.89 mmol, 1.2 *eq*) and HATU (718 mg, 1.89 mmol, 1.2 *eq*) in DMF (5 mL) at 20 °C was added DIPEA (407 mg, 3.15 mmol, 0.5 mL, 2 *eq*), and the resulting mixture was stirred at 20 °C for 16 h. LCMS showed starting material was consumed completely and 64% of desired product was formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give compound **35-4** (400 mg, 0.99 mmol, 62.9% yield). LCMS (ESI): RT = 0.797 min, mass calc. for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_3$ 404.11, m/z found 405.0 $[\text{M}+1]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 10.50 (s, 1H), 10.19 (s, 1H), 9.45 (s, 1H), 8.41 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.53 - 7.44 (m, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.08 - 7.01 (m, 1H), 2.60 (s, 3H).

Step 4: 2-(5-(5-methyloxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00283] To a solution of compound **35-4** (200 mg, 0.49 mmol, 1 *eq*) and TEA (150.2 mg, 1.48 mmol, 0.2 mL, 3 *eq*) in DCM (2 mL) at 20 °C was added TsCl (94.3 mg, 0.49 mmol, 1 *eq*), and the resulting mixture was stirred at 20 °C for 16 h. LCMS showed 7% of starting material still remained and 93% of desired product was formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 35** (160.90 mg, 0.42 mmol, 84.2% yield). LCMS (ESI): RT = 0.915 min, mass calc. for $\text{C}_{19}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_2$ 386.10, m/z found 386.9 $[\text{M}+1]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 9.24 (s, 1H), 8.61 - 8.51 (m, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.62 - 7.53 (m, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 2.70 (s, 3H).

Example 34: 2-(5-(oxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 36)



Step 1: N'-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazole-4-carbohydrazide

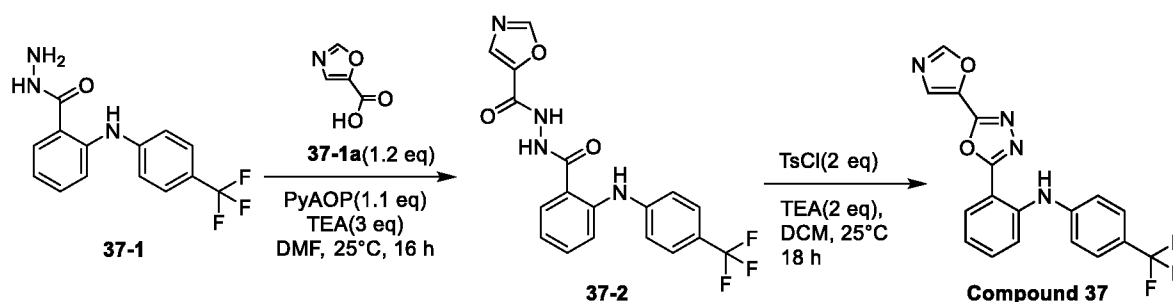
[00284] To a mixture of **36-1a** (137.9 mg, 1.22 mmol, 1.2 *eq*), PYAOP (635.7 mg, 1.22 mmol, 1.2 *eq*) and TEA (308.4 mg, 3.05 mmol, 424.27 μL , 3 *eq*) in DMF (3 mL) was added **36-1** (0.3 g, 1.02

mmol, 1 *eq*) in one portion at 20 °C under N₂. The mixture was stirred at 20 °C for 16 h. LCMS showed 7% of starting material was remained and 20% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine(15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **36-2** (0.05 g, 0.13 mmol, 12.61% yield). LCMS (ESI): RT = 0.767 min, mass calc. for C₁₈H₁₃F₃N₄O₃ 390.09, m/z found 390.9 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.57 (s, 1H), 10.40 (s, 1H), 9.43 (s, 1H), 8.78 (s, 1H), 8.60 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.60 (br d, *J* = 8.4 Hz, 2H), 7.53 - 7.43 (m, 2H), 7.30 (br d, *J* = 8.3 Hz, 2H), 7.05 (br t, *J* = 7.2 Hz, 1H).

Step 2: 2-(5-(oxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00285] To a mixture of **36-2** (33 mg, 85 μmol, 1 *eq*) and TEA (17.1 mg, 0.17 mmol, 24 μL, 2 *eq*) in DCM (3 mL) was added TsCl (16.1 mg, 85 μmol, 1 *eq*) in one portion at 20 °C under N₂. The mixture was stirred at 20 °C for 16 h. LCMS showed 78% of starting material was remained and 21% of desired product was detected. Then another batch of TsCl (21 mg, 0.11 mmol, 1.3 *eq*) was added and the mixture was stirred at 20 °C for 2 h. LCMS showed no starting material was remained and 77% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15mL), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 36** (5.52 mg, 15 μmol, 17.2% yield). LCMS (ESI): RT = 0.875 min, mass calc. for C₁₈H₁₁F₃N₄O₂ 372.08 m/z found 372.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 8.49 (d, *J* = 0.8 Hz, 1H), 8.12 (s, 1H), 8.04 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.56 - 7.50 (m, 1H), 7.45 - 7.37 (m, 3H), 7.27 (s, 1H), 7.04 - 6.97 (m, 1H).

Example 35: 2-(5-(oxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 37)



Step 1: N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazole-5-carbohydrazide

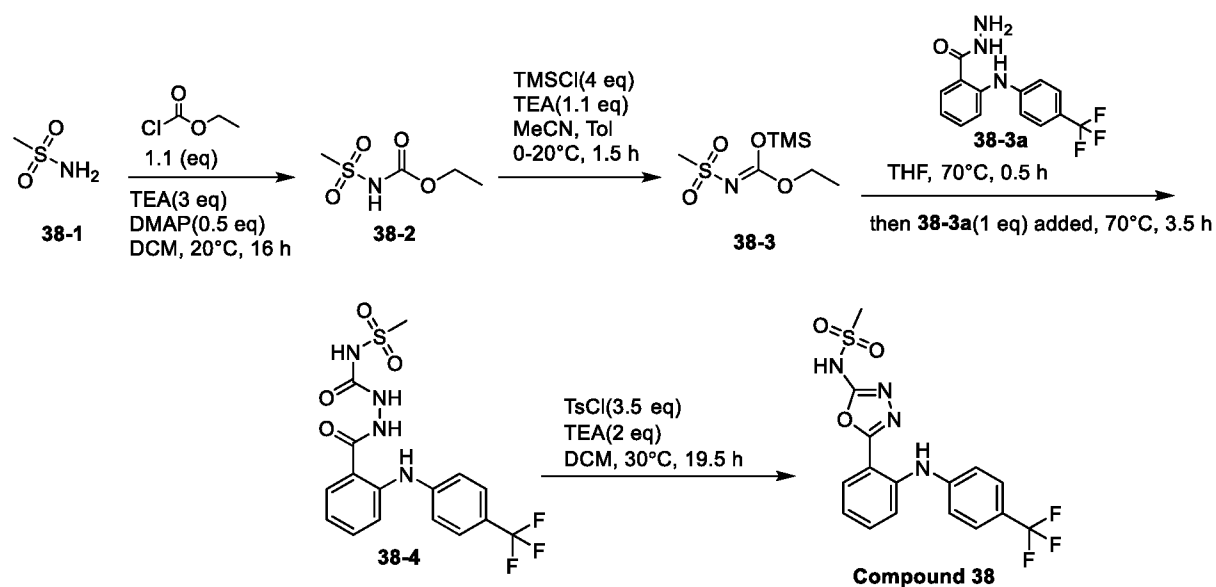
[00286] To a mixture of **37-1a** (138.4 mg, 1.22 mmol, 1.2 *eq*), PYAOP (638.2 mg, 1.22 mmol, 1.2 *eq*) and TEA (309.6 mg, 3.06 mmol, 425.92 μL, 3 *eq*) in DMF (3 mL) was added **37-1** (0.3 g, 1.02 mmol, 1 *eq*) in one portion at 20 °C under N₂. The mixture was stirred at 20 °C for 16 h. LCMS showed 9% of starting material and 15% of desired product was detected. The mixture was diluted

with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **37-2** (0.04 g, 0.10 mmol, 10.1% yield). LCMS (ESI): RT = 0.749 min, mass calc. for C₁₈H₁₃F₃N₄O₃ 390.09, m/z found 390.9 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.79 (s, 1H), 10.67 (s, 1H), 9.38 (s, 1H), 8.67 (s, 1H), 7.94 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.53 - 7.43 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.13 - 6.99 (m, 1H).

Step 2: 2-(5-(oxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00287] To a mixture of **37-2** (23 mg, 59 μmol, 1 *eq*) and TEA (14.9 mg, 0.15 mmol, 21 μL, 2.5 *eq*) in DCM (2 mL) was added TsCl (11.2 mg, 59 μmol, 1 *eq*) in one portion at 20 °C under N₂. The mixture was stirred at 20 °C for 16 h. LCMS showed 51% of starting material was remained and 46% of desired product was detected. Then another batch of TsCl (11.2 mg, 59 μmol, 1 *eq*) was added and the mixture was stirred at 20 °C for 2 h. LCMS showed no starting material was remained and 70% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15mL), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 37** (2.39 mg, 6 μmol, 10.8% yield). LCMS (ESI): RT = 0.888 min, mass calc. for C₁₈H₁₁F₃N₄O₂ 372.08 m/z found 372.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 8.21 - 8.12 (m, 1H), 7.99 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.95 - 7.90 (m, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.55 - 7.49 (m, 1H), 7.48 - 7.36 (m, 3H), 7.07 - 6.96 (m, 1H).

Example 36: N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide (Compound 38)



Step 1: ethyl methanesulfonylcarbamate

[00288] To a mixture of **38-1** (5 g, 52.56 mmol, 1 *eq*), TEA (15.96 g, 157.69 mmol, 22 mL, 3 *eq*) and DMAP (3.21 g, 26.28 mmol, 0.5 *eq*) in DCM (20 mL) was added ethyl carbonochloridate (6.27 g, 57.82 mmol, 5.5 mL, 1.1 *eq*) at 20 °C. The resulting mixture was stirred at 20 °C for 16 hr. TLC (Ethyl acetate:Petroleum ether = 2:1 I₂) showed new spots were formed. The filtrate was concentrated to give a residue. The residue was dissolved in EtOAc (100 mL) and washed with 1 N HCl (30 mL*2), water (30 mL*2), and brine (30 mL*2). The organic layer was dried over anhydrous and concentrated in vacuo to give **38-2** (2.1 g, 12.56 mmol, 23.9% yield), which was used directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.57 (br s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.28 - 3.17 (m, 3H), 1.22 (t, *J* = 7.2 Hz, 3H).

Step 2: (Z)-ethyl (trimethylsilyl) methylsulfonylcarbonimide

[00289] To a solution of **38-2** (0.5 g, 2.99 mmol, 1 *eq*) in a mixture of MeCN (1 mL) and toluene (6 mL) was added TMSCl (1.30 g, 11.96 mmol, 1.5 mL, 4 *eq*) and the resulting mixture was cooled in an ice bath. After slowly adding a solution of TEA (332.9 mg, 3.29 mmol, 0.5 mL, 1.1 *eq*) in Toluene (2 mL), the reaction mixture was stirred at 20 °C for 1.5 hr. The excess trimethylchlorosilane was evaporated in vacuo at 20 °C and diluted with water (15 mL) and extracted with DCM (20 mL) twice. The combined organic layer was dried by anhydrous Na₂SO₄, filtered and concentrated at 20 °C to give crude product compound **38-3** (0.28 g, 1.17 mmol, 39.1% yield), which was used directly.

Step 3: N-(methylsulfonyl)-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazine carboxamide

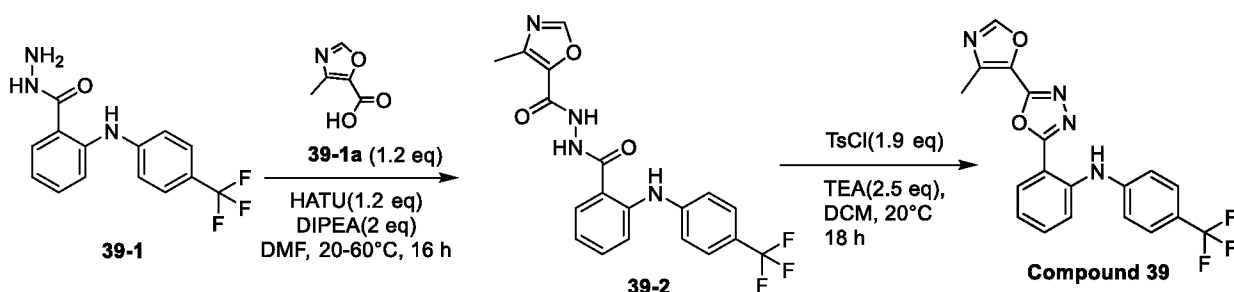
[00290] A solution of **38-3** (0.14 g, 0.58 mmol, 1 *eq*) in THF (5 mL) was stirred at 70 °C for 0.5 hr and cooled to 20 °C. Then **38-3a** (172.7 mg, 0.58 mmol, 1 *eq*) was added and the resulting mixture was stirred at 70 °C for 3.5 hr. LCMS showed 73% of **38-3a** was remained and 21% of desired product was formed. The mixture was concentrated in vacuo to yield a residue. The residue was purified by prep-HPLC to give **38-4** (15 mg, 24 μmol, 4.1% yield). LCMS (ESI): RT = 0.754 min, mass calc. for C₁₆H₁₅F₃N₄O₄S 416.08, *m/z* found 438.9 [M+23]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.46 (br s, 1H), 9.41 - 9.22 (m, 1H), 7.78 - 7.56 (m, 2H), 7.48 (br s, 2H), 7.26 (br dd, *J* = 8.3, 17.1 Hz, 2H), 7.14 - 6.97 (m, 1H), 3.26 (s, 3H).

Step 4: N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methane sulfonamide

[00291] To a mixture of compound **38-4** (13 mg, 31 μmol, 1 *eq*) and TEA (6.3 mg, 62 μmol, 8 uL, 2 *eq*) in DCM (2 mL) was added TsCl (9 mg, 47 μmol, 1.5 *eq*) at 20 °C. Then the mixture was stirred at 30 °C for 1.5 hr. LCMS showed 23% of compound **38-4** was remained and 25% of desired product was formed. Then the mixture was stirred at 30 °C for 16 hr. LCMS showed 21%

of compound **38-4** was remained and 29% of desired product was formed. Another batch of TsCl (11.9 mg, 62 μ mol, 2 *eq*) was added and the mixture was stirred at 30 °C for 2 hr. LCMS showed no compound **38-4** was remained and 30% of desired product was formed. The mixture was diluted with DCM (50 mL) and washed with brine (10 mL). The organic layer was dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 38** (2.78 mg, 7 μ mol, 22.4% yield). LCMS (ESI): RT = 0.801 min, mass calc. for C₁₆H₁₃F₃N₄O₃S 398.07, *m/z* found 399.0 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.88 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.58 - 7.46 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 3.11 (s, 3H).

Example 37: 2-(5-(4-methyloxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 39)



Step 1: 4-methyl-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazole-5-carbohydrazide

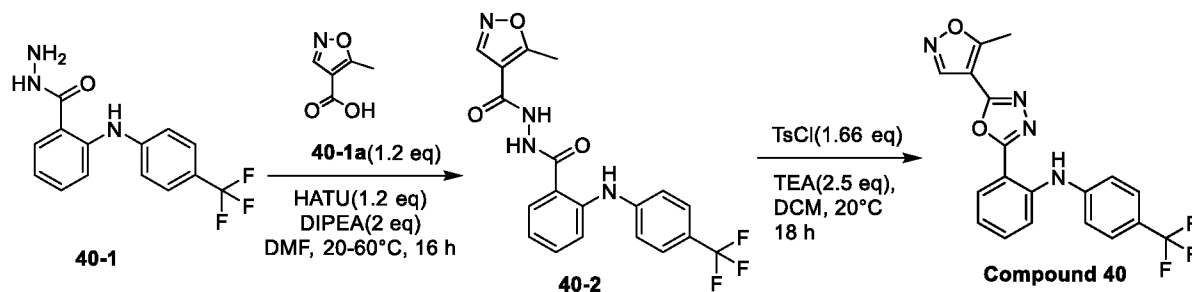
[00292] To a solution of **39-1** (0.3 g, 1.02 mmol, 1 *eq*), **39-1a** (155.0 mg, 1.22 mmol, 1.2 *eq*) and HATU (463.6 mg, 1.22 mmol, 1.2 *eq*) in DMF (4 mL) at 20 °C was added DIPEA (262.6 mg, 2.03 mmol, 0.4 mL, 2 *eq*), and the resulting mixture was stirred at 60 °C for 16 h. LCMS showed 11% of starting material was remained and 32% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **39-2** (85.05 mg, 0.21 mmol, 20.7% yield). LCMS (ESI): RT = 0.766 min, mass calc. for C₁₉H₁₅F₃N₄O₃ 404.11, *m/z* found 405.0 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.56 (d, *J* = 18.0 Hz, 2H), 9.43 (s, 1H), 8.53 (s, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.45 (m, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.06 (ddd, *J* = 2.0, 6.3, 7.9 Hz, 1H), 2.41 (s, 3H).

Step 2: 2-(5-(4-methyloxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00293] To a mixture of **39-2** (0.08 g, 0.2 mmol, 1 *eq*) and TEA (50.0 mg, 0.5 mmol, 68 μ L, 2.5 *eq*) in DCM (3 mL) was added TsCl (56.6 mg, 0.3 mol, 1.5 *eq*) in one portion at 20 °C. The mixture was stirred at 20 °C for 16 h. LCMS showed 9% of starting material was remained and 75% of desired product was detected. Then another batch of TsCl (15.1 mg, 79 μ mol, 0.4 *eq*) was added and the mixture was stirred at 20 °C for another 2 h. LCMS showed no starting material was remained and 44% of desired product was detected. The mixture was diluted with DCM (50 mL),

washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 39** (34.15 mg, 88 μ mol, 44.7% yield). LCMS (ESI): RT = 0.922 min, mass calc. for C₁₉H₁₃F₃N₄O₂ 386.10, m/z found 386.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.50 (s, 1H), 8.04 (s, 1H), 7.97 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.46 - 7.37 (m, 3H), 7.05 - 6.98 (m, 1H), 2.67 (s, 3H).

Example 38: 2-(5-(5-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 40)



Step 1: 5-methyl-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)isoxazole-4-carbohydrazide

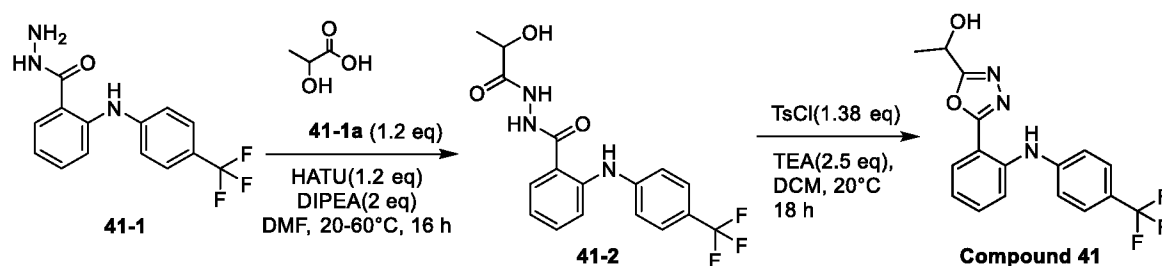
[00294] To a solution of **40-1** (0.3 g, 1.02 mmol, 1 *eq*), **40-1a** (155.6 mg, 1.22 mmol, 1.2 *eq*) and HATU (465.4 mg, 1.22 mmol, 1.2 *eq*) in DMF (4 mL) at 20 °C was added DIPEA (263.7 mg, 2.04 mmol, 0.4 mL, 2 *eq*), and the resulting mixture was stirred at 60 °C for 16 h. LCMS showed no starting material was remained and 43% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **40-2** (0.21 g, 0.52 mmol, 50.9% yield). LCMS (ESI): RT = 0.801 min, mass calc. for C₁₉H₁₅F₃N₄O₃ 404.11, m/z found 404.9 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.57 (br s, 1H), 9.40 (br s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 - 7.43 (m, 3H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.07 - 6.99 (m, 1H), 2.26 (d, *J* = 2.0 Hz, 3H).

Step 2: 2-(5-(5-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00295] To a mixture of compound **40-2** (0.21 g, 0.52 mmol, 1 *eq*) and TEA (131.4 mg, 1.30 mmol, 0.2 mL, 2.5 *eq*) in DCM (8 mL) was added TsCl (148.5 mg, 0.78 mmol, 1.5 *eq*) in one portion at 20 °C. The mixture was stirred at 20 °C for 16 h. LCMS showed 10% of starting material was remained and 65% of desired product was detected. Then another batch of TsCl (15.8 mg, 83 μ mol, 0.16 *eq*) was added and the mixture was stirred at 20 °C for another 2 h. LCMS showed no starting material was remained and 54% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 40** (7.8

mg, 20 μ mol, 3.8% yield). LCMS (ESI): RT = 0.922 min, mass calc. for $C_{19}H_{13}F_3N_4O_2$ 386.10, m/z found 386.9 $[M+1]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.99 (dd, J = 1.3, 8.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.54 - 7.41 (m, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.07 - 6.98 (m, 1H), 2.51 (s, 3H).

Example 39: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol (Compound 41)



Step 1: N'-(2-hydroxypropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

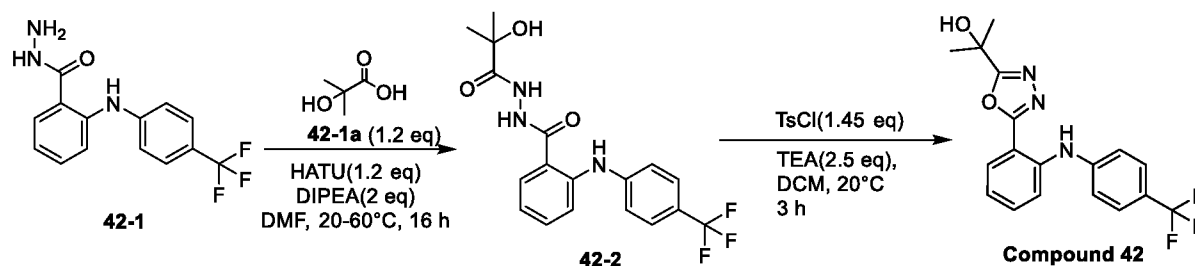
[00296] To a solution of **41-1** (0.3 g, 1.02 mmol, 1 *eq*), **41-1a** (110.3 mg, 1.22 mmol, 91 μ L, 1.2 *eq*) and HATU (465.4 mg, 1.22 mmol, 1.2 *eq*) in DMF (4 mL) at 20 °C was added DIPEA (263.7 mg, 2.04 mmol, 0.36 mL, 2 *eq*), and the resulting mixture was stirred at 60 °C for 16 h. LCMS showed no starting material was remained and 43% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **41-2** (92 mg, 0.25 mmol, 24.6% yield). LCMS (ESI): RT = 0.727 min, mass calc. for $C_{17}H_{16}F_3N_3O_3$ 367.11, m/z found 367.0 $[M+1]^+$. ^1H NMR (400 MHz, $DMSO-d_6$) δ 10.37 (s, 1H), 9.81 (s, 1H), 9.39 (s, 1H), 7.70 - 7.65 (m, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.51 - 7.39 (m, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.08 - 6.96 (m, 1H), 4.15 (q, J = 6.8 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H).

Step 2: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

[00297] To a mixture of **41-2** (86 mg, 0.23 mmol, 1 *eq*) and TEA (59.2 mg, 0.58 mmol, 81 μ L, 2.5 *eq*) in DCM (1 mL) was added TsCl (53.6 mg, 0.28 mmol, 1.2 *eq*) in one portion at 20 °C. The mixture was stirred at 20 °C for 16 h. LCMS showed 7% of starting material was remained and 65% of desired product was detected. Then another batch of TsCl (8.0 mg, 42 μ mol, 0.18 *eq*) was added and the mixture was stirred at 20 °C for another 2 h. LCMS and HPLC showed no starting material was remained and 59% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 41** (18.63 mg, 53 μ mol, 22.6% yield). LCMS (ESI): RT = 0.841 min, mass calc. for $C_{17}H_{14}F_3N_3O_2$ 349.10, m/z found 349.9 $[M+1]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.91 (dd, J = 1.4, 7.9

Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.53 - 7.48 (m, 1H), 7.43 - 7.38 (m, 1H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.02 - 6.90 (m, 1H), 5.22 (m, 1H), 2.89 (br d, $J = 5.4$ Hz, 1H), 1.76 (d, $J = 6.8$ Hz, 3H).

Example 40: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol (Compound 42)



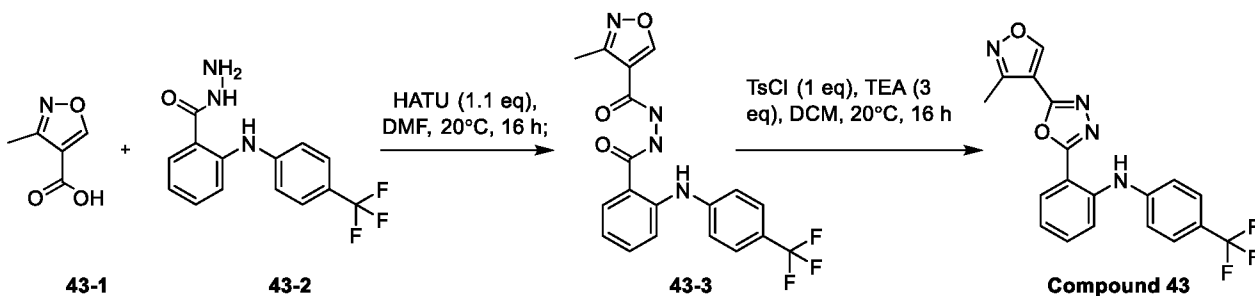
Step 1: N'-(2-hydroxy-2-methylpropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzo hydrazide

[00298] To a solution of **42-1** (0.3 g, 1.02 mmol, 1 *eq*), **42-1a** (127.4 mg, 1.22 mmol, 91 μ L, 1.2 *eq*) and HATU (465.4 mg, 1.22 mmol, 1.2 *eq*) in DMF (4 mL) at 20 °C was added DIPEA (263.7 mg, 2.04 mmol, 0.36 mL, 2 *eq*), and the resulting mixture was stirred at 60 °C for 16 h. LCMS showed no starting material was remained and 31% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **42-2** (76.2 mg, 0.2 mmol, 19.6% yield). LCMS (ESI): RT = 0.758 min, mass calc. for $\text{C}_{18}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_3$ 381.13, m/z found 382.0 $[\text{M}+1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H), 9.67 (s, 1H), 9.40 (s, 1H), 7.67 (d, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.50 - 7.41 (m, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 7.05 - 6.98 (m, 1H), 1.33 (s, 6H).

Step 2: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol

[00299] To a mixture of **42-2** (71 mg, 0.18 mmol, 1 *eq*) and TEA (37.7 mg, 0.37 mmol, 51 μ L, 2 *eq*) in DCM (3 mL) was added TsCl (42.6 mg, 0.22 mmol, 1.2 *eq*) in one portion at 15 °C. The mixture was stirred at 15 °C for 2 h. LCMS and HPLC showed 33% of starting material was remained and 65% of desired product was detected. Then another batch of TsCl (8.9 mg, 46 μ mol, 0.25 *eq*) was added and the mixture was stirred at 20 °C for another 1 h. LCMS showed 18% starting material was remained and 61% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 42** (19.76 mg, 54 μ mol, 29.2% yield). LCMS (ESI): RT = 0.854 min, mass calc. for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_2$ 363.12, m/z found 363.9 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.48 (s, 1H), 7.91 (dd, $J = 1.4$, 7.9 Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.40 (dt, $J = 1.5$, 7.9 Hz, 1H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.01 - 6.94 (m, 1H), 2.87 (br s, 1H), 1.80 (s, 6H).

Example 41: 2-(5-(3-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 43)



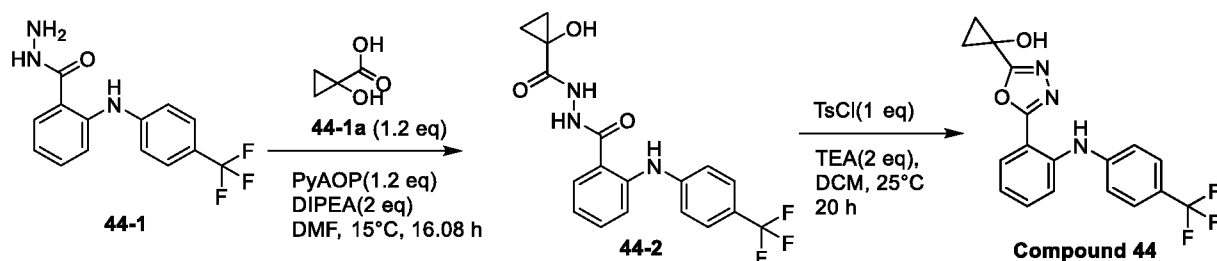
Step 1: 3-methyl-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)isoxazole-4-carbohydrazide

[00300] To a solution of compound **43-1** (200 mg, 1.57 mmol, 1 *eq*) and HATU (658.2 mg, 1.73 mmol, 1.1 *eq*) in DMF (1 mL) at 20 °C was added compound **43-2** (511.1 mg, 1.73 mmol, 1.1 *eq*) and DIPEA (406.7 mg, 3.15 mmol, 0.5 mL, 2 *eq*), and the resulting mixture was stirred at 20 °C for 16 h. LCMS showed starting material was consumed completely, and 29% of guanidine-byproduct and 63% of desired product were formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give compound **43-3** (334 mg, 0.83 mmol, 52.5% yield). LCMS (ESI): RT = 0.781 min, mass calc. for C₁₉H₁₅F₃N₄O₃ 404.11, m/z found 405.0[M+1]⁺. ¹H NMR (400MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 10.53 (s, 1H), 9.37 (s, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 - 7.45 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.11 - 7.02 (m, 1H), 2.41 (s, 3H).

Step 2: 2-(5-(3-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00301] To a solution of compound **43-3** (230 mg, 0.57 mmol, 1 *eq*) and TEA (172.7 mg, 1.71 mmol, 0.2 mL, 3 *eq*) in DCM (3 mL) at 20 °C was added TsCl (108.4 mg, 0.57 mmol, 1 *eq*), and the resulting mixture was stirred at 20 °C for 16 h. LCMS showed starting material was consumed completely, and 90% of desired product were formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 43** (176.96 mg, 0.46 mmol, 80.5% yield). LCMS (ESI): RT = 0.946 min, mass calc. for C₁₉H₁₃F₃N₄O₂ 386.10, m/z found 387.0[M+1]⁺. ¹H NMR (400MHz, DMSO-*d*₆) δ 9.82 (s, 1H), 9.22 (s, 1H), 8.06 - 8.00 (m, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.62 - 7.54 (m, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.22 - 7.15 (m, 1H), 2.57 (s, 3H).

Example 42: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropanol (Compound 44)



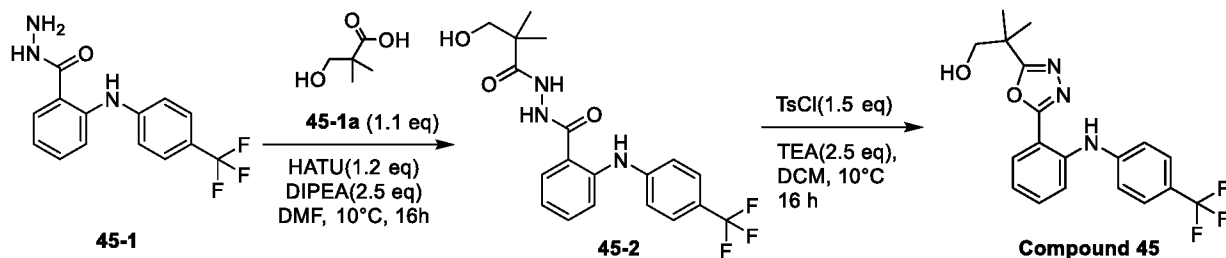
Step 1: N'-((1-hydroxycyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00302] To a mixture of **44-1a** (207.4 mg, 2.03 mmol, 1.2 *eq*) and PYAOP (1.07 g, 2.05 mmol, 1.21 *eq*) in DMF (5 mL) was added DIPEA (547.2 mg, 4.23 mmol, 0.7 mL, 2.5 *eq*) in one portion at 15 °C. After stirring for 5 min, **44-1** (0.5 g, 1.69 mmol, 1 *eq*) was added and the mixture was stirred at 15 °C for 16 h. LCMS showed no starting material was remained and 43% of desired product was detected. The mixture was diluted with EA (100 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **44-2** (15 mg, 40 μmol, 2.3% yield). LCMS (ESI): RT = 0.749 min, mass calc. for C₁₈H₁₆F₃N₃O₃ 379.11, m/z found 380.0 [M+1]⁺.

Step 2: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropanol

[00303] To a mixture of **44-2** (15 mg, 40 μmol, 1 *eq*) and TEA (8 mg, 79 μmol, 11 uL, 2 *eq*) in DCM (2 mL) was added TsCl (11 mg, 59 μmol, 1.5 *eq*) in one portion at 10 °C. The mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 52% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 44** (3.41 mg, 9 μmol, 23.9% yield). LCMS (ESI): RT = 0.850 min, mass calc. for C₁₈H₁₄F₃N₃O₂ 361.10, m/z found 361.9 [M+1]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.94 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.67 - 7.55 (m, 3H), 7.52 - 7.45 (m, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.07 (t, *J* = 7.7 Hz, 1H), 1.48 - 1.32 (m, 4H).

Example 43: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol (Compound 45)



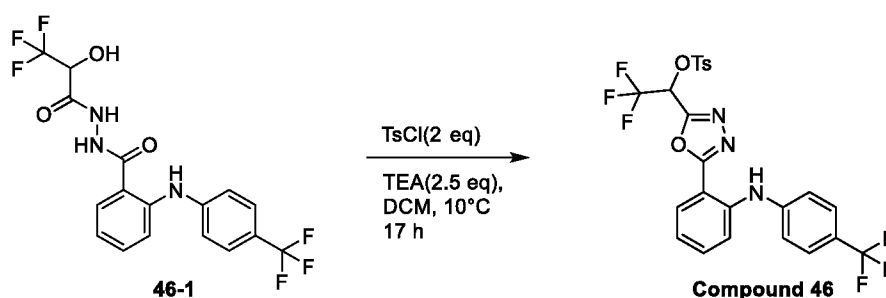
Step 1: N'-((3-hydroxy-2,2-dimethylpropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00304] To a solution of **45-1a** (132.5 mg, 1.12 mmol, 1.1 *eq*) and HATU (465.4 mg, 1.22 mmol, 1.2 *eq*) in DMF (3 mL) at 10 °C was added DIPEA (329.6 mg, 2.55 mmol, 0.5 mL, 2.5 *eq*). After stirring for 10 min, **45-1** (0.3 g, 1.02 mmol, 1 *eq*) was added and the resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 60% of desired product was detected. TLC (Petroleum ether:Ethyl acetate = 1:1,UV) indicated reactant 1 was consumed completely and one new spot formed. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂) to give compound **45-2** (350 mg, 0.89 mmol, 86.8% yield). LCMS (ESI): RT = 0.763 min, mass calc. for C₁₉H₂₀F₃N₃O₃ 395.15, m/z found 396.0 [M+1]⁺.

Step 2: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol

[00305] To a solution of **45-2** (0.25 g, 0.63 mmol, 1 *eq*) and TEA (160 mg, 1.58 mmol, 0.2 mL, 2.5 *eq*) in DCM (5 mL) at 10 °C was added TsCl (180.8 mg, 0.95 mmol, 1.5 *eq*). The resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 60% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 45** (22.61 mg, 59 umol, 9.4% yield). LCMS (ESI): RT = 0.876 min, mass calc. for C₁₉H₁₈F₃N₃O₂ 377.14, m/z found 377.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.48 (br s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.57 (br d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.42 - 7.31 (m, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 3.85 (s, 2H), 2.83 (br s, 1H), 1.48 (s, 6H).

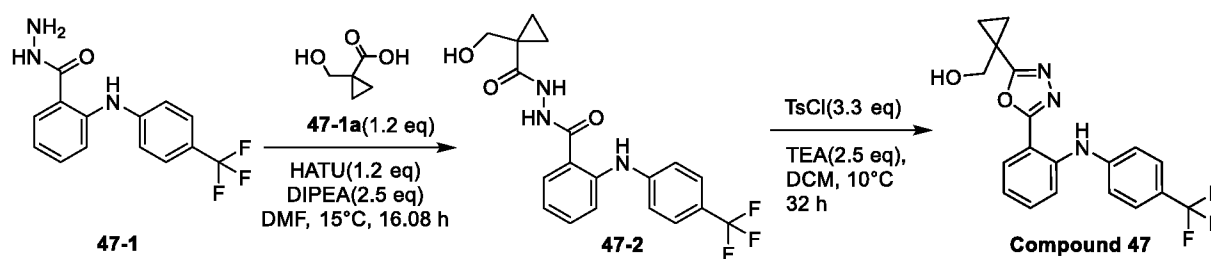
Example 44: 2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl 4-methylbenzenesulfonate (Compound 46)



[00306] To a solution **46-1** (0.24 g, 0.57 mmol, 1 *eq*) and TEA (144.1 mg, 1.42 mmol, 0.2 mL, 2.5 *eq*) in DCM (5 mL) at 10 °C was added TsCl (162.9 mg, 0.85 mmol, 1.5 *eq*). The resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 46% of **Compound 46** was formed. Then another batch of TsCl (54.3 mg, 0.28 mmol, 0.5 *eq*) was added and the resulting mixture was stirred at 10 °C for another 1 h. LCMS showed no starting material was remained and 60% of **Compound 46** was formed. The mixture was diluted with EA (50 mL),

washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 46** (20 mg, 35 μmol , 6.2% yield). LCMS (ESI): RT = 1.007 min, mass calc. for $\text{C}_{24}\text{H}_{17}\text{F}_6\text{N}_3\text{O}_4\text{S}$ 557.08, m/z found 558.0 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.19 (s, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.62 (dd, J = 1.4, 7.9 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.44 - 7.33 (m, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.16 (s, 2H), 6.93 - 6.86 (m, 1H), 6.05 (q, J = 5.8 Hz, 1H), 2.17 (s, 3H).

Example 45: (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methanol (Compound 47)



Step 1: N'-(1-(hydroxymethyl)cyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00307] To a mixture of **47-1a** (70.8 mg, 0.61 mmol, 1.2 *eq*) and HATU (231.8 mg, 0.61 mmol, 1.2 *eq*) in DMF (3 mL) was added DIPEA (164.2 mg, 1.27 mmol, 0.2 mL, 2.5 *eq*) in one portion at 15 °C. After stirring for 5 min, **47-1** (0.15 g, 0.51 mmol, 1 *eq*) was added and the mixture was stirred at 15 °C for 16 h. LCMS and HPLC showed no starting material was remained and 43% of desired product was detected. The mixture was diluted with EA (100 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **47-2** (60 mg, 0.15 mmol, 29.4% yield). LCMS (ESI): RT = 0.758 min, mass calc. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_3$ 393.13, m/z found 394.0 $[\text{M}+1]^+$.

Step 2: (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methanol

[00308] To a solution of **47-2** (20 mg, 51 μmol , 1 *eq*) and TEA (12.9 mg, 0.13 mmol, 18 μL , 2.5 *eq*) in DCM (5 mL) at 10 °C was added TsCl (12.6 mg, 66 μmol , 1.3 *eq*). The resulting mixture was stirred at 10 °C for 16 h. LCMS showed 57% of starting material was remained and 14% of desired product was detected. TsCl (29.1 mg, 0.15 mmol, 3 *eq*) was added to the mixture, and the resulting mixture was stirred at 10 °C for 16 h. LCMS showed 16% of starting material was remained and 30% of desired product was detected. The mixture was diluted with EA (100 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 47** (27.56 mg, 73 μmol , 36.1% yield). LCMS (ESI): RT = 0.849 min, mass calc. for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_2$ 375.12, m/z found 376.0 $[\text{M}+1]^+$. ^1H

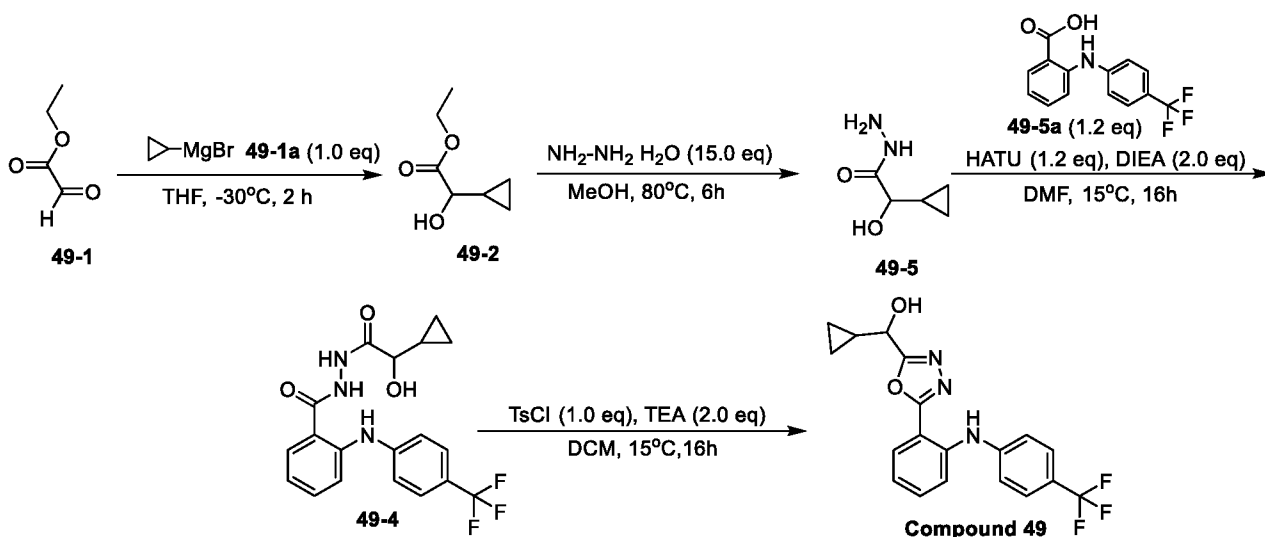
NMR (400 MHz, DMSO-*d*₆) δ 9.21 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.59 - 7.49 (m, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.19 - 7.10 (m, 1H), 5.02 (t, *J* = 5.9 Hz, 1H), 3.79 (d, *J* = 6.0 Hz, 2H), 1.23 - 1.17 (m, 2H), 1.16 - 1.09 (m, 2H).

Example 46: 2-[5-(2H-tetrazol-5-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 48)



[00309] To a solution of **48-1** (30 mg, 90.8 μ mol, 1 eq) in DMF (0.5 mL) were added NaN₃ (0.1 g, 1.1 mmol, 11.9 eq) and NH₄Cl (24.3 mg, 0.5 mmol, 15.9 μ L, 5.0 eq). The mixture was stirred at 120 °C for 2 hr. LC-MS showed **48-1** was consumed completely and 98% of desired compound was detected. The reaction mixture was diluted with (H₂O 1 mL). The residue was purified by prep-HPLC to give **Compound 48** (2.54 mg, 6.8 μ mol, 7% yield). LCMS (ESI): RT = 0.948 min, mass calc. for C₁₆H₁₀F₃N₇O 373.09, *m/z* found 374.4 [M+H]⁺; ¹H NMR (400MHz, CDCl₃) δ 8.17-8.15 (m, *J* = 1.1, 7.9 Hz, 1H), 7.66-7.57 (m, 3H), 7.54-7.48 (m, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H).

Example 47: cyclopropyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol (Compound 49)



Step 1: ethyl 2-cyclopropyl-2-hydroxyacetate

[00310] To a solution of compound **49-1** (10 g, 48.98 mmol, 1 eq) in THF (100 mL) was added compound **49-1a** (0.5 M, 97.9 mL, 1 eq) dropwise at -20~-30 °C bath. The mixture was stirred at -30 °C for 2 hr. TLC (PE/EA = 1/1, KMnO₄) showed that the starting material was remained and

new spots were formed. The reaction mixture was quenched with water (200 mL) dropwise at -20 °C and the aqueous phase was extracted with EA (30 mL*4). The combined organic phase was washed with water (25 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂). **49-2** (1.2 g, 8.32 mmol, 17.0% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 4.24 (m, 2H), 3.76 - 3.71 (m, 1H), 2.85 (br s, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.13 - 1.02 (m, 1H), 0.55 - 0.45 (m, 3H), 0.44 - 0.35 (m, 1H).

Step 2: 2-cyclopropyl-2-hydroxyacetohydrazide

[00311] To a solution of compound **49-2** (100 mg, 0.69 mmol, 1 *eq*) in MeOH (1 mL) was added NH₂NH₂·H₂O (651 mg, 10.40 mmol, 0.6 mL, 15 *eq*). The mixture was stirred at 80 °C for 6 hr. TLC (PE/EA = 1/1, I₂) showed that the starting material was consumed completely. The reaction mixture was concentrated in vacuum. The crude product was used for the next step directly. **49-3** (40 mg, 0.31 mmol, 44.3% yield) was obtained. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (br s, 1H), 5.17 (br s, 1H), 4.27 (br s, 2H), 1.07 - 0.97 (m, 1H), 0.40 - 0.23 (m, 4H).

Step 3: N'-(2-cyclopropyl-2-hydroxyacetyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

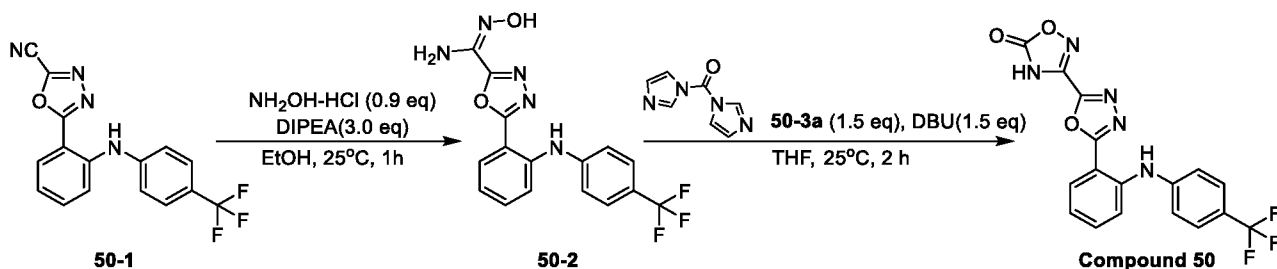
[00312] To a solution of compound **49-3a** (77.8 mg, 0.28 mmol, 1.2 *eq*) in DMF (1 mL) were added DIPEA (59.6 mg, 0.46 mmol, 80 uL, 2 *eq*), HATU (105.2 mg, 0.28 mmol, 1.2 *eq*) and compound **3** (30 mg, 0.23 mmol, 1 *eq*). The mixture was stirred at 15 °C for 16 hr. LCMS showed that the starting material was consumed completely and desired product was detected. The reaction mixture was concentrated in vacuum. The crude product was purified by prep-HPLC. **49-4** (30 mg, 76.3 umol, 33.1% yield) was obtained. ¹H NMR (400MHz, DMSO-*d*₆) δ 9.93 (br s, 1H), 8.23 (br s, 1H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.49 - 7.36 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 5.48 (br d, *J* = 4.8 Hz, 1H), 3.65 (br t, *J* = 5.1 Hz, 1H), 1.18 - 1.06 (m, 1H), 0.52 - 0.28 (m, 4H).

Step 4: cyclopropyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol

[00313] To a solution of compound **49-4** (25 mg, 63 umol, 1 *eq*) in DCM (0.5 mL) were added TEA (13 mg, 0.13 mmol, 17.7 uL, 2 *eq*) and TsCl (12 mg, 63.6 umol, 1 *eq*). The mixture was stirred at 10 °C for 2 hr. LCMS showed that the starting material was remained and 58% of desired product was detected. The reaction mixture was concentrated in vacuum. The crude product was purified by prep-HPLC. **Compound 49** (10 mg, 26.6 umol, 41.9% yield) was obtained. LCMS (ESI): RT = 0.885 min, mass calcd. for C₁₉H₁₆F₃N₃O₂, 375.12 m/z found 375.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.55 (s, 1H), 8.07 (br d, *J* = 7.78 Hz, 1H), 7.86 (d, *J* = 8.78 Hz, 1H), 7.75 (d, *J* = 8.04 Hz, 2H), 7.64 (d, *J* = 9.04 Hz, 1H), 7.57 (d, *J* = 8.04 Hz, 2H), 7.48 (d, *J* = 8.04 Hz, 1H), 7.13

(br s, 1H), 6.07 (br d, $J = 8.28$ Hz, 1H), 4.36 (dq, $J = 13.62, 6.76$ Hz, 1H), 1.59 (s, 9H), 1.32 (d, $J = 6.54$ Hz, 6H).

Example 48: 3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-4H-1,2,4-oxadiazol-5-one (Compound 50)



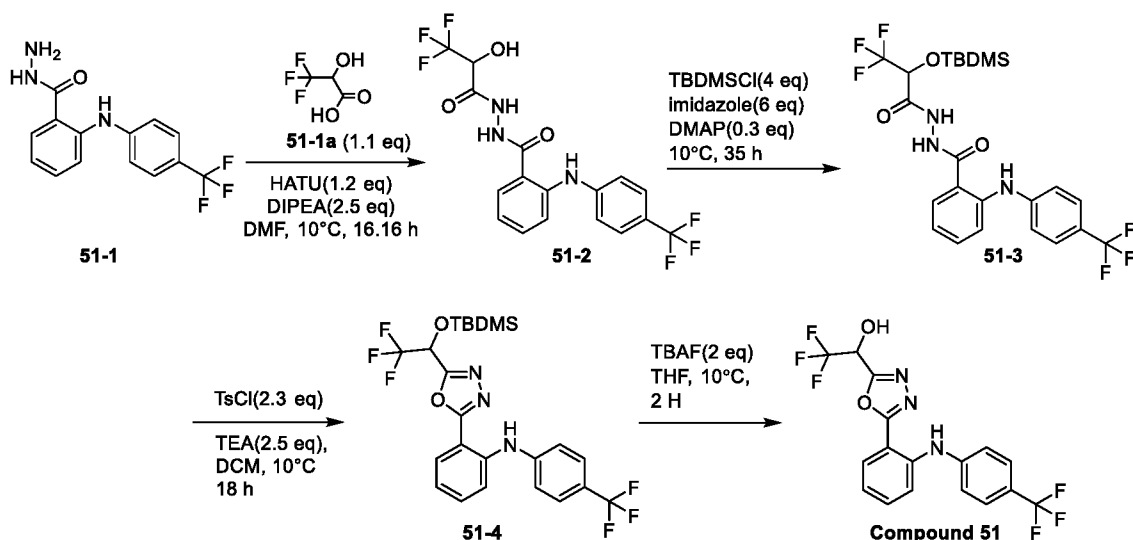
Step 1: N'-hydroxy-5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carboxamide

[00314] To a solution of **50-1** (70 mg, 0.2 mmol, 1 eq) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (22.1 mg, 0.2 mmol, 0.98 eq, HCl) in EtOH (2 mL) was added DIPEA (82.2 mg, 0.6 mmol, 0.1 mL, 3.0 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed **50-1** was consumed completely and 99% of desired compound was detected. The reaction mixture was filtered to give **50-2** (35 mg, 96.3 μmol , 45.4% yield). LCMS (ESI): RT = 0.953 min, mass calc. for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{N}_5\text{O}_2$ 363.09, m/z found 364.4 $[\text{M}+\text{H}]^+$.

Step 2: 3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-4H-1,2,4-oxadiazol-5-one

[00315] To a solution of **50-2** (35 mg, 96.3 μmol , 1 eq) and **50-3a** (23.4 mg, 0.1 mmol, 1.5 eq) in THF (1 mL) was added DBU (22.0 mg, 0.1 mmol, 22 μL , 1.5 eq). The mixture was stirred at 25 °C for 2 h. LC-MS showed 30% of **50-2** was remained and 68% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 50** (8.68 mg, 22.3 μmol , 23.1% yield). LCMS (ESI): RT = 1.146 min, mass calc. for $\text{C}_{12}\text{H}_6\text{BrN}_5$ 253.05, m/z found 254.3 $[\text{M}+\text{H}]^+$.

Example 49: 2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol (Compound 51)



Step 1: N'-(3,3,3-trifluoro-2-hydroxypropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00316] To a solution of **51-1a** (268.3 mg, 1.86 mmol, 1.1 *eq*) and HATU (772.7 mg, 2.03 mmol, 1.2 *eq*) in DMF (5 mL) at 10 °C was added DIPEA (547.2 mg, 4.23 mmol, 0.7 mL, 2.5 *eq*). After stirring for 10 min, **51-1** (0.5 g, 1.69 mmol, 1 *eq*) was added and the resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 14% desired product was detected. The mixture was directly purified by prep-HPLC to give **51-2** (50 mg, 0.11 mmol, 45% yield. LCMS (ESI): RT = 0.797 min, mass calc. for C₁₇H₁₃F₆N₃O₃ 421.09, m/z found 421.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (br s, 1H), 8.89 (br s, 1H), 8.52 (br s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.41 - 7.31 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.86 (t, *J* = 7.8 Hz, 1H), 4.61 (br d, *J* = 7.0 Hz, 1H), 3.91 (br s, 1H).

Step 2: N'-(2-((tert-butyldimethylsilyl)oxy)-3,3,3-trifluoropropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00317] To a solution of **51-2** (40 mg, 95 umol, 1 *eq*), DMAP (3.5 mg, 28 umol, 0.3 *eq*) and imidazole (38.8 mg, 0.57 mmol, 6 *eq*) in DCM (3 mL) at 10 °C was added TBDMSCl (28.6 mg, 0.19 mmol, 23 uL, 2 *eq*). The resulting mixture was stirred at 10 °C for 16 h. LCMS showed 52% of starting material was remained and 44% desired product was detected. Then another batch of TBDMSCl (14.3 mg, 95 umol, 12 uL, 1 *eq*) was added and the resulting mixture was stirred at 10 °C for 3 h. LCMS showed 31% of starting material was remained and 65% desired product was detected. Then another batch of TBDMSCl (14.3 mg, 95 umol, 12 uL, 1 *eq*) was added and the resulting mixture was stirred at 10 °C for another 16 h. LCMS showed no starting material was remained and 89.9% desired product was detected. TLC (Petroleum ether:Ethyl acetate = 3:1 UV) showed new spots were formed. The mixture diluted with water (10 mL), extracted with dichloromethane (15 mL*3) and the extracts dried over anhydrous Na₂SO₄, filtered and evaporated

to give crude product. The mixture was directly purified-TLC to give **51-3** (34 mg, 60 μ mol, 63.5% yield).

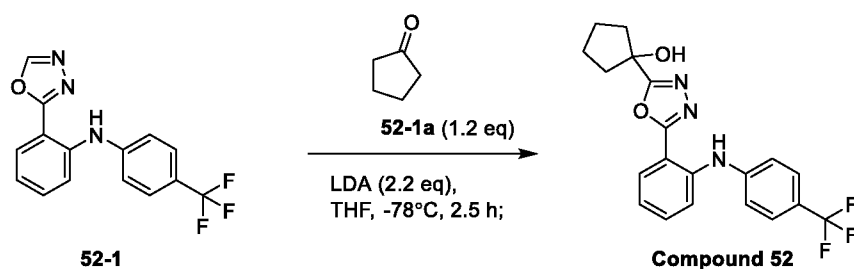
Step 3: 2-(5-(1-((tert-butyldimethylsilyl)oxy)-2,2,2-trifluoroethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00318] To a solution of compound **51-3** (34 mg, 64 μ mol, 1 *eq*) and TEA (16.06 mg, 0.16 mmol, 22 μ L, 2.5 *eq*) in DCM (1 mL) at 10 °C was added TsCl (18.2 mg, 95 μ mol, 1.5 *eq*). The resulting mixture was stirred at 10 °C for 2 h. LCMS showed 54% of starting material was remained and 14% of desired product was detected. Then another batch of TsCl (9.68 mg, 51 μ mol, 0.8 *eq*) was added and the solution was continuously stirred at 10 °C for 16 h. LCMS showed 18% of starting material was remained and 39% of desired product was detected. TLC (Petroleum ether : Ethyl acetate = 5:1 UV) showed some of starting material was remained and new spot was formed. The mixture was directly purified by prep-TLC to give **51-4** (11 mg, 21 μ mol, 32.8% yield).

Step 4: 2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

[00319] To a mixture of **51-4** (9 mg, 17 μ mol, 1 *eq*) in THF (1 mL) was added TBAF (1 M, 35 μ L, 2 *eq*). Then the resulting solution was stirred at 10 °C for 2 h. LCMS showed starting material was consumed completely and 100% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The combined mixture was directly purified by prep-HPLC to give **Compound 51** (4.15 mg, 10 μ mol, 59.2% yield). LCMS (ESI): RT = 0.896 min, mass calc. for C₁₇H₁₁F₆N₃O₂ 403.08, m/z found 403.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.26 (s, 1H), 7.84 (d, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.47 - 7.40 (m, 1H), 7.39 - 7.33 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.92 (t, *J* = 7.5 Hz, 1H), 5.39 (q, *J* = 5.9 Hz, 1H), 3.63 (br s, 1H).

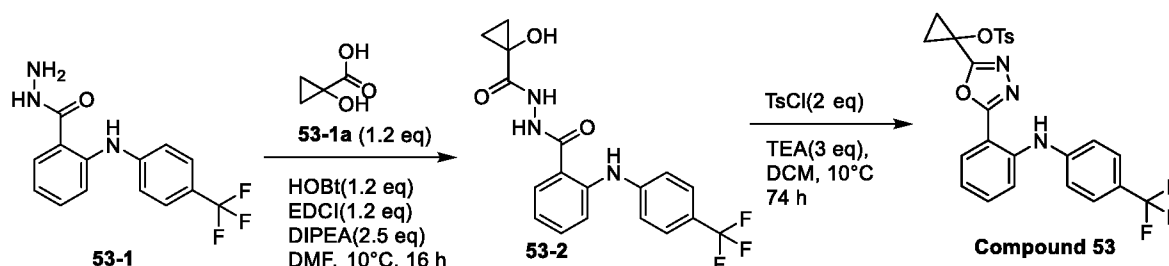
Example 50: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopentanol (Compound 52)



[00320] To a solution of **52-1** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then **52-1a** (33.1 mg, 0.39 mmol, 35 μ L, 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C into the above mixture. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE: EA = 5:1, UV) showed some

starting material still remained and one new spot was formed. LCMS showed 27% of starting material still remained and 68% of desired product was formed. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) at -78°C , and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **Compound 52** (66.97 mg, 0.17 mmol, 52.5% yield). LCMS (ESI): RT = 0.898 min, mass calc. for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_2$ 389.14, m/z found 390.0 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.51 (s, 1H), 7.91 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, $J = 8.3$ Hz, 2H), 7.01 - 6.95 (m, 1H), 2.58 (s, 1H), 2.38 - 2.28 (m, 2H), 2.21 - 2.13 (m, 2H), 2.11 - 2.00 (m, 2H), 1.98 - 1.86 (m, 2H).

Example 51: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl 4-methylbenzenesulfonate (Compound 53)



Step 1: N'-((1-hydroxycyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

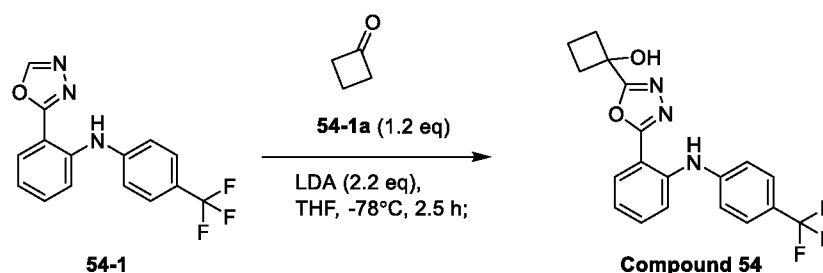
[00321] A mixture of **53-1** (450 mg, 1.52 mmol, 1 *eq*), **53-1a** (186.7 mg, 1.83 mmol, 1.2 *eq*), HOBT (247.1 mg, 1.83 mmol, 1.2 *eq*), EDCI (350.6 mg, 1.83 mmol, 1.2 *eq*) and DIPEA (492.4 mg, 3.81 mmol, 0.7 mL, 2.5 *eq*) in DMF (10 mL) was stirred at 10°C for 16 h. LCMS showed 35% of starting material was remained and 61% of desired product was detected. The mixture was diluted with EA (100 mL), washed with brine (15 mL), dried with Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give compound **53-2** (0.5 g, 1.28 mmol, 83.9% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H), 9.93 (s, 1H), 9.43 (br s, 1H), 7.67 (d, $J = 7.1$ Hz, 1H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.53 - 7.39 (m, 2H), 7.28 (d, $J = 8.5$ Hz, 2H), 7.02 (t, $J = 6.7$ Hz, 1H), 6.43 (s, 1H), 1.14 - 1.04 (m, 2H), 0.98 - 0.90 (m, 2H).

Step 2: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl 4-methylbenzenesulfonate

[00322] To a mixture of **53-2** (0.45 g, 1.19 mmol, 1 *eq*) and TEA (360.1 mg, 3.56 mmol, 0.5 mL, 3 *eq*) in DCM (15 mL) was added TsCl (226.2 mg, 1.19 mmol, 1 *eq*) at 10°C . The resulting mixture was stirred at 10°C for 1 h. LCMS showed 22% of starting material remained and 15% of **53** was formed. Then another TsCl (113.1 mg, 0.59 mmol, 0.5 *eq*) was added and the resulting mixture was

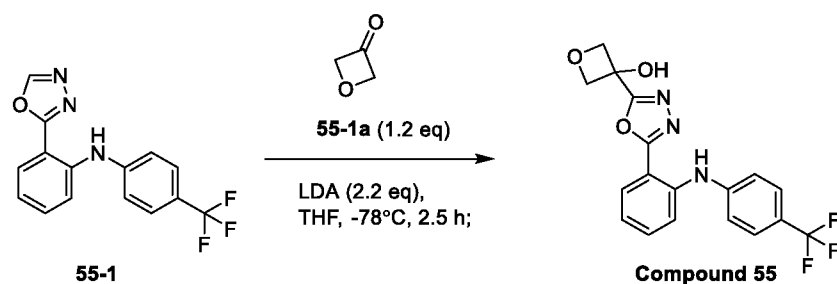
stirred at 10 °C for 1.5 h. LCMS and HPLC showed 8% of starting material remained, and 30% of **53** was formed. The mixture was directly diluted with EA (20 mL), washed with water (5 mL*3), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 53** (23 mg, 40 μ mol, 3.4% yield). LCMS (ESI): RT = 0.985 min, mass calc. for C₂₅H₂₀F₃N₃O₄S 515.11, m/z found 538.0 [M+23]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.66 (dd, *J* = 3.4, 8.1 Hz, 3H), 7.56 (d, *J* = 3.8 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.14 (td, *J* = 4.1, 8.1 Hz, 1H), 2.15 (s, 3H), 1.75 - 1.67 (m, 2H), 1.61 - 1.52 (m, 2H).

Example 52: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclobutanol (Compound 54)



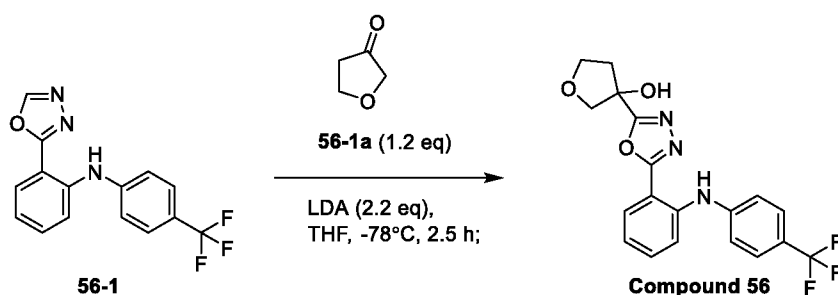
[00323] To a solution of **54-1** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then **54-1a** (27.6 mg, 0.39 mmol, 29 μ L, 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C into the above mixture. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE: EA = 5:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed starting material was consumed completely and 90% of desired product was formed. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL) at -78 °C, and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **Compound 54** (55.89 mg, 0.15 mmol, 45.5% yield). LCMS (ESI): RT = 0.881 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 376.0[M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.94 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.01 - 6.96 (m, 1H), 2.97 (s, 1H), 2.87 - 2.76 (m, 2H), 2.61 - 2.50 (m, 2H), 2.13 - 2.04 (m, 1H), 2.03 - 1.92 (m, 1H).

Example 53: (Compound 55) 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxetan-3-ol



[00324] To a solution of **55-1** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then oxetan-3-one (28.3 mg, 0.39 mmol, 29 μL , 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C into the above mixture. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE: EA = 2:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed 24% of starting material still remained and 76% of desired product was formed. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) at -78 °C, and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 55** (69.12 mg, 0.18 mmol, 55.9% yield). LCMS (ESI): RT = 0.826 min, mass calc. for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_3$ 377.10, m/z found 378.1 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.38 (s, 1H), 7.97 (dd, J = 1.4, 7.9 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.54 - 7.50 (m, 1H), 7.47 - 7.40 (m, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.03 - 6.97 (m, 1H), 5.14 (d, J = 7.8 Hz, 2H), 5.02 (d, J = 7.8 Hz, 2H), 3.78 (s, 1H).

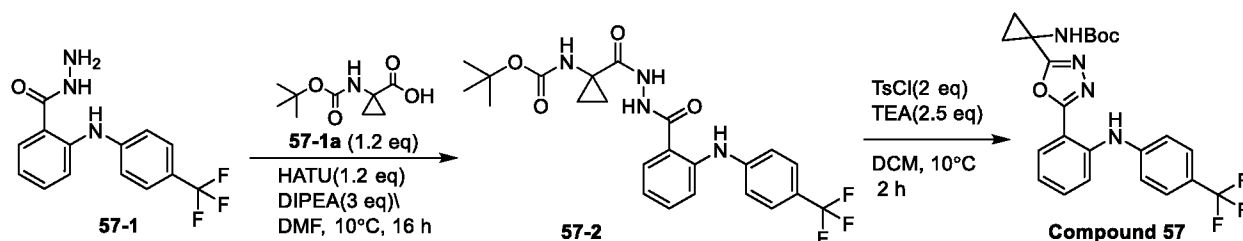
Example 54: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3-ol (Compound 56)



[00325] To a solution of **56-1** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then **56-1a** (33.8 mg, 0.39 mmol, 35 μL , 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C into the above mixture. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE:EA = 2:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed 38% of starting material still remained and 62% of desired product was formed. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) at -78 °C, and then diluted with water (20 mL) and extracted

with EA (20 mL *3). The combined organic layers were washed with brine (20mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 56** (51.73 mg, 0.13 mmol, 38.6% yield). LCMS (ESI): RT = 0.828 min, mass calc. for C₁₉H₁₆F₃N₃O₃ 391.11, m/z found 391.9[M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 7.91 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.95 (m, 1H), 4.29 - 4.12 (m, 4H), 3.17 (s, 1H), 2.71 (td, *J* = 8.6, 13.2 Hz, 1H), 2.51 - 2.42 (m, 1H).

Example 55: (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate (Compound 57)



Step 1: tert-butyl (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbonyl)cyclopropyl)carbamate

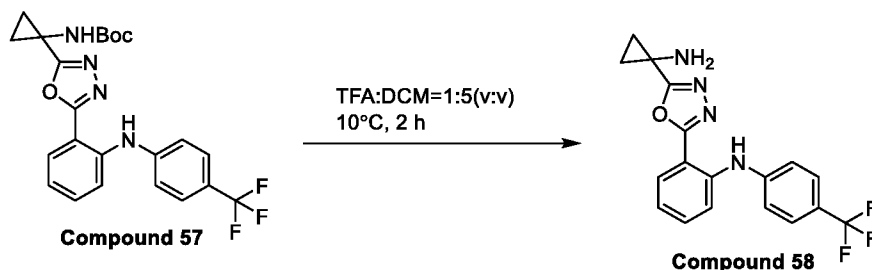
[00326] A mixture of **57-1** (600 mg, 2.03 mmol, 1 *eq*), **57-1a** (490.7 mg, 2.44 mmol, 1.2 *eq*), DIPEA (787.9 mg, 6.1 mmol, 1.1 mL, 3 *eq*) and HATU (927.2 mg, 2.44 mmol, 1.2 *eq*) in DMF (1 mL) was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 53% of desired product was detected. The mixture was diluted with EA (100 mL), washed with aq. saturated citric acid (15 mL*2), aq. saturated NaHCO₃ (15 mL*2) and brine (15 mL) in turns, dried with Na₂SO₄, filtered and concentrated to give crude compound **57-2** (850 mg, 1.78 mmol, 87.4% yield), which was used directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.39 (br s, 1H), 10.48 - 10.28 (m, 1H), 9.84 (s, 1H), 9.43 (s, 1H), 7.96 (s, 1H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.49 - 7.40 (m, 3H), 7.28 (br d, *J* = 8.3 Hz, 2H), 7.00 (br t, *J* = 7.1 Hz, 1H), 1.40 (s, 9H), 1.32 - 1.27 (m, 2H), 1.01 - 0.95 (m, 2H).

Step 2: tert-butyl (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate

[00327] To a mixture of **57-2** (50 mg, 0.1 mmol, 1 *eq*) and TEA (26.4 mg, 0.26 mmol, 36 uL, 2.5 *eq*) in DCM (2 mL) was added TsCl (29.9 mg, 0.16 mmol, 1.5 *eq*) at 10 °C. Then the resulting mixture was stirred at 10 °C for 1 h. LCMS showed 16% of starting material was remained and 48% of desired product was detected. Then another portion of TsCl (9.9 mg, 52 umol, 0.5 *eq*) was added and the mixture was stirred at 10 °C for another 1 h. LCMS showed 15% of starting material was remained and 56% of desired product was detected. The solution was diluted with EA (100 mL), washed with brine (15 mL), dried with Na₂SO₄, filtered and concentrated to give a residue.

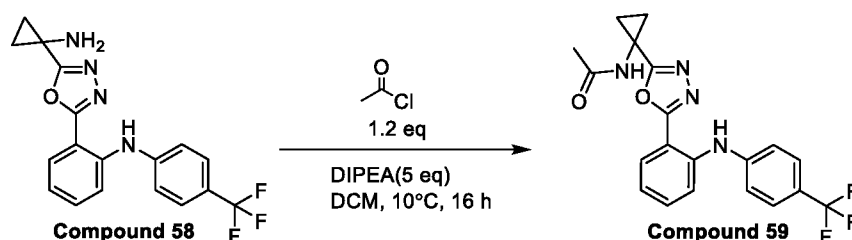
The residue was purified by prep-HPLC to give **Compound 57** (25 mg, 53 μ mol, 51.3% yield). LCMS (ESI): RT = 0.942 min, mass calc. for $C_{23}H_{23}F_3N_4O_3$ 460.17, m/z found 482.9 $[M+23]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.05 (s, 1H), 7.85 (br d, J = 7.9 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.58 - 7.50 (m, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 1.53 - 1.48 (m, 2H), 1.40 (s, 9H), 1.34 - 1.30 (m, 2H).

Example 56: 2-(5-(1-aminocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 58)



[00328] To a solution of **Compound 57** (50 mg, 0.11 mmol, 1 *eq*) in DCM (1 mL) was added TFA (309.5 mg, 2.71 mmol, 0.2 mL, 25 *eq*) at 10 °C. Then the mixture was stirred at 10 °C for 2 h. LCMS showed no starting material was remained and 96% of desired product was formed. The mixture was concentrated at 10 °C to give a residue. The residue was purified by prep-HPLC to give **Compound 58** (3.51 mg, 9 μ mol, 8.9% yield). LCMS (ESI): RT = 0.729 min, mass calc. for $C_{18}H_{15}F_3N_4O$ 360.12, m/z found 361.0 $[M+1]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.32 - 9.12 (m, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.62 (br d, J = 8.4 Hz, 2H), 7.57 - 7.47 (m, 2H), 7.32 (br d, J = 8.4 Hz, 2H), 7.19 - 7.07 (m, 1H), 3.02 - 2.61 (m, 1H), 1.29 - 1.20 (m, 2H), 1.14 - 1.05 (m, 2H).

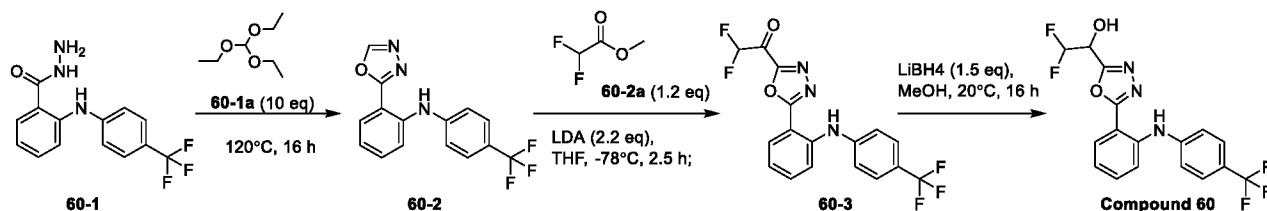
Example 57: N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)acetamide (Compound 59)



[00329] To a mixture of **Compound 58** (100 mg, 0.21 mmol, 1 *eq*, TFA) and DIPEA (136.2 mg, 1.05 mmol, 0.2 mL, 5 *eq*) in DCM (3 mL) was added a solution of acetyl chloride (19.9 mg, 0.25 mmol, 18 μ L, 1.2 *eq*) in DCM (1 mL) at 10 °C. Then the resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 42% of desired product was detected. The mixture was quenched methanol (0.01 mL) and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 59** (9.59 mg, 23 μ mol, 10.8% yield). LCMS (ESI): RT = 0.808 min, mass calc. for $C_{20}H_{17}F_3N_4O_2$ 402.13, m/z found 425.0 $[M+23]^+$. ^1H NMR (400 MHz,

CDCl₃) δ 9.37 (s, 1H), 7.69 (dd, J = 1.5, 7.9 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 1H), 7.33 - 7.24 (m, 3H), 6.87 (t, J = 7.6 Hz, 1H), 6.20 (s, 1H), 3.85 (s, 1H), 2.11 (s, 1H), 2.03 (s, 3H), 1.71 - 1.65 (m, 2H), 1.46 - 1.41 (m, 2H).

Example 58: 2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol (Compound 60)



Step 1: 2-(1, 3, 4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00330] The mixture of compound **60-1** (1.50 g, 5.08 mmol, 1 *eq*) and compound **60-1a** (7.53 g, 50.8 mmol, 8.5 mL, 10 *eq*) (neat reaction) was stirred at 120 °C under N₂ for 16 h. TLC (PE: EA = 1:1, UV) showed starting material was consumed completely, and one new spot was formed. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give compound **60-2** (1.40 g, 4.49 mmol, 88.5% yield). LCMS (ESI): RT = 0.989 min, mass calc. for C₁₅H₁₀F₃N₃O 305.08, m/z found 306.1[M+1]⁺.

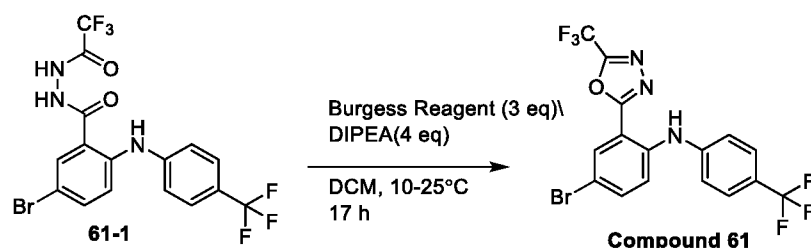
Step 2: 2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanone

[00331] To a solution of compound **60-2** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then compound **60-2a** (43.3 mg, 0.39 mmol, 35 μ L, 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE:EA = 2:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed 40% of starting material still remained and 59% of one new peak was formed. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL) at -78 °C, and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give compound **60-3** (40.0 mg, 90.1 μ mol, 27.5% yield). LCMS (ESI): RT = 0.815 min, mass calc. for C₁₇H₁₀F₅N₃O₂ 383.07, m/z found 401.9[M+H₂O+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.69 - 7.57 (m, 2H), 7.54 - 7.46 (m, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.02 (ddd, J = 2.4, 5.8, 8.2 Hz, 1H), 6.86 - 6.59 (m, 1H).

Step 3: 2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

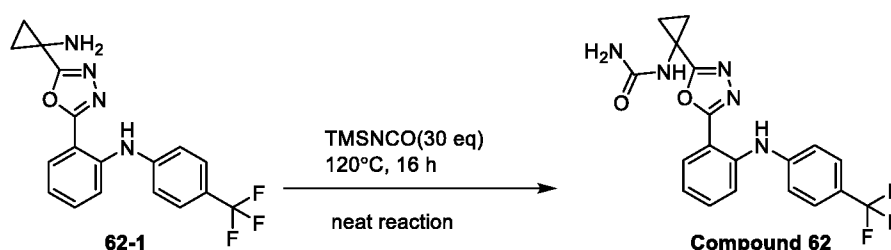
[00332] To a solution of compound **60-3** (20 mg, 52.2 μmol , 1 *eq*) in MeOH (1 mL) at 20 °C was added LiBH_4 (1.7 mg, 78.3 μmol , 1.5 *eq*), and the mixture was stirred at 20 °C for 16 h. TLC (PE:EA = 2:1, UV) showed starting material was consumed completely and one new spot was formed. LCMS showed starting material was consumed completely and 97% of desired product was formed. The reaction mixture was quenched with water (0.5 mL) at 20 °C, and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **Compound 60** (14.63 mg, 38.0 μmol , 72.8% yield). LCMS (ESI): RT = 0.865 min, mass calc. for $\text{C}_{17}\text{H}_{12}\text{F}_5\text{N}_3\text{O}_2$ 385.05, m/z found 385.7 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.39 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.00 (t, J = 7.5 Hz, 1H), 6.34 - 6.07 (m, 1H), 5.31 - 5.24 (m, 1H), 3.13 (d, J = 7.3 Hz, 1H).

Example 59: 4-bromo-2-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 61)



[00333] To a mixture of compound **61-1** (10 mg, 21 μmol , 1 *eq*) and DIPEA (11 mg, 85 μmol , 15 μL , 4 *eq*) in DCM (1 mL) was added Burgess reagent (15.2 mg, 64 μmol , 3 *eq*) in one portion at 10 °C. The mixture was stirred at 25 °C for 1 h. LCMS showed 65% of compound **61-1** was remained and 26% of desired product was detected. Then the mixture was continuously stirred at 25 °C for 16 h. TLC (Petroleum ether:Ethyl acetate = 2:1 UV) showed no compound **61-1** was remained and one main new spot was detected. The mixture was purified by prep-TLC to give **Compound 61** (5.84 mg, 13 μmol , 58.9% yield). MS (ESI): mass calc. for $\text{C}_{16}\text{H}_8\text{BrF}_6\text{N}_3\text{O}$ 450.98, m/z found 453.9721 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.28 (s, 1H), 8.04 (d, J = 2.3 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.53 (dd, J = 2.3, 9.1 Hz, 1H), 7.37 (d, J = 9.0 Hz, 3H).

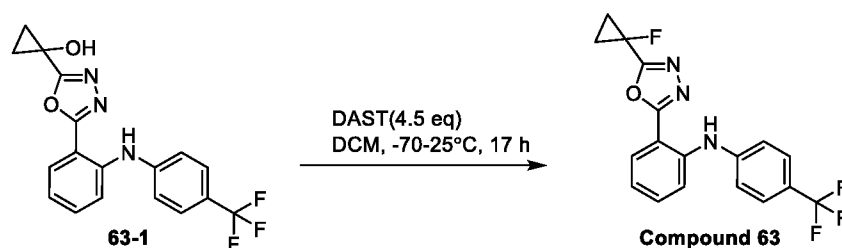
Example 60: 1-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)urea (Compound 62)



[00334] A mixture of **62-1** (100 mg, 0.21 mmol, 1 *eq*, TFA) and isocyanato(trimethyl)silane (728.6 mg, 6.32 mmol, 0.8 mL, 30 *eq*) was stirred at 120 °C for 16 h. LCMS showed no starting material was remained and 67% of desired product was detected. The mixture was quenched with diluted with DCM (50 mL), washed with brine (15 mL), dried by anhydrous Na₂SO₄, filtered and concentrated at 10 °C to give a residue. The residue was purified by prep-HPLC to give

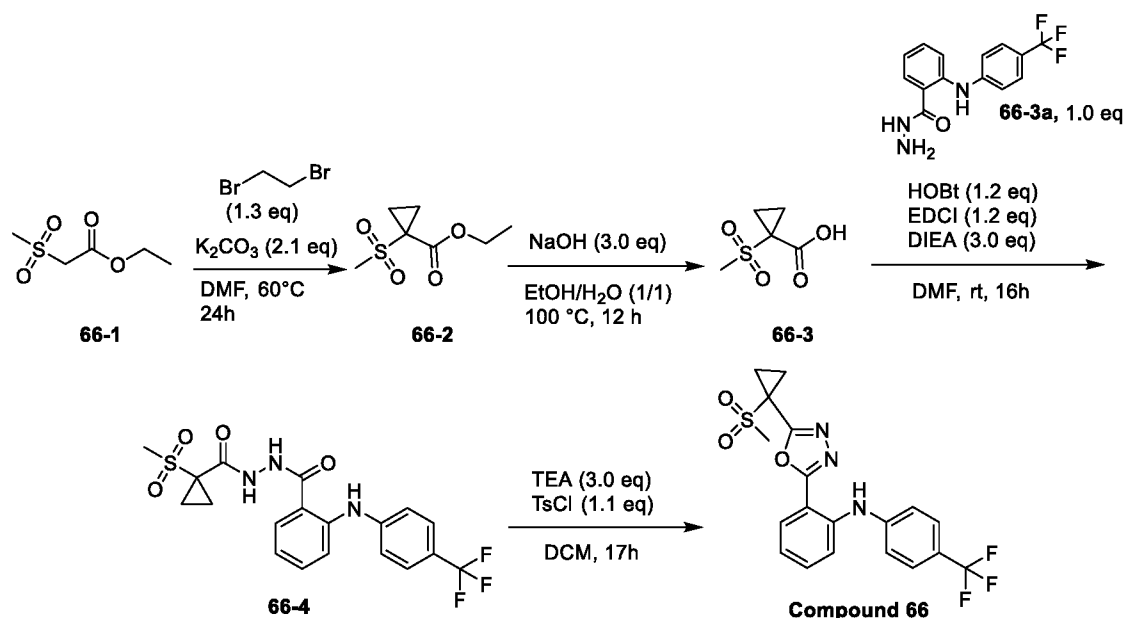
Compound 62 (11.85 mg, 29.13 μ mol, 13.82% yield). LCMS (ESI): RT = 0.882 min, mass calc. for C₁₉H₁₆F₃N₅O₂ 403.13, m/z found 404.1[M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.18 (s, 1H), 7.85 (d, *J* = 7.1 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.58 - 7.48 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.19 - 7.06 (m, 2H), 5.77 (s, 2H), 1.58 - 1.43 (m, 2H), 1.37 - 1.22 (m, 2H).

Example 61: 2-(5-(1-fluorocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 63)



[00335] To a mixture of **63-1** (5 mg, 14 μ mol, 1 *eq*) in DCM (1 mL) was added DAST (3.3 mg, 21 μ mol, 3 μ L, 1.5 *eq*) in one portion at -70 °C. The mixture was stirred at 25 °C for 1 h. LCMS showed 78% of starting material was remained and no desired product was detected. Then another batch of DAST (6.7 mg, 41 μ mol, 5 μ L, 3 *eq*) was added and the mixture was continuously stirred at 25 °C for 16 h. LCMS showed the starting material was consumed completely and 52% of desired product was formed. TLC (Petroleum ether:Ethyl acetate = 2:1 UV) the starting material was consumed completely and two main new spots were formed. The mixture was purified directly by prep-TLC to give **Compound 63** (4.2 mg, 11 μ mol, 80.6% yield). LCMS (ESI): RT = 1.064 min, mass calc. for C₁₈H₁₃F₄N₃O 363.10, m/z found 364.1 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆+CD₃OD) δ 7.92 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.57 - 7.49 (m, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 1.78 - 1.63 (m, 2H), 1.51 - 1.41 (m, 2H).

Example 62: 2-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 66)



Step 1: ethyl 1-methylsulfonylcyclopropanecarboxylate

[00336] To a solution of compound **66-1** (1 g, 6 mmol, 1 *eq*) in DMF (10 mL) were added 1,2-dibromoethane (1.5 g, 8.4 mmol, 0.6 mL, 1.4 *eq*) and K_2CO_3 (1.6 g, 12 mmol, 2 *eq*). The reaction was heated at 60 °C for 24 hr. TLC (EA:PE = 1:5, $KMnO_4$) showed that starting material was consumed completely. The reaction was diluted with EA (50 mL) and washed with brine (2*20 mL). The organic layer was dried over Na_2SO_4 and concentrated. Compound **66-2** (0.8 g, crude) was used for next step directly. ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 - 4.15 (m, 2H), 3.22 (s, 3H), 1.85 - 1.70 (m, 2H), 1.70 - 1.60 (m, 2H), 1.35 - 1.20 (m, 3H).

Step 2: 1-methylsulfonylcyclopropanecarboxylic acid

[00337] To a solution of compound **66-2** (0.8 g, 3.1 mmol, 1 *eq*) in EtOH (10 mL) and H₂O (10 mL) was added NaOH (374.5 mg, 9.3 mmol, 3 *eq*). The reaction was heated at 100 °C for 12 hr. The reaction was concentrated. The residue was adjusted pH to 5 with 1 N. aq. HCl and extracted with EA (3*15 mL). The organic layer was dried over Na_2SO_4 and concentrated. Compound **66-3** (0.3 g, 1.8 mmol, 58% yield) was used for next step directly. ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (br, 1H), 3.23 (s, 3H), 1.95 - 1.80 (m, 2H), 1.80 - 1.70 (m, 2H).

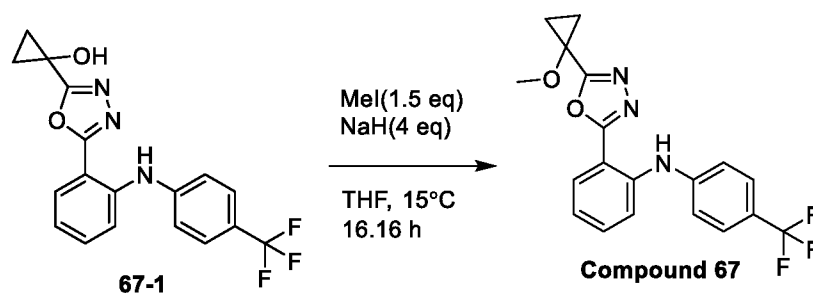
Step 3: N'-(1-methylsulfonylcyclopropanecarbonyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00338] To a mixture of compound **66-3** (0.1 g, 0.6 mmol, 1 *eq*), HOBt (98 mg, 0.7 mmol, 1.2 *eq*) and EDCI (140 mg, 0.7 mmol, 1.2 *eq*) in DMF (4 mL) was added compound **66-3a** (179 mg, 0.6 mmol, 1 *eq*) followed by DIEA (236 mg, 1.8 mmol, 0.3 mL, 3 *eq*). The reaction was stirred at 20 °C for 16 hr. LCMS showed that 28% of desired product was detected. The reaction was concentrated. The crude product was purified by prep-HPLC to give compound **66-4** (30 mg, 67 μ mol, 11% yield).

Step 4: 2-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

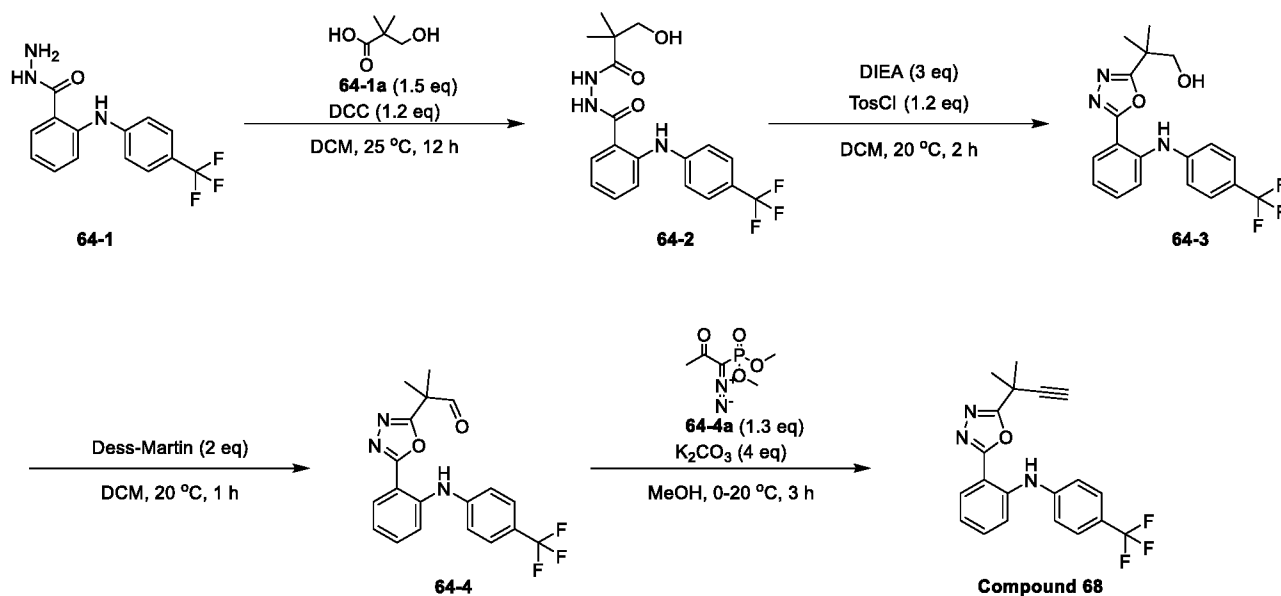
[00339] To a solution of compound **66-4** (30 mg, 67 μ mol, 1 *eq*) and TsCl (14 mg, 74 μ mol, 1.1 *eq*) in DCM (1 mL) was added Et₃N (20.6 mg, 0.2 mmol, 28 μ L, 3 *eq*). The reaction was stirred at 20 °C for 16 hr. LCMS showed that 27% of starting material was remained and 29% of desired product was detected. Additional of TsCl (14 mg) was added. The reaction was stirred at 20 °C for 1 hr. LCMS showed that 29% of desired product was detected. The reaction was diluted with DCM (15 mL) and washed with water (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 66** (2.01 mg, 4.7 μ mol, 6.9% yield). LCMS (ESI): RT = 0.862 min, mass calc. for: C₁₉H₁₆F₃N₃O₃S 423.09, m/z found 423.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.13 (s, 1H), 7.97 (d, *J* = 8.03 Hz, 1H), 7.63 (d, *J* = 8.53 Hz, 2H), 7.58 (d, *J* = 3.01 Hz, 2H), 7.33 (d, *J* = 8.53 Hz, 2H), 7.18 (ddd, *J* = 7.91, 4.89, 3.26 Hz, 1H), 3.32 (s, 3H), 1.83 - 1.90 (m, 2H), 1.76 - 1.82 (m, 2H).

Example 63: 2-(5-(1-methoxycyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 67)



[00340] To a mixture of **67-1** (17 mg, 47 μ mol, 1 *eq*) in THF (2 mL) was added NaH (7.5 mg, 0.19 mmol, 60% purity, 4 *eq*) in one portion at 15 °C. After stirring for 10 min, a solution of MeI (10 mg, 70.6 μ mol, 4 μ L, 1.5 *eq*) in THF (1 mL) was added and then the mixture was stirred at 15 °C for 16 h. LCMS showed no starting material was remained and 85% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (10 mL*2), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 67** (2.48 mg, 6.6 μ mol, 14.0% yield). LCMS (ESI): RT = 1.050 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.34, m/z found 376.1 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (br s, 1H), 7.92 (br d, *J* = 8.0 Hz, 1H), 7.67 - 7.46 (m, 4H), 7.29 (br d, *J* = 8.3 Hz, 2H), 7.16 (br s, 1H), 3.43 (s, 3H), 1.44 - 1.25 (m, 4H).

Example 64: 2-(5-(2-methylbut-3-yn-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 68)



Step 1: N'-(3-hydroxy-2,2-dimethyl-propanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide [00341] To a solution of **64-1** (50 mg, 0.17 mmol, 1 *eq*) and **64-1a** (30.0 mg, 0.25 mmol, 1.5 *eq*) in DCM (1 mL) was added DCC (41.9 mg, 0.20 mmol, 41 μ L, 1.2 *eq*). The mixture was stirred at 25 °C for 12 h. The mixture was diluted with H₂O (10 mL), extracted with EA (20 mL *3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **64-2** (60 mg, 0.15 mmol, 89.6% yield).

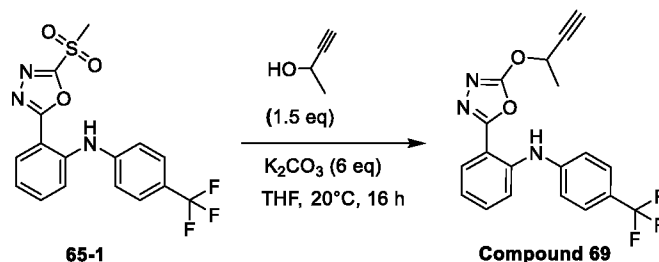
Step 2: 2-methyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]propan-1-ol [00342] To a solution of **64-2** (60 mg, 0.15 mmol, 1 *eq*) in DCM (1 mL) were added TosCl (34.7 mg, 0.18 mmol, 1.2 *eq*) and DIEA (58.8 mg, 0.46 mmol, 79 μ L, 3 *eq*). The mixture was stirred at 20 °C for 2 h. The mixture was diluted with H₂O (10 mL), extracted with EA (20 mL * 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **64-3** (30 mg, 79.5 μ mol, 52.4% yield).

Step 3: 2-methyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]propanal [00343] To a mixture of **64-3** (20 mg, 53.0 μ mol, 1 *eq*) in DCM (0.5 mL) was added Dess-Martin (45.0 mg, 0.11 mmol, 33 μ L, 2 *eq*). The mixture was stirred at 20 °C for 1 h. The mixture was diluted with NaS₂O₃ (8 mL), extracted with DCM (15 mL * 2). The combined organic layers were washed with NaHCO₃ (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **64-4** (15 mg, 34.8 μ mol, 65.6% yield).

Step 4: 2-(5-(2-methylbut-3-yn-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

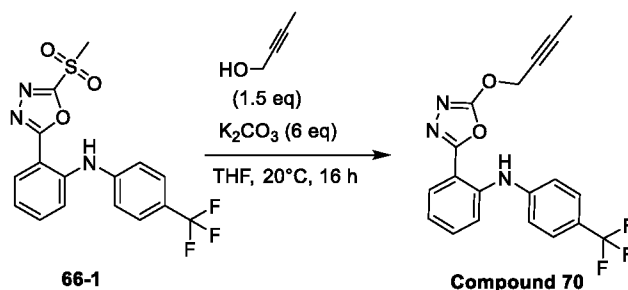
[00344] To a mixture of **64-4** (10 mg, 26.6 μmol , 1 *eq*) and **64-4a** (6.7 mg, 34.6 μmol , 1.3 *eq*) in MeOH (0.5 mL) was added K_2CO_3 (14.7 mg, 0.11 mmol, 4 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 h. Then the mixture was stirred at 20 °C for 1 h. The mixture was concentrated. The residue was diluted with H_2O (5 mL), extracted with EA (10 mL * 3). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was checked by HPLC. The residue was purified by prep-HPLC to give **Compound 68** (3.1 mg, 8.2 μmol , 30.8% yield). LCMS (ESI): RT = 1.072 min, mass calc. for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_3\text{O}$ 371.12, m/z found 372.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.54 (s, 1H), 7.94 (dd, $J = 1.3, 7.9$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.5$ Hz, 1H), 7.45 - 7.32 (m, 3H), 6.99 (t, $J = 7.6$ Hz, 1H), 2.40 (s, 1H), 1.82 (s, 6H).

Example 65: 2-(5-(but-3-yn-2-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 69)



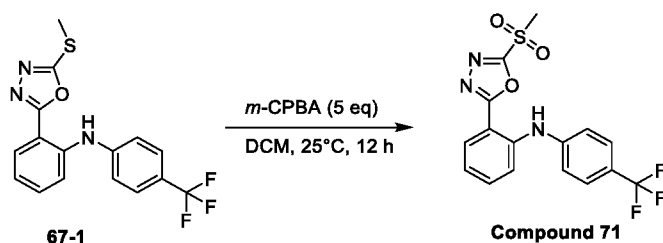
[00345] To a solution of but-3-yn-2-ol (8.2 mg, 0.12 mmol, 9 μL , 1.5 *eq*) in THF (1 mL) was added K_2CO_3 (64.9 mg, 0.47 mmol, 6 *eq*) and compound **65-1** (30 mg, 78 μmol , 1 *eq*) at 20 °C. The mixture was stirred at 20 °C for 16 hr. The reaction mixture was concentrated to give a residue which was purified by prep-HPLC to give **Compound 69** (10 mg, 25 μmol , 32.2% yield). LCMS (ESI): RT = 1.058 min, mass calc. for $\text{C}_{19}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$ 373.3, m/z found 374.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.36 (s, 1H), 7.77 (dd, $J = 1.4, 8.0$ Hz, 1H), 7.57 (d, $J = 8.5$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.40 - 7.36 (m, 1H), 7.34 (d, $J = 8.5$ Hz, 2H), 6.96 (t, $J = 7.5$ Hz, 1H), 5.65 - 5.59 (m, 1H), 2.68 (d, $J = 2.1$ Hz, 1H), 1.81 (d, $J = 6.6$ Hz, 3H).

Example 66: 2-(5-(but-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 70)



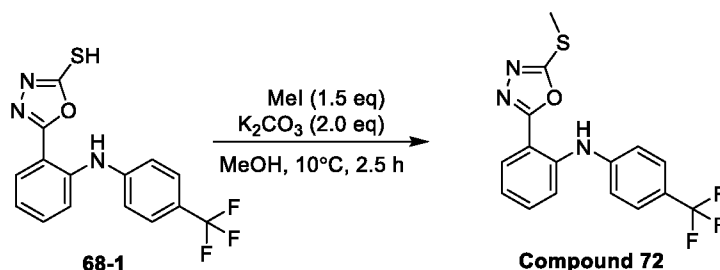
[00346] To a solution of but-2-yn-1-ol (13.7 mg, 0.20 mmol, 15 μ L, 1.5 *eq*) in THF (1 mL) was added K_2CO_3 (108.2 mg, 0.78 mmol, 6 *eq*) and compound **66-1** (50 mg, 0.13 mmol, 1 *eq*) at 20 °C. The mixture was stirred at 20 °C for 16 hr. The reaction mixture was concentrated to give a residue which was purified by prep-HPLC to give **Compound 70** (10 mg, 26 μ mol, 19.7% yield). LCMS (ESI): RT = 1.082 min, mass calc. for $C_{19}H_{14}F_3N_3O_2$ 373.3, m/z found 374.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.80 (dd, J = 1.3, 7.9 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.50 - 7.47 (m, 1H), 7.40 (dt, J = 1.4, 7.8 Hz, 1H), 7.30 (s, 2H), 7.02 - 6.97 (m, 1H), 5.43 (q, J = 3.3 Hz, 2H), 2.27 (t, J = 3.3 Hz, 3H).

Example 67: 2-(5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 71)



[00347] To a solution of compound **67-1** (50.0 mg, 0.14 mmol, 1 *eq*) in DCM (4 mL) was added *m*-CPBA (144.5 mg, 0.71 mmol, 85% purity, 5 *eq*) at 25°C. The mixture was stirred at 25°C for 12 hr. The mixture was diluted with H_2O (5 mL). The mixture was extracted with EA (10 mL*3). The organic layer was dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 71** (12.9 mg, 33.4 μ mol, 23.5% yield). LCMS (ESI): RT = 0.975 min, mass calc. for $C_{16}H_{12}F_3N_3O_3S$ 383.06, m/z found 384.0 $[M+H]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.01 (s, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.67 - 7.59 (m, 4H), 7.34 (br d, J = 8.4 Hz, 2H), 7.21 (br t, J = 7.1 Hz, 1H), 3.68 (s, 3H).

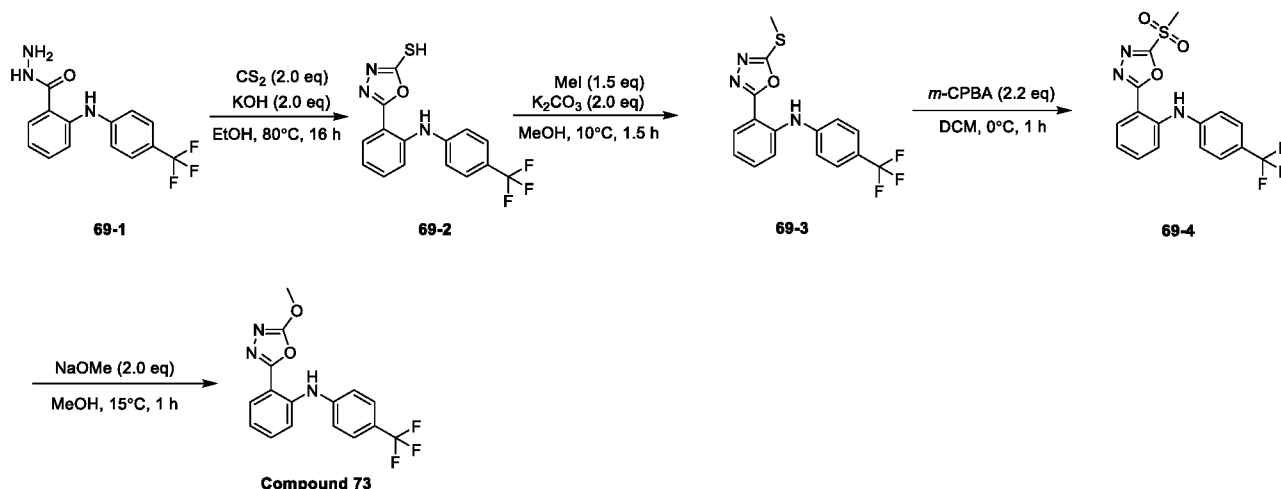
Example 68: 2-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 72)



[00348] To a solution of compound **68-1** (50.0 mg, 0.15 mmol, 1 *eq*) in MeOH (1 mL) was added K_2CO_3 (41.0 mg, 0.30 mmol, 2 *eq*). The mixture was stirred at 10°C for 0.5 hr. MeI (31.6 mg, 0.22 mmol, 14 μ L, 1.5 *eq*) was added. The mixture was stirred at 10°C for 2 hr. The mixture was diluted with H_2O (5 mL). The mixture was extracted with EA (5 mL*3). The organic layer was dried over

Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by *prep*-HPLC to give **Compound 72** (33.1 mg, 93.4 μ mol, 63.0% yield). LCMS (ESI): RT = 1.065 min, mass calc. for C₁₆H₁₂F₃N₃OS 351.07, m/z found 352.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.40 (s, 1H), 7.85 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.42 - 7.34 (m, 3H), 7.00 - 6.94 (m, 1H), 2.80 (s, 3H)

Example 69: 2-(5-methoxy-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 73)



Step 1: 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-thiol

[00349] To a solution of compound **69-1** (1.00 g, 3.39 mmol, 1 *eq*) and KOH (380.0 mg, 6.77 mmol, 2 *eq*) in EtOH (10 mL) was added CS₂ (515.8 mg, 6.77 mmol, 0.41 mL, 2 *eq*). The mixture was stirred at 80°C for 16 hr. The mixture was concentrated. 1 N HCl was added to the residue until pH = 6 -7. The mixture was extracted with EA (15 mL*3). The organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography to give compound **69-2** (700.0 mg, 2.08 mmol, 61.3% yield).

Step 2: 2-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00350] To a solution of compound **69-2** (650.0 mg, 1.93 mmol, 1 *eq*) in MeOH (10 mL) was added K₂CO₃ (532.6 mg, 3.85 mmol, 2 *eq*). The mixture was stirred at 10°C for 0.5 hr. MeI (410.3 mg, 2.89 mmol, 0.18 mL, 1.5 *eq*) was added. The mixture was stirred at 10°C for 1 hr. The mixture was concentrated. The residue was diluted with H₂O (10 mL). The mixture was extracted with EA (15 mL*3). The organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **69-3** (500.0 mg, crude).

Step 3: 2-(5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

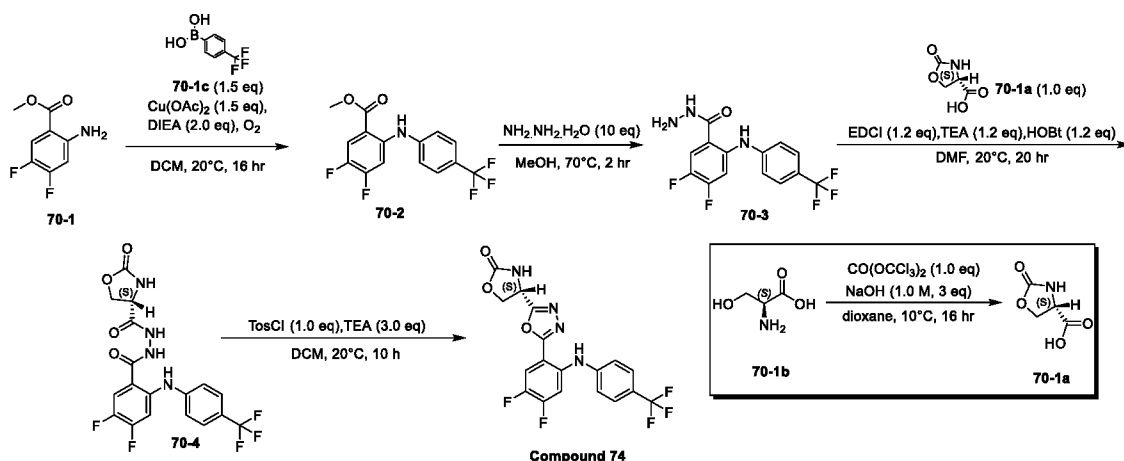
[00351] To a solution of compound **69-3** (50.0 mg, 0.14 mmol, 1 *eq*) in DCM (2 mL) was added *m*-CPBA (63.6 mg, 0.31 mmol, 85% purity, 2.2 *eq*) at 0°C. The mixture was stirred at 0°C for 1 hr.

The mixture was diluted with H₂O (5 mL). The mixture was extracted with EA (10 mL*3). The organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography to give compound **69-4** (35.0 mg, 54.8 μ mol, 38.5% yield).

Step 4: 2-(5-methoxy-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00352] To a solution of compound **69-4** (35.0 mg, 54.8 μ mol, 1 *eq*) in MeOH (1 mL) was added NaOMe (5.9 mg, 0.11 mmol, 2 *eq*). The mixture was stirred at 15°C for 1 hr. The mixture was diluted with H₂O (5 mL). The mixture was extracted with EA (10 mL*3). The organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by *prep*-HPLC to give **Compound 73** (8.4 mg, 25.1 μ mol, 45.7% yield). LCMS (ESI): RT = 1.018 min, mass calc. for C₁₆H₁₂F₃N₃O₂ 335.09, *m/z* found 336.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.35 (br s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.58 (br d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.40 - 7.32 (m, 3H), 6.96 (t, *J* = 7.5 Hz, 1H), 4.27 (s, 3H).

Example 70: (S)-4-(5-(4,5-difluoro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 74)



Step 1: methyl 4,5-difluoro-2-[4-(trifluoromethyl)anilino]benzoate

[00353] To a solution of **70-1** (1.00 g, 5.34 mmol, 1 *eq*) and **70-1c** (1.50 g, 8.02 mmol, 1.5 *eq*) in DCM (15 mL) were added Cu(OAc)₂ (1.40 g, 8.02 mmol, 1.5 *eq*) and DIEA (1.30 g, 10.69 mmol, 1.8 mL, 2 *eq*). The mixture was degassed, purged with O₂ for 3 times and stirred at 20°C for 16 hr. The mixture was concentrated. The residue was dissolved in EA (10 mL) and washed with H₂O (3 mL *3). The combined organic layers were washed with brine (3 mL *3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give **70-2** (650.0 mg, 1.96 mmol, 36.7% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.61 (br s, 1H), 7.79 (dd, *J* = 9.0, 11.1 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.10 (dd, *J* = 6.9, 12.8 Hz, 1H), 3.92 - 3.88 (m, 3H)

Step 2: 4,5-difluoro-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00354] To a solution of compound **70-2** (650.0 mg, 1.96 mmol, 1.0 *eq*) in MeOH (10 mL) was added $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (1.16 g, 19.62 mmol, 1.1 mL, 10 *eq*). The mixture was stirred at 70°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (15 mL), washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography to give **70-3** (470.0 mg, 1.42 mmol, 72.3% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.91 (s, 1H), 9.71 (s, 1H), 7.68 (dd, $J = 8.9$, 11.3 Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.47 - 7.39 (m, 1H), 7.28 (d, $J = 8.5$ Hz, 2H), 4.55 (br s, 2H)

Step 3: (4S)-2-oxooxazolidine-4-carboxylic acid

[00355] To a solution of NaOH (1 M, 14.2 mL, 3 *eq*) was added compound **70-1b** (500.0 mg, 4.76 mmol, 1 *eq*) at 10°C, followed by addition of a solution of bis(trichloromethyl) carbonate (1.40 g, 4.76 mmol, 1 *eq*) in dioxane (6 mL). The solution was stirred at 10°C for 16 hr. The reaction was concentrated in vacuum. Then the residue was diluted with MeCN (20 mL), filtered and the filtrate was concentrated in vacuum to give **70-1a** (600.0 mg, crude), which was used for the next step directly. ^1H NMR confirmed that compound. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.15 (s, 1H), 4.51 - 4.43 (m, 1H), 4.36 - 4.31 (m, 1H), 4.27 (dd, $J = 4.1$, 8.4 Hz, 1H).

Step 4: (4S)-N'-[4,5-difluoro-2-[4-(trifluoromethyl)anilino]benzoyl]-2-oxo-oxazolidine-4-carbohydrazide

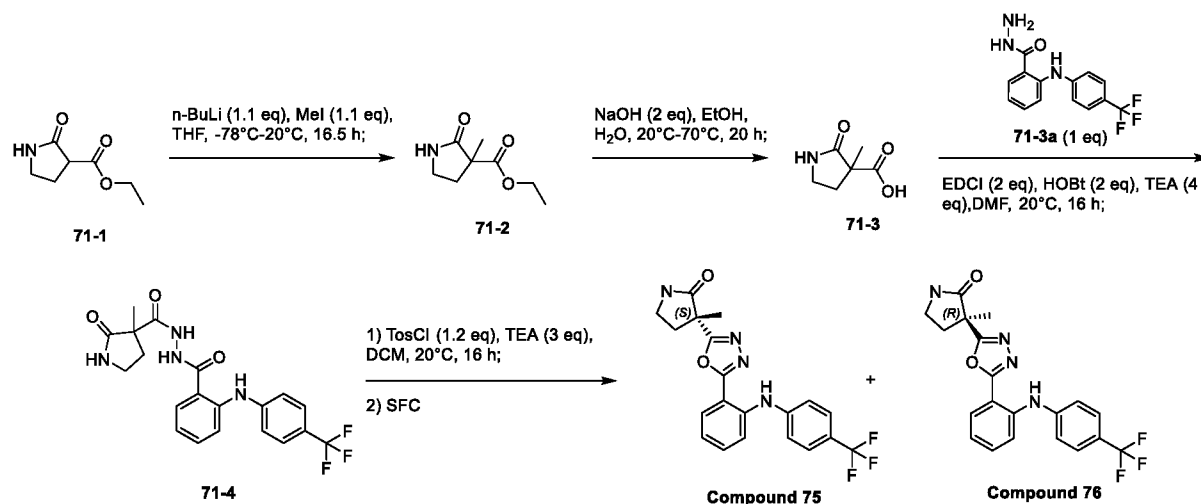
[00356] To a solution of **70-1a** (65.9 mg, 0.50 mmol, 1 *eq*), EDCI (115.7 mg, 0.60 mmol, 1.2 *eq*) and HOBt (81.5 mg, 0.60 mmol, 1.2 *eq*) in DMF (2 mL) were added **70-3** (200.0 mg, 0.60 mmol, 1.2 *eq*) and TEA (61.1 mg, 0.60 mmol, 84 μL , 1.2 *eq*) at 20°C. The mixture was stirred at 20°C for 20 hr. The solution was diluted with H_2O (2 mL) and extracted with EA (4 mL * 3). Then the combined organic layers were washed with brine (4 mL * 3) and H_2O (4 mL * 3). Finally, the organic layer was dried by Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was triturated with DCM (5 mL) to give **70-4** (80.0 mg, crude). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.84 - 10.61 (m, 1H), 10.49 (br s, 1H), 9.50 (br s, 1H), 8.15 (s, 1H), 7.88 - 7.76 (m, 1H), 7.60 (d, $J = 8.5$ Hz, 2H), 7.53 - 7.40 (m, 1H), 7.31 (br d, $J = 8.4$ Hz, 2H), 4.60 - 4.51 (m, 1H), 4.48 - 4.40 (m, 1H), 4.22 (dd, $J = 4.3$, 8.3 Hz, 1H)

Step 5: (S)-4-(5-(4,5-difluoro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one

[00357] To a solution of **70-4** (70.0 mg, 0.16 mmol, 1.0 *eq*) in DCM (1 mL) were added TosCl (30.0 mg, 0.16 mmol, 1.0 *eq*) and TEA (47.8 mg, 0.47 mmol, 65 μL , 3.0 *eq*), the solution was stirred at 20°C for 10 hr. The solution was diluted with H_2O (1 mL) and extracted with EA (1 mL * 3). Then the combined organic layers were washed with brine (1 mL * 3) and H_2O (1 mL * 3). Finally, the organic layer was dried by Na_2SO_4 , filtered and concentrated under reduced pressure to

give a residue. The residue was purified by prep-HPLC. Then the product was purified by column chromatography. LCMS, MS and ^1H NMR confirmed that **Compound 74** (3.39 mg, 7.1 μmol , 4.5% yield) was obtained. LCMS (ESI): RT = 1.041 min, mass calc. for $\text{C}_{18}\text{H}_{11}\text{F}_5\text{N}_4\text{O}_3$ 426.08, m/z found 427.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.33 (s, 1H), 7.69 (dd, J = 8.4, 10.3 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.23 (dd, J = 6.8, 12.5 Hz, 1H), 6.19 (s, 1H), 5.39 - 5.30 (m, 1H), 4.91 - 4.85 (m, 1H), 4.82 - 4.77 (m, 1H).

Example 71: (S)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (Compound 75) and (R)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (Compound 76)



Step 1: ethyl 3-methyl-2-oxopyrrolidine-3-carboxylate

[00358] To a solution of **71-1** (800 mg, 5.09 mmol, 1 eq) in THF (10 mL) at -78°C was added $n\text{-BuLi}$ (2.5 M, 2.24 mL, 1.1 eq) and the mixture was stirred at -78°C for 0.5 h. And then MeI (794.7 mg, 5.60 mmol, 0.35 mL, 1.1 eq) was added into the above mixture at -78°C , and the mixture was stirred at 20°C for 16 h. The reaction mixture was quenched with saturated NH_4Cl (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **71-2** (720 mg, 3.79 mmol, 74.4% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.16 (brs, 1H), 4.21 (dq, J = 1.8, 7.1 Hz, 2H), 3.54 - 3.42 (m, 1H), 3.40 - 3.30 (m, 1H), 2.69 - 2.59 (m, 1H), 2.04 (ddd, J = 7.0, 8.4, 13.0 Hz, 1H), 1.46 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H).

Step 2: 3-methyl-2-oxopyrrolidine-3-carboxylic acid

[00359] To a solution of **71-2** (350 mg, 2.04 mmol, 1 eq) in EtOH (2 mL) at 20°C was added NaOH (2 M, 2.04 mL, 2 eq) and the mixture was stirred at 20°C for 16 h, and then stirred at 70°C for 4 h. The reaction mixture was concentrated to remove EtOH . The residue was diluted with water (20 mL), acidified with 2 N HCl to pH = 1-2, and then extracted with EA (20 mL *3). The

combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 30 mg sample. The liquid layer was lyophilized to give a residue, which was dissolved in MeOH and then filtered to remove the precipitate. The filtrate was concentrated to give 350 mg sample. The above two batches were combined to give **71-3** (380 mg, 1.86 mmol, 90.9% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 (brs, 1H), 3.25 - 3.18 (m, 2H), 2.43 - 2.38 (m, 1H), 1.92 - 1.84 (m, 1H), 1.19 (s, 3H).

Step 3: 3-methyl-2-oxo-*N'*-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)pyrrolidine-3-carbohydrazide

[00360] To a solution of **71-3a** (220 mg, 0.75 mmol, 1 *eq*), **71-3** (304.7 mg, 1.49 mmol, 2 *eq*), EDCI (285.7 mg, 1.49 mmol, 2 *eq*) and HOBt (201.4 mg, 1.49 mmol, 2 *eq*) in DMF (5 mL) at 20°C was added TEA (301.6 mg, 2.98 mmol, 0.41 mL, 4 *eq*), and the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **71-4** (400 mg, 0.67 mmol, 89.4% yield), which was used directly for next step. LCMS (ESI): RT = 0.987 min, mass calc. for C₂₀H₁₉F₃N₄O₃ 420.14, m/z found 442.9 [M+Na]⁺.

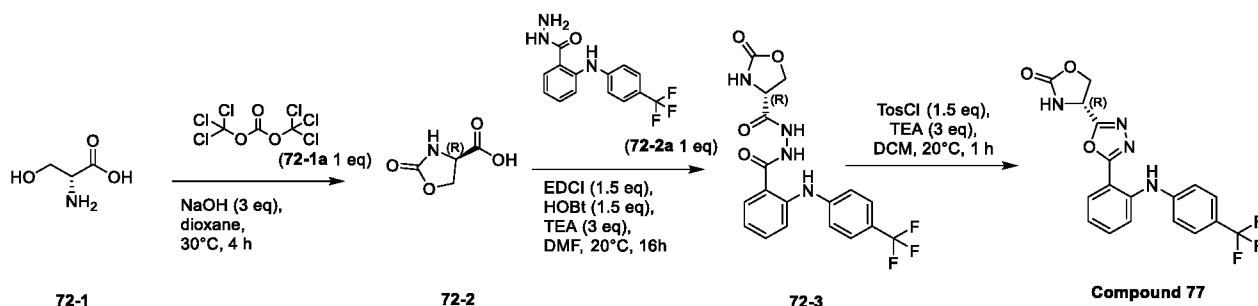
Step 4: (S)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (Compound 75) and (R)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (Compound 76)

[00361] To a solution of **71-4** (400 mg, 0.67 mmol, 1 *eq*) and TEA (202.2 mg, 2.00 mmol, 0.28 mL, 3 *eq*) in DCM (5 mL) at 20°C was added TosCl (152.4 mg, 0.80 mmol, 1.2 *eq*), and the mixture was stirred at 20°C for 16 h. The mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 170 mg of desired product as a mixture (R/S isomers = 1:1 ratio) by LCMS and SFC. The 100 mg of desired product as a mixture (R/S, from the above 170 mg batch) was purified further by SFC to give **Compound 75** (24.7 mg, 61.5 umol, 9.2% yield, 99.8% ee) and **Compound 76** (19.3 mg, 47.5 umol, 7.1% yield, 99.8% ee).

Compound 75: LCMS (ESI): RT = 0.944 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 402.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.48 (brs, 1H), 7.92 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.40 (dt, *J* = 1.5, 7.9 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.93 (m, 1H), 5.94 (brs, 1H), 3.72 - 3.63 (m, 1H), 3.53 (dt, *J* = 4.8, 8.8 Hz, 1H), 3.03 (ddd, *J* = 4.8, 7.9, 12.9 Hz, 1H), 2.39 - 2.30 (m, 1H), 1.80 (s, 3H). **Compound 76:** LCMS (ESI): RT = 0.942 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 402.9 [M+H]⁺; ¹H NMR (400

MHz, CDCl₃) δ 9.48 (s, 1H), 7.92 (dd, J = 1.4, 8.0 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.39 (dt, J = 1.5, 7.9 Hz, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.01 - 6.93 (m, 1H), 6.37 (br s, 1H), 3.71 - 3.62 (m, 1H), 3.53 (dt, J = 5.0, 8.8 Hz, 1H), 3.01 (ddd, J = 4.9, 7.9, 12.9 Hz, 1H), 2.33 (ddd, J = 6.3, 7.8, 13.2 Hz, 1H), 1.79 (s, 3H).

Example 72: (R)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 77)



Step 1: (R)-2-oxooxazolidine-4-carboxylic acid

[00362] To a solution of NaOH (1 M, 11.43 mL, 3 *eq*) was added **72-1** at 30°C, followed by addition of a solution **72-1a** (1.1 g, 3.81 mmol, 1 *eq*) in dioxane (4 mL) along with gas evolved. After stirring for 2 h, the mixture was clear, then the mixture was stirred for another 2 hr at 30°C. The reaction mixture was concentrated under reduced pressure and then extracted with hot acetonitrile (150 mL). The mixture was filtered and concentrated under reduced pressure to give **72-2** (260 mg, 1.79 mmol, 46.9% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (brs, 1H), 4.36 - 4.31 (m, 2H), 4.27 (brdd, J = 3.3, 8.3 Hz, 1H).

Step 2: (R)-2-oxo-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazolidine-4-carbohydrazide

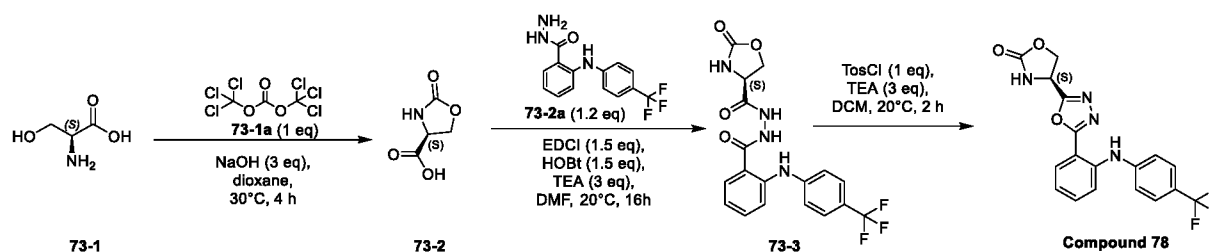
[00363] To a solution of **72-2**, EDCI (288.8 mg, 1.51 mmol, 1.5 *eq*) and HOBt (203.6 mg, 1.51 mmol, 1.5 *eq*) in DMF (2 mL) at 20°C were added **72-2a** (296.6 mg, 1.00 mmol, 1 *eq*) and TEA (304.9 mg, 3.01 mmol, 0.42 mL, 3 *eq*). The mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **72-3** (330 mg, 0.59 mmol, 58.7% yield). LCMS (ESI): RT = 0.782 min, mass calc. for C₁₈H₁₅F₃N₄O₄ 408.33, *m/z* found 408.9 [M+H]⁺.

Step 3: (R)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one

[00364] To a solution of **72-3** (300 mg, 0.73 mmol, 1 *eq*) in DCM (3 mL) were added TEA (223.0 mg, 2.20 mmol, 0.31 mL, 3 *eq*) and TosCl (210.1 mg, 1.10 mmol, 1.5 *eq*). The mixture was stirred at 20°C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue.

The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 77** (60 mg, 0.15 mmol, 20.1% yield). LCMS (ESI): RT = 0.822 min, mass calc. for C₁₈H₁₃F₃N₄O₃ 390.32, m/z found 390.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.90 (brd, *J* = 7.9 Hz, 1H), 7.62 (brd, *J* = 8.1 Hz, 2H), 7.53 - 7.49 (m, 1H), 7.44 (brd, *J* = 7.5 Hz, 1H), 7.36 (brd, *J* = 8.1 Hz, 3H), 6.99 (t, *J* = 7.5 Hz, 1H), 5.42 (brdd, *J* = 4.8, 8.2 Hz, 1H), 4.93 - 4.88 (m, 1H), 4.84 - 4.79 (m, 1H).

Example 73: (S)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 78)



Step 1: (S)-2-oxooxazolidine-4-carboxylic acid

[00365] To a solution of NaOH (1 M, 11.43 mL, 3 eq) was added **73-1** at 30°C, followed by addition of a solution **73-1a** (1.1 g, 3.81 mmol, 1 eq) in dioxane (4 mL) along with gas evolved. After stirring for 2 h, the mixture was clear, then the mixture was stirred for another 2 hr at 30°C. The reaction mixture was concentrated under reduced pressure and then extracted with hot acetonitrile (150 mL). The mixture was filtered and concentrated under reduced pressure to give **73-2** (664 mg, 2.76 mmol, 94.0% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (s, 1H), 4.52 - 4.42 (m, 1H), 4.37 - 4.24 (m, 2H).

Step 2: (S)-2-oxo-*N'*-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazolidine-4-carbohydrazide

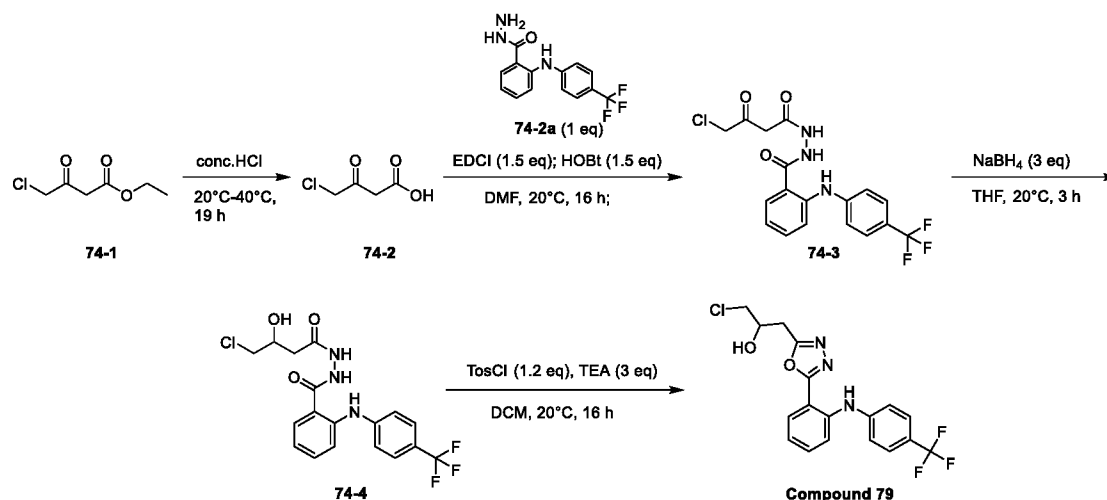
[00366] To a solution of **73-2** (300 mg, 2.29 mmol, 1 eq), EDCI (658.1 mg, 3.43 mmol, 1.5 eq) and HOBT (463.9 mg, 3.43 mmol, 1.5 eq) in DMF (3 mL) at 30°C was added **73-2a** (810.9 mg, 2.75 mmol, 1.2 eq) and TEA (694.8 mg, 6.87 mmol, 1 mL, 3 eq). The mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **73-3** (900 mg, 1.81 mmol, 79% yield). LCMS (ESI): RT = 0.768 min, mass calc. for C₁₈H₁₅F₃N₄O₄ 408.33, m/z found 430.9 [M+Na]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.85 (brs, 1H), 9.58 (s, 1H), 7.95 (s, 2H), 7.55 (s, 3H),

7.44 - 7.42 (m, 2H), 7.23 (s, 2H), 6.99 (s, 1H), 4.52 (br s, 1H), 4.41 (dd, $J = 4.4, 9.2$ Hz, 1H), 4.23 (dd, $J = 4.5, 8.3$ Hz, 1H).

Step 3: (S)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one

[00367] To a solution of **73-3** (100 mg, 0.24 mmol, 1 eq) in DCM (1 mL) were added TEA (74.3 mg, 0.73 mmol, 0.1 mL, 3 eq) and TosCl (46.7 mg, 0.24 mmol, 1 eq). The mixture was stirred at 20°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 78** (20 mg, 0.50 mmol, 20.1% yield). LCMS (ESI): RT = 0.850 min, mass calc. for C₁₈H₁₃F₃N₄O₃ 390.32, m/z found 390.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.33 (brs, 1H), 7.88 (brd, $J = 7.9$ Hz, 1H), 7.60 (brd, $J = 8.3$ Hz, 2H), 7.52 - 7.48 (m, 1H), 7.45 - 7.40 (m, 1H), 7.36 (br d, $J = 8.1$ Hz, 2H), 6.98 (t, $J = 7.5$ Hz, 1H), 5.99 (brs, 1H), 5.35 (br s, 1H), 4.91 - 4.85 (m, 1H), 4.82 - 4.77 (m, 1H).

Example 74: 1-chloro-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol (Compound 79)



Step 1: 4-chloro-3-oxobutanoic acid

[00368] The solution of **74-1** (300 mg, 1.82 mmol, 0.25 mL, 1 eq) in conc. HCl (2 mL) was stirred at 20°C for 16 h, and then stirred at 40°C for another 3 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (10 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **74-2** (190 mg, 1.39 mmol, 76.5% yield), which was used directly for next step. ¹H NMR (400 MHz, CDCl₃) δ 4.24 (s, 2H), 3.76 (s, 2H).

Step 2: N'-(4-chloro-3-oxobutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00369] To a solution of **74-2a** (180 mg, 0.61 mmol, 1 *eq*), **74-2** (99.9 mg, 0.73 mmol, 1.2 *eq*) and HOBt (123.6 mg, 0.91 mmol, 1.5 *eq*) in DMF (1 mL) at 20°C was added EDCI (175.3 mg, 0.91 mmol, 1.5 *eq*), and the mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **74-3** (180 mg, 0.21 mmol, 34.3% yield), which was used directly for next step. LCMS (ESI): RT = 0.981 min, mass calc. for C₁₈H₁₅ClF₃N₃O₃ 413.08, m/z found 435.9 [M+Na]⁺.

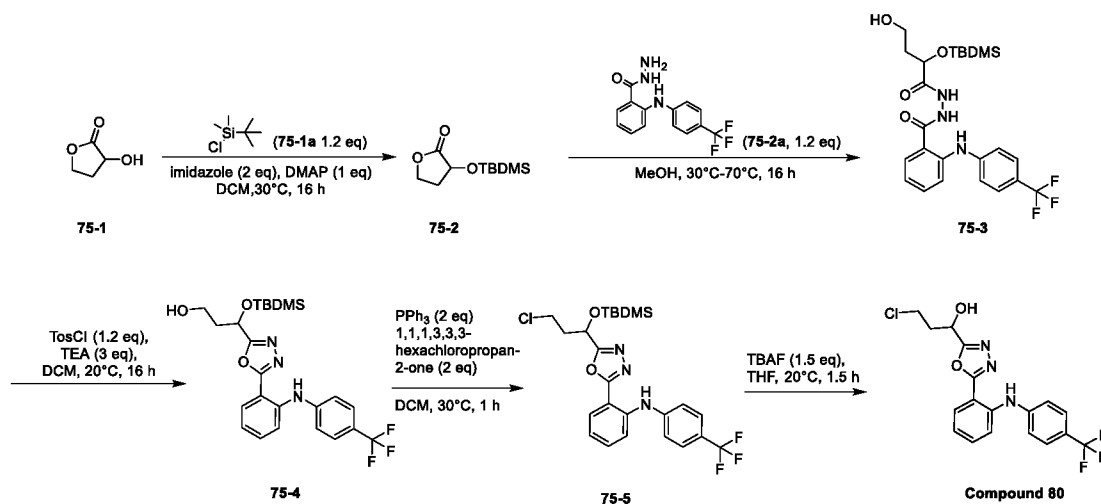
Step 3: N'-(4-chloro-3-hydroxybutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00370] To a solution of **74-3** (160 mg, 0.19 mmol, 1 *eq*) in THF (1 mL) at 20°C was added NaBH₄ (21.1 mg, 0.56 mmol, 3 *eq*), and the mixture was stirred at 20°C for 3 h. The reaction mixture was quenched with water (20 mL) at 20°C, and then extracted with EA (10 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **74-4** (80 mg, 0.13 mmol, 70.5% yield), which was used directly for next step. LCMS (ESI): RT = 0.980 min, mass calc. for C₁₈H₁₇ClF₃N₃O₃ 415.09, m/z found 437.9 [M+Na]⁺.

Step 4: 1-chloro-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol

[00371] To a solution of **74-4** (70 mg, 0.11 mmol, 1 *eq*) and TEA (34.8 mg, 0.34 mmol, 48 uL, 3 *eq*) in DCM (1 mL) at 20°C was added TosCl (26.2 mg, 0.14 mmol, 1.2 *eq*), and the mixture was stirred at 20°C for 16 h. The residue was concentrated to give a residue. The residue was purified by flash silica gel chromatography and prep-HPLC to give **Compound 79** (4.4 mg, 11.1 umol, 9.7% yield). LCMS (ESI): RT = 0.986 min, mass calc. for C₁₈H₁₅ClF₃N₃O₂ 397.08, m/z found 398.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.89 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.95 (m, 1H), 4.49 (br d, *J* = 4.4 Hz, 1H), 3.78 (dd, *J* = 4.0, 5.1 Hz, 2H), 3.35 - 3.21 (m, 2H), 3.06 (d, *J* = 4.8 Hz, 1H).

Example 75: 3-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol (Compound 80)



Step 1: 3-((tert-butyldimethylsilyl)oxy)dihydrofuran-2(3H)-one

[00372] To a solution of **75-1** (300 mg, 2.94 mmol, 0.23 mL, 1 *eq*) in DCM (3 mL) were added imidazole (400.1 mg, 5.88 mmol, 2 *eq*), DMAP (359.0 mg, 2.94 mmol, 1 *eq*) and **75-1a** (531.5 mg, 3.53 mmol, 0.43 mL, 1.2 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL*2), dried over Na₂SO₄, filtered and concentrated under reduced pressure give **75-2** (664 mg, 2.76 mmol, 94.0% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.44 - 4.33 (m, 2H), 4.18 (dt, *J* = 6.4, 9.2 Hz, 1H), 2.50 - 2.42 (m, 1H), 2.21 (qd, *J* = 8.8, 12.6 Hz, 1H), 0.90 (s, 9H), 0.15 (d, *J* = 9.3 Hz, 6H)

Step 2: *N'*-(2-((tert-butyldimethylsilyl)oxy)-4-hydroxybutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00373] To a solution of **75-2** (300 mg, 1.11 mmol, 1 *eq*) in MeOH (3 mL) at 30°C was added **75-2a** (393.0 mg, 1.33 mmol, 1.2 *eq*). The mixture was stirred at 70°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL*2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **75-3** (600 mg, 0.56 mmol, 50.8% yield). LCMS (ESI): RT = 0.906 min, mass calc. for C₂₃H₃₀F₃N₃O₃Si 511.21, *m/z* found 534.1 [M+Na]⁺.

Step 3: 3-((tert-butyldimethylsilyl)oxy)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol

[00374] To a solution of **75-3** (600 mg, 1.17 mmol, 1 *eq*) in DCM (7 mL) at 30°C were added TEA (356.0 mg, 3.52 mmol, 0.49 mL, 3 *eq*) and TosCl (268.3 mg, 1.41 mmol, 1.2 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **75-4** (192 mg, 0.23 mmol, 19.9% yield). LCMS (ESI): RT = 1.042 min, mass calc. for C₂₄H₃₀F₃N₃O₃Si 493.59, *m/z* found 494.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.59 (br

d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 1H), 7.44 - 7.40 (m, 1H), 7.38 (brd, $J = 8.4$ Hz, 2H), 6.99 (t, $J = 7.5$ Hz, 1H), 5.31 (t, $J = 6.3$ Hz, 1H), 4.46 (t, $J = 5.6$ Hz, 1H), 3.89 (brd, $J = 5.1$ Hz, 2H), 3.79 (brd, $J = 4.4$ Hz, 1H), 3.75 (s, 1H), 2.25 (quin, $J = 6.1$ Hz, 2H), 2.12 - 1.89 (m, 2H), 0.93 (s, 13H), 0.19 (s, 3H), 0.09 (s, 4H).

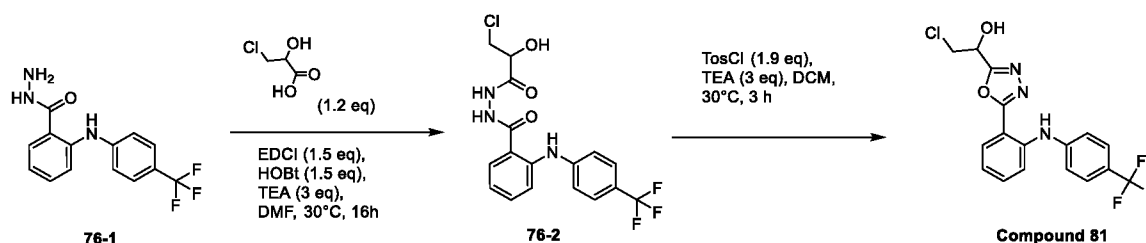
Step 4: 2-(5-(1-((tert-butyldimethylsilyl)oxy)-3-chloropropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00375] To a solution of **75-4** (160 mg, 0.32 mmol, 1 *eq*) and PPh_3 (170.0 mg, 0.65 mmol, 2 *eq*) in DCM (2 mL) at 30°C was added 1, 1, 1, 3, 3, 3-hexachloropropan-2-one (171.6 mg, 0.65 mmol, 98 μL , 2 *eq*). The mixture was stirred at 30°C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give to give **75-5** (120 mg, 0.14 mmol, 43.38% yield). LCMS (ESI): RT = 1.152 min, mass calc. for $\text{C}_{24}\text{H}_{29}\text{ClF}_3\text{N}_3\text{O}_2\text{Si}$ 512.04, m/z found 512.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, $J = 7.8$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.44 - 7.36 (m, 3H), 6.99 (t, $J = 7.5$ Hz, 1H), 5.32 (dd, $J = 4.3, 8.7$ Hz, 1H), 3.84 - 3.76 (m, 2H), 3.75 (s, 1H), 3.70 - 3.64 (m, 1H), 2.50 (tdd, $J = 4.7, 9.1, 14.0$ Hz, 1H), 2.35 (tdd, $J = 4.8, 9.4, 14.3$ Hz, 1H), 2.22 - 2.08 (m, 1H), 0.92 (s, 12H), 0.21 (s, 3H), 0.13 - 0.07 (m, 6H).

Step 5: 3-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol

[00376] To a solution of **75-5** (50 mg, 97 μmol , 1 *eq*) in THF (1 mL) at 30°C was added TBAF (1 M, 0.15 mL, 1.5 *eq*). The mixture was stirred at 30°C for 1.5 h. The reaction mixture was concentrated under reduced pressure to remove solvent and then extracted with petroleum ether (5 mL *2) to give the residue. The residue was diluted with water (5 mL), then acidified with 2N HCl at 30°C to pH = 7, and then extracted with EA (5 mL *3). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 80** (10 mg, 25 μmol , 25.5% yield). LCMS (ESI): RT = 0.910 min, mass calc. for $\text{C}_{18}\text{H}_{15}\text{ClF}_3\text{N}_3\text{O}_2$ 397.78, m/z found 398.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1H), 7.91 (d, $J = 7.9$ Hz, 1H), 7.59 (d, $J = 8.3$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.44 - 7.33 (m, 3H), 6.98 (t, $J = 7.6$ Hz, 1H), 5.40 - 5.31 (m, 1H), 3.95 - 3.87 (m, 1H), 3.84 - 3.76 (m, 1H), 2.98 (brd, $J = 5.4$ Hz, 1H), 2.57 - 2.40 (m, 2H).

Example 76: 2-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 81)



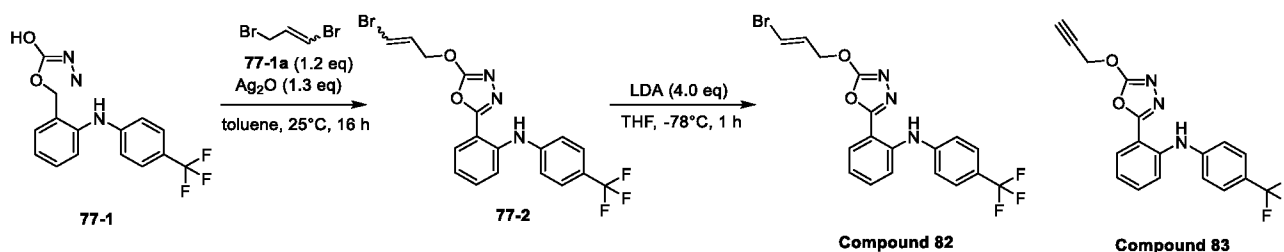
Step 1: 2-((4-(trifluoromethyl) phenyl) amino)benzohydrazide

[00377] To a solution of **76-1a** (101.2 mg, 0.81 mmol, 1.2 *eq*), EDCI (194.8 mg, 1.02 mmol, 1.5 *eq*) and HOBt (137.3 mg, 1.02 mmol, 1.5 *eq*) in DMF (2 mL) at 30°C were added **76-1** (200 mg, 0.68 mmol, 1 *eq*) and TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give to give **76-2** (484 mg, 0.89 mmol, 87.1% yield). LCMS (ESI): RT = 0.755 min, mass calc. for C₁₇H₁₅ClF₃N₃O₃ 401.08, m/z found 401.9 [M+H]⁺

Step 2: 2-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol

[00378] To a solution of **76-2** (262 mg, 0.65 mmol, 1 *eq*) in DCM (3 mL) at 30°C were added TEA (198 mg, 1.96 mmol, 0.27 mL, 3 *eq*) and TosCl (236.2 mg, 1.24 mmol, 1.9 *eq*). The mixture was stirred at 30°C for 3 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography, prep-HPLC and prep-TLC to give **Compound 81** (10 mg, 26 umol, 4.00% yield). **Compound 81**: LCMS (ESI): RT = 0.871 min, mass calc. for C₁₇H₁₃ClF₃N₃O₂ 383.06, m/z found 384.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (brs, 1H), 7.92 (brd, *J* = 7.8 Hz, 1H), 7.60 (brd, *J* = 8.5 Hz, 2H), 7.51 (brd, *J* = 8.0 Hz, 1H), 7.43 (brd, *J* = 8.3 Hz, 1H), 7.37 (brd, *J* = 7.5 Hz, 2H), 6.99 (brt, *J* = 6.9 Hz, 1H), 5.33 (brs, 1H), 4.13 - 4.03 (m, 2H), 3.16 (brs, 1H).

Example 77: (E)-2-(5-((3-bromoallyl)oxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 82) and 2-(5-(prop-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 83)



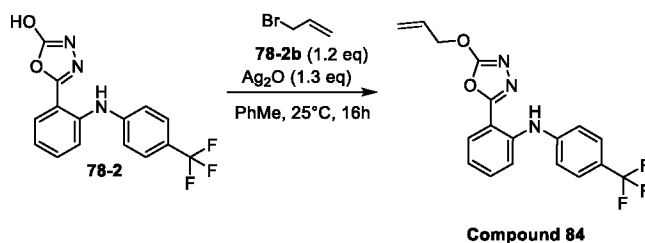
Step 1: 2-[5-[(Z)-3-bromoallyloxy]-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00379] To a solution of compound 77-1 (0.4 g, 1.25 mmol, 1 *eq*) and compound 77-1a (298.6 mg, 1.49 mmol, 1.2 *eq*) in toluene (6 mL) was added Ag₂O (375.1 mg, 1.62 mmol, 1.3 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was filtered and concentrated. The crude product was purified by column chromatography on silica gel to give compound 77-2 (120 mg, 0.27 mmol, 21.8% yield).

Step 2: (E)-2-(5-((3-bromoallyl)oxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 82) and 2-(5-(prop-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 83)

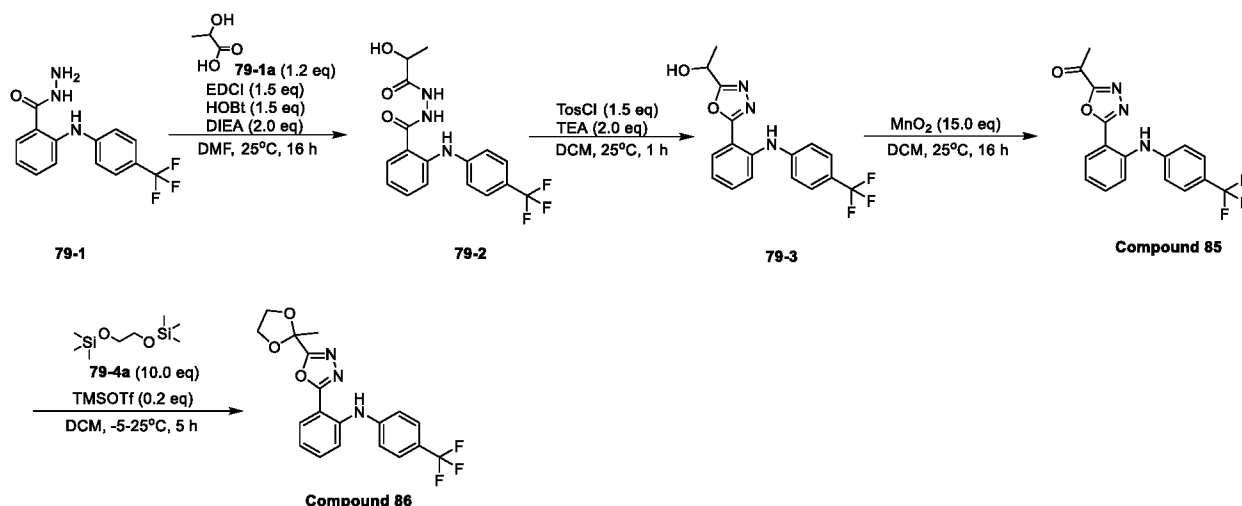
[00380] To a solution of compound 77-2 (40 mg, 90.8 μmol, 1 *eq*) in THF (2 mL) was added LDA (2 M, 0.18 mL, 4 *eq*) at -78°C. The reaction was stirred at -78°C for 1 hr. The reaction was quenched by sat. NH₄Cl (5 mL) and extracted with EA (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 82** (6.8 mg, 14.8 μmol, 16.2% yield) LCMS (ESI): RT = 1.115 min, mass calcd. for C₁₈H₁₃BrF₃N₃O₂ 439.01, m/z found 439.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.30 (s, 1H), 7.76 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.39 - 7.33 (m, 3H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 13.8 Hz, 1H), 6.53 (td, *J* = 6.8, 13.6 Hz, 1H), 4.99 (d, *J* = 6.9 Hz, 2H); and **Compound 83** (1.6 mg, 4.4 μmol, 4.8% yield) LCMS (ESI): RT = 1.049 min, mass calcd. for C₁₈H₁₂F₃N₃O₂ 359.09, m/z found 359.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.78 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.40 - 7.31 (m, 3H), 7.00 - 6.91 (m, 1H), 5.16 (d, *J* = 2.5 Hz, 2H), 2.72 (t, *J* = 2.4 Hz, 1H).

Example 78: 2-(5-(allyloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 84)



[00381] To a solution of compound **78-2** (50 mg, 0.15 mmol, 1 *eq*) and compound **78-2b** (22.5 mg, 0.18 mmol, 16 μ L, 1.2 *eq*) in toluene (1 mL) was added Ag₂O (46.8 mg, 0.20 mmol, 9 μ L, 1.3 *eq*) at 25°C. The reaction was stirred at 25°C for 16 hr. The reaction was diluted with EA (20 mL), filtered and concentrated. The residue was purified by prep-HPLC to give **Compound 84** (3.4 mg, 8.8 μ mol, 5.6% yield). LCMS (ESI): RT = 1.078 min, mass calcd. For C₁₈H₁₄F₃N₃O₂, 361.10 m/z found 362.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.35 (s, 1H), 7.77 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.39 - 7.33 (m, 3H), 6.99 - 6.93 (m, 1H), 6.18 - 6.05 (m, 1H), 5.62 - 5.52 (m, 1H), 5.45 (dd, *J* = 1.0, 10.4 Hz, 1H), 5.04 (td, *J* = 1.1, 6.0 Hz, 2H).

Example 79: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-one (Compound 85) and 2-(5-(2-methyl-1,3-dioxolan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 86)



Step 1: N'-(2-hydroxypropanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00382] To a solution of compound **79-1** (500 mg, 1.69 mmol, 1 *eq*) and compound **79-1a** (183.0 mg, 2.03 mmol, 0.15 mL, 1.2 *eq*) in DMF (8 mL) were added HOBt (343.2 mg, 2.54 mmol, 1.5 *eq*), EDCI (486.9 mg, 2.54 mmol, 1.5 *eq*) and DIEA (437.7 mg, 3.39 mmol, 0.59 mL, 2 *eq*). The mixture was stirred at 25°C for 16 hr. The reaction mixture was quenched with H₂O (15 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (10 mL) and brine (10 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. LCMS confirmed that compound **79-2** (310 mg, 0.82 mmol, 48.3% yield) was obtained.

Step 2: 1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethanol

[00383] To a solution of compound **79-2** (310 mg, 0.84 mmol, 1 *eq*) in DCM (2 mL) were added TEA (170.8 mg, 1.69 mmol, 0.23 mL, 2 *eq*) and TosCl (241.3 mg, 1.27 mmol, 1.5 *eq*). The mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered

and concentrated in vacuum. The residue was purified by flash silica gel chromatography. LCMS confirmed that the compound **79-3** (135 mg, 0.14 mmol, 16.9% yield) was obtained.

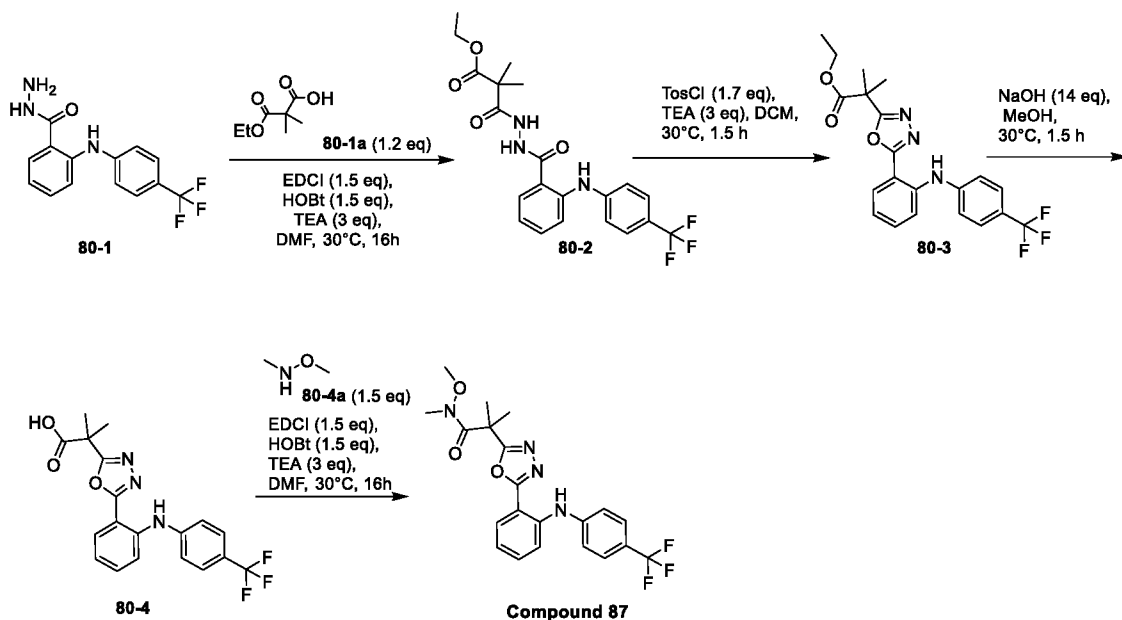
Step 3: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-one (Compound 85)

[00384] To a solution of compound **79-3** (135 mg, 0.39 mmol, 1 *eq*) in DCM (5 mL) was added MnO₂ (504 mg, 5.80 mmol, 15 *eq*). The mixture was stirred at 25°C for 16 hr. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The crude product was purified by prep-TLC. LCMS and ¹HNMR confirmed that **Compound 85** (80 mg, 0.22 mmol, 57.2% yield) was obtained. LCMS (ESI): RT = 0.939 min, mass calcd. For C₁₇H₁₂F₃N₃O₂, 347.09 m/z found 347.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 8.03 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.61 - 7.60 (m, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.53 - 7.48 (m, 1H), 7.48 - 7.42 (m, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.00 (ddd, *J* = 1.3, 6.9, 7.9 Hz, 1H), 2.83 (s, 3H).

Step 4: 2-(5-(2-methyl-1,3-dioxolan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 86)

[00385] To a solution of **Compound 85** (50 mg, 0.14 mmol, 1 *eq*) and compound **79-4a** (297.2 mg, 1.44 mmol, 10 *eq*) in DCM (1 mL) was added TMSOTf (6.4 mg, 28 μmol, 5 uL, 0.2 *eq*) at -5°C. Then the mixture was warmed to 25°C and stirred at 25°C for 5 hr. The reaction mixture was quenched with TEA (5 drops), concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-TLC. LCMS, HPLC and ¹HNMR confirmed that **Compound 86** (17.4 mg, 42 μmol, 29.6% yield) was obtained. LCMS (ESI): RT = 1.037 min, mass calcd. For C₁₉H₁₃F₃N₄O, 391.34 m/z found 392.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.62 - 9.37 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.59 (br d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44 - 7.33 (m, 3H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.30 - 4.18 (m, 1H), 4.24 (br d, *J* = 5.3 Hz, 3H), 1.96 (s, 3H).

Example 80: N-methoxy-N,2-dimethyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 87)



Step 1: ethyl 2,2-dimethyl-3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propanoate

[00386] To a solution of **80-1a** (195.3 mg, 1.22 mmol, 1.2 eq), EDCI (292.2 mg, 1.52 mmol, 1.5 eq) and HOBT (205.9 mg, 1.52 mmol, 1.5 eq) in DMF (20 mL) at 30°C were added **80-1** (300 mg, 1.02 mmol, 1 eq) and TEA (308.4 mg, 3.05 mmol, 0.42 mL, 3 eq). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give to give **80-2** (484 mg, 0.89 mmol, 87.1% yield). LCMS (ESI): RT = 0.835 min, mass calc. for C₂₁H₂₂F₃N₃O₄ 437.41, m/z found 438.0 [M+H]⁺.

Step 2: ethyl 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoate

[00387] To a solution of **80-2** (480 mg, 1.10 mmol, 1 eq) in DCM (6 mL) at 30°C were added TEA (333.1 mg, 3.29 mmol, 0.46 mL, 3 eq) and TosCl (355.7 mg, 1.87 mmol, 1.7 eq). The mixture was stirred at 30°C for 1.5 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **80-3** (375 mg, 0.82 mmol, 75.0% yield). LCMS (ESI): RT = 0.976 min, mass calc. for C₂₁H₂₀F₃N₃O₃ 419.40, m/z found 420.0 [M+H]⁺.

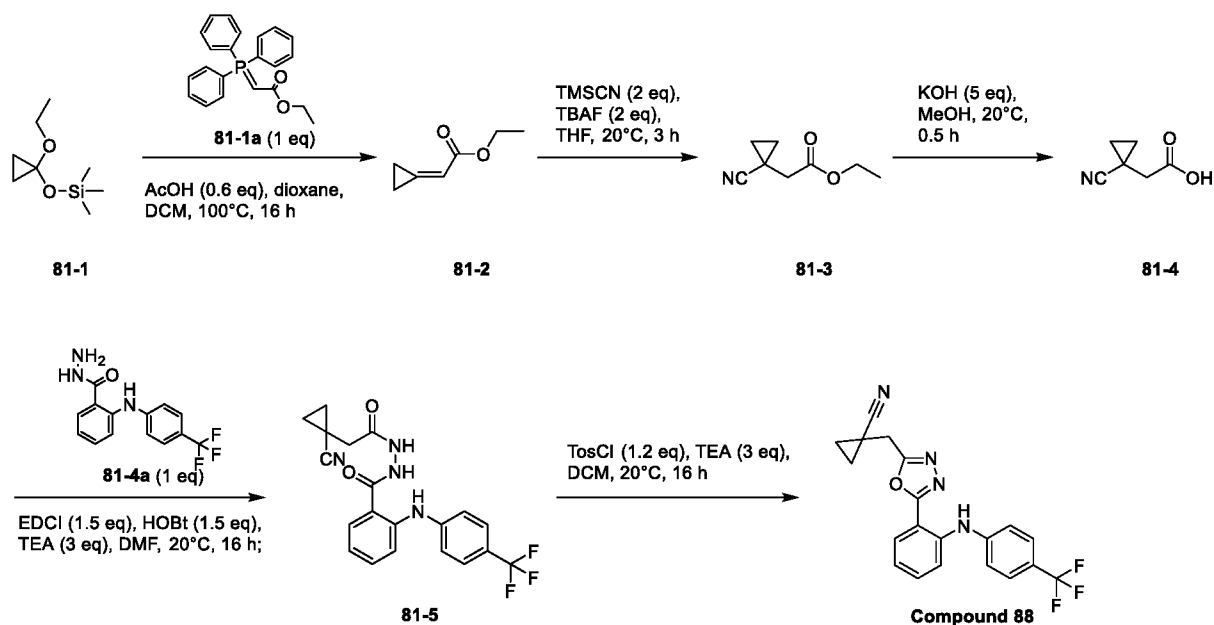
Step 3: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoic acid

[00388] To a solution of **80-3** (370 mg, 0.88 mmol, 1 *eq*) in MeOH (12 mL) at 30°C was added NaOH (2 M, 6.18 mL, 14 *eq*). The mixture was stirred at 30°C for 1.5 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water (20 mL), then acidified with 2N HCl at 0°C to pH = 2-3, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **80-4** (340 mg, 0.78 mmol, 88.6% yield). LCMS (ESI): RT = 0.875 min, mass calc. for C₁₉H₁₆F₃N₃O₃ 391.34, m/z found 392.0 [M+H]⁺;

Step 4: N-methoxy-N,2-dimethyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide

[00389] To a solution of **80-4** (51 mg, 0.13 mmol, 1 *eq*) and HATU (74.3 mg, 0.20 mmol, 1.5 *eq*) in DMF (10 mL) at 30°C were added **80-4a** (19.1 mg, 0.20 mmol, 1.5 *eq*) and TEA (66.0 mg, 0.65 mmol, 91 μ L, 5 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (40 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL *2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography and prep-HPLC to give **Compound 87** (24 mg, 52 μ mol, 39.9% yield). LCMS (ESI): RT = 0.912 min, mass calc. for C₂₁H₂₁F₃N₄O₃ 434.41, m/z found 435.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.43 - 7.35 (m, 3H), 7.02 - 6.95 (m, 1H), 3.32 (s, 3H), 3.23 (s, 3H), 1.75 (s, 6H)

Example 81: 1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyclopropane-1-carbonitrile (Compound 88)



Step 1: ethyl 2-cyclopropylideneacetate

[00390] To a solution of **81-1** (2 g, 11.47 mmol, 2.31 mL, 1.1 *eq*) and AcOH (375.7 mg, 6.26 mmol, 0.36 mL, 0.6 *eq*) in dioxane (30 mL) at 100°C was added **81-1a** (3.63 g, 10.43 mmol, 1 *eq*) in DCM (10 mL) drop-wise, and the mixture was stirred at 100°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give **81-2** (450 mg, 3.57 mmol, 34.2% yield) (volatile). ¹H NMR (400 MHz, CDCl₃) δ 6.23 (quin, *J* = 1.9 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.49 - 1.42 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.26 - 1.21 (m, 2H).

Step 2: ethyl 2-(1-cyanocyclopropyl)acetate

[00391] To a solution of TBAF (1 M, 1.59 mL, 2 *eq*) at 20°C was added TMSCN (157.3 mg, 1.59 mmol, 0.20 mL, 2 *eq*). And then the mixture was stirred at 20°C for 0.5 h. And then a solution of **81-2** (100 mg, 0.79 mmol, 1 *eq*) in THF (0.5 mL) was added at 20°C into the above mixture. The resulting mixture was stirred at 20°C for 2.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **81-3** (110 mg, 0.72 mmol, 90.6% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.23 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 2H), 1.40 - 1.35 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 0.98 - 0.93 (m, 2H).

Step 3: 2-(1-cyanocyclopropyl)acetic acid

[00392] To a solution of KOH (201.5 mg, 3.59 mmol, 5 *eq*) in MeOH (4 mL) at 20°C was added **81-3** (110 mg, 0.72 mmol, 1 *eq*). And then the mixture was stirred at 20°C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (10 mL), then acidified with 2 N HCl to pH = 1-2, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **81-4** (86 mg, 0.69 mmol, 95.7% yield). ¹H NMR (400 MHz, CDCl₃) δ 2.58 (s, 2H), 1.45 - 1.37 (m, 2H), 1.02 - 0.95 (m, 2H).

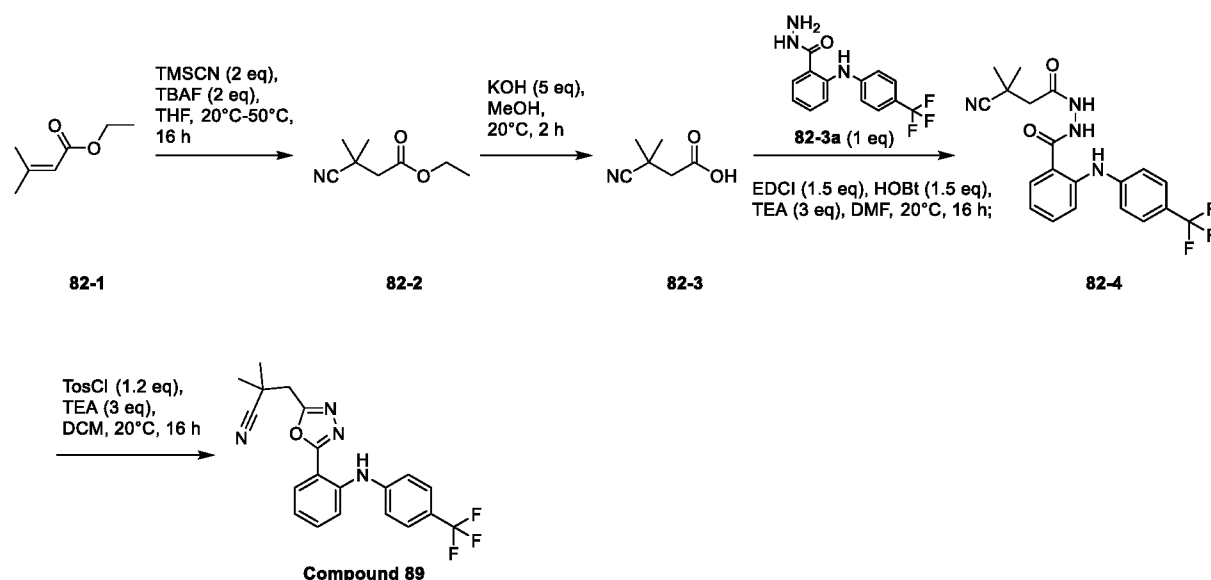
Step 4: *N'*-(2-(1-cyanocyclopropyl)acetyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00393] To a solution of **81-4** (81.4 mg, 0.65 mmol, 1.2 *eq*), EDCI (155.8 mg, 0.81 mmol, 1.5 *eq*), HOBt (109.8 mg, 0.81 mmol, 1.5 *eq*) and **81-4a** (160 mg, 0.54 mmol, 1 *eq*) in DMF (2 mL) at 20°C was added TEA (164.5 mg, 1.63 mmol, 0.23 mL, 3 *eq*). And then the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **81-5** (240 mg, 0.45 mmol, 83.7% yield), which was used directly for next step. LCMS (ESI): RT = 0.788 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 403.0 [M+H]⁺.

Step 5: 1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyclopropane-1-carbonitrile

[00394] To a solution of **81-5** (140 mg, 0.26 mmol, 1 *eq*) and TEA (80.3 mg, 0.79 mmol, 0.11 mL, 3 *eq*) in DCM (1 mL) at 20°C was added TosCl (60.5 mg, 0.32 mmol, 1.2 *eq*). And then the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 88** (55 mg, 0.14 mmol, 54.1% yield). LCMS (ESI): RT = 0.876 min, mass calc. for C₂₀H₁₅F₃N₄O 384.12, m/z found 385.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.93 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.44 - 7.39 (m, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.00 (t, *J* = 7.7 Hz, 1H), 3.19 (s, 2H), 1.52 - 1.46 (m, 2H), 1.20 - 1.14 (m, 2H).

Example 82: 2,2-dimethyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile (Compound 89)



Step 1: ethyl 3-cyano-3-methylbutanoate

[00395] To a solution of TBAF (1 M, 3.12 mL, 2 *eq*) in THF (0.5 mL) at 20°C was added TMSCN (309.6 mg, 3.12 mmol, 0.39 mL, 2 *eq*). And then the mixture was stirred at 20°C for 0.5 h. And then ethyl **82-1** (200 mg, 1.56 mmol, 0.22 mL, 1 *eq*) was added at 20°C into the above mixture. The resulting mixture was stirred at 50°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **82-2** (130 mg, 0.84 mmol, 53.7% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 4.21 (q, *J* = 6.9 Hz, 2H), 2.57 (s, 2H), 1.48 (s, 6H), 1.30 (t, *J* = 7.1 Hz, 3H).

Step 2: 3-cyano-3-methylbutanoic acid

[00396] To a solution of KOH (235.0 mg, 4.19 mmol, 5 *eq*) in MeOH (3 mL) at 20°C was added **82-2** (130 mg, 0.84 mmol, 1 *eq*). And then the mixture was stirred at 20°C for 2 h. The reaction

mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (10 mL), then acidified with 2 N HCl to pH = 1-2, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **82-3** (105 mg, 0.83 mmol, 98.6% yield), which was used directly for next step. ¹H NMR (400 MHz, CDCl₃) δ 2.65 (s, 2H), 1.51 (s, 6H).

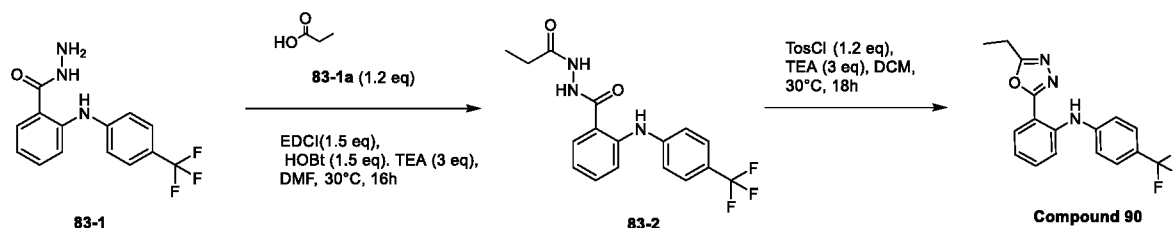
Step 3: *N'*-(3-cyano-3-methylbutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00397] To a solution of **82-3** (103.4 mg, 0.81 mmol, 1.2 eq), EDCI (194.8 mg, 1.02 mmol, 1.5 eq), HOBt (137.3 mg, 1.02 mmol, 1.5 eq) and **82-3a** (200 mg, 0.68 mmol, 1 eq) in DMF (2 mL) at 20°C was added TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 eq). And then the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **82-4** (320 mg, 0.58 mmol, 85.3% yield), which was used directly for next step. LCMS (ESI): RT = 0.841 min, mass calc. for C₂₀H₁₉F₃N₄O₂ 404.15, m/z found 405.0 [M+H]⁺.

Step 4: 2,2-dimethyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile

[00398] To a solution of **82-4** (180 mg, 0.32 mmol, 1 eq) and TEA (98.6 mg, 0.97 mmol, 0.14 mL, 3 eq) in DCM (1 mL) at 20°C was added TosCl (74.3 mg, 0.39 mmol, 1.2 eq). And then the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 89** (45 mg, 0.11 mmol, 34.1% yield). LCMS (ESI): RT = 0.895 min, mass calc. for C₂₀H₁₇F₃N₄O 386.14, m/z found 387.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.44 (s, 1H), 7.93 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.01 - 6.97 (m, 1H), 3.27 (s, 2H), 1.57 (s, 6H).

Example 83: 2-(5-ethyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 90)



Step 1: *N'*-propionyl-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

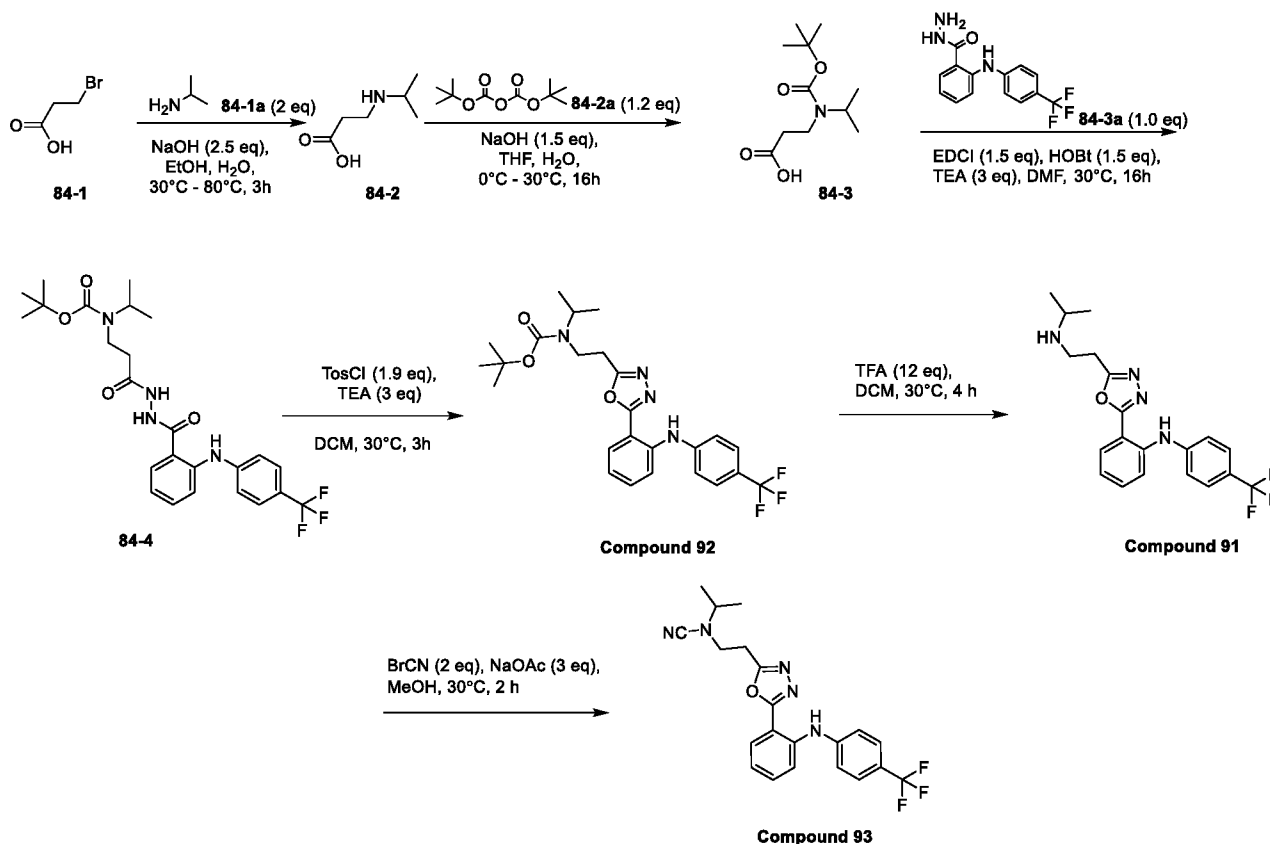
[00399] To a solution of **83-1a** (30.1 mg, 0.41 mmol, 30 uL, 1.2 eq), EDCI (97.4 mg, 0.51 mmol, 1.5 eq) and HOBt (68.7 mg, 0.51 mmol, 1.5 eq) in DMF (1 mL) at 30°C were added **83-1** (100 mg, 0.34 mmol, 1 eq) and TEA (102.8 mg, 1.02 mmol, 0.14 mL, 3 eq). The mixture was stirred at 30°C

for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **83-2** (140 mg, 0.20 mmol, 58.8% yield). LCMS (ESI): RT = 0.764 min, mass calc. for C₁₇H₁₆F₃N₃O₂ 351.12, m/z found 351.9 [M+H]⁺.

Step 2: 2-(5-ethyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00400] To a solution of **83-2** (134 mg, 0.19 mmol, 1 *eq*) in DCM (2 mL) at 30°C were added TEA (57.9 mg, 0.57 mmol, 80 μ L, 3 *eq*) and TosCl (43.6 mg, 0.23 mmol, 1.2 *eq*). The mixture was stirred at 30°C for 18 h. The reaction mixture was concentrated under reduced pressure to give the residue which was purified by prep-HPLC to give **Compound 90** (32 mg, 96.0 μ mol, 50.3% yield). LCMS (ESI): RT = 0.935 min, mass calc. for C₁₇H₁₄F₃N₃O 333.11, m/z found 333.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.41 - 7.35 (m, 3H), 7.00 - 6.95 (m, 1H), 2.99 (q, *J* = 7.5 Hz, 2H), 1.47 (t, *J* = 7.5 Hz, 3H).

Example 84: 2-(5-(2-(isopropylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 91), tert-butyl isopropyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 92), and N-isopropyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 93)



Step 1: 3-(isopropylamino)propanoic acid

[00401] To a solution of **84-1** (1.6 g, 10.72 mmol, 1.11 mL, 1 *eq*) in EtOH (30 mL) at 30°C was added **84-1a** (1.3 g, 21.44 mmol, 1.84 mL, 2 *eq*). The mixture was stirred at 80°C for 3 h. To the resulting mixture was added the solution of NaOH (1.1 g, 26.80 mmol, 2.5 *eq*) in water (10 mL). The reaction mixture was concentrated under reduced pressure to give **84-2** (2.05 g, 10.71 mmol, 99.9% yield) was obtained. Crude ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.70 - 2.61 (m, 1H), 2.56 (t, *J* = 6.6 Hz, 2H), 2.04 - 2.00 (m, 2H), 0.93 (d, *J* = 6.1 Hz, 6H).

Step 2: 3-((tert-butoxycarbonyl)(isopropyl)amino)propanoic acid compound

[00402] To a solution **84-2** (2.1 g, 10.71 mmol, 1 *eq*) and NaOH (642.4 mg, 16.06 mmol, 1.5 *eq*) in THF (10 mL) and water (10 mL) at 0°C was added **84-2a** (2.8 g, 12.85 mmol, 2.95 mL, 1.2 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to remove solvent and then extracted with petroleum ether (20 mL *2) to give the residue. The residue was diluted with water (20 mL), then acidified with 2N HCl at 0°C to pH = 2.5, and then extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **84-3** (920 mg, 3.58 mmol, 33.4% yield). Crude ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.22 (brs, 1H), 4.18 - 3.92 (m, 1H), 3.27 - 3.21 (m, 2H), 2.44 - 2.36 (m, 2H), 1.39 (s, 9H), 1.06 (brd, *J* = 6.8 Hz, 6H).

Step 3: tert-butyl isopropyl(3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propyl)carbamate

[00403] To a solution of **84-3** (188.0 mg, 0.81 mmol, 1.2 *eq*), EDCI (194.8 mg, 1.02 mmol, 1.5 *eq*) and HOBt (137.3 mg, 1.02 mmol, 1.5 *eq*) in DMF (4 mL) at 30°C were added **84-3a** (200 mg, 0.68 mmol, 1 *eq*) and TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **84-4** (370 mg, 0.51 mmol, 75.2% yield). LCMS (ESI): R = 0.877 min, mass calcd. For C₂₅H₃₁F₃N₄O₄ 508.23 m/z found 531.1 [M+Na]⁺.

Step 4: tert-butyl isopropyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 92)

[00404] To a solution of **84-4** (338 mg, 0.47 mmol, 1 *eq*) in DCM (3 mL) at 30°C were added TEA (141.2 mg, 1.40 mmol, 0.19 mL, 3 *eq*) and TosCl (168.5 mg, 0.88 mmol, 1.9 *eq*). The mixture was stirred at 30°C for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 92** (180 mg, 0.34 mmol, 74.1% yield). LCMS (ESI): RT = 1.017 min, mass calc. for C₂₅H₂₉F₃N₄O₃

490.22, *m/z* found 491.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.87 (brd, $J = 7.5$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.42 - 7.35 (m, 3H), 6.97 (t, $J = 7.2$ Hz, 1H), 4.45 - 4.08 (m, 1H), 3.57 (brd, $J = 7.0$ Hz, 2H), 3.23 (brd, $J = 8.6$ Hz, 2H), 1.47 (s, 9H), 1.16 (d, $J = 6.9$ Hz, 6H).

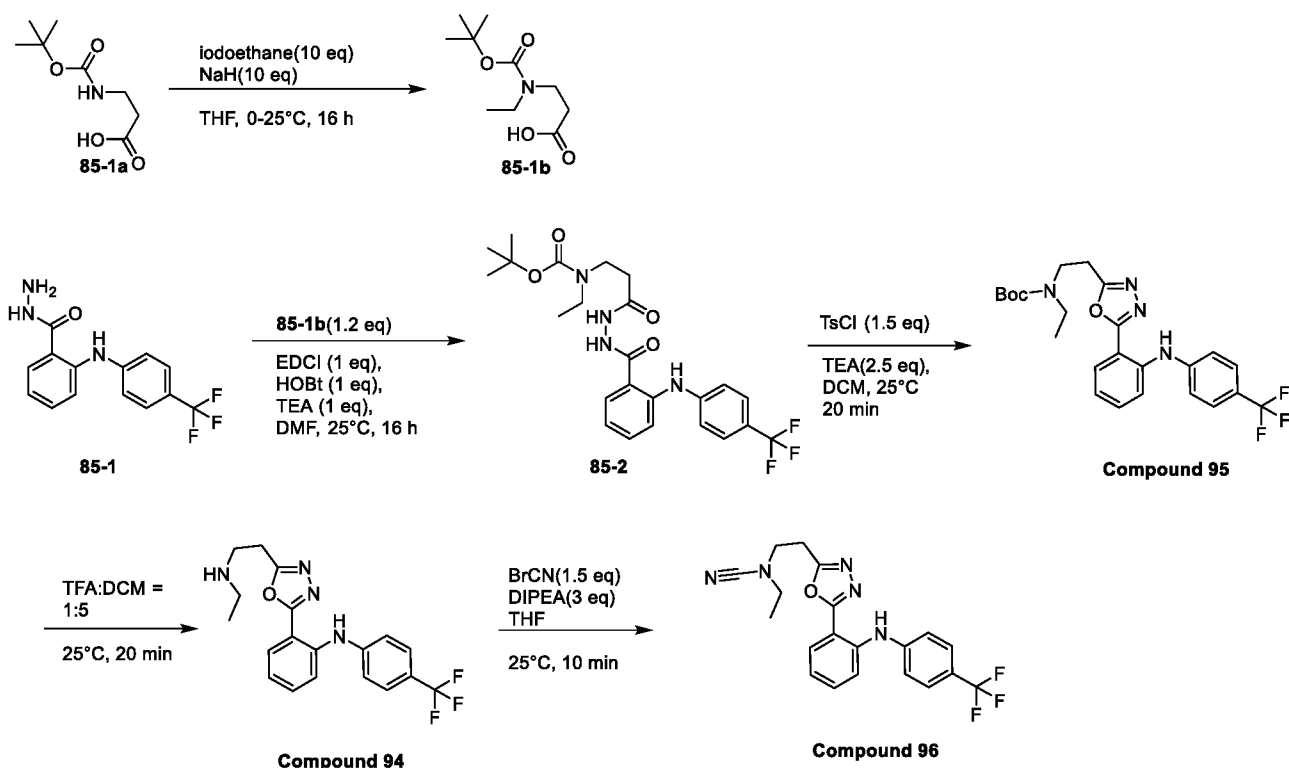
Step 5: 2-(5-(2-(isopropylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 91)

[00405] To a solution of **Compound 92** (160 mg, 0.33 mmol, 1 *eq*) in DCM (3 mL) at 30°C was added TFA (446.3 mg, 3.91 mmol, 0.29 mL, 12 *eq*). The mixture was stirred at 30°C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL), Na_2CO_3 (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purification by prep-HPLC to give **Compound 91** (90 mg, 0.23 mmol, 70.0% yield). LCMS (ESI): RT = 0.750 min, mass calc. for $C_{20}H_{21}F_3N_4O$ 390.17, *m/z* found 391.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.89 - 7.84 (m, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.42 - 7.35 (m, 3H), 6.97 (t, $J = 7.5$ Hz, 1H), 3.24 (s, 4H), 3.06 - 2.96 (m, 1H), 1.18 (d, $J = 6.3$ Hz, 6H)

Step 6: N-isopropyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 93)

[00406] To a solution of **Compound 91** (40.0 mg, 0.10 mmol, 1 *eq*) and NaOAc (25.2 mg, 0.31 mmol, 3 *eq*) in MeOH (1 mL) at 30°C was added cyanogen bromide (21.7 mg, 0.20 mmol, 15 μ L, 2 *eq*), and the resulting mixture was stirred at 30°C for 2 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 93** (14.9 mg, 36 μ mol, 35.0% yield). LCMS (ESI): RT = 0.896 min, mass calc. for $C_{21}H_{20}F_3N_5O$ 415.16, *m/z* found 438.0 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.89 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.58 (d, $J = 8.3$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.43 - 7.34 (m, 3H), 6.98 (t, $J = 7.5$ Hz, 1H), 3.60 - 3.55 (m, 2H), 3.33 (t, $J = 7.0$ Hz, 2H), 3.30 - 3.25 (m, 1H), 1.30 (d, $J = 6.5$ Hz, 6H).

Example 85: 2-(5-(2-(ethylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 94), tert-butyl ethyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 95), and N-ethyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 96)



Step 1: 3-((tert-butoxycarbonyl)(ethyl)amino)propanoic acid

[00407] To a solution of 3-(tert-butoxycarbonylamino)propanoic acid **85-1a** (500 mg, 2.64 mmol, 1 eq) and iodoethane (4.12 g, 26.43 mmol, 2.11 mL, 10 eq) in THF (20 mL) was added NaH (1.06 g, 26.43 mmol, 60% purity, 10 eq) slowly in portions (gas evolved) over a period of 1 hr at 0°C. Then the mixture was stirred at 25°C for 16 h. The mixture was quenched with water (20 mL) at 0°C and extracted with EA (20 mL) twice. The separated aqueous layer was cooled in ice-water bath and adjusted to pH~3 with 1 M HCl and then extracted with EA (30 mL) twice. The combined organic layer was washed with brine (15 mL), dried by anhydrous Na₂SO₄, filtered and concentrated to give 3-[tert-butoxycarbonyl(ethyl)amino]propanoic acid **85-1b** (500 mg, 2.30 mmol, 87.1% yield). No purification and used directly for next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.39 - 3.29 (m, 2H), 3.21 - 3.13 (m, 2H), 2.46 - 2.38 (m, 2H), 1.92 (s, 1H), 1.42 - 1.38 (m, 9H), 1.06 - 0.97 (m, 3H).

Step 2: tert-butyl ethyl(3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propyl)carbamate

[00408] To a solution of **85-1** (250 mg, 0.85 mmol, 1 eq) and 3-[tert-butoxycarbonyl(ethyl)amino]propanoic acid (220.7 mg, 1.02 mmol, 1.2 eq), HOBt (114.4 mg, 0.85 mmol, 1 eq) and EDCI (162.3 mg, 0.85 mmol, 1 eq) in DMF (3 mL) was added TEA (85.7 mg, 0.85 mmol, 0.12 mL, 1 eq) at 25°C. Then the mixture was stirred at 25°C for 16 hr. The mixture was diluted with EA (100 mL), washed with saturated aq. NH₄Cl (15 mL*2) and brine (15 mL*2) in

turns, dried by anhydrous Na₂SO₄, filtered and concentrated to give **85-2** (600 mg, crude). No purification and used directly for next step. LCMS (ESI): R = 0.979 min, mass calcd. For C₂₄H₂₉F₃N₄O₄ 494.21 m/z found 517 [M+23]⁺.

Step 3: tert-butyl ethyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 95)

[00409] To a solution of **85-2** (500 mg, 1.01 mmol, 1 *eq*) and TosCl (289.1 mg, 1.52 mmol, 1.5 *eq*) in DCM (15 mL) was added TEA (255.8 mg, 2.53 mmol, 0.35 mL, 2.5 *eq*) at 25°C. Then the mixture was stirred at 25°C for 20 min. The reaction mixture was quenched with water (5 mL) and diluted with DCM (100 mL), washed with saturated aq. NH₄Cl(15 mL*2) and brine(15 mL*2) in turns, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue (500 mg). The residue was purified by prep-HPLC to give **Compound 95** (140 mg, 0.29 mmol, 28.5% yield). LCMS (ESI): R = 1.112 min, mass calcd. For C₂₄H₂₇F₃N₄O₃ 476.20 m/z found 477.1 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.24 (br d, *J* = 16.1 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.48 (m, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.19 - 7.10 (m, 1H), 3.56 (t, *J* = 6.5 Hz, 2H), 3.27 - 3.06 (m, 4H), 1.38 - 1.10 (m, 9H), 1.04 (br t, *J* = 6.9 Hz, 3H).

Step 4: 2-(5-(2-(ethylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 94)

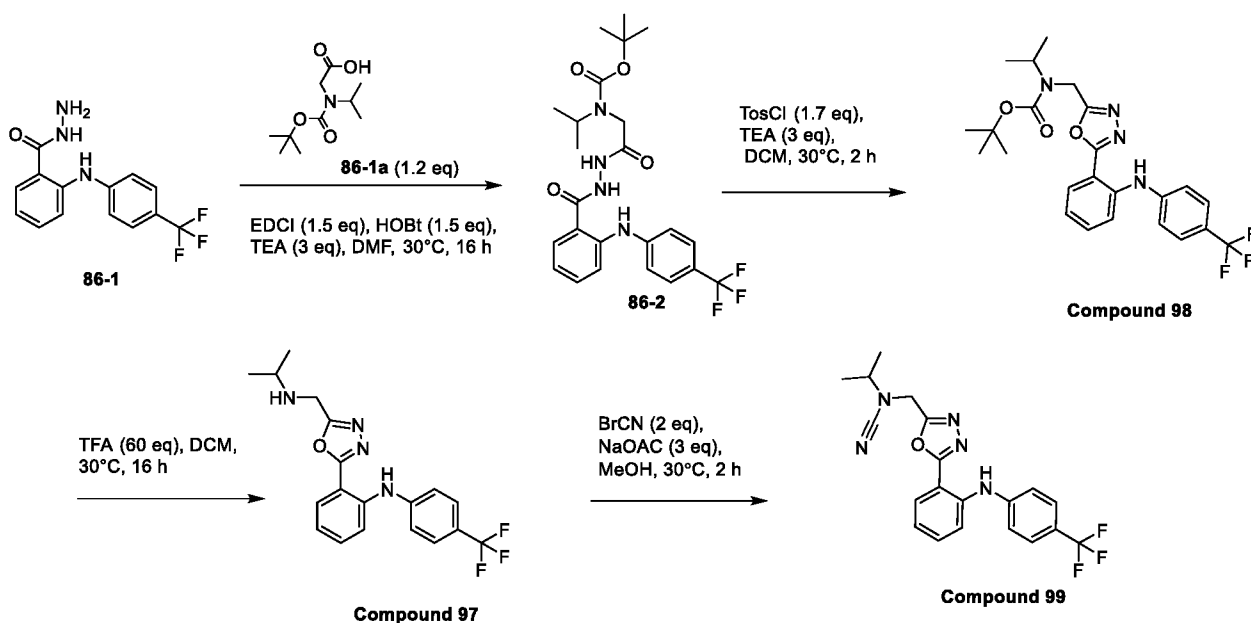
[00410] To a solution of **Compound 95** (130 mg, 0.27 mmol, 1 *eq*) in DCM (3 mL) was added TFA (933.3 mg, 8.18 mmol, 0.61 mL, 30 *eq*) at 25°C. Then the resulting mixture was stirred at 25°C for 20 min. The mixture was concentrated at 25°C to give a residue. The residue was lyophilized to give **Compound 94** (130 mg, 0.26 mmol, 93.9% yield, TFA). LCMS (ESI): R = 0.845 min, mass calcd. For C₁₉H₁₉F₃N₄O 376.15 m/z found 377.1 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.24 (s, 1H), 8.64 (br s, 2H), 7.94 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.62 - 7.51 (m, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.20 - 7.12 (m, 1H), 3.47 - 3.35 (m, 4H), 3.05 (q, *J* = 7.3 Hz, 2H), 1.20 (t, *J* = 7.3 Hz, 3H).

Step 5: N-ethyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 96)

[00411] To a solution of **Compound 94** (50 mg, 0.1 mmol, 1 *eq*, TFA) and DIPEA (39.5 mg, 0.3 mmol, 53 uL, 3 *eq*) in THF (2 mL) was added BrCN (16.2 mg, 0.15 mmol, 11 uL, 1.5 *eq*) at 25°C. Then the resulting mixture was stirred at 25°C for 10 min. The mixture was quenched with water (5 mL) and diluted with EA (100 mL), washed with saturated aq. NH₄Cl(15 mL*2) and brine(15 mL*2) in turns, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 96** (20.3 mg, 50 umol, 49.3% yield). LCMS (ESI): R = 0.992 min, mass calcd. For C₂₀H₁₈F₃N₅O 401.15 m/z found 402.0 [M+1]⁺; ¹H

NMR (400 MHz, DMSO-*d*₆) δ 9.24 (s, 1H), 7.95 (br d, *J* = 7.5 Hz, 1H), 7.64 (br d, *J* = 8.5 Hz, 2H), 7.60 - 7.45 (m, 2H), 7.38 (br d, *J* = 8.3 Hz, 2H), 7.14 (br t, *J* = 7.0 Hz, 1H), 3.54 (br t, *J* = 6.7 Hz, 2H), 3.27 (br t, *J* = 6.5 Hz, 2H), 3.10 (q, *J* = 7.3 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H).

Example 86: 2-(5-((isopropylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 97), tert-butyl isopropyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 98), and N-isopropyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 99)



Step 1: tert-butyl isopropyl(2-oxo-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)ethyl)carbamate

[00412] To a solution of **86-1** (200.0 mg, 0.68 mmol, 1.0 *eq*), EDCI (194.8 mg, 1.02 mmol, 1.5 *eq*) and HOBT (137.3 mg, 1.02 mmol, 1.5 *eq*) in DMF (3 mL) at 30°C were added **86-1a** (176.6 mg, 0.81 mmol, 1.2 *eq*) and TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give to give **86-2** (230 mg, 0.39 mmol, 57.7% yield). LCMS (ESI): RT = 0.861 min, mass calc. for C₂₄H₂₉F₃N₄O₄ 494.21, *m/z* found 517.1 [M+Na]⁺.

Step 2: tert-butyl isopropyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 98)

[00413] To a solution of **86-2** (220 mg, 0.44 mmol, 1 *eq*) in DCM (3 mL) at 30°C were added TEA (135.1 mg, 1.33 mmol, 0.19 mL, 3 *eq*) and TosCl (144.2 mg, 0.76 mmol, 1.7 *eq*), and the mixture was stirred at 30°C for 2 h. The reaction mixture was diluted with water (20 mL), and then

extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 98** (150 mg, 0.31 mmol, 70.8% yield). LCMS (ESI): RT = 1.002 min, mass calc. for C₂₄H₂₇F₃N₄O₃ 476.20, m/z found 499.0 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.50 (s, 1H), 7.84 (brs, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.42 - 7.36 (m, 3H), 6.96 (t, *J* = 7.5 Hz, 1H), 4.58 (brs, 3H), 1.44 (brs, 9H), 1.22 (d, *J* = 6.8 Hz, 6H).

Step 3: 2-(5-((isopropylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 97)

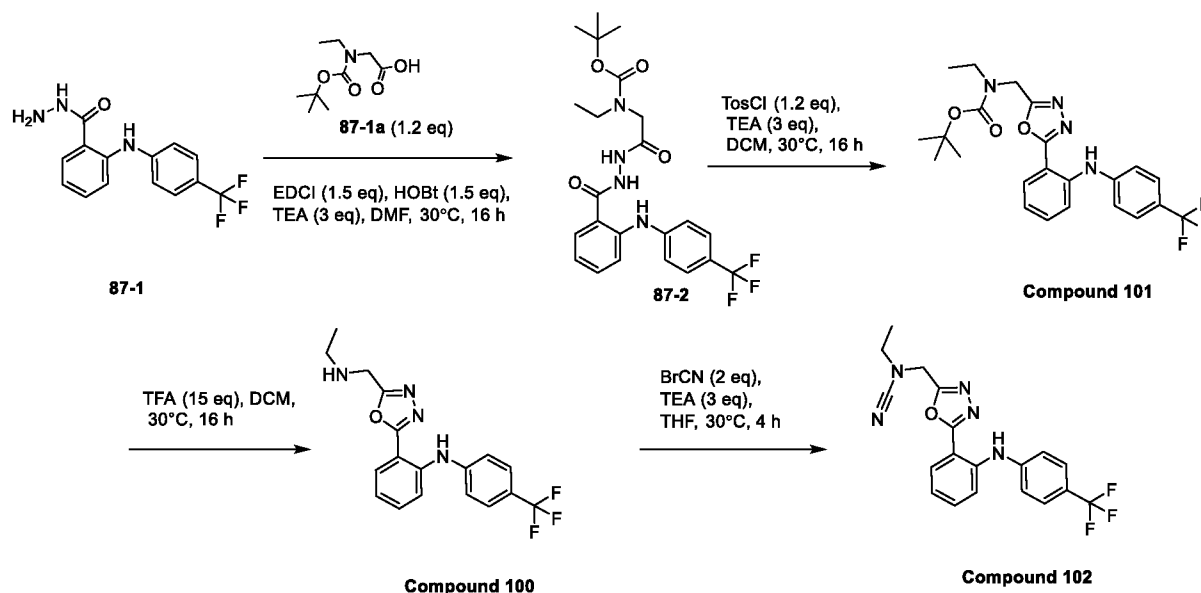
[00414] To a solution of **Compound 98** (140 mg, 0.29 mmol, 1 *eq*) in DCM (3 mL) at 30°C was added TFA (2.0 g, 17.63 mmol, 1.31 mL, 60 *eq*) and the mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with saturation Na₂CO₃ solution (20 mL) and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 97** (70 mg, 0.19 mmol, 63.3% yield). LCMS (ESI): RT = 0.745 min, mass calc. for C₁₈H₁₇F₃N₄O 376.15, m/z found 377 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.91 (dd, *J* = 1.5, 80 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.42 - 7.36 (m, 3H), 6.98 (t, *J* = 7.1 Hz, 1H), 4.16 (s, 2H), 4.16 (s, 2H), 2.96 (quin, *J* = 6.2 Hz, 1H), 1.15 (d, *J* = 6.3 Hz, 6H).

Step 4: N-isopropyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 99)

[00415] To a solution of **Compound 97** (25.0 mg, 66 μmol, 1 *eq*) and NaOAc (16.4 mg, 0.20 mmol, 3 *eq*) in MeOH (1 mL) at 30°C was added cyanogen bromide (14.1 mg, 0.13 mmol, 10 μL, 2 *eq*), and the resulting mixture was stirred at 30°C for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 99** (13.0 mg, 32 μmol, 48.8% yield). LCMS (ESI): RT = 0.888 min, mass calc. for C₂₀H₁₈F₃N₅O 401.15, m/z found 402.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 7.94 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.03 - 6.98 (m, 1H), 4.57 (s, 2H), 3.37 (spt, *J* = 6.5 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 6H).

Example 87: 2-(5-((ethylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 100), and tert-butyl ethyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound

101), and N-ethyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 102)



Step 1: tert-butyl ethyl(2-oxo-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)ethyl carbamate

[00416] To a solution of **87-1a** (123.9 mg, 0.61 mmol, 1.2 *eq*), EDCI (146.1 mg, 0.76 mmol, 1.5 *eq*) and HOBt (103 mg, 0.76 mmol, 1.5 *eq*) in DMF (3 mL) at 30°C was added **87-1** (150 mg, 0.51 mmol, 1 *eq*) and TEA (154.2 mg, 1.52 mmol, 0.21 mL, 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **87-2** (170 mg, 0.34 mmol, 67.3% yield) was obtained. LCMS (ESI): R = 0.846 min, mass calcd. For C₂₃H₂₇F₃N₄O₄ 480.20 m/z found 503.0 [M+23]⁺.

Step 2: tert-butyl ethyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 101)

[00417] To a solution of **87-2** (170 mg, 0.35 mmol, 1 *eq*) in DCM (3 mL) at 30°C was added TEA (107.4 mg, 1.06 mmol, 0.15 mL, 3 *eq*) and TosCl (80.9 mg, 0.42 mmol, 1.2 *eq*), and the mixture was stirred at 30°C for 2 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 101** (150 mg, 0.32 mmol, 91.7% yield). LCMS (ESI): RT = 0.988 min, mass calc. for C₂₃H₂₅F₃N₄O₃ 462.19, m/z found 485.0 [M+23]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 7.86

(brs, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.43 - 7.34 (m, 3H), 6.97 (t, $J = 7.5$ Hz, 1H), 4.82 - 4.64 (m, 2H), 3.40 (brs, 2H), 1.50 (brs, 9H), 1.18 (brs, 3H).

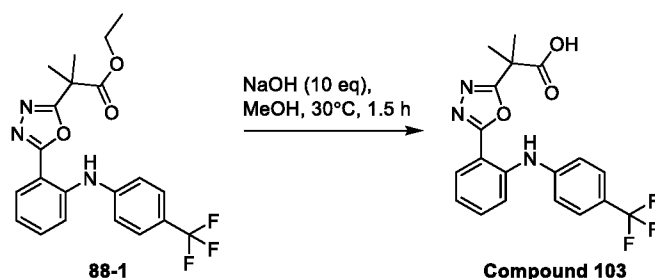
Step 3: 2-(5-((ethylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 100)

[00418] To a solution of **Compound 101** (140 mg, 0.35 mmol, 1 *eq*) in DCM (3 mL) at 30°C was added TFA (517.8 mg, 4.54 mmol, 0.34 mL, 15 *eq*) and the mixture was stirred at 30°C for 1 h. The reaction mixture was diluted with water (20 mL), saturated Na₂CO₃ solution (20 mL) and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 100** (70.0 mg, 0.19 mmol, 61.1% yield). LCMS (ESI): RT = 0.722 min, mass calc. for C₁₈H₁₇F₃N₄O 362.14, m/z found 363 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.91 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.42 - 7.36 (m, 3H), 7.00 - 6.94 (m, 1H), 4.45 (brs, 1H), 4.15 (s, 2H), 2.80 (q, $J = 7.1$ Hz, 2H), 1.18 (t, $J = 7.1$ Hz, 3H).

Step 4: N-ethyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 102)

[00419] To a solution of **Compound 100** (30 mg, 82.8 μ mol, 1 *eq*) and TEA (25.1 mg, 0.25 mmol, 35 μ L, 3 *eq*) in THF (2 mL) at 30°C was added cyanogen bromide (17.5 mg, 0.17 mmol, 12 μ L, 2 *eq*), and the resulting mixture was stirred at 30°C for 4 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 102** (5.0 mg, 12.9 μ mol, 15.6% yield). LCMS (ESI): RT = 0.869 min, mass calc. for C₁₈H₁₇F₃N₄O 387.36, m/z found 388.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 7.94 (dd, $J = 1.3, 7.9$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.04 - 6.97 (m, 1H), 4.56 (s, 2H), 3.22 (q, $J = 7.3$ Hz, 2H), 1.36 (t, $J = 7.3$ Hz, 3H).

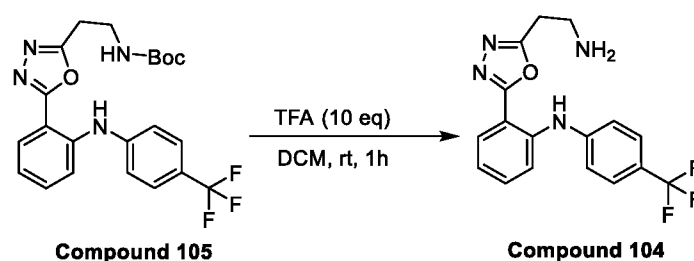
Example 88: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoic acid (Compound 103)



[00420] To a solution of **88-1** (250 mg, 0.60 mmol, 1 *eq*) in MeOH (6 mL) at 30°C was added NaOH (2 M, 2.98 mL, 10 *eq*), and the mixture was stirred at 30°C for 1.5 h. The reaction mixture

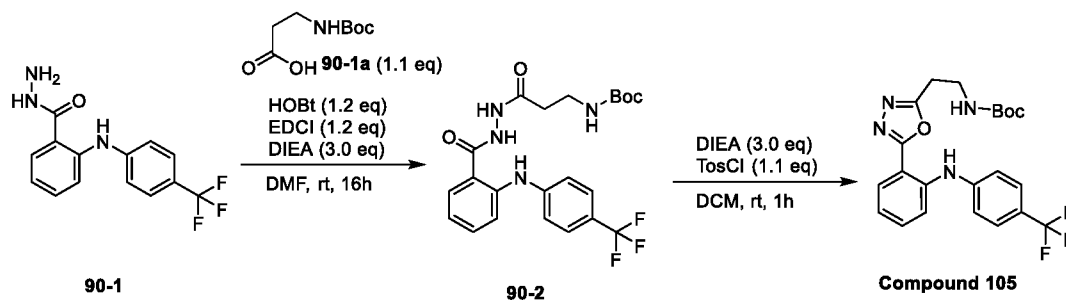
was concentrated under reduced pressure to remove solvent. The residue was diluted with water (20 mL), then acidified with 2N HCl at 0°C to pH = 2-3, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 103** (220 mg, 0.55 mmol, 91.8% yield). LCMS (ESI): RT = 0.988 min, mass calc. for C₁₉H₁₆F₃N₃O₃ 391.11, m/z found 392 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.00 - 6.94 (m, 1H), 1.83 (s, 6H).

Example 89: 2-(5-(2-aminoethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 104)



[00421] To a solution of **Compound 105** (100 mg, 0.22 mmol, 1 eq) in DCM (2 mL) was added TFA (254.2 mg, 2.23 mmol, 0.16 mL, 10 eq). The reaction was stirred at 25°C for 1 hr. The reaction was neutralized with sat. Na₂CO₃ and extracted with DCM (3*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. **Compound 104** (70 mg, 0.19 mmol, 87% yield) was used for next step without further purification. LCMS (ESI): RT = 0.825 min, mass calc. for C₁₇H₁₅F₃N₄O 348.12, m/z found 349.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.88 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.43 - 7.32 (m, 3H), 7.01 - 6.94 (m, 1H), 4.59 (br s, 1H), 3.26 (br s, 2H), 3.13 - 3.06 (m, 2H).

Example 90: tert-butyl (2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 105)



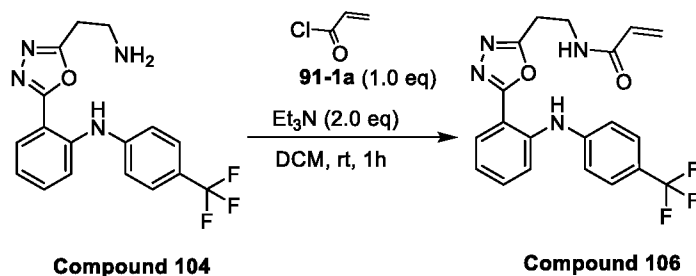
Step 1: tert-butyl N-[3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]carbamate

[00422] To a mixture of compound **90-1** (0.2 g, 0.67 mmol, 1 *eq*), compound **90-1a** (140.9 mg, 0.74 mmol, 1.1 *eq*), HOBt (109.8 mg, 0.81 mmol, 1.2 *eq*) and EDCI (155.8 mg, 0.81 mmol, 1.2 *eq*) in DMF (4 mL) was added DIEA (262.6 mg, 2 mmol, 0.35 mL, 3 *eq*) at 25°C under N₂. The mixture was stirred at 25 °C for 16 hr. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The compound **90-2** (0.3 g, crude) was used for next step directly.

Step 2: tert-butyl (2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

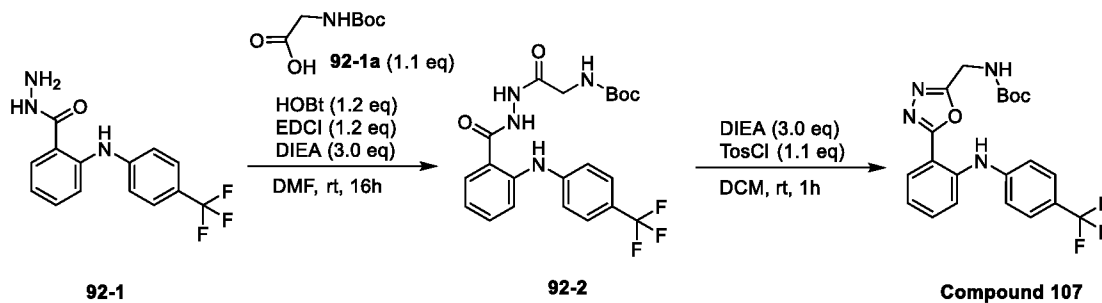
[00423] To a solution of compound **90-2** (0.3 g, 0.64 mmol, 1 *eq*) and DIEA (249.3 mg, 1.9 mmol, 0.33 mL, 3 *eq*) in DCM (4 mL) was added TosCl (134.8 mg, 0.7 mmol, 1.1 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) and washed with water (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give **Compound 105** (130 mg, 0.28 mmol, 45% yield). LCMS (ESI): RT = 1.048 min, mass calc. for C₂₂H₂₃F₃N₄O₃ 448.16, m/z found 449.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.47 (s, 1H), 7.88 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.54 - 7.47 (m, 1H), 7.44 - 7.33 (m, 3H), 7.02 - 6.95 (m, 1H), 3.69 (q, *J* = 6.0 Hz, 2H), 3.16 (t, *J* = 6.3 Hz, 2H), 1.44 (s, 9H).

Example 91: N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)acrylamide (Compound 106)



[00424] To a solution of **Compound 104** (60 mg, 0.17 mmol, 1 *eq*) and Et₃N (34.8 mg, 0.34 mmol, 47.9 uL, 2 *eq*) in DCM (2 mL) was added **91-1a** (15.5 mg, 0.17 mmol, 14 uL, 1 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (20 mL) and washed with H₂O (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 106** (11.2 mg, 27 umol, 16% yield). LCMS (ESI): RT = 0.942 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 403.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.47 - 7.34 (m, 3H), 7.03 - 6.91 (m, 1H), 6.33 (dd, *J* = 1.3, 16.9 Hz, 2H), 6.18 - 6.06 (m, 1H), 5.69 (dd, *J* = 1.3, 10.3 Hz, 1H), 3.93 (q, *J* = 6.1 Hz, 2H), 3.23 (t, *J* = 6.0 Hz, 2H).

Example 92: tert-butyl ((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 107)



Step 1: tert-butyl N-[2-oxo-2-[2-[2-[4-

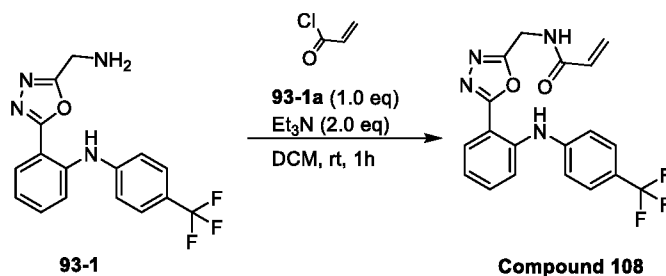
(trifluoromethyl)anilino]benzoyl]hydrazino]ethyl]carbamate

[00425] To a mixture of compound **92-1** (0.2 g, 0.67 mmol, 1 *eq*), compound **92-1a** (130.5 mg, 0.74 mmol, 1.1 *eq*), HOBT (109.8 mg, 0.81 mmol, 1.2 *eq*) and EDCI (155.8 mg, 0.81 mmol, 1.2 *eq*) in DMF (4 mL) was added DIEA (262.6 mg, 2 mmol, 0.35 mL, 3 *eq*) at 25°C under N₂. The mixture was stirred at 25 °C for 16 hr. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The compound **92-2** (0.3 g, crude) was used for next step directly.

Step 2: tert-butyl ((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate

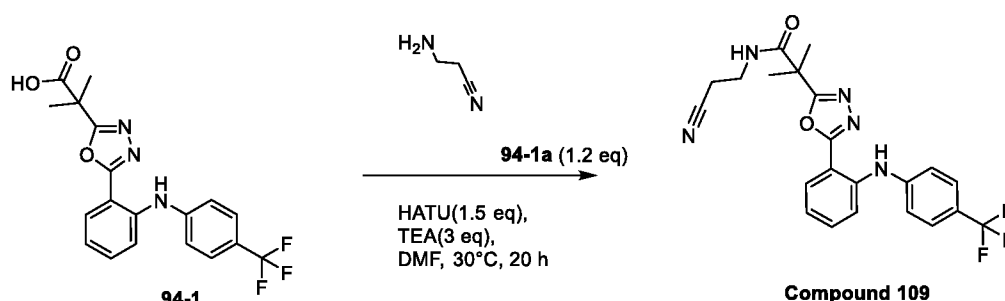
[00426] To a solution of compound **92-2** (0.3 g, 0.66 mmol, 1 *eq*) and DIEA (257 mg, 1.99 mmol, 0.34 mL, 3 *eq*) in DCM (4 mL) was added TosCl (139 mg, 0.72 mmol, 1.1 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) and washed with water (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give **Compound 107** (120 mg, 0.26 mmol, 40.7% yield). LCMS (ESI): RT = 1.040 min, mass calc. for C₂₁H₂₁F₃N₄O₃ 434.16, m/z found 435.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.88 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.43 - 7.33 (m, 3H), 7.01 - 6.93 (m, 1H), 5.24 - 5.12 (m, 1H), 4.67 (d, *J* = 5.8 Hz, 2H), 1.49 (s, 9H).

Example 93: N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)acrylamide (Compound 108)



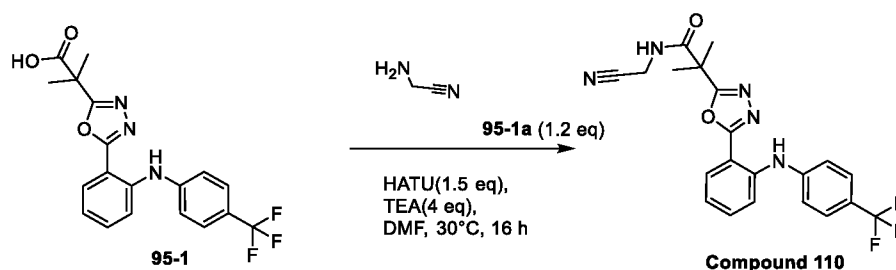
[00427] To a solution of **93-1** (60 mg, 0.17 mmol, 1 *eq*) and Et₃N (36.3 mg, 0.35 mmol, 49.9 uL, 2 *eq*) in DCM (2 mL) was added **93-1a** (16.2 mg, 0.17 mmol, 14.6 uL, 1 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (20 mL) and washed with H₂O (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 108** (17.3 mg, 44 umol, 24.6% yield). LCMS (ESI): RT = 0.942 min, mass calc. for C₁₉H₁₅F₃N₄O₂ 388.11, m/z found 349.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ = 9.42 (s, 1H), 7.90 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.57 - 7.49 (m, 1H), 7.45 - 7.33 (m, 2H), 7.45 - 7.33 (m, 1H), 7.05 - 6.95 (m, 1H), 6.43 (dd, *J* = 1.0, 17.1 Hz, 1H), 6.33 - 6.14 (m, 2H), 5.80 (dd, *J* = 1.3, 10.3 Hz, 1H), 4.90 (d, *J* = 5.8 Hz, 2H).

Example 94: N-(2-cyanoethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 109)



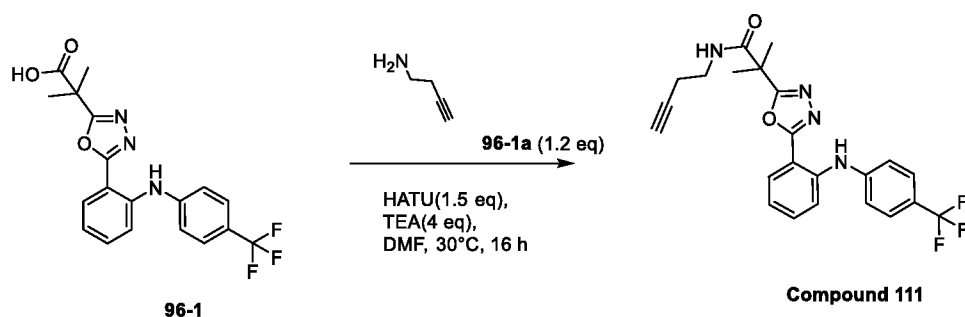
[00428] To a solution of **94-1** (40 mg, 0.10 mmol, 1 *eq*) and HATU (58.3 mg, 0.15 mmol, 1.5 *eq*) in DMF (1 mL) at 30°C were added **94-1a** (8.6 mg, 0.12 mmol, 9 uL, 1.2 *eq*) and TEA (31.0 mg, 0.31 mmol, 43 uL, 3 *eq*). The mixture was stirred at 30°C for 20 h. The reaction mixture was concentrated under reduced pressure to give the residue which was purified by prep-HPLC to give **Compound 109** (20 mg, 45.1 umol, 44.1% yield). LCMS (ESI): RT = 0.853 min, mass calc. for C₂₂H₂₀F₃N₅O₂ 443.16, m/z found 444.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.37 (s, 1H), 7.88 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.52 - 7.48 (m, 1H), 7.43 - 7.38 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.31 (brd, *J* = 5.9 Hz, 1H), 7.01 - 6.95 (m, 1H), 3.54 (q, *J* = 6.3 Hz, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 1.79 (s, 6H).

Example 95: N-(cyanomethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 110)



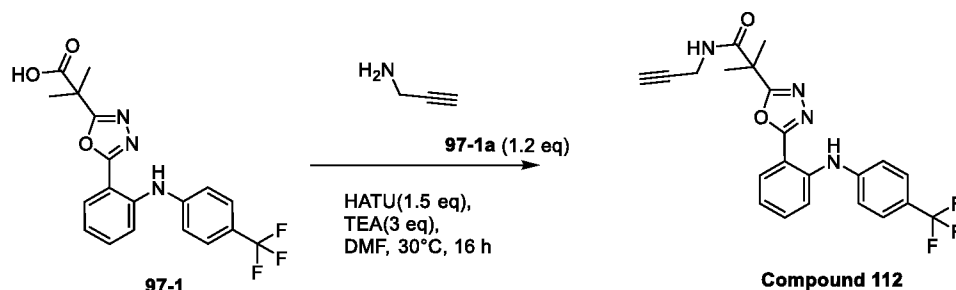
[00429] To a solution of **95-1** (40 mg, 0.1 mmol, 1 *eq*) and HATU (58.3 mg, 0.15 mmol, 1.5 *eq*) in DMF (1 mL) at 30°C were added **95-1a** (15.8 mg, 0.12 mmol, 1.2 *eq*, HCl) and TEA (41.4 mg, 0.41 mmol, 57 μ L, 4 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to give **Compound 110** (13 mg, 30 μ mol, 29.3% yield). LCMS (ESI): RT = 0.860 min, mass calc. for $C_{21}H_{18}F_3N_5O_2$ 429.14, m/z found 430.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.87 (dd, J = 1.4, 7.9 Hz, 1H), 7.74 (brs, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.52 - 7.49 (m, 1H), 7.44 - 7.40 (m, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.02 - 6.97 (m, 1H), 4.22 (d, J = 5.5 Hz, 2H), 1.80 (s, 6H).

Example 96: N-(but-3-yn-1-yl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 111)



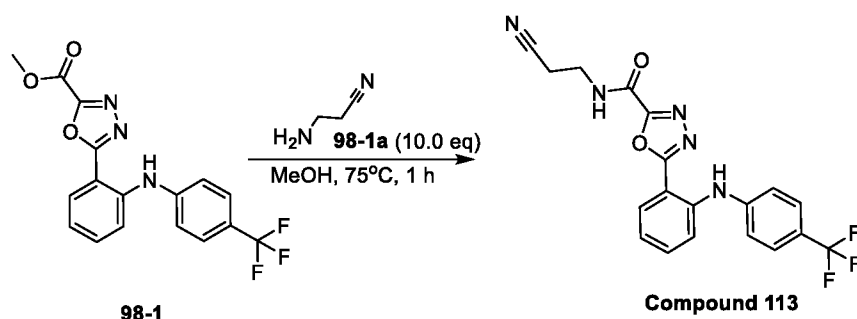
[00430] To a solution of **96-1** (40 mg, 0.10 mmol, 1 *eq*) and HATU (58.3 mg, 0.15 mmol, 1.5 *eq*) in DMF (1 mL) at 30°C were added **96-1a** (17.4 mg, 0.12 mmol, 1.2 *eq*, HCl) and TEA (41.4 mg, 0.41 mmol, 57 μ L, 4 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to give the residue which was purified by prep-HPLC to give **Compound 111** (32 mg, 72.3 μ mol, 70.8% yield). LCMS (ESI): RT = 0.891 min, mass calc. for $C_{23}H_{21}F_3N_4O_2$ 442.16, m/z found 443.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.89 (dd, J = 1.4, 7.9 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.3 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.01 - 6.96 (m, 1H), 6.72 (brs, 1H), 3.42 (q, J = 6.3 Hz, 2H), 2.42 (dt, J = 2.6, 6.4 Hz, 2H), 1.91 (t, J = 2.6 Hz, 1H), 1.79 (s, 6H).

Example 97: 2-methyl-N-(prop-2-yn-1-yl)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 112)



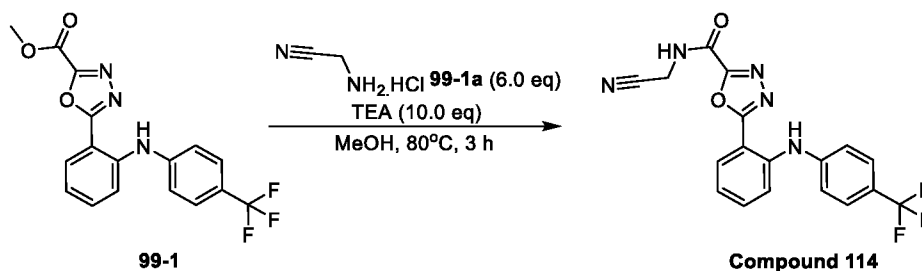
[00431] To a solution of **97-1** (30 mg, 76.7 μmol , 1 *eq*) and HATU (43.7 mg, 0.11 mmol, 1.5 *eq*) in DMF (1 mL) at 30°C were added **97-1a** (5.1 mg, 92.0 μmol , 5.9 μL , 1.2 *eq*) and TEA (23.3 mg, 0.23 mmol, 32 μL , 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to give **Compound 112** (13.0 mg, 30.4 μmol , 39.6% yield). LCMS (ESI): RT = 0.884 min, mass calc. for $\text{C}_{22}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_2$ 428.15, m/z found 429.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ = 9.41 (s, 1H), 7.88 (dd, J = 1.4, 8.0 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.53 - 7.50 (m, 1H), 7.44 - 7.39 (m, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.01 - 6.97 (m, 1H), 6.92 (brs, 1H), 4.07 (dd, J = 2.6, 5.1 Hz, 2H), 2.24 (t, J = 2.6 Hz, 1H), 1.79 (s, 6H)

Example 98: N-(2-cyanoethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 113)



[00432] To a solution of compound **98-1** (50 mg, 0.14 mmol, 1 *eq*) in MeOH (1 mL) was added compound **98-1a** (96.4 mg, 1.38 mmol, 0.1 mL, 10 *eq*). The mixture was stirred at 75°C for 1 hr. The reaction mixture was filtered and the solid was collected to give **Compound 113** (39 mg, 97 μmol , 70.6% yield). LCMS (ESI): RT = 0.841 min, mass calc. For $\text{C}_{19}\text{H}_{14}\text{F}_3\text{N}_5\text{O}_2$, 401.11 m/z found 402.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.64 (t, J = 5.8 Hz, 1H), 9.11 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 3.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.23 - 7.14 (m, 1H), 3.56 (q, J = 6.4 Hz, 2H), 2.82 (t, J = 6.5 Hz, 2H).

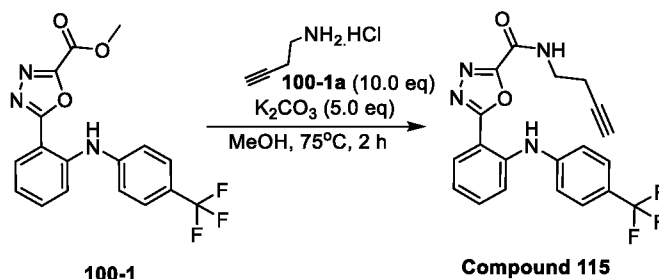
Example 99: N-(cyanomethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 114)



[00433] To a solution of compound **99-1** (50 mg, 0.14 mmol, 1 *eq*) in MeOH (1 mL) were added compound **99-1a** (77.1 mg, 0.83 mmol, 6 *eq*, HCl) and TEA (139.2 mg, 1.38 mmol, 0.19 mL, 10 *eq*). The mixture was stirred at 80°C for 3 hr. The reaction mixture was concentrated in vacuum.

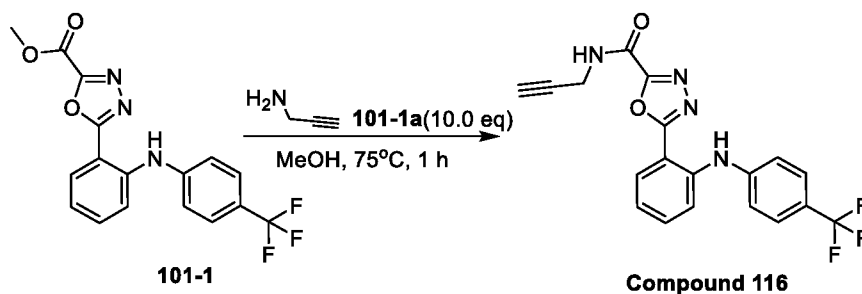
The crude product was purified by prep-HPLC. LCMS and ^1H NMR confirmed that **Compound 114** (24.1 mg, 62.4 μmol , 45.3% yield) was obtained. LCMS (ESI): RT = 0.834 min, mass calcd. For $\text{C}_{18}\text{H}_{12}\text{F}_3\text{N}_5\text{O}_2$, 387.09 m/z found 388.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.27 (s, 1H), 8.05 (d, $J = 7.8$ Hz, 1H), 7.76 (br s, 1H), 7.62 (d, $J = 8.5$ Hz, 2H), 7.52 - 7.42 (m, 2H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.05 - 6.97 (m, 1H), 4.47 (d, $J = 6.0$ Hz, 2H).

Example 100: N-(but-3-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 115)



[00434] To a solution of compound **100-1** (50 mg, 0.14 mmol, 1 *eq*) in MeOH (2 mL) were added K_2CO_3 (95.1 mg, 0.69 mmol, 5 *eq*) and compound **100-1a** (145.2 mg, 1.38 mmol, 10 *eq*). The mixture was stirred at 75°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with H_2O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by prep-TLC. LCMS and ^1H NMR confirmed that **Compound 115** (4.33 mg, 10.8 μmol , 7.8% yield) was obtained. LCMS (ESI): RT = 0.881 min, mass calcd. For $\text{C}_{20}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_2$, 400.11 m/z found 400.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.29 (s, 1H), 7.99 (dd, $J = 1.2, 8.1$ Hz, 1H), 7.53 (d, $J = 8.5$ Hz, 2H), 7.45 - 7.33 (m, 3H), 7.30 (d, $J = 8.5$ Hz, 2H), 6.93 (t, $J = 7.5$ Hz, 1H), 3.62 (q, $J = 6.4$ Hz, 2H), 2.51 (dt, $J = 2.6, 6.4$ Hz, 2H), 2.02 (t, $J = 2.6$ Hz, 1H).

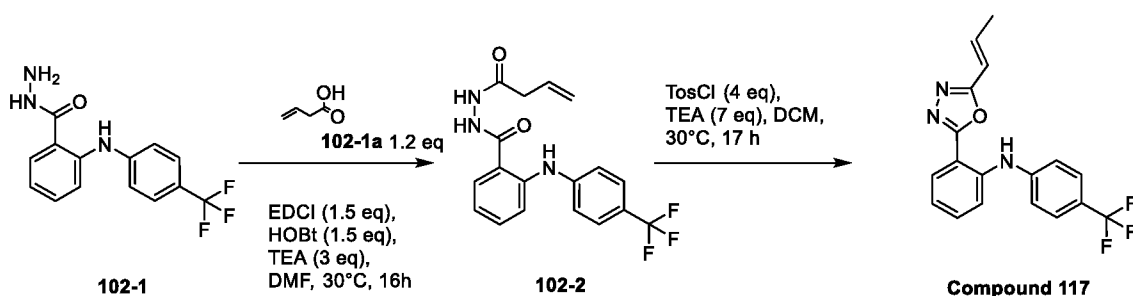
Example 101: N-(prop-2-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 116)



[00435] To a solution of compound **101-1** (50 mg, 0.14 mmol, 1 *eq*) in MeOH (1 mL) was added compound **101-1a** (75.8 mg, 1.38 mmol, 88 μL , 10 *eq*). The mixture was stirred at 75°C for 1 hr. The reaction mixture was filtered and the solid was collected to give **Compound 116** (27 mg, 69

umol, 50.7% yield). LCMS (ESI): RT = 0.862 min, mass calcd. For $C_{19}H_{13}F_3N_4O_2$, 386.10 m/z found 386.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.10 - 8.01 (m, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.52 - 7.47 (m, 1H), 7.47 - 7.42 (m, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.36 - 7.29 (m, 1H), 7.00 (t, J = 7.4 Hz, 1H), 4.33 (dd, J = 2.5, 5.5 Hz, 2H), 2.36 (t, J = 2.5 Hz, 1H).

Example 102: (E)-2-(5-(prop-1-en-1-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 117)



Step 1: N'-(but-3-enoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

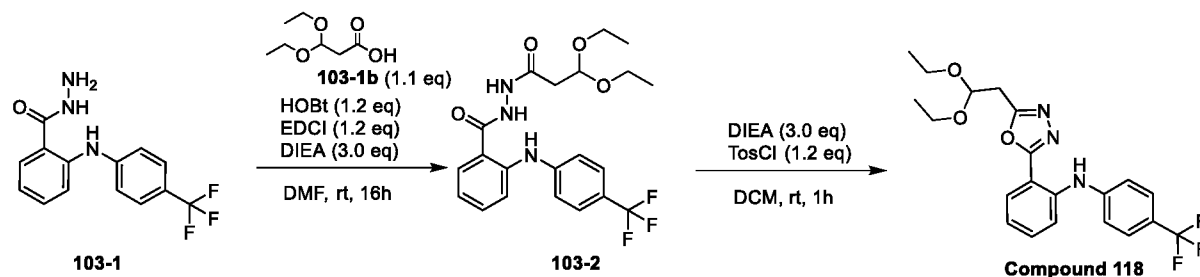
[00436] To a solution of **102-1a** (105 mg, 1.22 mmol, 1.2 eq), EDCI (292.2 mg, 1.52 mmol, 1.5 eq) and HOBt (206 mg, 1.52 mmol, 1.5 eq) in DMF (3 mL) at 30°C were added **102-1** (300 mg, 1.02 mmol, 1 eq) and TEA (308.4 mg, 3.05 mmol, 0.42 mL, 3 eq). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **102-2** (175 mg, 0.45 mmol, 44.6% yield). LCMS (ESI): RT = 0.775 min, mass calc. for $C_{18}H_{16}F_3N_3O_2$ 363.12, m/z found 363.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.18 (brs, 1H), 7.61 (t, J = 7.1 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.46 - 7.43 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.5 Hz, 3H), 7.07 - 6.95 (m, 1H), 6.92 - 6.89 (m, 1H), 6.03 - 5.92 (m, 1H), 5.36 - 5.31 (m, 1H), 3.17 (d, J = 7.0 Hz, 1H), 1.91 (dd, J = 1.2, 6.9 Hz, 2H).

Step 2: (E)-2-(5-(prop-1-en-1-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00437] To a solution of **102-2** (120 mg, 0.33 mmol, 1 eq) in DCM (2 mL) at 30°C were added TEA (234.0 mg, 2.31 mmol, 0.32 mL, 7 eq) and TosCl (251.9 mg, 1.32 mmol, 4 eq). The mixture was stirred at 30°C for 17 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography and prep-HPLC to give **Compound 117** (40 mg, 0.11 mmol, 34.4% yield). LCMS (ESI): RT = 0.968 min, mass calc. for $C_{18}H_{14}F_3N_3O$ 345.11, m/z found 345.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.58

(s, 1H), 7.91 (dd, $J = 1.3$, 7.9 Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.41 - 7.36 (m, 3H), 7.01 - 6.91 (m, 2H), 6.51 (dd, $J = 1.7$, 15.9 Hz, 1H), 2.05 (dd, $J = 1.7$, 6.9 Hz, 3H)

Example 103: 2-(5-(2,2-diethoxyethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 118)



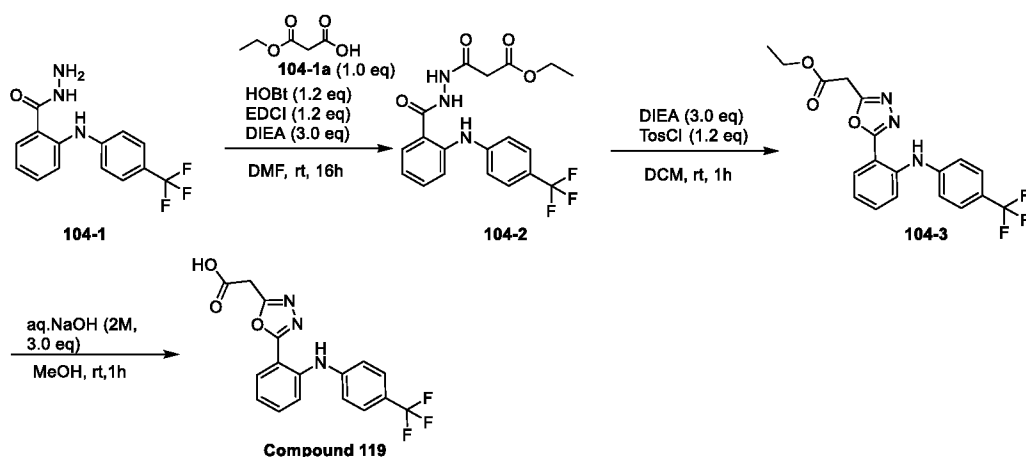
Step 1: N'-(3,3-diethoxypropanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00438] To a solution of **103-1b** (301.5 mg, 1.86 mmol, 1.1 *eq*), EDCI (388.7 mg, 2.03 mmol, 1.2 *eq*) and HOBT (274.0 mg, 2.03 mmol, 1.2 *eq*) in DMF (5 mL) was added compound **103-1** (0.5 g, 1.69 mmol, 1 *eq*) followed by DIEA (655.2 mg, 5.07 mmol, 0.88 mL, 3 *eq*). The reaction mixture was stirred at 25°C for 16 hours. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give compound **103-2** (0.45 g, 0.94 mmol, 55.7% yield).

Step 2: 2-(5-(2,2-diethoxyethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

To a solution of compound **103-2** (0.35 g, 0.79 mmol, 1 *eq*) and DIEA (308.8 mg, 2.39 mmol, 0.41 mL, 3 *eq*) in DCM (6 mL) was added TosCl (182.2 mg, 0.95 mmol, 1.2 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (10 mL) and washed with water (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give **Compound 118** (250 mg, 0.58 mmol, 73.6% yield). LCMS (ESI): RT = 1.075 min, mass calc. for C₂₁H₂₂F₃N₃O₃ 421.16, m/z found 422.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.54 (s, 1H), 7.89 (d, $J = 7.9$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.6$ Hz, 1H), 7.44 - 7.31 (m, 3H), 6.97 (t, $J = 7.6$ Hz, 1H), 5.06 (t, $J = 5.8$ Hz, 1H), 3.81 - 3.72 (m, 2H), 3.66 - 3.55 (m, 2H), 3.31 (d, $J = 5.8$ Hz, 2H), 1.22 (t, $J = 7.0$ Hz, 6H).

Example 104: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetic acid (Compound 119)



Step 1: ethyl 3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propanoate

[00439] To a solution of compound **104-1a** (223.2 mg, 1.6 mmol, 1 *eq*), EDCI (388.7 mg, 2.0 mmol, 1.2 *eq*) and HOBt (274.0 mg, 2.0 mmol, 1.2 *eq*) in DMF (5 mL) was added compound **104-1** (0.5 g, 1.6 mmol, 1 *eq*) followed by DIEA (655.2 mg, 5.0 mmol, 0.88 mL, 3 *eq*). The reaction mixture was stirred at 25°C for 16 hours. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated to give compound **104-2** (700 mg, crude), which was used for next step directly.

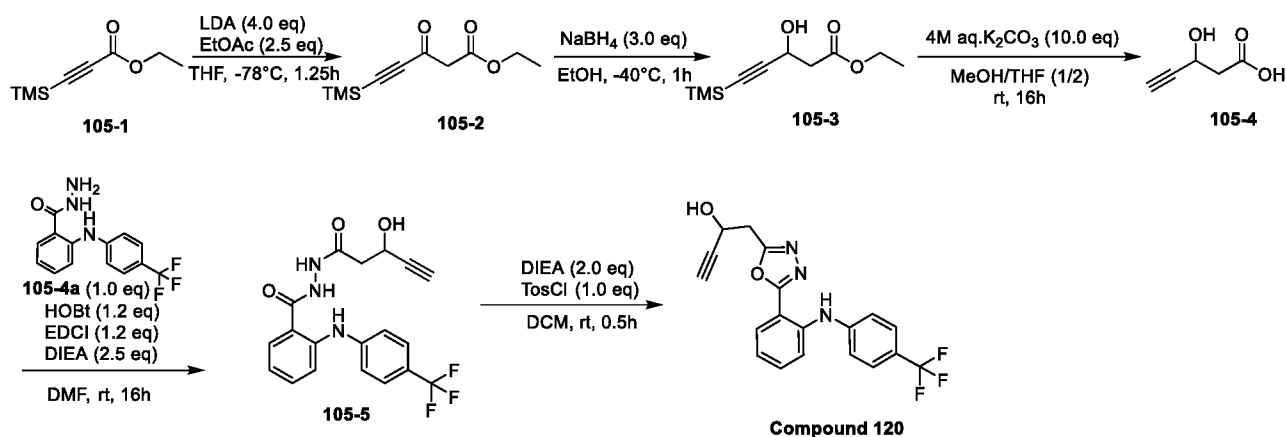
Step 2: ethyl 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]acetate

[00440] To a solution of compound **104-2** (700 mg, 1.7 mmol, 1 *eq*) and DIEA (663.0 mg, 5.1 mmol, 0.89 mL, 3 *eq*) in DCM (10 mL) was added TosCl (391.2 mg, 2.0 mmol, 1.2 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) and washed with water (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give compound **104-3** (410 mg, 0.99 mmol, 58.2% yield).

Step 3: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetic acid

[00441] To a solution of compound **104-3** (310 mg, 0.79 mmol, 1 *eq*) in MeOH (1 mL) was added NaOH (2 M, 1.19 mL, 3 *eq*). The reaction was stirred at 25°C for 1 hr. Another batch was combined. The reaction was concentrated. The aqueous layer was adjusted pH to 3-4 with 2N aq. HCl and filtered. **Compound 119** (350 mg, 0.94 mmol, 79.4% yield) was obtained and then used for next step directly. LCMS (ESI): RT = 0.936 min, mass calc. for C₁₇H₁₂F₃N₃O₃ 363.08, m/z found 363.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.44 - 12.87 (m, 1H), 9.22 (s, 1H), 7.89 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.50 (m, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.19 - 7.09 (m, 1H), 4.17 (s, 2H).

Example 105: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-2-ol (Compound 120)



Step 1: Ethyl 3-oxo-5-trimethylsilyl-pent-4-ynoate

[00442] To a solution of EtOAc (1.29 g, 14.6 mmol, 1.4 mL, 2.5 *eq*) in THF (20 mL) was added drop-wise LDA (2 M, 11.7 mL, 4 *eq*) at -78°C . After 15 min, compound **105-1** (1 g, 5.8 mmol, 1.1 mL, 1 *eq*) in THF (5 mL) was added drop-wise at -78°C . The reaction was stirred at -78°C for 1 hr. AcOH (1 mL) was added to the solution. The reaction was poured into ice/water slurry with 2N aq. HCl maintaining aqueous layer at the pH 3 and extracted with EA (2*50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel to give compound **105-2** (100 mg, 0.47 mmol, 8% yield).

Step 2: ethyl 3-hydroxy-5-trimethylsilyl-pent-4-ynoate

[00443] To a solution of compound **105-2** (0.1 g, 0.47 mmol, 1 *eq*) in EtOH (3 mL) was added NaBH_4 (53.4 mg, 1.4 mmol, 3 *eq*) at -40°C and the reaction was stirred at this temperature for 1 hr. The reaction was quenched by 2M aq. HCl (5 mL) and washed with EA (2*20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to give compound **105-3** (20 mg, 93.3 μmol , 19.8% yield).

Step 3: 3-hydroxypent-4-ynoic acid

[00444] A solution of K_2CO_3 (128.9 mg, 0.93 mmol, 10 *eq*) in H_2O (1 mL) was added to the solution of compound **105-3** (20 mg, 93.3 μmol , 1 *eq*) in MeOH (1 mL) and THF (2 mL). The reaction was stirred at 25°C for 16 hr. The reaction was concentrated. EtOH (5 mL) was added and the solution was filtered. The filtrate was concentrated to give compound **105-4** (10 mg, crude), which was used for next step directly.

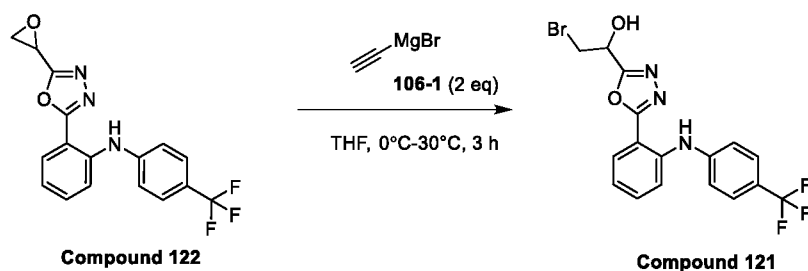
Step 4: N'-(3-hydroxypent-4-ynoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00445] To a solution of compound **105-4** (10 mg, 87.6 μmol , 1 *eq*), HOBt (14.2 mg, 0.1 mmol, 1.2 *eq*) and EDCI (20.1 mg, 0.1 mmol, 1.2 *eq*) in DMF (1 mL) was added compound **105-4a** (25.8 mg, 87.6 μmol , 1 *eq*) followed by DIEA (28.3 mg, 0.21 mmol, 38 μL , 2.5 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was diluted with EA (15 mL) and washed with brine (2*5

mL). The organic layer was dried over Na₂SO₄ and concentrated to give compound **105-5** (25 mg, crude), which was used for next step directly.

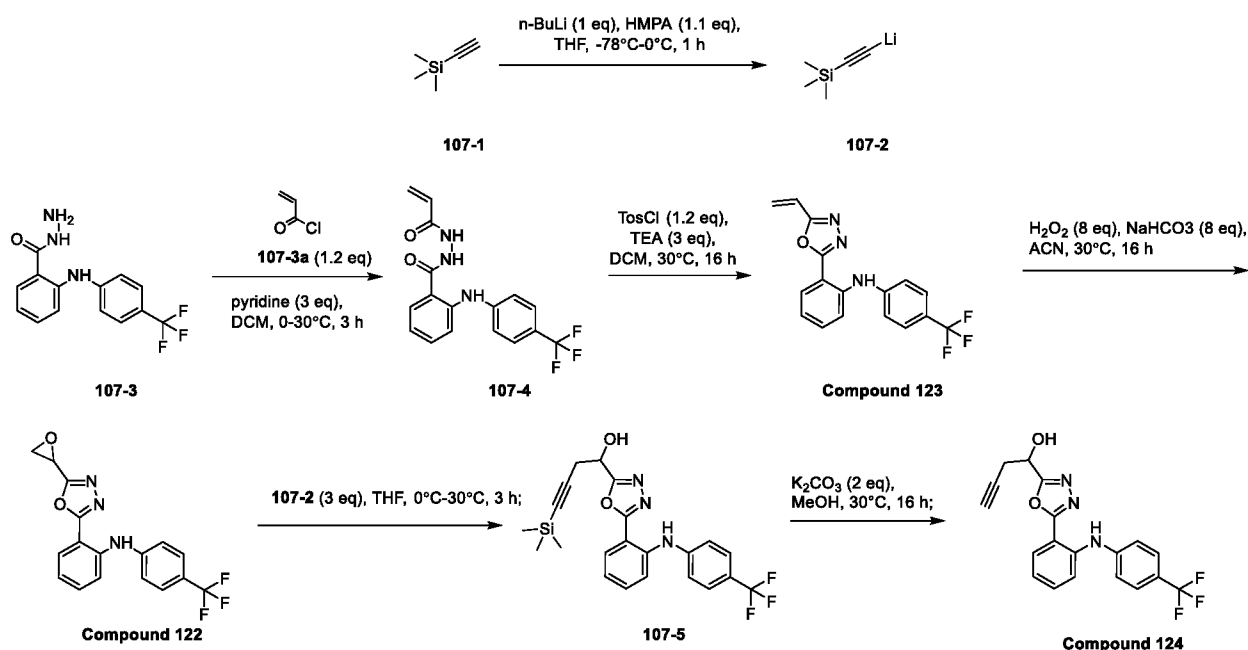
Step 5: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-2-ol [00446] To a solution of compound **105-5** (25 mg, 63.8 μ mol, 1 *eq*) and TosCl (12.1 mg, 63.8 μ mol, 1.0 *eq*) in DCM (1 mL) was added DIEA (16.5 mg, 0.12 mmol, 22 μ L, 2.0 *eq*). The reaction was stirred at 25°C for 30 min. The reaction was diluted with DCM (10 mL) and washed with H₂O (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The reaction was purified by prep-HPLC to give **Compound 120** (1.3 mg, 3.5 μ mol, 5.5% yield). LCMS (ESI): RT = 0.961 min, mass calc. for C₁₉H₁₄F₃N₃O₂ 373.14, m/z found 374.0 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.48 (br s, 1H), 7.89 (br d, *J* = 8.1 Hz, 1H), 7.59 (br d, *J* = 8.0 Hz, 2H), 7.52 (br d, *J* = 8.3 Hz, 1H), 7.42 (br d, *J* = 7.3 Hz, 1H), 7.37 (br d, *J* = 8.6 Hz, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 5.03 - 4.94 (m, 1H), 3.41 (br d, *J* = 5.5 Hz, 2H), 2.57 (s, 1H).

Example 106: 2-bromo-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 121)



[00447] To a solution of **Compound 122** (15.0 mg, 43.2 μ mol, 1 *eq*) in THF (1 mL) at 0°C was added **106-1** (0.5 M, 0.17 mL, 2 *eq*), and the mixture was stirred at 30°C for 3 h. The reaction mixture was quenched with saturated NH₄Cl (10 mL), diluted with water (10 mL) and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 121** (10.4 mg, 23.7 μ mol, 54.8% yield). LCMS (ESI): RT = 0.867 min, mass calc. for C₁₇H₁₃BrF₃N₃O₂ 427.01, m/z found 429.8 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 7.92 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.45 - 7.39 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.01 - 6.96 (m, 1H), 5.38 - 5.29 (m, 1H), 3.98 - 3.88 (m, 2H), 3.18 (d, *J* = 6.8 Hz, 1H).

Example 107: 2-(5-(oxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 122), N-(4-(trifluoromethyl)phenyl)-2-(5-vinyl-1,3,4-oxadiazol-2-yl)aniline (Compound 123), and 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-1-ol (Compound 124)



Step 1: ((trimethylsilyl)ethynyl)lithium

[00448] To a solution of **107-1** (1 g, 10.18 mmol, 1.41 mL, 1 *eq*) and HMPA (2.01 g, 11.20 mmol, 1.97 mL, 1.1 *eq*) in THF (20 mL) at -78°C was added *n*-BuLi (2.5 M, 4.07 mL, 1.0 *eq*) drop-wise, and the mixture was stirred at 0°C for 1 h. The mixture was used directly for next step.

Step 2: *N'*-acryloyl-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00449] To a solution of **107-3** (500 mg, 1.69 mmol, 1 *eq*) and pyridine (401.9 mg, 5.08 mmol, 0.41 mL, 3 *eq*) in DCM (10 mL) at 0°C was added **107-3a** (183.9 mg, 2.03 mmol, 0.17 mL, 1.2 *eq*), and the mixture was stirred at 30°C for 3 h. The mixture was quenched with water (1 mL) and concentrated to give a residue. The residue was purified by flash silica gel chromatography to give **107-4** (170 mg, 0.49 mmol, 28.7% yield). LCMS (ESI): RT = 0.762 min, mass calc. for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$ 349.10, m/z found 349.9 $[\text{M}+\text{H}]^{+}$.

Step 3: N-(4-(trifluoromethyl)phenyl)-2-(5-vinyl-1,3,4-oxadiazol-2-yl)aniline (Compound 123)

[00450] To a solution of **107-4** (70.0 mg, 0.20 mmol, 1 *eq*) and TEA (60.8 mg, 0.60 mmol, 84 μL , 3 *eq*) in DCM (3 mL) at 30°C was added TosCl (45.8 mg, 0.24 mmol, 1.2 *eq*), and the mixture was stirred at 30°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 123** (30 mg, 90.6 μmol , 45.2% yield). LCMS (ESI): RT = 0.933 min, mass calc. for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_3\text{O}$ 331.09, m/z found 331.9 $[\text{M}+\text{H}]^{+}$; ^1H NMR (400 MHz, CDCl_3) δ 9.55 (s, 1H), 7.94 (dd, J = 1.5, 8.0 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.44 - 7.35 (m, 3H), 7.02 - 6.96 (m, 1H), 6.81 (dd, J = 11.3, 17.6 Hz, 1H), 6.40 (d, J = 17.8 Hz, 1H), 5.95 - 5.89 (m, 1H), 5.92 (d, J = 11.8 Hz, 1H).

Step 4: 2-(5-(oxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 122)

[00451] To a solution of **Compound 123** (120 mg, 0.36 mmol, 1 *eq*) in ACN (4 mL) at 30°C were added H₂O₂ (328.6 mg, 2.90 mmol, 0.28 mL, 30% purity, 8 *eq*) and NaHCO₃ (243.4 mg, 2.90 mmol, 8 *eq*), and the mixture was stirred at 30°C for 16 h. The reaction mixture was quenched with saturated Na₂SO₃ (30 mL), concentrated under reduced pressure to remove ACN. The residue was extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 122** (19.0 mg, 53.1 umol, 14.7% yield). LCMS (ESI): RT = 0.877 min, mass calc. for C₁₇H₁₂F₃N₃O₂ 347.09, m/z found 347.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 7.86 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 - 7.48 (m, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.00 - 6.94 (m, 1H), 4.26 (dd, *J* = 2.4, 4.1 Hz, 1H), 3.46 (dd, *J* = 2.4, 5.4 Hz, 1H), 3.36 (dd, *J* = 4.1, 5.4 Hz, 1H).

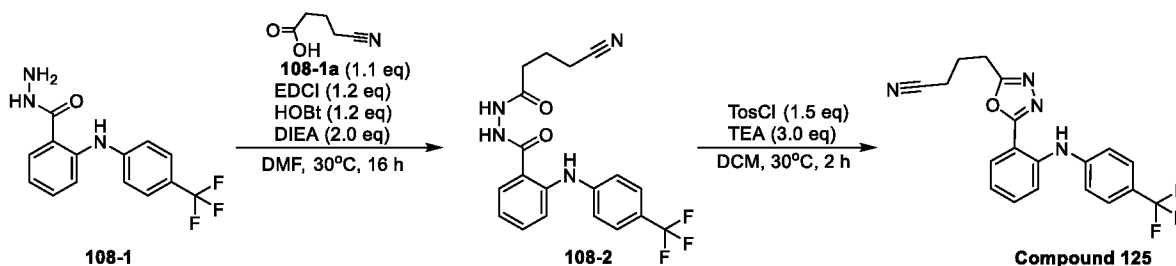
Step 5: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)-4-(trimethylsilyl)but-3-yn-1-ol

[00452] To a solution of **Compound 122** (20 mg, 57.6 umol, 1 *eq*) in THF (0.5 mL) at 0°C was added compound **107-2** (0.37 M, 0.47 mL, 3 *eq*), and the resulting mixture was stirred at 30°C for 3 h. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL), then diluted with water (5 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **107-5** (25.0 mg, 56.1 umol, 97.4% yield) as crude, which was used directly for next step. LCMS (ESI): RT = 0.975 min, mass calc. for C₂₂H₂₂F₃N₃O₂Si 445.14, m/z found 446.2 [M+H]⁺.

Step 6: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-1-ol (Compound 124)

[00453] To a solution of **107-5** (23.0 mg, 51.6 umol, 1 *eq*) in MeOH (1 mL) at 30°C was added K₂CO₃ (14.3 mg, 0.10 mmol, 2 *eq*), and the resulting mixture was stirred at 30°C for 16 h. The reaction mixture was filtered to remove the solid. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 124** (6.5 mg, 17.4 umol, 33.7% yield). LCMS (ESI): RT = 0.855 min, mass calc. for C₁₉H₁₄F₃N₃O₂ 373.10, m/z found 373.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 7.92 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 5.23 (t, *J* = 5.8 Hz, 1H), 3.08 (brs, 1H), 3.04 - 2.97 (m, 2H), 2.16 (t, *J* = 2.6 Hz, 1H).

Example 108: 4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile (Compound 125)



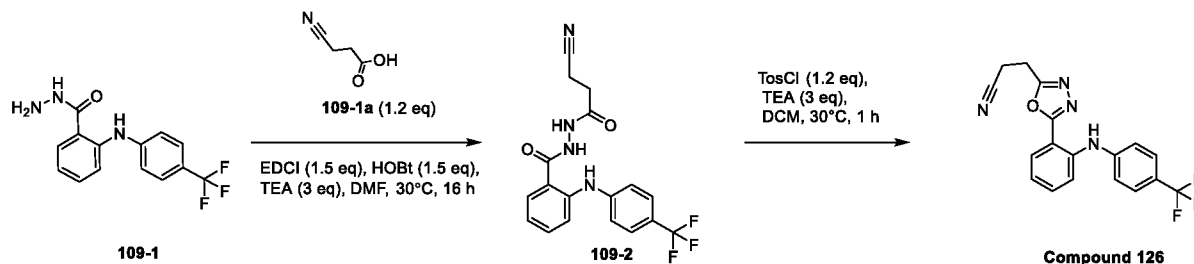
Step 1: N'-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00454] To a solution of compound **108-1** (200 mg, 0.68 mmol, 1 *eq*) and compound **108-1a** (84 mg, 0.75 mmol, 1.1 *eq*) in DMF (3 mL) were added EDCI (155 mg, 0.71 mmol, 1.2 *eq*), HOBt (110 mg, 0.81 mmol, 1.2 *eq*) and DIEA (175 mg, 1.35 mmol, 0.24 mL, 2 *eq*). The mixture was stirred at 30°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL*2) and brine (5 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. Compound **108-2** (165 mg, 0.42 mmol, 62% yield) was obtained.

Step 2: 4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile

[00455] To a solution of compound **108-2** (100 mg, 0.26 mmol, 1 *eq*) in DCM (1 mL) were added TosCl (73 mg, 0.38 mmol, 1.5 *eq*) and TEA (78 mg, 0.77 mmol, 0.1 mL, 3 *eq*). The mixture was stirred at 30°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 125** (47.8 mg, 0.13 mmol, 50% yield) was obtained. LCMS (ESI): RT = 0.879 min, mass calcd. For C₁₉H₁₅F₃N₄O, 372.12 m/z found 372.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.47 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.45 - 7.40 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.06 - 6.94 (m, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.31 (quin, *J* = 7.2 Hz, 2H).

Example 109: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile (Compound 126)



Step 1: N'-((3-cyanopropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

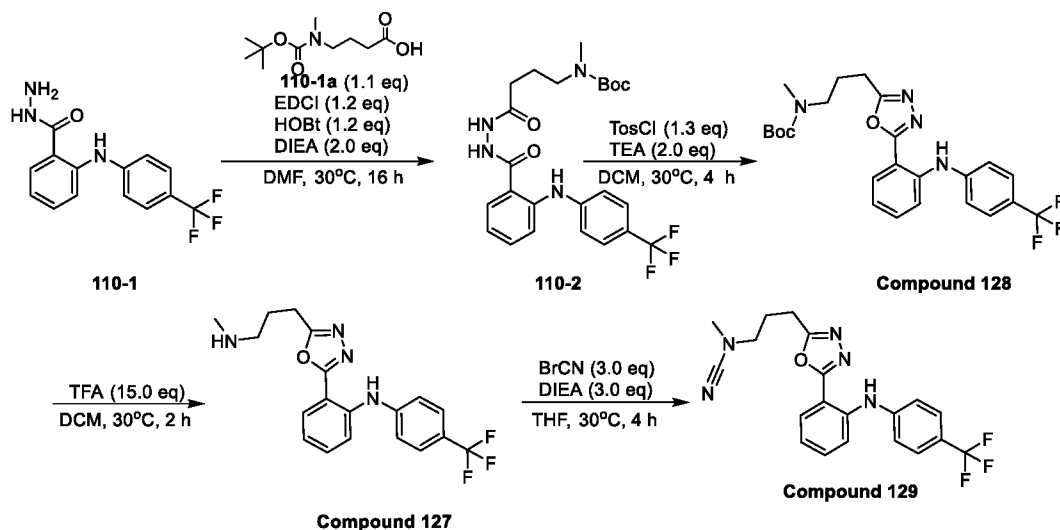
[00456] To a solution of **109-1a** (40.3 mg, 0.41 mmol, 1.2 *eq*), EDCI (97.4 mg, 0.51 mmol, 1.5 *eq*) and HOBt (68.7 mg, 0.51 mmol, 1.5 *eq*) in DMF (2 mL) at 30°C was added **109-1** (100 mg, 0.34

mmol, 1 *eq*) and then TEA (102.8 mg, 1.02 mmol, 0.14 mL, 3 *eq*), and the resulting mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **109-2** (160 mg, 0.29 mmol, 86.2% yield), which was used directly for next step. LCMS (ESI): RT = 0.749 min, mass calc. for C₁₈H₁₅F₃N₄O₂ 376.11, m/z found 399.0 [M+23]⁺.

Step 2: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile [00457]

To a solution of **109-2** (150 mg, 0.27 mmol, 1 *eq*) and TEA (83.1 mg, 0.82 mmol, 0.11 mL, 3 *eq*) in DCM (1 mL) at 30°C was added TosCl (62.7 mg, 0.33 mmol, 1.2 *eq*), and the resulting mixture was stirred at 30°C for 1 h. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give 50 mg sample. The 50 mg sample was purified further by prep-HPLC to give **Compound 126** (14.0 mg, 39.1 μmol, 14.3% yield). LCMS (ESI): RT = 0.862 min, mass calc. for C₁₈H₁₃F₃N₄O 358.10, m/z found 358.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 7.88 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.95 (m, 1H), 3.36 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.4 Hz, 2H).

Example 110: 2-(5-(3-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 127), tert-butyl methyl(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 128), and N-methyl-N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 129)



Step 1: tert-butyl N-methyl-N-[4-oxo-4-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]butyl]carbamate

[00458] To a solution of compound **110-1** (200 mg, 0.68 mmol, 1 *eq*) and compound **110-1a** (161 mg, 0.75 mmol, 1.1 *eq*) in DMF (3 mL) were added EDCI (155 mg, 0.81 mmol, 1.2 *eq*), HOBT (109 mg, 0.81 mmol, 1.2 *eq*) and DIEA (175 mg, 1.35 mmol, 0.24 mL, 2 *eq*). The mixture was stirred at 30°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL*2) and brine (5 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS confirmed that compound **110-2** (260 mg, 0.49 mmol, 72% yield) was obtained.

Step 2: tert-butyl methyl(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 128)

[00459] To a solution of compound **110-2** (260 mg, 0.53 mmol, 1 *eq*) in DCM (3 mL) were added TEA (106 mg, 1.05 mmol, 0.15 mL, 2 *eq*) and TosCl (130 mg, 0.68 mmol, 1.3 *eq*). The mixture was stirred at 30°C for 4 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that **Compound 128** (162 mg, 0.33 mmol, 63% yield) was obtained. LCMS (ESI): RT = 0.973 min, mass calcd. For C₂₄H₂₇F₃N₄O₃, 476.20 m/z found 499.0 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.53 (s, 1H), 7.88 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.42 - 7.33 (m, 3H), 6.97 (t, *J* = 7.2 Hz, 1H), 3.41 (br t, *J* = 6.7 Hz, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.90 (s, 3H), 2.12 (quin, *J* = 7.3 Hz, 2H), 1.45 (s, 9H).

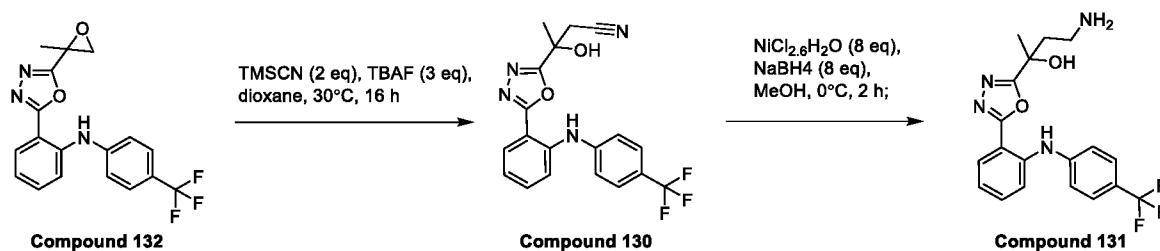
Step 3: 2-(5-(3-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 127)

[00460] To a solution of **Compound 128** (150 mg, 0.31 mmol, 1 *eq*) in DCM (2 mL) was added TFA (538 mg, 4.72 mmol, 0.35 mL, 15 *eq*). The mixture was stirred at 30°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with saturated aq. Na₂CO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. LCMS and ¹H NMR confirmed that **Compound 127** (110 mg, 0.29 mmol, 91% yield) was obtained. LCMS (ESI): RT = 2.008 min, mass calcd. For C₁₉H₁₉F₃N₄O, 376.15 m/z found 377.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.46 (br s, 1H), 7.56 - 7.44 (m, 4H), 7.37 - 7.30 (m, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.90 (t, *J* = 7.2 Hz, 1H), 3.41 (t, *J* = 7.0 Hz, 2H), 2.96 (s, 3H), 2.74 - 2.63 (m, 2H), 2.08 - 1.94 (m, 2H).

Step 4: N-methyl-N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 129)

[00461] To a solution of **Compound 128** (70 mg, 0.19 mmol, 1 *eq*) in THF (1 mL) were added BrCN (59 mg, 0.56 mmol, 41 μ L, 3 *eq*) and DIEA (72 mg, 0.56 mmol, 97 μ L, 3 *eq*). The mixture was stirred at 30°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 129** (4.5 mg, 11 μ mol, 6% yield) was obtained. LCMS (ESI): RT = 2.008 min, mass calcd. For C₂₀H₁₈F₃N₅O, 401.15 m/z found 402.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.47 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.45 - 7.34 (m, 3H), 7.03 - 6.93 (m, 1H), 3.20 (t, *J* = 6.9 Hz, 2H), 3.09 (t, *J* = 7.3 Hz, 2H), 2.93 (s, 3H), 2.27 (quin, *J* = 7.0 Hz, 2H).

Example 111: 3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile (Compound 130) and 4-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol (Compound 131)



Step 1: 3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile (Compound 130)

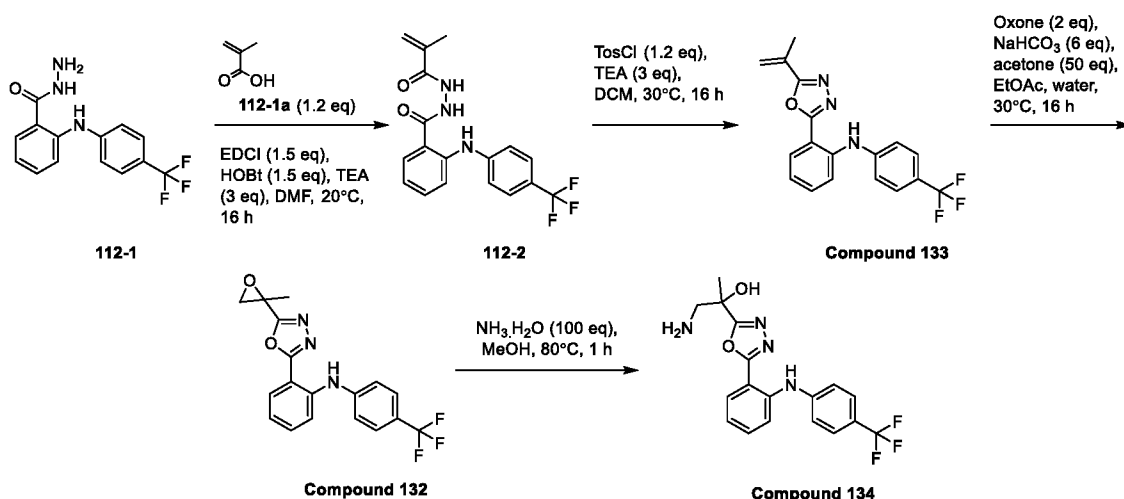
[00462] To a solution of **Compound 132** (25 mg, 69.2 μ mol, 1 *eq*) in dioxane (2 mL) at 30°C was added TMSCN (13.7 mg, 0.14 mmol, 17 μ L, 2 *eq*) and then TBAF (1 M, 0.21 mL, 3 *eq*), and the resulting mixture was stirred at 30°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 130** (20.0 mg, 50.2 μ mol, 72.5% yield). LCMS (ESI): RT = 0.841 min, mass calc. for C₁₉H₁₅F₃N₄O₂ 388.11, m/z found 388.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.36 (s, 1H), 7.91 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 - 7.49 (m, 1H), 7.42 (dt, *J* = 1.4, 7.8 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.97 (m, 1H), 3.44 (brs, 1H), 3.17 (q, *J* = 16.8 Hz, 2H), 1.95 (s, 3H).

Step 2: 4-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol (Compound 131)

[00463] To a solution of **Compound 130** (140 mg, 0.36 mmol, 1 *eq*) in MeOH (3 mL) at 0°C was added NiCl₂·6H₂O (685.5 mg, 2.88 mmol, 8 *eq*) and then NaBH₄ (109.1 mg, 2.88 mmol, 8 *eq*), and the resulting mixture was stirred at 0°C for 2 h. After quenched with saturated NH₄Cl solution (20 mL) at 0°C, it was stirred at 30°C for 16 h. The mixture was concentrated to give a residue. The

residue was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. The collected pure fractions was basified with saturated NaHCO₃ solution to pH = 8-9, then concentrated to remove ACN and then extracted with EA (50 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 131** (45.0 mg, 0.11 mmol, 31.8% yield). LCMS (ESI): RT = 0.705 min, mass calc. for C₁₉H₁₉F₃N₄O₂ 392.15, m/z found 393.0 [M+1]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.73 (d, *J* = 6.9 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.48 - 7.44 (m, 1H), 7.42 - 7.36 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 3.48 (brs, 1H), 3.40 - 3.32 (m, 1H), 2.12 (d, *J* = 6.4 Hz, 2H), 1.50 (s, 3H).

Example 112: 2-(5-(2-methyloxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 132), 2-(5-(prop-1-en-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 133), and 1-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol (Compound 134)



Step 1: *N'*-methacryloyl-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00464] To a solution of **112-1a** (174.9 mg, 2.03 mmol, 0.17 mL, 1.2 eq), EDCI (487.0 mg, 2.54 mmol, 1.5 eq) and HOBt (343.2 mg, 2.54 mmol, 1.5 eq) in DMF (10 mL) at 20°C was added **112-1** (500 mg, 1.69 mmol, 1 eq) and then TEA (514.1 mg, 5.08 mmol, 0.71 mL, 3 eq), and the mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **112-2** (440 mg, 1.17 mmol, 69.2% yield). LCMS (ESI): RT = 0.783 min, mass calc. for C₁₈H₁₆F₃N₃O₂ 363.12, m/z found 363.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.18 (s, 1H), 9.02 (brs, 1H), 8.72 (brs,

1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 2H), 7.48 - 7.44 (m, 1H), 7.43 - 7.38 (m, 1H), 7.24 (d, $J = 8.3$ Hz, 2H), 6.94 (t, $J = 7.5$ Hz, 1H), 5.95 (s, 1H), 5.53 (s, 1H), 2.06 (s, 3H).

Step 2: 2-(5-(prop-1-en-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 133)

[00465] To a solution of **112-2** (200 mg, 0.55 mmol, 1 *eq*) and TEA (167.1 mg, 1.65 mmol, 0.23 mL, 3 *eq*) in DCM (3 mL) at 30°C was added TosCl (125.9 mg, 0.66 mmol, 1.2 *eq*), and the mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 133** (120 mg, 0.34 mmol, 61.2% yield). LCMS (ESI): RT = 0.978 min, mass calc. for C₁₈H₁₄F₃N₃O 345.11, m/z found 345.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.62 (s, 1H), 7.94 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.03 - 6.95 (m, 1H), 6.13 (s, 1H), 5.63 (d, $J = 0.6$ Hz, 1H), 2.30 (s, 3H).

Step 3: 2-(5-(2-methyloxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 132)

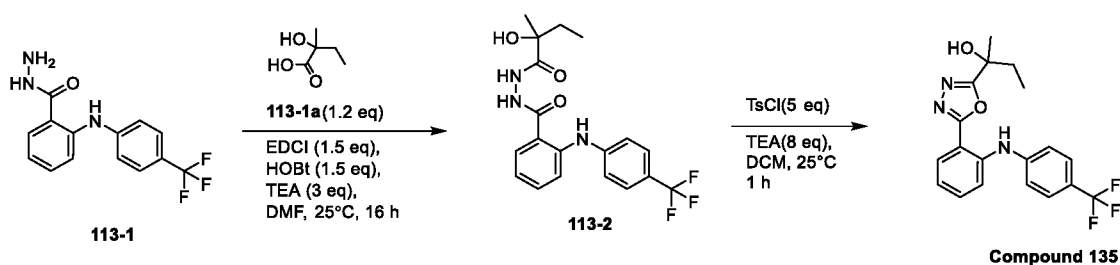
[00466] To a solution of **Compound 133** (120 mg, 0.35 mmol, 1 *eq*) and NaHCO₃ (175.2 mg, 2.09 mmol, 81 μ L, 6 *eq*) in water (2 mL) and EtOAc (2 mL) at 30°C was added acetone (1.01 g, 17.38 mmol, 1.28 mL, 50 *eq*) and then Oxone (427.3 mg, 0.70 mmol, 2 *eq*), and the mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 132** (35.0 mg, 95.3 μ mol, 27.4% yield). LCMS (ESI): RT = 0.914 min, mass calc. for C₁₈H₁₄F₃N₃O₂ 361.10, m/z found 361.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.85 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 7.8$ Hz, 1H), 7.40 (dt, $J = 1.5, 7.9$ Hz, 1H), 7.36 (d, $J = 8.3$ Hz, 2H), 6.97 (ddd, $J = 1.1, 7.2, 8.0$ Hz, 1H), 3.54 (d, $J = 5.5$ Hz, 1H), 3.16 (d, $J = 5.0$ Hz, 1H), 1.94 (s, 3H).

Step 4: 1-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol (Compound 134)

[00467] To a solution of **Compound 132** (30 mg, 83.0 μ mol, 1 *eq*) in MeOH (1 mL) at 30°C was added NH₃.H₂O (1.16 g, 8.30 mmol, 1.28 mL, 25% solution, 100 *eq*), and the mixture was stirred at 80°C for 1 h. The reaction mixture was concentrated under reduced pressure to give **Compound 134** (23.0 mg, 60.8 μ mol, 73.2% yield). LCMS (ESI): RT = 0.718 min, mass calc. for

$C_{18}H_{17}F_3N_4O_2$ 378.13, m/z found 379.0 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.93 (d, $J = 7.0$ Hz, 1H), 7.56 (d, $J = 8.3$ Hz, 2H), 7.49 (d, $J = 8.3$ Hz, 1H), 7.41 - 7.36 (m, 1H), 7.33 (d, $J = 8.5$ Hz, 2H), 6.96 (t, $J = 7.4$ Hz, 1H), 3.59 (d, $J = 12.5$ Hz, 1H), 2.89 (d, $J = 12.5$ Hz, 1H), 2.72 (brs, 3H), 1.66 (s, 3H).

Example 113: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol (Compound 135)



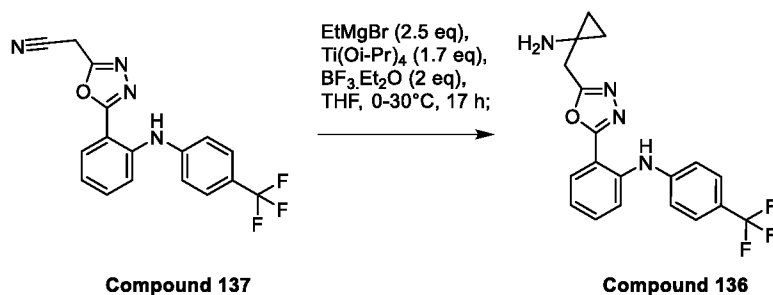
Step 1: N'-(2-hydroxy-2-methylbutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00468] To a solution of 2-hydroxy-2-methyl-butanoic acid **113-1a** (48.0 mg, 0.41 mmol, 1.2 *eq*), EDCI (97.39 mg, 508.04 μ mol, 1.5 *eq*) and TEA (102.8 mg, 1.02 mmol, 0.14 mL, 3 *eq*) in DMF (1.5 mL) at 25°C were added **113-1** (100 mg, 0.34 mmol, 1 *eq*) and then HOBt (68.6 mg, 0.51 mmol, 1.5 *eq*) and the resulting mixture was stirred at 25°C for 16 h. The mixture was directly purified by prep-HPLC to give **113-2** (30 mg, 75.88 μ mol, 22.40% yield). LCMS (ESI): $R = 0.775$ min, mass calcd. For $C_{19}H_{20}F_3N_3O_3$ 418.0 found $[M+23]^+$.

Step 2: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol

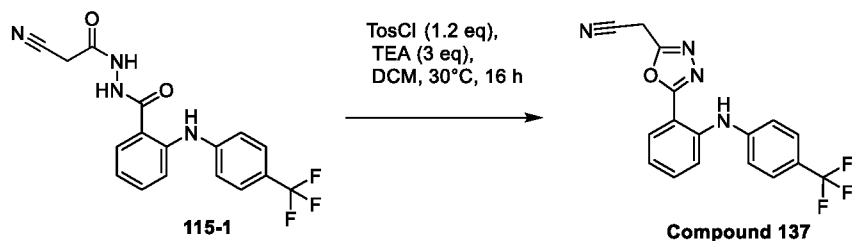
[00469] To a solution of compound **113-2** (25 mg, 63.2 μ mol, 1 *eq*) and TosCl (60.3 mg, 0.32 mmol, 5 *eq*) in DCM (3 mL) was added TEA (51.2 mg, 0.51 mmol, 70 μ L, 8 *eq*) at 25°C and the resulting mixture was stirred at 25°C for 1 h. The mixture was diluted with water (5 mL) and then diluted with EA (30 mL) and separated. The separated organic layer was washed with brine (10 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated under pressure to give a residue. The residue was directly purified by prep-HPLC to give **Compound 135** (7.7 mg, 20.54 μ mol, 32.48% yield). LCMS (ESI): $R = 0.898$ min, mass calcd. For $C_{19}H_{18}F_3N_3O_2$ 377.14 m/z found 377.9 $[M+1]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.24 (s, 1H), 7.94 (d, $J = 7.9$ Hz, 1H), 7.63 (d, $J = 8.6$ Hz, 2H), 7.59 - 7.51 (m, 2H), 7.33 (d, $J = 8.5$ Hz, 2H), 7.22 - 7.11 (m, 1H), 5.97 - 5.79 (m, 1H), 1.96 - 1.80 (m, 2H), 1.63 - 1.45 (m, 3H), 0.83 (t, $J = 7.4$ Hz, 3H).

Example 114: 2-(5-((1-aminocyclopropyl)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 136)



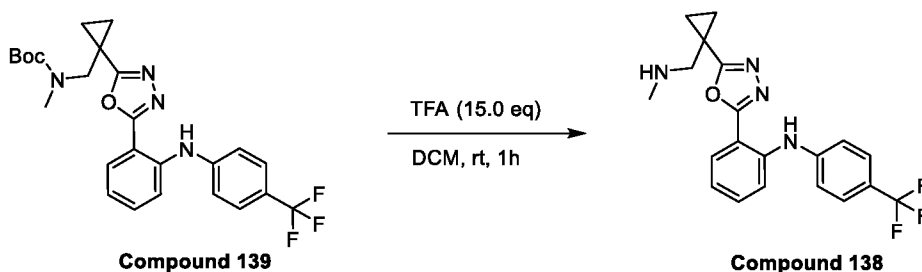
[00470] To a solution of **Compound 137** (50 mg, 0.15 mmol, 1 *eq*) in THF (1 mL) at 0°C were added Ti(*i*-PrO)₄ (70.2 mg, 0.25 mmol, 73 μ L, 1.7 *eq*) and then EtMgBr (3.0 M, 0.12 mL, 2.5 *eq*), and the mixture was stirred at 30°C for 1 h. After BF₃.Et₂O (137.4 mg, 0.29 mmol, 0.12 mL, 30% solution, 2 *eq*) was added at 0°C into the above mixture, the resulting mixture was stirred at 30°C for 16 h. The mixture was quenched with water (1 mL), diluted with saturated Na₂CO₃ solution (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 136** (5.0 mg, 12.6 μ mol, 8.6% yield). LCMS (ESI): RT = 0.739 min, mass calc. for C₁₉H₁₇F₃N₄O 374.14, m/z found 375.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H), 7.91 (s, 1H), 7.60 (d, *J* = 7.0 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.45 - 7.36 (m, 3H), 7.02 (s, 1H), 3.08 (brs, 2H), 0.83 (brs, 4H).

Example 115: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetonitrile (Compound 137)



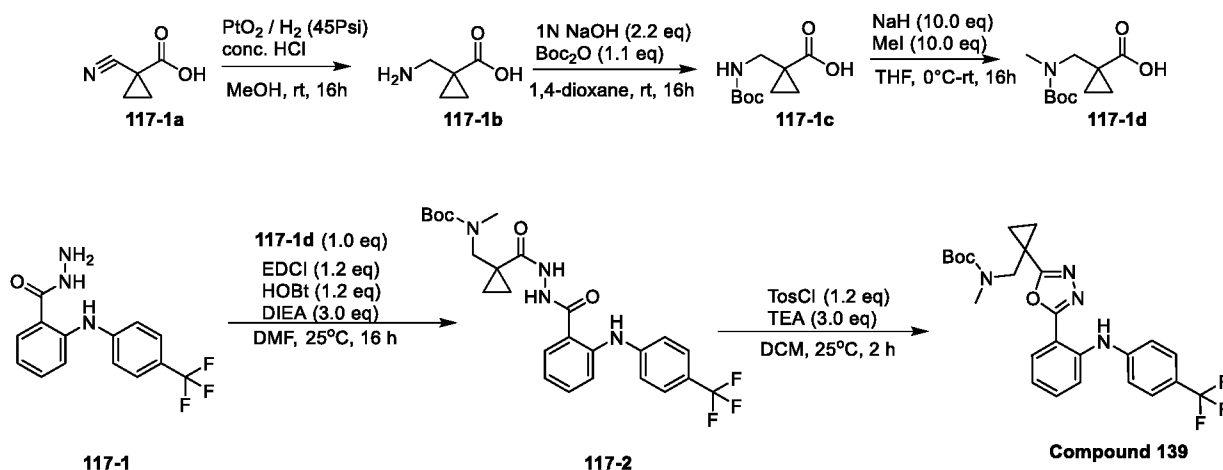
[00471] To a solution of **115-1** (350 mg, 0.97 mmol, 1 *eq*) and TEA (293.3 mg, 2.90 mmol, 0.40 mL, 3 *eq*) in DCM (5 mL) at 30°C was added TosCl (221.0 mg, 1.16 mmol, 1.2 *eq*), and the resulting mixture was stirred at 30°C for 16 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 137** (160 mg, 0.46 mmol, 48.1% yield). LCMS (ESI): RT = 0.857 min, mass calc. for C₁₇H₁₁F₃N₄O 344.09, m/z found 344.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.33 (s, 1H), 7.90 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.53 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.03 - 6.97 (m, 1H), 4.17 (s, 2H).

Example 116: 2-(5-(1-((methylamino)methyl)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 138)



[00472] To a solution of **Compound 139** (0.2 g, 0.4 mmol, 1 *eq*) in DCM (2 mL) was added TFA (700 mg, 6.14 mmol, 0.45 mL, 15 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) adjusted pH to 8-9 with Sat. Na₂CO₃ and washed with H₂O (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. **Compound 138** (120 mg, 0.3 mmol, 74% yield) was obtained without further purification. LCMS (ESI): RT = 0.836 min, mass calc. for C₂₀H₁₉F₃N₄O 388.15, m/z found 389.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 7.71 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.34 - 7.24 (m, 3H), 6.88 (t, *J* = 7.6 Hz, 1H), 2.94 (s, 2H), 2.46 - 2.39 (m, 3H), 1.40 - 1.31 (m, 2H), 1.12 - 1.04 (m, 2H).

Example 117: tert-butyl methyl((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)carbamate (Compound 139)



Step 1: 1-(aminomethyl)cyclopropanecarboxylic acid

[00473] To a solution of compound **117-1a** (1 g, 9 mmol, 1 *eq*) and HCl (12 M, 0.5 mL) in MeOH (40 mL) was added PtO₂ (0.3 g, 0.26 mmol, 2.94e-2 *eq*) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (45psi) at 25°C for 16 hours. The reaction was filtered and concentrated. Compound **117-1b** (1.2 g, 7.92 mmol, 87.9% yield, HCl) was used for next step directly. ¹H NMR (400 MHz, CD₃OD) δ 3.33 (td, *J* = 1.6, 3.3 Hz, 2H), 3.04 (s, 3H), 1.32 - 1.25 (m, 3H), 0.93 - 0.84 (m, 3H).

Step 2: 1-[(tert-butoxycarbonylamino)methyl]cyclopropanecarboxylic acid

[00474] A solution of compound **117-1b** (1.2 g, 7.9 mmol, 1 *eq*, HCl) and NaOH (1 M, 17 mL, 2.2 *eq*) in 1,4-dioxane (25 mL) was stirred at 25°C for 15 min. Boc₂O (1.9 g, 8.7 mmol, 2 mL, 1.1 *eq*)

was added to the solution. The reaction was stirred at 25°C for 16 hr. 1,4-dioxane was removed. The aqueous layer was adjusted pH to 3 with Sat. citric acid and extracted with EA (2*40 mL). The organic layer was dried over Na₂SO₄ and concentrated. Compound **117-1c** (1.5 g, 6.97 mmol, 88% yield) was used for next step directly. ¹H NMR (400 MHz, CD₃OD) δ 3.30 (s, 2H), 1.45 (s, 9H), 1.21 - 1.13 (m, 2H), 0.95 - 0.90 (m, 2H).

Step 3: 1-[[tert-butoxycarbonyl(methyl)amino]methyl]cyclopropanecarboxylic acid

[00475] To a solution of compound **117-1c** (0.7 g, 3.2 mmol, 1 *eq*) and MeI (4.6 g, 32.5 mmol, 2 mL, 10 *eq*) in THF (15 mL) was added NaH (1.30 g, 32.52 mmol, 60% purity, 10 *eq*) in portions at 0°C. The reaction was stirred at 25°C for 16 hr. The precipitate was formed. PE (15 mL) was added. The reaction was washed with water (2*20 mL). The aqueous layer was adjusted pH to 4 with Sat. citric acid and extracted with EA (2*30 mL). The organic layer was dried over Na₂SO₄ and concentrated. The compound **117-1d** (0.45 g, 1.9 mmol, 60% yield) was used for next step directly. ¹H NMR (400 MHz, CDCl₃) δ 3.58 (s, 2H), 2.92 (s, 3H), 1.46 (s, 9H), 1.40 - 1.25 (m, 2H), 1.10 - 1.00 (m, 2H).

Step 4: tert-butyl N-methyl-N-[[1-[[[2-[4-

(trifluoromethyl)anilino]benzoyl]amino]carbonyl]cyclopropyl]methyl]carbamate

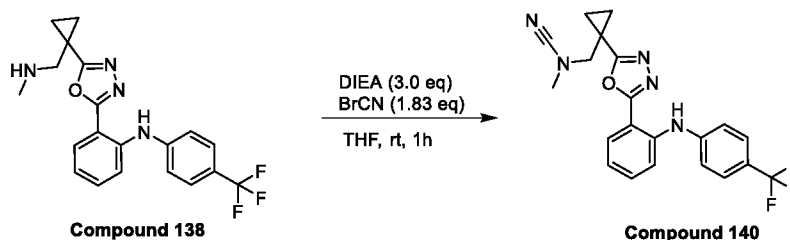
[00476] To a solution of compound **117-1** (300 mg, 1 mmol, 1 *eq*), HOBt (164.7 mg, 1.2 mmol, 1.2 *eq*) and EDCI (233.7 mg, 1.22 mmol, 1.2 *eq*) in DMF (5 mL) was added compound **117-1d** (232.9 mg, 1 mmol, 1 *eq*) followed by DIEA (393.9 mg, 3.05 mmol, 0.53 mL, 3 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was diluted with EA (60 mL) and washed with brine (2*20 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give compound **117-2** (360 mg, 0.68 mmol, 67% yield). LCMS confirmed that desired product was obtained. LCMS (ESI): RT = 1.018 min, mass calc. for C₂₅H₂₉F₃N₄O₄ 506.21, m/z found 507.1 [M+1]⁺.

Step 5: tert-butyl methyl((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)carbamate

[00477] To a solution of compound **117-2** (0.36 g, 0.71 mmol, 1 *eq*) and TosCl (162.6 mg, 0.85 mmol, 1.2 *eq*) in DCM (8 mL) was added DIEA (275.5 mg, 2.13 mmol, 0.37 mL, 3 *eq*). The reaction was stirred at 25°C for 2 hr. The reaction was diluted with DCM (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The reaction was purified by column chromatography on silica gel to give **Compound 139** (0.27 g, 0.55 mmol, 76.9% yield). LCMS (ESI): RT = 1.131 min, mass calc. for C₂₅H₂₇F₃N₄O₃ 488.20, m/z found 489.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (br s, 1H), 7.88 (br s, 1H), 7.59 (d, *J* = 8.5 Hz, 2H),

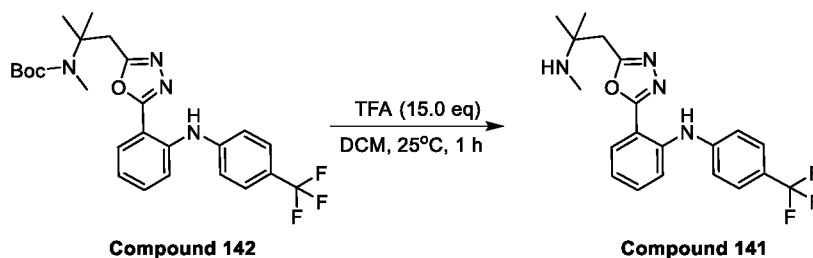
7.55 - 7.50 (m, 1H), 7.44 - 7.33 (m, 3H), 6.98 (t, $J = 7.4$ Hz, 1H), 3.90 - 3.79 (m, 2H), 2.99 (s, 3H), 1.44 (s, 11H), 1.31 - 1.19 (m, 2H).

Example 118: N-methyl-N-((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)cyanamide (Compound 140)



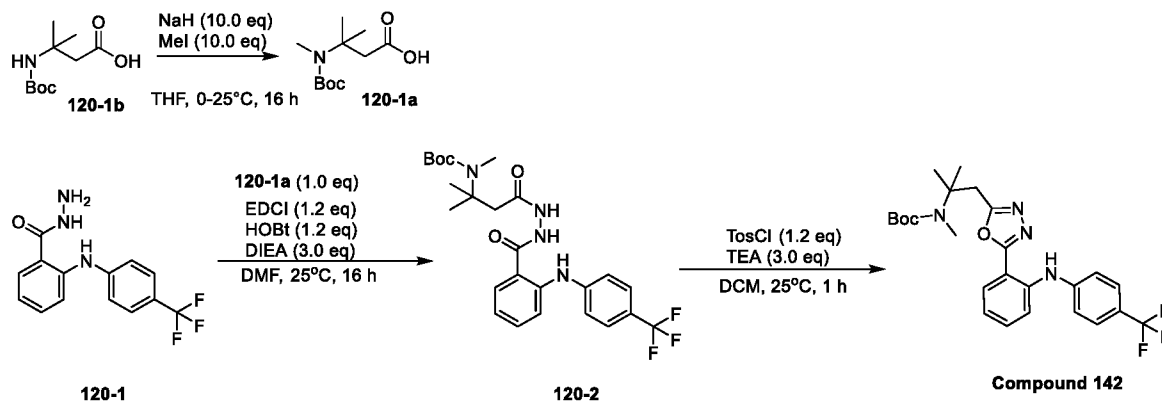
[00478] To a solution of **Compound 138** (0.1 g, 0.25 mmol, 1 *eq*) and DIEA (99.8 mg, 0.77 mmol, 0.13 mL, 3 *eq*) in THF (2 mL) was added BrCN (50 mg, 0.47 mmol, 34 μ L, 1.83 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with EA (30 mL) and washed with brine (3*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was triturated with EA (3 mL) and PE (10 mL), filtered to give **Compound 140** (60.5 mg, 0.14 mmol, 54.5% yield). LCMS (ESI): RT = 1.002 min, mass calc. for C₂₁H₁₈F₃N₅O 413.15, m/z found 414.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.36 (s, 1H), 7.76 (dd, $J = 1.2, 7.9$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 1H), 7.35 - 7.25 (m, 3H), 6.90 (t, $J = 7.4$ Hz, 1H), 3.44 (s, 2H), 2.99 (s, 3H), 1.50 - 1.40 (m, 2H), 1.31 - 1.18 (m, 2H).

Example 119: 2-(5-(2-methyl-2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 141)



[00479] To a solution of **Compound 142** (70 mg, 0.14 mmol, 1 *eq*) in DCM (2 mL) was added TFA (244 mg, 2.1 mmol, 0.15 mL, 15 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (5 mL) and washed with water (10 mL). The aqueous layer was adjusted pH to 8-9 with Sat. Na₂CO₃ and extracted with EA (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. 60 mg of crude **Compound 141** was obtained. 20 mg of crude product was purified by prep-HPLC to give pure **Compound 141** (1.9 mg, 4.8 μ mol, 3% yield). LCMS (ESI): RT = 0.847 min, mass calc. for C₂₀H₂₁F₃N₄O 390.17, m/z found 391.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H), 7.89 (d, $J = 6.8$ Hz, 1H), 7.60 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.44 - 7.36 (m, 3H), 6.99 (t, $J = 7.2$ Hz, 1H), 3.09 (s, 2H), 2.47 (s, 3H), 1.27 (s, 6H). 40 mg of remained crude product was used directly in the synthesis of **Compound 143**.

Example 120: tert-butyl methyl(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate (Compound 142)



Step 1: 3-[tert-butoxycarbonyl(methyl)amino]-3-methyl-butanoic acid

[00480] To a solution of **120-1b** (0.3 g, 1.3 mmol, 1 *eq*) and MeI (1.9 g, 13 mmol, 0.86 mL, 10 *eq*) in THF (8 mL) was added NaH (551.9 mg, 13.8 mmol, 60% purity, 10 *eq*) at 0°C. The reaction was warmed to 25°C and stirred at 25°C for 16 hr. PE (10 mL) was added to the solution. The reaction was washed with water (2*10 mL). The aqueous layer was adjusted pH to 4-5 with Sat. citric acid solution and extracted with EA (2*15 mL). The organic layer was dried over Na₂SO₄ and concentrated. Compound **120-1a** (140 mg, 0.6 mmol, 43% yield) was used for next step directly. ¹H NMR (400 MHz, CDCl₃) δ 2.88 (s, 2H), 2.79 (s, 3H), 1.37 (s, 9H), 1.37 (s, 6H).

Step 2: tert-butyl N-[1,1-dimethyl-3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]-N-methyl-carbamate

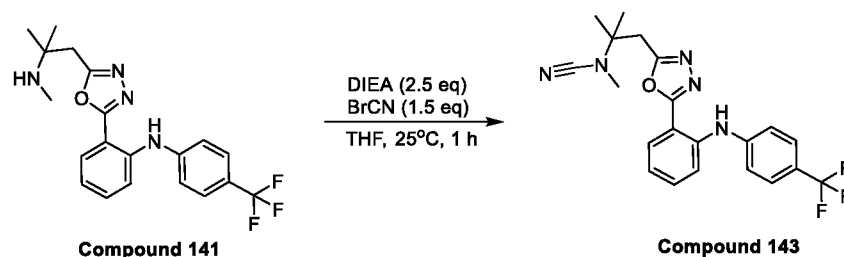
[00481] To a solution of **120-1** (178.7 mg, 0.6 mmol, 1 *eq*), **120-1a** (140 mg, 0.6 mmol, 1 *eq*), EDCI (139.2 mg, 0.72 mmol, 1.2 *eq*) and HOBt (98 mg, 0.72 mmol, 1.2 *eq*) in DMF (5 mL) was added DIEA (234 mg, 1.82 mmol, 0.31 mL, 3 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give **120-2** (170 mg, 0.29 mmol, 49% yield). LCMS (ESI): RT = 1.018 min, mass calc. for C₂₅H₃₁F₃N₄O₄ 508.23, m/z found 509.1 [M+1]⁺.

Step 3: tert-butyl methyl(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate

[00482] To a solution of **120-2** (170 mg, 0.33 mmol, 1 *eq*) and TosCl (76.4 mg, 0.4 mmol, 1.2 *eq*) in DCM (4 mL) was added Et₃N (101 mg, 1 mmol, 0.13 mL, 3 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) and washed with H₂O (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give crude **Compound 142** (90 mg). 20 mg of crude product was re-purified by prep-HPLC to give **Compound 142** (10.2 mg, 20.7 μmol, 6.2% yield). LCMS (ESI):

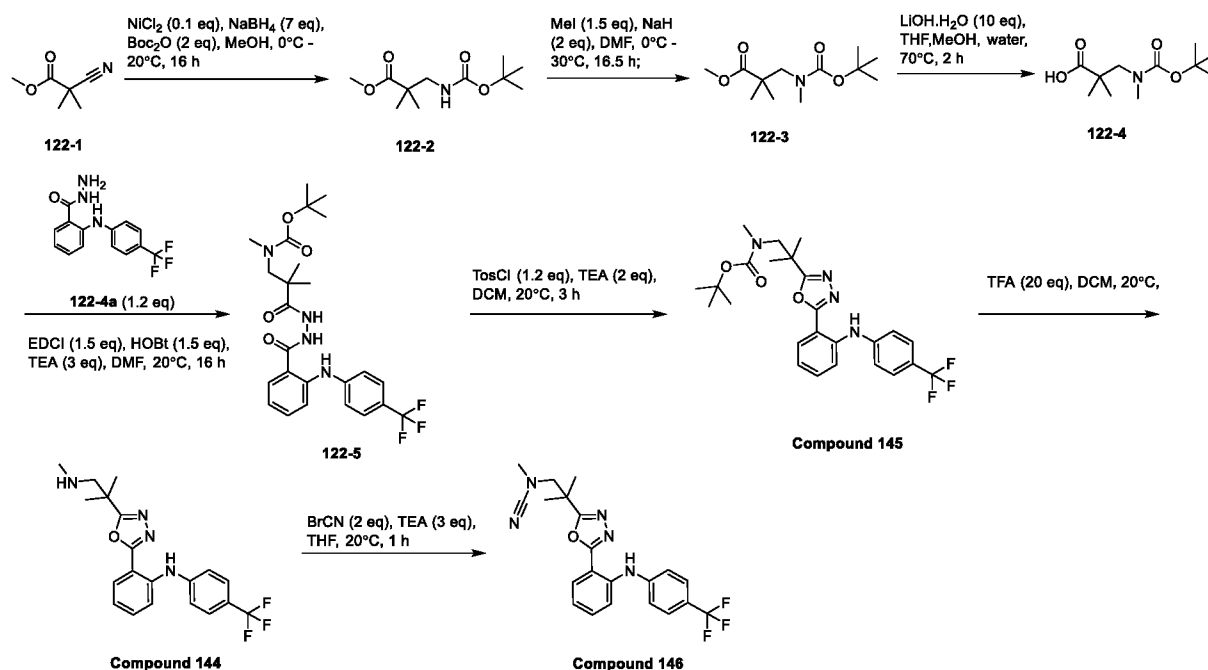
RT = 1.148 min, mass calc. for $C_{25}H_{29}F_3N_4O_3$ 490.22, m/z found 491.1 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.89 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.3$ Hz, 1H), 7.43 - 7.32 (m, 3H), 6.96 (t, $J = 7.2$ Hz, 1H), 3.60 (s, 2H), 2.78 (s, 3H), 1.54 (s, 6H), 1.53 (s, 9H).

Example 121: N-methyl-N-(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide (Compound 143)



[00483] To a solution of **Compound 141** (30 mg, 76 μmol , 1 eq) and DIEA (24.8 mg, 0.19 mmol, 33 μL , 2.5 eq) in THF (2 mL) was added BrCN (12 mg, 0.11 mmol, 8 μL , 1.5 eq). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with EA (20 mL) and washed with H_2O (2*10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was triturated with MeOH (5 mL) and filtered to give **Compound 143** (16.8 mg, 40 μmol , 52% yield). LCMS (ESI): RT = 0.993 min, mass calc. for $C_{21}H_{20}F_3N_5O$ 415.16, m/z found 416.1 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.3$ Hz, 1H), 7.44 - 7.32 (m, 3H), 6.99 (t, $J = 7.7$ Hz, 1H), 3.24 (s, 2H), 2.95 (s, 3H), 1.50 (s, 6H).

Example 122: 2-(5-(2-methyl-1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 144), tert-butyl methyl(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 145), and N-methyl-N-(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 146)



Step 1: methyl 3-((tert-butoxycarbonyl)amino)-2,2-dimethylpropanoate

[00484] To a solution of **122-1** (2.0 g, 15.73 mmol, 1 eq), $(\text{Boc})_2\text{O}$ (6.87 g, 31.46 mmol, 7.23 mL, 2 eq) and NiCl_2 (203.9 mg, 1.57 mmol, 0.1 eq) in MeOH (40 mL) at 0°C was added NaBH_4 (4.17 g, 110.11 mmol, 7 eq) slowly portion-wise, and the resulting mixture was stirred at 20°C for 16 h. The reaction mixture was quenched with $\text{NH}_4\cdot\text{H}_2\text{O}$ (10 mL), and then concentrated to remove solvent. And the residue was diluted with water (50 mL), and then extracted with EA (50 mL *3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **122-2** (600 mg, 2.59 mmol, 16.5% yield). ^1H NMR (400 MHz, CDCl_3) δ 4.97 (brs, 1H), 3.69 (s, 3H), 3.24 (d, J = 6.6 Hz, 2H), 1.44 (s, 9H), 1.19 (s, 6H).

Step 2: methyl 3-((tert-butoxycarbonyl)(methyl)amino)-2,2-dimethylpropanoate

[00485] To a solution of **122-2** (300 mg, 1.30 mmol, 1 eq) in DMF (3 mL) at 0°C was added NaH (103.8 mg, 2.59 mmol, 60% purity, 2 eq) slowly portion-wise, and then the mixture was stirred at 0°C for 0.5 h. And then iodomethane (276.2 mg, 1.95 mmol, 0.12 mL, 1.5 eq) was added drop-wise into the above mixture at 0°C , and the resulting mixture was stirred at 30°C for 16 h. The reaction mixture was quenched with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **122-3** (120 mg, 0.44 mmol, 33.9% yield). ^1H NMR (400 MHz, CDCl_3) δ 3.69 (s, 3H), 3.45 (s, 2H), 2.80 (s, 3H), 1.45 (s, 9H), 1.19 (s, 6H).

Step 3: 3-((tert-butoxycarbonyl)(methyl)amino)-2,2-dimethylpropanoic acid

[00486] To a solution of **122-3** (120 mg, 0.49 mmol, 1 *eq*) in THF (2 mL) and MeOH (2 mL) at 20°C was added LiOH.H₂O (205.3 mg, 4.89 mmol, 10 *eq*) in water (2 mL), and then the mixture was stirred at 70°C for 2 h. The reaction mixture was quenched with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **122-4** (110 mg, 0.43 mmol, 87.5% yield). ¹H NMR (400 MHz, CDCl₃) δ 3.48 (s, 2H), 2.88 (s, 3H), 1.45 (s, 9H), 1.22 (s, 6H).

Step 4: tert-butyl (2,2-dimethyl-3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propyl)(methyl)carbamate

[00487] To a solution of **122-4** (100 mg, 0.43 mmol, 1 *eq*), EDCI (124.3 mg, 0.65 mmol, 1.5 *eq*) and HOBt (87.6 mg, 0.65 mmol, 1.5 *eq*) in DMF (2 mL) at 20°C was added **122-4a** (153.2 mg, 0.52 mmol, 1.2 *eq*) and then TEA (131.3 mg, 1.30 mmol, 0.18 mL, 3 *eq*), and the mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **122-5** (310 mg, 0.41 mmol, 95.9% yield), which was used directly for next step. LCMS (ESI): RT = 0.875 min, mass calc. for C₂₅H₃₁F₃N₄O₄ 508.23, m/z found 531.1 [M+23]⁺.

Step 5: tert-butyl methyl(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 145)

[00488] To a solution of **122-5** (300 mg, 0.40 mmol, 1 *eq*) and TEA (81.2 mg, 0.80 mol, 0.11 mL, 2 *eq*) in DCM (1 mL) at 20°C was added TosCl (91.8 mg, 0.48 mmol, 1.2 *eq*), and the mixture was stirred at 20°C for 3 h. The reaction mixture was combined with that of ES8223-478, and then was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EA = 5:1, UV) to give **Compound 145** (140 mg, 0.28 mmol, 70.4% yield). LCMS (ESI): RT = 1.008 min, mass calc. for C₂₅H₂₉F₃N₄O₃ 490.22, m/z found 513.0 [M+23]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.56 (brs, 1H), 7.89 (brs, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.99 (t, *J* = 7.0 Hz, 1H), 3.60 (s, 2H), 2.81 - 2.74 (m, 3H), 1.53 (s, 6H), 1.36 (s, 9H).

Step 6: 2-(5-(2-methyl-1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 144)

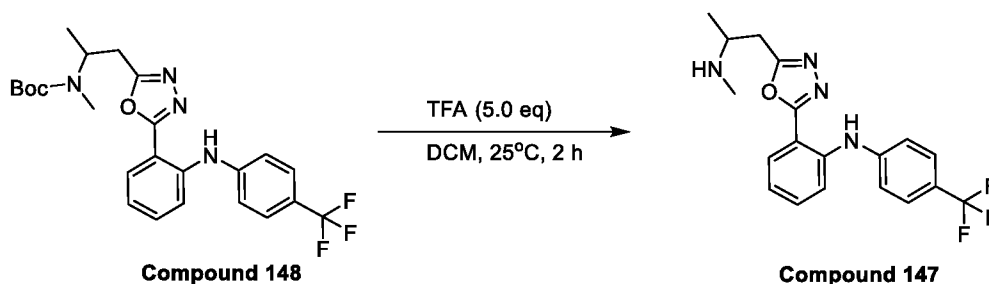
[00489] To a solution of **Compound 145** (130 mg, 0.27 mmol, 1 *eq*) in DCM (2 mL) at 20°C was added TFA (604.4 mg, 5.30 mmol, 0.39 mL, 20 *eq*), and the mixture was stirred at 20°C for 1 h. The mixture was concentrated to remove solvent. The residue was diluted with saturated Na₂CO₃

solution (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 144** (100 mg, 0.25 mmol, 93.9% yield), which was used directly for next step. LCMS (ESI): RT = 0.752 min, mass calc. for C₂₀H₂₁F₃N₄O 390.17, m/z found 391.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.44 (s, 1H), 7.88 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 3.14 (s, 2H), 2.63 (s, 3H), 1.56 (s, 6H).

Step 7: N-methyl-N-(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 146)

[00490] To a solution of **Compound 144** (50 mg, 0.13 mmol, 1 *eq*) and TEA (38.9 mg, 0.38 mmol, 53 uL, 3 *eq*) in THF (2 mL) at 20°C was added BrCN (27.1 mg, 0.26 mmol, 19 uL, 2 *eq*), and the mixture was stirred at 20°C for 1 h. The residue was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 146** (13.0 mg, 31.3 umol, 24.4% yield). LCMS (ESI): RT = 0.895 min, mass calc. for C₂₁H₂₀F₃N₅O 415.16, m/z found 437.9 [M+23]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 7.90 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.96 (m, 1H), 3.44 (s, 2H), 2.89 (s, 3H), 1.60 (s, 6H).

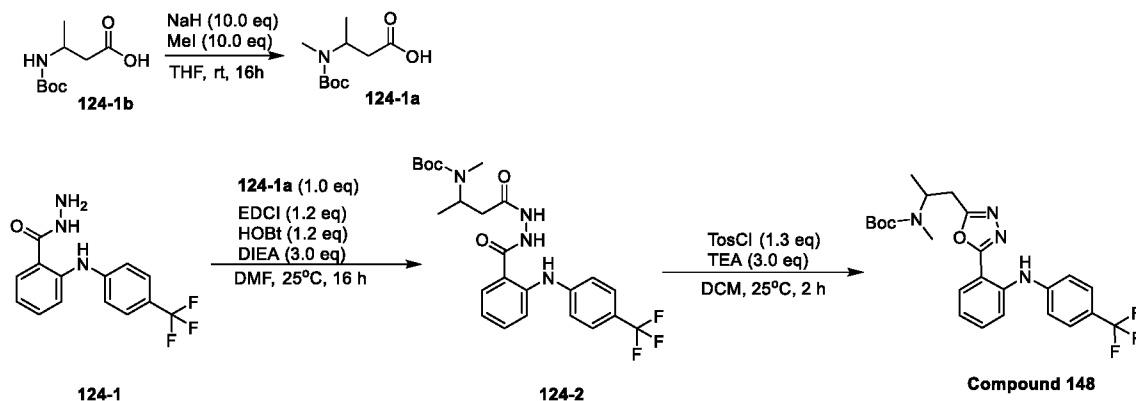
Example 123: 2-(5-(2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 147)



[00491] To a solution of **Compound 148** (130 mg, 0.27 mmol, 1 *eq*) in DCM (3 mL) was added TFA (155.5 mg, 1.36 mmol, 0.1 mL, 5 *eq*). The reaction was stirred at 25°C for 2 hr. The reaction was adjusted pH to 8-9 with sat. Na₂CO₃ and extracted with DCM (2*15 mL). The organic layer was dried over Na₂SO₄ and concentrated. 80 mg of crude product was obtained. Crude **Compound 147** (60 mg, 0.14 mmol, 52% yield) was used for next step directly. 20 mg of crude product was purified by prep-HPLC to give **Compound 147** (4.2 mg, 11 umol, 4% yield). LCMS and ¹H NMR confirmed that desired product was obtained. LCMS (ESI): RT = 0.831 min, mass calc. for C₁₉H₁₉F₃N₄O 376.18, m/z found 377.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.53 (s, 1H), 7.88

(d, $J = 7.03$ Hz, 1H), 7.58 (d, $J = 8.53$ Hz, 2H), 7.52 (d, $J = 8.53$ Hz, 1H), 7.32 - 7.43 (m, 3H), 6.98 (t, $J = 7.40$ Hz, 1H), 3.15 - 3.24 (m, 1H), 2.97 - 3.13 (m, 2H), 1.24 (d, $J = 6.27$ Hz, 3 H).

Example 124: tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate (Compound 148)



Step 1: 3-[tert-butoxycarbonyl(methyl)amino]butanoic acid

[00492] To a solution of compound **124-1b** (0.2 g, 1 mmol, 1 *eq*) and MeI (1.4 g, 10.3 mmol, 0.64 mL, 10 *eq*) in THF (8 mL) was added NaH (411.9 mg, 10.3 mmol, 60% purity, 10 *eq*) at 0°C. The reaction was warmed to 25°C and stirred at 25°C for 16 hr. The reaction was quenched by PE (10 mL). The aqueous layer was adjusted pH to 4-5 with Sat. Citric acid and extracted with EA (2*20 mL). The organic layer was dried over Na₂SO₄ and concentrated to give **124-1a** (0.22 g, 1 mmol, 98% yield), which was used for next step directly. ¹H NMR (400 MHz, CDCl₃) δ 4.44 (br, 1H), 2.66 (s, 3H), 2.51 (dd, $J = 15.06, 8.03$ Hz, 1H), 2.35 (dd, $J = 15.06, 6.53$ Hz, 1H), 1.36 (s, 9H), 1.11 (d, $J = 6.78$ Hz, 3H).

Step 2: tert-butyl N-methyl-N-[1-methyl-3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]carbamate

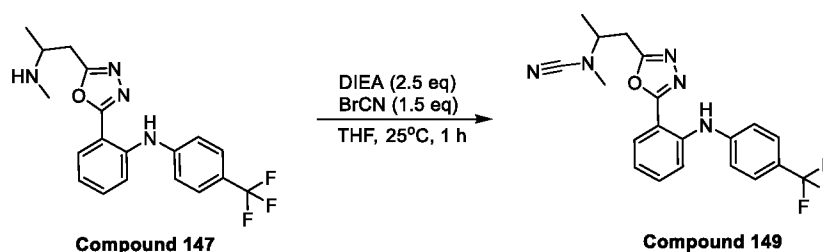
[00493] To a mixture of compound **124-1** (300 mg, 1 mmol, 1 *eq*) and compound **124-1a** (220.7 mg, 1.0 mmol, 1 *eq*) and EDCI (233.7 mg, 1.2 mmol, 1.2 *eq*) in DMF (6 mL) was added HOBt (164.7 mg, 1.2 mmol, 1.2 *eq*), followed by DIEA (393.9 mg, 3 mmol, 0.53 mL, 3 *eq*). The mixture was stirred at 25 °C for 16 hr. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give compound **124-2** (340 mg, 0.6 mmol, 62% yield). LCMS (ESI): RT = 0.962 min, mass calc. for C₂₄H₂₉F₃N₄O₄ 494.21, m/z found 495.1 [M+1]⁺.

Step 3: tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate

[00494] To a solution of compound **124-2** (200 mg, 0.4 mmol, 1 *eq*) in DCM (3 mL) was added TEA (122.7 mg, 1.2 mmol, 0.17 mL, 3 *eq*) followed by TosCl (100 mg, 0.5 mmol, 1.3 *eq*). The reaction was stirred at 25°C for 2 hr. The reaction was diluted with DCM (20 mL) and washed with

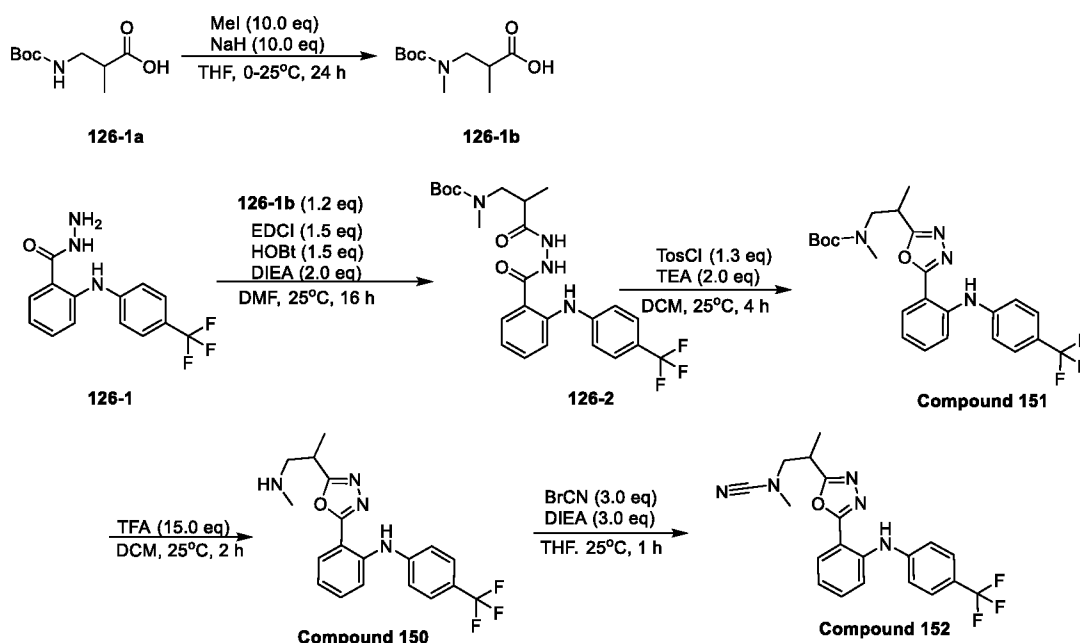
H₂O (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated to give **Compound 148** (130 mg, 0.25 mmol, 62% yield), which was used for next step directly. LCMS (ESI): RT = 1.091 min, mass calc. for C₂₄H₂₇F₃N₄O₃ 476.20, m/z found 477.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.46 (br s, 1H), 7.90 (br s, 1H), 7.58 (d, *J* = 8.53 Hz, 2H), 7.50 (d, *J* = 8.28 Hz, 1H), 7.31 - 7.43 (m, 3H), 6.94 - 7.01 (m, 1H), 4.44 - 4.93 (m, 1H), 3.11 - 3.23 (m, 1H), 3.00 - 3.09 (m, 1H), 2.82 (br d, *J* = 19.58 Hz, 3H), 1.57 (s, 9H), 1.34 - 1.36 (m, 3H).

Example 125: N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide (Compound 149)



[00495] To a solution of **Compound 147** (60 mg, 0.16 mmol, 1 *eq*) and DIEA (51 mg, 0.39 mmol, 69 μ L, 2.5 *eq*) in THF (2 mL) was added BrCN (25.3 mg, 0.23 mmol, 17 μ L, 1.5 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with EA (10 mL) and washed with H₂O (2*3 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 149** (5.5 mg, 13.5 μ mol, 8.5% yield). LCMS (ESI): RT = 0.991 min, mass calc. for C₂₀H₁₈F₃N₅O 401.15, m/z found 402.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.90 (dd, *J* = 7.88, 1.38 Hz, 1H), 7.59 (d, *J* = 8.50 Hz, 2H), 7.51 (d, *J* = 8.13 Hz, 1H), 7.35 - 7.44 (m, 3H), 6.93 - 7.02 (m, 1H), 3.59 - 3.68 (m, 1H), 3.27 - 3.36 (m, 1H), 3.10 - 3.19 (m, 1H), 1.47 (d, *J* = 6.63 Hz, 3H).

Example 126: 2-(5-(1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 150), tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 151), and N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 152)



Step 1: 3-[tert-butoxycarbonyl(methyl)amino]-2-methyl-propanoic acid

[00496] To a solution of compound **126-1a** (200 mg, 0.98 mmol, 1 *eq*) and MeI (1.40 g, 9.84 mmol, 0.6 mL, 10 *eq*) in THF (2 mL) was added NaH (393 mg, 9.84 mmol, 60% purity, 10 *eq*) slowly in portions over a period of 1 hr at 0°C. Then the mixture was stirred at 20°C for 23 hr. The reaction mixture was diluted with petro ether (5 mL). Then the organic phase was removed, the aqueous phase was adjusted pH = 3 with aqueous solution of citric acid and extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹H NMR showed that compound **126-1b** (155 mg, 0.71 mmol, 72.5% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 3.44 - 3.34 (m, 1H), 3.28 (br dd, *J* = 6.9, 13.3 Hz, 1H), 2.83 - 2.69 (m, 4H), 1.41 - 1.35 (m, 9H), 1.11 (d, *J* = 7.1 Hz, 3H).

Step 2: tert-butyl N-methyl-N-[2-methyl-3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]carbamate

[00497] To a solution of compound **126-1** (170 mg, 0.57 mmol, 1 *eq*) and compound **126-1b** (150 mg, 0.69 mmol, 1.2 *eq*) in DMF (2 mL) were added HOBt (116 mg, 0.86 mmol, 1.5 *eq*), EDCI (165 mg, 0.86 mmol, 1.5 *eq*) and DIEA (148 mg, 1.15 mmol, 0.2 mL, 2 *eq*). The mixture was stirred at 25°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. Compound **126-2** (120 mg, 0.22 mmol, 38% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.40 - 8.43 (m, 3H), 7.59 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.45 -

7.41 (m, 1H), 7.39 - 7.33 (m, 1H), 7.21 (d, $J = 8.3$ Hz, 2H), 6.88 (t, $J = 7.4$ Hz, 1H), 3.67 - 3.16 (m, 2H), 2.88 (s, 4H), 1.46 (s, 9H), 1.21 (d, $J = 7.0$ Hz, 3H).

Step 3: tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 151)

[00498] To a solution of compound **126-2** (120 mg, 0.22 mmol, 1 *eq*) in DCM (3 mL) were added TEA (44 mg, 0.44 mmol, 61 μ L, 2 *eq*) and TosCl (54 mg, 0.28 mmol, 1.3 *eq*). The mixture was stirred at 25°C for 4 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. **Compound 151** (95 mg, 0.19 mmol, 88% yield) was obtained. LCMS (ESI): RT = 0.976 min, mass calcd. For C₂₄H₂₇F₃N₄O₃, 476.20 m/z found 499.0 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.52 (br d, $J = 11.4$ Hz, 1H), 7.93 - 7.85 (m, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.43 - 7.33 (m, 3H), 7.01 - 6.95 (m, 1H), 3.73 - 3.46 (m, 3H), 2.98 - 2.84 (m, 3H), 1.46 (br s, 3H), 1.39 (s, 9H).

Step 4: 2-(5-(1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 150)

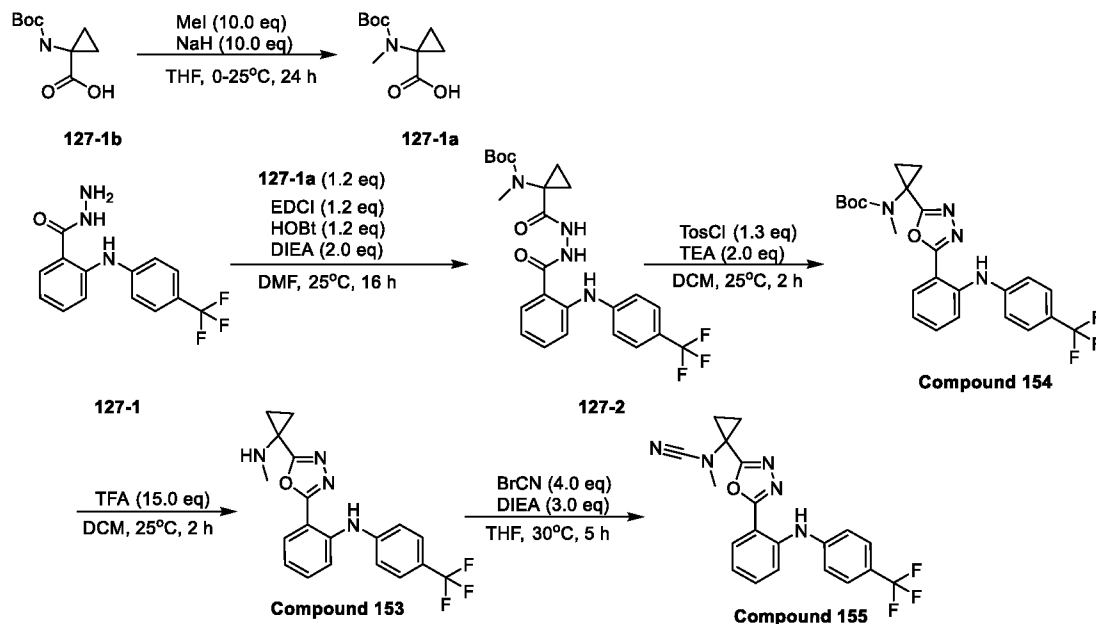
[00499] To a solution of **Compound 151** (90 mg, 0.19 mmol, 1 *eq*) in DCM (2 mL) was added TFA (323 mg, 2.83 mmol, 0.2 mL, 15 *eq*). The mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with saturated aq. Na₂CO₃ (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. LCMS and ¹H NMR confirmed that **Compound 150** (65 mg, 0.16 mmol, 87% yield) was obtained. LCMS (ESI): RT = 0.736 min, mass calcd. For C₁₉H₁₉F₃N₄O, 376.15 m/z found 377.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.54 (s, 1H), 7.89 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.43 - 7.33 (m, 3H), 7.01 - 6.95 (m, 1H), 3.43 (qd, $J = 7.1, 13.9$ Hz, 1H), 3.11 (dd, $J = 8.2, 12.1$ Hz, 1H), 2.93 (dd, $J = 5.6, 12.1$ Hz, 1H), 2.50 (s, 3H), 1.47 (d, $J = 7.0$ Hz, 3H).

Step 5: N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 152)

[00500] To a solution of **Compound 150** (60 mg, 0.16 mmol, 1 *eq*) in THF (2 mL) were added DIEA (61 mg, 0.48 mmol, 83 μ L, 3 *eq*) and BrCN (50 mg, 0.48 mmol, 35 μ L, 3 *eq*). The mixture was stirred at 25°C for 1 hr. The reaction mixture was diluted with EA (15 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 152** (19 mg, 47 μ mol, 29% yield) was obtained. LCMS (ESI): RT = 0.875 min, mass calcd. For C₂₀H₁₈F₃N₅O, 401.15 m/z found 401.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 7.92 (dd, $J = 1.4, 7.9$

Hz, 1H), 7.60 (d, $J = 8.3$ Hz, 2H), 7.53 (d, $J = 8.3$ Hz, 1H), 7.45 - 7.36 (m, 3H), 7.01 (t, $J = 7.3$ Hz, 1H), 3.63 - 3.53 (m, 2H), 3.45 - 3.36 (m, 1H), 2.98 (s, 3H), 1.56 (d, $J = 6.8$ Hz, 3H).

Example 127: 2-(5-(1-(methylamino)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 153), tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate (Compound 154), and N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)cyanamide (Compound 155)



Step 1: 1-[tert-butoxycarbonyl(methyl)amino]cyclopropanecarboxylic acid

[00501] To a solution of compound **127-1b** (300 mg, 1.49 mmol, 1 *eq*) and MeI (2.12 g, 14.91 mmol, 0.93 mL, 10 *eq*) in THF (5 mL) was added a mixture of NaH (596 mg, 14.91 mmol, 60% purity, 10 *eq*) in THF (5 mL) slowly at 0°C. Then the mixture was stirred at 25°C for 24 hr. The reaction mixture was diluted with petro ether (5 mL). Then the organic phase was removed, the aqueous phase was adjusted pH = 3 with aqueous solution of citric acid and extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹H NMR confirmed that compound **127-1a** (303 mg, 1.41 mmol, 94% yield) was obtained. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.48 (br s, 1H), 2.75 (s, 3H), 1.35 (s, 8H), 1.37 - 1.34 (m, 1H), 1.28 - 1.07 (m, 4H).

Step 2: tert-butyl N-methyl-N-[1-[[[2-[4-(trifluoromethyl)anilino]benzoyl]amino]carbonyl]cyclopropyl]carbamate

[00502] To a solution of compound **127-1** (228 mg, 0.77 mmol, 1 *eq*) and compound **127-1a** (200 mg, 0.93 mmol, 1.2 *eq*) in DMF (5 mL) were added HOBt (125 mg, 0.93 mmol, 1.2 *eq*), EDCI (178 mg, 0.93 mmol, 1.2 *eq*) and DIEA (200 mg, 1.55 mmol, 0.3 mL, 2 *eq*). The mixture was stirred at

25°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. Compound **127-2** (235 mg, 0.45 mmol, 58% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.20 (br s, 1H), 8.91 - 8.62 (m, 2H), 7.59 (br d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.47 - 7.43 (m, 1H), 7.41 - 7.35 (m, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 2.99 (s, 3H), 1.69 - 1.64 (m, 2H), 1.51 (s, 9H), 1.22 (br s, 2H).

Step 3: tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate (Compound 154)

[00503] To a solution of compound **127-2** (150 mg, 0.30 mmol, 1 *eq*) in DCM (2 mL) were added TEA (92 mg, 0.91 mmol, 0.13 mL, 3 *eq*) and TosCl (75 mg, 0.4 mmol, 1.3 *eq*). The mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. **Compound 154** (134 mg, 0.27 mmol, 90% yield) was obtained. LCMS (ESI): RT = 0.997 min, mass calcd. For C₂₄H₂₅F₃N₄O₃, 474.19 m/z found 497.1 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.50 (br s, 1H), 7.79 (br s, 1H), 7.57 (br d, *J* = 8.3 Hz, 2H), 7.51 (br d, *J* = 8.3 Hz, 1H), 7.42 - 7.32 (m, 3H), 6.96 (br t, *J* = 7.2 Hz, 1H), 3.08 (s, 3H), 1.73 (br s, 2H), 1.57 - 1.40 (m, 11H).

Step 4: 2-(5-(1-(methylamino)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 153)

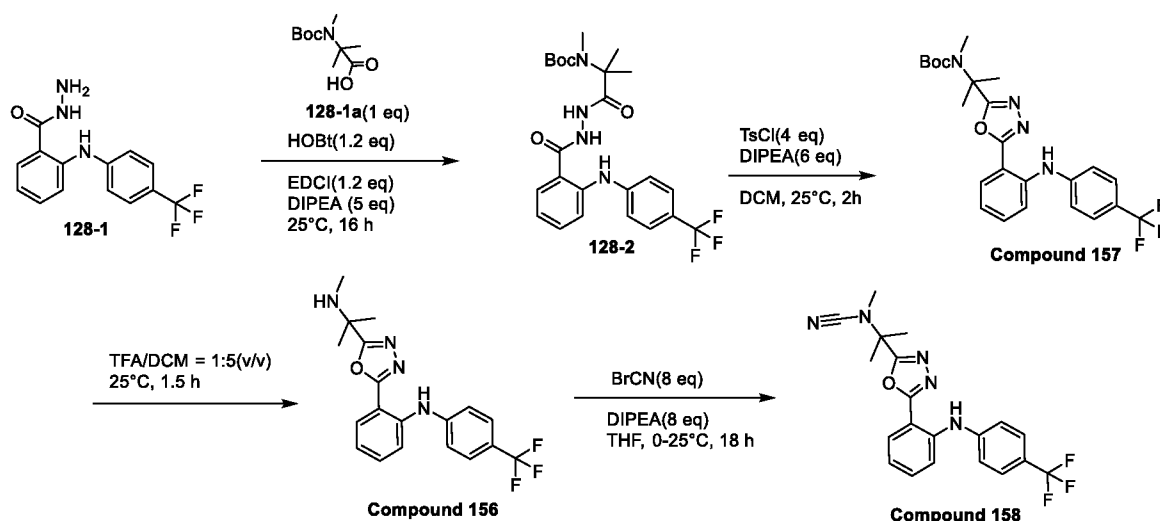
[00504] To a solution of **Compound 154** (120 mg, 0.25 mmol, 1 *eq*) in DCM (2 mL) was added TFA (432 mg, 3.79 mmol, 0.28 mL, 15 *eq*). The mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with saturated aq. Na₂CO₃ (10 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The product was used for the next step directly. LCMS and ¹H NMR showed that **Compound 153** (88 mg, 0.23 mmol, 92% yield) was obtained. LCMS (ESI): RT = 0.736 min, mass calcd. For C₁₉H₁₇F₃N₄O, 374.14 m/z found 374.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.73 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.34 - 7.26 (m, 3H), 6.89 (t, *J* = 7.5 Hz, 1H), 2.56 - 2.53 (m, 1H), 2.55 (s, 2H), 1.35 - 1.30 (m, 2H), 1.25 - 1.19 (m, 2H).

Step 5: N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)cyanamide (Compound 155)

[00505] To a solution of **Compound 153** (80 mg, 0.21 mmol, 1 *eq*) in THF (2 mL) were added DIEA (82 mg, 0.64 mmol, 0.11 mL, 3 *eq*) and BrCN (90 mg, 0.85 mmol, 62 uL, 4 *eq*). The mixture

was stirred at 30°C for 5 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 155** (52 mg, 0.13 mmol, 60% yield) was obtained. LCMS (ESI): RT = 0.897 min, mass calcd. For C₂₀H₁₆F₃N₅O, 399.13 m/z found 399.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.40 (s, 1H), 7.85 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.01 - 6.96 (m, 1H), 3.12 (s, 3H), 1.76 - 1.71 (m, 2H), 1.69 - 1.64 (m, 2H).

Example 128: 2-(5-(2-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 156), tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate (Compound 157), and N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide (Compound 158)



Step 1: tert-butyl methyl(2-methyl-1-oxo-1-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propan-2-yl)carbamate

[00506] To a solution of **128-1a** (200 mg, 0.92 mmol, 1 *eq*), **128-1** (271.8 mg, 0.92 mmol, 1 *eq*), HOBt (149.3 mg, 1.10 mmol, 1.2 *eq*) and EDCI (211.8 mg, 1.10 mmol, 1.2 *eq*) was added DIPEA (594.9 mg, 4.60 mmol, 0.8 mL, 5 *eq*) at 25°C. Then the resulting mixture was stirred at 25°C for 16 h. The mixture was directly purified by prep-HPLC to give **128-2** (130 mg, 0.26 mmol, 28.6% yield). LCMS (ESI): RT = 0.852 min, mass calcd. For C₂₄H₂₉F₃N₄O₄ 494.21 m/z found 517.0 [M+23]⁺.

Step 2: tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate (Compound 157)

[00507] To a solution of **128-2** (125 mg, 0.25 mmol, 1 *eq*) and TosCl (192.8 mg, 1.01 mmol, 4 *eq*) in DCM (4 mL) was added DIPEA (196.0 mg, 1.52 mmol, 0.3 mL, 6 *eq*) at 25°C. Then the

resulting mixture was stirred at 25°C for 2 h. The solution was concentrated to give a residue. The residue was purified by column chromatography to give **Compound 157** (95 mg, 0.20 mmol, 78.5% yield). LCMS (ESI): RT = 0.993 min, mass calcd. For C₂₄H₂₇F₃N₄O₃ 476.20 m/z found 477.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.62 (s, 1H), 7.87 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.62 - 7.50 (m, 3H), 7.42 - 7.33 (m, 3H), 7.00 - 6.93 (m, 1H), 3.09 (s, 3H), 1.78 (s, 6H), 1.26 (s, 9H).

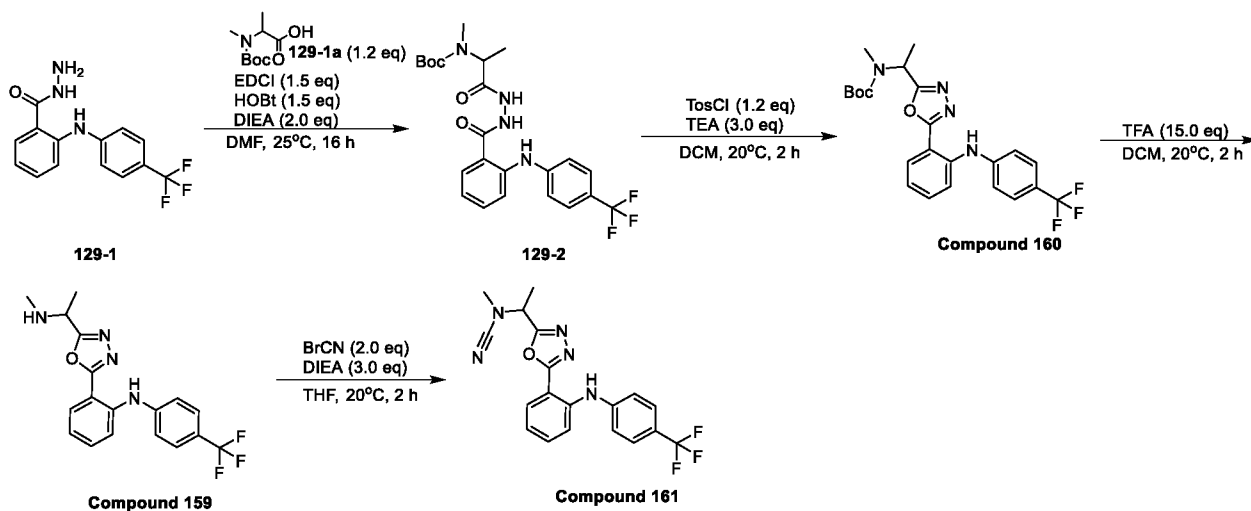
Step 3: 2-(5-(2-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 156)

[00508] To a solution of **Compound 157** (80 mg, 0.17 mmol, 1 *eq*) in DCM (4 mL) was added TFA (0.8 mL) at 25°C. Then the resulting mixture was stirred at 25°C for 1.5 h. The solution was concentrated at 20°C to give a residue. The residue was diluted with 20 mL of water and lyophilized to give **Compound 156** (82 mg, 0.16 mmol, 97.1% yield, TFA). LCMS (ESI): RT = 0.739 min, mass calcd. For C₁₉H₁₉F₃N₄O 376.15 m/z found 376.9 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.53 (br s, 1H), 9.03 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.59 - 7.46 (m, 4H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.15 - 7.07 (m, 1H), 2.48 (s, 3H), 1.64 (s, 6H).

Step 4: N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide (Compound 158)

[00509] To a solution of **Compound 156** (60 mg, 0.16 mmol, 1 *eq*) and DIPEA (82.4 mg, 0.64 mmol, 0.1 mL, 4 *eq*) in THF (3 mL) was added cyanogen bromide (33.8 mg, 0.32 mmol, 24 uL, 2 *eq*) at 0°C. The mixture was stirred at 25°C for 2 hr. Then another batch of cyanogen bromide (101.3 mg, 0.96 mmol, 70 uL, 6 *eq*) and DIPEA (82.4 mg, 0.64 mmol, 0.1 mL, 4 *eq*) was added and the resulting mixture was stirred for another 16 h at 25°C. The solution was quenched with water (10 mL) and then diluted with EA(50 mL), washed with brine (15 mL*3). The combined organic layer was dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography to give **Compound 158** (14 mg, 35 umol, 21.9% yield). LCMS (ESI): R = 0.885 min, mass calcd. For C₂₀H₁₈F₃N₅O 401.15 m/z found 401.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 7.94 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.55 - 7.49 (m, 1H), 7.43 (dt, *J* = 1.5, 7.8 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.05 - 6.98 (m, 1H), 2.86 (s, 3H), 1.94 - 1.84 (m, 6H).

Example 129: 2-(5-(1-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 159), tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 160), and N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 161)



Step 1: tert-butyl N-methyl-N-[1-methyl-2-oxo-2-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]ethyl]carbamate

[00510] To a solution of compound **129-1** (200 mg, 0.67 mmol, 1 eq) and compound **129-1a** (165 mg, 0.81 mmol, 1.2 eq) in DMF (2 mL) were added HOBt (137 mg, 1.02 mmol, 1.5 eq), EDCI (194 mg, 1.02 mmol, 1.5 eq) and DIEA (175 mg, 1.35 mmol, 0.24 mL, 2 eq). The mixture was stirred at 25°C for 16 hr. The reaction mixture was quenched with water (5 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS confirmed that compound **129-2** (120 mg, 0.23 mmol, 34% yield) was obtained.

Step 2: tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 160)

[00511] To a solution of compound **129-2** (120 mg, 0.25 mmol, 1 eq) in DCM (2 mL) were added TEA (75 mg, 0.75 mmol, 0.1 mL, 3 eq) and TosCl (57 mg, 0.3 mmol, 1.2 eq). The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that **Compound 160** (104 mg, 0.22 mmol, 90% yield) was obtained. LCMS (ESI): RT = 0.994 min, mass calcd. For C₂₃H₂₅F₃N₄O₃, 462.19 m/z found 485.0 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H), 7.86 (br d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.43 - 7.34 (m, 3H), 7.00 - 6.95 (m, 1H), 5.94 - 5.34 (m, 1H), 2.81 (br s, 3H), 1.71 (br s, 3H), 1.51 (br s, 9H).

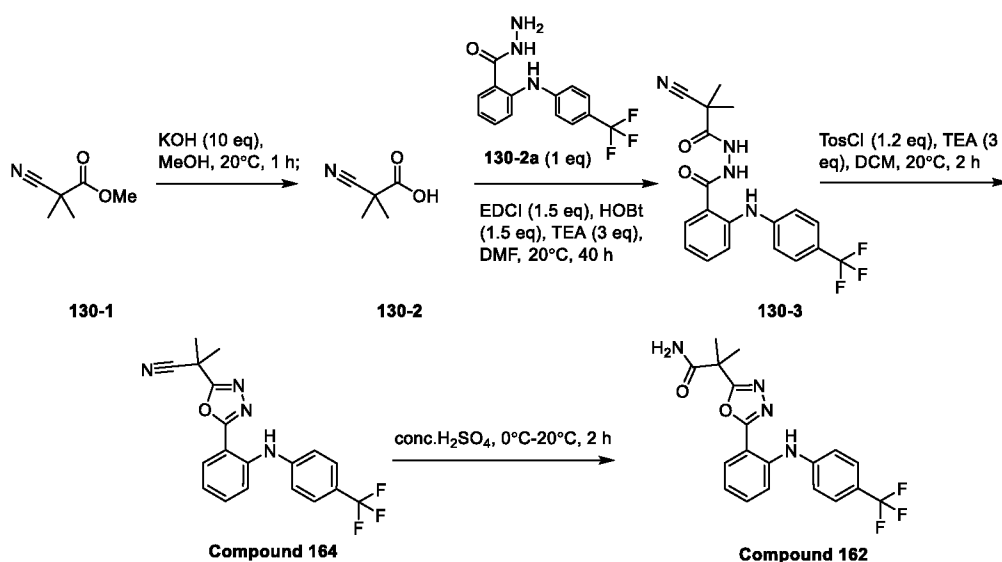
Step 3: 2-(5-(1-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 159)

[00512] To a solution of **Compound 160** (100 mg, 0.22 mmol, 1 *eq*) in DCM (2 mL) was added TFA (369 mg, 3.24 mmol, 0.24 mL, 15 *eq*). The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with saturated aq. Na₂CO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. LCMS and ¹H NMR confirmed that **Compound 159** (65 mg, 0.17 mmol, 80% yield) was obtained. LCMS (ESI): RT = 0.717 min, mass calcd. For C₁₈H₁₇F₃N₄O, 362.14 m/z found 362.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.54 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.44 - 7.35 (m, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 4.15 (q, *J* = 6.9 Hz, 1H), 2.48 (s, 3H), 1.60 (s, 3H).

Step 4: N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 161)

[00513] To a solution of **Compound 159** (60 mg, 0.16 mmol, 1 *eq*) in THF (2 mL) were added DIEA (64 mg, 0.5 mmol, 86 uL, 3 *eq*) and BrCN (35 mg, 0.33 mmol, 24 uL, 2 *eq*). The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 161** (30 mg, 77 umol, 46% yield) was obtained. LCMS (ESI): RT = 0.875 min, mass calcd. For C₁₉H₁₆F₃N₅O, 387.13 m/z found 387.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.86 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.46 - 7.41 (m, 1H), 7.38 - 7.26 (m, 3H), 6.96 - 6.90 (m, 1H), 4.46 (q, *J* = 7.0 Hz, 1H), 2.90 (s, 3H), 1.79 (d, *J* = 7.3 Hz, 3H).

Example 130: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 162)



Step 1: 2-cyano-2-methylpropanoic acid

[00514] To a solution of KOH (2.21 g, 39.33 mmol, 10 *eq*) in MeOH (20 mL) at 20°C was added **130-1** (500 mg, 3.93 mmol, 1 *eq*), and the resulting mixture was stirred at 20°C for 1 h. The reaction mixture was concentrated to remove most of MeOH, and the residue was diluted with water (20 mL), acidified with conc. HCl to pH = 1-2, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue **130-2** (430 mg, 3.80 mmol, 96.7% yield). ¹H NMR (400 MHz, CDCl₃) δ 1.67 (s, 6H).

Step 2: *N'*-(2-cyano-2-methylpropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00515] To a solution of **130-2** (137.9 mg, 1.22 mmol, 1.2 *eq*), EDCI (292.2 mg, 1.52 mmol, 1.5 *eq*) and HOBT (205.9 mg, 1.52 mmol, 1.5 *eq*) in DMF (4 mL) at 20°C was added **130-2a** (300 mg, 1.02 mmol, 1 *eq*) and then TEA (308.4 mg, 3.05 mmol, 0.42 mL, 3 *eq*), and the resulting mixture was stirred at 20°C for 40 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **130-3** (290 mg, 0.71 mmol, 69.5% yield). LCMS (ESI): RT = 0.799 min, mass calc. for C₁₉H₁₇F₃N₄O₂ 390.13, m/z found 390.9 [M+1]⁺.

Step 3: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile (Compound 164)

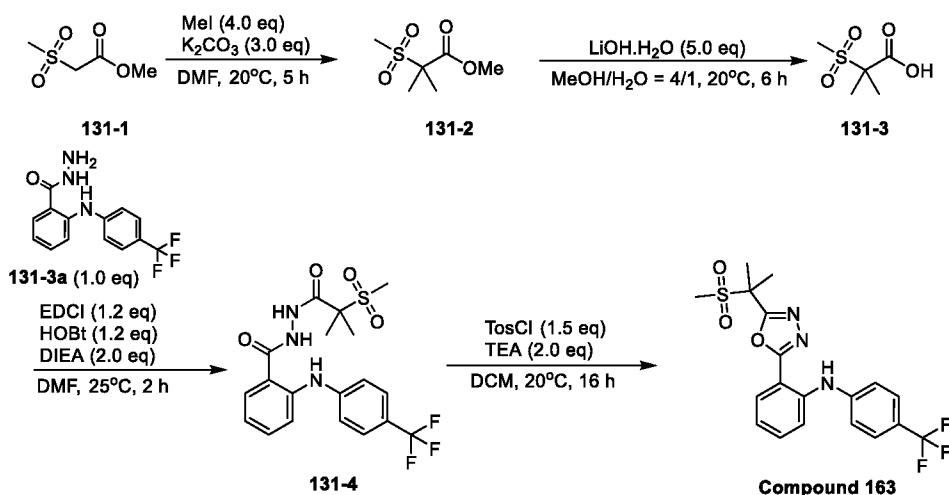
[00516] To a solution of **130-3** (150 mg, 0.38 mmol, 1 *eq*) and TEA (116.7 mg, 1.15 mmol, 0.16 mL, 3 *eq*) in DCM (2 mL) at 20°C was added TosCl (87.9 mg, 0.46 mmol, 1.2 *eq*), and the resulting mixture was stirred at 20°C for 2 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 164** (110 mg, 0.29 mmol, 74.3% yield). LCMS (ESI): RT = 0.924 min, mass calc. for C₁₉H₁₅F₃N₄O 372.12, m/z found 372.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 7.93 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 1.97 (s, 6H).

Step 4: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 162)

[00517] The sample of **Compound 164** (50 mg, 0.13 mmol, 1 *eq*) was added slowly to H₂SO₄ (1 mL) at 0°C, and the resulting mixture was stirred at 20°C for 2 h. The reaction mixture was added drop-wise into the ice-water (10 mL) under stirring, then basified with saturated Na₂CO₃ solution to

pH = 8-9, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 162** (45.3 mg, 0.12 mmol, 86.4% yield). LCMS (ESI): RT = 0.843 min, mass calc. for C₁₉H₁₇F₃N₄O₂ 390.13, m/z found 390.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.42 (dt, *J* = 1.4, 7.8 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.03 - 6.96 (m, 1H), 6.52 (brs, 1H), 5.50 (brs, 1H), 1.80 (s, 6H).

Example 131: 2-(5-(2-(methylsulfonyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 163)



Step 1: methyl 2-methyl-2-methylsulfonyl-propanoate

[00518] To a solution of compound **131-1** (600 mg, 3.94 mmol, 1 *eq*) and MeI (2.24 g, 15.77 mmol, 1 mL, 4 *eq*) in DMF (8 mL) was added K₂CO₃ (1.63 g, 11.83 mmol, 3 *eq*). The mixture was stirred at 20°C for 5 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL*2), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹HNMR confirmed that compound **131-2** (525 mg, crude) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 3.82 (s, 3H), 3.05 (s, 3H), 1.66 (s, 6H).

Step 2: 2-methyl-2-methylsulfonyl-propanoic acid

[00519] To a solution of compound **131-2** (520 mg, 2.89 mmol, 1 *eq*) in MeOH (2 mL) and H₂O (0.5 mL) was added LiOH.H₂O (605 mg, 14.43 mmol, 5 *eq*). The mixture was stirred at 20°C for 6 hr. The reaction mixture was concentrated in vacuum. The aqueous phase was adjusted pH = 3 with aqueous solution of citric acid and extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹HNMR confirmed that compound **131-3** (230 mg, crude) was obtained. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.09 (s, 3H), 1.50 (s, 6H).

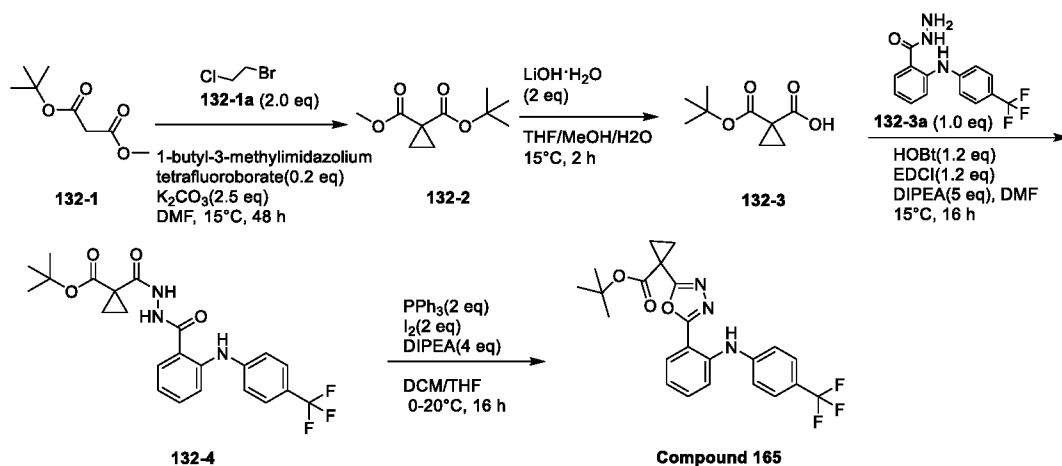
Step 3: N'-(2-methyl-2-methylsulfonyl-propanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00520] To a solution of compound **131-3a** (325 mg, 1.10 mmol, 1 eq), compound **131-3** (220 mg, 1.32 mmol, 1.2 eq), EDCI (253 mg, 1.32 mmol, 1.2 eq) and HOBt (178 mg, 1.32 mmol, 1.2 eq) in DMF (4 mL) was added DIEA (285 mg, 2.21 mmol, 0.4 mL, 2 eq). The mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched with H₂O (5 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. ¹H NMR confirmed that compound **131-4** (240 mg, 0.54 mmol, 49% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.02 (br d, *J* = 15.1 Hz, 2H), 8.15 (br s, 1H), 7.57 - 7.40 (m, 3H), 7.40 - 7.29 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.85 (t, *J* = 7.4 Hz, 1H), 3.08 (s, 3H), 1.66 (s, 6H).

Step 4: 2-(5-(2-(methylsulfonyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00521] To a solution of compound **131-4** (100 mg, 0.22 mmol, 1 eq) in DCM (2 mL) were added TosCl (64 mg, 0.33 mmol, 1.5 eq) and TEA (45 mg, 0.45 mmol, 62 uL, 2 eq). The mixture was stirred at 20°C for 16 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and NMR confirmed that **Compound 163** (25 mg, 57 umol, 25% yield) was obtained. LCMS (ESI): RT = 0.879 min, mass calcd. For C₁₉H₁₈F₃N₃O₃S, 425.10 m/z found 425.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.37 (s, 1H), 7.93 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.54 - 7.48 (m, 1H), 7.46 - 7.40 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.04 - 6.96 (m, 1H), 3.02 (s, 3H), 2.01 (s, 6H).

Example 132: tert-butyl 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylate (Compound 165)



Step 1: O1'-tert-butyl O1-methyl cyclopropane-1,1-dicarboxylate

[00522] To a mixture of compound **132-1** (4 g, 23.0 mmol, 3.9 mL, 1.0 eq) in DMF (35 mL) were added **132-1a** (6.59 g, 45.9 mmol, 3.8 mL, 2.0 eq), 1-butyl-3-methyl-imidazol-3-ium; tetrafluoroborate(1.04 g, 4.59 mmol, 0.9 mL, 0.2 eq) and K₂CO₃ (7.93 g, 57.4 mmol, 2.5 eq). Then the resulting mixture was stirred at 15°C for 48 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with EA(100 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **132-2** (4.1 g, 20.48 mmol, 89.2% yield). ¹H NMR (400 MHz DMSO-*d*₆) δ 3.61-3.69 (m, 3H), 1.37-1.45 (m, 9H), 1.21-1.32 (m, 3H).

Step 2: 1-tert-butoxycarbonylcyclopropanecarboxylic acid

[00523] To a mixture of compound **132-2** (3.1 g, 15.48 mmol, 1 eq) in MeOH (10 mL) and THF (25 mL) was drop-wise added a solution of LiOH.H₂O (1.3 g, 30.96 mmol, 2.0 eq) in H₂O (10 mL) over 2 min at 15°C. The resulting mixture was stirred at 15 °C for 2 h. The solution was concentrated at 15°C to remove most of organic solvent and extracted with EA(10 mL) twice. The separated aqueous layer was adjusted with cold aq 2 M HCl to pH~ 2, along with lots of solid formed. Then the suspension was filtered and washed with water (10 mL). The filter cake was collected to give compound **132-3** (1.1 g, 5.91 mmol, 38.2% yield). The filtrate was extracted with EA (15 mL*4). The combined organic layer was washed with brine (15 mL), dried with Na₂SO₄, filtered and concentrated to give compound **132-3** (500 mg, 2.69 mmol, 17.3% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.43 - 1.36 (m, 9H), 1.26 - 1.18 (m, 4H).

Step 3: tert-butyl 1-[[[2-[4-

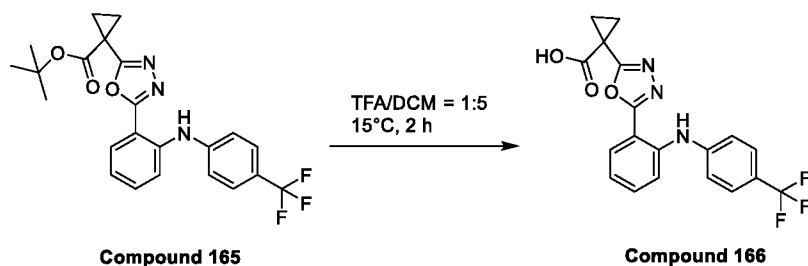
(trifluoromethyl)anilino]benzoyl]amino]carbamoyle]cyclopropanecarboxylate

[00524] To a mixture of compound **132-3a** (800 mg, 2.71 mmol, 1.0 eq), compound **132-3** (605.4 mg, 3.25 mmol, 1.2 eq), HOBt (439.3 mg, 3.25 mmol, 1.2 eq) and EDCI (623.3 mg, 3.25 mmol, 1.2 eq) in DMF (10 mL) was added DIPEA (1.75 g, 13.55 mmol, 2.4 mL, 5 eq) at 15°C. The resulting mixture was stirred at 15 °C for 16 h. The mixture was concentrated at 40°C to remove most of organic solvent, diluted with water (30 mL) and extracted with EA (50 mL) twice. The separated aqueous layer was cooled to 0°C and adjusted with cold aq 2 M HCl to pH~ 2 and then extracted with EA (15 mL*4). The combined organic layer was washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography to give compound **132-4** (780 mg, 1.65 mmol, 60.9% yield). LCMS (ESI): RT = 0.892 min, mass calc. for C₂₃H₂₄F₃N₃O₄ 463.17, m/z found 485.9 [M+23]⁺.

Step 4: tert-butyl 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylate

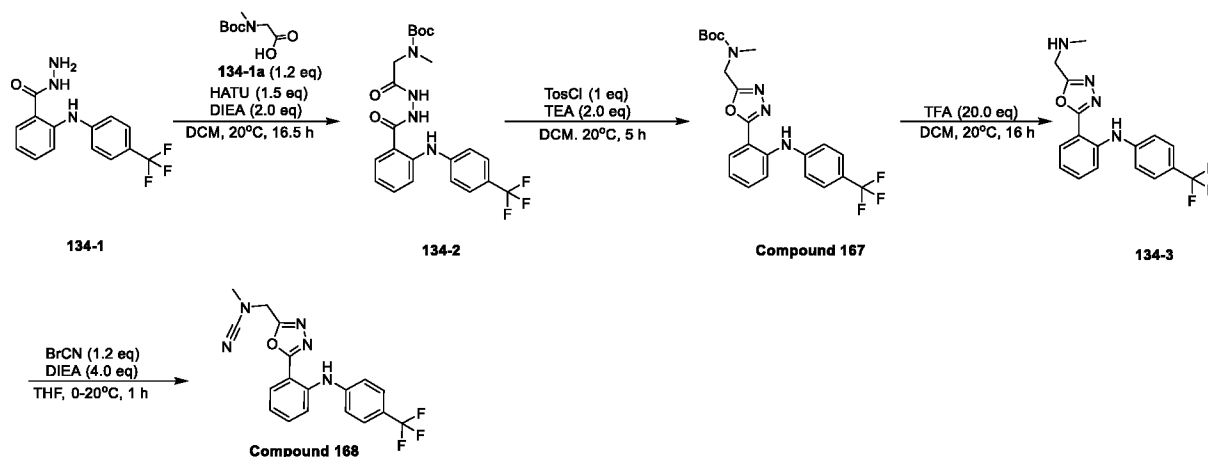
[00525] To a mixture of PPh₃ (860.3 mg, 3.28 mmol, 2.0 eq) in DCM (10 mL) was added iodine (832.5 mg, 3.28 mmol, 0.7 mL, 2.0 eq) in one portion at 0°C. After the iodine was dissolved completely, DIPEA (847.8 mg, 6.6 mmol, 1.2 mL, 4.0 eq) was added, followed by a solution of compound **132-4** (760 mg, 1.64 mmol, 1.0 eq) in THF (10 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EA (50 mL * 2). The combined organic layers were washed with NaHCO₃ (20 mL * 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give **Compound 165** (700 mg, 1.5 mmol, 93.9% yield). LCMS (ESI): RT = 1.018 min, mass calc. for C₂₃H₂₂F₃N₃O₃ 445.16, m/z found 446 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 7.84-8.05 (m, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.52-7.60 (m, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.13-7.21 (m, 1H), 1.55-1.66 (m, 4H), 1.28-1.47 (m, 9H).

Example 133: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylic acid (Compound 166)



[00526] To a mixture of **Compound 165** (300 mg, 0.7 mmol, 1 eq) in DCM (2 mL) was added TFA (0.4 mL) in one portion at 15°C. The mixture was stirred at 15 °C for 2 h. The reaction mixture was concentrated at 15°C to give a residue. The residue was purified by prep-HPLC to give the product (290 mg, 0.75 mmol, 5.5% yield). ¹HNMR and HPLC showed the product was not pure. 30 mg of the product was repurified by prep-HPLC to give **Compound 166** (10.18 mg, 0.03 mmol, 1.94e-1% yield). LCMS (ESI): RT = 0.848 min, mass calc. for C₁₉H₁₄F₃N₃O₃ 389.10, m/z found 389.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.31 (br s, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.63 (br d, *J* = 8.3 Hz, 2H), 7.59 - 7.49 (m, 2H), 7.35 (br d, *J* = 8.5 Hz, 2H), 7.13 (br t, *J* = 7.3 Hz, 1H), 1.39 (br s, 2H), 1.22 (br s, 2H).

Example 134: tert-butyl methyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 167) and N-methyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 168)



Step 1: tert-butyl N-methyl-N-[2-oxo-2-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]ethyl]carbamate

[00527] A solution of compound **134-1a** (153.8 mg, 0.81 mmol, 1.2 *eq*) and HATU (386 mg, 1.02 mmol, 1.5 *eq*) in DCM (2 mL) was stirred at 20°C for 30 min. Then compound **134-1** (200 mg, 0.67 mmol, 1 *eq*) and DIEA (175 mg, 1.35 mmol, 0.24 mL, 2 *eq*) were added to the mixture and stirred at 20°C for 16 hr. The reaction mixture was concentrated in vacuum to give the residue. The residue was diluted with EA (20 mL), washed with H₂O (10 mL*2) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS confirmed that compound **134-2** (105 mg, 0.21 mmol, 30.9% yield) was obtained.

Step 2: tert-butyl methyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 167)

[00528] To a solution of compound **134-2** (100 mg, 0.21 mmol, 1 *eq*) in DCM (1 mL) were added TosCl (40.8 mg, 0.21 mmol, 1 *eq*) and TEA (43 mg, 0.43 mmol, 59 μ L, 2 *eq*). The mixture was stirred at 20°C for 5 hr. The reaction mixture was concentrated in vacuum to give a residue. Then the residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that **Compound 167** (35 mg, 78 μ mol, 36.4% yield) was obtained. LCMS (ESI): RT = 0.938 min, mass calcd. For C₂₂H₂₃F₃N₄O₃, 448.17 m/z found 471.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 7.87 (br s, 1H), 7.59 (br d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.44 - 7.34 (m, 3H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.83 - 4.68 (m, 2H), 3.03 (br d, *J* = 11.1 Hz, 3H), 1.51 (br s, 9H).

Step 3: 2-[5-(methylaminomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00529] To a solution of **Compound 167** (30 mg, 66.9 μ mol, 1 *eq*) in DCM (1 mL) was added TFA (152 mg, 1.34 mmol, 99 μ L, 20 *eq*). The mixture was stirred at 20°C for 16 hr. The reaction

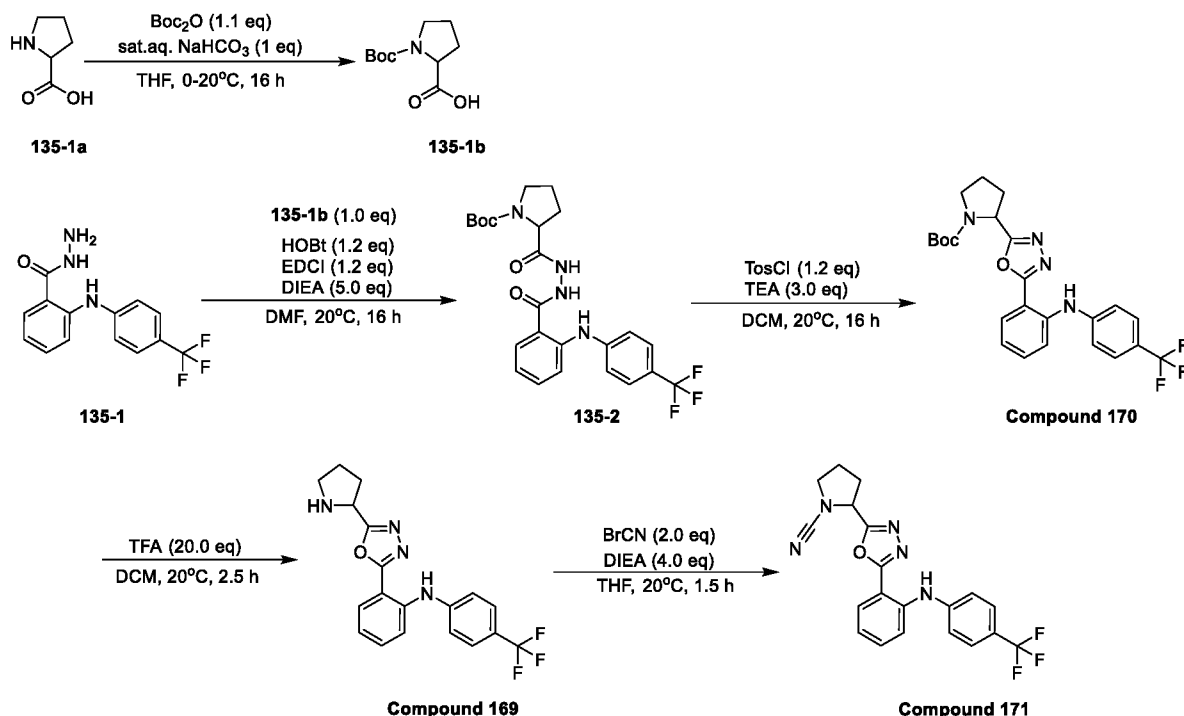
mixture was concentrated in vacuum. The crude product was used for the next step directly.

Compound **134-3** (40 mg, crude) was obtained.

Step 4: N-methyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 168)

[00530] To a solution of compound **134-3** (40 mg, 0.11 mmol, 1 *eq*) and DIEA (59 mg, 0.46 mmol, 80 μ L, 4 *eq*) in THF (1 mL) was added BrCN (14.6 mg, 0.14 mmol, 10 μ L, 1.2 *eq*) at 0°C. The mixture was stirred at 20°C for 1 hr. The reaction mixture was concentrated in vacuum to give a residue and the residue was diluted with EA (15 mL), filtered, the filtrate was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 168** (14 mg, 37 μ mol, 32.3% yield) was obtained. LCMS (ESI): RT = 0.862 min, mass calcd. For C₁₈H₁₄F₃N₅O, 373.12 m/z found 373.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 7.94 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.03 - 6.97 (m, 1H), 4.53 (s, 2H), 3.03 (s, 3H).

Example 135: 2-(5-(pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 169), and tert-butyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate (Compound 170), and 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile (Compound 171)



Step 1: 1-tert-butoxycarbonylpyrrolidine-2-carboxylic acid

[00531] To a solution of compound **135-1a** (1 g, 8.69 mmol, 1 *eq*) in NaHCO₃ (1 M, 8.7 mL, 1 *eq*) was added Boc₂O (2.1 g, 9.55 mmol, 2.2 mL, 1.1 *eq*) in THF (5 mL) at 0°C. Then the mixture was stirred at 20°C for 16 hr. The reaction mixture was concentrated in vacuum to remove THF, then the aqueous phase was adjusted pH = 2 with 1M. aq. HCl. The aqueous phase was extracted with EA (20 mL*3), washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹H NMR confirmed that compound **135-1b** (1.8 g, 8.36 mmol, 96.2% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.87 - 7.76 (m, 1H), 4.42 - 4.21 (m, 1H), 3.63 - 3.29 (m, 2H), 2.35 - 2.06 (m, 2H), 2.01 - 1.85 (m, 2H), 1.51 - 1.38 (m, 9H).

Step 2: tert-butyl 2-[[[2-[4-(trifluoromethyl)anilino]benzoyl]amino]carbamoyl]pyrrolidine -1-carboxylate

[00532] To a solution of compound **135-1** (300 mg, 1.02 mmol, 1 *eq*) and compound **135-1b** (218 mg, 1.02 mmol, 1 *eq*) in DMF (3 mL) were added HOBT (164.7 mg, 1.22 mmol, 1.2 *eq*), EDCI (233.7 mg, 1.22 mmol, 1.2 *eq*) and DIEA (656 mg, 5.08 mmol, 0.89 mL, 5 *eq*). The mixture was stirred at 20°C for 16 hr. The reaction mixture was quenched with H₂O (15 mL), extracted with EA (15 mL*3). The combined organic phase was washed with brine (10 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that compound **135-2** (300 mg, 0.58 mmol, 56.9% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.72 (br s, 1H), 9.22 (br s, 1H), 8.95 - 8.53 (m, 1H), 7.58 (br d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.48 - 7.42 (m, 1H), 7.41 - 7.33 (m, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.90 (br t, *J* = 7.4 Hz, 1H), 4.45 (br s, 1H), 3.64 - 3.32 (m, 2H), 2.50 - 2.15 (m, 1H), 2.05 - 1.87 (m, 3H), 1.50 (s, 9H).

Step 3: tert-butyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate (Compound 170)

[00533] To a solution of compound **135-2** (200 mg, 0.4 mmol, 1 *eq*) in DCM (3 mL) were added TosCl (92.9 mg, 0.48 mmol, 1.2 *eq*) and TEA (123 mg, 1.22 mmol, 0.17 mL, 3 *eq*). The mixture was stirred at 20°C for 16 hr. The reaction mixture was concentrated in vacuum to give a residue and the residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give the crude product (160 mg). Crude **Compound 170** (120 mg, 0.25 mmol, 62% yield) was used for the next step directly. 40 mg of the crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 170** (10 mg, 21 umol, 5.2% yield) was obtained. LCMS (ESI): RT = 0.969 min, mass calcd. For C₂₄H₂₅F₃N₄O₃, 474.19 m/z found 497.0 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.53 (br s, 1H), 7.86 (br d, *J* = 7.5 Hz, 1H), 7.61 - 7.55 (m, 2H), 7.55 - 7.48 (m, 1H), 7.44 - 7.32 (m, 3H), 7.01 -

6.93 (m, 1H), 5.28 - 5.09 (m, 1H), 3.78 - 3.43 (m, 2H), 2.49 - 2.29 (m, 1H), 2.28 - 2.11 (m, 2H), 2.11 - 2.00 (m, 1H), 1.49 - 1.33 (m, 9H).

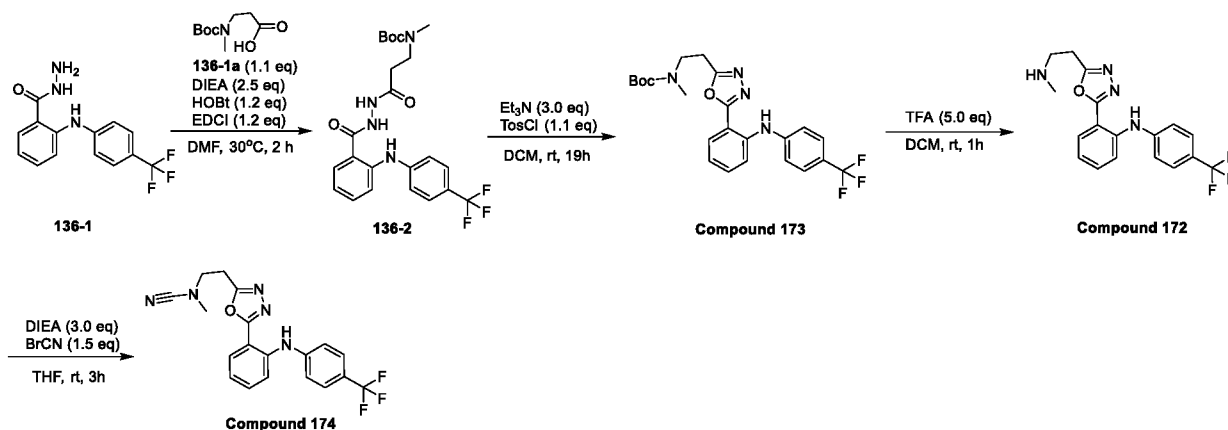
Step 4: 2-(5-(pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 169)

[00534] To a solution of **Compound 170** (120 mg, 0.25 mmol, 1 *eq*) in DCM (3 mL) was added TFA (576.7 mg, 5.06 mmol, 0.4 mL, 20 *eq*). The mixture was stirred at 20°C for 2.5 hr. The reaction mixture was concentrated in vacuum to give a residue and the residue was diluted with EA (10 mL), the precipitate was collected to give **Compound 169** (60 mg, 0.16 mmol, 63.4% yield). The crude product was purified by prep-HPLC. LCMS and ¹HNMR confirmed that **Compound 169** (7.89 mg, 19.8 μ mol, 7.8% yield) was obtained. LCMS (ESI): RT = 0.718 min, mass calcd. For C₁₉H₁₇F₃N₄O, 374.14 m/z found 374.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.41 (br s, 1H), 9.09 (s, 1H), 8.03 - 7.95 (m, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.58 - 7.54 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.18 (m, 1H), 5.09 (t, *J* = 7.4 Hz, 1H), 3.36 (t, *J* = 7.3 Hz, 2H), 2.48 - 2.29 (m, 2H), 2.20 - 2.04 (m, 2H).

Step 5: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile (Compound 171)

[00535] To a solution of **Compound 169** (60 mg, 0.16 mmol, 1 *eq*) in THF (2 mL) were added DIEA (82.8 mg, 0.64 mmol, 0.11 mL, 4 *eq*) and BrCN (33.9 mg, 0.32 mmol, 23 μ L, 2 *eq*). The mixture was stirred at 20°C for 1.5 hr. The reaction mixture was concentrated in vacuum to give a residue and the residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹HNMR confirmed that **Compound 171** (31 mg, 76 μ mol, 47.9% yield) was obtained. LCMS (ESI): RT = 0.874 min, mass calcd. For C₂₀H₁₆F₃N₅O, 399.13 m/z found 421.9 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.41 (s, 1H), 7.92 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.39 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.97 (m, 1H), 5.05 (dd, *J* = 4.3, 7.8 Hz, 1H), 3.74 (dt, *J* = 5.0, 8.4 Hz, 1H), 3.67 - 3.59 (m, 1H), 2.58 - 2.41 (m, 2H), 2.29 - 2.13 (m, 2H).

Example 136: 2-(5-(2-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 172), tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 173), and N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 174)



Step 1: tert-butyl N-methyl-N-[3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]carbamate

[00536] To a solution of compound **136-1a** (151 mg, 0.7 mmol, 1.1 *eq*), HOBt (109.8 mg, 0.8 mmol, 1.2 *eq*) and EDCI (155.8 mg, 0.8 mmol, 1.2 *eq*) in DMF (3 mL) was added compound **136-1** (200 mg, 0.6 mmol, 1 *eq*) followed by DIEA (218.8 mg, 1.6 mmol, 0.3 mL, 2.5 *eq*). The reaction was stirred at 30°C for 2 hr. The reaction was diluted with EA (30 mL) and washed with Sat.NaHCO₃ (2*10 mL) and brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude compound **136-2** (0.3 g, 0.5 mmol, 73% yield) was used for next step directly. LCMS confirmed that desired product was obtained.

Step 2: tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 173)

[00537] To a solution of compound **136-2** (0.2 g, 0.3 mmol, 1 *eq*) and Et₃N (101 mg, 0.9 mmol, 0.1 mL, 3 *eq*) in DCM (2 mL) was added TosCl (25.8 mg, 0.4 mmol, 1.1 *eq*). The reaction was stirred at 30°C for 16 hr. Additional TosCl (26 mg) was added. The reaction was continued to stir at 30°C for 3 hr. The reaction was diluted with DCM (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product (100 mg, crude) was used for next step directly. 60 mg crude product was purified by prep-HPLC to give **Compound 173** (2.88 mg, 6.1 umol, 1.8% yield). LCMS and ¹HNMR confirmed that desired product was obtained. LCMS (ESI): RT = 1.067 min, mass calc. for C₂₃H₂₅F₃N₄O₃ 462.19, m/z found 463.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.41 (s, 1H), 7.81 (s, 1H), 7.50 (d, *J* = 8.50 Hz, 2H), 7.43 (d, *J* = 8.50 Hz, 1H), 7.25 - 7.35 (m, 3H), 6.87 - 6.93 (m, 1H), 3.65 (s, 2H), 3.13 (s, 2H), 2.86 (d, *J* = 10.76 Hz, 3H), 1.33 (s, 9H).

Step 3: 2-(5-(2-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 172)

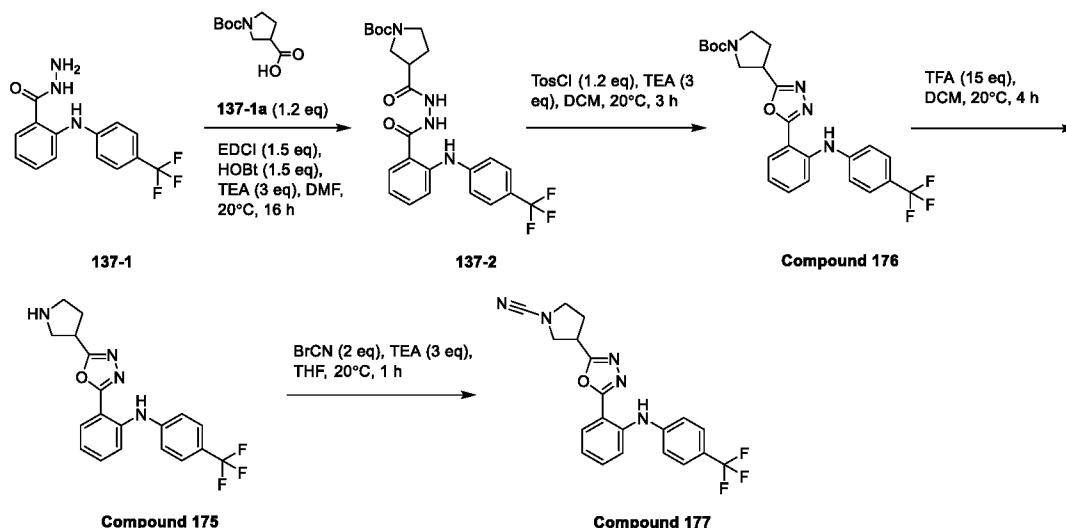
[00538] To a solution of **Compound 173** (70 mg, 0.15 mmol, 1 *eq*) in DCM (1 mL) was added TFA (86 mg, 0.75 mmol, 56 uL, 5 *eq*). The reaction was stirred at 25°C for 1hr. The reaction was

adjusted pH to 7-8 with Sat. NaHCO₃ and extracted with DCM (3*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. 10 mg crude product was purified by prep-HPLC to give **Compound 172** (4.81 mg, 13.14 μ mol, 8.68% yield). 30 mg **Compound 172** (30 mg, 82 μ mol, 54% yield) was used for next step directly. ¹H NMR and LCMS confirmed that desired product was obtained. LCMS (ESI): RT = 0.892 min, mass calc. for C₂₃H₂₅F₃N₄O₃ 362.19, m/z found 363.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.80 (dd, *J* = 7.91, 1.38 Hz, 1H), 7.50 (d, *J* = 8.53 Hz, 2H), 7.43 (d, *J* = 8.53 Hz, 1H), 7.25 - 7.35 (m, 3H), 6.85 - 6.95 (m, 1H), 2.99 - 3.13 (m, 4H), 2.43 (s, 3H).

Step 4: N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 174)

[00539] To a solution of **Compound 172** (30 mg, 82 μ mol, 1 *eq*) and DIEA (32 mg, 0.25 mmol, 43 μ L, 3 *eq*) in THF (2 mL) was added BrCN (13 mg, 0.12 mmol, 9 μ L, 1.5 *eq*). The reaction was stirred at 25°C for 3hr. The reaction was diluted with EA (10 mL) and washed with water (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The reaction was purified by prep-HPLC to give **Compound 174** (14.06 mg, 35 μ mol, 43% yield). LCMS and ¹H NMR confirmed that desired product was obtained. LCMS (ESI): RT = 0.996 min, mass calc. for C₂₃H₂₅F₃N₄O₃ 387.13, m/z found 388.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 7.91 (dd, *J* = 7.91, 1.13 Hz, 1H), 7.60 (d, *J* = 8.53 Hz, 2H), 7.52 (d, *J* = 8.53 Hz, 1H), 7.34 - 7.45 (m, 3H), 7.00 (t, *J* = 7.40 Hz, 1H), 3.54 - 3.65 (m, 2H), 3.30 - 3.39 (m, 2H), 3.00 (s, 3 H).

Example 137: 2-(5-(pyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 175), tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate (Compound 176), and 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile (Compound 177)



Step 1: tert-butyl 3-(2-(2-((4-**(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbonyl)pyrrolidine-1-carboxylate**

[00540] To a solution of **137-1a** (175.0 mg, 0.81 mmol, 1.2 eq), EDCI (194.8 mg, 1.02 mmol, 1.5 eq) and HOBt (137.3 mg, 1.02 mmol, 1.5 eq) in DMF (2 mL) at 20°C was added **137-1** (200 mg, 0.68 mmol, 1 eq) and TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 eq), and the resulting mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **137-2** (250 mg, 0.49 mmol, 72.7% yield). LCMS (ESI): RT = 0.826 min, mass calc. for C₂₄H₂₇F₃N₄O₄ 492.20, m/z found 515.0 [M+23]⁺.

Step 2: tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate (Compound 176)

[00541] To a solution of **137-2** (250 mg, 0.51 mmol, 1 eq) and TEA (154.1 mg, 1.52 mmol, 0.21 mL, 3 eq) in DCM (2 mL) at 20°C was added TosCl (116.1 mg, 0.61 mmol, 1.2 eq), and the resulting mixture was stirred at 20°C for 3 h. The reaction mixture was quenched with MeOH (0.5 mL) and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 176** (210 mg, 0.44 mmol, 87.2% yield). LCMS (ESI): RT = 0.976 min, mass calc. for C₂₄H₂₅F₃N₄O₃ 474.19, m/z found 475.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 3.89 (brs, 1H), 3.81 - 3.62 (m, 3H), 3.53 (brs, 1H), 2.47 - 2.33 (m, 2H), 1.49 (s, 9H).

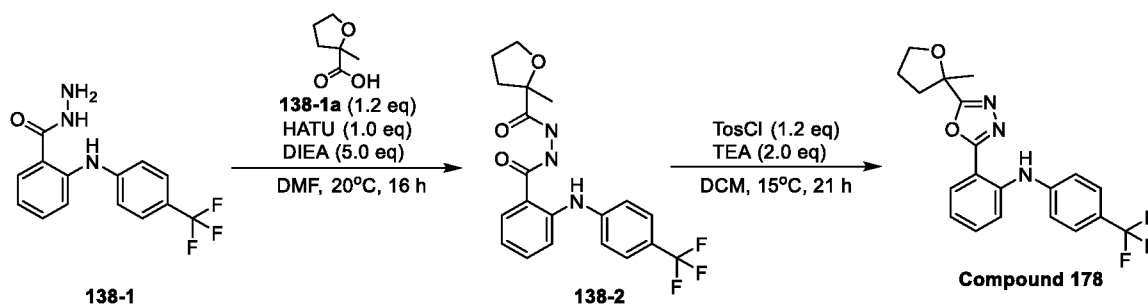
Step 3: 2-(5-(pyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 175)

[00542] To a solution of **Compound 176** (200 mg, 0.42 mmol, 1 eq) in DCM (4 mL) at 20°C was added TFA (720.9 mg, 6.32 mmol, 0.47 mL, 15 eq), and the resulting mixture was stirred at 20°C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with saturated Na₂CO₃ solution (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 175** (150 mg, 0.39 mmol, 93.6% yield). LCMS (ESI): RT = 0.732 min, mass calc. for C₁₉H₁₇F₃N₄O 374.14, m/z found 374.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 7.86 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.95 (m, 1H), 3.95 - 3.78 (m, 3H), 3.76 - 3.60 (m, 2H), 2.54 - 2.43 (m, 2H).

Step 4: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile (Compound 177)

[00543] To a solution of **Compound 175** (70 mg, 0.19 mmol, 1 *eq*) and TEA (56.8 mg, 0.56 mmol, 78 μ L, 3 *eq*) in THF (2 mL) at 20°C was added BrCN (39.6 mg, 0.37 mmol, 27 μ L, 2 *eq*), and the resulting mixture was stirred at 20°C for 1 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 177** (62.4 mg, 0.16 mmol, 83.6% yield). LCMS (ESI): RT = 0.867 min, mass calc. for C₂₀H₁₆F₃N₅O 399.13, m/z found 399.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H), 7.88 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 3.67 - 3.57 (m, 1H), 3.41 - 3.28 (m, 2H), 3.24 (ddd, *J* = 5.8, 8.1, 11.4 Hz, 1H), 3.12 - 3.04 (m, 1H), 2.38 - 2.19 (m, 2H).

Example 138: 2-(5-(2-methyltetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 178)



Step 1: 2-methyl-N'-[2-[4-(trifluoromethyl)anilino]benzoyl]tetrahydrofuran-2-carbohydrazide

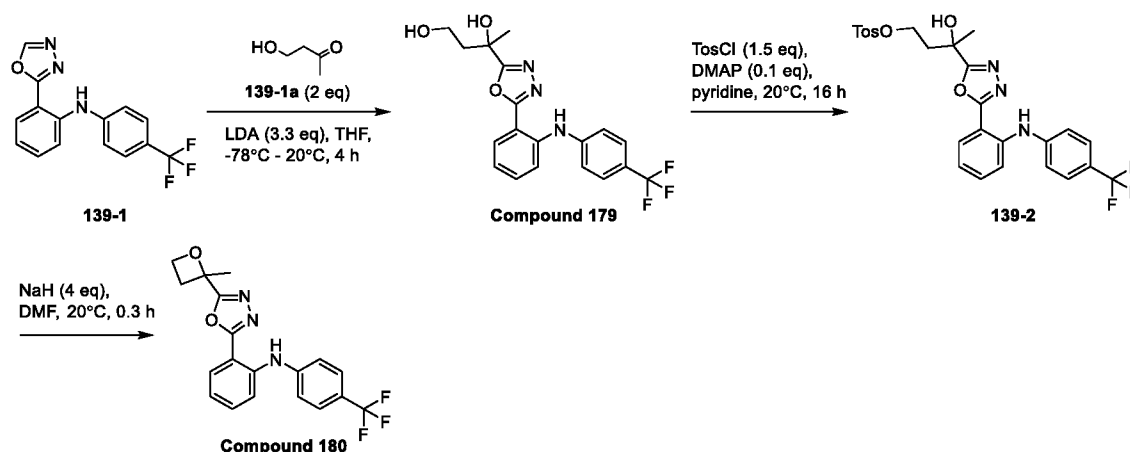
[00544] To a solution of compound **138-1** (113 mg, 0.38 mmol, 1 *eq*), compound **138-1a** (60 mg, 0.46 mmol, 1.2 *eq*) and HATU (146 mg, 0.38 mmol, 1 *eq*) in DMF (1 mL) was added DIEA (248 mg, 1.92 mmol, 0.3 mL, 5 *eq*). The mixture was stirred at 20°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL). Then the precipitate was collected. The crude product was used for the next step directly. LCMS confirmed that compound **138-2** (91 mg, 0.21 mmol, 55.8% yield) was obtained.

Step 2: 2-(5-(2-methyltetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00545] To a mixture of compound **138-2** (60 mg, 0.15 mmol, 1 *eq*) in DCM (1 mL) were added TosCl (33 mg, 0.17 mmol, 1.2 *eq*) and TEA (29 mg, 0.30 mmol, 41 μ L, 2 *eq*). The mixture was stirred at 15°C for 21 hr. The reaction mixture was concentrated in vacuum to give a residue and

then the residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 178** (26 mg, 67 μmol, 45.3% yield) was obtained. LCMS (ESI): RT = 0.940 min, mass calcd. For C₂₀H₁₈F₃N₃O₂, 389.14 m/z found 390.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.55 (s, 1H), 7.93 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 7.7 Hz, 1H), 4.16 - 4.06 (m, 1H), 3.99 (q, *J* = 7.6 Hz, 1H), 2.76 (m, 1H), 2.28 - 2.01 (m, 3H), 1.79 (s, 3H).

Example 139: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butane-1,3-diol (Compound 179) and 2-(5-(2-methyloxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 180)



Step 1: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butane-1,3-diol (Compound 179)

[00546] To a solution of **139-1** (50 mg, 0.16 mmol, 1 eq) in THF (2 mL) at -78°C was added LDA (2 M, 0.3 mL, 3.3 eq) drop-wise, and the mixture was stirred at -78°C for 0.5 h. And then the solution of 4-hydroxybutan-2-one (28.9 mg, 0.33 mmol, 28 μL, 2.0 eq) in THF (1 mL) was added at -78°C into the above solution. The resulting mixture was stirred at 20°C for 3.5 h. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL), then diluted with water (5 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EA = 1:1, UV) to give **Compound 179** (10 mg, 24.3 μmol, 14.8% yield). LCMS (ESI): RT = 0.798 min, mass calc. for C₁₉H₁₈F₃N₃O₃ 393.13, m/z found 394.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 7.93 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.02 - 6.94 (m, 1H), 4.53 (s, 1H), 4.09 - 3.93 (m, 2H), 2.41 - 2.25 (m, 3H), 1.78 (s, 3H).

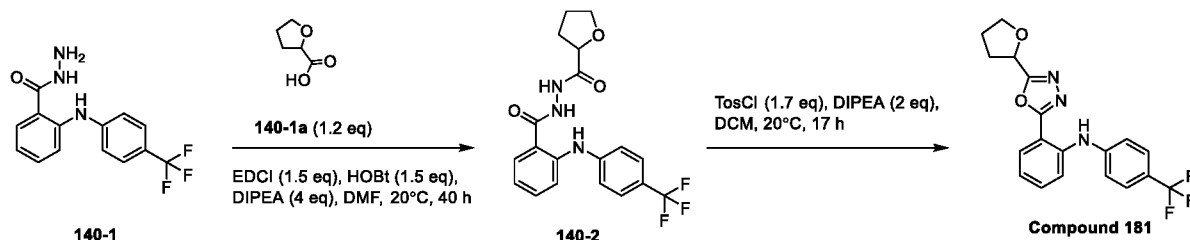
Step 2: 3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butyl 4-methylbenzenesulfonate

[00547] To a solution of **Compound 179** (90 mg, 0.23 mmol, 1 *eq*) in pyridine (2 mL) at 20°C was added TosCl (65.4 mg, 0.34 mmol, 1.5 *eq*) and DMAP (2.8 mg, 23 μ mol, 0.1 *eq*). The resulting mixture was stirred at 20°C for 16 h. The combined mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **139-2** (10 mg, 13 μ mol, 5.6% yield) was obtained. LCMS (ESI): RT = 0.917 min, mass calc. for $C_{26}H_{24}F_3N_3O_5S$ 547.14, *m/z* found 570.0 $[M+23]^+$.

Step 3: 2-(5-(2-methyloxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 180)

[00548] To a solution of **139-2** (22 mg, 40.2 μ mol, 1 *eq*) in DMF (1 mL) at 0°C was added NaH (6.4 mg, 0.16 mmol, 60% purity, 4 *eq*). The resulting mixture was stirred at 20°C for 0.3 h. The reaction mixture was quenched with water (0.5 mL) and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 180** (2.27 mg, 6.1 μ mol, 15.1% yield). LCMS (ESI): RT = 0.897 min, mass calc. for $C_{19}H_{16}F_3N_3O_2$ 375.12, *m/z* found 375.9 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.97 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.00 (t, *J* = 7.6 Hz, 1H), 4.89 - 4.80 (m, 1H), 4.70 (td, *J* = 6.1, 9.0 Hz, 1H), 3.36 (ddd, *J* = 6.3, 8.7, 11.5 Hz, 1H), 2.97 - 2.87 (m, 1H), 2.00 (s, 3H).

Example 140: 2-(5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 181)



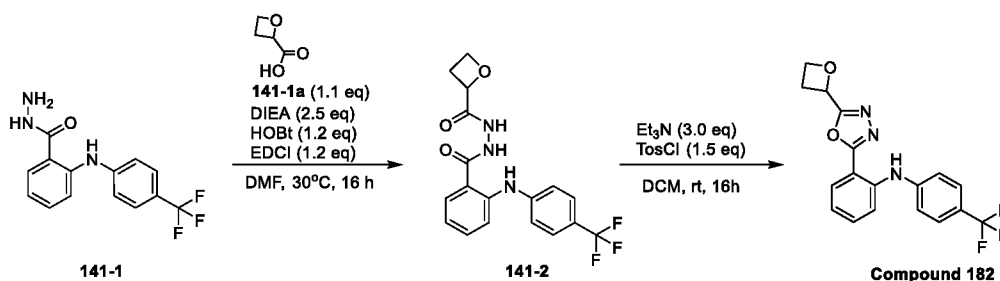
Step 1: *N'*-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)tetrahydrofuran-2-carbohydrazide

[00549] To a solution of **140-1a** (94.4 mg, 0.81 mmol, 78.0 μ L, 1.2 *eq*), EDCI (194.8 mg, 1.02 mmol, 1.5 *eq*) and HOBt (137.3 mg, 1.02 mmol, 1.5 *eq*) in DMF (3 mL) at 20°C was added **140-1** (200 mg, 0.68 mmol, 1 *eq*) and then DIPEA (350.2 mg, 2.71 mmol, 0.5 mL, 4 *eq*), and the resulting mixture was stirred at 20°C for 40 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give **140-2** (340 mg, 0.44 mmol, 66.1% yield) as a crude, which was used directly for next step. LCMS (ESI): RT = 0.768 min, mass calc. for $C_{19}H_{18}F_3N_3O_3$ 393.13, *m/z* found 393.9 $[M+1]^+$.

Step 2: 2-(5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00550] To a solution of **140-2** (340 mg, 0.45 mmol, 1 *eq*) and DIPEA (115.7 mg, 0.90 mmol, 0.2 mL, 2 *eq*) in DCM (4 mL) at 20°C was added TosCl (102.4 mg, 0.54 mmol, 1.2 *eq*), and the resulting mixture was stirred at 20°C for 16 h. After additional 0.5 *eq* TosCl the reaction was further stirred for 1 h. The mixture was quenched with water (1 mL), and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 181** (104.96 mg, 0.28 mmol, 62.5% yield). LCMS (ESI): RT = 0.912 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 375.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.20 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 3.0 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.23 - 7.14 (m, 1H), 5.25 (dd, *J* = 5.3, 7.8 Hz, 1H), 3.94 - 3.84 (m, 2H), 2.36 - 2.20 (m, 2H), 2.10 - 1.93 (m, 2H).

Example 141: 2-(5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 182)



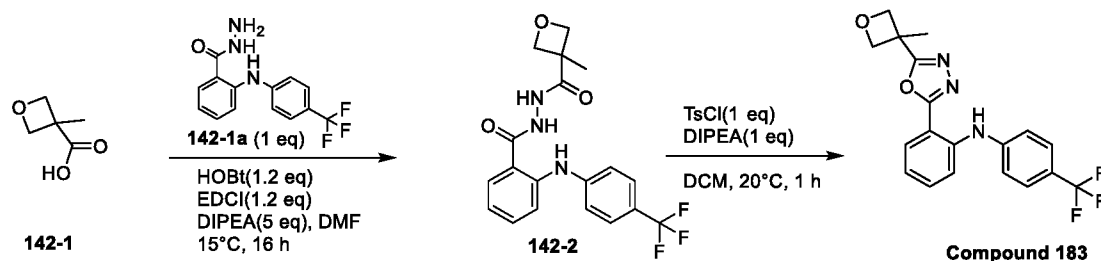
Step 1: N'-[2-[4-(trifluoromethyl)anilino]benzoyl]oxetane-2-carbohydrazide

[00551] To a solution of compound **141-1a** (38 mg, 0.3 mmol, 1.1 *eq*), HOBt (54.9 mg, 0.4 mmol, 1.2 *eq*) and EDCI (77.9 mg, 0.4 mmol, 1.2 *eq*) in DMF (3 mL) was added compound **141-1** (100 mg, 0.3 mmol, 1 *eq*) followed by DIEA (109.4 mg, 0.8 mmol, 0.1 mL, 2.5 *eq*). The reaction was stirred at 30°C for 16 hr. The reaction was diluted with EA (40 mL), washed with Sat. NaHCO₃ (2*10 mL) and brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give compound **141-2** (70 mg, 0.1 mmol, 47% yield). LCMS confirmed that desired product was obtained.

Step 2: 2-(5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00552] To a solution of compound **141-2** (70 mg, 0.1 mmol, 1 *eq*) and Et₃N (48.7 mg, 0.4 mmol, 67 μ L, 3 *eq*) in DCM (2 mL) was added TosCl (45.9 mg, 0.2 mmol, 1.5 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was diluted with DCM (20 mL) and washed with brine (10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 182** (18.07 mg, 49 μ mol, 30% yield). LCMS (ESI): RT = 0.999 min, mass calc. for C₁₈H₁₄F₃N₃O₂ 361.10, m/z found 362.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.44 (s, 1H), 7.91 (dd, *J* = 7.78, 1.51 Hz, 1H), 7.52 (d, *J* = 8.28 Hz, 2H), 7.42 - 7.48 (m, 1H), 7.25 - 7.39 (m, 3H), 6.88 - 6.96 (m, 1H), 5.92 (t, *J* = 7.40 Hz, 1H), 4.75 - 4.90 (m, 2H), 3.15 (q, *J* = 7.78 Hz, 2H).

Example 142: 2-(5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 183)



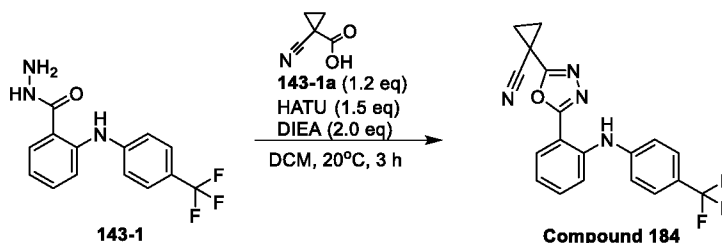
Step 1: 3-methyl-N'-[2-[4-(trifluoromethyl)anilino]benzoyl]oxetane-3-carbohydrazide

[00553] To a mixture of **142-1a** (150 mg, 0.51 mmol, 1.0 eq), compound **142-1** (70.79 mg, 0.61 mmol, 1.2 eq), HOBt (82.4 mg, 0.61 mmol, 1.2 eq) and EDCI (116.9 mg, 0.61 mmol, 1.2 eq) in DMF (3 mL) was added DIPEA (328.3 mg, 2.54 mmol, 0.5 mL, 5 eq) at 15°C. The resulting mixture was stirred at 15 °C for 16 h. The solution was diluted with H₂O (15 mL) and extracted with EA (50 mL) twice. The combined organic layer was washed with Na₂HCO₃ (30 mL), dried with Na₂SO₄, filtered and concentrated to give crude product compound **142-2** (260 mg, crude), which was used directly. LCMS (ESI): RT = 0.751 min, mass calc. for C₁₉H₁₈F₃N₃O₃ 393.13, m/z found 393.9 [M+1]⁺.

Step 2: 2-(5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

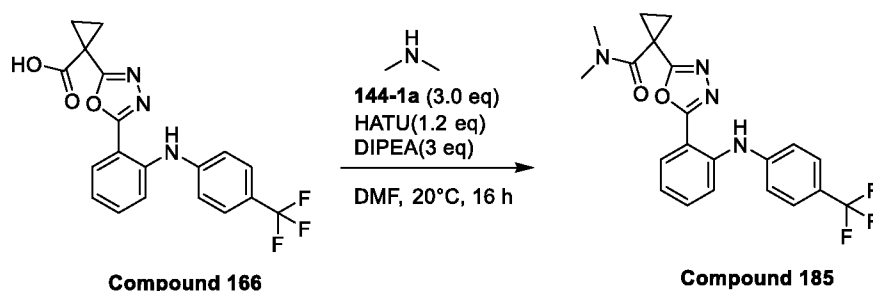
[00554] To a mixture of compound **142-2** (240 mg, 0.61 mmol, 1 eq) and DIPEA (78.8 mg, 0.61 mmol, 0.1 mL, 1 eq) in DCM (10 mL) was added TosCl (116.3 mg, 0.61 mmol, 1 eq) at 20°C. The resulting mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EA (50 mL * 2). The combined organic layers were washed with NaHCO₃ (20 mL * 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 183** (27.31 mg, 70.6 umol, 11.6% yield). LCMS (ESI): RT = 0.889 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 375.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.22-9.57 (m, 1H), 7.84 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.29-7.35 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.08 (d, *J* = 6.0 Hz, 2H), 4.60 (d, *J* = 6.0 Hz, 2H), 1.81-1.88 (m, 3H).

Example 143: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carbonitrile (Compound 184)



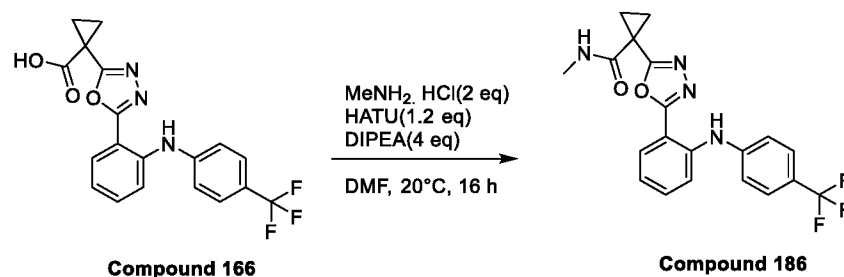
[00555] A solution of compound **143-1a** (90.3 mg, 0.81 mmol, 1.2 *eq*) and HATU (386 mg, 1.02 mmol, 1.5 *eq*) in DCM (6 mL) was stirred at 20°C for 30 min. Then compound **143-1** (200 mg, 0.68 mmol, 1 *eq*) and DIEA (175 mg, 1.35 mmol, 0.23 mL, 2 *eq*) were added to the mixture and stirred at 20°C for 2.5 hr. The reaction mixture was concentrated in vacuum to give a residue. The residue was diluted with EA (30 mL), washed with H₂O (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that **Compound 184** (28 mg, 74.8 μmol, 11% yield) was obtained. LCMS (ESI): RT = 1.022 min, mass calcd. For C₁₉H₁₃F₃N₄O, 370.10 m/z found 371.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.91 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.53 - 7.48 (m, 1H), 7.46 - 7.39 (m, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.03 - 6.96 (m, 1H), 2.03 - 1.98 (m, 4H).

Example 144: N,N-dimethyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (Compound 185)



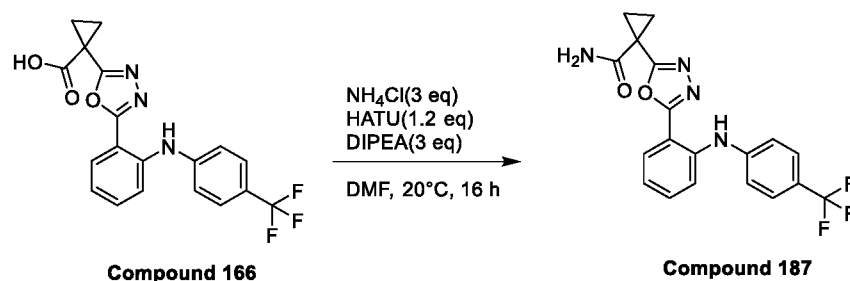
[00556] A mixture of **Compound 166** (40 mg, 0.1 mmol, 1 *eq*), HATU (46.9 mg, 0.12 mmol, 1.2 *eq*), DIPEA (39.8 mg, 0.3 mmol, 0.1 mL, 3 *eq*) and **144-1a** (2 M, 0.15 mL, 3 *eq*) in DMF (1 mL) was stirred at 20 °C for 16 hr under N₂ atmosphere. The mixture was directly purified by prep-HPLC to give **Compound 185** (4.20 mg, 10.1 μmol, 9.8% yield). LCMS (ESI): RT = 0.856 min, mass calc. for C₂₁H₁₉F₃N₄O₂ 416.15, m/z found 438.9 [M+23]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.14 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 3.8 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.12-7.20 (m, 1H), 2.90 (br d, *J* = 14.1 Hz, 6H), 1.47-1.65 (m, 4H).

Example 145: N-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (Compound 186)



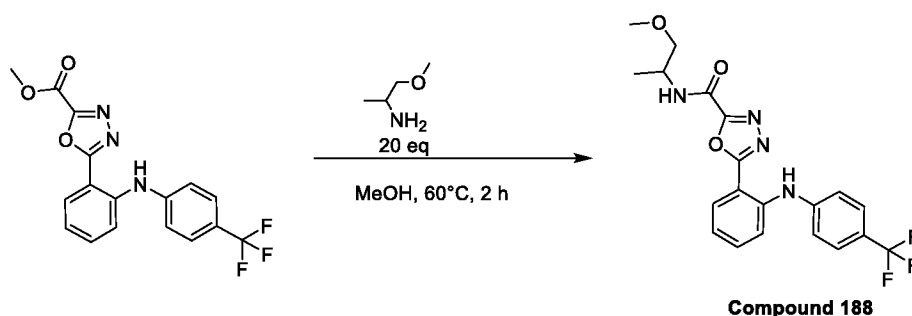
[00557] A mixture of **Compound 166** (40 mg, 0.1 mmol, 1.0 eq), HATU (46.9 mg, 0.12 mmol, 1.2 eq), DIPEA (53.1 mg, 0.4 mmol, 0.1 mL, 4.0 eq) and methanamine hydrochloride (13.9 mg, 0.2 mmol, 2.0 eq) in DMF (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20 °C for 16 hr under N₂ atmosphere. The mixture was directly purified by prep-HPLC to give **Compound 186** (18.19 mg, 0.1 mmol, 44.0% yield). LCMS (ESI): RT = 0.874 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 402.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.25 (s, 1H), 8.08 (br d, *J* = 4.4 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.51 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 2.65 (d, *J* = 4.4 Hz, 3H), 1.58 - 1.51 (m, 2H), 1.47 - 1.40 (m, 2H).

Example 146: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (Compound 187)



[00558] A mixture of **Compound 166** (40 mg, 0.1 mmol, 1.0 eq), HATU (46.9 mg, 0.1 mmol, 1.2 eq), DIPEA (39.8 mg, 0.3 mmol, 0.05 mL, 3.0 eq) and NH₄Cl (16.5 mg, 0.3 mmol, 0.01 mL, 3.0 eq) in DMF (1 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20 °C for 16 hr under N₂ atmosphere. The mixture was directly purified by prep-HPLC to give **Compound 187** (28.61 mg, 73.7 μmol, 71.7% yield). LCMS (ESI): RT = 0.843 min, mass calc. for C₁₉H₁₅F₃N₄O₂ 388.11, m/z found 388.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 7.69 (br s, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.47 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 1.61 - 1.52 (m, 2H), 1.49 - 1.42 (m, 2H).

Example 147: N-(1-methoxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 188)

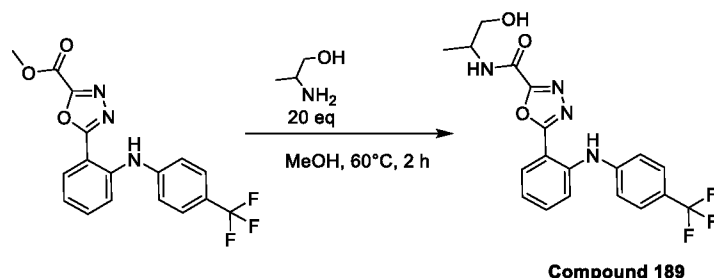


[00559] A mixture of compound methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (50 mg, 0.14 mmol, 1 eq) and 1-methoxypropan-2-amine (245.4 mg,

2.75 mmol, 0.3 mL, 20 *eq*) in MeOH (0.5 mL) was heated at 60°C for 2 h. The mixture was directly purified by prep-HPLC to give **Compound 188** (24.42 mg, 58.1 μ mol, 42.2% yield).

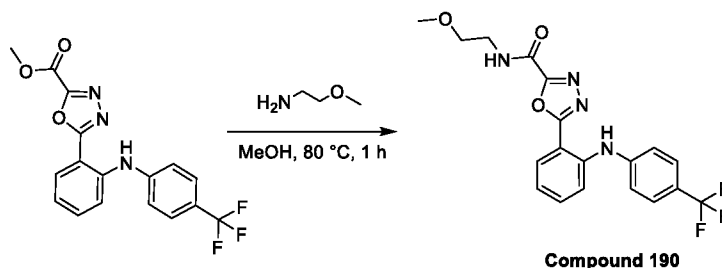
LCMS (ESI): RT = 0.880 min, mass calc. for $C_{20}H_{19}F_3N_4O_3$ 420.14, m/z found 442.9 $[M+23]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.18 (d, J = 8.3 Hz, 1H), 9.13 (s, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 3.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.21 - 7.12 (m, 1H), 4.23 (m, 1H), 3.49 - 3.41 (m, 1H), 3.33 (br d, J = 5.5 Hz, 1H), 3.28 (s, 3H), 1.17 (d, J = 6.8 Hz, 3H).

Example 148: N-(1-hydroxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 189)



[00560] A mixture of methyl compound methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (50 mg, 0.14 mmol, 1.0 *eq*) and compound **1a** (206.8 mg, 2.6 mmol, 0.22 mL, 20 *eq*) in MeOH (0.5 mL) was heated at 60°C for 2 h. The residue was directly purified by prep-HPLC to give **Compound 189** (28.39 mg, 0.07 mmol, 50.76% yield). LCMS (ESI): RT = 0.809 min, mass calc. for $C_{19}H_{17}F_3N_4O_3$ 406.13, m/z found 406.9 $[M+1]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.14 (s, 1H), 9.01 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 3.5 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.11-7.24 (m, 1H), 4.85 (t, J = 5.8 Hz, 1H), 3.84-4.26 (m, 1H), 3.41-3.53 (m, 2H), 1.17 (d, J = 6.8 Hz, 3H).

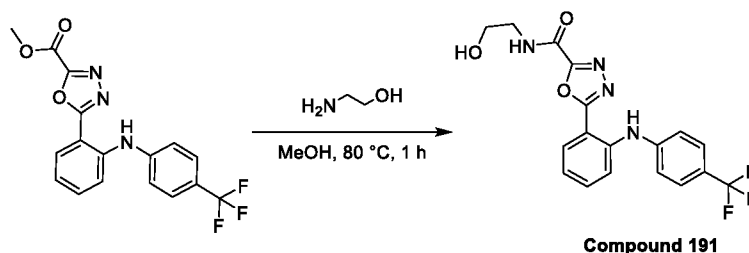
Example 149: N-(2-methoxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 190)



[00561] To a mixture of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60 mg, 0.17 mmol, 1 *eq*) in MeOH (3 mL) was added 2-methoxyethan-1-amine (62.0 mg, 0.82 mmol, 5 *eq*). The mixture was stirred at 80 °C for 1 h. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC. **Compound 190** (47.47 mg, 116.82 μ mol, 70.73% yield) was obtained, which was confirmed by LCMS and ^1H NMR. LCMS (ESI): RT = 0.844 min, mass calc. for $C_{19}H_{17}F_3N_4O_3$ 406.13, m/z found 406.9 $[M+H]^+$. ^1H NMR

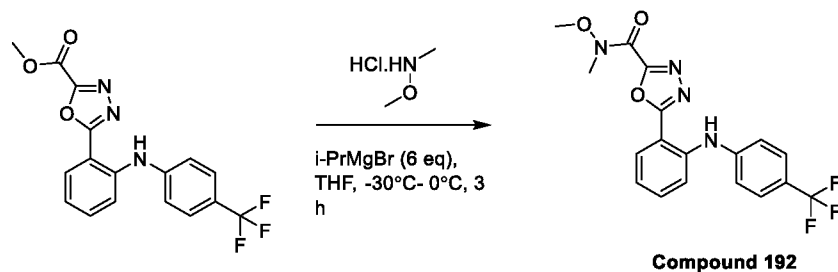
(400MHz, DMSO- d_6) δ 9.38 - 9.33 (m, 1H), 9.13 (s, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.59 - 7.54 (m, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.17 (ddd, J = 3.0, 5.3, 8.0 Hz, 1H), 3.52 - 3.44 (m, 4H), 3.27 (s, 3H).

Example 150: N-(2-hydroxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 191)



[00562] To a mixture of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60 mg, 0.17 mmol, 1 *eq*) in MeOH (3 mL) was added 2-aminoethan-1-ol (50.4 mg, 0.83 mmol, 5 *eq*). The mixture was stirred at 80 °C for 1 h. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC. **Compound 191** (32.95 mg, 83.2 μ mol, 50.3% yield) was obtained, which was confirmed by LCMS and ^1H NMR. LCMS (ESI): RT = 0.787 min, mass calcd. for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_3$ 392.11, m/z found 414.9 $[\text{M}+\text{Na}]^+$. ^1H NMR (400MHz, DMSO- d_6) δ 9.26 (t, J = 5.5 Hz, 1H), 9.14 (s, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.60 - 7.54 (m, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.17 (ddd, J = 2.9, 5.3, 7.9 Hz, 1H), 4.83 (t, J = 5.6 Hz, 1H), 3.54 (q, J = 5.9 Hz, 2H), 3.40 - 3.36 (m, 2H).

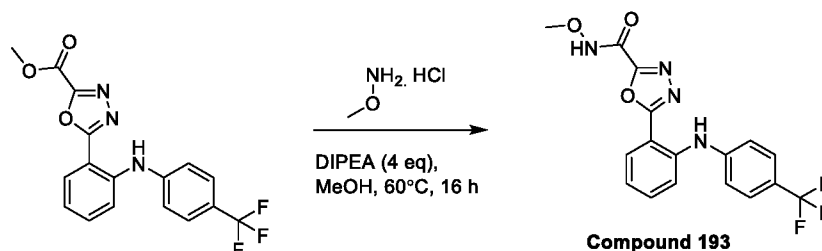
Example 151: N-methoxy-N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 192)



[00563] To a solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and N,O-dimethylhydroxylamine hydrochloride (48.3 mg, 0.50 mmol, 3 *eq*) in THF (2 mL) at -30 °C was added *i*-PrMgBr (0.5 M, 2.0 mL, 6 *eq*) dropwise, and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution (3 mL) at 0 °C, and then diluted with water (20 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **Compound 192** (6.84 mg, 16.8 μ mol, 10.2% yield). LCMS (ESI): RT = 0.876

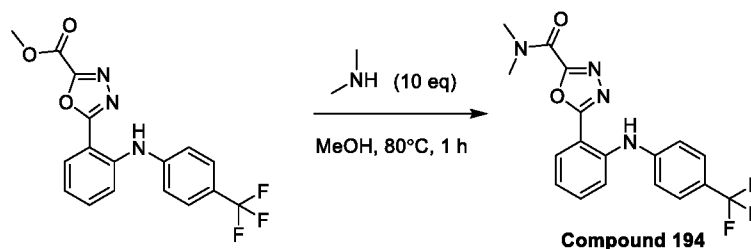
min, mass calc. for $C_{18}H_{15}F_3N_4O_3$ 392.11, m/z found 392.9 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (brs, 1H), 8.02 (d, $J = 7.8$ Hz, 1H), 7.60 (d, $J = 8.3$ Hz, 2H), 7.53 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.02 - 6.97 (m, 1H), 3.97 (s, 3H), 3.45 (s, 3H).

Example 152: N-methoxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 193)



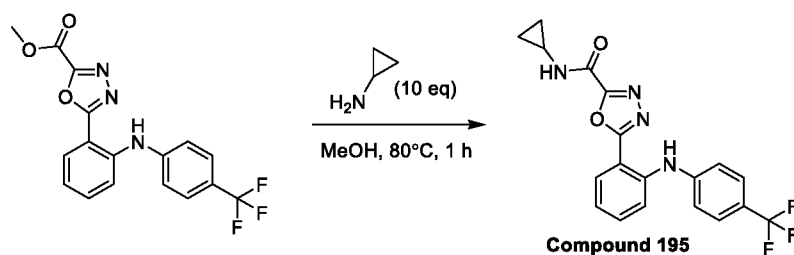
[00564] To a solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and O-methylhydroxylamine hydrochloride (3 *eq*) in MeOH (1 mL) at 20°C was added DIPEA (85.4 mg, 0.66 mmol, 0.1 mL, 4 *eq*), and the mixture was stirred at 60°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 193** (22.02 mg, 58.2 μ mol, 35.2% yield). LCMS (ESI): RT = 0.833 min, mass calc. for $C_{17}H_{13}F_3N_4O_3$ 378.09, m/z found 378.8 $[M+1]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 12.80 (brs, 1H), 9.10 (s, 1H), 7.98 (d, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.57 (d, $J = 3.8$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.17 (td, $J = 4.1, 8.0$ Hz, 1H), 3.76 (s, 3H).

Example 153: N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 194)



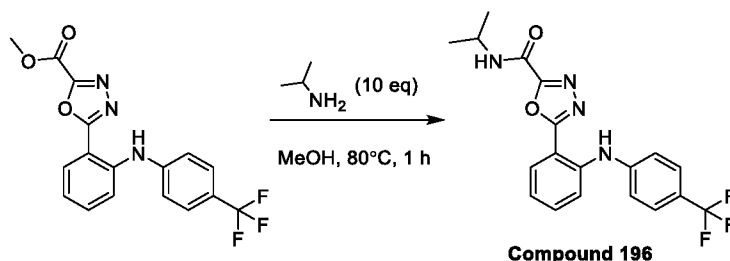
[00565] The solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and dimethylamine (2.0 M, 0.8 mL, 10 *eq*) in MeOH (1 mL) was stirred at 80°C for 1 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 194** (36.42 mg, 96.8 μ mol, 58.6% yield). LCMS (ESI): RT = 0.869 min, mass calc. for $C_{18}H_{15}F_3N_4O_2$ 376.11, m/z found 376.9 $[M+1]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.18 (s, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 8.5$ Hz, 2H), 7.59 - 7.53 (m, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.20 - 7.12 (m, 1H), 3.31 (s, 3H), 3.07 (s, 3H).

Example 154: N-cyclopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 195)



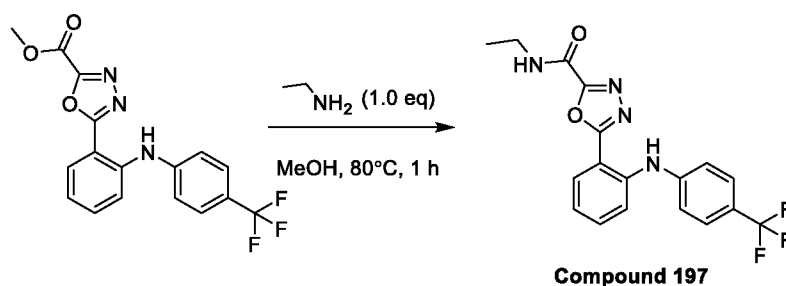
[00566] The solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and cyclopropylamine (94.3 mg, 1.65 mmol, 0.1 mL, 10 *eq*) in MeOH (1 mL) was stirred at 80°C for 1 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 195** (45.52 mg, 0.12 mmol, 71.0% yield). LCMS (ESI): RT = 0.865 min, mass calc. for C₁₉H₁₅F₃N₄O₂ 388.11, m/z found 388.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.42 (d, *J* = 4.5 Hz, 1H), 9.13 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 3.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.20 - 7.14 (m, 1H), 2.93 - 2.88 (m, 1H), 0.79 - 0.73 (m, 2H), 0.72 - 0.66 (m, 2H).

Example 155: N-isopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 196)



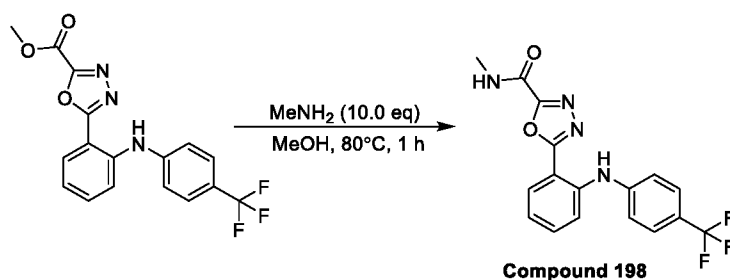
[00567] The solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and *iso*-propylamine (97.6 mg, 1.65 mmol, 0.1 mL, 10 *eq*) in MeOH (1 mL) was stirred at 80°C for 1 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 196** (33.33 mg, 85.4 μmol, 51.7% yield). LCMS (ESI): RT = 0.890 min, mass calc. for C₁₉H₁₇F₃N₄O₂ 390.13, m/z found 390.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.20 (d, *J* = 8.3 Hz, 1H), 9.14 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.59 - 7.53 (m, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.20 - 7.12 (m, 1H), 4.18 - 4.06 (m, 1H), 1.20 (d, *J* = 6.5 Hz, 6H).

Example 156: N-ethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 197)



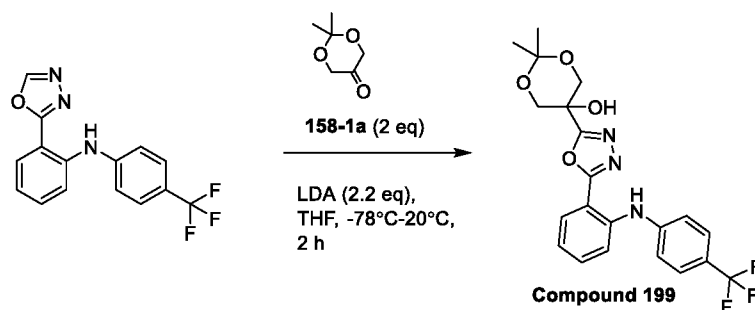
[00568] To a solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60 mg, 0.17 mmol, 1 eq) in MeOH (1 mL) was added ethylamine (7.5 mg, 165.16 μ mol, 10.8 μ L, 1 eq). The mixture was stirred at 80 °C for 1 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 197** (19.53 mg, 51.38 μ mol, 31% yield). LCMS (ESI): RT = 0.986 min, mass calc. for $C_{18}H_{15}F_3N_4O_2$ 376.11, m/z found 377.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.37 (t, J = 5.8 Hz, 1H), 9.14 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 2.8 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.19 - 7.12 (m, 1H), 3.34 - 3.27 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H).

Example 157: N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 198)



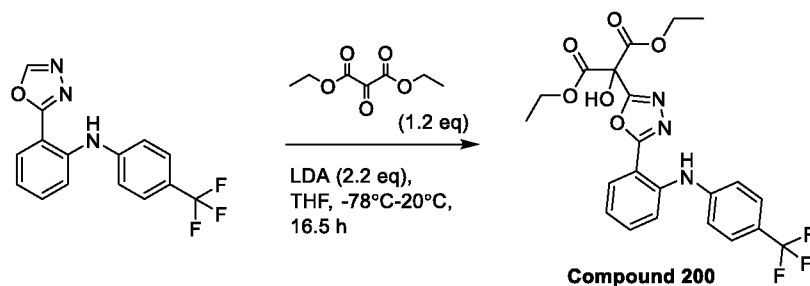
[00569] To a solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60 mg, 0.17 mmol, 1 eq) in MeOH (1 mL) was added MeNH₂ (2 M, 0.82 mL, 10 eq). The mixture was stirred at 80 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 198** (5.24 mg, 14.17 μ mol, 8% yield). LCMS (ESI): RT = 0.953 min, mass calc. for $C_{17}H_{13}F_3N_4O_2$ 362.10, m/z found 363.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.28 (d, J = 4.8 Hz, 1H), 9.14 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 2.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.18-7.14 (m, 1H), 2.84 (d, J = 4.8 Hz, 3H).

Example 158: 2,2-dimethyl-5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)-1,3-dioxan-5-ol (Compound 199)



[00570] To a solution of 2-(1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78°C was added LDA (2 M, 0.4 mL, 2.2 *eq*) drop-wise, and the mixture was stirred at -78°C for 0.5 h. And then the solution of **158-1a** (85.3 mg, 0.66 mmol, 0.2 mL, 2.0 *eq*) in THF (1 mL) was added at -78°C into the above solution. The resulting mixture was stirred at 20°C for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL), then diluted with water (5 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EA = 2:1, UV) to give **Compound 199** (80.13 mg, 0.18 mmol, 56.2% yield). LCMS (ESI): RT = 0.861 min, mass calc. for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_4$ 435.14, m/z found 436.0 $[\text{M}+1]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1H), 7.96 (dd, $J = 1.4, 8.0$ Hz, 1H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, $J = 8.5$ Hz, 2H), 6.99 (t, $J = 7.6$ Hz, 1H), 4.42 (d, $J = 11.9$ Hz, 2H), 4.08 (d, $J = 11.9$ Hz, 2H), 3.70 (s, 1H), 1.57 - 1.55 (m, 6H).

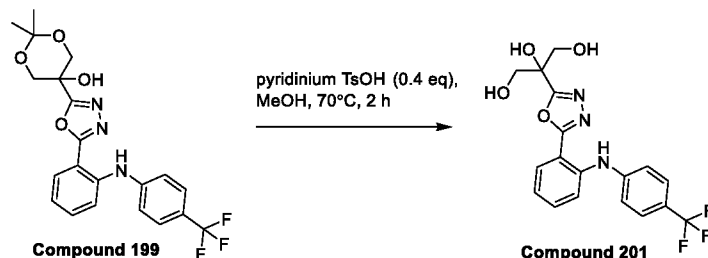
Example 159: diethyl 2-hydroxy-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)malonate (Compound 200)



[00571] To a solution of 2-(1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (50 mg, 0.16 mmol, 1 *eq*) in THF (2 mL) at -78°C was added LDA (2 M, 0.2 mL, 2.2 *eq*) drop-wise, and the mixture was stirred at -78°C for 0.5 h. And then the above solution was added at -78°C into the solution of diethyl 2-oxopropanedioate (34.2 mg, 0.20 mmol, 30 μL , 1.2 *eq*) in THF (1 mL). The resulting mixture was stirred at 20°C for 16 h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL), then diluted with water (5 mL) and extracted with EA (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC

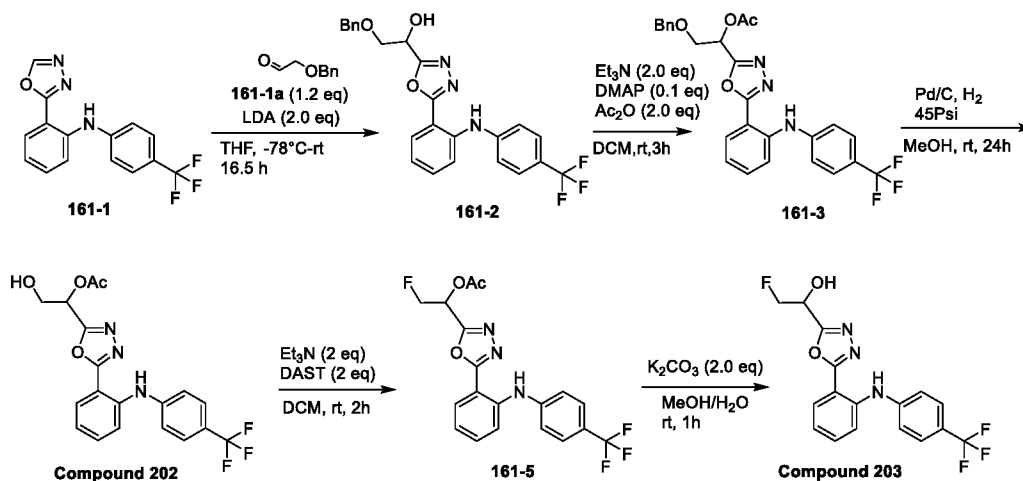
(PE:EA = 2:1, UV) to give **Compound 200** (25.0 mg, 50.1 μ mol, 30.6% yield). LCMS (ESI): RT = 0.902 min, mass calc. for $C_{22}H_{20}F_3N_3O_6$ 479.13, m/z found 480.0 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, J = 8.3 Hz, 2H), 6.98 (t, J = 7.0 Hz, 1H), 4.53 (s, 1H), 4.46 (ttt, J = 3.6, 7.1, 10.6 Hz, 4H), 1.38 (t, J = 7.0 Hz, 6H).

Example 160: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propane-1,2,3-triol (Compound 201)



[00572] The solution of **Compound 199** (70.0 mg, 0.16 mmol, 1 *eq*) and pyridinium TsOH (16.2 mg, 64.3 μ mol, 0.4 *eq*) in MeOH (3 mL) was stirred at 70°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 201** (32.41 mg, 82.0 μ mol, 51.0% yield). LCMS (ESI): RT = 0.742 min, mass calc. for $C_{18}H_{16}F_3N_3O_4$ 395.11, m/z found 395.9 $[M+1]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.60 - 8.75 (m, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.57 - 7.48 (m, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.14 (dt, J = 1.9, 7.1 Hz, 1H), 3.89 - 3.78 (m, 4H).

Example 161: 2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl acetate (Compound 202) and 2-fluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 203)



Step 1: 2-benzyloxy-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethanol

[00573] To a solution of compound 2-(1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline **161-1** (0.5 g, 1.6 mmol, 1 *eq*) in THF (8 mL) was added LDA (2 M, 1.6 mL, 2 *eq*) at -78°C. The

mixture was stirred at -78°C for 30 min. Compound **161-1a** (295.1 mg, 1.9 mmol, 0.3 mL, 1.2 *eq*) in THF (2 mL) was added drop wise to the solution and the reaction was warmed to 20°C. The reaction was stirred at 20°C for 16 hr. The reaction was quenched by Sat.NH₄Cl (10 mL) and extracted with EA (2*30 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give compound **161-2** (207 mg, 0.4 mmol, 27% yield).

Step 2: [2-benzyloxy-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethyl] acetate

[00574] To a solution of compound **161-2** (207 mg, 0.4 mmol, 1 *eq*), DMAP (5.5 mg, 45 μ mol, 0.1 *eq*) and Et₃N (91 mg, 0.9 mmol, 0.1 mL, 2 *eq*) in DCM (5 mL) was added Ac₂O (92.8 mg, 0.9 mmol, 85 μ L, 2 *eq*). The reaction was stirred at 25°C for 3 hr. The reaction was diluted with DCM (30 mL) and washed with brine (3*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give compound **161-3** (160 mg, 0.2 mmol, 61% yield). LCMS confirmed that desired product was obtained.

Step 3: 2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl acetate (Compound 202)

[00575] To a solution of compound **161-3** (130 mg, 0.2 mmol, 1 *eq*) in MeOH (20 mL) was added Pd/C (30 mg, 10%) under Ar. The suspension was degassed under vacuum and purged with H₂ 3 times. The mixture was stirred under H₂ (50 psi) at 30°C for 16 hours. The reaction was filtered and concentrated. The residue was purified by prep-HPLC to give **Compound 202** (4.63 mg, 10.7 μ mol, 4.1% yield) and compound **3** (20 mg, 40.2 μ mol, 15.4% yield). LCMS (ESI): RT = 0.825 min, mass calc. for C₁₉H₁₆F₃N₃O₄ 407.11, m/z found 407.9 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.99 (dd, *J* = 7.91, 1.38 Hz, 1H), 7.56 - 7.68 (m, 3H), 7.50 (td, *J* = 7.91, 1.51 Hz, 1H), 7.42 (d, *J* = 8.53 Hz, 2H), 7.04 - 7.12 (m, 1H), 2.02 - 2.10 (m, 3H).

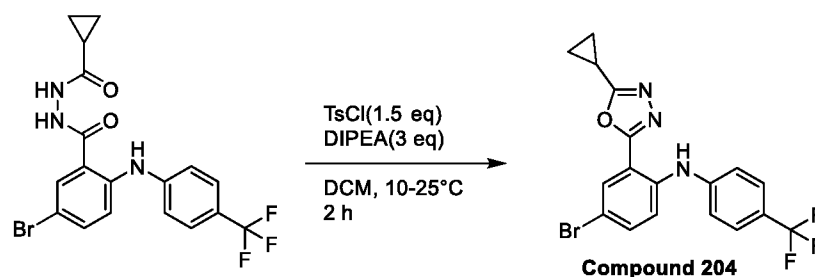
Step 4: [2-fluoro-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethyl] acetate

[00576] To a solution of **Compound 202** (90 mg, 0.22 mmol, 1 *eq*) and Et₃N (44 mg, 0.44 mmol, 61 μ L, 2 *eq*) in DCM (3 mL) was added DAST (71 mg, 0.44 mmol, 58 μ L, 2 *eq*). The reaction was stirred at 25°C for 2 hr. The reaction was diluted with DCM (15 mL) and washed with water (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The reaction was purified by column chromatography on silica gel to give compound **161-5** (20 mg, 46 μ mol, 21% yield). LCMS confirmed that desired product was obtained. LCMS (ESI): RT = 1.027 min, mass calc. for C₁₉H₁₅F₄N₃O₃ 409.10, m/z found 410.0 [M+H]⁺.

Step 5: 2-fluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 203)

[00577] To a solution of compound **161-5** (10 mg, 24 μmol , 1 *eq*) in MeOH (1 mL) was added K_2CO_3 (6.7 mg, 48 μmol , 2 *eq*) in H_2O (0.1 mL). The reaction was stirred at 25°C for 1 hr. The solution was concentrated. The aqueous layer was extracted with EA (2*5 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give **Compound 203** (1.3 mg, 3.4 μmol , 7% yield). LCMS (ESI): RT = 0.946 min, mass calc. for $\text{C}_{17}\text{H}_{13}\text{F}_4\text{N}_3\text{O}_2$ 367.09, m/z found 368.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.41 (s, 1H), 7.95 (dd, $J = 7.91, 1.38$ Hz, 1H), 7.61 (d, $J = 8.53$ Hz, 2H), 7.49 - 7.56 (m, 1H), 7.44 (td, $J = 7.84, 1.38$ Hz, 1H), 7.38 (d, $J = 8.53$ Hz, 2H), 6.96 - 7.05 (m, 1H), 5.72 - 5.92 (m, 1H), 4.23 - 4.43 (m, 2H), 2.48 (br s, 1H).

Example 162: 4-bromo-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 204)



[00578] To a mixture of compound 5-bromo- N' -(cyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide (860 mg, 1.94 mmol, 1 *eq*) and DIPEA (754.0 mg, 5.83 mmol, 1.0 mL, 3 *eq*) in DCM (15 mL) was added TsCl (556.1 mg, 2.92 mmol, 1.5 *eq*) at 10°C. Then the mixture was stirred at 25°C for 2 h. The mixture was diluted with DCM (200 mL), washed with 1 M HCl (20 mL) and brine (15 mL*2) in turns, dried with Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography to give the product (800 mg, 1.89 mmol, 97.2% yield). 50 mg of the crude product was purified by TLC to give **Compound 204** (10.64 mg, 24.9 μmol , 1.3% yield). MS: mass calc. for $\text{C}_{18}\text{H}_{13}\text{BrF}_3\text{N}_3\text{O}$ 423.02, m/z found 426.04 $[\text{M}+1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.21 (s, 1H), 8.01 (d, $J = 2.3$ Hz, 1H), 7.69 - 7.59 (m, 3H), 7.48 (d, $J = 8.8$ Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 2H), 2.38 - 2.27 (m, 1H), 1.21 - 1.09 (m, 4H).

II. Biological Evaluation

Example A1: YAP Reporter Assay

[00579] HEK293T cells stably transfected with 8XTBD luciferase reporter and pRLTK in 384-well plates were treated with the test compounds, starting from 3 μM (final concentration in assay

plate), 1:3 dilution, and 10 points in quadruplicates. Post 24-hr incubation with compounds at 37°C and 5% CO₂, cells were lysed and 8XTBD-driven firefly luciferase and control TK-driven renilla luciferase activities were measured using Promega Dual-Luciferase Reporter Assay System.

[00580] Reagents: The reagents used for this study are: DMEM: Invitrogen# 11960077, Dual-Glo Luciferase Assay System: Promega-E2980, Puromycin Dihydrochloride: Invitrogen-A1113803, 384-well plate: PerkinElmer-6007480, L-GLUTAMINE: Invitrogen-25030164, Hygromycin B: Invitrogen-10687010, and Penicillin-Streptomycin: Merk-TMS-AB2-C

[00581] Media: The media used for this assay were: Culture Medium: DMEM+ 1ug/mL puromycin + 200 ug/mL hygromycin (with 10% FBS + 1mM L-glutamine); and Assay Medium: DMEM (with 10% FBS + 1mM L-glutamine + 1x P/S).

[00582] Cell Plating: The appropriate media was warmed at 37°C by water bath: Culture Medium, Assay Medium, 1* D-PBS, 0.05% trypsin-EDTA. The cells were trypsinized after removing all media, then washed with 1* sterile D-PBS and then with 2 ml 0.05% trypsin-EDTA. The cells were then incubated at RT for one minute. Then 10 ml/75cm² flask Assay Medium was added to each flask. Using a 10 ml pipette, the cells were then gently resuspended in the media, until the clumps completely disappeared. The cells were then transferred into 50 ml centrifuge tubes and were centrifuged at 800 rpm for 5 mins. The medium was removed and the cells were resuspended with Assay Medium. An aliquot of cells was used to count the cell density (cells/ml). The cell suspension was then diluted with Assay Medium to a concentration of 6x10⁴ cells/ml. 50ul cells suspension was then plated to 384-well plate (PerkinElmer-6007480), 3x10³ cells/well and the cells were incubated in an incubator at 37°C, 5% CO₂.

[00583] Compound Treatment: In the afternoon (incubation of the plate with 3-4 hrs), the test compounds were added by Echo, starting from 3uM (final concentration in the assay plate), 1:3 dilution, 10 points, quadruplicates. The plate was placed at 37°C, 5% CO₂ incubator for 24hrs.

[00584] Detection: The Dual-Glo Luciferase Reagent was prepared by transferring the contents of one bottle of Dual-Glo Luciferase Buffer to one bottle of Dual-Glo Luciferase Substrate to create the Dual-Glo Luciferase Reagent. Mixing was performed by inversion until the substrate was thoroughly dissolved. After mixing, the reagent was aliquoted into 15 ml tubes. In the afternoon (24hrs post compound treatment), the DMEM+ medium in the 384 well plates were aspirated by Microplate Washer.

[00585] Measuring firefly luciferase activity: 20ul Dual-Glo Luciferase Reagent was added to the 384-well plates. The plates were protected from light to prevent interference with the assay. The plates were shaken for 1min followed centrifuging plates at 1000rpm for 30 seconds. After waiting at least 10 minutes, the firefly luminescence was measured by Envision.

[00586] Measuring renilla luciferase activity: 20ul Stop-Glo Reagent was added to the 384-well plates. The plates were shaken for 1min and then centrifuged at 1000rpm for 30 seconds. After waiting at least 10 minutes, the renilla luminescence was measured by Envision.

[00587] Compound IC₅₀ and maximum inhibition on the firefly luciferase and renilla luciferase activities were reported separately. IC₅₀ for firefly luciferase activity are shown in the table below.

TABLE 2

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
1	ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate	B
2	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol	A
3	ethyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate	A
4	5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine	B
5	(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol	A
6	N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine	C
8	methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate	B
9	ethyl (5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate	C
10	2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol	B
11	ethyl N-methyl-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate	B
12	N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine	B
13	5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	B
14	N-hydroxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
15	5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
16	3-tosyl-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	B
17	4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	A
19	2-(methyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol	B
20	2-(1,3,4-oxadiazol-2-yl)-N-[4-(trifluoromethyl)phenyl]aniline	B
22	5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carbonitrile	A
24	2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide	B
25	1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethane-1,2-diol	A
26	2-oxo-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidine-3-carboxylate	A
28	2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline	B
29	4-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-1,3-dioxolan-2-one	A
30	2-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol	B
31	2-[5-(azidomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline	B
32	N-(2-hydroxyethyl)-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide	B
34	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)imidazolidin-2-one	B
35	2-(5-(5-methyloxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
36	2-(5-(oxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
37	2-(5-(oxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
38	N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
40	2-(5-(5-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
41	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol	A
42	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol	A
44	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropanol	A
45	2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol	A
46	2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl 4-methylbenzenesulfonate	B
47	(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methanol	A
48	2-[5-(2H-tetrazol-5-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline	C
49	cyclopropyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol	A
50	3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-4H-1,2,4-oxadiazol-5-one	C
51	2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol	A
52	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopentanol	A
53	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl 4-methylbenzenesulfonate	B
54	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclobutanol	A
55	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxetan-3-ol	A
56	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3-ol	A
57	(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate	B
58	2-(5-(1-aminocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
59	N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)acetamide	B
60	2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol	A
62	1-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)urea	B
63	2-(5-(1-fluorocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
66	2-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline	A
67	2-(5-(1-methoxycyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
68	2-(5-(2-methylbut-3-yn-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
69	2-(5-(but-3-yn-2-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
70	2-(5-(but-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
71	2-(5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
72	2-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
73	2-(5-methoxy-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
75	(S)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one	A
76	(R)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one	A
77	(R)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	A
78	(S)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	B
79	1-chloro-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol	A
80	3-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol	A

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
81	2-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol	A
82	(E)-2-(5-((3-bromoallyl)oxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
83	2-(5-(prop-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
84	2-(5-(allyloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
85	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-one	A
86	2-(5-(2-methyl-1,3-dioxolan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
87	N-methoxy-N,2-dimethyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide	A
88	1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyclopropane-1-carbonitrile	B
89	2,2-dimethyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile	B
90	2-(5-ethyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
91	2-(5-(2-(isopropylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
93	N-isopropyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide	B
94	2-(5-(2-(ethylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
96	N-ethyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide	A
97	2-(5-((isopropylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
99	N-isopropyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide	B
100	2-(5-((ethylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
102	N-ethyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide	A

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
103	2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoic acid	B
104	2-(5-(2-aminoethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
108	N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)acrylamide	A
110	N-(cyanomethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide	C
112	2-methyl-N-(prop-2-yn-1-yl)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide	C
113	N-(2-cyanoethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
114	N-(cyanomethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
115	N-(but-3-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
116	N-(prop-2-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
117	(E)-2-(5-(prop-1-en-1-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
119	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetic acid	B
120	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-2-ol	A
121	2-bromo-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol	A
122	2-(5-(oxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
123	N-(4-(trifluoromethyl)phenyl)-2-(5-vinyl-1,3,4-oxadiazol-2-yl)aniline	A
124	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-1-ol	A
126	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
129	N-methyl-N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide	A
130	3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile	A
132	2-(5-(2-methyloxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
133	2-(5-(prop-1-en-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
134	1-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol	B
135	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol	A
136	2-(5-((1-aminocyclopropyl)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
137	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetonitrile	B
140	N-methyl-N-((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)cyanamide	A
143	N-methyl-N-(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide	C
144	2-(5-(2-methyl-1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
146	N-methyl-N-(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide	A
147	2-(5-(2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
149	N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide	A
150	2-(5-(1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
152	N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide	A
153	2-(5-(1-(methylamino)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
155	N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)cyanamide	A
156	2-(5-(2-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
158	N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide	A
159	2-(5-(1-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
161	N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide	A
162	2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide	A
163	2-(5-(2-(methylsulfonyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
164	2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile	A
166	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylic acid	A
167	tert-butyl methyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate	C
168	N-methyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide	A
169	2-(5-(pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
171	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile	A
172	2-(5-(2-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
174	N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide	A
175	2-(5-(pyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
177	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile	B
178	2-(5-(2-methyltetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
179	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butane-1,3-diol	A
180	2-(5-(2-methyloxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
181	2-(5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
182	2-(5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
183	2-(5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
184	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carbonitrile	A
185	N,N-dimethyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide	B
186	N-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide	B
187	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide	A
188	N-(1-methoxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B
189	N-(1-hydroxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B
190	N-(2-methoxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
191	N-(2-hydroxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
192	N-methoxy-N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B
194	N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	C
195	N-cyclopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B
196	N-isopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
197	N-ethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
198	N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
199	2,2-dimethyl-5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)-1,3-dioxan-5-ol	C
200	diethyl 2-hydroxy-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)malonate	B
201	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propane-1,2,3-triol	A
202	2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl acetate	A
203	2-fluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol	A
204	4-bromo-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B

Note: Biochemical assay IC₅₀ data are designated within the following ranges:

A: ≤ 0.100 μM

B: > 0.100 μM to ≤ 1.000 μM

C: > 1.000 μM to ≤ 5.000 μM

D: > 5.000 μM

Example A2: Tumor Suppression Assay

[00588] The procedures described herein for the tumor suppression assay is as described in PCT/US2013/043752 (WO 2013/188138). Mouse procedures are performed according to the guidelines of approved animal protocol and based on the methods. After the cells are grown to 90%> confluence, these cells are harvested by trypsinization, washed in phosphate-buffered saline (PBS), and resuspended in PBS supplemented with 50% matrigel (BD Biosciences). An appropriate amount of cells is prepared for administration, such as 200 μL per injection site. Immuno-compromised mice are injected on the dorsolateral sites subcutaneously. Any one of the compounds described herein is formulated accordingly and is then administered at a suitable dose. Control mice received vehicle alone. The average tumor diameter (two perpendicular axes of the tumor are measured) are recorded. The data are expressed in tumor volume estimated by $(\text{width})^2 \times \text{length} / 2$. Paired, two-tailed Student's t-test is performed to access the statistical significance.

Example A3: Cell Proliferation Assay

[00589] Cancer cell lines are plated in 384-well plates 24h before drug treatment. Post incubation for various time periods with the test compounds, starting from 3 μ M (final concentration in assay plate), 1:3 dilution, and 10 points in duplicates, the number of viable cells and proliferative cells are determined using CellTiter-Glo® Luminescent Cell Viability Assay Kit (Promega) and Click-iT EdU HCS Assay Kit (Invitrogen) according to the manufacturers' protocols. The IC₅₀ values and maximum % inhibition of the test compounds are calculated using the dose response curves.

[00590] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

OXADIAZOLE COMPOUNDS

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 62/672,370 filed on May 16, 2018, which is incorporated herein by reference in its entirety.

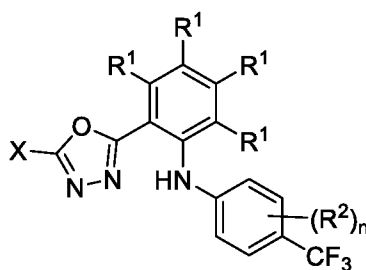
BACKGROUND OF THE DISCLOSURE

[0002] YAP and TAZ are transcriptional co-activators of the Hippo pathway network and regulate cell proliferation, migration, and apoptosis. Inhibition of the Hippo pathway promotes YAP/TAZ translocation to the nucleus, wherein YAP/TAZ interact with transcriptional enhancer associate domain (TEAD) transcription factors and coactivate the expression of target genes and promote cell proliferation. Hyperactivation of YAP and TAZ and/or mutations in one or more members of the Hippo pathway network have been implicated in numerous cancers. Described herein are inhibitors associated with one or more members of the Hippo pathway network, such as inhibitors of YAP/TAZ or inhibitors that modulate the interaction between YAP/TAZ and TEAD.

SUMMARY OF THE DISCLOSURE

[0003] Provided herein are substituted oxadiazole compounds and pharmaceutical compositions comprising said compounds. In some embodiments, the subject compounds are useful for the treatment of cancer.

[0004] Provided in one aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

X is H, -CN, halogen, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, -L²-L³-Y², -L²-L³-L⁴-Y², -L⁵-L⁶-L³-Y², or -L⁶-L⁵-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y^1 is N_3 , substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^2 is absent, substituted or unsubstituted C_1 - C_6 alkylene, substituted or unsubstituted C_3 - C_{10} cycloalkylene, or substituted or unsubstituted C_2 - C_{10} heterocycloalkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-, -O(C=O)-NR³(SO₂)-NR³-, -NR³(SO₂)NR³-(C=O)O-, -O-(SO₂)-, or -(SO₂)-O-;

each R³ is independently H, -CN, -S(=O)₂(C₁-C₄alkyl), or substituted or unsubstituted C_1 - C_6 alkyl;

L^4 is substituted or unsubstituted C_1 - C_6 alkylene;

L^5 is substituted or unsubstituted C_1 - C_6 alkylene;

L^6 is substituted or unsubstituted C_3 - C_{10} cycloalkylene;

Y^2 is H, -CN, -N₃, halogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂;

or R³ and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R⁶ is independently H or substituted or unsubstituted C_1 - C_6 alkyl;

or two R⁶ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or -L⁷-Y³;

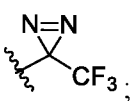
L^7 is substituted or unsubstituted C_1 - C_6 alkylene;

Y^3 is -Si(R⁷)₂;

each R⁷ is independently substituted or unsubstituted C_1 - C_6 alkyl;

n is 0, 1, 2, 3, or 4;

each R^2 is independently H, halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R^4 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^4 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

each R^5 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[0005] In some embodiments, if X, L^1 , L^2 , L^4 , L^5 , L^6 , L^7 , Y^1 , Y^2 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , or R^7 is substituted, then X, L^1 , L^2 , L^4 , L^5 , L^6 , L^7 , Y^1 , Y^2 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , or R^7 is substituted with 1-5 R^8 groups; each R^8 is independently selected from halogen, $-N_3$, $-CN$, $-NO_2$, $-OR^9$, $-SR^9$, $-S(=O)R^{10}$, $-S(=O)_2R^{10}$, $-S(=O)_2N(R^9)_2$, $-NR^9S(=O)_2R^{10}$, $-C(=O)R^{10}$, $-OC(=O)R^{10}$, $-CO_2R^9$, $-OCO_2R^{10}$, $-N(R^9)_2$, $-C(=O)N(R^9)_2$, $-OC(=O)N(R^9)_2$, $-NHC(=O)R^{10}$, $-NHC(=O)OR^{10}$, $-(CH_2)_r-R^9$, $-(CH_2)_r$ -halogen, unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or substituted C_1 - C_6 fluoroalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, unsubstituted or substituted C_1 - C_6 heteroalkyl, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_{10} heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; each R^9 is independently selected from H, substituted or unsubstituted C_1 - C_6 alkyl, unsubstituted or substituted C_1 - C_6 fluoroalkyl, unsubstituted or substituted C_1 - C_6 heteroalkyl, unsubstituted or substituted C_3 - C_{10} cycloalkyl,

unsubstituted or substituted C₂-C₁₀heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; or two R⁹ on the same N atom are taken together with the N atom to which they are attached to form a N-containing heterocycle; each R¹⁰ is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, unsubstituted or substituted C₁-C₆fluoroalkyl, unsubstituted or substituted C₁-C₆heteroalkyl, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₁₀heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; and r is 1, 2, 3, or 4.

[0006] In some embodiments, X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0007] In some embodiments, X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0008] In some embodiments, X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[0009] In some embodiments, X is substituted or unsubstituted C₁-C₄alkyl. In some embodiments, X is -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃.

[0010] In some embodiments, X is substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, X is -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.

[0011] In some embodiments, X is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, X is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl.

[0012] In some embodiments, X is substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, X is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-

dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl.

[0013] In some embodiments, X is substituted or unsubstituted heteroaryl. In some embodiments, X is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, X is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[0014] In some embodiments, X is $-L^1-Y^1$. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, Y^1 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, Y^1 is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted phenyl. In some embodiments, L^1 is substituted or unsubstituted C_1 - C_4 alkylene; and Y^1 is substituted or unsubstituted heteroaryl. In some embodiments, Y^1 is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, Y^1 is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or

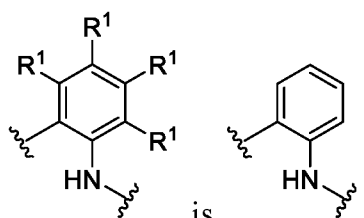
unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[0015] In some embodiments, X is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1 - C_4 alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-; Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂. In some embodiments, L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-; Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C_1 - C_4 alkyl.

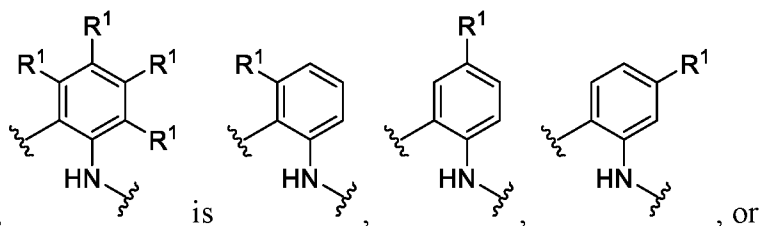
[0016] In some embodiments, L^2 is absent; L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-; Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂. In some embodiments, L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-; Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl,

substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$; and each R^6 is independently H or substituted or unsubstituted C_1 - C_4 alkyl.

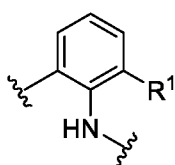
[0017] In some embodiments, X is $-\text{L}^2-\text{L}^3-\text{L}^4-\text{Y}^2$. In some embodiments, L^2 is substituted or unsubstituted C_1 - C_4 alkylene; L^3 is $-\text{O}-$, $-\text{S}-$, $-(\text{S}=\text{O})-$, $-(\text{SO}_2)-$, $-\text{NR}^3-$, $-(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{O}-$, $-\text{O}(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{NR}^3-$, $-(\text{C}=\text{O})\text{NR}^3-\text{O}-$, $-\text{NR}^3(\text{C}=\text{O})-$, $-\text{NR}^3(\text{C}=\text{O})\text{NR}^3-$, $-\text{O}(\text{C}=\text{O})\text{NR}^3-$, $-\text{NR}^3(\text{C}=\text{O})\text{O}-$, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-$, $-\text{NR}^3(\text{SO}_2)-$, $-(\text{SO}_2)\text{NR}^3-$, $-(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})-$, $-(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})-$, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$, or $-\text{O}-(\text{SO}_2)-$; L^4 is substituted or unsubstituted C_1 - C_4 alkylene; Y^2 is independently H, $-\text{CN}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$. In some embodiments, L^3 is $-\text{O}-$, $-\text{S}-$, $-(\text{S}=\text{O})-$, $-(\text{SO}_2)-$, $-\text{NR}^3-$, $-(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{O}-$, $-\text{O}(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{NR}^3-$, $-(\text{C}=\text{O})\text{NR}^3-\text{O}-$, $-\text{NR}^3(\text{C}=\text{O})-$, $-\text{NR}^3(\text{C}=\text{O})\text{NR}^3-$, $-\text{NR}^3(\text{C}=\text{O})\text{O}-$, $-\text{NR}^3(\text{SO}_2)-$, $-(\text{SO}_2)\text{NR}^3-$, or $-\text{O}-(\text{SO}_2)-$; Y^2 is independently H, $-\text{CN}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$; and each R^6 is independently H or substituted or unsubstituted C_1 - C_4 alkyl.



[0018] In some embodiments,



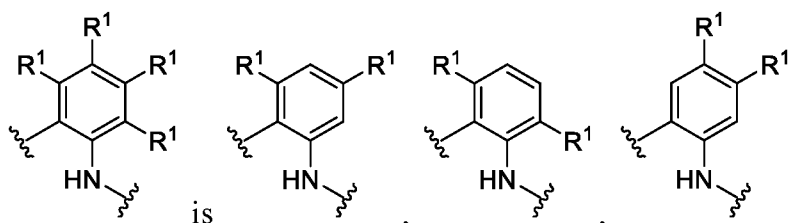
[0019] In some embodiments,



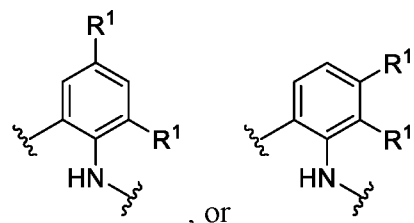
and R^1 is halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl,

substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0020] In some embodiments, R¹ is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R¹ is halogen, substituted or unsubstituted C₁-C₄alkyl, or substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, R¹ is F, Cl, Br, I, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -C(CH₃)₃, -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.

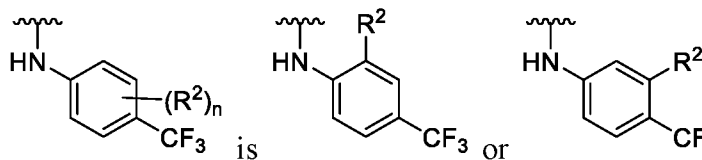


[0021] In some embodiments,



; and each R¹ is independently halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0022] In some embodiments, each R¹ is independently halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R¹ is independently halogen, substituted or unsubstituted C₁-C₄alkyl, or substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R¹ is independently F, Cl, Br, I, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -C(CH₃)₃, -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.



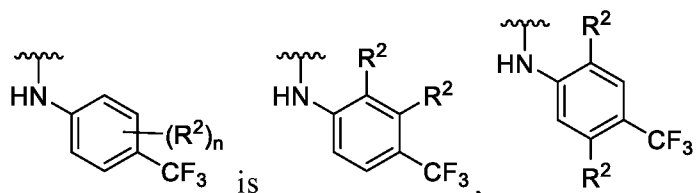
[0023] In some embodiments, halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl, or

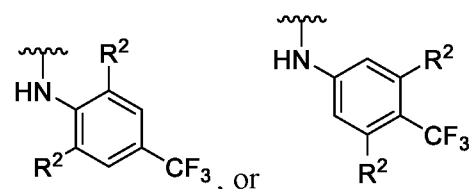
[0024] In some embodiments, R^2 is halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted

phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and each R^5 is independently H, or substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, R^2 is halogen, $-N_3$, $-OR^5$, $-(SO_2)R^5$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted

C_1 - C_4 haloalkyl, or



[0025] In some embodiments, wherein:

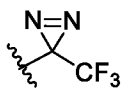


; and each R^2 is independently halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted aralkyl,

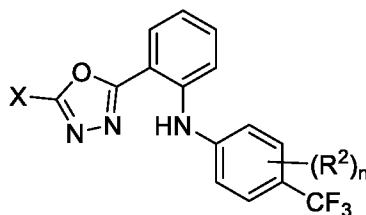
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or In some embodiments, each R^2 is independently halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted

phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and each R^5 is

independently H, or substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R² is independently halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl,

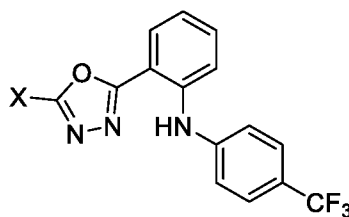
substituted or unsubstituted C₁-C₄haloalkyl, or .

[0026] In some embodiments, the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



Formula (Ia).

[0027] In some embodiments, the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:



Formula (Ib).

[0028] In some embodiments, the compound exhibits an IC₅₀ of no more than about 5.000 μM.

[0029] Provided in another aspect is a compound, or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1, or a pharmaceutically acceptable salt thereof.

[0030] Provided in another aspect is a pharmaceutical composition comprising a pharmaceutically acceptable excipient and any one of the compounds disclosed herein or a pharmaceutically acceptable salt thereof.

[0031] Provided herein is a method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound of any one of the compounds disclosed herein or a pharmaceutically acceptable salt thereof.

INCORPORATION BY REFERENCE

[0032] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0034] **FIG. 1** illustrates a schematic representation of the Hippo signaling network. Hippo pathway components shaded in dark gray indicate components that inhibit YAP/TAZ activity. Hippo pathway components shaded in light gray indicate components that promote YAP/TAZ activity. Pointed and blunt arrowheads indicate activating and inhibitory interactions, respectively. Abbreviations: α -CAT (α -Catenin), AJUB (Ajuba), AMOT (Angiomotin), β -TRCP (β -transducing repeat containing protein), CK1 (Casein Kinase 1), CRB (Crumbs), E-CAD (E-cadherin), EX (Expanded), GPCR (G-protein coupled receptor), HIPK (Homeodomain interacting protein kinase), KIBRA (Kidney brain), LATS (Large tumor suppressor), LGL (Lethal giant larvae), MASK (Multiple ankyrin single KH), MER (Merlin), MOB (Mps one binder), MST (Mammalian sterile 20 like), PALS (Protein Associated with Lin-7), PATJ (Pals1-associated tight junction protein), PP2A (Protein phosphatase 2A), PTPN14 (Protein tyrosine phosphatase non-receptor type 14), RASSF (Ras associated factor), SAV (Salvador), SCRIB (Scribble), SIK (Salt inducible kinase), TAO (Thousand and one amino acid protein), TAZ (transcriptional coactivator with PDZ-binding motif), TEAD (TEA domain protein), VGL4 (Vestigial-like 4), WBP2 (WW domain binding protein 2), YAP (Yes associated protein), ZO (Zonula occludens), ZYX (Zyxin).

[0035] **FIG. 2** illustrates a schematic representation of the Hippo signaling pathway regulated by G alpha proteins.

DETAILED DESCRIPTION OF THE DISCLOSURE

Certain Terminology

[0036] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

[0037] As used herein, in some embodiments, ranges and amounts are expressed as “about” a particular value or range. About also includes the exact amount. Hence “about 5 μL ” means “about 5 μL ” and also “5 μL .” Generally, the term “about” includes an amount that is expected to be within experimental error.

[0038] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0039] As used herein, the terms “individual(s)”, “subject(s)” and “patient(s)” mean any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g. constant or intermittent) of a health care worker (e.g. a doctor, a registered nurse, a nurse practitioner, a physician’s assistant, an orderly, or a hospice worker).

[0040] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0041] "Amino" refers to the $-\text{NH}_2$ radical.

[0042] "Cyano" refers to the $-\text{CN}$ radical.

[0043] "Nitro" refers to the $-\text{NO}_2$ radical.

[0044] "Oxa" refers to the $-\text{O}-$ radical.

[0045] "Oxo" refers to the $=\text{O}$ radical.

[0046] "Thioxo" refers to the $=\text{S}$ radical.

[0047] "Imino" refers to the $=\text{N}-\text{H}$ radical.

[0048] "Oximo" refers to the $=\text{N}-\text{OH}$ radical.

[0049] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to fifteen carbon atoms (e.g., $\text{C}_1\text{-C}_{15}$ alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (e.g., $\text{C}_1\text{-C}_{13}$ alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (e.g., $\text{C}_1\text{-C}_8$ alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (e.g., $\text{C}_1\text{-C}_5$ alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (e.g., $\text{C}_1\text{-C}_4$ alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (e.g., $\text{C}_1\text{-C}_3$ alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (e.g., $\text{C}_1\text{-C}_2$ alkyl). In other embodiments, an alkyl comprises one carbon atom (e.g., C_1 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (e.g., $\text{C}_5\text{-C}_{15}$ alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (e.g., $\text{C}_5\text{-C}_8$ alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (e.g., $\text{C}_2\text{-C}_5$ alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (e.g., $\text{C}_3\text{-C}_5$ alkyl). In other embodiments, the alkyl group is selected from methyl,

ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where *t* is 1 or 2), $-S(O)_tOR^a$ (where *t* is 1 or 2), $-S(O)_tR^f$ (where *t* is 1 or 2) and $-S(O)_tN(R^a)_2$ (where *t* is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl. In some embodiments, an alkyl chain is optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-CN$, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where *t* is 1 or 2), $-R^b-S(O)_tOR^a$ (where *t* is 1 or 2), $-R^b-S(O)_tR^a$ (where *t* is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where *t* is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0050] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula $-O$ -alkyl, where alkyl is an alkyl chain as defined above.

[0051] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to six carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification,

an alkenyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl.

[0052] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl comprises two to six carbon atoms. In other embodiments, an alkynyl has two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl.

[0053] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In some embodiments, the points of attachment of the alkylene chain to the rest of the molecule and to the radical group are through one carbon in the alkylene chain or through any two carbons within the chain. In certain embodiments, an alkylene comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C_1-C_2

alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C₁ alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C₅-C₈ alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C₂-C₅ alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C₃-C₅ alkylene). Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -C(O)N(R^a)₂, -N(R^a)C(O)OR^f, -OC(O)-NR^aR^f, -N(R^a)C(O)R^f, -N(R^a)S(O)_tR^f (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tR^f (where t is 1 or 2), and -S(O)_tN(R^a)₂ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl. In some embodiments, an alkylene chain is optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a, -R^b-N(R^a)S(O)_tR^a (where t is 1 or 2), -R^b-S(O)_tOR^a (where t is 1 or 2), -R^b-S(O)_tR^a (where t is 1 or 2), and -R^b-S(O)_tN(R^a)₂ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0054] "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from five to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π-electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl

radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-CN$, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0055] "Aryloxy" refers to a radical bonded through an oxygen atom of the formula $-O$ -aryl, where aryl is as defined above.

[0056] "Aralkyl" refers to a radical of the formula $-R^c$ -aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0057] "Aralkenyl" refers to a radical of the formula $-R^d$ -aryl where R^d is an alkenylene chain as defined above. The aryl part of the aralkenyl radical is optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical is optionally substituted as defined above for an alkenylene group.

[0058] "Aralkynyl" refers to a radical of the formula $-R^e$ -aryl, where R^e is an alkynylene chain as defined above. The aryl part of the aralkynyl radical is optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical is optionally substituted as defined above for an alkynylene chain.

[0059] "Carbocyclyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, and in some embodiments, include fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. In some embodiments, the carbocyclyl is saturated, (*i.e.*, containing single C-C bonds only)

or unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) A fully saturated carbocyclyl radical is also referred to as "cycloalkyl." Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In certain embodiments, a cycloalkyl comprises three to eight carbon atoms (*e.g.*, C₃-C₈ cycloalkyl). In other embodiments, a cycloalkyl comprises three to seven carbon atoms (*e.g.*, C₃-C₇ cycloalkyl). In other embodiments, a cycloalkyl comprises three to six carbon atoms (*e.g.*, C₃-C₆ cycloalkyl). In other embodiments, a cycloalkyl comprises three to five carbon atoms (*e.g.*, C₃-C₅ cycloalkyl). In other embodiments, a cycloalkyl comprises three to four carbon atoms (*e.g.*, C₃-C₄ cycloalkyl). An unsaturated carbocyclyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "carbocyclyl" is meant to include carbocyclyl radicals that are optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a, -R^b-N(R^a)S(O)_tR^a (where t is 1 or 2), -R^b-S(O)_tOR^a (where t is 1 or 2), -R^b-S(O)_tR^a (where t is 1 or 2), and -R^b-S(O)_tN(R^a)₂ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0060] The term "cycloalkylene" refers to a divalent cycloalkyl group and is optionally substituted as indicated for the term "cycloalkyl" or "carbocyclyl".

[0061] "Carbocyclylalkyl" refers to a radical of the formula -R^c-carbocyclyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0062] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo substituents.

[0063] The term “haloalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro-, or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2,2-difluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl. Other examples of haloalkyl include, but not limited to, chloromethyl, trichloromethyl, 2-chloroethyl, bromomethyl, and 2-bromoethyl. The term “perhaloalkyl” denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms. In some embodiments, the alkyl part of the haloalkyl radical is optionally substituted as defined above for an alkyl group.

[0064] “Heterocyclyl” or “heterocycle” refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which include fused or bridged ring systems in some embodiments. The heteroatoms in the heterocyclyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. In some embodiments, the heterocyclyl is attached to the rest of the molecule through any atom of the ring(s). In some embodiments, the heterocyclyl is saturated, (*i.e.*, containing single bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) A fully saturated heterocyclyl radical is also referred to as “heterocycloalkyl.” Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, oxazolidiny, piperidiny, piperaziny, 4-piperidonyl, pyrrolidiny, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl, tetrahydropyrany, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, and 1,1-dioxo-thiomorpholiny. Unless stated otherwise specifically in the specification, the term “heterocyclyl” is meant to include heterocyclyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, -R^b-CN, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-N(R^a)₂, -R^b-N(R^a)₂, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)N(R^a)₂, -R^b-O-R^c-C(O)N(R^a)₂, -R^b-N(R^a)C(O)OR^a, -R^b-N(R^a)C(O)R^a,

$-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0065] “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.* $-NH-$, $-N(alkyl)-$, sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1 - C_6 heteroalkyl. In some embodiments, the alkyl part of the heteroalkyl radical is optionally substituted as defined for an alkyl group.

[0066] A “heterocycloalkyl” or “heteroalicyclic” group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. In some embodiments, the heterocycloalkyl is dioxolanyl, oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidin-2-onyl, pyrrolidine-2,5-dithionyl, pyrrolidine-2,5-dionyl, pyrrolidinonyl, imidazolidinyl, imidazolidin-2-onyl, or thiazolidin-2-onyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C_2 - C_{10} heterocycloalkyl. In one aspect, a heterocycloalkyl is a C_2 - C_6 heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4 - C_{10} heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

[0067] The term “heterocycloalkylene” refers to a divalent heterocycloalkyl group and is optionally substituted as indicated for the term “heterocycloalkyl”.

[0068] “Heterocyclylalkyl” refers to a radical of the formula $-R^c$ -heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocyclyl group.

[0069] “Heterocyclylalkoxy” refers to a radical bonded through an oxygen atom of the formula $-O-R^c$ -heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a

nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkoxy radical is optionally substituted as defined above for a heterocyclyl group.

[0070] "Heteroaryl" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, in some embodiments, the heteroaryl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolyl, 5,6-dihydrobenzo[h]cinnolyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indolizyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolyl, quinoxalinyl, quinolyl, isoquinolyl, tetrahydroquinolyl, 5,6,7,8-tetrahydroquinazolyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl,

thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (*i.e.* thienyl). In some embodiments, the heteroaryl groups include monocyclic heteroaryls and bicyclic heteroaryls. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, haloalkenyl, haloalkynyl, oxo, thio, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0071] "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0072] "*C*-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A *C*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

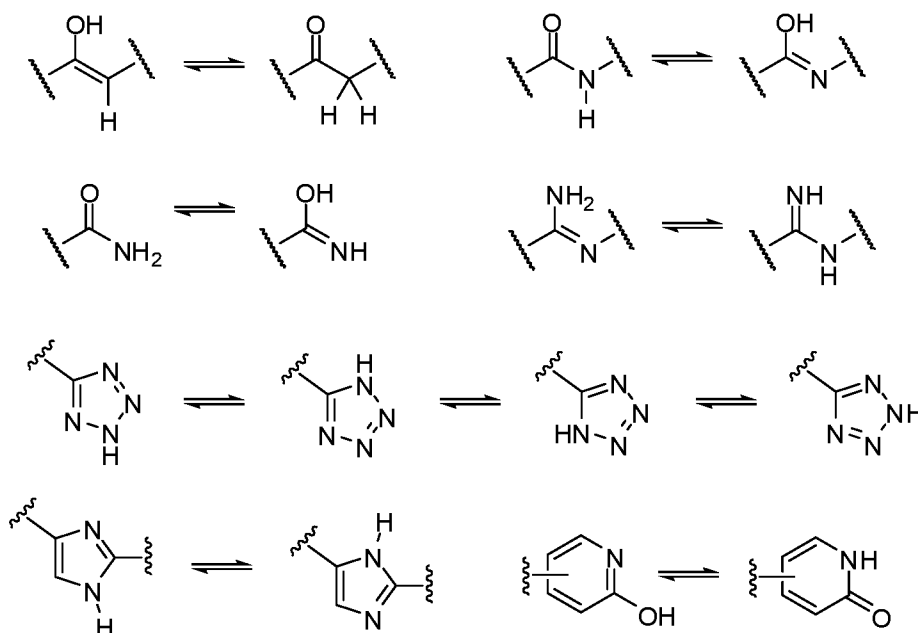
[0073] "Heteroaryloxy" refers to radical bonded through an oxygen atom of the formula –O-heteroaryl, where heteroaryl is as defined above.

[0074] "Heteroarylalkyl" refers to a radical of the formula –R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

[0075] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical is optionally substituted as defined above for a heteroaryl group.

[0076] In some embodiments, the compounds disclosed herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless stated otherwise, it is intended that all stereoisomeric forms of the compounds disclosed herein are contemplated by this disclosure. When the compounds described herein contain alkene double bonds, and unless specified otherwise, it is intended that this disclosure includes both *E* and *Z* geometric isomers (*e.g.*, *cis* or *trans*.) Likewise, all possible isomers, as well as their racemic and optically pure forms, and all tautomeric forms are also intended to be included. The term "geometric isomer" refers to *E* or *Z* geometric isomers (*e.g.*, *cis* or *trans*) of an alkene double bond. The term "positional isomer" refers to structural isomers around a central ring, such as *ortho*-, *meta*-, and *para*- isomers around a benzene ring.

[0077] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0078] "Optional" or "optionally" means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0079] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s). In some other embodiments, optional substituents are individually and independently selected from D, halogen, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, -OH, -C(=O)OH, -C(=O)Oalkyl, -OC(=O)alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -NHC(=O)alkyl, -N(alkyl)C(=O)alkyl, -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, -CH₂CO₂H, -CH₂CO₂alkyl, -CH₂C(=O)NH₂, -CH₂C(=O)NH(alkyl), -CH₂C(=O)N(alkyl)₂, -CH₂S(=O)₂NH₂, -CH₂S(=O)₂NH(alkyl), -CH₂S(=O)₂N(alkyl)₂, alkyl, alkenyl, alkynyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, optional substituents are individually and independently selected from D, halogen, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, -OH, -CO₂H, -CO₂alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄alkyl), -C(=O)NH₂, -C(=O)NH(C₁-C₄alkyl), -C(=O)N(C₁-C₄alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(C₁-C₄alkyl), -S(=O)₂N(C₁-C₄alkyl)₂, C₁-C₄alkyl,

C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄heteroalkyl, C₁-C₄alkoxy, C₁-C₄fluoroalkoxy, -SC₁-C₄alkyl, -S(=O)C₁-C₄alkyl, and -S(=O)₂C₁-C₄alkyl. In some embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -OH, -NH(CH₃), -N(CH₃)₂, -CH₃, -CH₂CH₃, -CF₃, -OCH₃, and -OCF₃. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, substituted groups are substituted with one of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O). In some embodiments, an optional substituent on a sulfur atom includes one or two oxo (=O) groups.

[0080] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Pharmaceutically acceptable salts of the compounds described herein are optionally pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[0081] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrate, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66:1-19 (1997), which is hereby incorporated by reference in its entirety). In some embodiments, acid addition salts of basic compounds are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[0082] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. In some embodiments, pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts, and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chlorprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins, and the like. See Berge et al., *supra*.

[0083] As used herein, "treatment" or "treating" or "palliating" or "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is afflicted with the underlying disorder in some embodiments. For prophylactic benefit, in some embodiments, the compositions are administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

[0084] "Prodrug" is meant to indicate a compound that is converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some embodiments, a prodrug is inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam)).

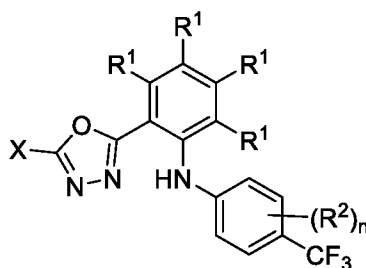
[0085] A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

[0086] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. In some embodiments, prodrugs of an active compound, as described herein, are prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino, or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol or amine functional groups in the active compounds and the like.

Compounds

[0087] In some embodiments, the compounds disclosed herein are oxadiazole compounds.

[0088] Provided in one aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

X is H, -CN, halogen, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, -L²-L³-Y², -L²-L³-L⁴-Y², -L⁵-L⁶-L³-Y², or -L⁶-L⁵-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y¹ is -N₃, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^2 is absent, substituted or unsubstituted C_1 - C_6 alkylene, substituted or unsubstituted C_3 -

C_{10} cycloalkylene, or substituted or unsubstituted C_2 - C_{10} heterocycloalkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-

O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -

NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -

(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-,

-O(C=O)-NR³(SO₂)-NR³-, -NR³(SO₂)NR³-(C=O)O-, -O-(SO₂)-, or -(SO₂)-O-;

each R³ is independently H, -CN, -S(=O)₂(C₁-C₄alkyl), or substituted or unsubstituted C_1 - C_6 alkyl;

L^4 is substituted or unsubstituted C_1 - C_6 alkylene;

L^5 is substituted or unsubstituted C_1 - C_6 alkylene;

L^6 is substituted or unsubstituted C_3 - C_{10} cycloalkylene;

Y^2 is H, -CN, -N₃, halogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 -

C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 -

C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 -

C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or

unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂;

or R³ and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R⁶ is independently H or substituted or unsubstituted C_1 - C_6 alkyl;

or two R⁶ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R¹ is independently H, halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted

C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 -

C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 -

C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted

C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted

aryl, substituted or unsubstituted heteroaryl, or -L⁷-Y³;

L^7 is substituted or unsubstituted C_1 - C_6 alkylene;

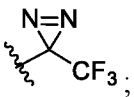
Y^3 is -Si(R⁷)₂;

each R⁷ is independently substituted or unsubstituted C_1 - C_6 alkyl;

n is 0, 1, 2, 3, or 4;

each R² is independently H, halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵,

substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R⁴ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R⁴ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

each R⁵ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R⁵ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[0089] In some embodiments, if X, L¹, L², L⁴, L⁵, L⁶, L⁷, Y¹, Y², R¹, R², R³, R⁴, R⁵, R⁶, or R⁷ is substituted, then X, L¹, L², L⁴, L⁵, L⁶, L⁷, Y¹, Y², R¹, R², R³, R⁴, R⁵, R⁶, or R⁷ is substituted with 1-5 R⁸ groups; each R⁸ is independently selected from halogen, -N₃, -CN, -NO₂, -OR⁹, -SR⁹, -S(=O)R¹⁰, -S(=O)₂R¹⁰, -S(=O)₂N(R⁹)₂, -NR⁹S(=O)₂R¹⁰, -C(=O)R¹⁰, -OC(=O)R¹⁰, -CO₂R⁹, -OCO₂R¹⁰, -N(R⁹)₂, -C(=O)N(R⁹)₂, -OC(=O)N(R⁹)₂, -NHC(=O)R¹⁰, -NHC(=O)OR¹⁰, -(CH₂)_r-R⁹, -(CH₂)_r-halogen, unsubstituted or substituted C₁-C₆alkyl, unsubstituted or substituted C₁-C₆fluoroalkyl, unsubstituted or substituted C₂-C₆alkenyl, unsubstituted or substituted C₂-C₆alkynyl, unsubstituted or substituted C₁-C₆heteroalkyl, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₁₀heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; each R⁹ is independently selected from H, substituted or unsubstituted C₁-C₆alkyl, unsubstituted or substituted C₁-C₆fluoroalkyl, unsubstituted or substituted C₁-C₆heteroalkyl, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₁₀heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; or two R⁹ on the same N atom are

taken together with the N atom to which they are attached to form a N-containing heterocycle; each R^{10} is independently selected from H, substituted or unsubstituted C_1 - C_6 alkyl, unsubstituted or substituted C_1 - C_6 fluoroalkyl, unsubstituted or substituted C_1 - C_6 heteroalkyl, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_{10} heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl, or unsubstituted or substituted heteroaryl; and r is 1, 2, 3, or 4.

[0090] In some embodiments, X is H. In some embodiments, X is $-CN$. In some embodiments, X is halogen. In some embodiments, X is substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, X is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, X is substituted or unsubstituted C_2 - C_6 alkenyl. In some embodiments, X is substituted or unsubstituted C_2 - C_6 alkynyl. In some embodiments, X is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, X is substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, X is substituted or unsubstituted aryl. In some embodiments, X is substituted or unsubstituted heteroaryl. In some embodiments, X is $-L^1-Y^1$. In some embodiments, X is $-L^2-L^3-Y^2$. In some embodiments, X is $-L^2-L^3-L^4-Y^2$. In some embodiments, X is $-L^5-L^6-L^3-Y^2$. In some embodiments, X is $-L^6-L^5-L^3-Y^2$.

[0091] In some embodiments, X is substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0092] In some embodiments, X is substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0093] In some embodiments, X is substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[0094] In some embodiments, X is substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, X is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$.

[0095] In some embodiments, X is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, X is $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$.

[0096] In some embodiments, X is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, X is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl.

[0097] In some embodiments, X is substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, X is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl.

[0098] In some embodiments, X is substituted or unsubstituted heteroaryl. In some embodiments, X is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, X is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[0099] In some embodiments, X is -L¹-Y¹. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene. In some embodiments, L¹ is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-. In some embodiments, Y¹ is substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted C₂-C₁₀ heterocycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted C₂-C₆ heterocycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted aryl. In some embodiments, Y¹ is or substituted or unsubstituted heteroaryl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is

substituted or unsubstituted C₂-C₆ heterocycloalkyl. In some embodiments, Y¹ is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted phenyl. In some embodiments, L¹ is substituted or unsubstituted C₁-C₄alkylene; and Y¹ is substituted or unsubstituted heteroaryl. In some embodiments, Y¹ is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, Y¹ is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

[00100] In some embodiments, L² is absent. In some embodiments, L² is substituted or unsubstituted C₁-C₆alkylene. In some embodiments, L² is substituted or unsubstituted C₁-C₄alkylene. In some embodiments, L² is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-. In some embodiments, L² is substituted or unsubstituted C₃-C₁₀cycloalkylene. In some embodiments, L² is substituted or unsubstituted C₃-C₆cycloalkylene. In some embodiments, L² is substituted or unsubstituted cyclopropylene, substituted or unsubstituted cyclobutylene, substituted or unsubstituted cyclopentylene, or substituted or unsubstituted cyclohexylene. In some embodiments, L² is substituted or unsubstituted C₂-C₁₀heterocycloalkylene. In some embodiments, L² is substituted or unsubstituted C₂-C₆heterocycloalkylene. In some embodiments, L² is substituted or unsubstituted aziridinylene, substituted or unsubstituted azetidinylene, substituted or unsubstituted pyrrolidinylene, substituted or unsubstituted piperidinylene, substituted or unsubstituted oxetanylene, substituted or unsubstituted tetrahydrofuranylene, or substituted or unsubstituted tetrahydropyranylene. In some embodiments, L³ is -O-. In some embodiments, L³ is

-S-. In some embodiments, L^3 is $-(S=O)-$. In some embodiments, L^3 is $-(SO_2)-$. In some embodiments, L^3 is $-NR^3-$. In some embodiments, L^3 is $-(C=O)-$. In some embodiments, L^3 is $-(C=O)O-$. In some embodiments, L^3 is $-O(C=O)-$. In some embodiments, L^3 is $-(C=O)NR^3-$. In some embodiments, L^3 is $-(C=O)NR^3-O-$. In some embodiments, L^3 is $-O-NR^3(C=O)-$. In some embodiments, L^3 is $-NR^3(C=O)-$. In some embodiments, L^3 is $-NR^3(C=O)NR^3-$. In some embodiments, L^3 is $-O(C=O)NR^3-$. In some embodiments, L^3 is $-NR^3(C=O)O-$. In some embodiments, L^3 is $-NR^3(SO_2)NR^3-$. In some embodiments, L^3 is $-NR^3(SO_2)-$. In some embodiments, L^3 is $-(SO_2)NR^3-$. In some embodiments, L^3 is $-(SO_2)NR^3-(C=O)-$. In some embodiments, L^3 is $-(C=O)-NR^3(SO_2)-$. In some embodiments, L^3 is $-(SO_2)NR^3-(C=O)O-$. In some embodiments, L^3 is $-O(C=O)-NR^3(SO_2)-$. In some embodiments, L^3 is $-NR^3(SO_2)NR^3-(C=O)-$. In some embodiments, L^3 is $-(C=O)-NR^3(SO_2)NR^3-$. In some embodiments, L^3 is $-O(C=O)-NR^3(SO_2)-NR^3-$. In some embodiments, L^3 is $-NR^3(SO_2)NR^3-(C=O)O-$. In some embodiments, L^3 is $-O-(SO_2)-$. In some embodiments, L^3 is $-(SO_2)-O-$. In some embodiments, R^3 is H. In some embodiments, R^3 is substituted or unsubstituted C_1 - C_6 alkylene. In some embodiments, R^3 is substituted or unsubstituted C_1 - C_4 alkylene. In some embodiments, R^3 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$. In some embodiments, L^4 is substituted or unsubstituted C_1 - C_6 alkylene. In some embodiments, L^4 is substituted or unsubstituted C_1 - C_4 alkylene. In some embodiments, L^4 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

[00101] In some embodiments, Y^2 is H. In some embodiments, Y^2 is $-CN$. In some embodiments, Y^2 is $-N_3$. In some embodiments, Y^2 is halogen. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, Y^2 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, Y^2 is $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_6 alkenyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_4 alkenyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_6 alkynyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_4 alkynyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, Y^2 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, Y^2 is substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, Y^2 is substituted or

unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, Y² is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, Y² is substituted or unsubstituted aralkyl. In some embodiments, Y² is substituted or unsubstituted benzyl. In some embodiments, Y² is substituted or unsubstituted aryl. In some embodiments, Y² is substituted or unsubstituted phenyl. In some embodiments, Y² is substituted or unsubstituted heteroaryl. In some embodiments, Y² is substituted or unsubstituted monocyclic heteroaryl. In some embodiments, Y² is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In some embodiments, Y² is -OR⁶. In some embodiments, Y² is -(C=O)OR⁶. In some embodiments, Y² is -N(R⁶)₂. In some embodiments, Y² is -(C=O)N(R⁶)₂. In some embodiments, R³ and Y² on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00102] In some embodiments, each R⁶ is independently H. In some embodiments, each R⁶ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁶ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁶ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, two R⁶ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

[00103] In some embodiments, X is -L²-L³-Y². In some embodiments, L² is substituted or unsubstituted C₁-C₄alkylene; L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -

NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-; Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂. In some embodiments, L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-; Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

[00104] In some embodiments, L² is absent; L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-; Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂. In some embodiments, L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-; Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

[00105] In some embodiments, X is -L²-L³-L⁴-Y². In some embodiments, L² is substituted or unsubstituted C₁-C₄alkylene; L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -

$\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})-$, $-\text{NR}^3(\text{SO}_2)\text{NR}^3-(\text{C}=\text{O})\text{O}-$, or $-\text{O}-(\text{SO}_2)-$; L^4 is substituted or unsubstituted C_1 - C_4 alkylene; Y^2 is independently H, $-\text{CN}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$. In some embodiments, L^3 is $-\text{O}-$, $-\text{S}-$, $-(\text{S}=\text{O})-$, $-(\text{SO}_2)-$, $-\text{NR}^3-$, $-(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{O}-$, $-\text{O}(\text{C}=\text{O})-$, $-(\text{C}=\text{O})\text{NR}^3-$, $-(\text{C}=\text{O})\text{NR}^3-\text{O}-$, $-\text{NR}^3(\text{C}=\text{O})-$, $-\text{NR}^3(\text{C}=\text{O})\text{NR}^3-$, $-\text{NR}^3(\text{C}=\text{O})\text{O}-$, $-\text{NR}^3(\text{SO}_2)-$, $-(\text{SO}_2)\text{NR}^3-$, or $-\text{O}-(\text{SO}_2)-$; Y^2 is independently H, $-\text{CN}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$; and each R^6 is independently H or substituted or unsubstituted C_1 - C_4 alkyl.

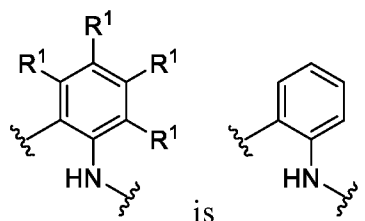
[00106] In some embodiments, X is $-\text{L}^5-\text{L}^6-\text{L}^3-\text{Y}^2$. In some embodiments, X is $-\text{L}^6-\text{L}^5-\text{L}^3-\text{Y}^2$. In some embodiments, L^5 is substituted or unsubstituted C_1 - C_4 alkylene. In some embodiments, L^5 is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. In some embodiments, L^6 is substituted or unsubstituted C_3 - C_6 cycloalkylene. In some embodiments, L^6 is substituted or unsubstituted cyclopropylene, substituted or unsubstituted cyclobutylene, substituted or unsubstituted cyclopentylene, or substituted or unsubstituted cyclohexylene.

[00107] In some embodiments, each R^1 is independently H. In some embodiments, each R^1 is independently halogen. In some embodiments, each R^1 is independently $-\text{CN}$. In some embodiments, each R^1 is independently $-\text{OR}^4$. In some embodiments, each R^1 is independently $-\text{SR}^4$. In some embodiments, each R^1 is independently $-\text{N}(\text{R}^4)_2$. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^1 is independently $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, or $-\text{C}(\text{CH}_3)_3$. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^1 is independently $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_6 alkenyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_4 alkenyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_6 alkynyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_4 alkynyl. In some

embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_6 heteroalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_1 - C_4 heteroalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_3 - C_{10} cycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_{10} heterocycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted C_2 - C_6 heterocycloalkyl. In some embodiments, each R^1 is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, each R^1 is independently substituted or unsubstituted aralkyl. In some embodiments, each R^1 is independently substituted or unsubstituted benzyl. In some embodiments, each R^1 is independently substituted or unsubstituted aryl. In some embodiments, each R^1 is independently substituted or unsubstituted phenyl. In some embodiments, each R^1 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^1 is independently substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R^1 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In some embodiments, each R^1 is independently $-L^7-Y^3$.

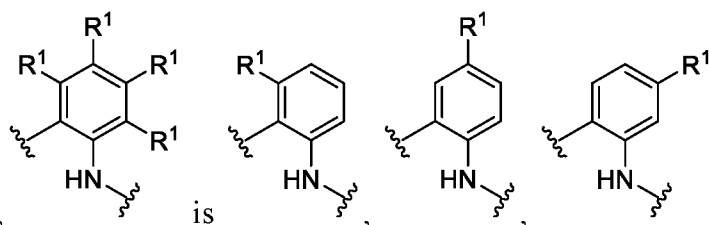
[00108] In some embodiments, L^7 is substituted or unsubstituted C_1 - C_6 alkylene. In some embodiments, L^7 is substituted or unsubstituted C_1 - C_4 alkylene. In some embodiments, L^7 is $-CH_2-$,

-CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-. In some embodiments, Y³ is -Si(R⁷)₂. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁷ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁷ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃.



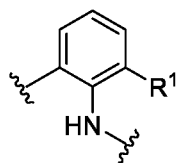
[00109] In some embodiments,

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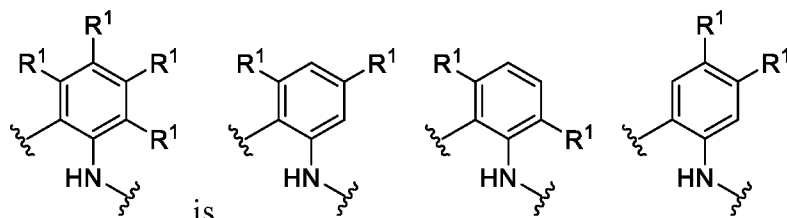
[00110] In some embodiments,

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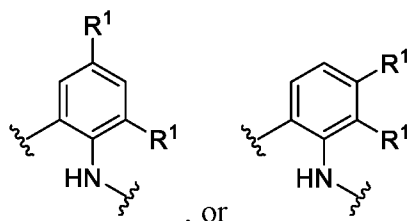
and R¹ is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00111] In some embodiments, R¹ is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R¹ is halogen, substituted or unsubstituted C₁-C₄alkyl, or substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, R¹ is F, Cl, Br, I, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -C(CH₃)₃, -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.



[00112] In some embodiments,

is



; and each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

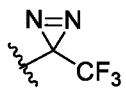
[00113] In some embodiments, each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R^1 is independently halogen, substituted or unsubstituted C_1 - C_4 alkyl, or substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^1 is independently F, Cl, Br, I, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$.

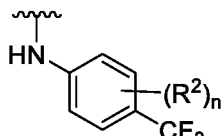
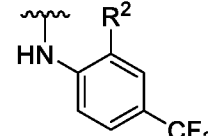
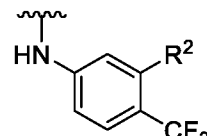
[00114] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

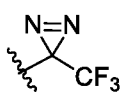
[00115] In some embodiments, each R^2 is independently H. In some embodiments, each R^2 is independently halogen. In some embodiments, each R^2 is independently $-\text{N}_3$. In some embodiments, each R^2 is independently $-\text{CN}$. In some embodiments, each R^2 is independently $-\text{OR}^5$. In some embodiments, each R^2 is independently $-\text{SR}^5$. In some embodiments, each R^2 is independently $-(\text{SO}_2)\text{R}^5$. In some embodiments, each R^2 is independently $-\text{N}(\text{R}^5)_2$. In some embodiments, each R^2 is independently $-\text{CO}_2\text{R}^5$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 alkyl. In some embodiments, each R^2 is independently $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, or $-\text{C}(\text{CH}_3)_3$. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_6 haloalkyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_1 - C_4 haloalkyl. In some embodiments, each R^2 is independently $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$. In some embodiments, each R^2 is independently substituted or unsubstituted C_2 - C_6 alkenyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_2 - C_4 alkenyl. In some embodiments, each R^2 is independently substituted or unsubstituted C_2 - C_6 alkynyl. In some embodiments, each R^2 is

independently substituted or unsubstituted C₂-C₄alkynyl. In some embodiments, each R² is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R² is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R² is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R² is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R² is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, each R² is independently substituted or unsubstituted aralkyl. In some embodiments, each R² is independently substituted or unsubstituted benzyl. In some embodiments, each R² is independently substituted or unsubstituted aryl. In some embodiments, each R² is independently substituted or unsubstituted phenyl. In some embodiments, each R² is independently substituted or unsubstituted heteroaryl. In some embodiments, each R² is independently substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R² is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In

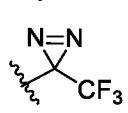
some embodiments, each R² is independently

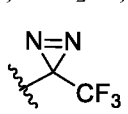


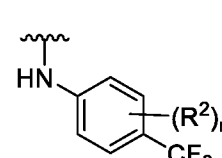
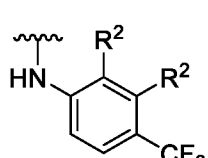
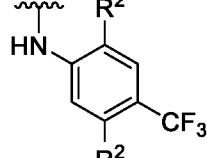
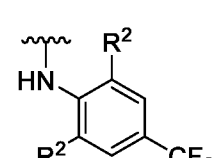
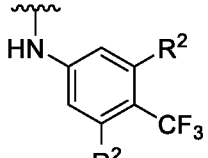
[00116] In some embodiments,  is  or ; and R² is halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted

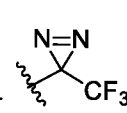
heteroaryl, or .

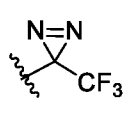
[00117] In some embodiments, R² is halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted

phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and each R⁵ is independently H, or substituted or unsubstituted C₁-C₄alkyl. In some embodiments, R² is halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted

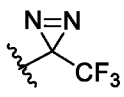
C₁-C₄haloalkyl, or .

[00118] In some embodiments, wherein:  is , , , or ; and each R² is independently halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted aralkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or . In some embodiments, each R² is independently halogen, -N₃, -CN, -OR⁵, -SR⁵, -(SO₂)R⁵, -N(R⁵)₂, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted

phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and each R⁵ is

independently H, or substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R² is independently halogen, -N₃, -OR⁵, -(SO₂)R⁵, -CO₂R⁵, substituted or unsubstituted C₁-C₄alkyl,

substituted or unsubstituted C₁-C₄haloalkyl, or .

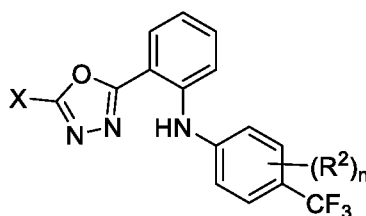
[00119] In some embodiments, each R⁴ is independently H. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁴ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R⁴ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aralkyl. In some embodiments, each R⁴ is independently substituted or unsubstituted benzyl. In some embodiments, each R⁴ is independently substituted or unsubstituted aryl. In some embodiments, each R⁴ is independently substituted or unsubstituted phenyl. In some embodiments, each R⁴ is independently substituted or unsubstituted heteroaryl. In some embodiments, each R⁴ is independently substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R⁴ is independently substituted or

unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In some embodiments, two R⁴ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00120] In some embodiments, each R⁵ is independently H. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₆alkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₄alkyl. In some embodiments, each R⁵ is independently -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₆haloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₄haloalkyl. In some embodiments, each R⁵ is independently -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₆heteroalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₁-C₄heteroalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₃-C₁₀cycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₃-C₆cycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₂-C₁₀heterocycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted C₂-C₆heterocycloalkyl. In some embodiments, each R⁵ is independently substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl. In some embodiments, each R⁵

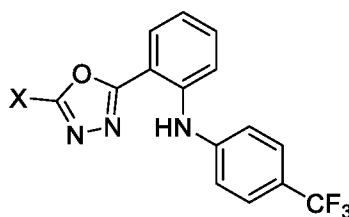
is independently substituted or unsubstituted aralkyl. In some embodiments, each R^5 is independently substituted or unsubstituted benzyl. In some embodiments, each R^5 is independently substituted or unsubstituted aryl. In some embodiments, each R^5 is independently substituted or unsubstituted phenyl. In some embodiments, each R^5 is independently substituted or unsubstituted heteroaryl. In some embodiments, each R^5 is independently substituted or unsubstituted monocyclic heteroaryl. In some embodiments, each R^5 is independently substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl. In some embodiments, two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00121] In some embodiments, the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



Formula (Ia).

[00122] In some embodiments, the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:

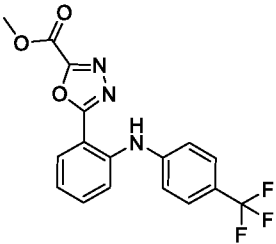
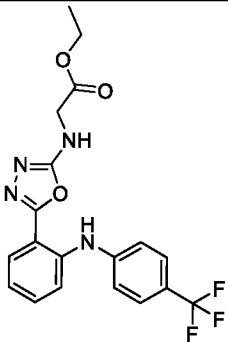
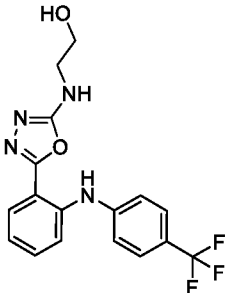
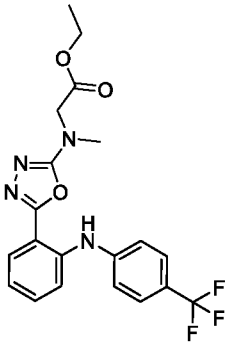
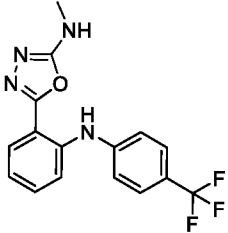


Formula (Ib).

[00123] In some embodiments, the compound disclosed herein has the structure provided in Table 1.

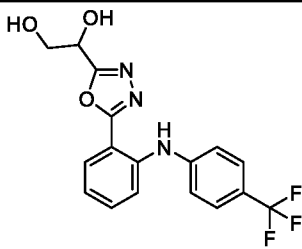
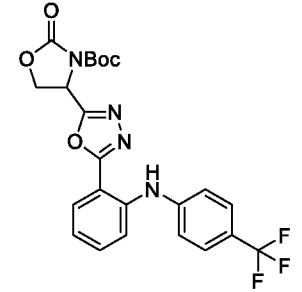
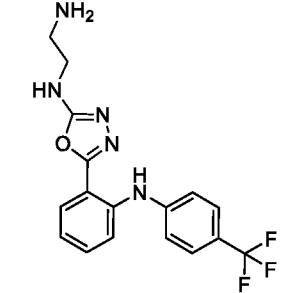
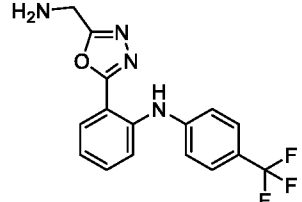
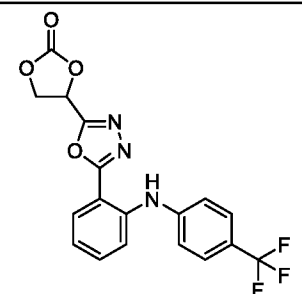
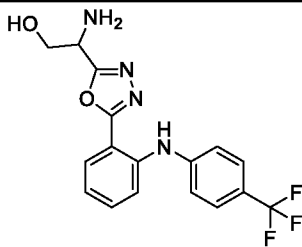
TABLE 1

Compound No.	Structure	Name
1		ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate
2		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol
3		ethyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate
4		5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine
5		(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol
6		N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine

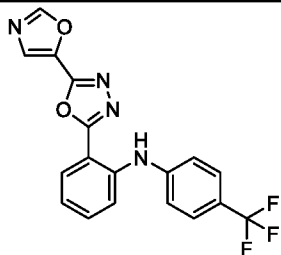
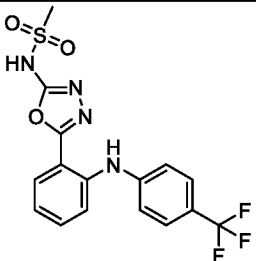
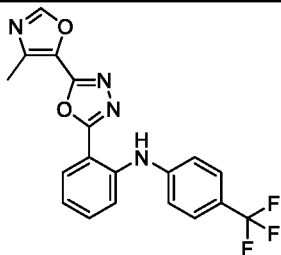
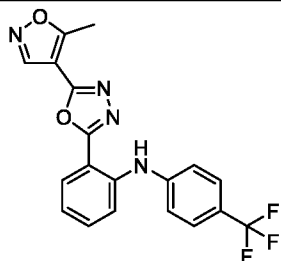
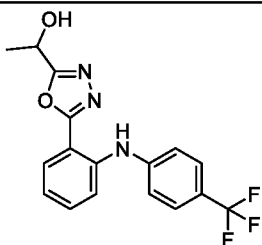
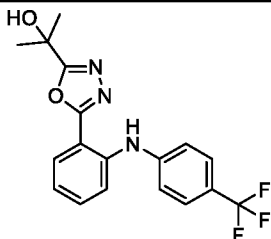
Compound No.	Structure	Name
8		methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate
9		ethyl (5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate
10		2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol
11		ethyl N-methyl-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate
12		N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine

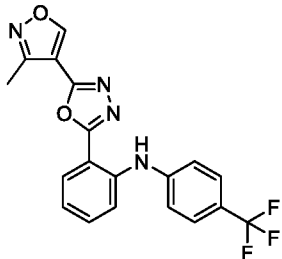
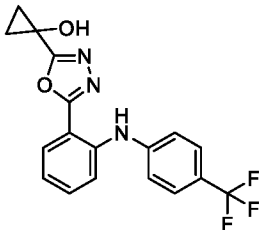
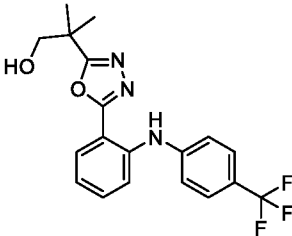
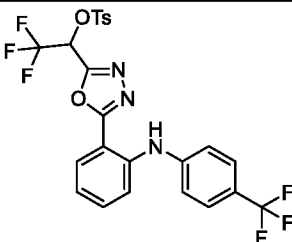
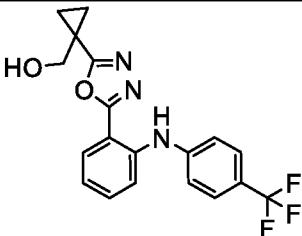
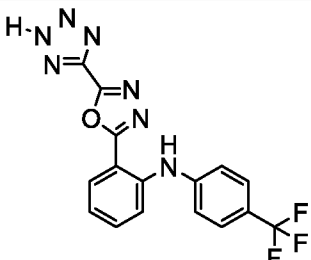
Compound No.	Structure	Name
13		5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
14		N-hydroxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
15		5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
16		3-tosyl-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
17		4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
18		(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycine

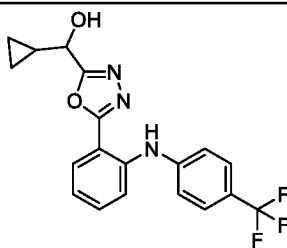
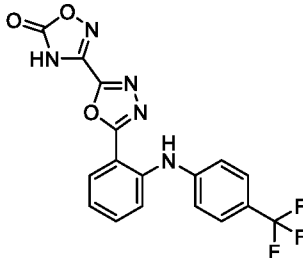
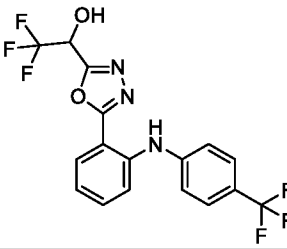
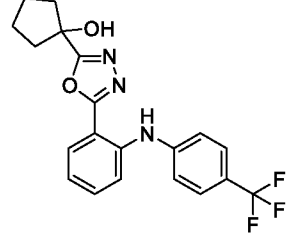
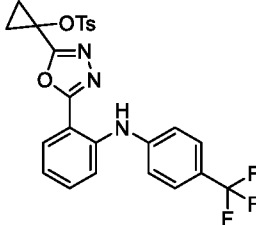
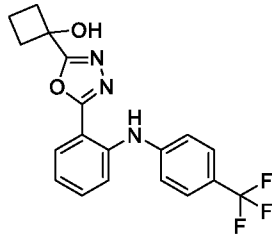
Compound No.	Structure	Name
19		2-(methyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol
20		2-(1,3,4-oxadiazol-2-yl)-N-[4-(trifluoromethyl)phenyl]aniline
21		2-[5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline
22		5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carbonitrile
23		1-(4-methoxybenzyl)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)urea
24		2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide

Compound No.	Structure	Name
25		1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethane-1,2-diol
26		2-oxo-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidine-3-carboxylate
27		N1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethane-1,2-diamine
28		2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline
29		4-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-1,3-dioxolan-2-one
30		2-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

Compound No.	Structure	Name
31		2-[5-(azidomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline
32		N-(2-hydroxyethyl)-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide
33		N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)benzenesulfonamide
34		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)imidazolidin-2-one
35		2-(5-(5-methyloxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
36		2-(5-(oxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
37		2-(5-(oxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
38		N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide
39		2-(5-(4-methyloxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
40		2-(5-(5-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
41		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol
42		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol

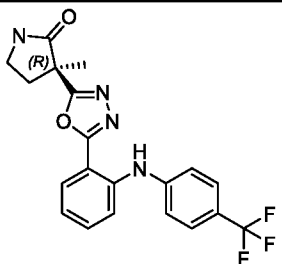
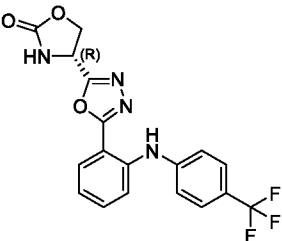
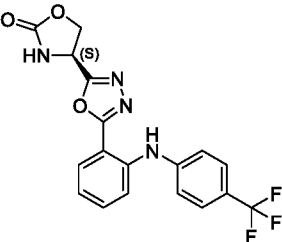
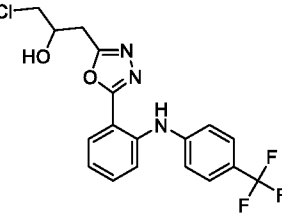
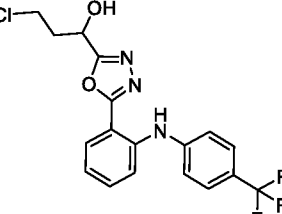
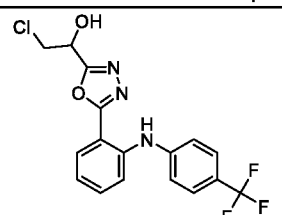
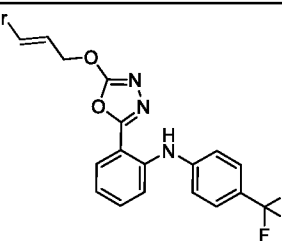
Compound No.	Structure	Name
43		2-(5-(3-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
44		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropanol
45		2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol
46		2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl 4-methylbenzenesulfonate
47		(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methanol
48		2-[5-(2H-tetrazol-5-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

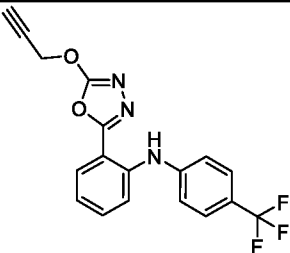
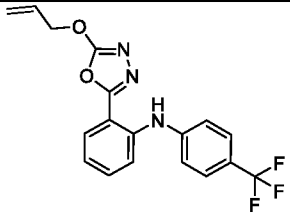
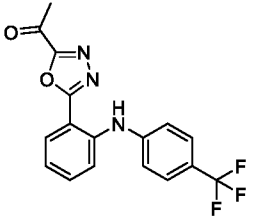
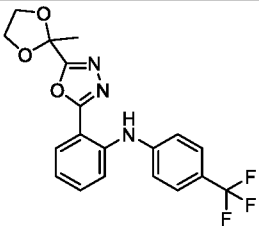
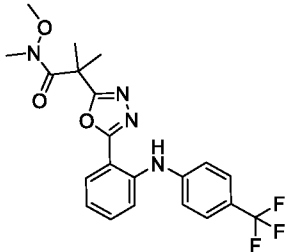
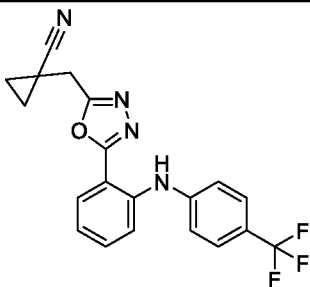
Compound No.	Structure	Name
49		cyclopropyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol
50		3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-5-one]
51		2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol
52		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopentanol
53		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl 4-methylbenzenesulfonate
54		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclobutanol

Compound No.	Structure	Name
55		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxetan-3-ol
56		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3-ol
57		(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate
58		2-(5-(1-aminocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
59		N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)acetamide
60		2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol
61		4-bromo-2-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

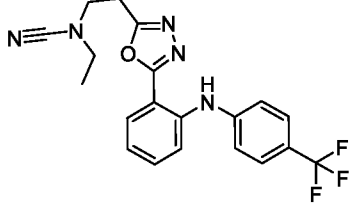
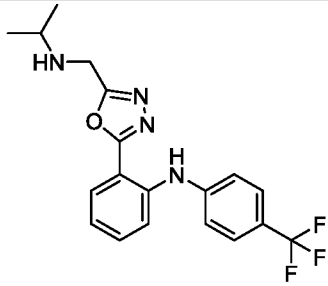
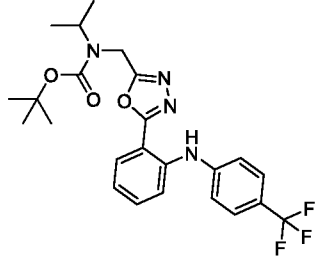
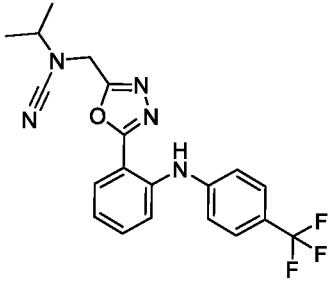
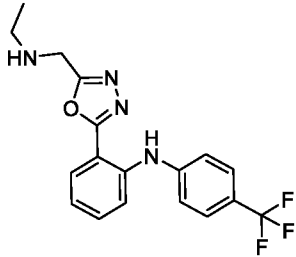
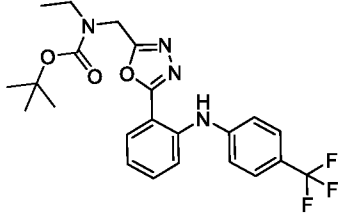
Compound No.	Structure	Name
62		1-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)urea
63		2-(5-(1-fluorocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
66		2-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline
67		2-(5-(1-methoxycyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
68		2-(5-(2-methylbut-3-yn-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
69		2-(5-(but-3-yn-2-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

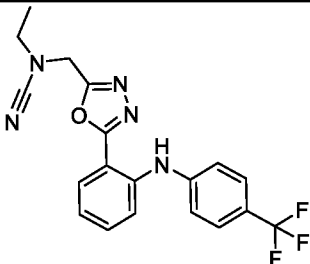
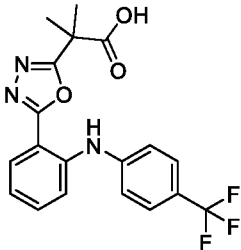
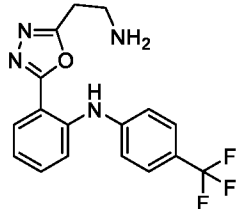
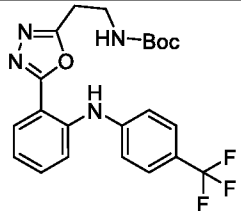
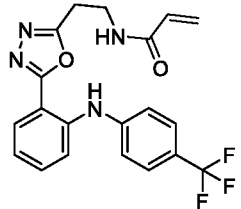
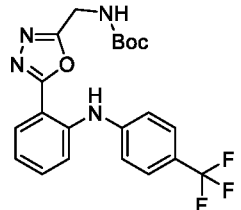
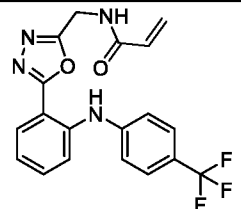
Compound No.	Structure	Name
70		2-(5-(but-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
71		2-(5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
72		2-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
73		2-(5-methoxy-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
74		(S)-4-(5-(4,5-difluoro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
75		(S)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one

Compound No.	Structure	Name
76		(R)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one
77		(R)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
78		(S)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one
79		1-chloro-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol
80		3-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol
81		2-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol
82		(E)-2-(5-((3-bromoallyl)oxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
83		2-(5-(prop-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
84		2-(5-(allyloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
85		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-one
86		2-(5-(2-methyl-1,3-dioxolan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
87		N-methoxy-N,2-dimethyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
88		1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyclopropane-1-carbonitrile

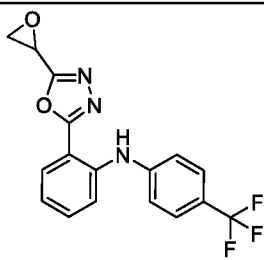
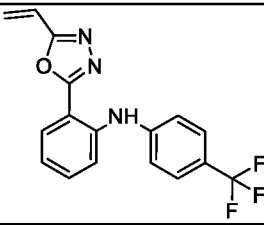
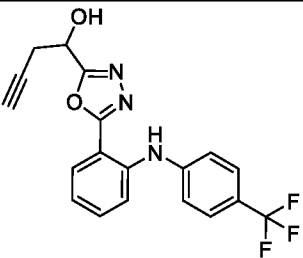
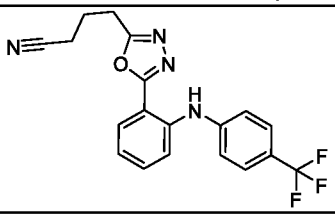
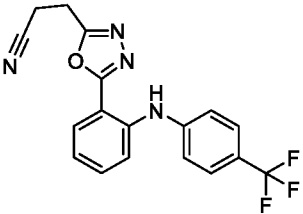
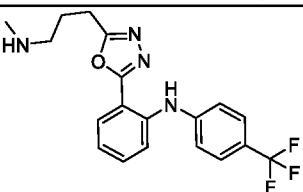
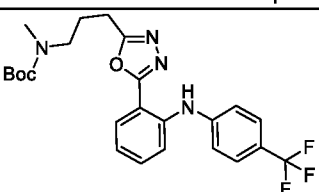
Compound No.	Structure	Name
89		2,2-dimethyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile
90		2-(5-ethyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
91		2-(5-(2-(isopropylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
92		tert-butyl isopropyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate
93		N-isopropyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide
94		2-(5-(2-(ethylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
95		tert-butyl ethyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

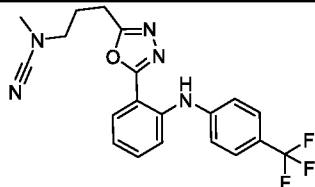
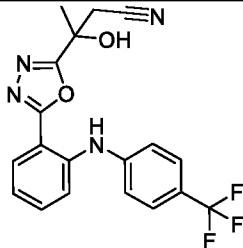
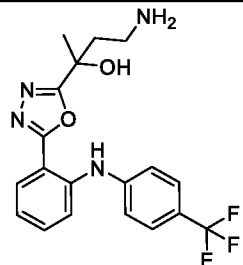
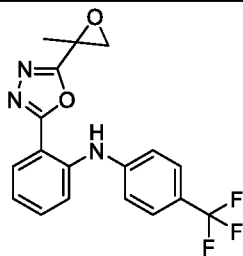
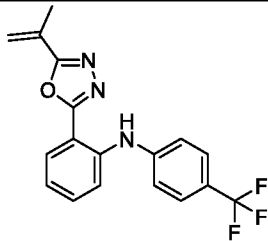
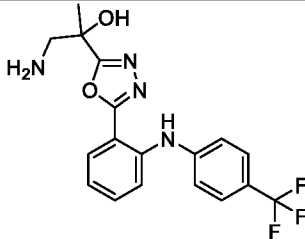
Compound No.	Structure	Name
96		N-ethyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide
97		2-(5-((isopropylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
98		tert-butyl isopropyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate
99		N-isopropyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide
100		2-(5-((ethylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
101		tert-butyl ethyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate

Compound No.	Structure	Name
102		N-ethyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide
103		2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoic acid
104		2-(5-(2-aminoethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
105		tert-butyl (2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate
106		N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)acrylamide
107		tert-butyl ((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate
108		N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)acrylamide

Compound No.	Structure	Name
109		N-(2-cyanoethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
110		N-(cyanomethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
111		N-(but-3-yn-1-yl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
112		2-methyl-N-(prop-2-yn-1-yl)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
113		N-(2-cyanoethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
114		N-(cyanomethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
115		N-(but-3-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide

Compound No.	Structure	Name
116		N-(prop-2-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
117		(E)-2-(5-(prop-1-en-1-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
118		2-(5-(2,2-diethoxyethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
119		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetic acid
120		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-2-ol
121		2-bromo-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol

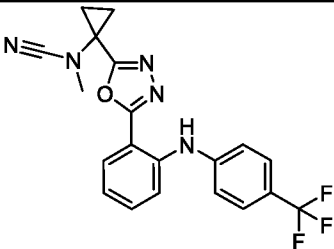
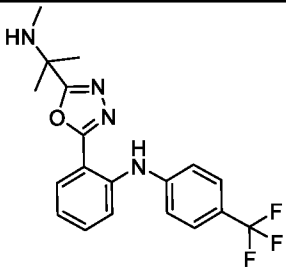
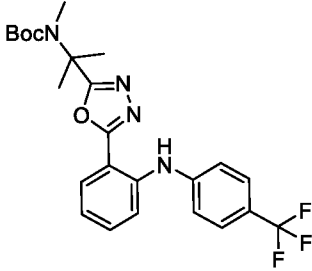
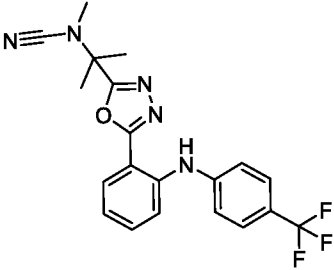
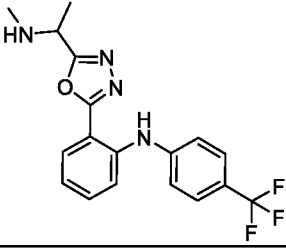
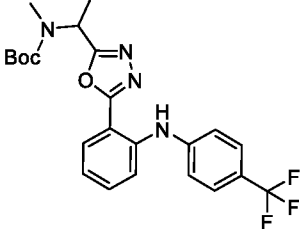
Compound No.	Structure	Name
122		2-(5-(oxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
123		N-(4-(trifluoromethyl)phenyl)-2-(5-vinyl-1,3,4-oxadiazol-2-yl)aniline
124		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-1-ol
125		4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile
126		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile
127		2-(5-(3-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
128		tert-butyl methyl(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate

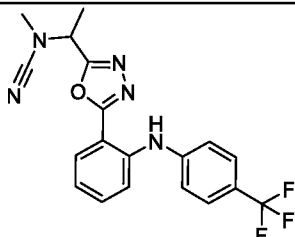
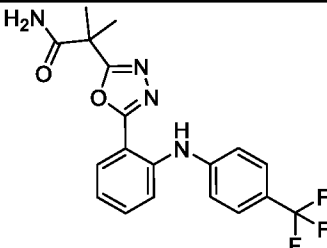
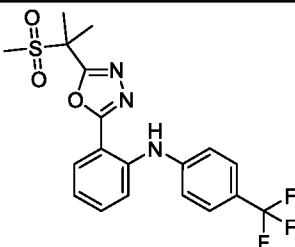
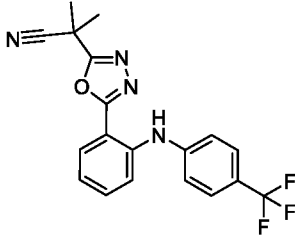
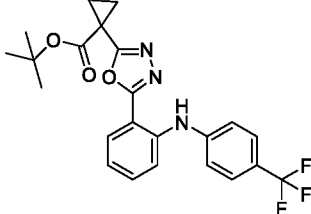
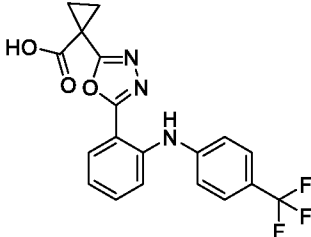
Compound No.	Structure	Name
129		N-methyl-N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide
130		3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile
131		4-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol
132		2-(5-(2-methyloxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
133		2-(5-(prop-1-en-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
134		1-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol

Compound No.	Structure	Name
135		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol
136		2-(5-((1-aminocyclopropyl)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
137		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetonitrile
138		2-(5-(1-((methylamino)methyl)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
139		tert-butyl methyl((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)carbamate
140		N-methyl-N-((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)cyanamide

Compound No.	Structure	Name
141		2-(5-(2-methyl-2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
142		tert-butyl methyl(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate
143		N-methyl-N-(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide
144		2-(5-(2-methyl-1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
145		tert-butyl methyl(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate
146		N-methyl-N-(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide
147		2-(5-(2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Compound No.	Structure	Name
148		tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate
149		N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide
150		2-(5-(1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
151		tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate
152		N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide
153		2-(5-(1-(methylamino)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
154		tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate

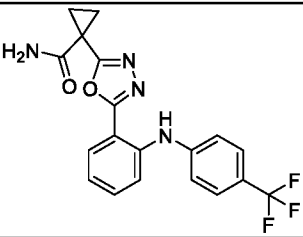
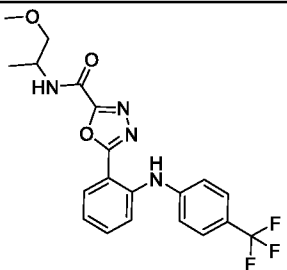
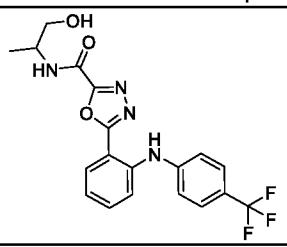
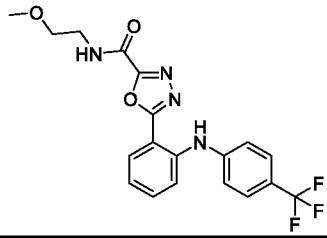
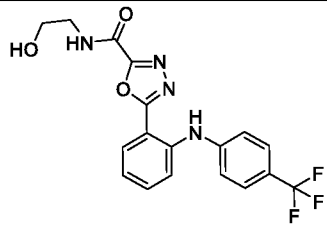
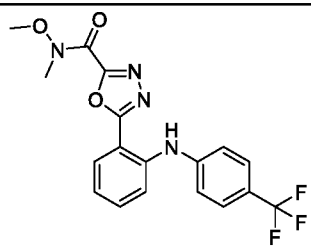
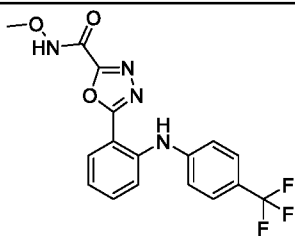
Compound No.	Structure	Name
155		N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)cyanamide
156		2-(5-(2-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
157		tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate
158		N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide
159		2-(5-(1-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
160		tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

Compound No.	Structure	Name
161		N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide
162		2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide
163		2-(5-(2-(methylsulfonyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
164		2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile
165		tert-butyl 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylate
166		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylic acid

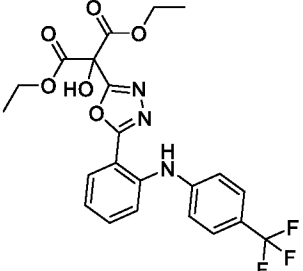
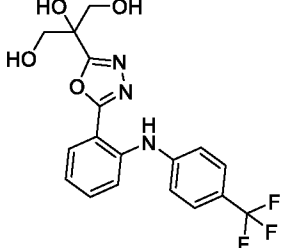
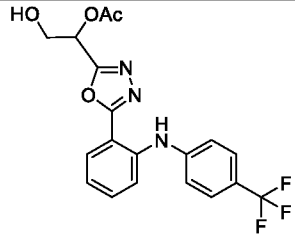
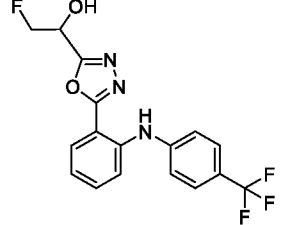
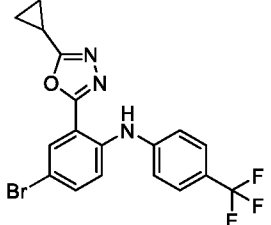
Compound No.	Structure	Name
167		tert-butyl methyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate
168		N-methyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide
169		2-(5-(pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
170		tert-butyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate
171		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile
172		2-(5-(2-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
173		tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

Compound No.	Structure	Name
174		N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide
175		2-(5-(pyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
176		tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate
177		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile
178		2-(5-(2-methyltetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
179		3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butane-1,3-diol

Compound No.	Structure	Name
180		2-(5-(2-methyloxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
181		2-(5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
182		2-(5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
183		2-(5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline
184		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carbonitrile
185		N,N-dimethyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide
186		N-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide

Compound No.	Structure	Name
187		1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide
188		N-(1-methoxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
189		N-(1-hydroxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
190		N-(2-methoxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
191		N-(2-hydroxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
192		N-methoxy-N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
193		N-methoxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide

Compound No.	Structure	Name
194		N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
195		N-cyclopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
196		N-isopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
197		N-ethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
198		N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide
199		2,2-dimethyl-5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)-1,3-dioxan-5-ol

Compound No.	Structure	Name
200		diethyl 2-hydroxy-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)malonate
201		2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propane-1,2,3-triol
202		2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl acetate
203		2-fluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol
204		4-bromo-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

Preparation of the Compounds

[00124] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH Inc. (Toronto, Canada), Bionet

(Cornwall, U.K.), Chemservice Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

[00125] Methods known to one of ordinary skill in the art are identified through various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R. V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[00126] In some instances, specific and analogous reactants are identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., is contacted for more details). Chemicals that are known but not commercially available in catalogs are prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

[00127] In some embodiments, the compounds disclosed herein are prepared as described in the Examples section.

Further Forms of Compounds Disclosed Herein

Isomers

[00128] Furthermore, in some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all *cis*, *trans*, *syn*, *anti*, *entgegen* (*E*), and *zusammen* (*Z*) isomers as well as the corresponding mixtures thereof. In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the *R* configuration, or *S* configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred (*e.g.*, crystalline diastereomeric salts). In some embodiments, the diastereomers have distinct physical properties (*e.g.*, melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Labeled compounds

[00129] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. In some embodiments, examples of isotopes that are incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, and the metabolites, pharmaceutically acceptable salts, esters, prodrugs, solvates, hydrates or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this disclosure. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^3H and carbon-14, i. e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, i.e., ^2H , produces certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof is prepared by any suitable method.

[00130] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00131] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00132] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ*

during the final isolation and purification of the compounds of the disclosure, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

Solvates

[00133] In some embodiments, the compounds described herein exist as solvates. The disclosure provides for methods of treating diseases by administering such solvates. The disclosure further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00134] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In some embodiments, solvates of the compounds described herein are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In some embodiments, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Prodrugs

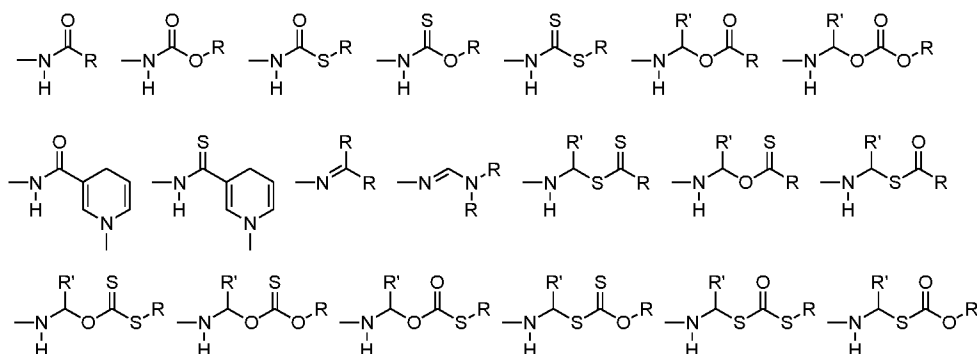
[00135] In some embodiments, the compounds described herein exist in prodrug form. The disclosure provides for methods of treating diseases by administering such prodrugs. The disclosure further provides for methods of treating diseases by administering such prodrugs as pharmaceutical compositions.

[00136] In some embodiments, prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e. g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy, or carboxylic acid group of compounds of the present disclosure. The amino acid residues include but are not limited to the 20 naturally occurring amino acids and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, cirtulline, homocysteine, homoserine, ornithine and methionine sulfone. In other embodiments, prodrugs include compounds wherein a nucleic acid residue, or an oligonucleotide of two or more (e. g., two, three or four) nucleic acid residues is covalently joined to a compound of the present disclosure.

[00137] Pharmaceutically acceptable prodrugs of the compounds described herein also include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, metal salts and sulfonate esters. In some embodiments, compounds having free amino, amido, hydroxy, or carboxylic groups are converted into prodrugs. For instance, free carboxyl groups are derivatized as amides or alkyl esters. In certain instances, all of these prodrug moieties incorporate groups including but not limited to ether, amine, and carboxylic acid functionalities.

[00138] Hydroxy prodrugs include esters, such as though not limited to, acyloxyalkyl (e.g. acyloxymethyl, acyloxyethyl) esters, alkoxycarbonyloxyalkyl esters, alkyl esters, aryl esters, sulfonate esters, sulfate esters and disulfide containing esters; ethers, amides, carbamates, hemisuccinates, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews* **1996**, 19, 115.

[00139] Amine derived prodrugs include, but are not limited to, the following groups and combinations of groups:



as well as sulfonamides and phosphonamides.

[00140] In certain instances, sites on any aromatic ring portions are susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, reduce, minimize, or eliminate this metabolic pathway.

Metabolites

[00141] In some embodiments, compounds described herein are susceptible to various metabolic reactions. Therefore, in some embodiments, incorporation of appropriate substituents into the structure will reduce, minimize, or eliminate a metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of an aromatic ring to metabolic reactions is, by way of example only, a halogen, or an alkyl group.

[00142] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

Pharmaceutical Compositions

[00143] In certain embodiments, the compound as described herein is administered as a pure chemical. In other embodiments, the compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)), the disclosure of which is hereby incorporated herein by reference in its entirety.

[00144] Accordingly, provided herein is a pharmaceutical composition comprising at least one compound described herein, or a stereoisomer, pharmaceutically acceptable salt, hydrate, solvate, or N-oxide thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.*, the subject) of the composition.

[00145] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[00146] Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[00147] In certain embodiments, the compound as described herein is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as contaminating intermediates or by-products that are created, for example, in one or more of the steps of a synthesis method.

[00148] These formulations include those suitable for oral, rectal, topical, buccal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, or intravenous), rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions are formulated as a unit dose, and/or are formulated for oral or subcutaneous administration.

[00149] In some instances, exemplary pharmaceutical compositions are used in the form of a pharmaceutical preparation, for example, in solid, semisolid, or liquid form, which includes one or more of a disclosed compound, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral applications. In some embodiments, the active ingredient is compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions,

and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[00150] For preparing solid compositions such as tablets in some instances, the principal active ingredient is mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a disclosed compound or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition is readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[00151] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions also comprise buffering agents in some embodiments. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[00152] In some instances, a tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets are prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets are made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, are optionally be scored or prepared with coatings and

shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[00153] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms contain optionally inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[00154] Suspensions, in addition to the subject composition, optionally contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00155] In some embodiments, formulations for rectal or vaginal administration are presented as a suppository, which are prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[00156] Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component is optionally mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which are required in some embodiments.

[00157] In some embodiments, the ointments, pastes, creams and gels contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[00158] In some embodiments, powders and sprays contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00159] Compositions and compounds disclosed herein are alternatively administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (*e.g.*, fluorocarbon propellant) suspension could be used. Sonic nebulizers are used because they minimize exposing the agent to shear, which result in degradation of the compounds contained in the subject compositions in some embodiments. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronic, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[00160] Pharmaceutical compositions suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which are reconstituted into sterile injectable solutions or dispersions just prior to use, which optionally contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[00161] Examples of suitable aqueous and non-aqueous carriers employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. In some embodiments, proper fluidity is maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00162] Also contemplated are enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about

8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (*e.g.*, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present disclosure.

[00163] In some embodiments, the dose of the composition comprising at least one compound as described herein differ, depending upon the patient's (*e.g.*, human) condition, that is, stage of the disease, general health status, age, and other factors that a person skilled in the medical art will use to determine dose.

[00164] In some instances, pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented) as determined by persons skilled in the medical arts. An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. In some embodiments, the optimal dose depends upon the body mass, weight, or blood volume of the patient.

[00165] In some embodiments, oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

The Hippo Signaling Network

[00166] The Hippo signaling network (also known as the Salvador/Warts/Hippo (SWH) pathway) is a master regulator of cell proliferation, death, and differentiation. In some embodiments, the main function of the Hippo signaling pathway is to regulate negatively the transcriptional co-activators Yes-associated protein (YAP) and its paralogue, the transcriptional co-activator with PDZ-binding motif (TAZ; also known as WWTR1) (**FIG. 1**). The Hippo kinase cascade phosphorylates and inhibits YAP/TAZ by promoting its cytoplasmic retention and degradation, thereby inhibiting the growth promoting function regulated under the YAP/TAZ control. In an un-phosphorylated/de-phosphorylated state, YAP, also known as YAP1 or YAP65, together with TAZ, are transported into the nucleus where they interact with TEAD family of transcription factors to upregulate genes that promote proliferation and migration, and inhibit apoptosis. In some instances, unregulated upregulation of these genes involved in proliferation, migration, and anti-apoptosis leads to development of cancer. In some instances, overexpression of YAP/TAZ is associated with cancer.

[00167] Additional core members of the Hippo signaling pathway comprise the serine/threonine kinases MST1/2 (homologues of *Hippo/Hpo* in *Drosophila*), Lats1/2 (homologues of *Warts/Wts*), and their adaptor proteins Sav1 (homologue of *Salvador/Sav*) and Mob (MOBKL1A and MOBKL1B; homologues of *Mats*), respectively (**FIG. 1**). In general, MST1/2 kinase complexes with the scaffold protein Sav1, which in turn phosphorylates and activates Lats1/2 kinase. Lats1/2 is also activated by the scaffold protein Mob. The activated Lats1/2 then phosphorylates and inactivates YAP or its paralog TAZ. The phosphorylation of YAP/TAZ leads to their nuclear export, retention within the cytoplasm, and degradation by the ubiquitin proteasome system.

[00168] In some instances, Lats1/2 phosphorylates YAP at the [HXRXXS] consensus motifs. YAP comprises five [HXRXXS] consensus motifs, wherein X denotes any amino acid residue. In some instances, Lats1/2 phosphorylates YAP at one or more of the consensus motifs. In some instances, Lats1/2 phosphorylates YAP at all five of the consensus motifs. In some instances, Lats1/2 phosphorylate at the S127 amino acid position. The phosphorylation of YAP S127 promotes 14-3-3 protein binding and results in cytoplasmic sequestration of YAP. Mutation of YAP at the S127 position thereby disrupts its interaction with 14-3-3 and subsequently promotes nuclear translocation.

[00169] Additional phosphorylation occurs at the S381 amino acid position in YAP. Phosphorylation of YAP at the S381 position and on the corresponding site in TAZ primes both proteins for further phosphorylation events by CK1 δ/ϵ in the degradation motif, which then signals

for interaction with the β -TRCP E3 ubiquitin ligase, leading to polyubiquitination and degradation of YAP.

[00170] In some instances, Lats1/2 phosphorylates TAZ at the [HXRXXS] consensus motifs. TAZ comprises four [HXRXXS] consensus motifs, wherein X denotes any amino acid residues. In some instances, Lats1/2 phosphorylates TAZ at one or more of the consensus motifs. In some instances, Lats1/2 phosphorylates TAZ at all four of the consensus motifs. In some instances, Lats1/2 phosphorylate at the S89 amino acid position. The phosphorylation of TAZ S89 promotes 14-3-3 protein binding and results in cytoplasmic sequestration of TAZ. Mutation of TAZ at the S89 position thereby disrupts its interaction with 14-3-3 and subsequently promotes nuclear translocation.

[00171] In some embodiments, phosphorylated YAP/TAZ accumulates in the cytoplasm, and undergoes SCF ^{β -TRCP}-mediated ubiquitination and subsequent proteasomal degradation. In some instances, the Skp, Cullin, F-box containing complex (SCF complex) is a multi-protein E3 ubiquitin ligase complex that comprises a F-box family member protein (e.g. Cdc4), Skp1, a bridging protein, and RBX1 which contains a small RING Finger domain which interacts with E2-ubiquitin conjugating enzyme. In some cases, the F-box family comprises more than 40 members, in which exemplary members include F-box/WD repeat-containing protein 1A (FBXW1A, β TrCP1, Fbxw1, hsSlimb, plkappaBalpha-E3 receptor subunit) and S-phase kinase-associated proteins 2 (SKP2). In some embodiments, the SCF complex (e.g. SCF ^{β TrCP1}) interacts with an E1 ubiquitin-activating enzyme and an E2 ubiquitin-conjugating enzyme to catalyze the transfer of ubiquitin to the YAP/TAZ substrate. Exemplary E1 ubiquitin-activating enzymes include those encoded by the following genes: *UBA1*, *UBA2*, *UBA3*, *UBA5*, *UBA5*, *UBA7*, *ATG7*, *NAE1*, and *SAE1*. Exemplary E2 ubiquitin-conjugating enzymes include those encoded by the following genes: *UBE2A*, *UBE2B*, *UBE2C*, *UBE2D1*, *UBE2D2*, *UBE2D3*, *UBE2E1*, *UBE2E2*, *UBE2E3*, *UBE2F*, *UBE2G1*, *UBE2G2*, *UBE2H*, *UBE2I*, *UBE2J1*, *UBE2J2*, *UBE2K*, *UBE2L3*, *UBE2L6*, *UBE2M*, *UBE2N*, *UBE2O*, *UBE2Q1*, *UBE2Q2*, *UBE2R1*, *UBE2R2*, *UBE2S*, *UBE2T*, *UBE2U*, *UBE2V1*, *UBE2V2*, *UBE2Z*, *ATG2*, *BIRC5*, and *UFC1*. In some embodiments, the ubiquitinated YAP/TAZ further undergoes the degradation process through the 26S proteasome.

[00172] In some embodiments, the Hippo pathway is regulated upstream by several different families of regulators (**FIG. 1**). In some instances, the Hippo pathway is regulated by the G-protein and its coupled receptors, the Crumbs complex, regulators upstream of the MST kinases, and the adherens junction.

YAP/TAZ Interaction with TEAD

[00173] In some embodiments, un-phosphorylated and/or dephosphorylated YAP/TAZ accumulates in the nucleus. Within the nucleus, YAP/TAZ interacts with the TEAD family of transcription factors (e.g. TEAD1, TEAD2, TEAD3, or TEAD4) to activate genes involved in anti-apoptosis and proliferation, such as for example *CTFG*, *Cyr61*, and *FGF1*.

[00174] In some embodiments, the compounds disclosed herein modulate the interaction between YAP/TAZ and TEAD. In some embodiments, the compounds disclosed herein bind to TEAD, YAP, or TAZ and prevent the interaction between YAP/TAZ and TEAD.

YAP/TAZ regulation mediated by G-proteins/GPCRs

[00175] In some embodiments, the Hippo pathway is regulated by the G protein-coupled receptor (GPCR) and G protein (also known as guanine nucleotide-binding proteins) family of proteins (**FIG. 2**). G proteins are molecular switches that transmit extracellular stimuli into the cell through GPCRs. In some instances, there are two classes of G proteins: monomeric small GTPases; and heterotrimeric G protein complexes. In some instances, the latter class of complexes comprise of alpha (G_α), beta (G_β), and gamma (G_γ) subunits. In some cases, there are several classes of G_α subunits: $G_{q/11}\alpha$, $G_{12/13}\alpha$, $G_{i/o}\alpha$ (G inhibitory, G other), and $G_s\alpha$ (G stimulatory).

[00176] In some instances, $G_i\alpha$ (G inhibitory), $G_o\alpha$ (G other), $G_{q/11}\alpha$, and $G_{12/13}\alpha$ coupled GPCRs activate YAP/TAZ and promote nuclear translocation. In other instances, $G_s\alpha$ (G stimulatory) coupled GPCRs suppress YAP/TAZ activity, leading to YAP/TAZ degradation.

[00177] In some cases, $G_i\alpha$ (G inhibitory), $G_o\alpha$ (G other), $G_{q/11}\alpha$, and $G_{12/13}\alpha$ coupled GPCRs activate YAP/TAZ through repression of Lats1/2 activities. In contrast, $G_s\alpha$, in some embodiments, induces Lats1/2 activity, thereby promoting YAP/TAZ degradation.

G_q Family

[00178] $G_q\alpha$ (also known as $G_{q/11}$ protein), participates in the inositol trisphosphate (IP_3) signal transduction pathway and calcium (Ca^{2+}) release from intracellular storage through the activation of phospholipase C (PLC). The activated PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacyl glycerol (DAG) and IP_3 . In some instances, IP_3 then diffuses through the cytoplasm into the ER or the sarcoplasmic reticulum (SR) in the case of muscle cells, and then binds to inositol trisphosphate receptor ($InsP3R$), which is a Ca^{2+} channel. In some cases, the binding triggers the opening of the Ca^{2+} channel, and thereby increases the release of Ca^{2+} into the cytoplasm.

[00179] In some embodiments, the GPCRs that interact with $G_q\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT₂ and 5-HT₃; alpha-1 adrenergic receptor; vasopressin type 1 receptors 1A and 1B; angiotensin II receptor type 1; calcitonin receptor;

histamine H1 receptor; metabotropic glutamate receptor, group I; muscarinic receptors M₁, M₃, and M₅; and trace amine-associated receptor 1.

[00180] In some instances, there are several types of G_qα: G_q, G_{q/11}, G_{q/14}, and G_{q/15}. The G_q protein is encoded by *GNAQ*. G_{q/11} is encoded by *GNAI1*. G_{q/14} is encoded by *GNAI4*. G_{q/15} is encoded by *GNAI5*.

[00181] In some instances, mutations or modifications of the G_qα genes have been associated with cancer. Indeed, studies have shown that mutations in G_qα promote uveal melanoma (UM) tumorigenesis. In some instances, about 80% of UM cases have been detected to contain a mutation in *GNAQ* and/or *GNAI1*.

[00182] In some instances, mutations or modifications of the G_qα genes have been associated with congenital diseases. In some instances, mutations of G_qα have been observed in congenital diseases such as Port-Wine Stain and/or Sturge-Weber Syndrome. In some instances, about 92% of Port-Wine stain cases harbors a mutation in *GNAQ*. In some instances, about 88% of Sturge-Weber Syndrome harbors a mutation in *GNAQ*.

G_{12/13} Family

[00183] G_{12/13}α modulates actin cytoskeletal remodeling in cells and regulates cell processes through guanine nucleotide exchange factors (GEFs). GEFs participate in the activation of small GTPases which acts as molecular switches in a variety of intracellular signaling pathways. Examples of small GTPases include the Ras-related GTPase superfamily (e.g. Rho family such as Cdc42), which is involved in cell differentiation, proliferation, cytoskeletal organization, vesicle trafficking, and nuclear transport.

[00184] In some embodiments, the GPCRs that interact with G_{12/13}α include, but are not limited to, purinergic receptors (e.g. P2Y₁, P2Y₂, P2Y₄, P2Y₆); muscarinic acetylcholine receptors M1 and M3; receptors for thrombin [protease-activated receptor (PAR)-1, PAR-2]; thromboxane (TXA₂); sphingosine 1-phosphate (e.g. S1P₂, S1P₃, S1P₄ and S1P₅); lysophosphatidic acid (e.g. LPA₁, LPA₂, LPA₃); angiotensin II (AT1); serotonin (5-HT_{2c} and 5-HT₄); somatostatin (sst₅); endothelin (ET_A and ET_B); cholecystikinin (CCK₁); V_{1a} vasopressin receptors; D₅ dopamine receptors; fMLP formyl peptide receptors; GAL₂ galanin receptors; EP₃ prostanoid receptors; A₁ adenosine receptors; α₁ adrenergic receptors; BB₂ bombesin receptors; B₂ bradykinin receptors; calcium-sensing receptors; KSHV-ORF74 chemokine receptors; NK₁ tachykinin receptors; and thyroid-stimulating hormone (TSH) receptors.

[00185] In some instances, G_{12/13}α is further subdivided into G₁₂ and G₁₃ types which are encoded by *GNA12* and *GNA13*, respectively.

G_{i/o} Family

[00186] $G_{i/o}\alpha$ (G inhibitory, G other) (also known as G_i/G_o or G_i protein) that suppresses the production of 3',5'-cyclic AMP (cAMP) from adenosine triphosphate (ATP) through an inhibition of adenylate cyclase activity, which converts ATP to cAMP.

[00187] In some embodiments, the GPCRs that interact with $G_i\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT₁ and 5-HT₅; muscarinic acetylcholine receptors such as M₂ and M₄; adenosine receptors such as A₁ and A₃; adrenergic receptors such as α_{2A} , α_{2B} , and α_{2C} ; apelin receptors; calcium-sensing receptor; cannabinoid receptors CB1 and CB2; chemokine CXCR4 receptor; dopamines D₂, D₃, and D₄; GABA_B receptor; glutamate receptors such as metabotropic glutamate receptor 2 (mGluR2), metabotropic glutamate receptor 3 (mGluR3), metabotropic glutamate receptor 4 (mGluR4), metabotropic glutamate receptor 6 (mGluR6), metabotropic glutamate receptor 7 (mGluR7), and metabotropic glutamate receptor 8 (mGluR8); histamine receptors such as H₃ and H₄ receptors; melatonin receptors such as melatonin receptor type 1 (MT1), melatonin receptor type 2 (MT2), and melatonin receptor type 3 (MT3); niacin receptors such as NIACR1 and NIACR2; opioid receptors such as δ , κ , μ , and nociceptin receptors; prostaglandin receptors such as prostaglandin E receptor 1 (EP₁), prostaglandin E receptor 3 (EP₃), prostaglandin F receptor (FP), and thromboxane receptor (TP); somatostatin receptors sst1, sst2, sst3, sst4, and sst5; and trace amine-associated receptor 8.

[00188] In some instances, there are several types of $G_i\alpha$: $G_{i\alpha 1}$, $G_{i\alpha 2}$, $G_{i\alpha 3}$, $G_{i\alpha 4}$, $G_{o\alpha}$, G_t , G_{gust} , and G_z . $G_{i\alpha 1}$ is encoded by *GNAI1*. $G_{i\alpha 2}$ is encoded by *GNAI2*. $G_{i\alpha 3}$ is encoded by *GNAI3*. $G_{o\alpha}$, the α_o subunit, is encoded by *GNAO1*. G_t is encoded by *GNAT1* and *GNAT2*. G_{gust} is encoded by *GNAT3*. G_z is encoded by *GNAZ*.

G_s Family

[00189] $G_s\alpha$ (also known as G stimulatory, G_s alpha subunit, or G_s protein) activates the cAMP-dependent pathway through the activation of adenylate cyclase, which converts adenosine triphosphate (ATP) to 3',5'-cyclic AMP (cAMP) and pyrophosphate. In some embodiments, the GPCRs that interact with $G_s\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT₄, 5-HT₆, and 5-HT₇; adrenocorticotrophic hormone receptor (ACTH receptor) (also known as melanocortin receptor 2 or MC2R); adenosine receptor types A_{2a} and A_{2b}; arginine vasopressin receptor 2 (AVPR2); β -adrenergic receptors β_1 , β_2 , and β_3 ; calcitonin receptor; calcitonin gene-related peptide receptor; corticotropin-releasing hormone receptor; dopamine receptor D₁-like family receptors such as D₁ and D₅; follicle-stimulating hormone receptor (FSH-receptor); gastric inhibitory polypeptide receptor; glucagon receptor; histamine H₂ receptor; luteinizing hormone/choriogonadotropin receptor; melanocortin receptors such as MC1R, MC2R, MC3R, MC4R, and MC5R; parathyroid hormone receptor 1; prostaglandin receptor types D₂ and

I₂; secretin receptor; thyrotropin receptor; trace amine-associated receptor 1; and box jellyfish opsin.

[00190] In some instances, there are two types of G_sα: G_s and G_{olf}. G_s is encoded by *GNAS*. G_{olf} is encoded by *GNAL*.

Additional Regulators of the Hippo signaling network

[00191] In some embodiments, the additional regulator of the Hippo signaling pathway is the Crumbs (Crb) complex. The Crumbs complex is a key regulator of cell polarity and cell shape. In some instances, the Crumbs complex comprises transmembrane CRB proteins which assemble multi-protein complexes that function in cell polarity. In some instances, CRB complexes recruit members of the Angiomotin (AMOT) family of adaptor proteins that interact with the Hippo pathway components. In some instances, studies have shown that AMOT directly binds to YAP, promotes YAP phosphorylation, and inhibits its nuclear localization.

[00192] In some instances, the additional regulator of the Hippo signaling pathway comprises regulators of the MST kinase family. MST kinases monitor actin cytoskeletal integrity. In some instances, the regulators include TAO kinases and cell polarity kinase PAR-1.

[00193] In some instances, the additional regulator of the Hippo signaling pathway comprises molecules of the adherens junction. In some instances, E-Cadherin (E-cad) suppresses YAP nuclear localization and activity through regulating MST activity. In some embodiments, E-cad-associated protein α-catenin regulates YAP through sequestering YAP/14-3-3 complexes in the cytoplasm. In other instances, Ajuba protein family members interact with Lats1/2 kinase activity, thereby preventing inactivation of YAP/TAZ.

[00194] In some embodiments, additional proteins that interact with YAP/TAZ either directly or indirectly include, but are not limited to, Merlin, protocadherin Fat 1, MASK1/2, HIPK2, PTPN14, RASSF, PP2A, Salt-inducible kinases (SIKs), Scribble (SCRIB), the Scribble associated proteins Discs large (Dlg), KIBRA, PTPN14, NPHP3, LKB1, Ajuba, and ZO1/2.

[00195] In some embodiments, the compounds described herein are inhibitors of transcriptional coactivator with PDZ binding motif/Yes- associated protein transcriptional coactivator (TAZ/YAP). In some embodiments, the compounds described herein increase the phosphorylation of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP) or decrease the dephosphorylation of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP). In some embodiments, the compounds increase the ubiquitination of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP) or decrease the

deubiquitination of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP).

[00196] In some embodiments, the compounds disclosed herein are inhibitors of one or more of the proteins encompassed by, or related to, the Hippo pathway. In some instances, the one or more proteins comprise a protein shown in Figs. 1 and/or 2. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein and/or its coupled GPCR. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of the $G_q\alpha$ family proteins such as G_q , $G_{q/11}$, $G_{q/14}$, and $G_{q/15}$; the $G_{12/13}\alpha$ family of proteins such as G_{12} and G_{13} ; or the $G_i\alpha$ family of proteins such as $G_{i\alpha1}$, $G_{i\alpha2}$, $G_{i\alpha3}$, $G_{i\alpha4}$, $G_{o\alpha}$, G_t , G_{gust} , and G_z . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_q . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/11}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/14}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/15}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{12} . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{13} . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha1}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha2}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha3}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{i\alpha4}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{o\alpha}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_t . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{gust} . In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_z .

[00197] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a core protein of the Hippo pathway. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Sav1. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Mob. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of YAP. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of TAZ. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of TEAD.

[00198] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a protein associated with the ubiquitination and proteasomal degradation pathway. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a proteasomal degradation pathway protein (e.g. 26S proteasome).

[00199] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a protein of the Ras superfamily of proteins. In some embodiments, an inhibitor of the Hippo pathway is an

inhibitor of a protein of the Rho family of proteins. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Cdc42.

[00200] Cdc42 is a member of the Ras superfamily of small GTPases. Specifically, Cdc42 belongs to the Rho family of GTPases, in which the family members participate in diverse and critical cellular processes such as gene transcription, cell-cell adhesion, and cell cycle progression. Cdc42 is involved in cell growth and polarity, and in some instances, Cdc42 is activated by guanine nucleotide exchange factors (GEFs). In some cases, an inhibitor of Cdc42 is a compound disclosed herein.

[00201] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a deubiquitinating enzyme. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a cysteine protease or a metalloprotease. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of an ubiquitin-specific protease. USP47 is a member of the ubiquitin-specific protease (USP/UBP) superfamily of cysteine proteases. In some embodiments, the compounds disclosed herein are inhibitors of USP47.

[00202] Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

Diseases

Cancer

[00203] In some embodiments, the compounds disclosed herein are useful for treating cancer. In some embodiments, the cancer is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes-associated protein transcription coactivator (TAZ/YAP). In some embodiments, the cancer is mediated by modulation of the interaction of YAP/TAZ with TEAD. In some embodiments, the cancer is characterized by a mutant $G\alpha$ -protein. In some embodiments, the mutant $G\alpha$ -protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant $G\alpha$ -protein is G12. In some embodiments, the mutant $G\alpha$ -protein is G13. In some embodiments, the mutant $G\alpha$ -protein is Gq. In some embodiments, the mutant $G\alpha$ -protein is G11. In some embodiments, the mutant $G\alpha$ -protein is Gi. In some embodiments, the mutant $G\alpha$ -protein is Go. In some embodiments, the mutant $G\alpha$ -protein is Gs.

[00204] In some embodiments, the cancer is a solid tumor. In some instances, the cancer is a hematologic malignancy. In some instances, the solid tumor is a sarcoma or carcinoma. In some instances, the solid tumor is a sarcoma. In some instances, the solid tumor is a carcinoma.

[00205] Exemplary sarcoma includes, but is not limited to, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastoma, angiosarcoma, chondrosarcoma, chordoma, clear cell sarcoma of soft tissue, dedifferentiated liposarcoma, desmoid, desmoplastic small round cell tumor, embryonal

rhabdomyosarcoma, epithelioid fibrosarcoma, epithelioid hemangioendothelioma, epithelioid sarcoma, esthesioneuroblastoma, Ewing sarcoma, extrarenal rhabdoid tumor, extraskeletal myxoid chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, giant cell tumor, hemangiopericytoma, infantile fibrosarcoma, inflammatory myofibroblastic tumor, Kaposi sarcoma, leiomyosarcoma of bone, liposarcoma, liposarcoma of bone, malignant fibrous histiocytoma (MFH), malignant fibrous histiocytoma (MFH) of bone, malignant mesenchymoma, malignant peripheral nerve sheath tumor, mesenchymal chondrosarcoma, myxofibrosarcoma, myxoid liposarcoma, myxoinflammatory fibroblastic sarcoma, neoplasms with perivascular epithelioid cell differentiation, osteosarcoma, parosteal osteosarcoma, neoplasm with perivascular epithelioid cell differentiation, periosteal osteosarcoma, pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, PNET/extraskeletal Ewing tumor, rhabdomyosarcoma, round cell liposarcoma, small cell osteosarcoma, solitary fibrous tumor, synovial sarcoma, and telangiectatic osteosarcoma.

[00206] Exemplary carcinoma includes, but is not limited to, adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer. In some instances, the liver cancer is primary liver cancer.

[00207] In some instances, the cancer is selected from uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the cancer is uveal melanoma. In some cases, the cancer is mesothelioma. In some cases, the cancer is esophageal cancer. In some cases, the cancer is liver cancer. In some cases, the cancer is primary liver cancer.

[00208] In some instances, the cancer is a hematologic malignancy. In some embodiments, a hematologic malignancy is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, a T-cell malignancy, or a B-cell malignancy. In some instances, a hematologic malignancy is a T-cell malignancy. Exemplary T-cell malignancy includes, but is not limited to, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma, angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), blastic NK-cell lymphoma, enteropathy-type T-cell lymphoma, hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma, nasal NK/T-cell lymphomas, and treatment-related T-cell lymphomas.

[00209] In some instances, a hematologic malignancy is a B-cell malignancy. Exemplary B-cell malignancy includes, but is not limited to, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, and a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

[00210] In some instances, the cancer is a relapsed or refractory cancer. In some embodiments, the relapsed or refractory cancer is a relapsed or refractory solid tumor. In some embodiments, the relapsed or refractory solid tumor is a relapsed or refractory sarcoma or a relapsed or refractory carcinoma. In some embodiments, the relapsed or refractory carcinoma includes adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer.

[00211] In some instances, the relapsed or refractory cancer is selected from relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular

carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma. In some cases, the relapsed or refractory cancer is relapsed or refractory mesothelioma. In some cases, the relapsed or refractory cancer is relapsed or refractory esophageal cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory liver cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory primary liver cancer.

[00212] In some instances, the relapsed or refractory cancer is a relapsed or refractory hematologic malignancy. In some embodiments, a relapsed or refractory hematologic malignancy is a relapsed or refractory leukemia, a relapsed or refractory lymphoma, a relapsed or refractory myeloma, a relapsed or refractory non-Hodgkin's lymphoma, a relapsed or refractory Hodgkin's lymphoma, a relapsed or refractory T-cell malignancy, or a relapsed or refractory B-cell malignancy. In some instances, a relapsed or refractory hematologic malignancy is a relapsed or refractory T-cell malignancy. In some instances, a relapsed or refractory hematologic malignancy is a relapsed or refractory B-cell malignancy, such as for example, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

[00213] In some instances, the cancer is a metastasized cancer. In some instances, the metastasized cancer is a metastasized solid tumor. In some instances, the metastasized solid tumor is a metastasized sarcoma or a metastasized carcinoma. In some embodiments, the metastasized

carcinoma includes adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer.

[00214] In some instances, the metastasized cancer is selected from metastasized uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the metastasized cancer is metastasized uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the metastasized cancer is metastasized uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the metastasized cancer is metastasized uveal melanoma. In some cases, the metastasized cancer is metastasized mesothelioma. In some cases, the metastasized cancer is metastasized esophageal cancer. In some cases, the metastasized cancer is metastasized liver cancer. In some cases, the metastasized cancer is metastasized primary liver cancer.

[00215] In some instances, the metastasized cancer is a metastasized hematologic malignancy. In some embodiments, the metastasized hematologic malignancy is a metastasized leukemia, a metastasized lymphoma, a metastasized myeloma, a metastasized non-Hodgkin's lymphoma, a metastasized Hodgkin's lymphoma, a metastasized T-cell malignancy, or a metastasized B-cell malignancy. In some instances, a metastasized hematologic malignancy is a metastasized T-cell malignancy. In some instances, a metastasized hematologic malignancy is a metastasized B-cell malignancy, such as for example, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell

lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

Congenital Diseases

[00216] In some embodiments, the compounds disclosed herein are useful for treating a congenital disease. In some embodiments, the congenital disease is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes- associated protein transcription coactivator (TAZ/YAP). In some embodiments, the congenital disease is characterized by a mutant G α -protein. In some embodiments, the mutant G α -protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant G α -protein is G12. In some embodiments, the mutant G α -protein is G13. In some embodiments, the mutant G α -protein is Gq. In some embodiments, the mutant G α -protein is G11. In some embodiments, the mutant G α -protein is Gi. In some embodiments, the mutant G α -protein is Go. In some embodiments, the mutant G α -protein is Gs.

[00217] In some embodiments, the congenital disease is the result of a genetic abnormality, an intrauterine environment, errors related to morphogenesis, infection, epigenetic modifications on a parental germline, or a chromosomal abnormality. Exemplary congenital diseases include, but are not limited to, Sturge-Weber Syndrome, Port-Wine stain, Holt-Oram syndrome, abdominal wall defects, Becker muscular dystrophy (BMD), biotinidase deficiency, Charcot-Marie-Tooth (CMT), cleft lip, cleft palate, congenital adrenal hyperplasia, congenital heart defects, congenital hypothyroidism, congenital muscular dystrophy, cystic fibrosis, Down syndrome, Duchenne muscular dystrophy, Fragile X syndrome, Friedreich's ataxia, galactosemia, hemoglobinopathies, Krabbe disease, limb-girdle muscular dystrophy, medium chain acyl-CoA dehydrogenase deficiency, myasthenia gravis, neural tube defects, phenylketonuria, Pompe disease, severe combined immunodeficiency (SCID), Stickler syndrome (or hereditary progressive arthropathopathy), spinal muscular atrophy, and trisomy 18. In some embodiments, the congenital disease is Sturge-Weber Syndrome or Port-Wine stain. In some embodiments, the congenital disease is Sturge-Weber Syndrome. In some embodiments, the congenital disease is Port-Wine stain.

EXAMPLES

[00218] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

List of abbreviations

[00219] As used above, and throughout the disclosure, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN or MeCN	acetonitrile
Bn	benzyl
BOC or Boc	<i>tert</i> -butyl carbamate
t-Bu	tert-butyl
Cy	cyclohexyl
DBA	dibenzylideneacetone
DCE	dichloroethane (ClCH ₂ CH ₂ Cl)
DCM	dichloromethane (CH ₂ Cl ₂)
DIPEA or DIEA	diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	dimethylformamide
DMA	<i>N,N</i> -dimethylacetamide
DMSO	dimethylsulfoxide
Dppf or dppf	1,1'-bis(diphenylphosphino)ferrocene
eq	equivalent(s)
Et	ethyl
Et ₂ O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
HPLC	high performance liquid chromatography
LAH	lithium aluminum anhydride
LCMS	liquid chromatography mass spectrometry
Me	methyl
MeOH	methanol
MS	mass spectroscopy
NMM	<i>N</i> -methyl-morpholine
NMP	<i>N</i> -methyl-pyrrolidin-2-one
NMR	nuclear magnetic resonance
RP-HPLC	reverse phase-high pressure liquid chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran

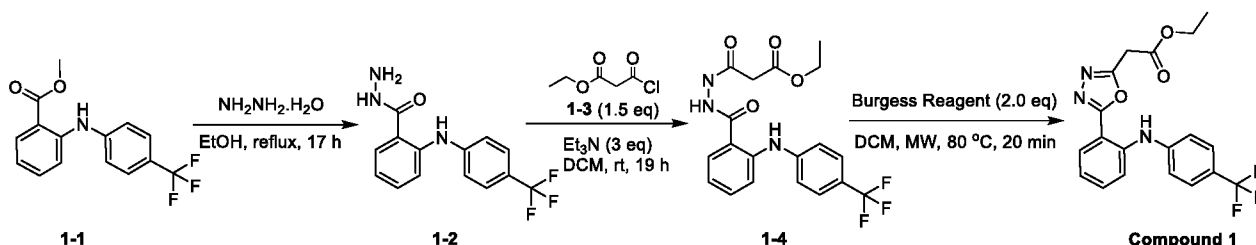
TLC

thin layer chromatography

I. Chemical Synthesis

[00220] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times were approximate and were not optimized. Column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted. Same reagents might have different assigned numbers throughout Examples.

Example 1: ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate (Compound 1)



Step 1: 2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00221] To a mixture of **1-1** (2.0 g, 6.8 mmol, 1 *eq*) in EtOH (20 mL) was added $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (4.1 g, 70.0 mmol, 4 mL, 85% purity, 10.33 *eq*). The resulted mixture was stirred at 80 °C for 17 h. LCMS and TLC showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography. **1-2** (1.8 g, 6.0 mmol, 89.1% yield) was obtained.

Step 2: ethyl 3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propanoate

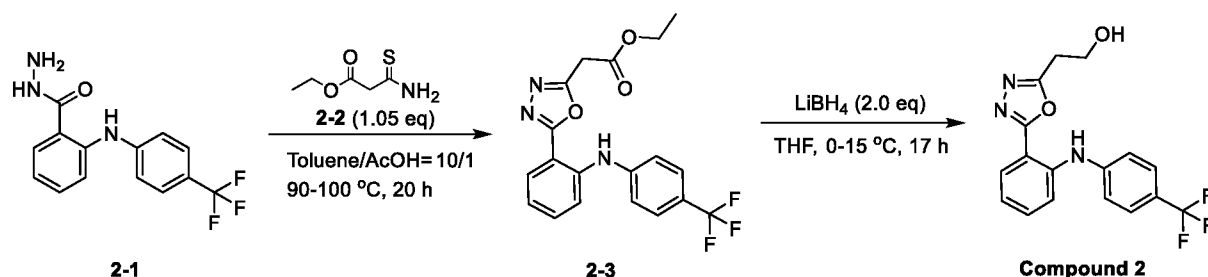
[00222] To a mixture of **1-2** (500 mg, 1.7 mmol, 1 *eq*) and TEA (514.1 mg, 5.1 mmol, 0.7 mL, 3 *eq*) in DCM (6 mL) was added **1-3** (382.4 mg, 2.5 mmol, 0.3 mL, 1.5 *eq*) dropwise. The resulting mixture was stirred at 15 °C for 19 h. LCMS showed the reaction was complete. The mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The organic layer was dried over anhydrous Na_2SO_4 , concentrated in vacuum. The residue was purified by silica gel chromatography. **1-4** (0.6 g, 1.2 mmol, 70.1% yield) was obtained.

Step 3: ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate

[00223] To a mixture of **1-4** (50 mg, 0.12 mmol, 1 *eq*) in DCM (3 mL) was added Burgess reagent (58.2 mg, 0.24 mmol, 2 *eq*). The resulted mixture was stirred at 80 °C under microwave condition for 20 min. LCMS and HPLC showed about 34% desired compound was detected, and 42% starting material was remained. The mixture was concentrated in vacuum. The residue was purified

by prep-HPLC. **Compound 1** (4.33 mg, 11.1 μmol , 9.1% yield) was obtained. LCMS (ESI): RT = 0.876 min, mass calcd. for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_3$ 391.11, m/z found 392.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.48 (s, 1H), 7.90 (dd, J = 1.1, 7.9 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.3 Hz, 1H), 7.43 - 7.35 (m, 3H), 6.97 (t, J = 7.5 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 4.06 (s, 2H), 1.32 (t, J = 7.2 Hz, 3H).

Example 2: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 2)



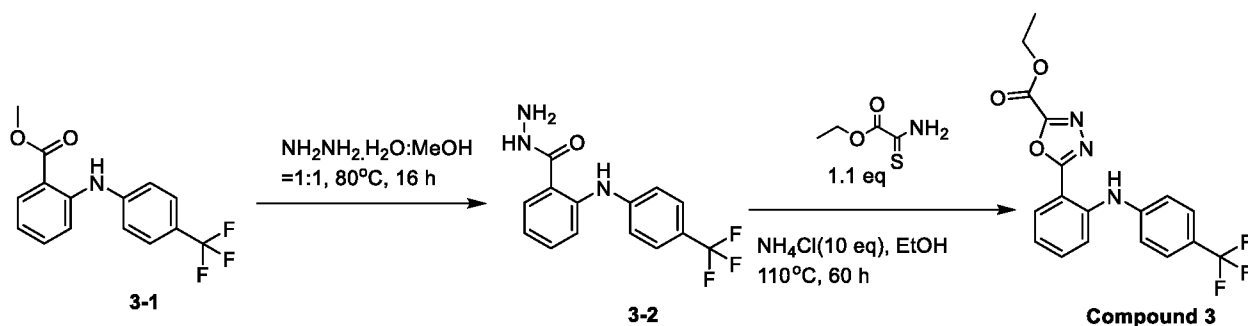
Step 1: ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate [00224]

To a mixture of **2-1** (50 mg, 0.17 mmol, 1 *eq*) in toluene (3 mL) and AcOH (0.3 mL) was added **2-2** (26.2 mg, 0.18 mmol, 1.05 *eq*). The resulted mixture was stirred at 90 $^\circ\text{C}$ for 17 h. LCMS showed the starting material was consumed completely, and 9% desired compound was detected. The mixture was stirred at 100 $^\circ\text{C}$ for 3 h. LCMS showed there's no obvious change. The mixture was concentrated in vacuum. The residue was checked by HPLC. The residue was purified by prep-HPLC. **2-3** (10 mg, 25.6 μmol , 15.1% yield) was obtained.

Step 2: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol [00225]

To a mixture of **2-3** (10 mg, 25.6 μmol , 1 *eq*) in THF (2 mL) was added LiBH_4 (1.1 mg, 51.1 μmol , 2 *eq*) at 0 $^\circ\text{C}$. The resulted mixture was stirred at 15 $^\circ\text{C}$ for 17 h. LCMS showed there's about 42% desired compound. The mixture was diluted with MeOH (3 mL), concentrated in vacuum. The residue was purified by prep-HPLC. **Compound 2** (3.9 mg, 11.2 μmol , 43.7% yield) was obtained. LCMS (ESI): RT = 0.788 min, mass calcd. for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$ 349.10, m/z found 349.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.48 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.5 Hz, 1H), 7.43 - 7.35 (m, 3H), 6.98 (t, J = 7.5 Hz, 1H), 4.17 (t, J = 5.8 Hz, 2H), 3.21 (t, J = 5.8 Hz, 2H).

Example 3: ethyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (Compound 3)



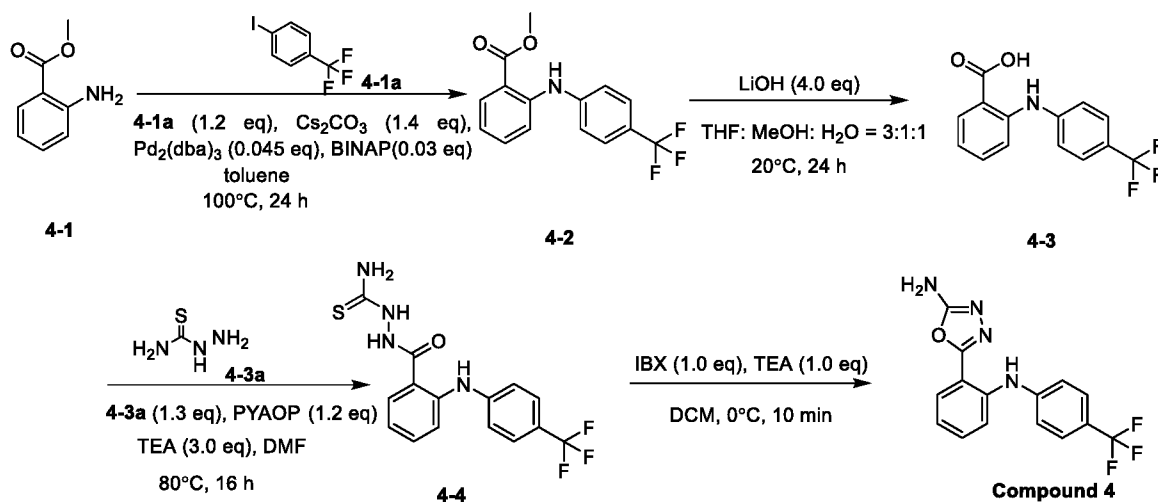
Step 1: 2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00226] To a solution of **3-1** (2.2 g, 7.45 mmol, 1 *eq*) in MeOH (5.5 mL) were added hydrazine-hydrate (5.7 g, 96.87 mmol, 5.5 mL, 13 *eq*) at 25 °C. The resulting solution was stirred at 80 °C for 16 h and cooled to 25 °C, along with lots of solid formed. LCMS showed no starting material was remained and 90% of desired product was detected. TLC (PE:EA = 2:1 UV) showed the reaction was complete. The mixture was filtered. The filter cake was washed with water (20 mL) and dried to give 1.9 g of residue. The filtrate was concentrated to remove most of methanol and extracted with EA (30 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was combined with 1.9 g of filter cake to give **3-2** (2.1 g, 7.11 mmol, 95.4% yield), which was used directly without purification. ¹H NMR (400MHz, CDCl₃) δ 9.25 (s, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.49 - 7.34 (m, 4H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.94 - 6.86 (m, 1H), 4.38 - 3.78 (m, 2H).

Step 2: ethyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate

[00227] A flask containing **3-2** (2.1 g, 7.11 mmol, 1 *eq*), NH₄Cl (3.8 g, 71.12 mmol, 2.5 mL, 10 *eq*) and ethyl 2-amino-2-thioxo-acetate (1.04 g, 7.82 mmol, 1.1 *eq*) in EtOH (60 mL) was heated at 110 °C for 60 h. (Note: ethyl 2-amino-2-thioxo-acetate was forgotten to add at the beginning, it was added after heating for about 1 h.) LCMS showed 34% of starting material was remained and 16% of desired product was formed. TLC (PE:EA = 2:1 UV) showed starting material was remained and new spots were formed. The mixture was filtered and the filter cake was washed with EA (30 mL). The filtrate was concentrated to give a residue. The residue was purified by column chromatography to give **Compound 3** (0.2 g) and recovery compound **3-2** (0.64 g, 2.17 mmol, 30.5% yield). **Compound 3** (0.2 g) was purified by prep-HPLC to give the title compound (112.8 mg, 0.30 mmol, 4.2% yield). LCMS (ESI): RT = 2.054 min, mass calc. for C₁₈H₁₄F₃N₃O₃ 377.10, *m/z* found 377.9[M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 10.27 (s, 1H), 9.44 (s, 1H), 8.07 - 7.97 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.52 - 7.31 (m, 4H), 6.99 (t, *J* = 7.5 Hz, 1H), 4.61 - 4.52 (m, 2H), 1.50 (t, *J* = 7.3 Hz, 3H).

Example 4: 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine (Compound 4)



Step 1: methyl 2-[4-(trifluoromethyl)anilino]benzoate

[00228] A mixture of **4-1** (2.32 g, 15.3 mmol, 2 mL, 1.0 eq), **4-1a** (5.0 g, 18.4 mmol, 2.7 mL, 1.2 eq), Cs_2CO_3 (7.0 g, 21.4 mmol, 1.4 eq), $\text{Pd}_2(\text{dba})_3$ (631.1 mg, 0.7 mmol, 0.1 eq) and BINAP (286.1 mg, 0.5 mmol, 0.03 eq) in toluene (80 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 24 hr under N_2 atmosphere. TLC (Petroleum ether:Ethyl acetate = 10: 1) indicated that **4-1** remained and three major new spots were detected. LCMS showed **4-1** was consumed completely and desired MS (m/z = 295.9; RT = 0.888 min) was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to give **4-2** (1.3 g, 4.3 mmol, 28.1% yield). LCMS showed the desired MS (m/z = 295.9; RT = 0.888 min) was detected. LCMS (ESI): RT = 0.888 min, mass calc. for: $\text{C}_{15}\text{H}_{12}\text{F}_3\text{NO}_2$ 295.08, m/z found 295.8 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 3.90-3.96 (m, 3H), 6.86 (ddd, J = 8.09, 5.58, 2.64 Hz, 1H), 7.26-7.33 (m, 2H), 7.36-7.43 (m, 2H), 7.56 (d, J = 8.53 Hz, 2H), 7.94-8.14 (m, 1H), 9.58-9.81 (m, 1H).

Step 2: 2-[4-(trifluoromethyl)anilino]benzoic acid

[00229] To a solution of **4-2** (1.1 g, 3.73 mmol, 1.0 eq) in THF (10 mL) and methanol (1 mL) was added LiOH (356.9 mg, 14.9 mmol, 4.0 eq) dissolved in H_2O (1 mL). The mixture was stirred at 20°C for 16 hr. TLC (Petroleum ether:Ethyl acetate = 1:1, UV) indicated compound **4-2** was remained, and one major new spot was detected. The mixture was concentrated to give a residue. The residue was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL). The aqueous phase was adjusted to pH~2 from 8 with HCl (2 M), along with lots of solid formed. **4-3** (0.7 g, crude) was obtained. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 6.96 (t, J = 7.40 Hz, 1 H), 7.39 (d, J = 8.28 Hz, 2 H), 7.43 - 7.53 (m, 2 H), 7.63 (d, J = 8.78 Hz, 2 H), 7.95 (dd, J = 7.91, 1.38 Hz, 1 H), 9.72-9.82 (s, 1 H), 13.23-13.32 (s, 1 H).

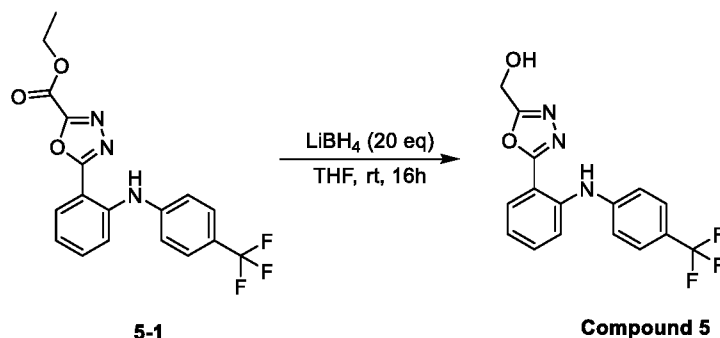
Step 3: [[2-[4-(trifluoromethyl)anilino]benzoyl]amino]thiourea

[00230] To a solution of **4-3** (30 mg, 0.1 mmol, 1.0 *eq*) in DMF (2 mL) was added PYAOP (66.7 mg, 0.1 mmol, 1.2 *eq*) and TEA (32.4 mg, 0.3 mmol, 0.1 mL, 3.0 *eq*). Then **4-3a** (12.6 mg, 0.1 mmol, 1.3 *eq*) was added to the mixture. The mixture was stirred at 80 °C for 16 hr. TLC (Petroleum ether:Ethyl acetate = 5:1, UV) indicated **4-3** was consumed and one new spot formed. LCMS showed **4-3** was consumed and 47% of desired MS ($m/z = 354.9$; RT = 0.720 min). The reaction mixture was concentrated under reduced pressure. The residue was diluted with H₂O (15 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂) to give **4-4**. LCMS (ESI): RT = 0.724 min, mass calc. for: C₁₅H₁₂F₃NO₂ 354.08, m/z found 354.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.33 (s, 1H), 6.94-7.03 (t, $J = 7.28$ Hz, 1H), 7.22-7.31 (d, $J = 8.53$ Hz, 2H), 7.38-7.50 (m, 3H), 7.59 (d, $J = 8.53$ Hz, 3H), 7.62-7.73 (m, 1H), 7.78-7.85 (d, $J = 7.53$ Hz, 1H), 9.24-9.34 (s, 1H), 9.44-9.53 (s, 1H), 10.41-10.51 (s, 1H).

Step 4: 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-amine

[00231] To a solution of **4-4** (40 mg, 0.1 mmol, 1.0 *eq*) in DCM (2 mL) was added IBX (31.6 mg, 0.1 mmol, 1.0 *eq*) and TEA (11.4 mg, 0.1 mmol, 1.0 *eq*). The mixture was stirred at 0 °C for 10 min. TLC (Petroleum ether:Ethyl acetate = 3:1, UV) indicated **4-4** remained and one major new spot was detected. LCMS showed **4-4** was consumed and desired product ($m/z = 320.9$; RT = 0.783 min) was detected. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **Compound 4** (6.5 mg, 19.7 μ mol, 17.4% yield). LCMS (ESI): RT = 0.769 min, mass calc. for: C₁₅H₁₁F₃N₄O 320.09, m/z found 320.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.08 (t, $J = 7.53$ Hz, 1H), 7.35-7.41 (m, 4H), 7.41-7.46 (m, 1H), 7.54 (d, $J = 8.03$ Hz, 1H), 7.64 (d, $J = 8.53$ Hz, 2H), 7.70 (d, $J = 8.03$ Hz, 1H), 9.34 (s, 1H).

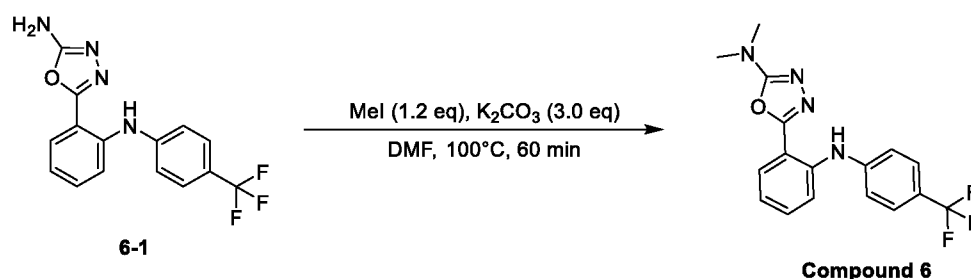
Example 5: (5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol (Compound 5)



[00232] To a solution of **5-1** (64 mg, 0.17 mmol, 1 *eq*) in THF (4 mL) was added LiBH₄ (73.9 mg, 3.4 mmol, 20 *eq*) at 0 °C. Then the mixture was stirred at 25 °C for 16 hr. TLC indicated that **5-1**

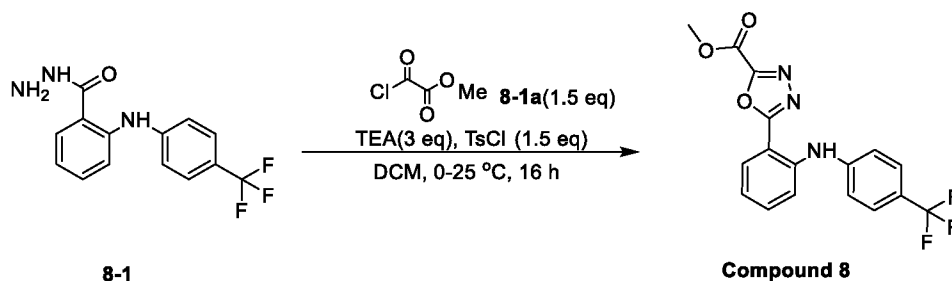
was consumed completely and four new spots formed. The reaction mixture was quenched by addition water 5 mL at 25 °C and the aqueous phase was extracted with ethyl acetate 40 mL (10 mL * 4). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 64 mg crude product. The crude product was purified by prep-TLC to give **Compound 5** (8 mg, 23.9 umol, 14.1% yield). LCMS (ESI): RT = 0.773 min, mass calcd. for C₁₆H₁₂N₃F₃O₂, 335.09 m/z found 335.9[M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 7.92 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.36 - 7.44 (m, 3H), 6.98 (t, *J* = 7.2 Hz, 1H), 4.99 (s, 2H), 2.51 (brs, 1H).

Example 6: N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine (Compound 6)



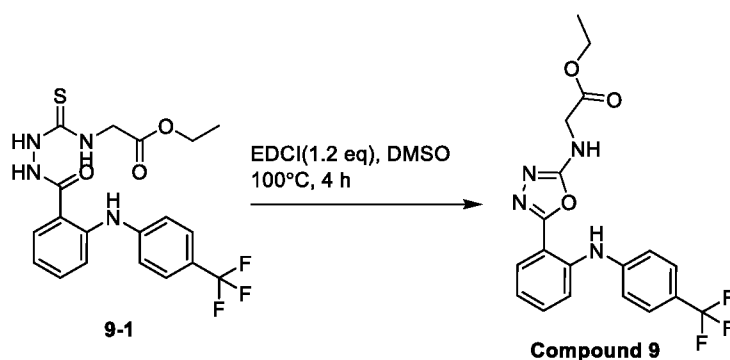
[00233] To a solution of **6-1** (40 mg, 0.1 mmol, 1.0 *eq*) in DMF (2 mL) were added K₂CO₃ (51.8 mg, 0.4 mmol, 3.0 *eq*) and MeI (35.5 mg, 0.3 mmol, 0.01 mL, 2.0 *eq*). The mixture was stirred under microwave tube at 100 °C for 60 min. LCMS showed **6-1** was consumed completely and two main peaks with desired mass was detected. TLC (Petroleum ether:Ethyl acetate = 1: 1, UV) indicated **6-1** was consumed, and two major new spots were detected. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 6** (3.5 mg, 0.01 mmol, 7.9% yield). LCMS (ESI): RT = 0.844 min, mass calc. for: C₁₇H₁₅F₃N₄O 348.12, m/z found 348.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.08-3.15 (m, 1H), 3.11 (s, 5H), 6.87 (t, *J* = 7.28 Hz, 1H), 7.22-7.30 (m, 3H), 7.43 (d, *J* = 8.28 Hz, 1H), 7.48 (d, *J* = 8.53 Hz, 2H), 7.58-7.75 (m, 1H), 9.44 (s, 1H).

Example 7: methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (Compound 8)



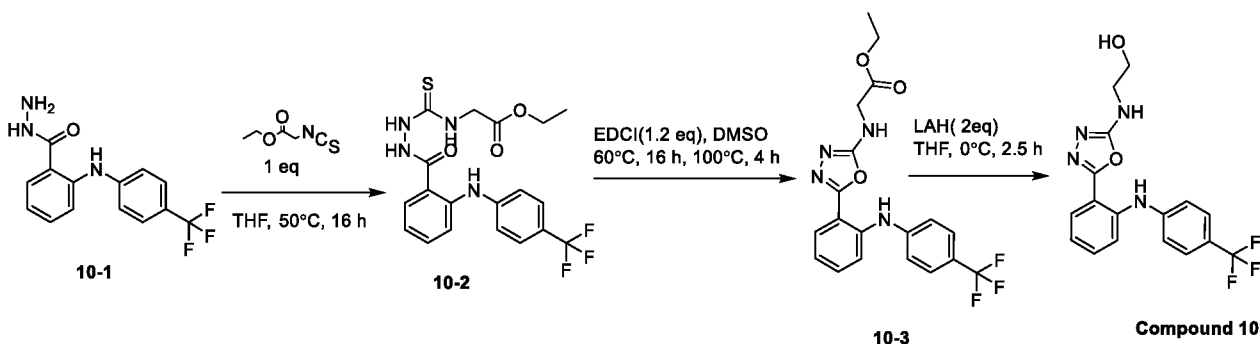
[00234] To a solution of **8-1a** (207.4 mg, 1.7 mmol, 0.2 mL, 1.0 eq) and TEA (514.1 mg, 5.1 mmol, 0.7 mL, 3.0 eq) in DCM (6.0 mL) was added **8-1** (0.5 g, 1.7 mmol, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 16 h. Then TsCl (322.8 mg, 1.7 mmol, 1.0 eq) was added and the mixture was stirred at 25 °C for 5 h. Several new peaks were shown and 47% of desired compound was detected on LC-MS. The reaction mixture was quenched by addition of saturated NaHCO₃ (30 mL), and then diluted with EtOAc (100 mL). The organic layers were washed with brine (50 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 8** (0.4 g, 1.1 mmol, 65.0% yield). 20 mg crude product was purified by prep-HPLC to give **Compound 8** (2.40 mg). LCMS (ESI): RT = 1.018 min, mass calc. for C₁₇H₁₂F₃N₃O₃ 363.08, m/z found 364.2 [M+H]⁺; ¹H NMR (400MHz, DMSO-*d*₆) δ 9.12 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 3.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.21-7.12 (m, 1H), 3.99 (s, 3H).

Example 8: ethyl (5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate (Compound 9)



[00235] A mixture of **9-1** (1.2 g, 2.72 mmol, 1 eq), EDCI (626.7 mg, 3.27 mmol, 1.2 eq) in DMSO (15 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 4 hr under N₂ atmosphere. LCMS showed the reaction was complete and 52% of desired product was formed. The mixture was combined with the another batch and diluted with EA (250 mL) and washed with brine (30 mL*5), dried by anhydrous Na₂SO₄, filtered and concentrated to give crude **Compound 9** (0.9 g, 2.21 mmol, 81.1% yield), which was used directly for next step. 50 mg of crude **Compound 9** was purified by prep-HPLC to give the title compound (21.07 mg, 51.8 umol, 1.9% yield). LCMS (ESI): RT = 0.821 min, mass calc. for C₁₉H₁₇F₃N₄O₃ 406.13, m/z found 406.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.27 (s, 1H), 8.42 (t, *J* = 6.4 Hz, 1H), 7.75 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 4.19 - 4.04 (m, 4H), 1.21 (t, *J* = 7.2 Hz, 3H).

Example 9: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol (Compound 10)



Step 1: 2-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbothioamido)acetate

[00236] To a solution of **10-1** (813.5 mg, 2.76 mmol, 1 eq) in THF (3.5 mL) was added ethyl 2-isothiocyanatoacetate (400 mg, 2.76 mmol, 0.4 mL, 1 eq). The mixture was stirred at 50 °C for 16 hr. LCMS showed **10-1** was consumed and 65% of desired mass was detected. The residue was concentrated under reduced pressure to give **10-2** (1.4 g, crude), which was used directly. LCMS (ESI): RT = 0.769 min, mass calc. for $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_3\text{S}$ 440.11, m/z found 441.0 $[\text{M}+1]^+$.

Step 2: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetate

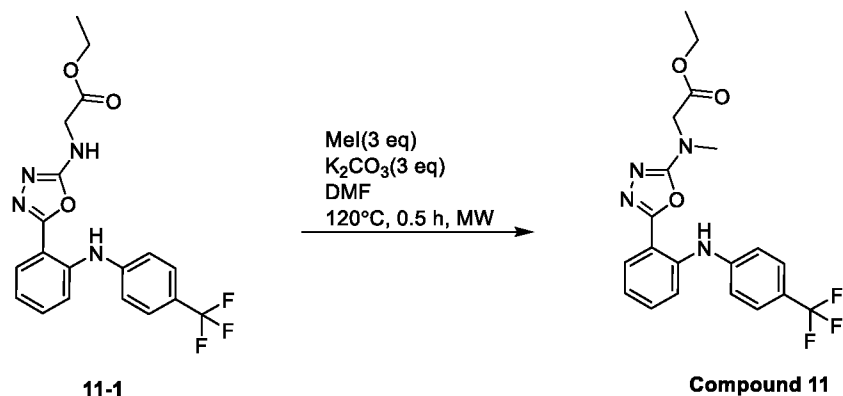
[00237] A mixture of **10-2** (1.2 g, 2.72 mmol, 1 eq), EDCI (626.7 mg, 3.27 mmol, 1.2 eq) in DMSO (15 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 4 hr under N_2 atmosphere. LCMS showed the reaction was complete and 52% of desired product was formed. The mixture was combined with another batch and diluted with EA (250 mL) and washed with brine (30 mL*5), dried by anhydrous Na_2SO_4 , filtered and concentrated to give crude **10-3** (0.9 g, 2.21 mmol, 81.1% yield), which was used directly for next step. 50 mg of crude **10-3** was purified by prep-HPLC to give **10-3** (21.07 mg, 51.85 μmol , 1.90% yield). LCMS (ESI): RT = 0.821 min, mass calc. for $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_4\text{O}_3$ 406.13, m/z found 406.9 $[\text{M}+1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.27 (s, 1H), 8.42 (t, J = 6.4 Hz, 1H), 7.75 (dd, J = 1.4, 7.9 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.10 (t, J = 7.2 Hz, 1H), 4.19 - 4.04 (m, 4H), 1.21 (t, J = 7.2 Hz, 3H).

Step 3: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethanol

[00238] A solution of **10-3** (0.04 g, 98 μmol , 1 eq) in THF (3 mL) was cooled to 0 °C. Then LiAlH_4 (7.5 mg, 0.20 mmol, 2 eq) was added, along with gas evolved. Then the mixture was stirred at 0 °C for 2.5 h. LCMS showed the reaction was complete and 93% of desired product was formed. The reaction was quenched with water (5 mL) and diluted with EA (50 mL) and separated. The separated organic layer was washed with brine (10 mL) and dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 10** (5.21 mg, 14 μmol , 14.4% yield). LCMS (ESI): RT = 0.747 min, mass calc. for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_2$ 364.11, m/z found 364.9 $[\text{M}+1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.32 (s, 1H),

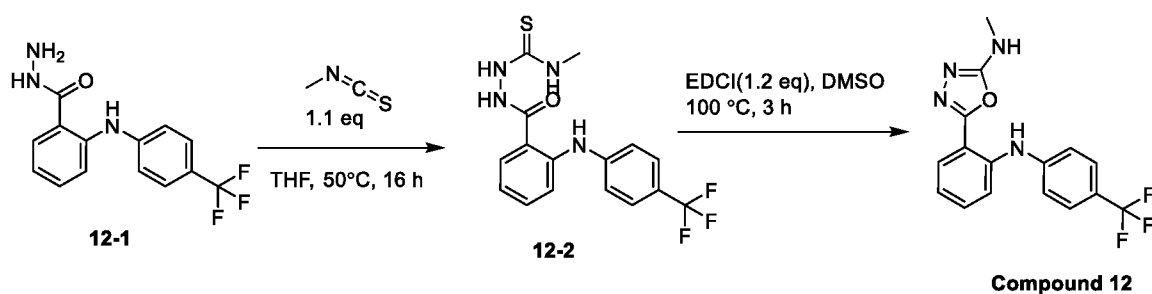
7.92 (br t, $J = 5.6$ Hz, 1H), 7.72 (d, $J = 7.5$ Hz, 1H), 7.64 (br d, $J = 8.5$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 1H), 7.46 - 7.32 (m, 3H), 7.08 (t, $J = 7.5$ Hz, 1H), 4.82 (t, $J = 5.4$ Hz, 1H), 3.62 - 3.51 (m, 2H), 3.32 (br d, $J = 5.8$ Hz, 2H).

Example 10: ethyl N-methyl-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate (Compound 11)



[00239] A mixture of **11-1** (200 mg, 0.49 mmol, 1 *eq*), MeI (209.58 mg, 1.48 mmol, 91.92 μL , 3 *eq*) and K_2CO_3 (204.07 mg, 1.48 mmol, 3 *eq*) in DMF (15 mL) was heated at 120 $^\circ\text{C}$ for 0.5 h under microwave. TLC (Petroleum ether:Ethyl acetate= 3:1, UV) indicated that **11-1** remained and one main spot was detected. LCMS showed **11-1** was consumed and desired mass (420.9) was detected. The mixture was combined with another batch, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2) to give **Compound 11** (66.17 mg, 0.15 mmol, 31.5% yield). LCMS (ESI): RT = 0.848 min, mass calc. for $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_3$ 420.14 m/z found 421.0 $[\text{M}+1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.18 (s, 1H), 7.86 (d, $J = 6.8$ Hz, 1H), 7.63 (d, $J = 8.5$ Hz, 2H), 7.56 - 7.50 (m, 1H), 7.48 - 7.41 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 2H), 7.11 (t, $J = 7.5$ Hz, 1H), 4.32 (s, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.15 (s, 3H), 1.20 (t, $J = 7.0$ Hz, 3H).

Example 11: N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine (Compound 12)



Step 1: N-methyl-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbothioamide

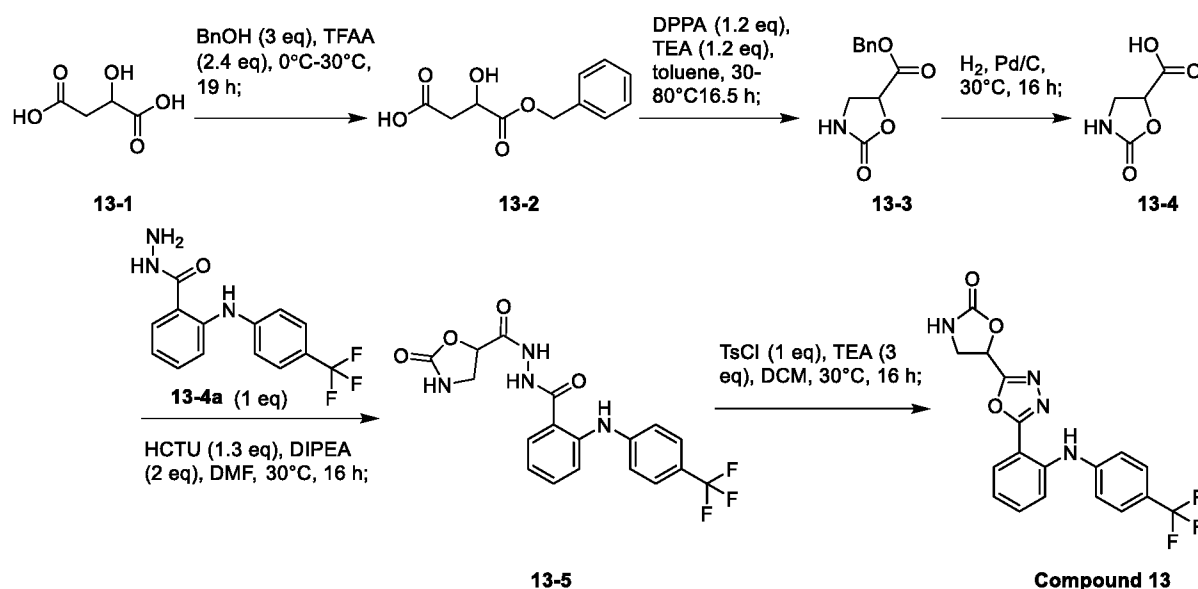
[00240] A tube containing **12-1** (0.2 g, 0.68 mmol, 1 *eq*) and methylimino(thioxo)methane (54.5 mg, 0.75 mmol, 51 μL , 1.1 *eq*) in THF (2.5 mL) was heated at 50 $^\circ\text{C}$ for 16 hr. LCMS showed the reaction was complete and 82% of desired product was formed. The mixture was concentrated to

give crude **12-2** (0.2 g, 0.54 mmol, 80.2% yield). LCMS (ESI): RT = 0.742 min, mass calc. for $C_{16}H_{15}F_3N_4OS$ 368.09, m/z found 368.9 $[M+1]^+$.

Step 2: N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine

[00241] A tube containing **12-2** (0.15 g, 0.41 mmol, 1 *eq*) and EDCI (93.67 mg, 0.49 mmol, 1.2 *eq*) in DMSO (1.5 mL) was heated at 100 °C for 3 hr. LCMS showed the reaction was complete and 64% of desired product was formed. The mixture was combined with another batch and filtered. The filtrate was purified by prep-HPLC to give **Compound 12** (6.54 mg, 19 μ mol, 4.8% yield). LCMS (ESI): RT = 1.366 min, mass calc. for $C_{16}H_{13}F_3N_4O$ 334.10, m/z found 334.9 $[M+1]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.31 (s, 1H), 7.79 - 7.70 (m, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.56 - 7.51 (m, 1H), 7.46 - 7.40 (m, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.08 (t, J = 7.3 Hz, 1H), 2.87 (d, J = 5.0 Hz, 3H).

Example 12: 5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 13)



Step 1: 4-(benzyloxy)-3-hydroxy-4-oxobutanoic acid

[00242] To a solution of TFAA (18.80 g, 89.49 mmol, 12.5 mL, 2.4 *eq*) at 0 °C was added **13-1** (5.0 g, 37.29 mmol, 1 *eq*). The mixture was stirred at 30 °C until the mixture was a clear solution (about 2 h). And then the mixture was concentrated to remove TFAA and the residue was dissolved in phenylmethanol (12.90 g, 119.33 mmol, 12.4 mL, 3.2 *eq*). The resulting mixture was stirred at 30 °C for 16 h. TLC (DCM:MeOH = 10:1, I₂) showed starting material was consumed completely and one new spot was formed. The mixture was diluted with EA (20 mL) and extracted with saturated Na₂CO₃ solution (100 mL). The aqueous layer was separated, then acidified with conc. HCl to pH = 1-2 and then extracted with EA (100 mL *3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced

pressure to give **13-2** (5.0 g, 22.30 mmol, 59.80% yield). ^1H NMR (400MHz, CDCl_3) δ 7.44 - 7.29 (m, 5H), 5.23 (s, 2H), 4.58 - 4.50 (m, 1H), 2.99 - 2.79 (m, 2H).

Step 2: benzyl 2-oxooxazolidine-5-carboxylate

[00243] To a solution of **13-2** (5.0 g, 22.30 mmol, 1 *eq*) and TEA (2.71 g, 26.76 mmol, 3.7 mL, 1.2 *eq*) in toluene (100 mL) at 30 °C was added DPPA (7.36 g, 26.76 mmol, 5.8 mL, 1.2 *eq*) dropwise. After stirred at 30 °C for 30 min, the mixture was stirred at 80 °C for 16 h. TLC (PE:EA = 1:1, I_2 , plate 1) showed most of starting material still remained but no new spot was formed. TLC (PE:EA = 1:1, KMnO_4 , plate 2) showed most of starting material still remained and two new spots were formed. The mixture was concentrated to remove solvent. And the residue was diluted with saturated Na_2CO_3 solution (100 mL), and then extracted with EA (100 mL *3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to give **13-3** (890 mg, 4.02 mmol, 18.04% yield), which was confirmed by ^1H NMR. ^1H NMR (400MHz, CDCl_3) δ 7.39 (s, 5H), 5.28 (s, 2H), 5.07 (dd, J = 5.6, 9.4 Hz, 1H), 3.90 (t, J = 9.4 Hz, 1H), 3.70 (dd, J = 5.5, 9.0 Hz, 1H).

Step 3: 2-oxooxazolidine-5-carboxylic acid

[00244] To a solution of benzyl 2-oxooxazolidine-5-carboxylate **13-3** (0.89 g, 4.02 mmol, 1 *eq*) in EtOH (10 mL) was added Pd/C (0.3 g, 0.282 μmol , 10% purity, $7.01\text{e-}2$ *eq*) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 30 °C for 16 h. TLC (Petroleum ether/Ethyl acetate = 1:1 stained by iodine) showed the starting material was consumed completely and new spot was formed. The reaction mixture was filtered and the filtrate was concentrated to give **13-4** (0.47 g, 3.59 mmol, 89.12% yield), which was used directly without purification. ^1H NMR (400MHz, CD_3OD) δ 5.13 - 5.08 (m, 1H), 3.91 (t, J = 9.4 Hz, 1H), 3.68 - 3.55 (m, 1H).

Step 4: 2-oxo-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazolidine-5-carbohydrazide

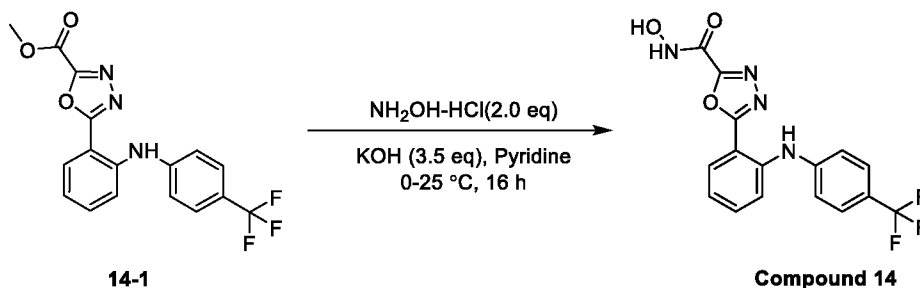
[00245] To a solution of **13-4** (20 mg, 0.153 mmol, 1.2 *eq*) in DMF (1 mL) at 30 °C was added HCTU (68.4 mg, 0.165 mmol, 1.3 *eq*), and the mixture was stirred at 30 °C for 20 min. And then **13-4a** (37.5 mg, 0.127 mmol, 1 *eq*) and DIPEA (32.9 mg, 0.254 mmol, 44.3 μL , 2 *eq*) was successively added at 30 °C into the above mixture. The resulting mixture was stirred at 30 °C for 16 h. TLC (DCM:MeOH = 10:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed starting material and desired product was included in one peak. The mixture was combined with another batch. The combined sample was purified by prep-HPLC to give **13-5** (18.46 mg, 45.2 μmol , 35.56% yield). LCMS (ESI): RT = 0.687 min, mass calc. for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_4$ 408.10, m/z found 431.0 $[\text{M}+23]^+$. ^1H NMR (400MHz, $\text{DMSO-}d_6$) δ 10.56 (s, 1H),

10.45 (s, 1H), 9.36 (s, 1H), 7.84 (s, 1H), 7.70 (d, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.48 (s, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 7.04 (s, 1H), 5.11 (d, $J = 3.5$ Hz, 1H), 3.79 (t, $J = 9.3$ Hz, 1H), 3.53 - 3.45 (m, 1H).

Step 5: 5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one

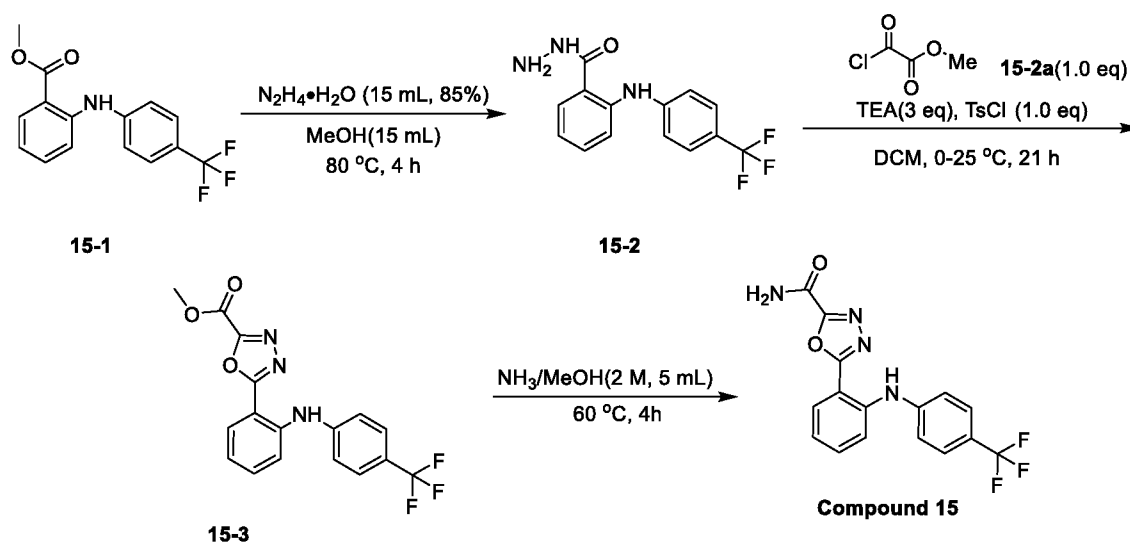
[00246] To a solution of **13-5** (80 mg, 0.20 mmol, 1 *eq*) and TEA (59.5 mg, 0.59 mmol, 81.8 μ L, 3 *eq*) in DCM (2 mL) at 30 °C was added TsCl (37.4 mg, 0.20 mmol, 1 *eq*), and the mixture was stirred at 30 °C for 16 h. TLC (DCM:MeOH = 10:1, UV) showed starting material was consumed completely and one new spot was formed. LCMS showed starting material was consumed completely and 54% of desired product was formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 13** (13.71 mg, 34.07 μ mol, 17.39% yield). LCMS (ESI): RT = 0.768 min, mass calc. for $C_{18}H_{13}F_3N_4O_3$ 390.09, m/z found 390.9[M+1]⁺. ¹H NMR (400MHz, DMSO- d_6) δ 9.13 (s, 1H), 8.09 (s, 1H), 7.93 (d, $J = 8.0$ Hz, 1H), 7.63 (d, $J = 8.5$ Hz, 2H), 7.59 - 7.52 (m, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.22 - 7.11 (m, 1H), 6.01 (dd, $J = 5.5, 9.0$ Hz, 1H), 3.99 - 3.92 (m, 1H), 3.90 - 3.84 (m, 1H).

Example 13: N-hydroxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 14)



[00247] To a solution of $\text{NH}_2\text{OH}\cdot\text{HCl}$ (58.3 mg, 0.6 mmol, 2.0 *eq*, HCl) in pyridine (2 mL) were added KOH (54.1 mg, 1.0 mmol, 3.5 *eq*) and **14-1** (0.1 g, 0.28 mmol, 1 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 h. LC-MS showed 16% of **14-1** remained and 39% of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 14** (13.06 mg, 36 μ mol, 13.0% yield). LCMS (ESI): RT = 0.743 min, mass calc. for $C_{16}H_{11}F_3N_4O_3$ 364.08, m/z found 364.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl_3) δ 12.20 (s, 1H), 9.79 (s, 1H), 9.12 (s, 1H), 8.01 (d, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.59-7.54 (m, 2H), 7.37 (d, $J = 8.5$ Hz, 2H), 7.18-7.14 (m, $J = 3.0, 5.1, 7.9$ Hz, 1H).

Example 14: 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 15)



Step 1: 2-[4-(trifluoromethyl)anilino]benzohydrazide

[00248] To a solution of **15-1** (2.0 g, 6.7 mmol, 1.0 eq) in MeOH (15.0 mL) was added $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (15.4 g, 262.3 mmol, 15 mL, 38.7 eq). The mixture was stirred at 80 °C for 4 h. TLC (PE:EA = 2:1 UV) showed that **15-1** was consumed completely and one new spot formed. The solution was concentrated (lots of solid formed) and then filtered. The filter cake was washed with water (20 mL), triturated with PE (50 mL), filtered and dried under vacuum to give **15-2** (1.9 g, 6.44 mmol, 95.0% yield).

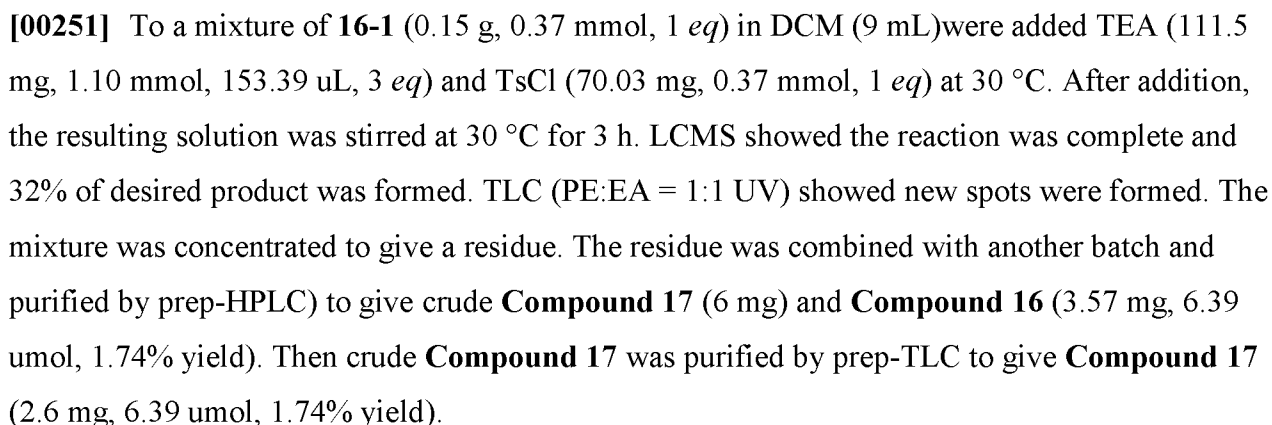
Step 2: methyl 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carboxylate

[00249] To a solution of **15-2a** (207.4 mg, 1.7 mmol, 0.2 mL, 1.0 eq) and TEA (514.1 mg, 5.1 mmol, 0.7 mL, 3.0 eq) in DCM (6.0 mL) was added **15-2** (0.5 g, 1.7 mmol, 1.0 eq) at 0 °C. The mixture was stirred at 25 °C for 16 h. Then TsCl (322.8 mg, 1.7 mmol, 1.0 eq) was added and the mixture was stirred at 25 °C for 5 h. Several new peaks were shown and 47% of desired compound was detected on LC-MS. The reaction mixture was quenched by addition of saturated NaHCO_3 (30 mL), and then diluted with EtOAc (100 mL). The organic layer was separated and washed with brine (50 mL * 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give **15-3** (0.4 g, 1.1 mmol, 65.0% yield). 20 mg crude product was purified by prep-HPLC to give to give desired compound (2.40 mg). LCMS (ESI): RT = 1.018 min, mass calc. for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_3\text{O}_3$ 363.08, m/z found 364.2 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.12 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 3.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.21-7.12 (m, 1H), 3.99 (s, 3H).

Step 3: methyl 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carboxylate

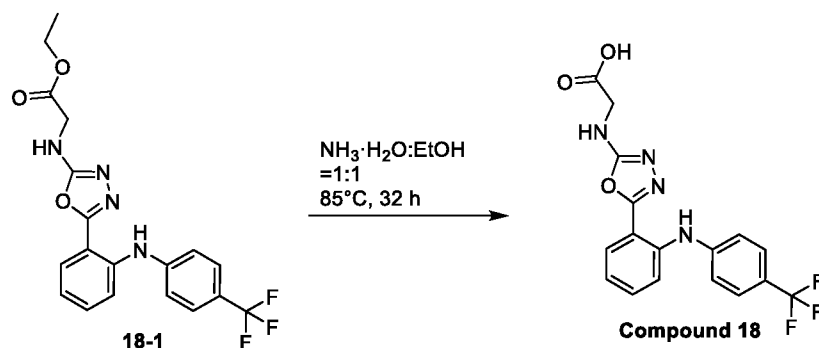
[00250] To a solution of NH_3 (46.9 mg, 2.75 mmol, 10 eq) in MeOH (5 mL) was added **15-3** (100.0 mg, 0.3 mmol, 1.0 eq) at 0 °C in seal pot. The mixture was stirred at 60 °C for 4 hr. Several new peaks were shown and 63% of desired compound was detected on LC-MS. The reaction

Example 15: 3-tosyl-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 16) and 4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 17)



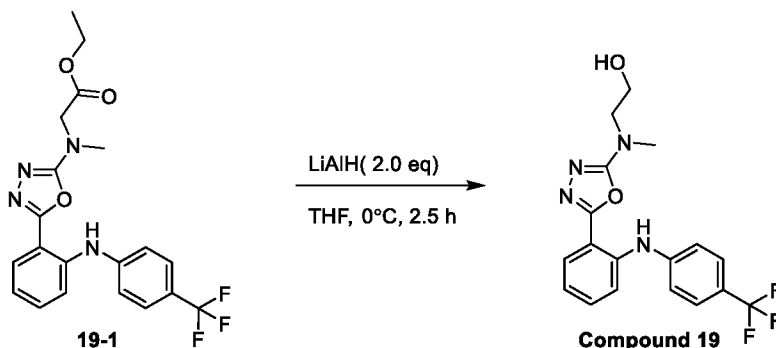
[00253] Compound 17: LCMS (ESI): RT = 0.760 min, mass calc. for C₁₈H₁₃F₃N₄O₃ 390.09, m/z found 391.3 [M+1]⁺. ¹H NMR (400MHz, DMSO-d₆) δ 9.16 (s, 1H), 8.57 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.70 - 7.53 (m, 4H), 7.36 (br d, *J* = 8.3 Hz, 2H), 7.17 (br t, *J* = 6.4 Hz, 1H), 5.37 (dd, *J* = 4.5, 8.5 Hz, 1H), 4.73 - 4.66 (m, 1H), 4.59 (dd, *J* = 4.4, 8.9 Hz, 1H).

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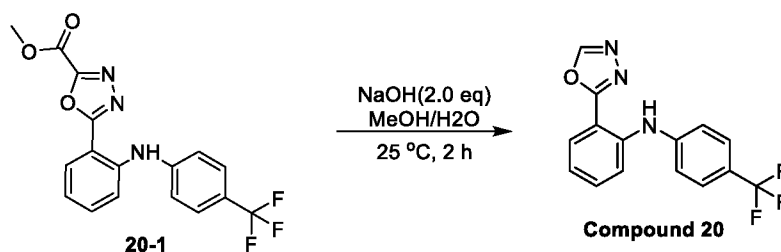


[00254] A solution of **18-1** (0.04 g, 98.44 μmol , 1 *eq*) in $\text{NH}_3\cdot\text{H}_2\text{O}$ (3.45 g, 24.61 mmol, 3.79 mL, 250 *eq*) was heated at 85 °C for 4 h. TLC (PE:EA = 1:1 UV) showed most of starting material remained. Then EtOH (4 mL) was added the mixture was heated at 85 °C for another 4 h. LCMS showed the reaction was complete and 52% of desired product was formed. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 18** (6.84 mg, 17.72 μmol , 18% yield). LCMS (ESI): RT = 0.747 min, mass calc. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_3$ 379.0, m/z found 378.09 $[\text{M}+23]^+$. ^1H NMR (400MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.09 (br s, 1H), 7.74 (br d, $J=7.8$ Hz, 1H), 7.64 (br d, $J=8.5$ Hz, 2H), 7.54 (br d, $J=8.3$ Hz, 1H), 7.47 - 7.35 (m, 3H), 7.08 (t, $J=7.5$ Hz, 1H), 3.88 (br s, 2H).

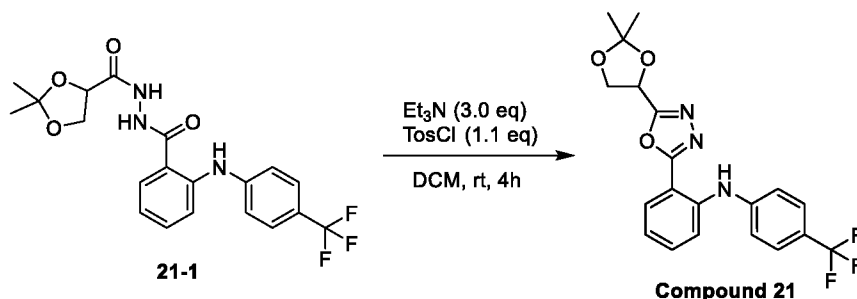
Example 17: 2-(methyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol (Compound 19)



[00255] A solution of **19-1** (50 mg, 0.1 mmol, 1.0 *eq*) in THF (4 mL) was cooled in ice-water bath. Then LiAlH_4 (9.0 mg, 0.2 mmol, 2.0 *eq*) was added, along with gas evolved. Then the mixture was stirred in ice-water bath for 2.5 hr. LCMS showed **19-1** was consumed and 67% of desired product was detected. Then the mixture was quenched with water (10 mL). The combined mixture was extracted with EA (20 mL*3), dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 19** (40.5 mg, 0.1 mmol, 89.1% yield). LCMS (ESI): RT = 0.766 min, mass calc. for: $\text{C}_{18}\text{H}_{17}\text{F}_3\text{N}_4\text{O}_2$ 378.13, m/z found 378.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 3.27 (s, 3H), 3.69 (t, $J=5.27$ Hz, 2H), 3.96 (t, $J=5.14$ Hz, 2H), 6.94 (t, $J=7.65$ Hz, 1H), 7.30-7.38 (m, 3H), 7.50 (d, $J=8.53$ Hz, 1H), 7.55 (d, $J=8.53$ Hz, 2H), 7.73 (d, $J=8.03$ Hz, 1H), 9.44 (s, 1H).

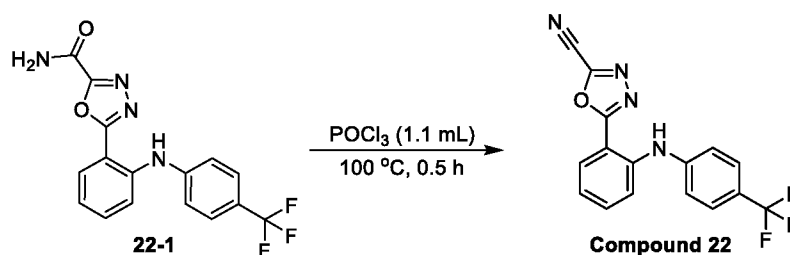
Example 18: 2-(1,3,4-oxadiazol-2-yl)-N-[4-(trifluoromethyl)phenyl]aniline (Compound 20)

[00256] To a solution of **20-1** (0.4 g, 1.1 mmol, 1.0 eq) in MeOH (0.8 mL) was added a solution of NaOH (88.1 mg, 2.2 mmol, 2.0 eq) in H₂O (0.5 mL). The mixture was stirred at 25 °C for 2 h. LC-MS showed **20-1** was consumed completely and 59% of desired mass was detected. The pH of the mixture was adjusted with HCl (1M) to 4-5, and then the mixture was filtered to give a residue. The residue was purified by prep-HPLC to give **Compound 20** (7.15 mg, 23.42 μmol, 2.13% yield). LCMS (ESI): RT = 0.824 min, mass calc. for C₁₅H₁₀F₃N₃O 305.08, m/z found 305.9 [M+H]⁺; ¹H NMR (400MHz, CDCl₃) δ 9.39 (s, 1H), 9.23 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.59-7.51 (m, 1H), 7.59-7.51 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.18-7.12 (m, 1H).

Example 19: 2-[5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 21)

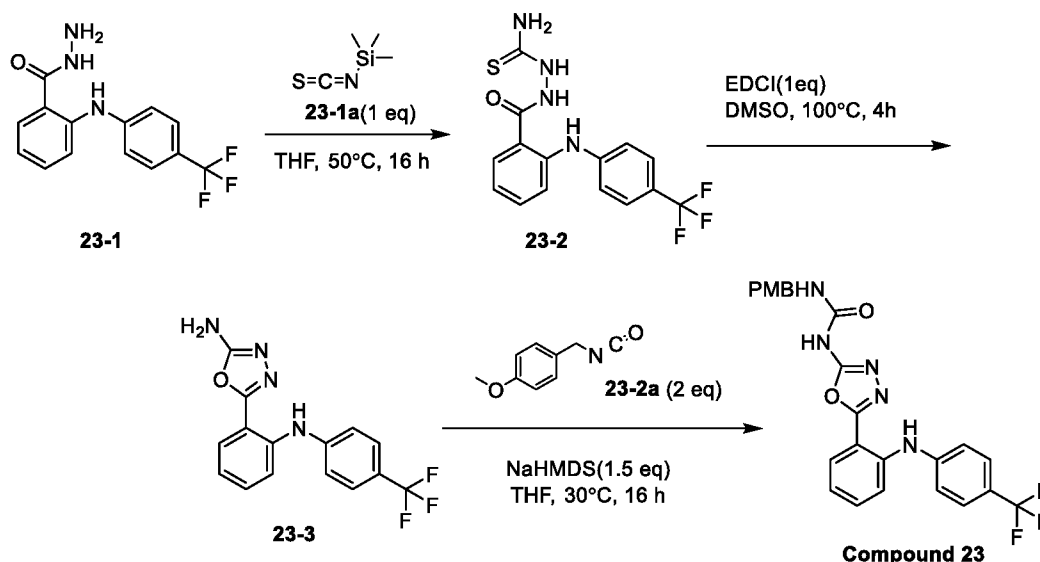
[00257] To a solution of **21-1** (62 mg, 0.15 mmol, 1 eq) and TEA (44.4 mg, 0.44 mmol, 61.15 μL, 3 eq) in DCM (2 mL) was added TsCl (29.3 mg, 0.16 mmol, 1.05 eq). The reaction was stirred at 25 °C for 3hr. LCMS showed that 78% of desired product was detected. HPLC showed that 89% of desired product was detected. The reaction was concentrated. The residue was purified by prep-HPLC to give **Compound 21** (18 mg, 44.40 μmol, 30.32% yield). LCMS (ESI): RT = 0.873 min, mass calcd. for C₂₀H₁₈F₃N₃O₃, 405.15 m/z found 406.0[M+H]⁺. ¹H NMR (400MHz, DMSO) δ 9.16 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.71 - 7.49 (m, 4H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.25 - 7.17 (m, 1H), 5.45 (t, *J* = 5.2 Hz, 1H), 4.50 - 4.25 (m, 1H), 1.43 (d, *J* = 4.0 Hz, 3H).

Example 20: 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carbonitrile (Compound 22)



[00258] A solution of **22-1** (50 mg, 0.1 mmol, 1.0 eq) in POCl₃ (1.76 g, 11.5 mmol, 1.1 mL, 80.0 eq) was stirred at 100 °C for 0.5 h. LC-MS showed **22-1** was consumed completely and 70% of desired compound was detected. The reaction mixture was quenched by addition of H₂O (10 mL) at 0 °C. The mixture was extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 22** (7.61 mg, 21.66 μmol, 15.1% yield). LCMS (ESI): RT = 1.582 min, mass calc. for C₁₆H₉F₃N₄O 330.07, m/z found 331.0 [M+H]⁺; ¹H NMR (400MHz, CDCl₃) δ 9.24 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.51-7.47 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.03-6.99 (m, 1H).

Example 21: 1-(4-methoxybenzyl)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)urea (Compound 23)



Step 1: 2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbothioamide

[00259] To a solution of **23-1** (1.5 g, 5.08 mmol, 1 eq) in THF (25 mL) was added **23-1a** (666.9 mg, 5.08 mmol, 63 μL, 1 eq). The mixture was stirred at 50 °C for 16 hr. LCMS showed reactant **23-1** was consumed completely and 69% of desired mass was detected. The solution was concentrated to give compound **23-2** (1.9 g, crude), which was used directly. LCMS (ESI): RT = 0.721 min, mass calc. for C₁₅H₁₃F₃N₄OS 354.08, m/z found 354.9 [M+1]⁺.

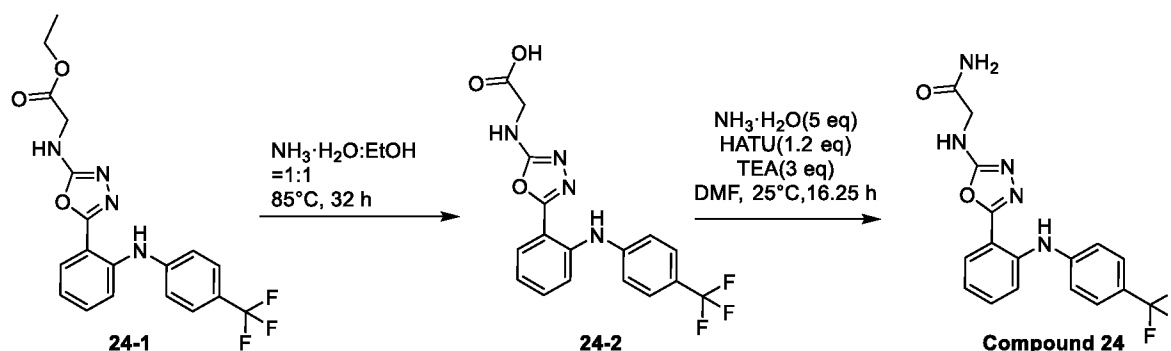
Step 2: 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine

[00260] To a solution of compound **23-2** (1.5 g, 4.23 mmol, 1 *eq*) in DMSO (10 mL) was added EDCI (811.5 mg, 4.23 mmol, 1 *eq*). The mixture was stirred at 100 °C for 4 hr. LCMS showed the reaction was complete and 52% of desired product was formed. TLC (PE:EA = 1:2 UV) showed the reaction was complete. The mixture was diluted with EA (250 mL) and washed with brine (30 mL*3), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂) to give **23-3** (0.7 g, 2.19 mmol, 51.6% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.28 (s, 1H), 7.76 - 7.67 (m, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.55 - 7.47 (m, 1H), 7.44 - 7.28 (m, 5H), 7.06 (t, *J* = 7.4 Hz, 1H).

Step 3: 1-(4-methoxybenzyl)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)urea

[00261] To a solution of **23-3** (0.1 g, 0.31 mmol, 1 *eq*) in THF (3 mL) were added NaHMDS (1 M, 0.5 mL, 1.5 *eq*) and **23-2a** (101.9 mg, 0.62 mmol, 89 uL, 2 *eq*) at 30 °C. The mixture was stirred at 30 °C for 16 h. LCMS showed no **23-3** was remained and 58% of desired compound was detected. The residue was purified by prep-HPLC to give **Compound 23** (105.84 mg, 0.22 mmol, 70.1% yield). LCMS (ESI): RT = 0.862 min, mass calc. for C₂₄H₂₀F₃N₅O₃ 483.15, *m/z* found 506.1 [M+23]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.10 (s, 1H), 9.11 (s, 1H), 7.96 (br t, *J* = 5.5 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.54 (m, 1H), 7.53 - 7.46 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.35 (d, *J* = 5.8 Hz, 2H), 3.74 (s, 3H), 3.31 (s, 1H).

Example 22: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide (Compound 24)



Step 1: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetic acid

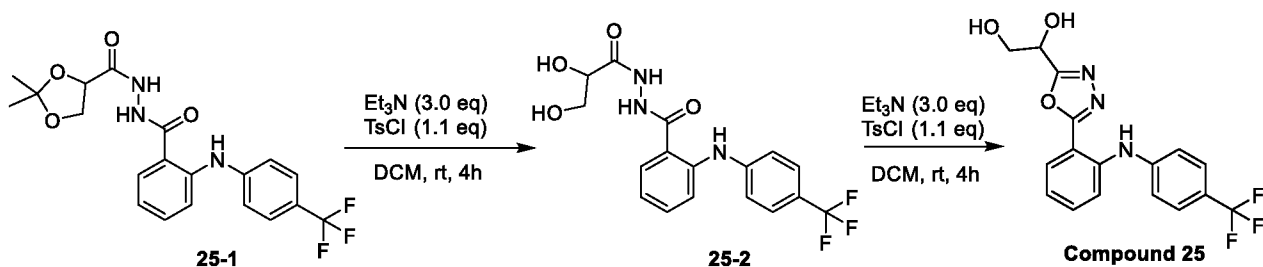
[00262] A solution of **24-1** (300 mg, 738.27 umol, 1 *eq*) in NH₃·H₂O (2.59 g, 73.83 mmol, 2.84 mL, 100 *eq*) was added EtOH (3 mL). The mixture was heated at 85 °C for 16 hr. TLC (PE:EA = 1:1 UV) showed most of material was remained. Then EtOH (3 mL) was added and the mixture was heated at 85 °C for another 16 h. LCMS showed **24-1** was consumed, 22% of **Compound 24** and 55% of **24-2** were formed. The reaction mixture was concentrated under reduced pressure to

give a mixture of **Compound 24** and **24-2** (300 mg), which was used into the next step without further purification. ^1H NMR (400MHz, DMSO- d_6) δ 9.37 (s, 1H), 9.27 (s, 1H), 7.76 - 7.69 (m, 3H), 7.64 (br d, J = 8.3 Hz, 4H), 7.54 (br dd, J = 3.8, 8.3 Hz, 3H), 7.48 - 7.43 (m, 2H), 7.42 - 7.35 (m, 5H), 7.08 (q, J = 7.9 Hz, 2H), 4.08 (s, 2H), 3.83 (s, 1H), 3.57 (s, 2H).

Step 2: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide

[00263] To a solution of **24-2** (0.3 g, 0.79 mmol, 1 *eq*) in DMF (10 mL) were added HATU (301.53 mg, 0.79 mmol, 1 *eq*) and TEA (240.73 mg, 2.38 mmol, 331.13 μL , 3 *eq*) at 25 °C. After stirring for 15 min, $\text{NH}_3 \cdot \text{H}_2\text{O}$ (555.8 mg, 3.97 mmol, 610.80 μL , 5 *eq*) was added and the resulting solution was stirred at 25 °C for 16 h. LCMS showed the reaction was complete and 78% of desired product was formed. TLC (PE:EA = 1:1 UV) showed the reaction was complete and new spot was formed. The reaction was diluted with EA (150 mL), washed with brine (20 mL*2) and saturated NaHCO_3 (20 mL*2) in turns, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2) and was lyophilized to give **Compound 24** (0.025 g, 63.14 μmol , 7.96% yield). LCMS (ESI): RT = 0.732 min, mass calc. for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_5\text{O}_2$ 377.11, m/z found 399.9 $[\text{M}+23]^+$. ^1H NMR (400MHz, DMSO- d_6) δ 9.32 (s, 1H), 8.15 (br s, 1H), 7.77 - 7.68 (m, 1H), 7.65 (br d, J = 8.3 Hz, 2H), 7.59 - 7.48 (m, 2H), 7.44 (br t, J = 7.2 Hz, 1H), 7.39 (br d, J = 8.3 Hz, 2H), 7.20 - 7.04 (m, 2H), 4.05 - 3.98 (m, 1H), 3.82 (br s, 2H), 1.19 - 1.14 (m, 1H).

Example 23: 1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethane-1,2-diol (Compound 25)



Step 1: N'-(2,3-dihydroxypropanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00264] To a solution of **25-1** (0.35 g, 0.83 mmol, 1 *eq*) and TEA (250.9 mg, 2.48 mmol, 0.34 mL, 3 *eq*) in DCM (10 mL) was added TsCl (165.4 mg, 0.86 mmol, 1.05 *eq*). The reaction was stirred at 25 °C for 16hr. LCMS showed that starting material was remained and 50% of desired product was detected. The reaction was concentrated. Compound **25-2** (300 mg, crude) was used for next step directly.

Step 2: 1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethane-1,2-diol

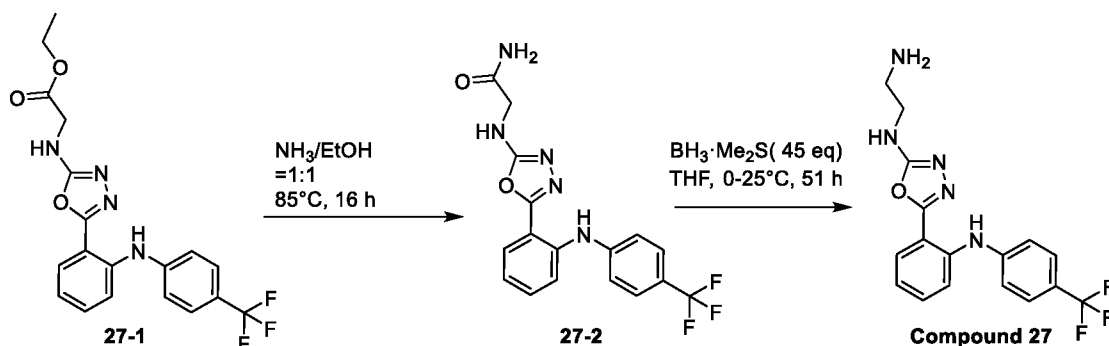
[00265] To a solution of compound **25-2** (250 mg, 0.65 mmol, 1 *eq*) and TEA (197.9 mg, 1.96 mmol, .27 mL, 3 *eq*) in DCM (10 mL) was added TsCl (136.7 mg, 0.72 mmol, 1.1 *eq*). The reaction was stirred at 25 °C for 16hr. LCMS showed that 38% of desired product was detected. HPLC showed that 30% of desired product was detected. The reaction was washed with water (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by prep-HPLC to give **Compound 25** (45 mg, 115.79 umol, 17.75% yield). LCMS and HNMR confirmed that desired product was obtained. LCMS (ESI): RT = 0.733 min, mass calcd. for C₁₇H₁₄F₃N₃O₃, 365.10 m/z found 365.9[M+H]⁺. ¹H NMR (400MHz, DMSO) δ 9.26 (s, 1H), 7.93 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.65 - 7.50 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 6.8 Hz, 1H), 6.19 (br, 1H), 5.05 (br, 1H), 4.95 - 4.80 (m, 1H), 3.85 - 3.70 (m, 2H).

Example 24: 2-oxo-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidine-3-carboxylate (Compound 26)



[00266] To a solution of **26-1** (0.25 g, 0.64 mmol, 1 *eq*), TEA (194.4 mg, 1.92 mmol, 0.3 mL, 3 *eq*) and DMAP (15.6 mg, 0.13 mmol, 0.2 *eq*) in DCM (5 mL) at 0 °C was added Boc₂O (139.8 mg, 0.64 mmol, 0.1 mL, 1 *eq*). Then the solution was stirred at 25 °C for 16 h. LCMS showed **26-1** was consumed completely and desired product was detected. TLC (Petroleum ether:Ethyl acetate = 2:1, UV) indicated **26-1** was consumed and two major new spots were detected. The reaction mixture was quenched with 10 mL of water and concentrated under reduced pressure to remove DCM. The resulting aqueous layer was extracted with ethyl acetate (20 mL*3). The combined organic layer was washed with brine (15 mL), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂) to give **Compound 26** (15.0 mg, 28.0 umol, 4.36% yield). LCMS (ESI): RT = 0.858 min, mass calc. for C₂₃H₂₁F₃N₄O₅ 490.15, m/z found 513.0 [M+23]⁺. ¹H NMR (400MHz, CDCl₃) δ 9.36 (s, 1H), 7.85 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.48 (m, 1H), 7.46 - 7.34 (m, 3H), 7.04 - 6.92 (m, 1H), 5.72 (dd, *J* = 4.1, 8.9 Hz, 1H), 4.73 (t, *J* = 9.2 Hz, 1H), 4.53 (dd, *J* = 4.0, 9.3 Hz, 1H), 1.52 - 1.45 (m, 9H).

Example 25: N1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethane-1,2-diamine (Compound 27)



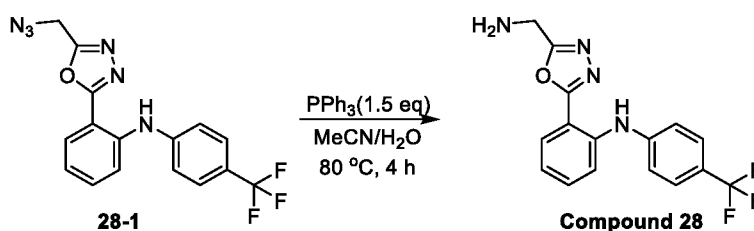
Step 1: 2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide

[00267] A solution of **27-1** (0.3 g, 0.74 mmol, 1 eq) in EtOH (15 mL) saturated with NH_3 (62.87 mg, 3.69 mmol) was stirred at 85°C for 16 h. LCMS showed 11% of **27-1** was remained and 77% of desired compound was detected. Then the solution was concentrated to give crude **27-2** (180 mg, 0.45 mmol, 61.58% yield), which was used directly without purification.

Step 2: N1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethane-1,2-diamine

[00268] To a solution of **27-2** (0.12 g, 0.32 mmol, 1 eq) in THF (5 mL) was added $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (10 M, 0.48 mL, 15 eq) at 0°C . The mixture was stirred at 25°C for 16 hr under N_2 atmosphere. LCMS showed 17% of **27-2** was remained and 57% of desired compound was detected. The mixture was quenched with 5 mL of methanol, stirred at 10 min at 25°C and concentrated to a residue. The residue was diluted with water (10 mL) and acidified to pH~2 with 1 M HCl and extracted with EA (15 mL*3). The combined organic layers dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue which was purified by prep-HPLC to give **Compound 27** (1.32 mg, 3.55 μmol , 1.12% yield). LCMS (ESI): RT = 0.639 min, mass calc. for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{N}_5\text{O}$ 363.13, m/z found 364.0 $[\text{M}+1]^+$. ^1H NMR (400MHz, METHANOL- d_4) δ 7.80 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.56 - 7.48 (m, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.05 - 6.99 (m, 1H), 3.82 (s, 4H).

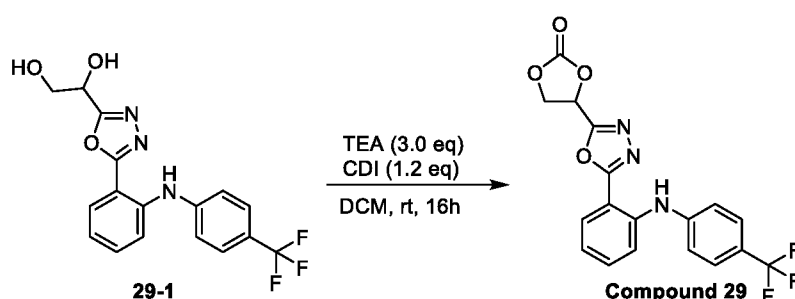
Example 26: 2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 28)



[00269] A solvent of **28-1** (50 mg, 0.1 mmol, 1.0 eq) and PPh_3 (54.6 mg, 0.2 mmol, 1.5 eq) in MeCN (1 mL) was stirred at 80°C for 1 h. After H_2O (0.2 mL) was added and the mixture was stirred at 80°C for 3 h. LC-MS showed reactant **28-1** was consumed completely and no desired

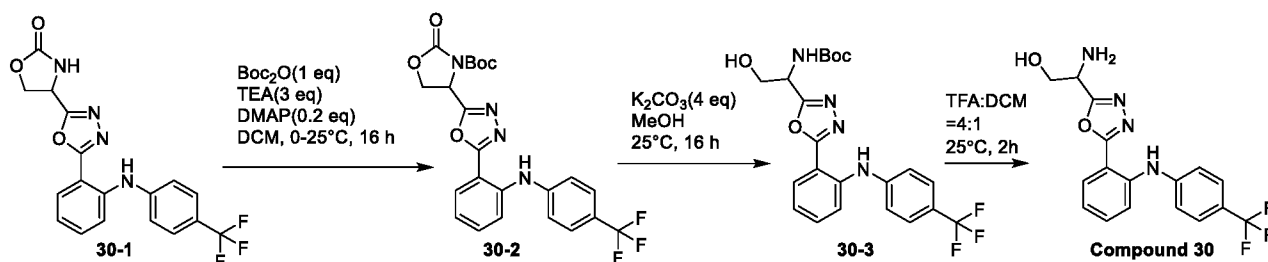
compound was detected. TLC (Petroleum ether:Ethyl acetate=0:1) indicated reactant **28-1** was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to give crude **Compound 28** (10 mg), which was purified by prep-HPLC to give **Compound 28** (2.13 mg, 6 μmol , 4.3% yield). LCMS (ESI): RT = 0.718 min, mass calcd. for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_4\text{O}$ 334.10 m/z found 335.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.50 (s, 1H), 7.90 (d, $J = 7.8$ Hz, 1H), 7.59 (d, $J = 8.3$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 1H), 7.44-7.33 (m, 3H), 6.98 (t, $J = 7.5$ Hz, 1H), 4.23-4.02 (m, 2H).

Example 27: 4-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-1,3-dioxolan-2-one (Compound 29)



[00270] To a solution of **29-1** (20 mg, 54.75 μmol , 1 eq) and Et_3N (16.6 mg, 0.16 mmol, 22.86 μL , 3 eq) in DCM (1 mL) was added triphosgene (24.3 mg, 82.12 μmol , 1.5 eq). The reaction was stirred at 25 °C for 16hr. LCMS showed that 85% of desired product was detected. The reaction was diluted with DCM (10 mL) and washed with water (2*5 mL). The organic was dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give **Compound 29** (15 mg, 33.35 μmol , 60.92% yield). LCMS (ESI): RT = 0.812 min, mass calcd. for $\text{C}_{18}\text{H}_{12}\text{F}_3\text{N}_3\text{O}_4$, 391.08 m/z found 392.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, CDCl_3) δ 9.32 (s, 1H), 7.92 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.50 - 7.40 (m, 1H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.00 (t, $J = 8.0$ Hz, 1H), 6.05 - 6.00 (m, 1H), 5.10 - 5.00 (m, 1H), 5.00 - 4.85 (m, 1H).

Example 28: 2-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol (Compound 30)



Step 1: tert-butyl 2-oxo-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidine-3-carboxylate

[00271] To a solution of **30-1** (0.25 g, 0.64 mmol, 1 *eq*), TEA (194.4 mg, 1.92 mmol, 0.3 mL, 3 *eq*) and DMAP (15.6 mg, 0.13 mmol, 0.2 *eq*) in DCM (5 mL) at 0 °C was added Boc₂O (139.8 mg, 0.64 mmol, 0.2 mL, 1 *eq*). Then the solution was stirred at 25 °C for 16 h. LCMS showed **30-1** was consumed completely and desired product was detected. TLC (Petroleum ether:Ethyl acetate = 2:1, UV) indicated **30-1** was consumed and two major new spots were detected. The reaction mixture was quenched with 10 mL of water and concentrated under reduced pressure to remove DCM. The resulting aqueous layer was extracted with ethyl acetate (20 mL*3). The combined organic layer was washed with brine (15 mL), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂) to give **30-2** (15.0 mg, 28 umol, 4.4% yield). LCMS (ESI): RT = 0.858 min, mass calc. for C₂₃H₂₁F₃N₄O₅ 490.15, m/z found 513.0 [M+23]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.36 (s, 1H), 7.85 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.48 (m, 1H), 7.46 - 7.34 (m, 3H), 7.04 - 6.92 (m, 1H), 5.72 (dd, *J* = 4.1, 8.9 Hz, 1H), 4.73 (t, *J* = 9.2 Hz, 1H), 4.53 (dd, *J* = 4.0, 9.3 Hz, 1H), 1.52 - 1.45 (m, 9H).

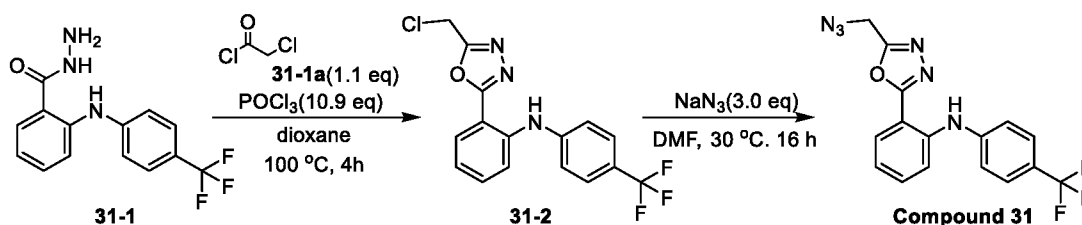
Step 2: tert-butyl (2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

[00272] A mixture of **30-2** (0.01 g, 20.4 umol, 1 *eq*) and K₂CO₃ (11.3 mg, 81.6 umol, 4 *eq*) in MeOH (1.5 mL) was stirred at 25 °C for 20 h. LCMS showed **30-2** was consumed and 58% of desired product was detected. The mixture was diluted with EA (50 mL), washed with water (10 mL*2), dried by anhydrous Na₂SO₄, filtered and concentrated to give compound **30-3** (0.01 g, crude), which was used directly.

Step 3: 2-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

[00273] To a solution of compound **30-3** (10.0 mg, 21.5 umol, 1 *eq*) in CH₂Cl₂ (1.6 mL) was added TFA (613.8 mg, 5.38 mmol, 0.4 mL, 250 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed compound **30-3** was consumed completely and 30% of desired product was formed. The mixture was concentrated at 25 °C to give a crude product and was diluted with water (10 mL), acidified to pH~2 with 1 M HCl and extracted with EA (5 mL*3). The combined organic layer was concentrated to crude product (15 mg), which was purified by prep-HPLC to give **Compound 30** (2.13 mg, 5.5 umol, 25.6% yield). LCMS (ESI): RT = 0.692 min, mass calc. for C₁₇H₁₅F₃N₄O₂ 364.11, m/z found 364.9 [M+1]⁺; ¹H NMR (400 MHz, CD₃OD) δ 8.03 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.68 - 7.57 (m, 3H), 7.50 (dt, *J* = 1.5, 7.9 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 4.43 - 4.32 (m, 1H), 4.02 - 3.92 (m, 2H).

Example 29: 2-[5-(azidomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 31)



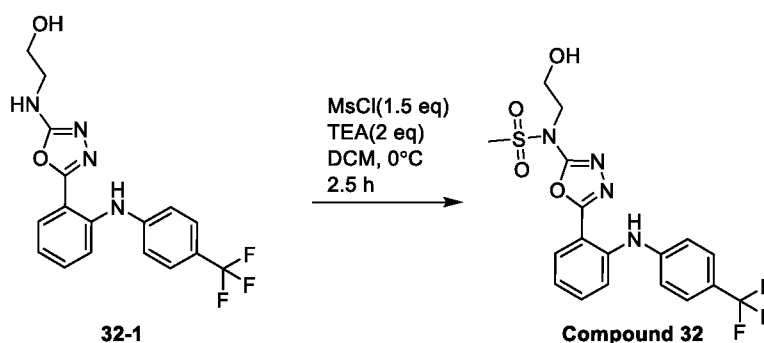
Step 1: 2-[5-(chloromethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00274] **31-1a** (84.1 mg, 0.7 mmol, 59 μ L, 1.1 eq) was added dropwise to the solution of **31-1** in dioxane (3 mL). The reaction mixture was refluxed 2 hours. POCl₃ (18 g, 117.2 mmol, 10.9 mL, 173.2 eq) was added to the reaction mixture, and the reaction was stirred at 100 °C for 2 h. LC-MS showed **31-1** was consumed completely and 43% of desired compound was detected. The mixture was poured into ice water, neutralized with saturated NaHCO₃, extracted with EtOAc (20 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to give **31-2** (100 mg, 0.28 mmol, 41.7% yield). LCMS (ESI): RT = 0.853 min, mass calc. for C₁₆H₁₁ClF₃N₃O 353.05 m/z found 353.9 [M+H]⁺.

Step 2: 2-[5-(azidomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

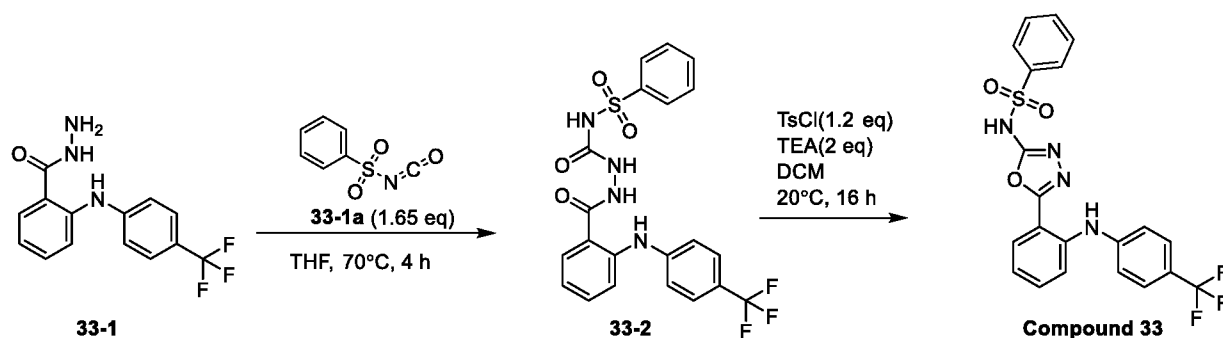
[00275] To a solution of **31-2** (100 mg, 0.3 mmol, 1 eq) in DMF (3 mL) was added NaN₃ (55.1 mg, 0.8 mmol, 3.0 eq). The mixture was stirred at 30 °C for 16 h. TLC indicated **31-2** was consumed completely and one new spot formed. The mixture was quenched by addition of H₂O (5 mL), and then extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 31** (100 mg, crude). 20 mg of the crude product was purified by prep-HPLC to give **Compound 31** (3.41 mg). LCMS (ESI): RT = 0.921 min, mass calc. for C₁₆H₁₁F₃N₆O 360.09 m/z found 361.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 7.91 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.55-7.49 (m, 1H), 7.46-7.34 (m, 3H), 7.03-6.96 (m, 1H), 4.67 (s, 2H).

Example 30: N-(2-hydroxyethyl)-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide (Compound 32)



[00276] To a stirred solution of **32-1** (0.03 g, 82 μ mol, 1 *eq*) and TEA (16.7 mg, 0.16 mmol, 23 μ L, 2 *eq*) in DCM (1 mL) was added MsCl (14.2 mg, 0.12 mmol, 10 μ L, 1.5 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2.5 h. LCMS showed the reaction was complete, 38% of **Compound 32** was detected. TLC (Petroleum ether:Ethyl acetate = 1:1 UV) showed new spots were formed. The mixture was concentrated to give a residue. The residue was purified by prep-TLC to give **Compound 32** (2.56 mg, 6 μ mol, 7.0% yield). LCMS (ESI): RT = 0.218 min, mass calc. for $C_{18}H_{17}F_3N_4O_4S$ 442.09, m/z found 443.0 $[M+1]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.65 (d, J = 6.8 Hz, 1H), 7.49 (br d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.3 Hz, 1H), 7.31 - 7.23 (m, 3H), 6.87 (t, J = 7.5 Hz, 1H), 5.27 (br d, J = 5.8 Hz, 1H), 4.45 (t, J = 4.9 Hz, 2H), 3.76 (q, J = 5.3 Hz, 2H), 3.15 - 2.84 (m, 3H).

Example 31: N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (Compound 33)



Step 1: N-(phenylsulfonyl)-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazine carboxamide

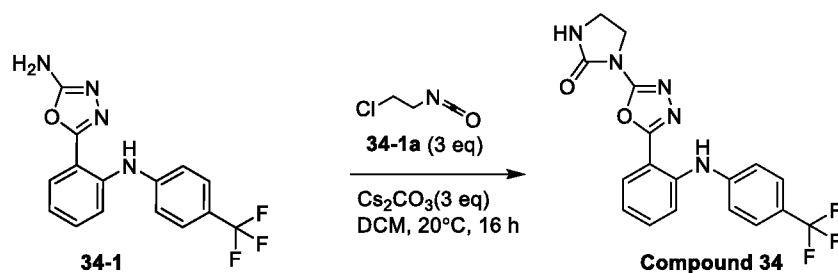
[00277] A mixture of 2-[4-(trifluoromethyl)anilino]benzohydrazide **33-1** (0.20 g, 0.68 mmol, 1 *eq*) and N-(oxomethylene)benzenesulfonamide **33-1a** (136.5 mg, 0.75 mmol, 99 μ L, 1.1 *eq*) in THF (3 mL) was stirred at 70 °C for 2 hr. LCMS showed 19% of starting material was remained and 40% of desired product was formed. Then N-(oxomethylene)benzenesulfonamide **33-1a** (68.3 mg, 0.37 mmol, 50 μ L, 0.55 *eq*) was added and the mixture was continuously stirred at 70 °C for another 2 h. LCMS showed starting material was consumed and 11% of desired product was formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give compound **33-2** (0.15 g, 0.16 mmol, 23.6% yield). LCMS (ESI): RT = 0.811 min, mass calc. for $C_{21}H_{17}F_3N_4O_4S$ 478.09, m/z found 501.0 $[M+23]^+$.

Step 2: N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)benzene sulfonamide

[00278] To a mixture of compound **33-2** (0.13 g, 0.27 mmol, 1 *eq*) and TEA (55.0 mg, 0.54 mmol, 76 μ L, 2 *eq*) in DCM (5 mL) was added TsCl (62.2 mg, 0.33 mmol, 1.2 *eq*) at 20 °C. The resulting mixture was stirred at 20 °C for 16 hr. LCMS showed no starting material was remained and 30%

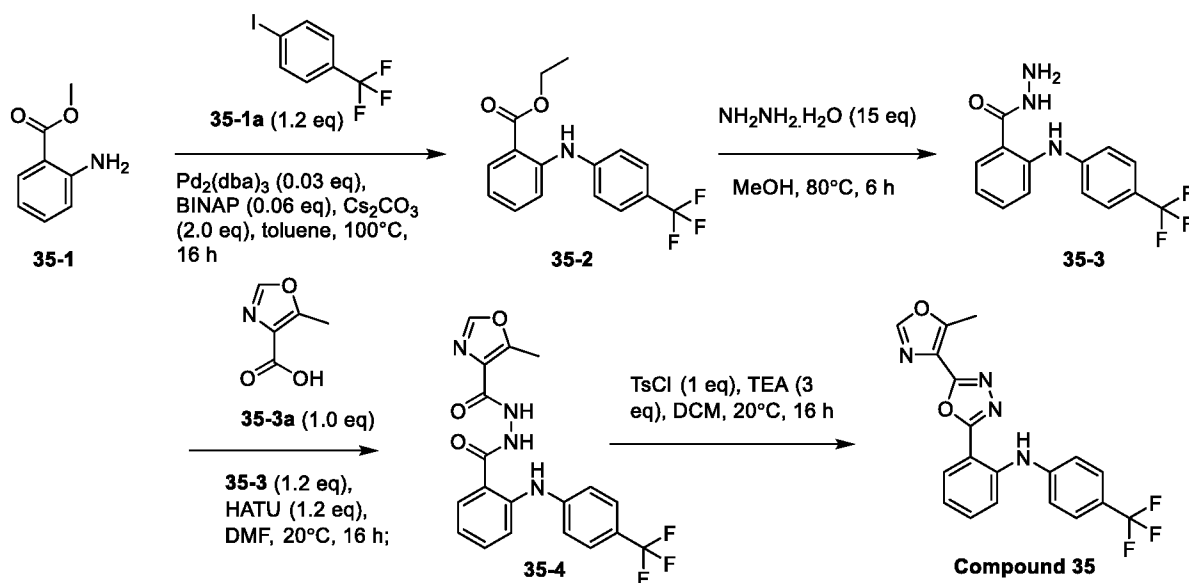
of desired product was formed. The mixture was concentrated at 25 °C to give a residue. The residue was purified by prep-HPLC to give **Compound 33** (2.48 mg, 6 μ mol, 2.0% yield). LCMS (ESI): RT = 0.867 min, mass calc. for C₂₁H₁₅F₃N₄O₃S 460.08, m/z found 461.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 11.13 - 10.59 (m, 1H), 8.22 (s, 1H), 8.03 - 7.97 (m, 2H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.63 - 7.56 (m, 3H), 7.55 - 7.48 (m, 2H), 7.45 - 7.38 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.97 (ddd, *J* = 2.1, 6.1, 8.1 Hz, 1H).

Example 32: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)imidazolidin-2-one (Compound 34)



[00279] To a stirred solution of 5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-amine **34-1** (40.0 mg, 0.13 mmol, 1 *eq*) and Cs₂CO₃ (122.1 mg, 0.37 mmol, 3 *eq*) in DCM (3 mL) was added **34-1a** (39.5 mg, 0.37 mmol, 3 *eq*) at 20 °C. The mixture was stirred at 20 °C for 16 h. LCMS showed 48% of starting material was remained and 27% of **Compound 34** was detected. The mixture was concentrated at 20 °C to give a residue. The residue was purified by prep-HPLC to give **Compound 34** (8.65 mg, 21.6 μ mol, 17.3% yield). LCMS (ESI): RT = 0.803 min, mass calc. for C₁₈H₁₄F₃N₅O₂ 389.11, m/z found 390.0 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.27 (br s, 1H), 7.89 (br d, *J* = 7.5 Hz, 1H), 7.50 (br d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.33 - 7.25 (m, 3H), 6.90 (t, *J* = 7.3 Hz, 1H), 4.95 (br s, 1H), 4.16 (br s, 2H), 3.68 (br s, 2H).

Example 33: 2-(5-(5-methyloxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 35)



Step 1: ethyl 2-((4-(trifluoromethyl)phenyl)amino)benzoate

[00280] The mixture of compound **35-1** (15.00 g, 99.23 mmol, 12.8 mL, 1 eq), compound **35-1a** (32.39 g, 119.08 mmol, 17.5 mL, 1.2 eq), $\text{Pd}_2(\text{dba})_3$ (2.73 g, 2.98 mmol, 0.03 eq), BINAP (3.71 g, 5.95 mmol, 0.06 eq) and Cs_2CO_3 (64.66 g, 198.46 mmol, 2 eq) in toluene (250 mL) at 30 °C was purged and degassed with N_2 for 3 times, and the resulting mixture was stirred at 100 °C under N_2 for 16 h. TLC (PE:EA = 10:1, UV) showed starting material was consumed completely and one new spot was formed. The mixture was concentrated to remove the solvent. The residue was diluted with EA (300 mL), and then filtered to remove the solid. The filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2) to give compound **35-2** (21.0 g, 66.54 mmol, 67.1% yield). LCMS (ESI): RT = 0.978 min, mass calc. for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{NO}_2$ 309.10, m/z found 309.9 $[\text{M}+1]^+$. ^1H NMR (400MHz, CDCl_3) δ 9.69 (s, 1H), 8.05 - 8.00 (m, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.44 - 7.36 (m, 2H), 7.30 (d, J = 8.5 Hz, 2H), 6.86 (ddd, J = 2.5, 5.9, 8.2 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H).

Step 2: 2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00281] To a solution of compound **35-2** (21.00 g, 67.90 mmol, 1 eq) in MeOH (60 mL) at 20 °C was added $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (59.98 g, 1.02 mol, 58.2 mL, 15 eq), and the resulting mixture was stirred at 80 °C for 6 h. TLC (PE:EA = 10:1, UV) showed starting material was consumed completely and one new spot was formed. LCMS showed starting material was consumed completely and 94% of desired product was formed. The mixture was concentrated to remove the solvent. The residue was diluted with water (100 mL), and then filtered to collect the solid. The filtrate was extracted with EA (100 mL *3) and the combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was combined with the filtered solid. The combined solid was purified by washed with

PE/EA (200 mL, PE: EA = 5:1), filtered and dried in vacuum to give compound **35-3** (19.00 g, 64.35 mmol, 94.8% yield). ^1H NMR (400MHz, CDCl_3) δ 9.28 (brs, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.51 - 7.35 (m, 4H), 7.24 (d, J = 8.5 Hz, 2H), 6.96 - 6.88 (m, 1H), 4.08 (brs, 2H).

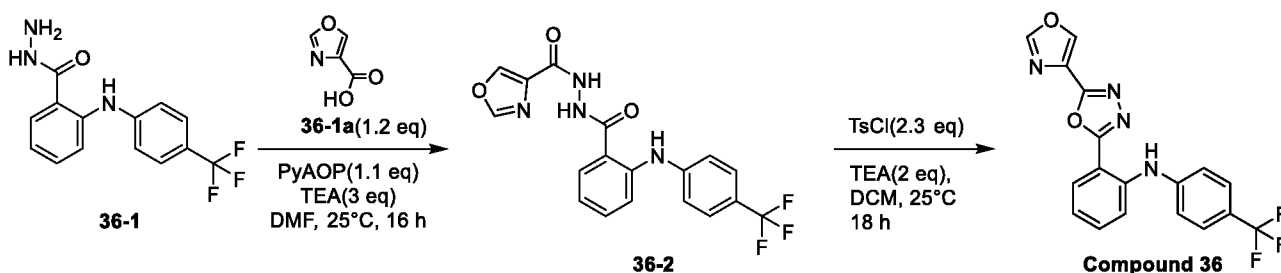
Step 3: 5-methyl-N'-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazole-4-carbohydrazide

[00282] To a solution of compound **35-3a** (200 mg, 1.57 mmol, 1 *eq*), compound **35-3** (557 mg, 1.89 mmol, 1.2 *eq*) and HATU (718 mg, 1.89 mmol, 1.2 *eq*) in DMF (5 mL) at 20 °C was added DIPEA (407 mg, 3.15 mmol, 0.5 mL, 2 *eq*), and the resulting mixture was stirred at 20 °C for 16 h. LCMS showed starting material was consumed completely and 64% of desired product was formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give compound **35-4** (400 mg, 0.99 mmol, 62.9% yield). LCMS (ESI): RT = 0.797 min, mass calc. for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_3$ 404.11, m/z found 405.0 $[\text{M}+1]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 10.50 (s, 1H), 10.19 (s, 1H), 9.45 (s, 1H), 8.41 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.53 - 7.44 (m, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.08 - 7.01 (m, 1H), 2.60 (s, 3H).

Step 4: 2-(5-(5-methyloxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00283] To a solution of compound **35-4** (200 mg, 0.49 mmol, 1 *eq*) and TEA (150.2 mg, 1.48 mmol, 0.2 mL, 3 *eq*) in DCM (2 mL) at 20 °C was added TsCl (94.3 mg, 0.49 mmol, 1 *eq*), and the resulting mixture was stirred at 20 °C for 16 h. LCMS showed 7% of starting material still remained and 93% of desired product was formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 35** (160.90 mg, 0.42 mmol, 84.2% yield). LCMS (ESI): RT = 0.915 min, mass calc. for $\text{C}_{19}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_2$ 386.10, m/z found 386.9 $[\text{M}+1]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 9.24 (s, 1H), 8.61 - 8.51 (m, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.62 - 7.53 (m, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 2.70 (s, 3H).

Example 34: 2-(5-(oxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 36)



Step 1: N'-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazole-4-carbohydrazide

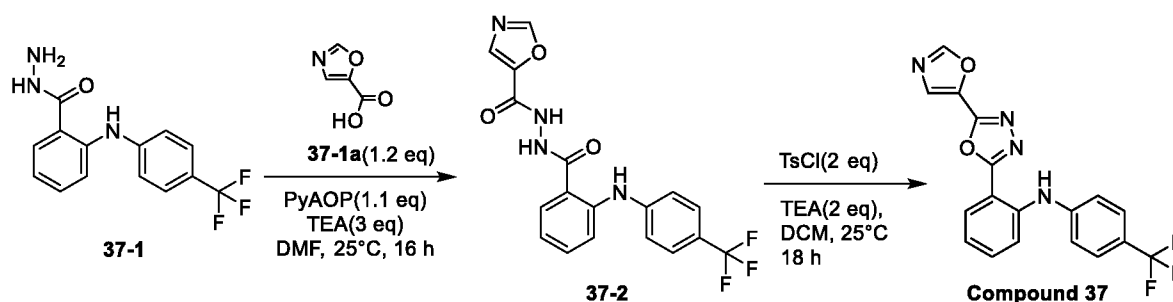
[00284] To a mixture of **36-1a** (137.9 mg, 1.22 mmol, 1.2 *eq*), PYAOP (635.7 mg, 1.22 mmol, 1.2 *eq*) and TEA (308.4 mg, 3.05 mmol, 424.27 μL , 3 *eq*) in DMF (3 mL) was added **36-1** (0.3 g, 1.02

mmol, 1 *eq*) in one portion at 20 °C under N₂. The mixture was stirred at 20 °C for 16 h. LCMS showed 7% of starting material was remained and 20% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine(15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **36-2** (0.05 g, 0.13 mmol, 12.61% yield). LCMS (ESI): RT = 0.767 min, mass calc. for C₁₈H₁₃F₃N₄O₃ 390.09, m/z found 390.9 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.57 (s, 1H), 10.40 (s, 1H), 9.43 (s, 1H), 8.78 (s, 1H), 8.60 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.60 (br d, *J* = 8.4 Hz, 2H), 7.53 - 7.43 (m, 2H), 7.30 (br d, *J* = 8.3 Hz, 2H), 7.05 (br t, *J* = 7.2 Hz, 1H).

Step 2: 2-(5-(oxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00285] To a mixture of **36-2** (33 mg, 85 μmol, 1 *eq*) and TEA (17.1 mg, 0.17 mmol, 24 μL, 2 *eq*) in DCM (3 mL) was added TsCl (16.1 mg, 85 μmol, 1 *eq*) in one portion at 20 °C under N₂. The mixture was stirred at 20 °C for 16 h. LCMS showed 78% of starting material was remained and 21% of desired product was detected. Then another batch of TsCl (21 mg, 0.11 mmol, 1.3 *eq*) was added and the mixture was stirred at 20 °C for 2 h. LCMS showed no starting material was remained and 77% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15mL), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 36** (5.52 mg, 15 μmol, 17.2% yield). LCMS (ESI): RT = 0.875 min, mass calc. for C₁₈H₁₁F₃N₄O₂ 372.08 m/z found 372.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 8.49 (d, *J* = 0.8 Hz, 1H), 8.12 (s, 1H), 8.04 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.56 - 7.50 (m, 1H), 7.45 - 7.37 (m, 3H), 7.27 (s, 1H), 7.04 - 6.97 (m, 1H).

Example 35: 2-(5-(oxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 37)



Step 1: N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazole-5-carbohydrazide

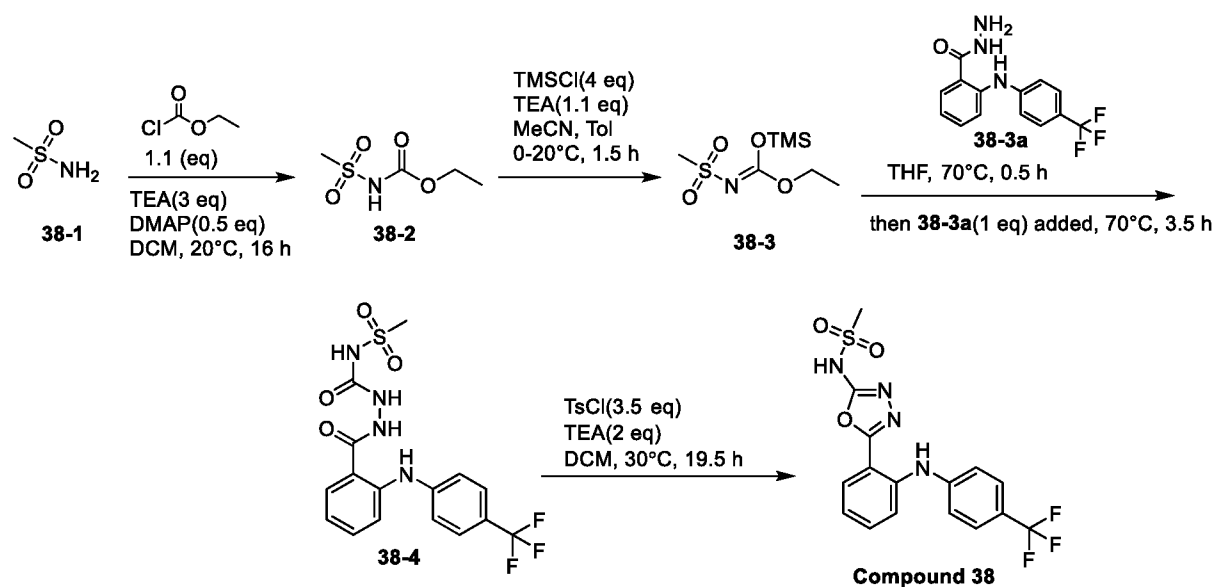
[00286] To a mixture of **37-1a** (138.4 mg, 1.22 mmol, 1.2 *eq*), PYAOP (638.2 mg, 1.22 mmol, 1.2 *eq*) and TEA (309.6 mg, 3.06 mmol, 425.92 μL, 3 *eq*) in DMF (3 mL) was added **37-1** (0.3 g, 1.02 mmol, 1 *eq*) in one portion at 20 °C under N₂. The mixture was stirred at 20 °C for 16 h. LCMS showed 9% of starting material and 15% of desired product was detected. The mixture was diluted

with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **37-2** (0.04 g, 0.10 mmol, 10.1% yield). LCMS (ESI): RT = 0.749 min, mass calc. for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_3$ 390.09, m/z found 390.9 $[\text{M}+1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.79 (s, 1H), 10.67 (s, 1H), 9.38 (s, 1H), 8.67 (s, 1H), 7.94 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.53 - 7.43 (m, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.13 - 6.99 (m, 1H).

Step 2: 2-(5-(oxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00287] To a mixture of **37-2** (23 mg, 59 μmol , 1 *eq*) and TEA (14.9 mg, 0.15 mmol, 21 μL , 2.5 *eq*) in DCM (2 mL) was added TsCl (11.2 mg, 59 μmol , 1 *eq*) in one portion at 20 °C under N_2 . The mixture was stirred at 20 °C for 16 h. LCMS showed 51% of starting material was remained and 46% of desired product was detected. Then another batch of TsCl (11.2 mg, 59 μmol , 1 *eq*) was added and the mixture was stirred at 20 °C for 2 h. LCMS showed no starting material was remained and 70% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15mL), dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 37** (2.39 mg, 6 μmol , 10.8% yield). LCMS (ESI): RT = 0.888 min, mass calc. for $\text{C}_{18}\text{H}_{11}\text{F}_3\text{N}_4\text{O}_2$ 372.08 m/z found 372.9 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.46 (s, 1H), 8.21 - 8.12 (m, 1H), 7.99 (dd, J = 1.4, 7.9 Hz, 1H), 7.95 - 7.90 (m, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.55 - 7.49 (m, 1H), 7.48 - 7.36 (m, 3H), 7.07 - 6.96 (m, 1H).

Example 36: N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide (Compound 38)



Step 1: ethyl methanesulfonylcarbamate

[00288] To a mixture of **38-1** (5 g, 52.56 mmol, 1 *eq*), TEA (15.96 g, 157.69 mmol, 22 mL, 3 *eq*) and DMAP (3.21 g, 26.28 mmol, 0.5 *eq*) in DCM (20 mL) was added ethyl carbonochloridate (6.27 g, 57.82 mmol, 5.5 mL, 1.1 *eq*) at 20 °C. The resulting mixture was stirred at 20 °C for 16 hr. TLC (Ethyl acetate:Petroleum ether = 2:1 I₂) showed new spots were formed. The filtrate was concentrated to give a residue. The residue was dissolved in EtOAc (100 mL) and washed with 1 N HCl (30 mL*2), water (30 mL*2), and brine (30 mL*2). The organic layer was dried over anhydrous and concentrated in vacuo to give **38-2** (2.1 g, 12.56 mmol, 23.9% yield), which was used directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.57 (br s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.28 - 3.17 (m, 3H), 1.22 (t, *J* = 7.2 Hz, 3H).

Step 2: (Z)-ethyl (trimethylsilyl) methylsulfonylcarbonimide

[00289] To a solution of **38-2** (0.5 g, 2.99 mmol, 1 *eq*) in a mixture of MeCN (1 mL) and toluene (6 mL) was added TMSCl (1.30 g, 11.96 mmol, 1.5 mL, 4 *eq*) and the resulting mixture was cooled in an ice bath. After slowly adding a solution of TEA (332.9 mg, 3.29 mmol, 0.5 mL, 1.1 *eq*) in Toluene (2 mL), the reaction mixture was stirred at 20 °C for 1.5 hr. The excess trimethylchlorosilane was evaporated in vacuo at 20 °C and diluted with water (15 mL) and extracted with DCM (20 mL) twice. The combined organic layer was dried by anhydrous Na₂SO₄, filtered and concentrated at 20 °C to give crude product compound **38-3** (0.28 g, 1.17 mmol, 39.1% yield), which was used directly.

Step 3: N-(methylsulfonyl)-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazine carboxamide

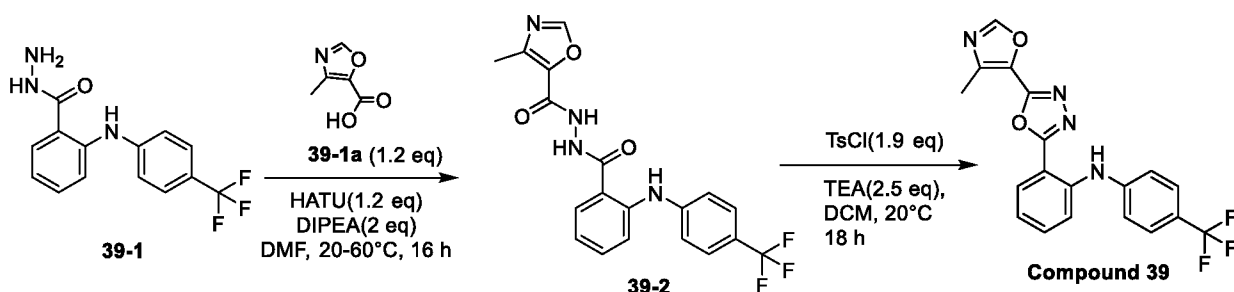
[00290] A solution of **38-3** (0.14 g, 0.58 mmol, 1 *eq*) in THF (5 mL) was stirred at 70 °C for 0.5 hr and cooled to 20 °C. Then **38-3a** (172.7 mg, 0.58 mmol, 1 *eq*) was added and the resulting mixture was stirred at 70 °C for 3.5 hr. LCMS showed 73% of **38-3a** was remained and 21% of desired product was formed. The mixture was concentrated in vacuo to yield a residue. The residue was purified by prep-HPLC to give **38-4** (15 mg, 24 μmol, 4.1% yield). LCMS (ESI): RT = 0.754 min, mass calc. for C₁₆H₁₅F₃N₄O₄S 416.08, *m/z* found 438.9 [M+23]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.46 (br s, 1H), 9.41 - 9.22 (m, 1H), 7.78 - 7.56 (m, 2H), 7.48 (br s, 2H), 7.26 (br dd, *J* = 8.3, 17.1 Hz, 2H), 7.14 - 6.97 (m, 1H), 3.26 (s, 3H).

Step 4: N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methane sulfonamide

[00291] To a mixture of compound **38-4** (13 mg, 31 μmol, 1 *eq*) and TEA (6.3 mg, 62 μmol, 8 μL, 2 *eq*) in DCM (2 mL) was added TsCl (9 mg, 47 μmol, 1.5 *eq*) at 20 °C. Then the mixture was stirred at 30 °C for 1.5 hr. LCMS showed 23% of compound **38-4** was remained and 25% of desired product was formed. Then the mixture was stirred at 30 °C for 16 hr. LCMS showed 21%

of compound **38-4** was remained and 29% of desired product was formed. Another batch of TsCl (11.9 mg, 62 μ mol, 2 *eq*) was added and the mixture was stirred at 30 °C for 2 hr. LCMS showed no compound **38-4** was remained and 30% of desired product was formed. The mixture was diluted with DCM (50 mL) and washed with brine (10 mL). The organic layer was dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 38** (2.78 mg, 7 μ mol, 22.4% yield). LCMS (ESI): RT = 0.801 min, mass calc. for C₁₆H₁₃F₃N₄O₃S 398.07, *m/z* found 399.0 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.88 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.58 - 7.46 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 3.11 (s, 3H).

Example 37: 2-(5-(4-methyloxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 39)



Step 1: 4-methyl-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazole-5-carbohydrazide

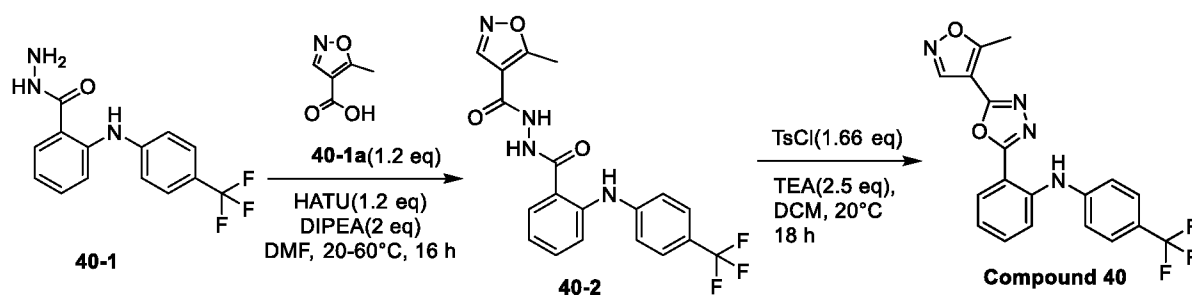
[00292] To a solution of **39-1** (0.3 g, 1.02 mmol, 1 *eq*), **39-1a** (155.0 mg, 1.22 mmol, 1.2 *eq*) and HATU (463.6 mg, 1.22 mmol, 1.2 *eq*) in DMF (4 mL) at 20 °C was added DIPEA (262.6 mg, 2.03 mmol, 0.4 mL, 2 *eq*), and the resulting mixture was stirred at 60 °C for 16 h. LCMS showed 11% of starting material was remained and 32% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **39-2** (85.05 mg, 0.21 mmol, 20.7% yield). LCMS (ESI): RT = 0.766 min, mass calc. for C₁₉H₁₅F₃N₄O₃ 404.11, *m/z* found 405.0 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.56 (d, *J* = 18.0 Hz, 2H), 9.43 (s, 1H), 8.53 (s, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.45 (m, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.06 (ddd, *J* = 2.0, 6.3, 7.9 Hz, 1H), 2.41 (s, 3H).

Step 2: 2-(5-(4-methyloxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00293] To a mixture of **39-2** (0.08 g, 0.2 mmol, 1 *eq*) and TEA (50.0 mg, 0.5 mmol, 68 μ L, 2.5 *eq*) in DCM (3 mL) was added TsCl (56.6 mg, 0.3 mol, 1.5 *eq*) in one portion at 20 °C. The mixture was stirred at 20 °C for 16 h. LCMS showed 9% of starting material was remained and 75% of desired product was detected. Then another batch of TsCl (15.1 mg, 79 μ mol, 0.4 *eq*) was added and the mixture was stirred at 20 °C for another 2 h. LCMS showed no starting material was remained and 44% of desired product was detected. The mixture was diluted with DCM (50 mL),

washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 39** (34.15 mg, 88 μ mol, 44.7% yield). LCMS (ESI): RT = 0.922 min, mass calc. for C₁₉H₁₃F₃N₄O₂ 386.10, m/z found 386.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.50 (s, 1H), 8.04 (s, 1H), 7.97 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.46 - 7.37 (m, 3H), 7.05 - 6.98 (m, 1H), 2.67 (s, 3H).

Example 38: 2-(5-(5-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 40)



Step 1: 5-methyl-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)isoxazole-4-carbohydrazide

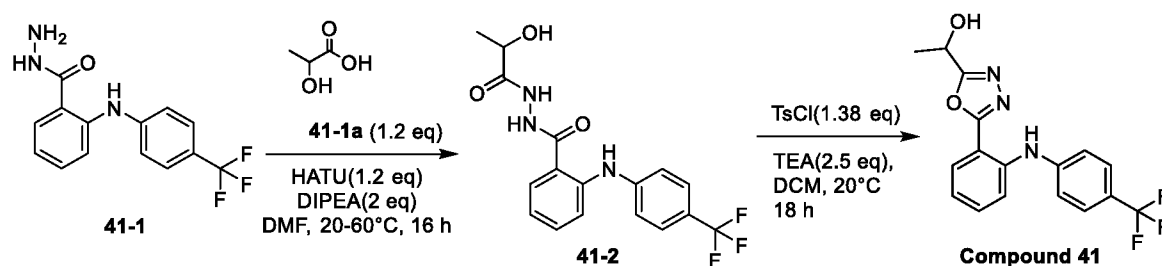
[00294] To a solution of **40-1** (0.3 g, 1.02 mmol, 1 *eq*), **40-1a** (155.6 mg, 1.22 mmol, 1.2 *eq*) and HATU (465.4 mg, 1.22 mmol, 1.2 *eq*) in DMF (4 mL) at 20 °C was added DIPEA (263.7 mg, 2.04 mmol, 0.4 mL, 2 *eq*), and the resulting mixture was stirred at 60 °C for 16 h. LCMS showed no starting material was remained and 43% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **40-2** (0.21 g, 0.52 mmol, 50.9% yield). LCMS (ESI): RT = 0.801 min, mass calc. for C₁₉H₁₅F₃N₄O₃ 404.11, m/z found 404.9 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.57 (br s, 1H), 9.40 (br s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 - 7.43 (m, 3H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.07 - 6.99 (m, 1H), 2.26 (d, *J* = 2.0 Hz, 3H).

Step 2: 2-(5-(5-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00295] To a mixture of compound **40-2** (0.21 g, 0.52 mmol, 1 *eq*) and TEA (131.4 mg, 1.30 mmol, 0.2 mL, 2.5 *eq*) in DCM (8 mL) was added TsCl (148.5 mg, 0.78 mmol, 1.5 *eq*) in one portion at 20 °C. The mixture was stirred at 20 °C for 16 h. LCMS showed 10% of starting material was remained and 65% of desired product was detected. Then another batch of TsCl (15.8 mg, 83 μ mol, 0.16 *eq*) was added and the mixture was stirred at 20 °C for another 2 h. LCMS showed no starting material was remained and 54% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 40** (7.8

mg, 20 μ mol, 3.8% yield). LCMS (ESI): RT = 0.922 min, mass calc. for $C_{19}H_{13}F_3N_4O_2$ 386.10, m/z found 386.9 $[M+1]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.99 (dd, J = 1.3, 8.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.54 - 7.41 (m, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.07 - 6.98 (m, 1H), 2.51 (s, 3H).

Example 39: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol (Compound 41)



Step 1: N'-(2-hydroxypropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

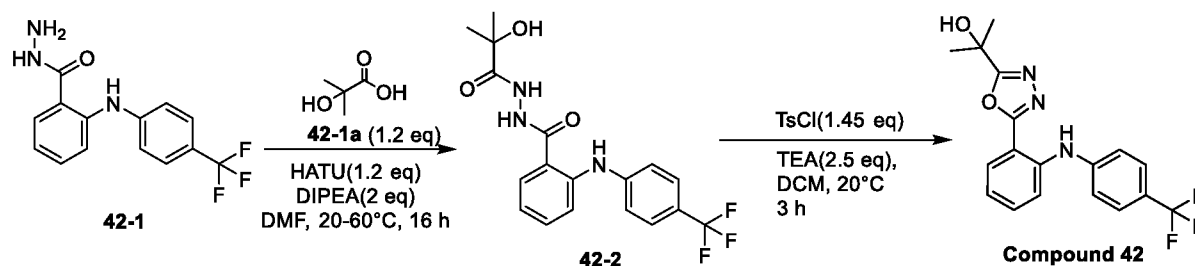
[00296] To a solution of **41-1** (0.3 g, 1.02 mmol, 1 *eq*), **41-1a** (110.3 mg, 1.22 mmol, 91 μ L, 1.2 *eq*) and HATU (465.4 mg, 1.22 mmol, 1.2 *eq*) in DMF (4 mL) at 20 °C was added DIPEA (263.7 mg, 2.04 mmol, 0.36 mL, 2 *eq*), and the resulting mixture was stirred at 60 °C for 16 h. LCMS showed no starting material was remained and 43% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **41-2** (92 mg, 0.25 mmol, 24.6% yield). LCMS (ESI): RT = 0.727 min, mass calc. for $C_{17}H_{16}F_3N_3O_3$ 367.11, m/z found 367.0 $[M+1]^+$. ^1H NMR (400 MHz, $DMSO-d_6$) δ 10.37 (s, 1H), 9.81 (s, 1H), 9.39 (s, 1H), 7.70 - 7.65 (m, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.51 - 7.39 (m, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.08 - 6.96 (m, 1H), 4.15 (q, J = 6.8 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H).

Step 2: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

[00297] To a mixture of **41-2** (86 mg, 0.23 mmol, 1 *eq*) and TEA (59.2 mg, 0.58 mmol, 81 μ L, 2.5 *eq*) in DCM (1 mL) was added TsCl (53.6 mg, 0.28 mmol, 1.2 *eq*) in one portion at 20 °C. The mixture was stirred at 20 °C for 16 h. LCMS showed 7% of starting material was remained and 65% of desired product was detected. Then another batch of TsCl (8.0 mg, 42 μ mol, 0.18 *eq*) was added and the mixture was stirred at 20 °C for another 2 h. LCMS and HPLC showed no starting material was remained and 59% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 41** (18.63 mg, 53 μ mol, 22.6% yield). LCMS (ESI): RT = 0.841 min, mass calc. for $C_{17}H_{14}F_3N_3O_2$ 349.10, m/z found 349.9 $[M+1]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.91 (dd, J = 1.4, 7.9

Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.53 - 7.48 (m, 1H), 7.43 - 7.38 (m, 1H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.02 - 6.90 (m, 1H), 5.22 (m, 1H), 2.89 (br d, $J = 5.4$ Hz, 1H), 1.76 (d, $J = 6.8$ Hz, 3H).

Example 40: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol (Compound 42)



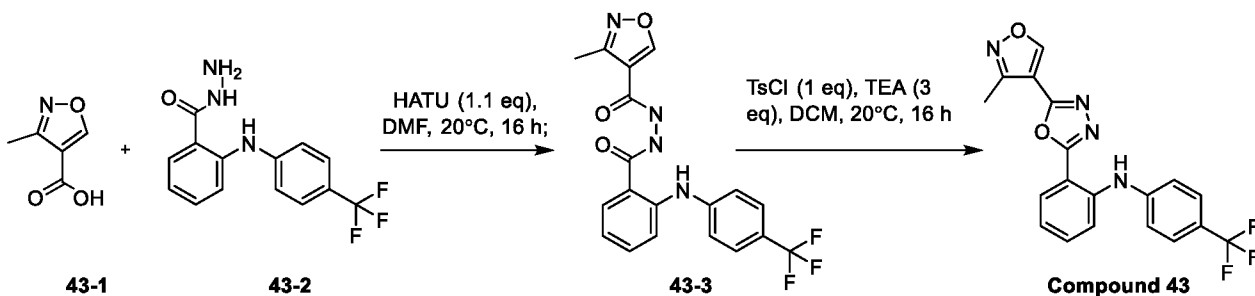
Step 1: N'-(2-hydroxy-2-methylpropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzo hydrazide

[00298] To a solution of **42-1** (0.3 g, 1.02 mmol, 1 *eq*), **42-1a** (127.4 mg, 1.22 mmol, 91 μ L, 1.2 *eq*) and HATU (465.4 mg, 1.22 mmol, 1.2 *eq*) in DMF (4 mL) at 20 °C was added DIPEA (263.7 mg, 2.04 mmol, 0.36 mL, 2 *eq*), and the resulting mixture was stirred at 60 °C for 16 h. LCMS showed no starting material was remained and 31% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **42-2** (76.2 mg, 0.2 mmol, 19.6% yield). LCMS (ESI): RT = 0.758 min, mass calc. for $\text{C}_{18}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_3$ 381.13, m/z found 382.0 $[\text{M}+1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H), 9.67 (s, 1H), 9.40 (s, 1H), 7.67 (d, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.50 - 7.41 (m, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 7.05 - 6.98 (m, 1H), 1.33 (s, 6H).

Step 2: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol

[00299] To a mixture of **42-2** (71 mg, 0.18 mmol, 1 *eq*) and TEA (37.7 mg, 0.37 mmol, 51 μ L, 2 *eq*) in DCM (3 mL) was added TsCl (42.6 mg, 0.22 mmol, 1.2 *eq*) in one portion at 15 °C. The mixture was stirred at 15 °C for 2 h. LCMS and HPLC showed 33% of starting material was remained and 65% of desired product was detected. Then another batch of TsCl (8.9 mg, 46 μ mol, 0.25 *eq*) was added and the mixture was stirred at 20 °C for another 1 h. LCMS showed 18% starting material was remained and 61% of desired product was detected. The mixture was diluted with DCM (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 42** (19.76 mg, 54 μ mol, 29.2% yield). LCMS (ESI): RT = 0.854 min, mass calc. for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_2$ 363.12, m/z found 363.9 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.48 (s, 1H), 7.91 (dd, $J = 1.4$, 7.9 Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.40 (dt, $J = 1.5$, 7.9 Hz, 1H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.01 - 6.94 (m, 1H), 2.87 (br s, 1H), 1.80 (s, 6H).

Example 41: 2-(5-(3-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 43)



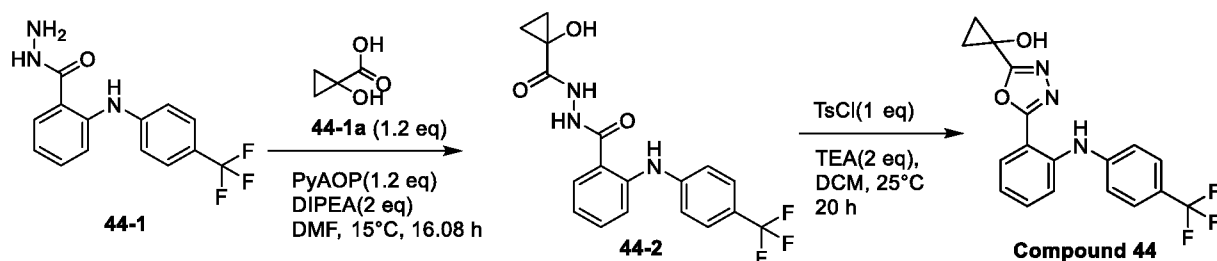
Step 1: 3-methyl-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)isoxazole-4-carbohydrazide

[00300] To a solution of compound **43-1** (200 mg, 1.57 mmol, 1 *eq*) and HATU (658.2 mg, 1.73 mmol, 1.1 *eq*) in DMF (1 mL) at 20 °C was added compound **43-2** (511.1 mg, 1.73 mmol, 1.1 *eq*) and DIPEA (406.7 mg, 3.15 mmol, 0.5 mL, 2 *eq*), and the resulting mixture was stirred at 20 °C for 16 h. LCMS showed starting material was consumed completely, and 29% of guanidine-byproduct and 63% of desired product were formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give compound **43-3** (334 mg, 0.83 mmol, 52.5% yield). LCMS (ESI): RT = 0.781 min, mass calc. for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_3$ 404.11, *m/z* found 405.0 $[\text{M}+1]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 10.61 (s, 1H), 10.53 (s, 1H), 9.37 (s, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 - 7.45 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.11 - 7.02 (m, 1H), 2.41 (s, 3H).

Step 2: 2-(5-(3-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00301] To a solution of compound **43-3** (230 mg, 0.57 mmol, 1 *eq*) and TEA (172.7 mg, 1.71 mmol, 0.2 mL, 3 *eq*) in DCM (3 mL) at 20 °C was added TsCl (108.4 mg, 0.57 mmol, 1 *eq*), and the resulting mixture was stirred at 20 °C for 16 h. LCMS showed starting material was consumed completely, and 90% of desired product were formed. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 43** (176.96 mg, 0.46 mmol, 80.5% yield). LCMS (ESI): RT = 0.946 min, mass calc. for $\text{C}_{19}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_2$ 386.10, *m/z* found 387.0 $[\text{M}+1]^+$. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 9.82 (s, 1H), 9.22 (s, 1H), 8.06 - 8.00 (m, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.62 - 7.54 (m, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.22 - 7.15 (m, 1H), 2.57 (s, 3H).

Example 42: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropanol (Compound 44)



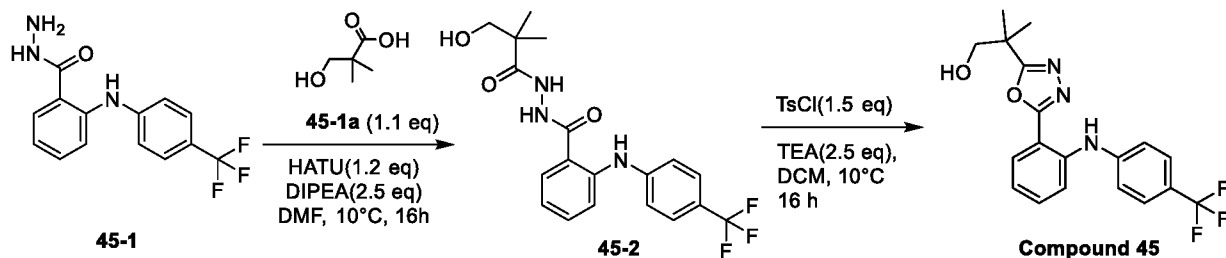
Step 1: N'-((1-hydroxycyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00302] To a mixture of **44-1a** (207.4 mg, 2.03 mmol, 1.2 *eq*) and PYAOP (1.07 g, 2.05 mmol, 1.21 *eq*) in DMF (5 mL) was added DIPEA (547.2 mg, 4.23 mmol, 0.7 mL, 2.5 *eq*) in one portion at 15 °C. After stirring for 5 min, **44-1** (0.5 g, 1.69 mmol, 1 *eq*) was added and the mixture was stirred at 15 °C for 16 h. LCMS showed no starting material was remained and 43% of desired product was detected. The mixture was diluted with EA (100 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **44-2** (15 mg, 40 μmol, 2.3% yield). LCMS (ESI): RT = 0.749 min, mass calc. for C₁₈H₁₆F₃N₃O₃ 379.11, m/z found 380.0 [M+1]⁺.

Step 2: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropanol

[00303] To a mixture of **44-2** (15 mg, 40 μmol, 1 *eq*) and TEA (8 mg, 79 μmol, 11 uL, 2 *eq*) in DCM (2 mL) was added TsCl (11 mg, 59 μmol, 1.5 *eq*) in one portion at 10 °C. The mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 52% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 44** (3.41 mg, 9 μmol, 23.9% yield). LCMS (ESI): RT = 0.850 min, mass calc. for C₁₈H₁₄F₃N₃O₂ 361.10, m/z found 361.9 [M+1]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.94 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.67 - 7.55 (m, 3H), 7.52 - 7.45 (m, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.07 (t, *J* = 7.7 Hz, 1H), 1.48 - 1.32 (m, 4H).

Example 43: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol (Compound 45)



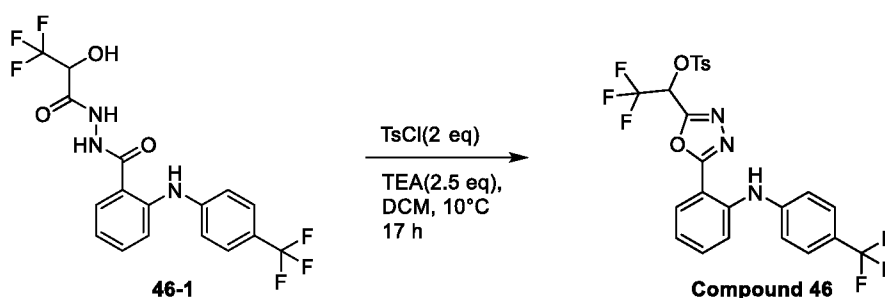
Step 1: N'-((3-hydroxy-2,2-dimethylpropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00304] To a solution of **45-1a** (132.5 mg, 1.12 mmol, 1.1 *eq*) and HATU (465.4 mg, 1.22 mmol, 1.2 *eq*) in DMF (3 mL) at 10 °C was added DIPEA (329.6 mg, 2.55 mmol, 0.5 mL, 2.5 *eq*). After stirring for 10 min, **45-1** (0.3 g, 1.02 mmol, 1 *eq*) was added and the resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 60% of desired product was detected. TLC (Petroleum ether:Ethyl acetate = 1:1,UV) indicated reactant 1 was consumed completely and one new spot formed. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂) to give compound **45-2** (350 mg, 0.89 mmol, 86.8% yield). LCMS (ESI): RT = 0.763 min, mass calc. for C₁₉H₂₀F₃N₃O₃ 395.15, m/z found 396.0 [M+1]⁺.

Step 2: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol

[00305] To a solution of **45-2** (0.25 g, 0.63 mmol, 1 *eq*) and TEA (160 mg, 1.58 mmol, 0.2 mL, 2.5 *eq*) in DCM (5 mL) at 10 °C was added TsCl (180.8 mg, 0.95 mmol, 1.5 *eq*). The resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 60% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 45** (22.61 mg, 59 umol, 9.4% yield). LCMS (ESI): RT = 0.876 min, mass calc. for C₁₉H₁₈F₃N₃O₂ 377.14, m/z found 377.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.48 (br s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.57 (br d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.42 - 7.31 (m, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 3.85 (s, 2H), 2.83 (br s, 1H), 1.48 (s, 6H).

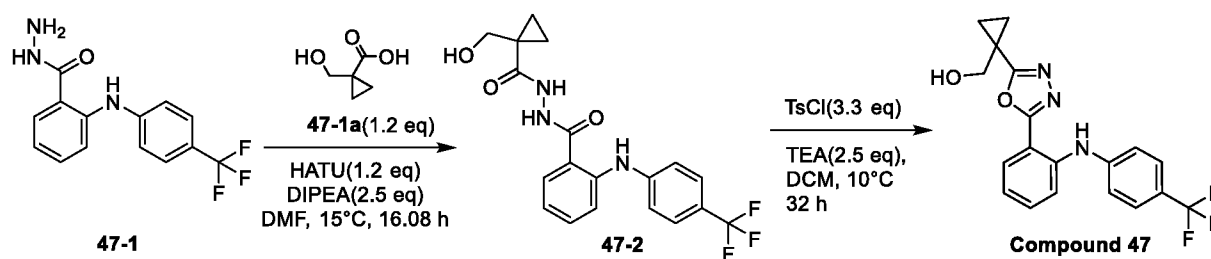
Example 44: 2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl 4-methylbenzenesulfonate (Compound 46)



[00306] To a solution **46-1** (0.24 g, 0.57 mmol, 1 *eq*) and TEA (144.1 mg, 1.42 mmol, 0.2 mL, 2.5 *eq*) in DCM (5 mL) at 10 °C was added TsCl (162.9 mg, 0.85 mmol, 1.5 *eq*). The resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 46% of **Compound 46** was formed. Then another batch of TsCl (54.3 mg, 0.28 mmol, 0.5 *eq*) was added and the resulting mixture was stirred at 10 °C for another 1 h. LCMS showed no starting material was remained and 60% of **Compound 46** was formed. The mixture was diluted with EA (50 mL),

washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 46** (20 mg, 35 μ mol, 6.2% yield). LCMS (ESI): RT = 1.007 min, mass calc. for C₂₄H₁₇F₆N₃O₄S 557.08, m/z found 558.0 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.19 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.62 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.44 - 7.33 (m, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.16 (s, 2H), 6.93 - 6.86 (m, 1H), 6.05 (q, *J* = 5.8 Hz, 1H), 2.17 (s, 3H).

Example 45: (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methanol (Compound 47)



Step 1: N'-((1-(hydroxymethyl)cyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00307] To a mixture of **47-1a** (70.8 mg, 0.61 mmol, 1.2 *eq*) and HATU (231.8 mg, 0.61 mmol, 1.2 *eq*) in DMF (3 mL) was added DIPEA (164.2 mg, 1.27 mmol, 0.2 mL, 2.5 *eq*) in one portion at 15 °C. After stirring for 5 min, **47-1** (0.15 g, 0.51 mmol, 1 *eq*) was added and the mixture was stirred at 15 °C for 16 h. LCMS and HPLC showed no starting material was remained and 43% of desired product was detected. The mixture was diluted with EA (100 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **47-2** (60 mg, 0.15 mmol, 29.4% yield). LCMS (ESI): RT = 0.758 min, mass calc. for C₁₉H₁₈F₃N₃O₃ 393.13, m/z found 394.0 [M+1]⁺.

Step 2: (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methanol

[00308] To a solution of **47-2** (20 mg, 51 μ mol, 1 *eq*) and TEA (12.9 mg, 0.13 mmol, 18 μ L, 2.5 *eq*) in DCM (5 mL) at 10 °C was added TsCl (12.6 mg, 66 μ mol, 1.3 *eq*). The resulting mixture was stirred at 10 °C for 16 h. LCMS showed 57% of starting material was remained and 14% of desired product was detected. TsCl (29.1 mg, 0.15 mmol, 3 *eq*) was added to the mixture, and the resulting mixture was stirred at 10 °C for 16 h. LCMS showed 16% of starting material was remained and 30% of desired product was detected. The mixture was diluted with EA (100 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 47** (27.56 mg, 73 μ mol, 36.1% yield). LCMS (ESI): RT = 0.849 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 376.0 [M+1]⁺. ¹H

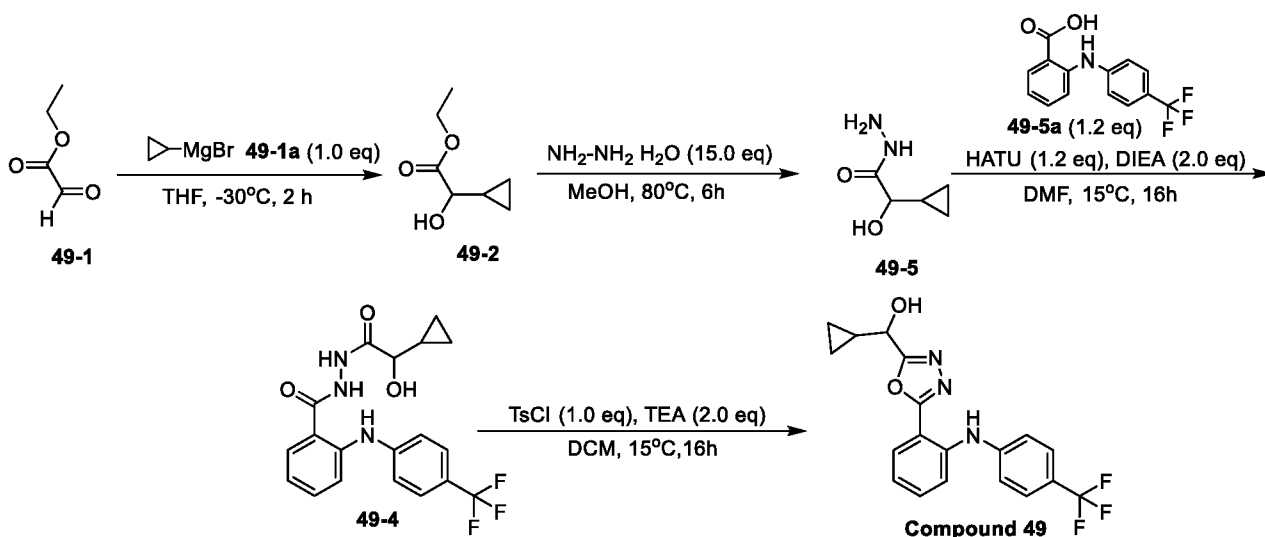
NMR (400 MHz, DMSO-*d*₆) δ 9.21 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.59 - 7.49 (m, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.19 - 7.10 (m, 1H), 5.02 (t, *J* = 5.9 Hz, 1H), 3.79 (d, *J* = 6.0 Hz, 2H), 1.23 - 1.17 (m, 2H), 1.16 - 1.09 (m, 2H).

Example 46: 2-[5-(2H-tetrazol-5-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 48)



[00309] To a solution of **48-1** (30 mg, 90.8 μ mol, 1 eq) in DMF (0.5 mL) were added NaN₃ (0.1 g, 1.1 mmol, 11.9 eq) and NH₄Cl (24.3 mg, 0.5 mmol, 15.9 μ L, 5.0 eq). The mixture was stirred at 120 °C for 2 hr. LC-MS showed **48-1** was consumed completely and 98% of desired compound was detected. The reaction mixture was diluted with (H₂O 1 mL). The residue was purified by prep-HPLC to give **Compound 48** (2.54 mg, 6.8 μ mol, 7% yield). LCMS (ESI): RT = 0.948 min, mass calc. for C₁₆H₁₀F₃N₇O 373.09, *m/z* found 374.4 [M+H]⁺; ¹H NMR (400MHz, CDCl₃) δ 8.17-8.15 (m, *J* = 1.1, 7.9 Hz, 1H), 7.66-7.57 (m, 3H), 7.54-7.48 (m, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H).

Example 47: cyclopropyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol (Compound 49)



Step 1: ethyl 2-cyclopropyl-2-hydroxyacetate

[00310] To a solution of compound **49-1** (10 g, 48.98 mmol, 1 eq) in THF (100 mL) was added compound **49-1a** (0.5 M, 97.9 mL, 1 eq) dropwise at -20~-30 °C bath. The mixture was stirred at -30 °C for 2 hr. TLC (PE/EA = 1/1, KMnO₄) showed that the starting material was remained and

new spots were formed. The reaction mixture was quenched with water (200 mL) dropwise at -20 °C and the aqueous phase was extracted with EA (30 mL*4). The combined organic phase was washed with water (25 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂). **49-2** (1.2 g, 8.32 mmol, 17.0% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 4.24 (m, 2H), 3.76 - 3.71 (m, 1H), 2.85 (br s, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.13 - 1.02 (m, 1H), 0.55 - 0.45 (m, 3H), 0.44 - 0.35 (m, 1H).

Step 2: 2-cyclopropyl-2-hydroxyacetohydrazide

[00311] To a solution of compound **49-2** (100 mg, 0.69 mmol, 1 *eq*) in MeOH (1 mL) was added NH₂NH₂·H₂O (651 mg, 10.40 mmol, 0.6 mL, 15 *eq*). The mixture was stirred at 80 °C for 6 hr. TLC (PE/EA = 1/1, I₂) showed that the starting material was consumed completely. The reaction mixture was concentrated in vacuum. The crude product was used for the next step directly. **49-3** (40 mg, 0.31 mmol, 44.3% yield) was obtained. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (br s, 1H), 5.17 (br s, 1H), 4.27 (br s, 2H), 1.07 - 0.97 (m, 1H), 0.40 - 0.23 (m, 4H).

Step 3: N'-(2-cyclopropyl-2-hydroxyacetyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

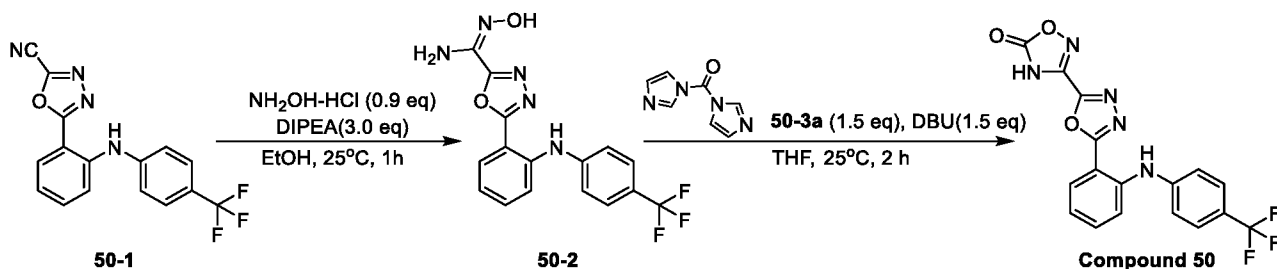
[00312] To a solution of compound **49-3a** (77.8 mg, 0.28 mmol, 1.2 *eq*) in DMF (1 mL) were added DIPEA (59.6 mg, 0.46 mmol, 80 uL, 2 *eq*), HATU (105.2 mg, 0.28 mmol, 1.2 *eq*) and compound **3** (30 mg, 0.23 mmol, 1 *eq*). The mixture was stirred at 15 °C for 16 hr. LCMS showed that the starting material was consumed completely and desired product was detected. The reaction mixture was concentrated in vacuum. The crude product was purified by prep-HPLC. **49-4** (30 mg, 76.3 umol, 33.1% yield) was obtained. ¹H NMR (400MHz, DMSO-*d*₆) δ 9.93 (br s, 1H), 8.23 (br s, 1H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.49 - 7.36 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 5.48 (br d, *J* = 4.8 Hz, 1H), 3.65 (br t, *J* = 5.1 Hz, 1H), 1.18 - 1.06 (m, 1H), 0.52 - 0.28 (m, 4H).

Step 4: cyclopropyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol

[00313] To a solution of compound **49-4** (25 mg, 63 umol, 1 *eq*) in DCM (0.5 mL) were added TEA (13 mg, 0.13 mmol, 17.7 uL, 2 *eq*) and TsCl (12 mg, 63.6 umol, 1 *eq*). The mixture was stirred at 10 °C for 2 hr. LCMS showed that the starting material was remained and 58% of desired product was detected. The reaction mixture was concentrated in vacuum. The crude product was purified by prep-HPLC. **Compound 49** (10 mg, 26.6 umol, 41.9% yield) was obtained. LCMS (ESI): RT = 0.885 min, mass calcd. for C₁₉H₁₆F₃N₃O₂, 375.12 m/z found 375.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.55 (s, 1H), 8.07 (br d, *J* = 7.78 Hz, 1H), 7.86 (d, *J* = 8.78 Hz, 1H), 7.75 (d, *J* = 8.04 Hz, 2H), 7.64 (d, *J* = 9.04 Hz, 1H), 7.57 (d, *J* = 8.04 Hz, 2H), 7.48 (d, *J* = 8.04 Hz, 1H), 7.13

(br s, 1H), 6.07 (br d, $J = 8.28$ Hz, 1H), 4.36 (dq, $J = 13.62, 6.76$ Hz, 1H), 1.59 (s, 9H), 1.32 (d, $J = 6.54$ Hz, 6H).

Example 48: 3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-4H-1,2,4-oxadiazol-5-one (Compound 50)



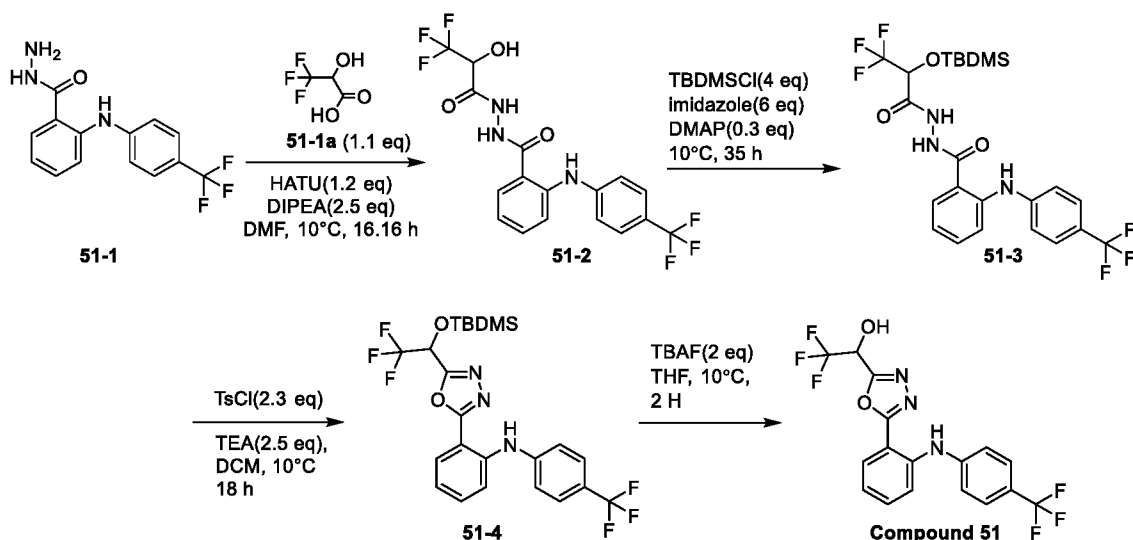
Step 1: N'-hydroxy-5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carboxamide

[00314] To a solution of **50-1** (70 mg, 0.2 mmol, 1 eq) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (22.1 mg, 0.2 mmol, 0.98 eq, HCl) in EtOH (2 mL) was added DIPEA (82.2 mg, 0.6 mmol, 0.1 mL, 3.0 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed **50-1** was consumed completely and 99% of desired compound was detected. The reaction mixture was filtered to give **50-2** (35 mg, 96.3 μmol , 45.4% yield). LCMS (ESI): RT = 0.953 min, mass calc. for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{N}_5\text{O}_2$ 363.09, m/z found 364.4 $[\text{M}+\text{H}]^+$.

Step 2: 3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-4H-1,2,4-oxadiazol-5-one

[00315] To a solution of **50-2** (35 mg, 96.3 μmol , 1 eq) and **50-3a** (23.4 mg, 0.1 mmol, 1.5 eq) in THF (1 mL) was added DBU (22.0 mg, 0.1 mmol, 22 μL , 1.5 eq). The mixture was stirred at 25 °C for 2 h. LC-MS showed 30% of **50-2** was remained and 68% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 50** (8.68 mg, 22.3 μmol , 23.1% yield). LCMS (ESI): RT = 1.146 min, mass calc. for $\text{C}_{12}\text{H}_8\text{F}_3\text{N}_6\text{O}_2$ 253.05, m/z found 254.3 $[\text{M}+\text{H}]^+$.

Example 49: 2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol (Compound 51)



Step 1: N'-(3,3,3-trifluoro-2-hydroxypropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00316] To a solution of **51-1a** (268.3 mg, 1.86 mmol, 1.1 *eq*) and HATU (772.7 mg, 2.03 mmol, 1.2 *eq*) in DMF (5 mL) at 10 °C was added DIPEA (547.2 mg, 4.23 mmol, 0.7 mL, 2.5 *eq*). After stirring for 10 min, **51-1** (0.5 g, 1.69 mmol, 1 *eq*) was added and the resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 14% desired product was detected. The mixture was directly purified by prep-HPLC to give **51-2** (50 mg, 0.11 mmol, 45% yield. LCMS (ESI): RT = 0.797 min, mass calc. for C₁₇H₁₃F₆N₃O₃ 421.09, m/z found 421.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (br s, 1H), 8.89 (br s, 1H), 8.52 (br s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.41 - 7.31 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.86 (t, *J* = 7.8 Hz, 1H), 4.61 (br d, *J* = 7.0 Hz, 1H), 3.91 (br s, 1H).

Step 2: N'-(2-((tert-butyldimethylsilyl)oxy)-3,3,3-trifluoropropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00317] To a solution of **51-2** (40 mg, 95 umol, 1 *eq*), DMAP (3.5 mg, 28 umol, 0.3 *eq*) and imidazole (38.8 mg, 0.57 mmol, 6 *eq*) in DCM (3 mL) at 10 °C was added TBDMSCl (28.6 mg, 0.19 mmol, 23 uL, 2 *eq*). The resulting mixture was stirred at 10 °C for 16 h. LCMS showed 52% of starting material was remained and 44% desired product was detected. Then another batch of TBDMSCl (14.3 mg, 95 umol, 12 uL, 1 *eq*) was added and the resulting mixture was stirred at 10 °C for 3 h. LCMS showed 31% of starting material was remained and 65% desired product was detected. Then another batch of TBDMSCl (14.3 mg, 95 umol, 12 uL, 1 *eq*) was added and the resulting mixture was stirred at 10 °C for another 16 h. LCMS showed no starting material was remained and 89.9% desired product was detected. TLC (Petroleum ether:Ethyl acetate = 3:1 UV) showed new spots were formed. The mixture diluted with water (10 mL), extracted with dichloromethane (15 mL*3) and the extracts dried over anhydrous Na₂SO₄, filtered and evaporated

to give crude product. The mixture was directly purified-TLC to give **51-3** (34 mg, 60 μ mol, 63.5% yield).

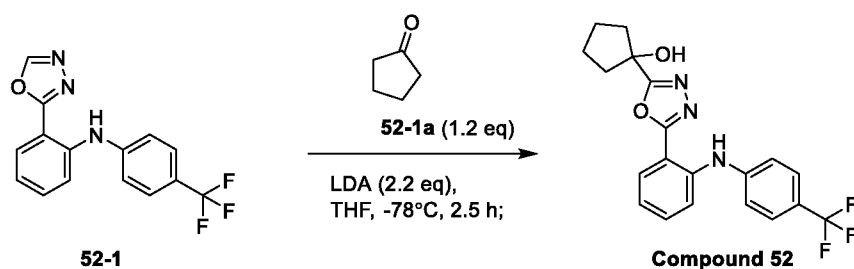
Step 3: 2-(5-(1-((tert-butyldimethylsilyl)oxy)-2,2,2-trifluoroethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00318] To a solution of compound **51-3** (34 mg, 64 μ mol, 1 *eq*) and TEA (16.06 mg, 0.16 mmol, 22 μ L, 2.5 *eq*) in DCM (1 mL) at 10 °C was added TsCl (18.2 mg, 95 μ mol, 1.5 *eq*). The resulting mixture was stirred at 10 °C for 2 h. LCMS showed 54% of starting material was remained and 14% of desired product was detected. Then another batch of TsCl (9.68 mg, 51 μ mol, 0.8 *eq*) was added and the solution was continuously stirred at 10 °C for 16 h. LCMS showed 18% of starting material was remained and 39% of desired product was detected. TLC (Petroleum ether : Ethyl acetate = 5:1 UV) showed some of starting material was remained and new spot was formed. The mixture was directly purified by prep-TLC to give **51-4** (11 mg, 21 μ mol, 32.8% yield).

Step 4: 2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

[00319] To a mixture of **51-4** (9 mg, 17 μ mol, 1 *eq*) in THF (1 mL) was added TBAF (1 M, 35 μ L, 2 *eq*). Then the resulting solution was stirred at 10 °C for 2 h. LCMS showed starting material was consumed completely and 100% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (15 mL) twice, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The combined mixture was directly purified by prep-HPLC to give **Compound 51** (4.15 mg, 10 μ mol, 59.2% yield). LCMS (ESI): RT = 0.896 min, mass calc. for C₁₇H₁₁F₆N₃O₂ 403.08, m/z found 403.9 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.26 (s, 1H), 7.84 (d, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.47 - 7.40 (m, 1H), 7.39 - 7.33 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.92 (t, *J* = 7.5 Hz, 1H), 5.39 (q, *J* = 5.9 Hz, 1H), 3.63 (br s, 1H).

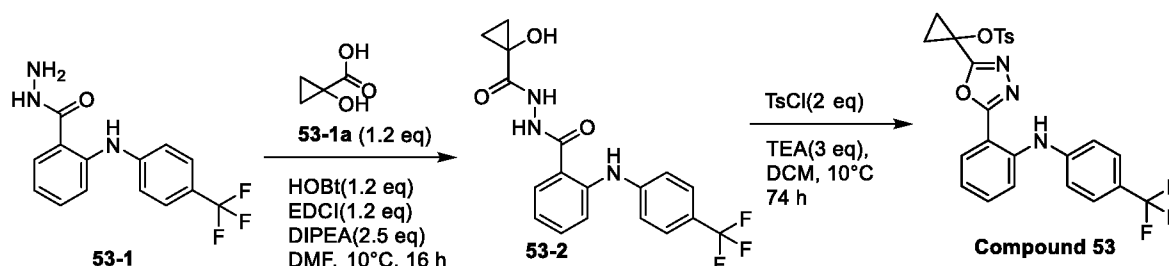
Example 50: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopentanol (Compound 52)



[00320] To a solution of **52-1** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then **52-1a** (33.1 mg, 0.39 mmol, 35 μ L, 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C into the above mixture. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE: EA = 5:1, UV) showed some

starting material still remained and one new spot was formed. LCMS showed 27% of starting material still remained and 68% of desired product was formed. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) at -78°C , and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **Compound 52** (66.97 mg, 0.17 mmol, 52.5% yield). LCMS (ESI): RT = 0.898 min, mass calc. for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_2$ 389.14, m/z found 390.0 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.51 (s, 1H), 7.91 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, $J = 8.3$ Hz, 2H), 7.01 - 6.95 (m, 1H), 2.58 (s, 1H), 2.38 - 2.28 (m, 2H), 2.21 - 2.13 (m, 2H), 2.11 - 2.00 (m, 2H), 1.98 - 1.86 (m, 2H).

Example 51: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl 4-methylbenzenesulfonate (Compound 53)



Step 1: N'-((1-hydroxycyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzo)hydrazide

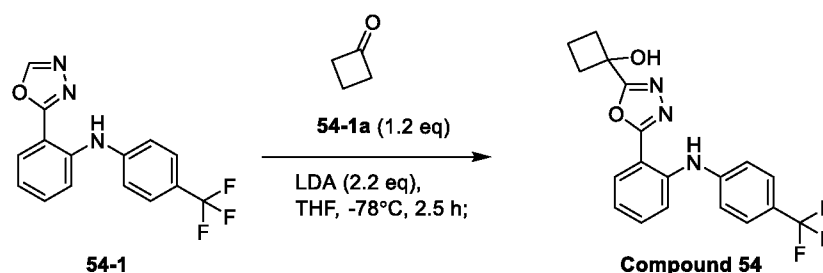
[00321] A mixture of **53-1** (450 mg, 1.52 mmol, 1 *eq*), **53-1a** (186.7 mg, 1.83 mmol, 1.2 *eq*), HOBT (247.1 mg, 1.83 mmol, 1.2 *eq*), EDCI (350.6 mg, 1.83 mmol, 1.2 *eq*) and DIPEA (492.4 mg, 3.81 mmol, 0.7 mL, 2.5 *eq*) in DMF (10 mL) was stirred at 10°C for 16 h. LCMS showed 35% of starting material was remained and 61% of desired product was detected. The mixture was diluted with EA (100 mL), washed with brine (15 mL), dried with Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give compound **53-2** (0.5 g, 1.28 mmol, 83.9% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H), 9.93 (s, 1H), 9.43 (br s, 1H), 7.67 (d, $J = 7.1$ Hz, 1H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.53 - 7.39 (m, 2H), 7.28 (d, $J = 8.5$ Hz, 2H), 7.02 (t, $J = 6.7$ Hz, 1H), 6.43 (s, 1H), 1.14 - 1.04 (m, 2H), 0.98 - 0.90 (m, 2H).

Step 2: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl 4-methylbenzenesulfonate

[00322] To a mixture of **53-2** (0.45 g, 1.19 mmol, 1 *eq*) and TEA (360.1 mg, 3.56 mmol, 0.5 mL, 3 *eq*) in DCM (15 mL) was added TsCl (226.2 mg, 1.19 mmol, 1 *eq*) at 10°C . The resulting mixture was stirred at 10°C for 1 h. LCMS showed 22% of starting material remained and 15% of **53** was formed. Then another TsCl (113.1 mg, 0.59 mmol, 0.5 *eq*) was added and the resulting mixture was

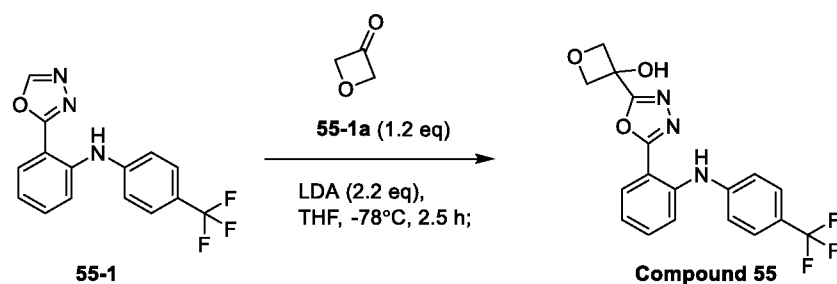
stirred at 10 °C for 1.5 h. LCMS and HPLC showed 8% of starting material remained, and 30% of **53** was formed. The mixture was directly diluted with EA (20 mL), washed with water (5 mL*3), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 53** (23 mg, 40 μ mol, 3.4% yield). LCMS (ESI): RT = 0.985 min, mass calc. for C₂₅H₂₀F₃N₃O₄S 515.11, m/z found 538.0 [M+23]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.66 (dd, *J* = 3.4, 8.1 Hz, 3H), 7.56 (d, *J* = 3.8 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.14 (td, *J* = 4.1, 8.1 Hz, 1H), 2.15 (s, 3H), 1.75 - 1.67 (m, 2H), 1.61 - 1.52 (m, 2H).

Example 52: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclobutanol (Compound 54)



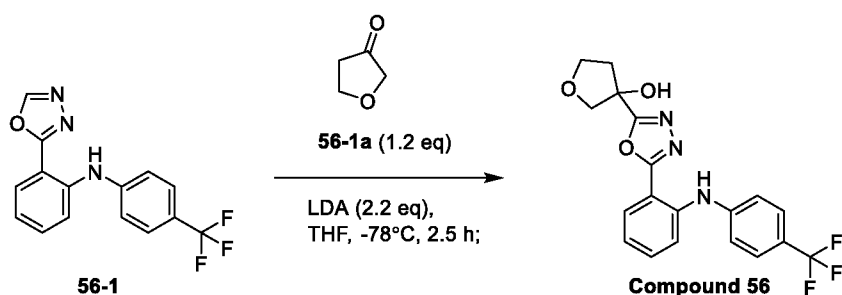
[00323] To a solution of **54-1** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then **54-1a** (27.6 mg, 0.39 mmol, 29 μ L, 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C into the above mixture. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE: EA = 5:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed starting material was consumed completely and 90% of desired product was formed. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL) at -78 °C, and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **Compound 54** (55.89 mg, 0.15 mmol, 45.5% yield). LCMS (ESI): RT = 0.881 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 376.0 [M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.94 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.01 - 6.96 (m, 1H), 2.97 (s, 1H), 2.87 - 2.76 (m, 2H), 2.61 - 2.50 (m, 2H), 2.13 - 2.04 (m, 1H), 2.03 - 1.92 (m, 1H).

Example 53: (Compound 55) 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxetan-3-ol



[00324] To a solution of **55-1** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then oxetan-3-one (28.3 mg, 0.39 mmol, 29 μ L, 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C into the above mixture. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE: EA = 2:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed 24% of starting material still remained and 76% of desired product was formed. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) at -78 °C, and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 55** (69.12 mg, 0.18 mmol, 55.9% yield). LCMS (ESI): RT = 0.826 min, mass calc. for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_3$ 377.10, m/z found 378.1 $[\text{M}+1]^+$. ^1H NMR (400 MHz, CDCl_3) δ 9.38 (s, 1H), 7.97 (dd, J = 1.4, 7.9 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.54 - 7.50 (m, 1H), 7.47 - 7.40 (m, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.03 - 6.97 (m, 1H), 5.14 (d, J = 7.8 Hz, 2H), 5.02 (d, J = 7.8 Hz, 2H), 3.78 (s, 1H).

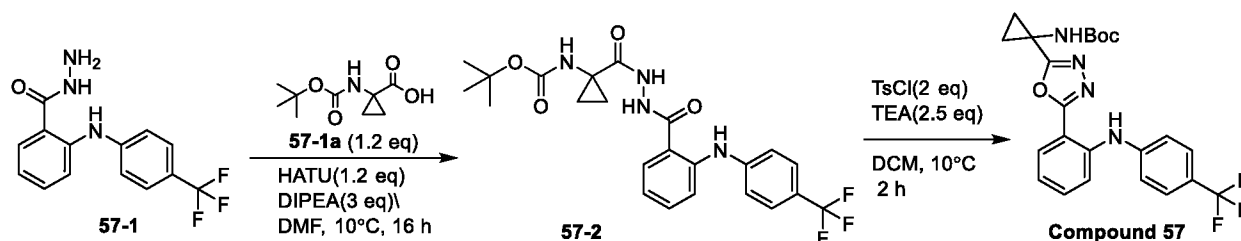
Example 54: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3-ol (Compound 56)



[00325] To a solution of **56-1** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then **56-1a** (33.8 mg, 0.39 mmol, 35 μ L, 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C into the above mixture. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE:EA = 2:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed 38% of starting material still remained and 62% of desired product was formed. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) at -78 °C, and then diluted with water (20 mL) and extracted

with EA (20 mL *3). The combined organic layers were washed with brine (20mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 56** (51.73 mg, 0.13 mmol, 38.6% yield). LCMS (ESI): RT = 0.828 min, mass calc. for C₁₉H₁₆F₃N₃O₃ 391.11, m/z found 391.9[M+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 7.91 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.95 (m, 1H), 4.29 - 4.12 (m, 4H), 3.17 (s, 1H), 2.71 (td, *J* = 8.6, 13.2 Hz, 1H), 2.51 - 2.42 (m, 1H).

Example 55: (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate (Compound 57)



Step 1: tert-butyl (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbonyl)cyclopropyl)carbamate

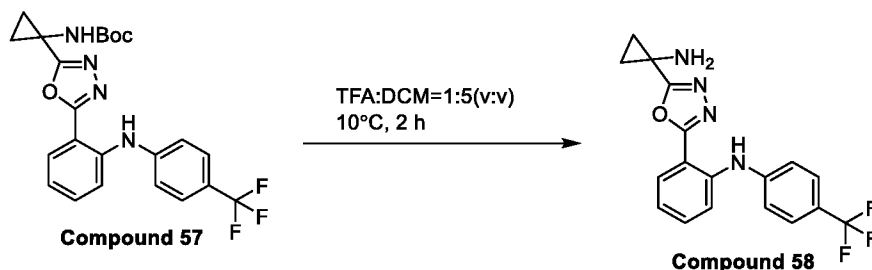
[00326] A mixture of **57-1** (600 mg, 2.03 mmol, 1 *eq*), **57-1a** (490.7 mg, 2.44 mmol, 1.2 *eq*), DIPEA (787.9 mg, 6.1 mmol, 1.1 mL, 3 *eq*) and HATU (927.2 mg, 2.44 mmol, 1.2 *eq*) in DMF (1 mL) was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 53% of desired product was detected. The mixture was diluted with EA (100 mL), washed with aq. saturated citric acid (15 mL*2), aq. saturated NaHCO₃ (15 mL*2) and brine (15 mL) in turns, dried with Na₂SO₄, filtered and concentrated to give crude compound **57-2** (850 mg, 1.78 mmol, 87.4% yield), which was used directly. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.39 (br s, 1H), 10.48 - 10.28 (m, 1H), 9.84 (s, 1H), 9.43 (s, 1H), 7.96 (s, 1H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.49 - 7.40 (m, 3H), 7.28 (br d, *J* = 8.3 Hz, 2H), 7.00 (br t, *J* = 7.1 Hz, 1H), 1.40 (s, 9H), 1.32 - 1.27 (m, 2H), 1.01 - 0.95 (m, 2H).

Step 2: tert-butyl (1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate

[00327] To a mixture of **57-2** (50 mg, 0.1 mmol, 1 *eq*) and TEA (26.4 mg, 0.26 mmol, 36 uL, 2.5 *eq*) in DCM (2 mL) was added TsCl (29.9 mg, 0.16 mmol, 1.5 *eq*) at 10 °C. Then the resulting mixture was stirred at 10 °C for 1 h. LCMS showed 16% of starting material was remained and 48% of desired product was detected. Then another portion of TsCl (9.9 mg, 52 umol, 0.5 *eq*) was added and the mixture was stirred at 10 °C for another 1 h. LCMS showed 15% of starting material was remained and 56% of desired product was detected. The solution was diluted with EA (100 mL), washed with brine (15 mL), dried with Na₂SO₄, filtered and concentrated to give a residue.

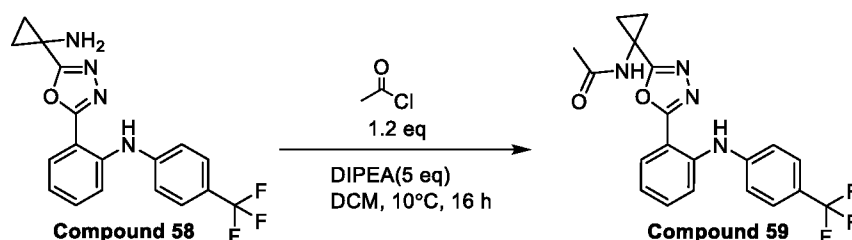
The residue was purified by prep-HPLC to give **Compound 57** (25 mg, 53 μ mol, 51.3% yield). LCMS (ESI): RT = 0.942 min, mass calc. for $C_{23}H_{23}F_3N_4O_3$ 460.17, m/z found 482.9 $[M+23]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.05 (s, 1H), 7.85 (br d, J = 7.9 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.58 - 7.50 (m, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 1.53 - 1.48 (m, 2H), 1.40 (s, 9H), 1.34 - 1.30 (m, 2H).

Example 56: 2-(5-(1-aminocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 58)



[00328] To a solution of **Compound 57** (50 mg, 0.11 mmol, 1 *eq*) in DCM (1 mL) was added TFA (309.5 mg, 2.71 mmol, 0.2 mL, 25 *eq*) at 10 °C. Then the mixture was stirred at 10 °C for 2 h. LCMS showed no starting material was remained and 96% of desired product was formed. The mixture was concentrated at 10 °C to give a residue. The residue was purified by prep-HPLC to give **Compound 58** (3.51 mg, 9 μ mol, 8.9% yield). LCMS (ESI): RT = 0.729 min, mass calc. for $C_{18}H_{15}F_3N_4O$ 360.12, m/z found 361.0 $[M+1]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.32 - 9.12 (m, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.62 (br d, J = 8.4 Hz, 2H), 7.57 - 7.47 (m, 2H), 7.32 (br d, J = 8.4 Hz, 2H), 7.19 - 7.07 (m, 1H), 3.02 - 2.61 (m, 1H), 1.29 - 1.20 (m, 2H), 1.14 - 1.05 (m, 2H).

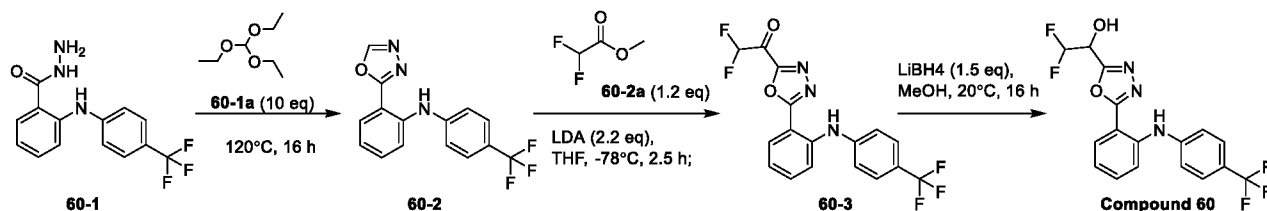
Example 57: N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)acetamide (Compound 59)



[00329] To a mixture of **Compound 58** (100 mg, 0.21 mmol, 1 *eq*, TFA) and DIPEA (136.2 mg, 1.05 mmol, 0.2 mL, 5 *eq*) in DCM (3 mL) was added a solution of acetyl chloride (19.9 mg, 0.25 mmol, 18 μ L, 1.2 *eq*) in DCM (1 mL) at 10 °C. Then the resulting mixture was stirred at 10 °C for 16 h. LCMS showed no starting material was remained and 42% of desired product was detected. The mixture was quenched methanol (0.01 mL) and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 59** (9.59 mg, 23 μ mol, 10.8% yield). LCMS (ESI): RT = 0.808 min, mass calc. for $C_{20}H_{17}F_3N_4O_2$ 402.13, m/z found 425.0 $[M+23]^+$. ^1H NMR (400 MHz,

CDCl₃) δ 9.37 (s, 1H), 7.69 (dd, J = 1.5, 7.9 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 1H), 7.33 - 7.24 (m, 3H), 6.87 (t, J = 7.6 Hz, 1H), 6.20 (s, 1H), 3.85 (s, 1H), 2.11 (s, 1H), 2.03 (s, 3H), 1.71 - 1.65 (m, 2H), 1.46 - 1.41 (m, 2H).

Example 58: 2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol (Compound 60)



Step 1: 2-(1, 3, 4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00330] The mixture of compound **60-1** (1.50 g, 5.08 mmol, 1 *eq*) and compound **60-1a** (7.53 g, 50.8 mmol, 8.5 mL, 10 *eq*) (neat reaction) was stirred at 120 °C under N₂ for 16 h. TLC (PE: EA = 1:1, UV) showed starting material was consumed completely, and one new spot was formed. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give compound **60-2** (1.40 g, 4.49 mmol, 88.5% yield). LCMS (ESI): RT = 0.989 min, mass calc. for C₁₅H₁₀F₃N₃O 305.08, m/z found 306.1[M+1]⁺.

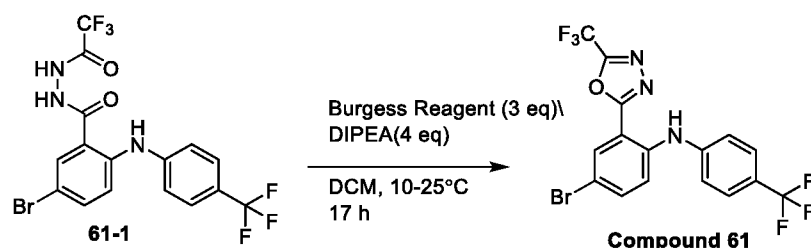
Step 2: 2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanone

[00331] To a solution of compound **60-2** (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78 °C was added LDA (2 M, 0.4 mL, 2.2 *eq*) dropwise, and the mixture was stirred at -78 °C for 0.5 h. And then compound **60-2a** (43.3 mg, 0.39 mmol, 35 μ L, 1.2 *eq*) in THF (1 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 2 h. TLC (PE:EA = 2:1, UV) showed some starting material still remained and one new spot was formed. LCMS showed 40% of starting material still remained and 59% of one new peak was formed. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL) at -78 °C, and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give compound **60-3** (40.0 mg, 90.1 μ mol, 27.5% yield). LCMS (ESI): RT = 0.815 min, mass calc. for C₁₇H₁₀F₅N₃O₂ 383.07, m/z found 401.9[M+H₂O+1]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.69 - 7.57 (m, 2H), 7.54 - 7.46 (m, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.02 (ddd, J = 2.4, 5.8, 8.2 Hz, 1H), 6.86 - 6.59 (m, 1H).

Step 3: 2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol

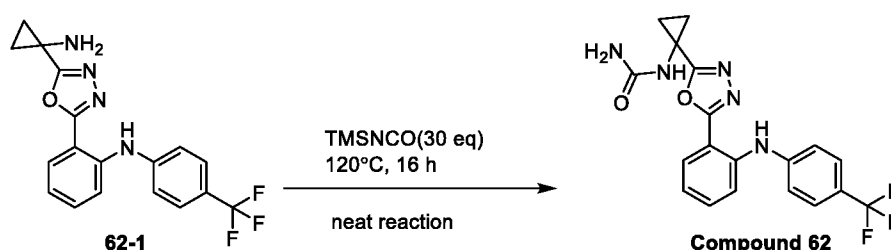
[00332] To a solution of compound **60-3** (20 mg, 52.2 μmol , 1 *eq*) in MeOH (1 mL) at 20 °C was added LiBH_4 (1.7 mg, 78.3 μmol , 1.5 *eq*), and the mixture was stirred at 20 °C for 16 h. TLC (PE:EA = 2:1, UV) showed starting material was consumed completely and one new spot was formed. LCMS showed starting material was consumed completely and 97% of desired product was formed. The reaction mixture was quenched with water (0.5 mL) at 20 °C, and then diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **Compound 60** (14.63 mg, 38.0 μmol , 72.8% yield). LCMS (ESI): RT = 0.865 min, mass calc. for $\text{C}_{17}\text{H}_{12}\text{F}_5\text{N}_3\text{O}_2$ 385.05, m/z found 385.7[M+1]⁺. ¹H NMR (400 MHz, CDCl_3) δ 9.39 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.43 (t, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.34 - 6.07 (m, 1H), 5.31 - 5.24 (m, 1H), 3.13 (d, *J* = 7.3 Hz, 1H).

Example 59: 4-bromo-2-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 61)



[00333] To a mixture of compound **61-1** (10 mg, 21 μmol , 1 *eq*) and DIPEA (11 mg, 85 μmol , 15 μL , 4 *eq*) in DCM (1 mL) was added Burgess reagent (15.2 mg, 64 μmol , 3 *eq*) in one portion at 10 °C. The mixture was stirred at 25 °C for 1 h. LCMS showed 65% of compound **61-1** was remained and 26% of desired product was detected. Then the mixture was continuously stirred at 25 °C for 16 h. TLC (Petroleum ether:Ethyl acetate = 2:1 UV) showed no compound **61-1** was remained and one main new spot was detected. The mixture was purified by prep-TLC to give **Compound 61** (5.84 mg, 13 μmol , 58.9% yield). MS (ESI): mass calc. for $\text{C}_{16}\text{H}_8\text{BrF}_6\text{N}_3\text{O}$ 450.98, m/z found 453.9721 [M+1]⁺. ¹H NMR (400 MHz, CDCl_3) δ 9.28 (s, 1H), 8.04 (d, *J* = 2.3 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.53 (dd, *J* = 2.3, 9.1 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 3H).

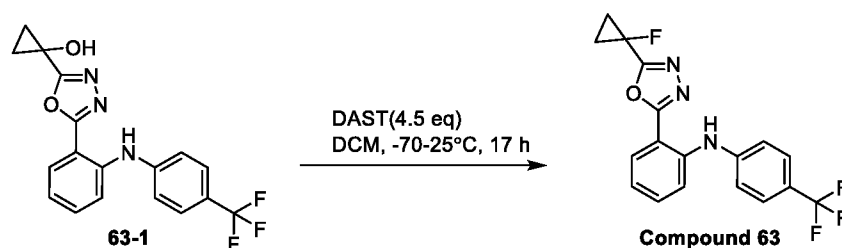
Example 60: 1-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)urea (Compound 62)



[00334] A mixture of **62-1** (100 mg, 0.21 mmol, 1 *eq*, TFA) and isocyanato(trimethyl)silane (728.6 mg, 6.32 mmol, 0.8 mL, 30 *eq*) was stirred at 120 °C for 16 h. LCMS showed no starting material was remained and 67% of desired product was detected. The mixture was quenched with diluted with DCM (50 mL), washed with brine (15 mL), dried by anhydrous Na₂SO₄, filtered and concentrated at 10 °C to give a residue. The residue was purified by prep-HPLC to give

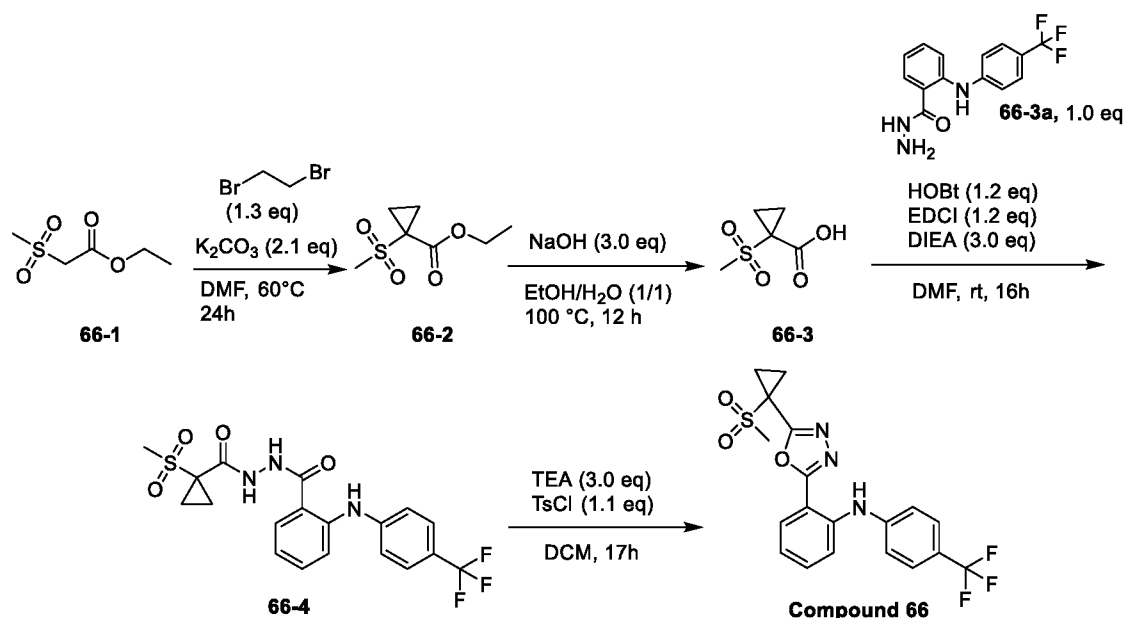
Compound 62 (11.85 mg, 29.13 μ mol, 13.82% yield). LCMS (ESI): RT = 0.882 min, mass calc. for C₁₉H₁₆F₃N₅O₂ 403.13, m/z found 404.1[M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.18 (s, 1H), 7.85 (d, *J* = 7.1 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.58 - 7.48 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.19 - 7.06 (m, 2H), 5.77 (s, 2H), 1.58 - 1.43 (m, 2H), 1.37 - 1.22 (m, 2H).

Example 61: 2-(5-(1-fluorocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 63)



[00335] To a mixture of **63-1** (5 mg, 14 μ mol, 1 *eq*) in DCM (1 mL) was added DAST (3.3 mg, 21 μ mol, 3 μ L, 1.5 *eq*) in one portion at -70 °C. The mixture was stirred at 25 °C for 1 h. LCMS showed 78% of starting material was remained and no desired product was detected. Then another batch of DAST (6.7 mg, 41 μ mol, 5 μ L, 3 *eq*) was added and the mixture was continuously stirred at 25 °C for 16 h. LCMS showed the starting material was consumed completely and 52% of desired product was formed. TLC (Petroleum ether:Ethyl acetate = 2:1 UV) the starting material was consumed completely and two main new spots were formed. The mixture was purified directly by prep-TLC to give **Compound 63** (4.2 mg, 11 μ mol, 80.6% yield). LCMS (ESI): RT = 1.064 min, mass calc. for C₁₈H₁₃F₄N₃O 363.10, m/z found 364.1 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆+CD₃OD) δ 7.92 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.57 - 7.49 (m, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 1.78 - 1.63 (m, 2H), 1.51 - 1.41 (m, 2H).

Example 62: 2-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline (Compound 66)



Step 1: ethyl 1-methylsulfonylcyclopropanecarboxylate

[00336] To a solution of compound **66-1** (1 g, 6 mmol, 1 eq) in DMF (10 mL) were added 1,2-dibromoethane (1.5 g, 8.4 mmol, 0.6 mL, 1.4 eq) and K_2CO_3 (1.6 g, 12 mmol, 2 eq). The reaction was heated at 60 °C for 24 hr. TLC (EA:PE = 1:5, $KMnO_4$) showed that starting material was consumed completely. The reaction was diluted with EA (50 mL) and washed with brine (2*20 mL). The organic layer was dried over Na_2SO_4 and concentrated. Compound **66-2** (0.8 g, crude) was used for next step directly. ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 - 4.15 (m, 2H), 3.22 (s, 3H), 1.85 - 1.70 (m, 2H), 1.70 - 1.60 (m, 2H), 1.35 - 1.20 (m, 3H).

Step 2: 1-methylsulfonylcyclopropanecarboxylic acid

[00337] To a solution of compound **66-2** (0.8 g, 3.1 mmol, 1 eq) in EtOH (10 mL) and H₂O (10 mL) was added NaOH (374.5 mg, 9.3 mmol, 3 eq). The reaction was heated at 100 °C for 12 hr. The reaction was concentrated. The residue was adjusted pH to 5 with 1 N. aq. HCl and extracted with EA (3*15 mL). The organic layer was dried over Na_2SO_4 and concentrated. Compound **66-3** (0.3 g, 1.8 mmol, 58% yield) was used for next step directly. ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (br, 1H), 3.23 (s, 3H), 1.95 - 1.80 (m, 2H), 1.80 - 1.70 (m, 2H).

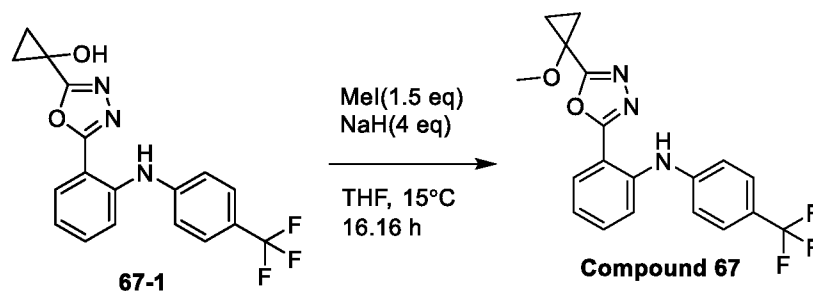
Step 3: N'-(1-methylsulfonylcyclopropanecarbonyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00338] To a mixture of compound **66-3** (0.1 g, 0.6 mmol, 1 eq), HOBt (98 mg, 0.7 mmol, 1.2 eq) and EDCI (140 mg, 0.7 mmol, 1.2 eq) in DMF (4 mL) was added compound **66-3a** (179 mg, 0.6 mmol, 1 eq) followed by DIEA (236 mg, 1.8 mmol, 0.3 mL, 3 eq). The reaction was stirred at 20 °C for 16 hr. LCMS showed that 28% of desired product was detected. The reaction was concentrated. The crude product was purified by prep-HPLC to give compound **66-4** (30 mg, 67 μ mol, 11% yield).

Step 4: 2-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

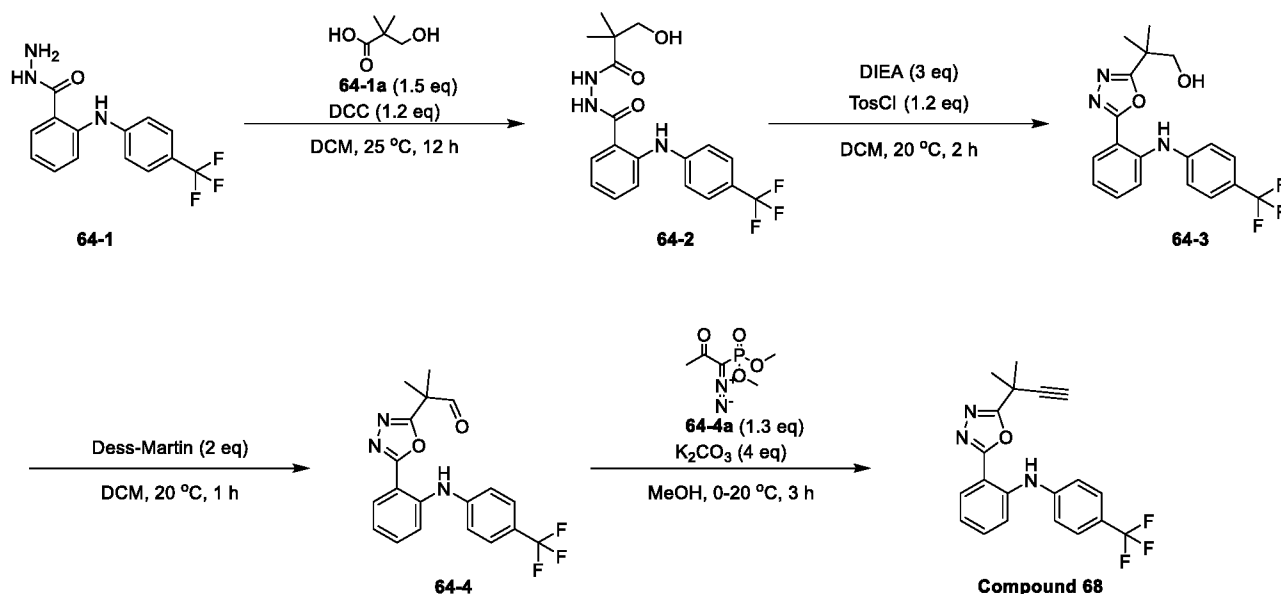
[00339] To a solution of compound **66-4** (30 mg, 67 μ mol, 1 *eq*) and TsCl (14 mg, 74 μ mol, 1.1 *eq*) in DCM (1 mL) was added Et₃N (20.6 mg, 0.2 mmol, 28 μ L, 3 *eq*). The reaction was stirred at 20 °C for 16 hr. LCMS showed that 27% of starting material was remained and 29% of desired product was detected. Additional of TsCl (14 mg) was added. The reaction was stirred at 20 °C for 1 hr. LCMS showed that 29% of desired product was detected. The reaction was diluted with DCM (15 mL) and washed with water (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 66** (2.01 mg, 4.7 μ mol, 6.9% yield). LCMS (ESI): RT = 0.862 min, mass calc. for: C₁₉H₁₆F₃N₃O₃S 423.09, m/z found 423.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.13 (s, 1H), 7.97 (d, *J* = 8.03 Hz, 1H), 7.63 (d, *J* = 8.53 Hz, 2H), 7.58 (d, *J* = 3.01 Hz, 2H), 7.33 (d, *J* = 8.53 Hz, 2H), 7.18 (ddd, *J* = 7.91, 4.89, 3.26 Hz, 1H), 3.32 (s, 3H), 1.83 - 1.90 (m, 2H), 1.76 - 1.82 (m, 2H).

Example 63: 2-(5-(1-methoxycyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 67)



[00340] To a mixture of **67-1** (17 mg, 47 μ mol, 1 *eq*) in THF (2 mL) was added NaH (7.5 mg, 0.19 mmol, 60% purity, 4 *eq*) in one portion at 15 °C. After stirring for 10 min, a solution of MeI (10 mg, 70.6 μ mol, 4 μ L, 1.5 *eq*) in THF (1 mL) was added and then the mixture was stirred at 15 °C for 16 h. LCMS showed no starting material was remained and 85% of desired product was detected. The mixture was diluted with EA (50 mL), washed with brine (10 mL*2), dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 67** (2.48 mg, 6.6 μ mol, 14.0% yield). LCMS (ESI): RT = 1.050 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.34, m/z found 376.1 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (br s, 1H), 7.92 (br d, *J* = 8.0 Hz, 1H), 7.67 - 7.46 (m, 4H), 7.29 (br d, *J* = 8.3 Hz, 2H), 7.16 (br s, 1H), 3.43 (s, 3H), 1.44 - 1.25 (m, 4H).

Example 64: 2-(5-(2-methylbut-3-yn-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 68)



Step 1: N'-(3-hydroxy-2,2-dimethyl-propanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide [00341] To a solution of **64-1** (50 mg, 0.17 mmol, 1 *eq*) and **64-1a** (30.0 mg, 0.25 mmol, 1.5 *eq*) in DCM (1 mL) was added DCC (41.9 mg, 0.20 mmol, 41 μ L, 1.2 *eq*). The mixture was stirred at 25 °C for 12 h. The mixture was diluted with H₂O (10 mL), extracted with EA (20 mL *3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **64-2** (60 mg, 0.15 mmol, 89.6% yield).

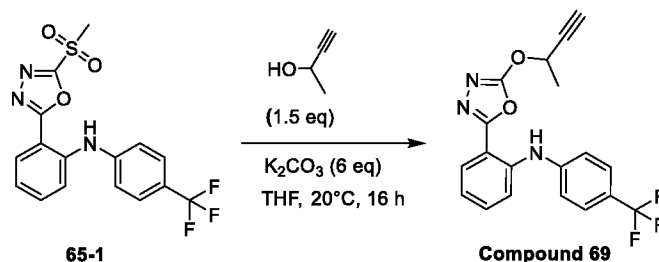
Step 2: 2-methyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]propan-1-ol [00342] To a solution of **64-2** (60 mg, 0.15 mmol, 1 *eq*) in DCM (1 mL) were added TosCl (34.7 mg, 0.18 mmol, 1.2 *eq*) and DIEA (58.8 mg, 0.46 mmol, 79 μ L, 3 *eq*). The mixture was stirred at 20 °C for 2 h. The mixture was diluted with H₂O (10 mL), extracted with EA (20 mL * 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **64-3** (30 mg, 79.5 μ mol, 52.4% yield).

Step 3: 2-methyl-2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]propanal [00343] To a mixture of **64-3** (20 mg, 53.0 μ mol, 1 *eq*) in DCM (0.5 mL) was added Dess-Martin (45.0 mg, 0.11 mmol, 33 μ L, 2 *eq*). The mixture was stirred at 20 °C for 1 h. The mixture was diluted with NaS₂O₃ (8 mL), extracted with DCM (15 mL * 2). The combined organic layers were washed with NaHCO₃ (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **64-4** (15 mg, 34.8 μ mol, 65.6% yield).

Step 4: 2-(5-(2-methylbut-3-yn-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

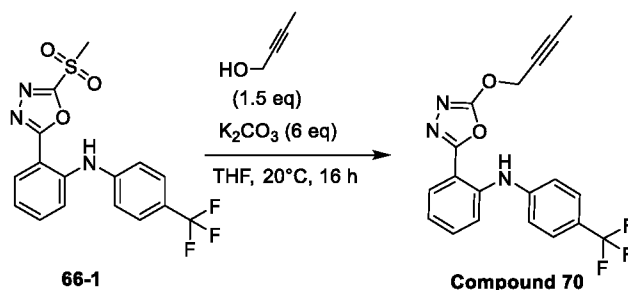
[00344] To a mixture of **64-4** (10 mg, 26.6 μmol , 1 *eq*) and **64-4a** (6.7 mg, 34.6 μmol , 1.3 *eq*) in MeOH (0.5 mL) was added K_2CO_3 (14.7 mg, 0.11 mmol, 4 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 h. Then the mixture was stirred at 20 °C for 1 h. The mixture was concentrated. The residue was diluted with H_2O (5 mL), extracted with EA (10 mL * 3). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was checked by HPLC. The residue was purified by prep-HPLC to give **Compound 68** (3.1 mg, 8.2 μmol , 30.8% yield). LCMS (ESI): RT = 1.072 min, mass calc. for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_3\text{O}$ 371.12, m/z found 372.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.54 (s, 1H), 7.94 (dd, $J = 1.3, 7.9$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.5$ Hz, 1H), 7.45 - 7.32 (m, 3H), 6.99 (t, $J = 7.6$ Hz, 1H), 2.40 (s, 1H), 1.82 (s, 6H).

Example 65: 2-(5-(but-3-yn-2-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 69)



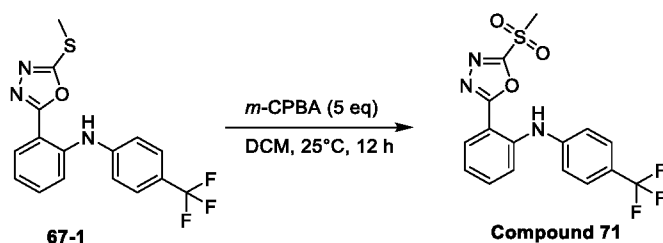
[00345] To a solution of but-3-yn-2-ol (8.2 mg, 0.12 mmol, 9 μL , 1.5 *eq*) in THF (1 mL) was added K_2CO_3 (64.9 mg, 0.47 mmol, 6 *eq*) and compound **65-1** (30 mg, 78 μmol , 1 *eq*) at 20 °C. The mixture was stirred at 20 °C for 16 hr. The reaction mixture was concentrated to give a residue which was purified by prep-HPLC to give **Compound 69** (10 mg, 25 μmol , 32.2% yield). LCMS (ESI): RT = 1.058 min, mass calc. for $\text{C}_{19}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$ 373.3, m/z found 374.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.36 (s, 1H), 7.77 (dd, $J = 1.4, 8.0$ Hz, 1H), 7.57 (d, $J = 8.5$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.40 - 7.36 (m, 1H), 7.34 (d, $J = 8.5$ Hz, 2H), 6.96 (t, $J = 7.5$ Hz, 1H), 5.65 - 5.59 (m, 1H), 2.68 (d, $J = 2.1$ Hz, 1H), 1.81 (d, $J = 6.6$ Hz, 3H).

Example 66: 2-(5-(but-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 70)



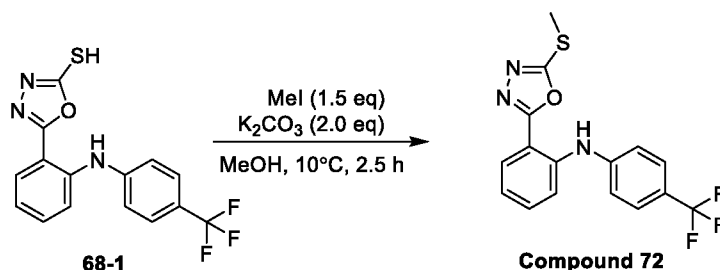
[00346] To a solution of but-2-yn-1-ol (13.7 mg, 0.20 mmol, 15 μ L, 1.5 *eq*) in THF (1 mL) was added K_2CO_3 (108.2 mg, 0.78 mmol, 6 *eq*) and compound **66-1** (50 mg, 0.13 mmol, 1 *eq*) at 20 °C. The mixture was stirred at 20 °C for 16 hr. The reaction mixture was concentrated to give a residue which was purified by prep-HPLC to give **Compound 70** (10 mg, 26 μ mol, 19.7% yield). LCMS (ESI): RT = 1.082 min, mass calc. for $C_{19}H_{14}F_3N_3O_2$ 373.3, m/z found 374.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.80 (dd, J = 1.3, 7.9 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.50 - 7.47 (m, 1H), 7.40 (dt, J = 1.4, 7.8 Hz, 1H), 7.30 (s, 2H), 7.02 - 6.97 (m, 1H), 5.43 (q, J = 3.3 Hz, 2H), 2.27 (t, J = 3.3 Hz, 3H).

Example 67: 2-(5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 71)



[00347] To a solution of compound **67-1** (50.0 mg, 0.14 mmol, 1 *eq*) in DCM (4 mL) was added *m*-CPBA (144.5 mg, 0.71 mmol, 85% purity, 5 *eq*) at 25°C. The mixture was stirred at 25°C for 12 hr. The mixture was diluted with H_2O (5 mL). The mixture was extracted with EA (10 mL*3). The organic layer was dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 71** (12.9 mg, 33.4 μ mol, 23.5% yield). LCMS (ESI): RT = 0.975 min, mass calc. for $C_{16}H_{12}F_3N_3O_3S$ 383.06, m/z found 384.0 $[M+H]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.01 (s, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.67 - 7.59 (m, 4H), 7.34 (br d, J = 8.4 Hz, 2H), 7.21 (br t, J = 7.1 Hz, 1H), 3.68 (s, 3H).

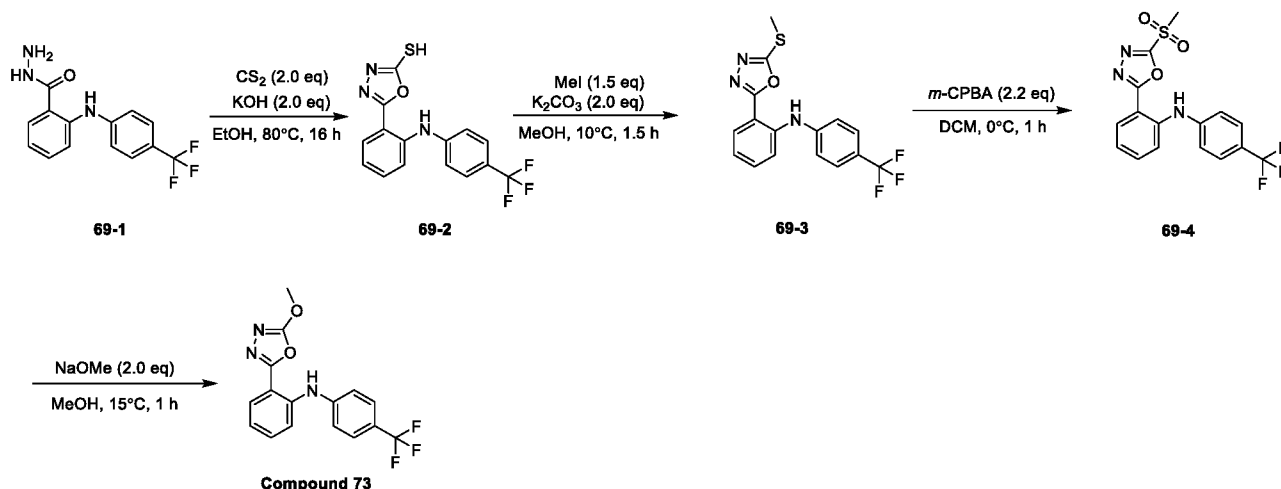
Example 68: 2-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 72)



[00348] To a solution of compound **68-1** (50.0 mg, 0.15 mmol, 1 *eq*) in MeOH (1 mL) was added K_2CO_3 (41.0 mg, 0.30 mmol, 2 *eq*). The mixture was stirred at 10°C for 0.5 hr. MeI (31.6 mg, 0.22 mmol, 14 μ L, 1.5 *eq*) was added. The mixture was stirred at 10°C for 2 hr. The mixture was diluted with H_2O (5 mL). The mixture was extracted with EA (5 mL*3). The organic layer was dried over

Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by *prep*-HPLC to give **Compound 72** (33.1 mg, 93.4 μ mol, 63.0% yield). LCMS (ESI): RT = 1.065 min, mass calc. for C₁₆H₁₂F₃N₃OS 351.07, m/z found 352.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.40 (s, 1H), 7.85 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.42 - 7.34 (m, 3H), 7.00 - 6.94 (m, 1H), 2.80 (s, 3H)

Example 69: 2-(5-methoxy-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 73)



Step 1: 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-thiol

[00349] To a solution of compound **69-1** (1.00 g, 3.39 mmol, 1 *eq*) and KOH (380.0 mg, 6.77 mmol, 2 *eq*) in EtOH (10 mL) was added CS₂ (515.8 mg, 6.77 mmol, 0.41 mL, 2 *eq*). The mixture was stirred at 80°C for 16 hr. The mixture was concentrated. 1 N HCl was added to the residue until pH = 6 -7. The mixture was extracted with EA (15 mL*3). The organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography to give compound **69-2** (700.0 mg, 2.08 mmol, 61.3% yield).

Step 2: 2-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00350] To a solution of compound **69-2** (650.0 mg, 1.93 mmol, 1 *eq*) in MeOH (10 mL) was added K₂CO₃ (532.6 mg, 3.85 mmol, 2 *eq*). The mixture was stirred at 10°C for 0.5 hr. MeI (410.3 mg, 2.89 mmol, 0.18 mL, 1.5 *eq*) was added. The mixture was stirred at 10°C for 1 hr. The mixture was concentrated. The residue was diluted with H₂O (10 mL). The mixture was extracted with EA (15 mL*3). The organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **69-3** (500.0 mg, crude).

Step 3: 2-(5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

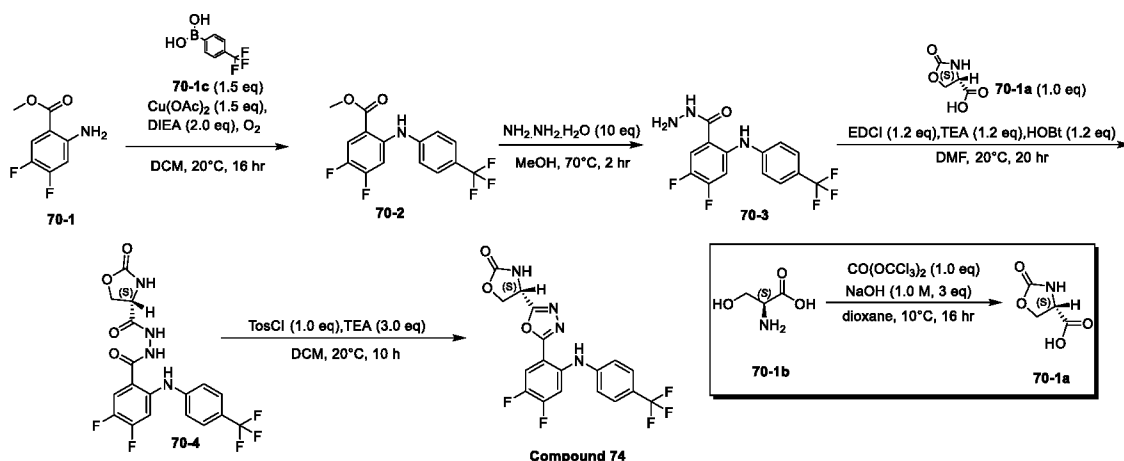
[00351] To a solution of compound **69-3** (50.0 mg, 0.14 mmol, 1 *eq*) in DCM (2 mL) was added *m*-CPBA (63.6 mg, 0.31 mmol, 85% purity, 2.2 *eq*) at 0°C. The mixture was stirred at 0°C for 1 hr.

The mixture was diluted with H₂O (5 mL). The mixture was extracted with EA (10 mL*3). The organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography to give compound **69-4** (35.0 mg, 54.8 μ mol, 38.5% yield).

Step 4: 2-(5-methoxy-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00352] To a solution of compound **69-4** (35.0 mg, 54.8 μ mol, 1 *eq*) in MeOH (1 mL) was added NaOMe (5.9 mg, 0.11 mmol, 2 *eq*). The mixture was stirred at 15°C for 1 hr. The mixture was diluted with H₂O (5 mL). The mixture was extracted with EA (10 mL*3). The organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by *prep*-HPLC to give **Compound 73** (8.4 mg, 25.1 μ mol, 45.7% yield). LCMS (ESI): RT = 1.018 min, mass calc. for C₁₆H₁₂F₃N₃O₂ 335.09, m/z found 336.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.35 (br s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.58 (br d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.40 - 7.32 (m, 3H), 6.96 (t, *J* = 7.5 Hz, 1H), 4.27 (s, 3H).

Example 70: (S)-4-(5-(4,5-difluoro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 74)



Step 1: methyl 4,5-difluoro-2-[4-(trifluoromethyl)anilino]benzoate

[00353] To a solution of **70-1** (1.00 g, 5.34 mmol, 1 *eq*) and **70-1c** (1.50 g, 8.02 mmol, 1.5 *eq*) in DCM (15 mL) were added Cu(OAc)₂ (1.40 g, 8.02 mmol, 1.5 *eq*) and DIEA (1.30 g, 10.69 mmol, 1.8 mL, 2 *eq*). The mixture was degassed, purged with O₂ for 3 times and stirred at 20°C for 16 hr. The mixture was concentrated. The residue was dissolved in EA (10 mL) and washed with H₂O (3 mL *3). The combined organic layers were washed with brine (3 mL *3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give **70-2** (650.0 mg, 1.96 mmol, 36.7% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.61 (br s, 1H), 7.79 (dd, *J* = 9.0, 11.1 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.10 (dd, *J* = 6.9, 12.8 Hz, 1H), 3.92 - 3.88 (m, 3H)

Step 2: 4,5-difluoro-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00354] To a solution of compound **70-2** (650.0 mg, 1.96 mmol, 1.0 *eq*) in MeOH (10 mL) was added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (1.16 g, 19.62 mmol, 1.1 mL, 10 *eq*). The mixture was stirred at 70°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (15 mL), washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography to give **70-3** (470.0 mg, 1.42 mmol, 72.3% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.91 (s, 1H), 9.71 (s, 1H), 7.68 (dd, $J = 8.9$, 11.3 Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.47 - 7.39 (m, 1H), 7.28 (d, $J = 8.5$ Hz, 2H), 4.55 (br s, 2H)

Step 3: (4S)-2-oxooxazolidine-4-carboxylic acid

[00355] To a solution of NaOH (1 M, 14.2 mL, 3 *eq*) was added compound **70-1b** (500.0 mg, 4.76 mmol, 1 *eq*) at 10°C, followed by addition of a solution of bis(trichloromethyl) carbonate (1.40 g, 4.76 mmol, 1 *eq*) in dioxane (6 mL). The solution was stirred at 10°C for 16 hr. The reaction was concentrated in vacuum. Then the residue was diluted with MeCN (20 mL), filtered and the filtrate was concentrated in vacuum to give **70-1a** (600.0 mg, crude), which was used for the next step directly. ^1H NMR confirmed that compound. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.15 (s, 1H), 4.51 - 4.43 (m, 1H), 4.36 - 4.31 (m, 1H), 4.27 (dd, $J = 4.1$, 8.4 Hz, 1H).

Step 4: (4S)-N'-[4,5-difluoro-2-[4-(trifluoromethyl)anilino]benzoyl]-2-oxo-oxazolidine-4-carbohydrazide

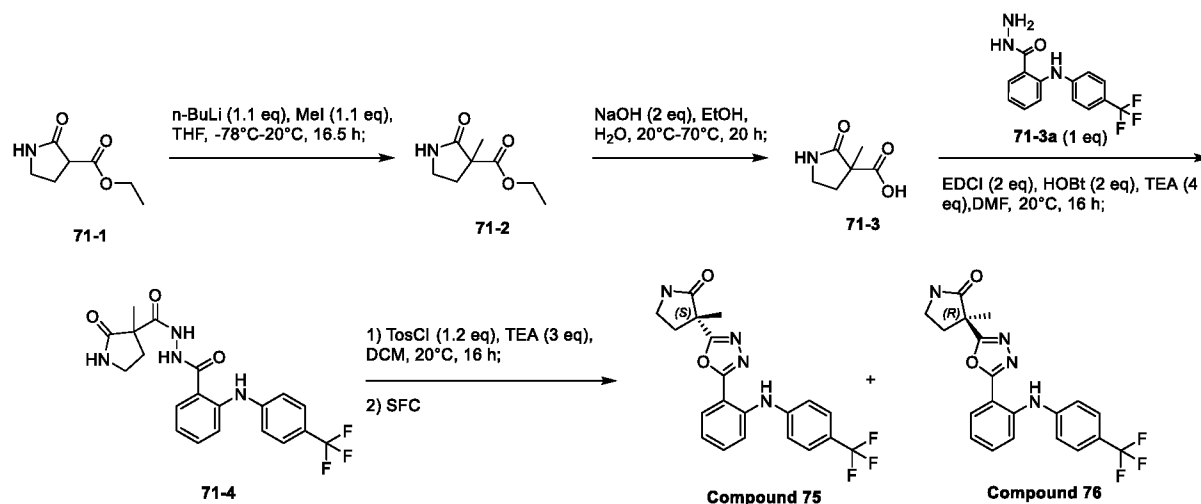
[00356] To a solution of **70-1a** (65.9 mg, 0.50 mmol, 1 *eq*), EDCI (115.7 mg, 0.60 mmol, 1.2 *eq*) and HOBt (81.5 mg, 0.60 mmol, 1.2 *eq*) in DMF (2 mL) were added **70-3** (200.0 mg, 0.60 mmol, 1.2 *eq*) and TEA (61.1 mg, 0.60 mmol, 84 μL , 1.2 *eq*) at 20°C. The mixture was stirred at 20°C for 20 hr. The solution was diluted with H_2O (2 mL) and extracted with EA (4 mL * 3). Then the combined organic layers were washed with brine (4 mL * 3) and H_2O (4 mL * 3). Finally, the organic layer was dried by Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was triturated with DCM (5 mL) to give **70-4** (80.0 mg, crude). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.84 - 10.61 (m, 1H), 10.49 (br s, 1H), 9.50 (br s, 1H), 8.15 (s, 1H), 7.88 - 7.76 (m, 1H), 7.60 (d, $J = 8.5$ Hz, 2H), 7.53 - 7.40 (m, 1H), 7.31 (br d, $J = 8.4$ Hz, 2H), 4.60 - 4.51 (m, 1H), 4.48 - 4.40 (m, 1H), 4.22 (dd, $J = 4.3$, 8.3 Hz, 1H)

Step 5: (S)-4-(5-(4,5-difluoro-2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one

[00357] To a solution of **70-4** (70.0 mg, 0.16 mmol, 1.0 *eq*) in DCM (1 mL) were added TosCl (30.0 mg, 0.16 mmol, 1.0 *eq*) and TEA (47.8 mg, 0.47 mmol, 65 μL , 3.0 *eq*), the solution was stirred at 20°C for 10 hr. The solution was diluted with H_2O (1 mL) and extracted with EA (1 mL * 3). Then the combined organic layers were washed with brine (1 mL * 3) and H_2O (1 mL * 3). Finally, the organic layer was dried by Na_2SO_4 , filtered and concentrated under reduced pressure to

give a residue. The residue was purified by prep-HPLC. Then the product was purified by column chromatography. LCMS, MS and ^1H NMR confirmed that **Compound 74** (3.39 mg, 7.1 μmol , 4.5% yield) was obtained. LCMS (ESI): RT = 1.041 min, mass calc. for $\text{C}_{18}\text{H}_{11}\text{F}_5\text{N}_4\text{O}_3$ 426.08, m/z found 427.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.33 (s, 1H), 7.69 (dd, J = 8.4, 10.3 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.23 (dd, J = 6.8, 12.5 Hz, 1H), 6.19 (s, 1H), 5.39 - 5.30 (m, 1H), 4.91 - 4.85 (m, 1H), 4.82 - 4.77 (m, 1H).

Example 71: (S)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (Compound 75) and (R)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (Compound 76)



Step 1: ethyl 3-methyl-2-oxopyrrolidine-3-carboxylate

[00358] To a solution of **71-1** (800 mg, 5.09 mmol, 1 eq) in THF (10 mL) at -78°C was added $n\text{-BuLi}$ (2.5 M, 2.24 mL, 1.1 eq) and the mixture was stirred at -78°C for 0.5 h. And then MeI (794.7 mg, 5.60 mmol, 0.35 mL, 1.1 eq) was added into the above mixture at -78°C , and the mixture was stirred at 20°C for 16 h. The reaction mixture was quenched with saturated NH_4Cl (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **71-2** (720 mg, 3.79 mmol, 74.4% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.16 (brs, 1H), 4.21 (dq, J = 1.8, 7.1 Hz, 2H), 3.54 - 3.42 (m, 1H), 3.40 - 3.30 (m, 1H), 2.69 - 2.59 (m, 1H), 2.04 (ddd, J = 7.0, 8.4, 13.0 Hz, 1H), 1.46 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H).

Step 2: 3-methyl-2-oxopyrrolidine-3-carboxylic acid

[00359] To a solution of **71-2** (350 mg, 2.04 mmol, 1 eq) in EtOH (2 mL) at 20°C was added NaOH (2 M, 2.04 mL, 2 eq) and the mixture was stirred at 20°C for 16 h, and then stirred at 70°C for 4 h. The reaction mixture was concentrated to remove EtOH . The residue was diluted with water (20 mL), acidified with 2 N HCl to pH = 1-2, and then extracted with EA (20 mL *3). The

combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 30 mg sample. The liquid layer was lyophilized to give a residue, which was dissolved in MeOH and then filtered to remove the precipitate. The filtrate was concentrated to give 350 mg sample. The above two batches were combined to give **71-3** (380 mg, 1.86 mmol, 90.9% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 (brs, 1H), 3.25 - 3.18 (m, 2H), 2.43 - 2.38 (m, 1H), 1.92 - 1.84 (m, 1H), 1.19 (s, 3H).

Step 3: 3-methyl-2-oxo-*N'*-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)pyrrolidine-3-carbohydrazide

[00360] To a solution of **71-3a** (220 mg, 0.75 mmol, 1 *eq*), **71-3** (304.7 mg, 1.49 mmol, 2 *eq*), EDCI (285.7 mg, 1.49 mmol, 2 *eq*) and HOBt (201.4 mg, 1.49 mmol, 2 *eq*) in DMF (5 mL) at 20°C was added TEA (301.6 mg, 2.98 mmol, 0.41 mL, 4 *eq*), and the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated to remove DMF. The residue was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **71-4** (400 mg, 0.67 mmol, 89.4% yield), which was used directly for next step. LCMS (ESI): RT = 0.987 min, mass calc. for C₂₀H₁₉F₃N₄O₃ 420.14, m/z found 442.9 [M+Na]⁺.

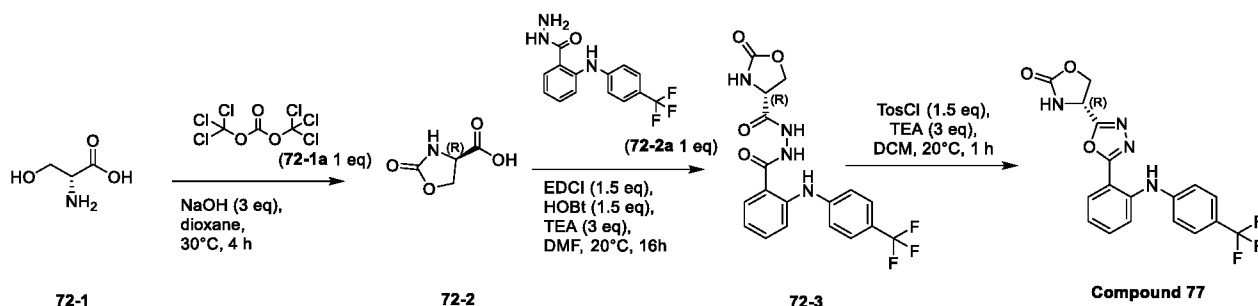
Step 4: (S)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (Compound 75) and (R)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one (Compound 76)

[00361] To a solution of **71-4** (400 mg, 0.67 mmol, 1 *eq*) and TEA (202.2 mg, 2.00 mmol, 0.28 mL, 3 *eq*) in DCM (5 mL) at 20°C was added TosCl (152.4 mg, 0.80 mmol, 1.2 *eq*), and the mixture was stirred at 20°C for 16 h. The mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 170 mg of desired product as a mixture (R/S isomers = 1:1 ratio) by LCMS and SFC. The 100 mg of desired product as a mixture (R/S, from the above 170 mg batch) was purified further by SFC to give **Compound 75** (24.7 mg, 61.5 umol, 9.2% yield, 99.8% ee) and **Compound 76** (19.3 mg, 47.5 umol, 7.1% yield, 99.8% ee).

Compound 75: LCMS (ESI): RT = 0.944 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 402.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.48 (brs, 1H), 7.92 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.40 (dt, *J* = 1.5, 7.9 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.93 (m, 1H), 5.94 (brs, 1H), 3.72 - 3.63 (m, 1H), 3.53 (dt, *J* = 4.8, 8.8 Hz, 1H), 3.03 (ddd, *J* = 4.8, 7.9, 12.9 Hz, 1H), 2.39 - 2.30 (m, 1H), 1.80 (s, 3H). **Compound 76:** LCMS (ESI): RT = 0.942 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 402.9 [M+H]⁺; ¹H NMR (400

MHz, CDCl₃) δ 9.48 (s, 1H), 7.92 (dd, J = 1.4, 8.0 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.39 (dt, J = 1.5, 7.9 Hz, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.01 - 6.93 (m, 1H), 6.37 (br s, 1H), 3.71 - 3.62 (m, 1H), 3.53 (dt, J = 5.0, 8.8 Hz, 1H), 3.01 (ddd, J = 4.9, 7.9, 12.9 Hz, 1H), 2.33 (ddd, J = 6.3, 7.8, 13.2 Hz, 1H), 1.79 (s, 3H).

Example 72: (R)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 77)



Step 1: (R)-2-oxooxazolidine-4-carboxylic acid

[00362] To a solution of NaOH (1 M, 11.43 mL, 3 eq) was added **72-1** at 30°C, followed by addition of a solution **72-1a** (1.1 g, 3.81 mmol, 1 eq) in dioxane (4 mL) along with gas evolved. After stirring for 2 h, the mixture was clear, then the mixture was stirred for another 2 hr at 30°C. The reaction mixture was concentrated under reduced pressure and then extracted with hot acetonitrile (150 mL). The mixture was filtered and concentrated under reduced pressure to give **72-2** (260 mg, 1.79 mmol, 46.9% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (brs, 1H), 4.36 - 4.31 (m, 2H), 4.27 (brdd, J = 3.3, 8.3 Hz, 1H).

Step 2: (R)-2-oxo-N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazolidine-4-carbohydrazide

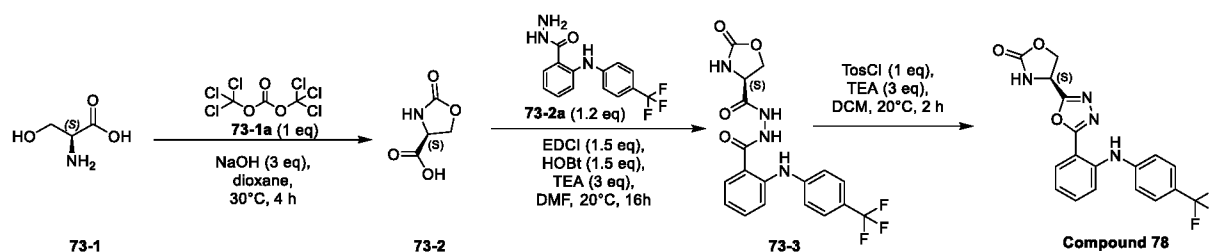
[00363] To a solution of **72-2**, EDCI (288.8 mg, 1.51 mmol, 1.5 eq) and HOBt (203.6 mg, 1.51 mmol, 1.5 eq) in DMF (2 mL) at 20°C were added **72-2a** (296.6 mg, 1.00 mmol, 1 eq) and TEA (304.9 mg, 3.01 mmol, 0.42 mL, 3 eq). The mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **72-3** (330 mg, 0.59 mmol, 58.7% yield). LCMS (ESI): RT = 0.782 min, mass calc. for C₁₈H₁₅F₃N₄O₄ 408.33, *m/z* found 408.9 [M+H]⁺.

Step 3: (R)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one

[00364] To a solution of **72-3** (300 mg, 0.73 mmol, 1 eq) in DCM (3 mL) were added TEA (223.0 mg, 2.20 mmol, 0.31 mL, 3 eq) and TosCl (210.1 mg, 1.10 mmol, 1.5 eq). The mixture was stirred at 20°C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue.

The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 77** (60 mg, 0.15 mmol, 20.1% yield). LCMS (ESI): RT = 0.822 min, mass calc. for C₁₈H₁₃F₃N₄O₃ 390.32, m/z found 390.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.90 (brd, *J* = 7.9 Hz, 1H), 7.62 (brd, *J* = 8.1 Hz, 2H), 7.53 - 7.49 (m, 1H), 7.44 (brd, *J* = 7.5 Hz, 1H), 7.36 (brd, *J* = 8.1 Hz, 3H), 6.99 (t, *J* = 7.5 Hz, 1H), 5.42 (brdd, *J* = 4.8, 8.2 Hz, 1H), 4.93 - 4.88 (m, 1H), 4.84 - 4.79 (m, 1H).

Example 73: (S)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one (Compound 78)



Step 1: (S)-2-oxooxazolidine-4-carboxylic acid

[00365] To a solution of NaOH (1 M, 11.43 mL, 3 eq) was added **73-1** at 30°C, followed by addition of a solution **73-1a** (1.1 g, 3.81 mmol, 1 eq) in dioxane (4 mL) along with gas evolved. After stirring for 2 h, the mixture was clear, then the mixture was stirred for another 2 hr at 30°C. The reaction mixture was concentrated under reduced pressure and then extracted with hot acetonitrile (150 mL). The mixture was filtered and concentrated under reduced pressure to give **73-2** (664 mg, 2.76 mmol, 94.0% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (s, 1H), 4.52 - 4.42 (m, 1H), 4.37 - 4.24 (m, 2H).

Step 2: (S)-2-oxo-*N'*-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)oxazolidine-4-carbohydrazide

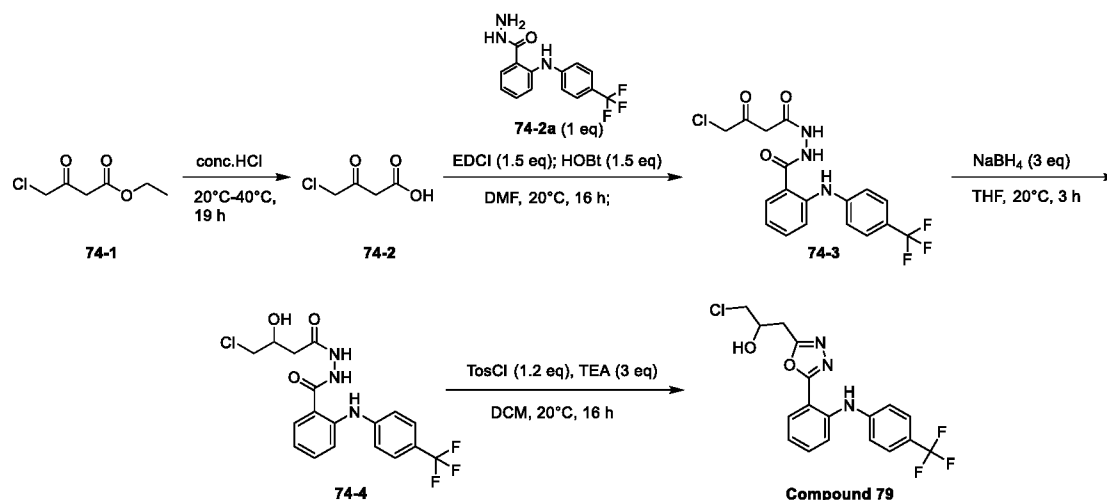
[00366] To a solution of **73-2** (300 mg, 2.29 mmol, 1 eq), EDCI (658.1 mg, 3.43 mmol, 1.5 eq) and HOBT (463.9 mg, 3.43 mmol, 1.5 eq) in DMF (3 mL) at 30°C was added **73-2a** (810.9 mg, 2.75 mmol, 1.2 eq) and TEA (694.8 mg, 6.87 mmol, 1 mL, 3 eq). The mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **73-3** (900 mg, 1.81 mmol, 79% yield). LCMS (ESI): RT = 0.768 min, mass calc. for C₁₈H₁₅F₃N₄O₄ 408.33, m/z found 430.9 [M+Na]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.85 (brs, 1H), 9.58 (s, 1H), 7.95 (s, 2H), 7.55 (s, 3H),

7.44 - 7.42 (m, 2H), 7.23 (s, 2H), 6.99 (s, 1H), 4.52 (br s, 1H), 4.41 (dd, $J = 4.4, 9.2$ Hz, 1H), 4.23 (dd, $J = 4.5, 8.3$ Hz, 1H).

Step 3: (S)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one

[00367] To a solution of **73-3** (100 mg, 0.24 mmol, 1 eq) in DCM (1 mL) were added TEA (74.3 mg, 0.73 mmol, 0.1 mL, 3 eq) and TosCl (46.7 mg, 0.24 mmol, 1 eq). The mixture was stirred at 20°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 78** (20 mg, 0.50 mmol, 20.1% yield). LCMS (ESI): RT = 0.850 min, mass calc. for C₁₈H₁₃F₃N₄O₃ 390.32, m/z found 390.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.33 (brs, 1H), 7.88 (brd, $J = 7.9$ Hz, 1H), 7.60 (brd, $J = 8.3$ Hz, 2H), 7.52 - 7.48 (m, 1H), 7.45 - 7.40 (m, 1H), 7.36 (br d, $J = 8.1$ Hz, 2H), 6.98 (t, $J = 7.5$ Hz, 1H), 5.99 (brs, 1H), 5.35 (br s, 1H), 4.91 - 4.85 (m, 1H), 4.82 - 4.77 (m, 1H).

Example 74: 1-chloro-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol (Compound 79)



Step 1: 4-chloro-3-oxobutanoic acid

[00368] The solution of **74-1** (300 mg, 1.82 mmol, 0.25 mL, 1 eq) in conc. HCl (2 mL) was stirred at 20°C for 16 h, and then stirred at 40°C for another 3 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (10 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **74-2** (190 mg, 1.39 mmol, 76.5% yield), which was used directly for next step. ¹H NMR (400 MHz, CDCl₃) δ 4.24 (s, 2H), 3.76 (s, 2H).

Step 2: N'-(4-chloro-3-oxobutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00369] To a solution of **74-2a** (180 mg, 0.61 mmol, 1 *eq*), **74-2** (99.9 mg, 0.73 mmol, 1.2 *eq*) and HOBt (123.6 mg, 0.91 mmol, 1.5 *eq*) in DMF (1 mL) at 20°C was added EDCI (175.3 mg, 0.91 mmol, 1.5 *eq*), and the mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **74-3** (180 mg, 0.21 mmol, 34.3% yield), which was used directly for next step. LCMS (ESI): RT = 0.981 min, mass calc. for C₁₈H₁₅ClF₃N₃O₃ 413.08, m/z found 435.9 [M+Na]⁺.

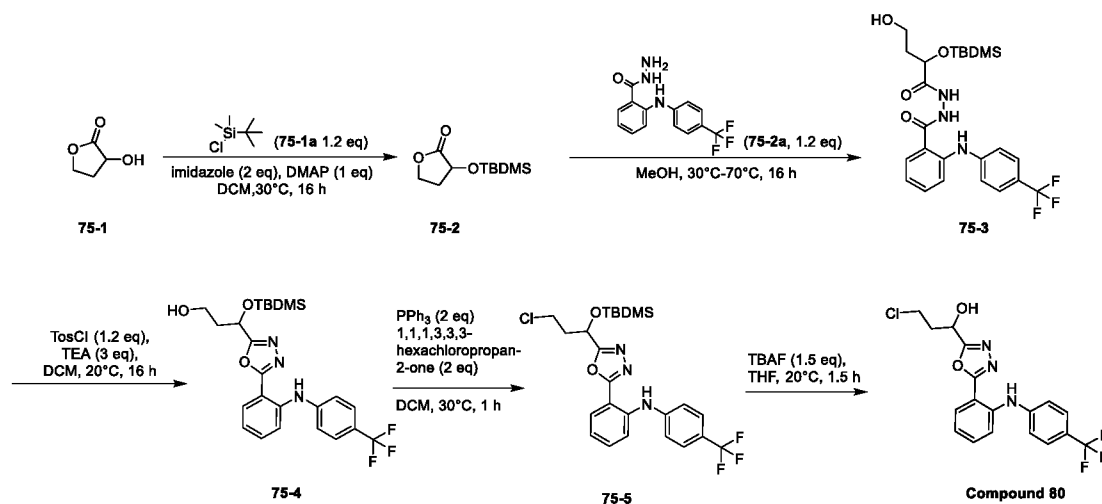
Step 3: N'-(4-chloro-3-hydroxybutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00370] To a solution of **74-3** (160 mg, 0.19 mmol, 1 *eq*) in THF (1 mL) at 20°C was added NaBH₄ (21.1 mg, 0.56 mmol, 3 *eq*), and the mixture was stirred at 20°C for 3 h. The reaction mixture was quenched with water (20 mL) at 20°C, and then extracted with EA (10 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **74-4** (80 mg, 0.13 mmol, 70.5% yield), which was used directly for next step. LCMS (ESI): RT = 0.980 min, mass calc. for C₁₈H₁₇ClF₃N₃O₃ 415.09, m/z found 437.9 [M+Na]⁺.

Step 4: 1-chloro-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol

[00371] To a solution of **74-4** (70 mg, 0.11 mmol, 1 *eq*) and TEA (34.8 mg, 0.34 mmol, 48 uL, 3 *eq*) in DCM (1 mL) at 20°C was added TosCl (26.2 mg, 0.14 mmol, 1.2 *eq*), and the mixture was stirred at 20°C for 16 h. The residue was concentrated to give a residue. The residue was purified by flash silica gel chromatography and prep-HPLC to give **Compound 79** (4.4 mg, 11.1 umol, 9.7% yield). LCMS (ESI): RT = 0.986 min, mass calc. for C₁₈H₁₅ClF₃N₃O₂ 397.08, m/z found 398.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.89 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.95 (m, 1H), 4.49 (br d, *J* = 4.4 Hz, 1H), 3.78 (dd, *J* = 4.0, 5.1 Hz, 2H), 3.35 - 3.21 (m, 2H), 3.06 (d, *J* = 4.8 Hz, 1H).

Example 75: 3-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol (Compound 80)



Step 1: 3-((tert-butyldimethylsilyl)oxy)dihydrofuran-2(3H)-one

[00372] To a solution of **75-1** (300 mg, 2.94 mmol, 0.23 mL, 1 *eq*) in DCM (3 mL) were added imidazole (400.1 mg, 5.88 mmol, 2 *eq*), DMAP (359.0 mg, 2.94 mmol, 1 *eq*) and **75-1a** (531.5 mg, 3.53 mmol, 0.43 mL, 1.2 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL*2), dried over Na₂SO₄, filtered and concentrated under reduced pressure give **75-2** (664 mg, 2.76 mmol, 94.0% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.44 - 4.33 (m, 2H), 4.18 (dt, *J* = 6.4, 9.2 Hz, 1H), 2.50 - 2.42 (m, 1H), 2.21 (qd, *J* = 8.8, 12.6 Hz, 1H), 0.90 (s, 9H), 0.15 (d, *J* = 9.3 Hz, 6H)

Step 2: *N'*-(2-(((*tert*-butyldimethylsilyl)oxy)-4-hydroxybutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00373] To a solution of **75-2** (300 mg, 1.11 mmol, 1 *eq*) in MeOH (3 mL) at 30°C was added **75-2a** (393.0 mg, 1.33 mmol, 1.2 *eq*). The mixture was stirred at 70°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL*2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **75-3** (600 mg, 0.56 mmol, 50.8% yield). LCMS (ESI): RT = 0.906 min, mass calc. for C₂₃H₃₀F₃N₃O₃Si 511.21, m/z found 534.1 [M+Na]⁺.

Step 3: 3-((tert-butyldimethylsilyl)oxy)-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol

[00374] To a solution of **75-3** (600 mg, 1.17 mmol, 1 *eq*) in DCM (7 mL) at 30°C were added TEA (356.0 mg, 3.52 mmol, 0.49 mL, 3 *eq*) and TosCl (268.3 mg, 1.41 mmol, 1.2 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **75-4** (192 mg, 0.23 mmol, 19.9% yield). LCMS (ESI): RT = 1.042 min, mass calc. for C₂₄H₃₀F₃N₃O₃Si 493.59, m/z found 494.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.59 (br

d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 1H), 7.44 - 7.40 (m, 1H), 7.38 (brd, $J = 8.4$ Hz, 2H), 6.99 (t, $J = 7.5$ Hz, 1H), 5.31 (t, $J = 6.3$ Hz, 1H), 4.46 (t, $J = 5.6$ Hz, 1H), 3.89 (brd, $J = 5.1$ Hz, 2H), 3.79 (brd, $J = 4.4$ Hz, 1H), 3.75 (s, 1H), 2.25 (quin, $J = 6.1$ Hz, 2H), 2.12 - 1.89 (m, 2H), 0.93 (s, 13H), 0.19 (s, 3H), 0.09 (s, 4H).

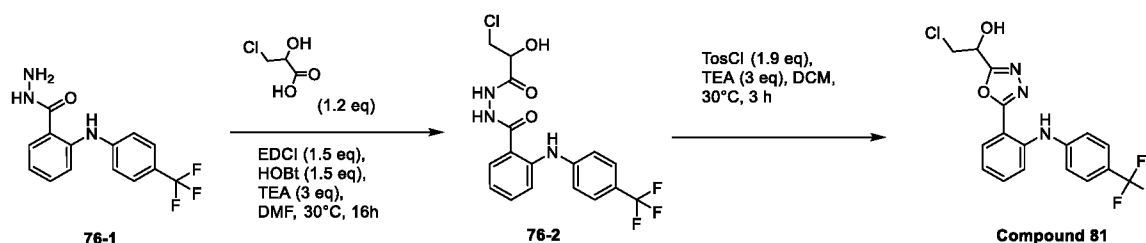
Step 4: 2-(5-(1-((tert-butyldimethylsilyl)oxy)-3-chloropropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00375] To a solution of **75-4** (160 mg, 0.32 mmol, 1 *eq*) and PPh_3 (170.0 mg, 0.65 mmol, 2 *eq*) in DCM (2 mL) at 30°C was added 1, 1, 1, 3, 3, 3-hexachloropropan-2-one (171.6 mg, 0.65 mmol, 98 μL , 2 *eq*). The mixture was stirred at 30°C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give to give **75-5** (120 mg, 0.14 mmol, 43.38% yield). LCMS (ESI): RT = 1.152 min, mass calc. for $\text{C}_{24}\text{H}_{29}\text{ClF}_3\text{N}_3\text{O}_2\text{Si}$ 512.04, m/z found 512.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, $J = 7.8$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.44 - 7.36 (m, 3H), 6.99 (t, $J = 7.5$ Hz, 1H), 5.32 (dd, $J = 4.3, 8.7$ Hz, 1H), 3.84 - 3.76 (m, 2H), 3.75 (s, 1H), 3.70 - 3.64 (m, 1H), 2.50 (tdd, $J = 4.7, 9.1, 14.0$ Hz, 1H), 2.35 (tdd, $J = 4.8, 9.4, 14.3$ Hz, 1H), 2.22 - 2.08 (m, 1H), 0.92 (s, 12H), 0.21 (s, 3H), 0.13 - 0.07 (m, 6H).

Step 5: 3-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol

[00376] To a solution of **75-5** (50 mg, 97 μmol , 1 *eq*) in THF (1 mL) at 30°C was added TBAF (1 M, 0.15 mL, 1.5 *eq*). The mixture was stirred at 30°C for 1.5 h. The reaction mixture was concentrated under reduced pressure to remove solvent and then extracted with petroleum ether (5 mL *2) to give the residue. The residue was diluted with water (5 mL), then acidified with 2N HCl at 30°C to pH = 7, and then extracted with EA (5 mL *3). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 80** (10 mg, 25 μmol , 25.5% yield). LCMS (ESI): RT = 0.910 min, mass calc. for $\text{C}_{18}\text{H}_{15}\text{ClF}_3\text{N}_3\text{O}_2$ 397.78, m/z found 398.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1H), 7.91 (d, $J = 7.9$ Hz, 1H), 7.59 (d, $J = 8.3$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.44 - 7.33 (m, 3H), 6.98 (t, $J = 7.6$ Hz, 1H), 5.40 - 5.31 (m, 1H), 3.95 - 3.87 (m, 1H), 3.84 - 3.76 (m, 1H), 2.98 (brd, $J = 5.4$ Hz, 1H), 2.57 - 2.40 (m, 2H).

Example 76: 2-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 81)



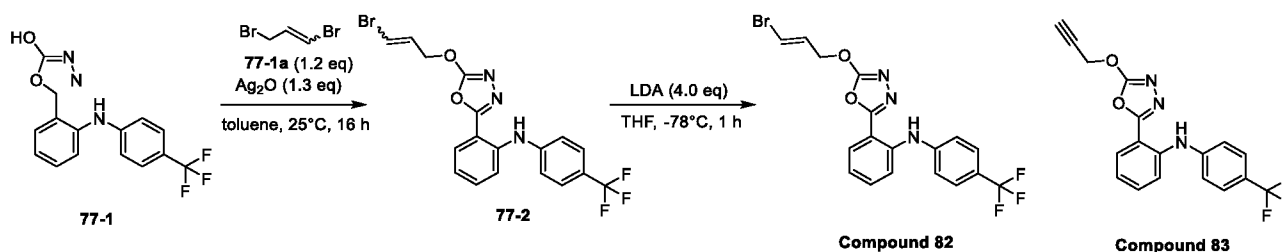
Step 1: 2-((4-(trifluoromethyl) phenyl) amino)benzohydrazide

[00377] To a solution of **76-1a** (101.2 mg, 0.81 mmol, 1.2 *eq*), EDCI (194.8 mg, 1.02 mmol, 1.5 *eq*) and HOBt (137.3 mg, 1.02 mmol, 1.5 *eq*) in DMF (2 mL) at 30°C were added **76-1** (200 mg, 0.68 mmol, 1 *eq*) and TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give to give **76-2** (484 mg, 0.89 mmol, 87.1% yield). LCMS (ESI): RT = 0.755 min, mass calc. for C₁₇H₁₅ClF₃N₃O₃ 401.08, m/z found 401.9 [M+H]⁺

Step 2: 2-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol

[00378] To a solution of **76-2** (262 mg, 0.65 mmol, 1 *eq*) in DCM (3 mL) at 30°C were added TEA (198 mg, 1.96 mmol, 0.27 mL, 3 *eq*) and TosCl (236.2 mg, 1.24 mmol, 1.9 *eq*). The mixture was stirred at 30°C for 3 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography, prep-HPLC and prep-TLC to give **Compound 81** (10 mg, 26 umol, 4.00% yield). **Compound 81**: LCMS (ESI): RT = 0.871 min, mass calc. for C₁₇H₁₃ClF₃N₃O₂ 383.06, m/z found 384.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (brs, 1H), 7.92 (brd, *J* = 7.8 Hz, 1H), 7.60 (brd, *J* = 8.5 Hz, 2H), 7.51 (brd, *J* = 8.0 Hz, 1H), 7.43 (brd, *J* = 8.3 Hz, 1H), 7.37 (brd, *J* = 7.5 Hz, 2H), 6.99 (brt, *J* = 6.9 Hz, 1H), 5.33 (brs, 1H), 4.13 - 4.03 (m, 2H), 3.16 (brs, 1H).

Example 77: (E)-2-(5-((3-bromoallyl)oxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 82) and 2-(5-(prop-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 83)



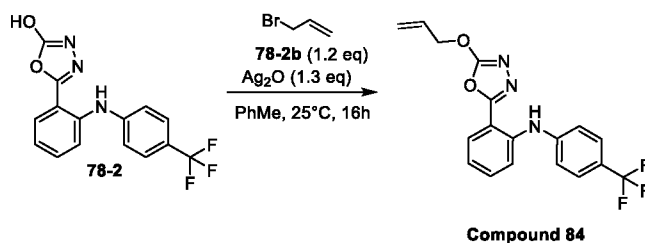
Step 1: 2-[5-[(Z)-3-bromoallyloxy]-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00379] To a solution of compound 77-1 (0.4 g, 1.25 mmol, 1 *eq*) and compound 77-1a (298.6 mg, 1.49 mmol, 1.2 *eq*) in toluene (6 mL) was added Ag₂O (375.1 mg, 1.62 mmol, 1.3 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was filtered and concentrated. The crude product was purified by column chromatography on silica gel to give compound 77-2 (120 mg, 0.27 mmol, 21.8% yield).

Step 2: (E)-2-(5-((3-bromoallyl)oxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 82) and 2-(5-(prop-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 83)

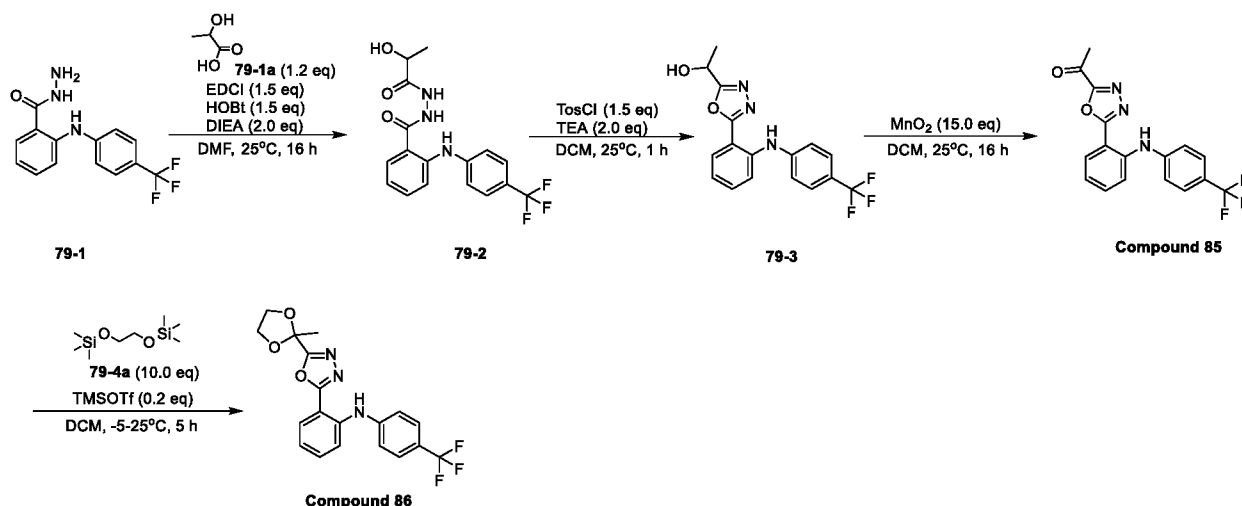
[00380] To a solution of compound 77-2 (40 mg, 90.8 μmol, 1 *eq*) in THF (2 mL) was added LDA (2 M, 0.18 mL, 4 *eq*) at -78°C. The reaction was stirred at -78°C for 1 hr. The reaction was quenched by sat. NH₄Cl (5 mL) and extracted with EA (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 82** (6.8 mg, 14.8 μmol, 16.2% yield) LCMS (ESI): RT = 1.115 min, mass calcd. for C₁₈H₁₃BrF₃N₃O₂ 439.01, m/z found 439.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.30 (s, 1H), 7.76 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.39 - 7.33 (m, 3H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 13.8 Hz, 1H), 6.53 (td, *J* = 6.8, 13.6 Hz, 1H), 4.99 (d, *J* = 6.9 Hz, 2H); and **Compound 83** (1.6 mg, 4.4 μmol, 4.8% yield) LCMS (ESI): RT = 1.049 min, mass calcd. for C₁₈H₁₂F₃N₃O₂ 359.09, m/z found 359.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.78 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.40 - 7.31 (m, 3H), 7.00 - 6.91 (m, 1H), 5.16 (d, *J* = 2.5 Hz, 2H), 2.72 (t, *J* = 2.4 Hz, 1H).

Example 78: 2-(5-(allyloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 84)



[00381] To a solution of compound **78-2** (50 mg, 0.15 mmol, 1 *eq*) and compound **78-2b** (22.5 mg, 0.18 mmol, 16 μ L, 1.2 *eq*) in toluene (1 mL) was added Ag₂O (46.8 mg, 0.20 mmol, 9 μ L, 1.3 *eq*) at 25°C. The reaction was stirred at 25°C for 16 hr. The reaction was diluted with EA (20 mL), filtered and concentrated. The residue was purified by prep-HPLC to give **Compound 84** (3.4 mg, 8.8 μ mol, 5.6% yield). LCMS (ESI): RT = 1.078 min, mass calcd. For C₁₈H₁₄F₃N₃O₂, 361.10 m/z found 362.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.35 (s, 1H), 7.77 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.39 - 7.33 (m, 3H), 6.99 - 6.93 (m, 1H), 6.18 - 6.05 (m, 1H), 5.62 - 5.52 (m, 1H), 5.45 (dd, *J* = 1.0, 10.4 Hz, 1H), 5.04 (td, *J* = 1.1, 6.0 Hz, 2H).

Example 79: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-one (Compound 85) and 2-(5-(2-methyl-1,3-dioxolan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 86)



Step 1: N'-(2-hydroxypropanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00382] To a solution of compound **79-1** (500 mg, 1.69 mmol, 1 *eq*) and compound **79-1a** (183.0 mg, 2.03 mmol, 0.15 mL, 1.2 *eq*) in DMF (8 mL) were added HOBt (343.2 mg, 2.54 mmol, 1.5 *eq*), EDCI (486.9 mg, 2.54 mmol, 1.5 *eq*) and DIEA (437.7 mg, 3.39 mmol, 0.59 mL, 2 *eq*). The mixture was stirred at 25°C for 16 hr. The reaction mixture was quenched with H₂O (15 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (10 mL) and brine (10 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. LCMS confirmed that compound **79-2** (310 mg, 0.82 mmol, 48.3% yield) was obtained.

Step 2: 1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethanol

[00383] To a solution of compound **79-2** (310 mg, 0.84 mmol, 1 *eq*) in DCM (2 mL) were added TEA (170.8 mg, 1.69 mmol, 0.23 mL, 2 *eq*) and TosCl (241.3 mg, 1.27 mmol, 1.5 *eq*). The mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered

and concentrated in vacuum. The residue was purified by flash silica gel chromatography. LCMS confirmed that the compound **79-3** (135 mg, 0.14 mmol, 16.9% yield) was obtained.

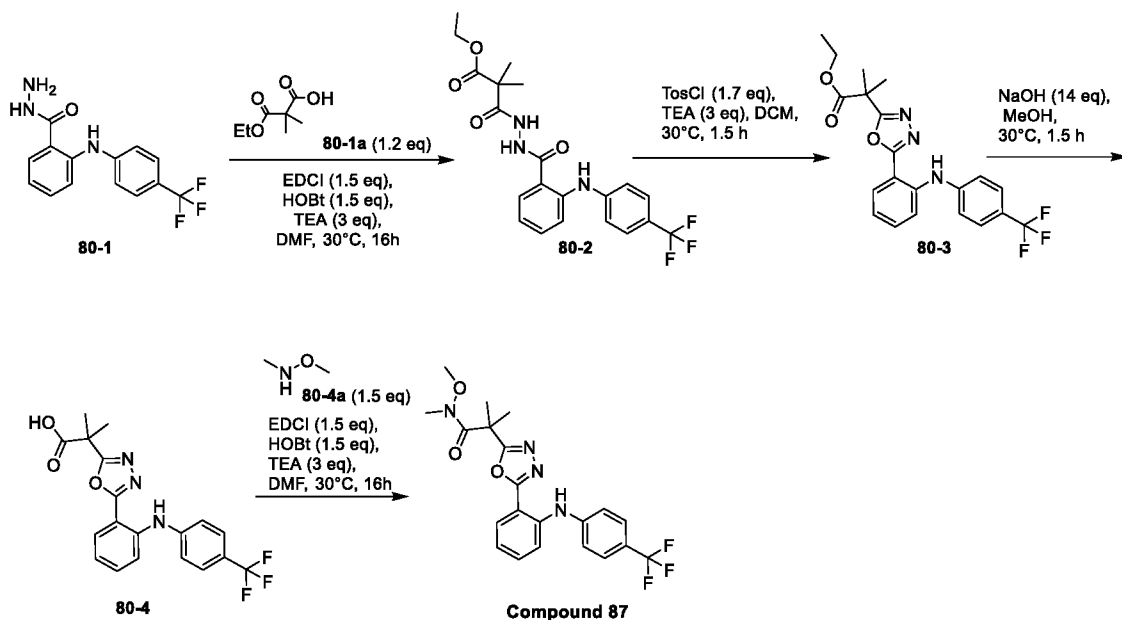
Step 3: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-one (Compound 85)

[00384] To a solution of compound **79-3** (135 mg, 0.39 mmol, 1 *eq*) in DCM (5 mL) was added MnO₂ (504 mg, 5.80 mmol, 15 *eq*). The mixture was stirred at 25°C for 16 hr. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The crude product was purified by prep-TLC. LCMS and ¹HNMR confirmed that **Compound 85** (80 mg, 0.22 mmol, 57.2% yield) was obtained. LCMS (ESI): RT = 0.939 min, mass calcd. For C₁₇H₁₂F₃N₃O₂, 347.09 m/z found 347.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 8.03 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.61 - 7.60 (m, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.53 - 7.48 (m, 1H), 7.48 - 7.42 (m, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.00 (ddd, *J* = 1.3, 6.9, 7.9 Hz, 1H), 2.83 (s, 3H).

Step 4: 2-(5-(2-methyl-1,3-dioxolan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 86)

[00385] To a solution of **Compound 85** (50 mg, 0.14 mmol, 1 *eq*) and compound **79-4a** (297.2 mg, 1.44 mmol, 10 *eq*) in DCM (1 mL) was added TMSOTf (6.4 mg, 28 μmol, 5 uL, 0.2 *eq*) at -5°C. Then the mixture was warmed to 25°C and stirred at 25°C for 5 hr. The reaction mixture was quenched with TEA (5 drops), concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-TLC. LCMS, HPLC and ¹HNMR confirmed that **Compound 86** (17.4 mg, 42 μmol, 29.6% yield) was obtained. LCMS (ESI): RT = 1.037 min, mass calcd. For C₁₉H₁₃F₃N₄O, 391.34 m/z found 392.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.62 - 9.37 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.59 (br d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44 - 7.33 (m, 3H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.30 - 4.18 (m, 1H), 4.24 (br d, *J* = 5.3 Hz, 3H), 1.96 (s, 3H).

Example 80: N-methoxy-N,2-dimethyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 87)



Step 1: ethyl 2,2-dimethyl-3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propanoate

[00386] To a solution of **80-1a** (195.3 mg, 1.22 mmol, 1.2 *eq*), EDCI (292.2 mg, 1.52 mmol, 1.5 *eq*) and HOBT (205.9 mg, 1.52 mmol, 1.5 *eq*) in DMF (20 mL) at 30°C were added **80-1** (300 mg, 1.02 mmol, 1 *eq*) and TEA (308.4 mg, 3.05 mmol, 0.42 mL, 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give to give **80-2** (484 mg, 0.89 mmol, 87.1% yield). LCMS (ESI): RT = 0.835 min, mass calc. for C₂₁H₂₂F₃N₃O₄ 437.41, m/z found 438.0 [M+H]⁺.

Step 2: ethyl 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoate

[00387] To a solution of **80-2** (480 mg, 1.10 mmol, 1 *eq*) in DCM (6 mL) at 30°C were added TEA (333.1 mg, 3.29 mmol, 0.46 mL, 3 *eq*) and TosCl (355.7 mg, 1.87 mmol, 1.7 *eq*). The mixture was stirred at 30°C for 1.5 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **80-3** (375 mg, 0.82 mmol, 75.0% yield). LCMS (ESI): RT = 0.976 min, mass calc. for C₂₁H₂₀F₃N₃O₃ 419.40, m/z found 420.0 [M+H]⁺.

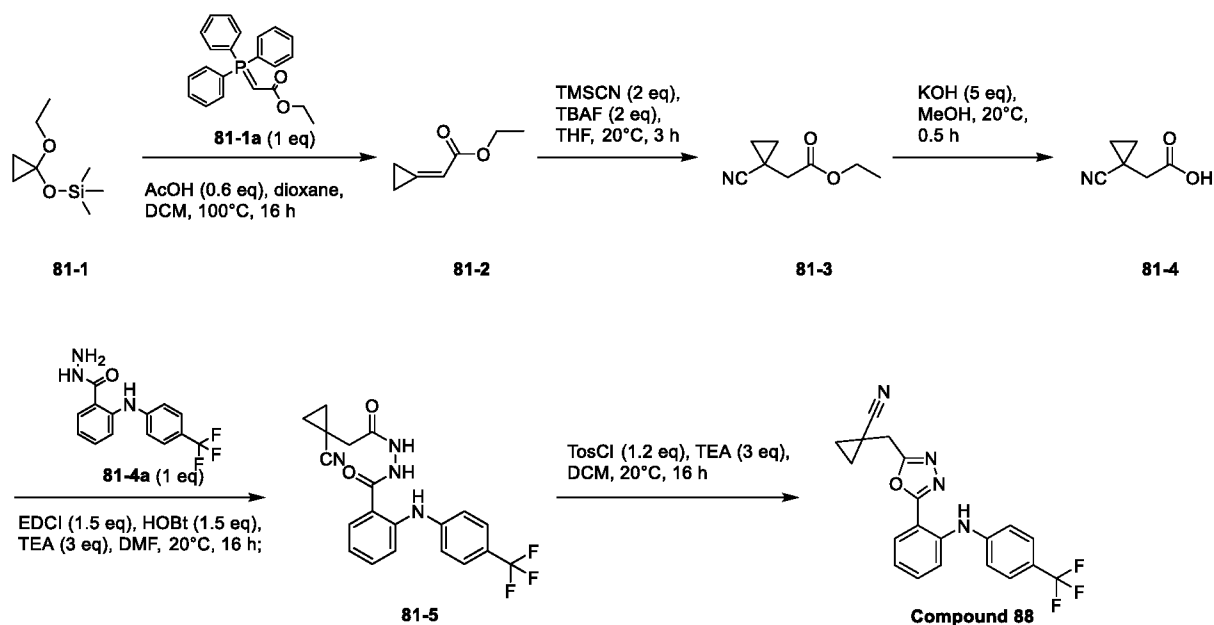
Step 3: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoic acid

[00388] To a solution of **80-3** (370 mg, 0.88 mmol, 1 *eq*) in MeOH (12 mL) at 30°C was added NaOH (2 M, 6.18 mL, 14 *eq*). The mixture was stirred at 30°C for 1.5 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water (20 mL), then acidified with 2N HCl at 0°C to pH = 2-3, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **80-4** (340 mg, 0.78 mmol, 88.6% yield). LCMS (ESI): RT = 0.875 min, mass calc. for C₁₉H₁₆F₃N₃O₃ 391.34, m/z found 392.0 [M+H]⁺;

Step 4: N-methoxy-N,2-dimethyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide

[00389] To a solution of **80-4** (51 mg, 0.13 mmol, 1 *eq*) and HATU (74.3 mg, 0.20 mmol, 1.5 *eq*) in DMF (10 mL) at 30°C were added **80-4a** (19.1 mg, 0.20 mmol, 1.5 *eq*) and TEA (66.0 mg, 0.65 mmol, 91 μ L, 5 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (40 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL *2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography and prep-HPLC to give **Compound 87** (24 mg, 52 μ mol, 39.9% yield). LCMS (ESI): RT = 0.912 min, mass calc. for C₂₁H₂₁F₃N₄O₃ 434.41, m/z found 435.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.43 - 7.35 (m, 3H), 7.02 - 6.95 (m, 1H), 3.32 (s, 3H), 3.23 (s, 3H), 1.75 (s, 6H)

Example 81: 1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyclopropane-1-carbonitrile (Compound 88)



Step 1: ethyl 2-cyclopropylideneacetate

[00390] To a solution of **81-1** (2 g, 11.47 mmol, 2.31 mL, 1.1 *eq*) and AcOH (375.7 mg, 6.26 mmol, 0.36 mL, 0.6 *eq*) in dioxane (30 mL) at 100°C was added **81-1a** (3.63 g, 10.43 mmol, 1 *eq*) in DCM (10 mL) drop-wise, and the mixture was stirred at 100°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give **81-2** (450 mg, 3.57 mmol, 34.2% yield) (volatile). ¹H NMR (400 MHz, CDCl₃) δ 6.23 (quin, *J* = 1.9 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.49 - 1.42 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.26 - 1.21 (m, 2H).

Step 2: ethyl 2-(1-cyanocyclopropyl)acetate

[00391] To a solution of TBAF (1 M, 1.59 mL, 2 *eq*) at 20°C was added TMSCN (157.3 mg, 1.59 mmol, 0.20 mL, 2 *eq*). And then the mixture was stirred at 20°C for 0.5 h. And then a solution of **81-2** (100 mg, 0.79 mmol, 1 *eq*) in THF (0.5 mL) was added at 20°C into the above mixture. The resulting mixture was stirred at 20°C for 2.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **81-3** (110 mg, 0.72 mmol, 90.6% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.23 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 2H), 1.40 - 1.35 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 0.98 - 0.93 (m, 2H).

Step 3: 2-(1-cyanocyclopropyl)acetic acid

[00392] To a solution of KOH (201.5 mg, 3.59 mmol, 5 *eq*) in MeOH (4 mL) at 20°C was added **81-3** (110 mg, 0.72 mmol, 1 *eq*). And then the mixture was stirred at 20°C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (10 mL), then acidified with 2 N HCl to pH = 1-2, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **81-4** (86 mg, 0.69 mmol, 95.7% yield). ¹H NMR (400 MHz, CDCl₃) δ 2.58 (s, 2H), 1.45 - 1.37 (m, 2H), 1.02 - 0.95 (m, 2H).

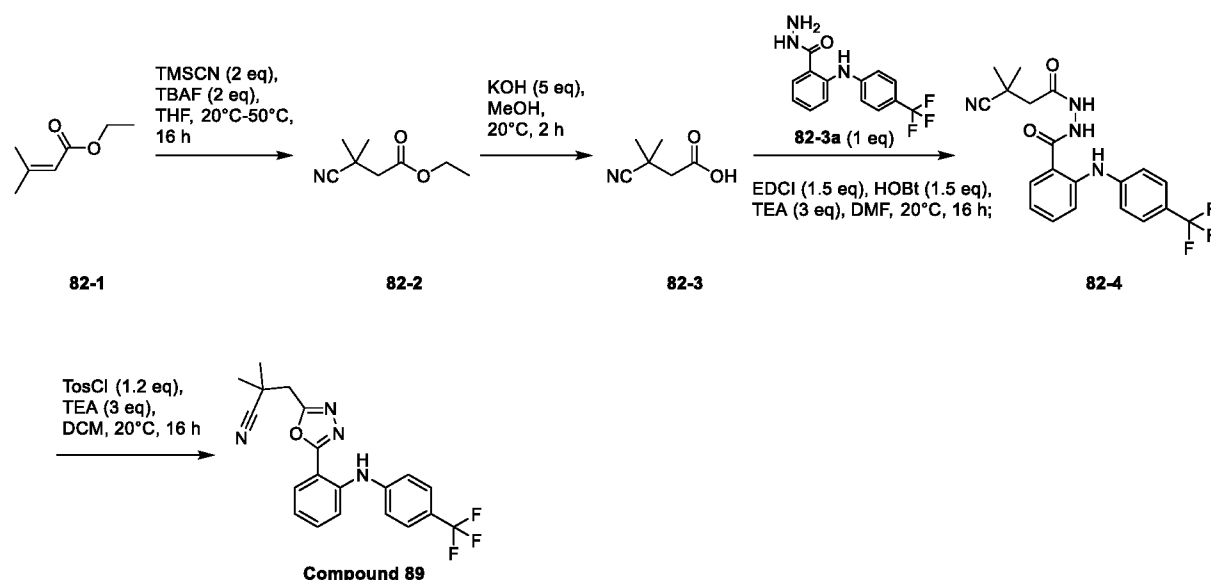
Step 4: *N'*-(2-(1-cyanocyclopropyl)acetyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00393] To a solution of **81-4** (81.4 mg, 0.65 mmol, 1.2 *eq*), EDCI (155.8 mg, 0.81 mmol, 1.5 *eq*), HOBt (109.8 mg, 0.81 mmol, 1.5 *eq*) and **81-4a** (160 mg, 0.54 mmol, 1 *eq*) in DMF (2 mL) at 20°C was added TEA (164.5 mg, 1.63 mmol, 0.23 mL, 3 *eq*). And then the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **81-5** (240 mg, 0.45 mmol, 83.7% yield), which was used directly for next step. LCMS (ESI): RT = 0.788 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 403.0 [M+H]⁺.

Step 5: 1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyclopropane-1-carbonitrile

[00394] To a solution of **81-5** (140 mg, 0.26 mmol, 1 *eq*) and TEA (80.3 mg, 0.79 mmol, 0.11 mL, 3 *eq*) in DCM (1 mL) at 20°C was added TosCl (60.5 mg, 0.32 mmol, 1.2 *eq*). And then the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 88** (55 mg, 0.14 mmol, 54.1% yield). LCMS (ESI): RT = 0.876 min, mass calc. for C₂₀H₁₅F₃N₄O 384.12, *m/z* found 385.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.93 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.44 - 7.39 (m, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.00 (t, *J* = 7.7 Hz, 1H), 3.19 (s, 2H), 1.52 - 1.46 (m, 2H), 1.20 - 1.14 (m, 2H).

Example 82: 2,2-dimethyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile (Compound 89)



Step 1: ethyl 3-cyano-3-methylbutanoate

[00395] To a solution of TBAF (1 M, 3.12 mL, 2 *eq*) in THF (0.5 mL) at 20°C was added TMSCN (309.6 mg, 3.12 mmol, 0.39 mL, 2 *eq*). And then the mixture was stirred at 20°C for 0.5 h. And then ethyl **82-1** (200 mg, 1.56 mmol, 0.22 mL, 1 *eq*) was added at 20°C into the above mixture. The resulting mixture was stirred at 50°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **82-2** (130 mg, 0.84 mmol, 53.7% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 4.21 (q, *J* = 6.9 Hz, 2H), 2.57 (s, 2H), 1.48 (s, 6H), 1.30 (t, *J* = 7.1 Hz, 3H).

Step 2: 3-cyano-3-methylbutanoic acid

[00396] To a solution of KOH (235.0 mg, 4.19 mmol, 5 *eq*) in MeOH (3 mL) at 20°C was added **82-2** (130 mg, 0.84 mmol, 1 *eq*). And then the mixture was stirred at 20°C for 2 h. The reaction

mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (10 mL), then acidified with 2 N HCl to pH = 1-2, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **82-3** (105 mg, 0.83 mmol, 98.6% yield), which was used directly for next step. ¹H NMR (400 MHz, CDCl₃) δ 2.65 (s, 2H), 1.51 (s, 6H).

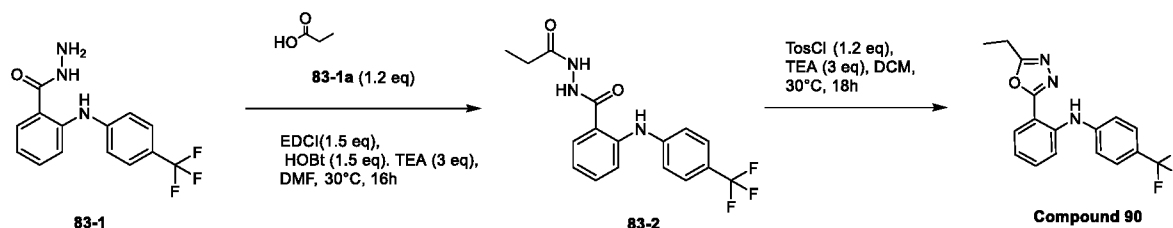
Step 3: *N'*-(3-cyano-3-methylbutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00397] To a solution of **82-3** (103.4 mg, 0.81 mmol, 1.2 eq), EDCI (194.8 mg, 1.02 mmol, 1.5 eq), HOBt (137.3 mg, 1.02 mmol, 1.5 eq) and **82-3a** (200 mg, 0.68 mmol, 1 eq) in DMF (2 mL) at 20°C was added TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 eq). And then the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **82-4** (320 mg, 0.58 mmol, 85.3% yield), which was used directly for next step. LCMS (ESI): RT = 0.841 min, mass calc. for C₂₀H₁₉F₃N₄O₂ 404.15, m/z found 405.0 [M+H]⁺.

Step 4: 2,2-dimethyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile

[00398] To a solution of **82-4** (180 mg, 0.32 mmol, 1 eq) and TEA (98.6 mg, 0.97 mmol, 0.14 mL, 3 eq) in DCM (1 mL) at 20°C was added TosCl (74.3 mg, 0.39 mmol, 1.2 eq). And then the mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 89** (45 mg, 0.11 mmol, 34.1% yield). LCMS (ESI): RT = 0.895 min, mass calc. for C₂₀H₁₇F₃N₄O 386.14, m/z found 387.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.44 (s, 1H), 7.93 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.01 - 6.97 (m, 1H), 3.27 (s, 2H), 1.57 (s, 6H).

Example 83: 2-(5-ethyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 90)



Step 1: *N'*-propionyl-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

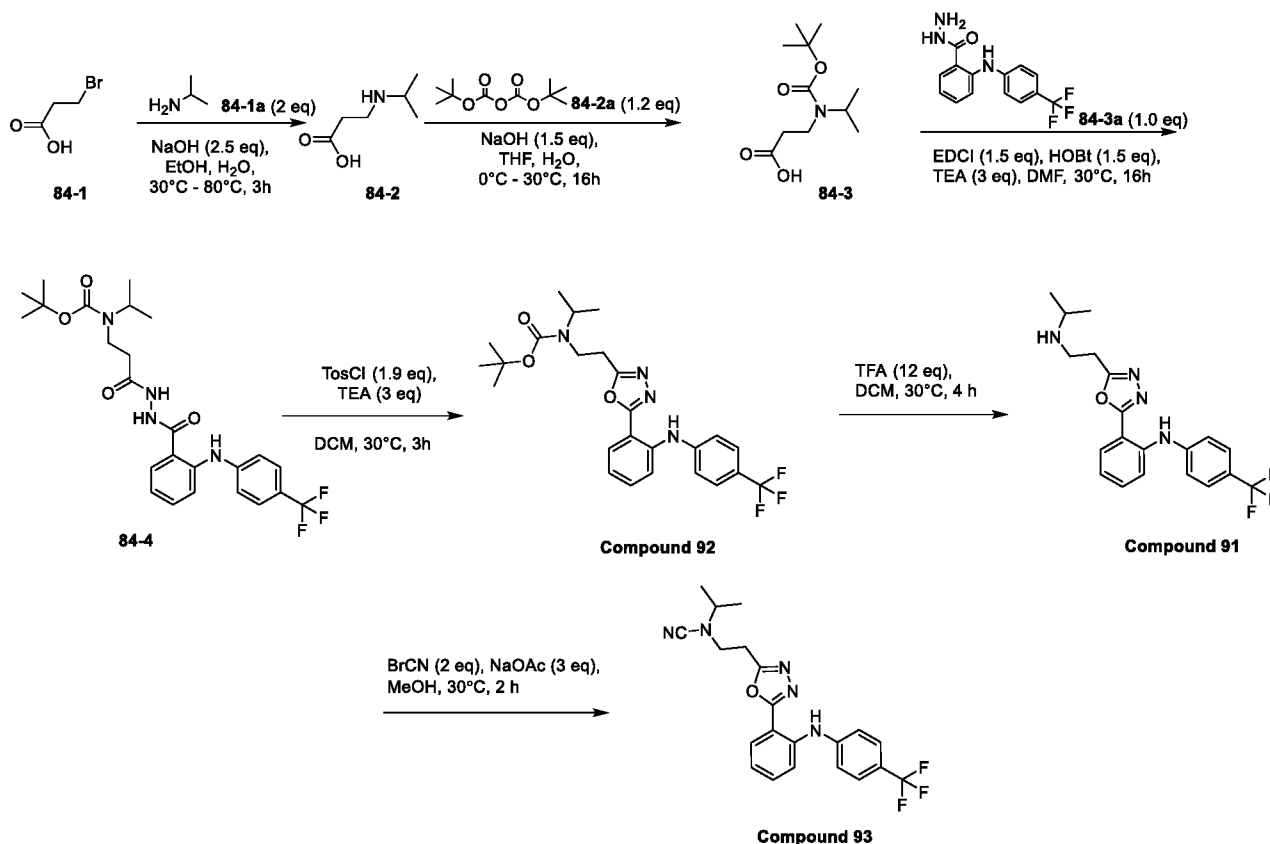
[00399] To a solution of **83-1a** (30.1 mg, 0.41 mmol, 30 uL, 1.2 eq), EDCI (97.4 mg, 0.51 mmol, 1.5 eq) and HOBt (68.7 mg, 0.51 mmol, 1.5 eq) in DMF (1 mL) at 30°C were added **83-1** (100 mg, 0.34 mmol, 1 eq) and TEA (102.8 mg, 1.02 mmol, 0.14 mL, 3 eq). The mixture was stirred at 30°C

for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **83-2** (140 mg, 0.20 mmol, 58.8% yield). LCMS (ESI): RT = 0.764 min, mass calc. for C₁₇H₁₆F₃N₃O₂ 351.12, m/z found 351.9 [M+H]⁺.

Step 2: 2-(5-ethyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00400] To a solution of **83-2** (134 mg, 0.19 mmol, 1 eq) in DCM (2 mL) at 30°C were added TEA (57.9 mg, 0.57 mmol, 80 uL, 3 eq) and TosCl (43.6 mg, 0.23 mmol, 1.2 eq). The mixture was stirred at 30°C for 18 h. The reaction mixture was concentrated under reduced pressure to give the residue which was purified by prep-HPLC to give **Compound 90** (32 mg, 96.0 umol, 50.3% yield). LCMS (ESI): RT = 0.935 min, mass calc. for C₁₇H₁₄F₃N₃O 333.11, m/z found 333.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.41 - 7.35 (m, 3H), 7.00 - 6.95 (m, 1H), 2.99 (q, *J* = 7.5 Hz, 2H), 1.47 (t, *J* = 7.5 Hz, 3H).

Example 84: 2-(5-(2-(isopropylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 91), tert-butyl isopropyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 92), and N-isopropyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 93)



Step 1: 3-(isopropylamino)propanoic acid

[00401] To a solution of **84-1** (1.6 g, 10.72 mmol, 1.11 mL, 1 *eq*) in EtOH (30 mL) at 30°C was added **84-1a** (1.3 g, 21.44 mmol, 1.84 mL, 2 *eq*). The mixture was stirred at 80°C for 3 h. To the resulting mixture was added the solution of NaOH (1.1 g, 26.80 mmol, 2.5 *eq*) in water (10 mL). The reaction mixture was concentrated under reduced pressure to give **84-2** (2.05 g, 10.71 mmol, 99.9% yield) was obtained. Crude ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.70 - 2.61 (m, 1H), 2.56 (t, *J* = 6.6 Hz, 2H), 2.04 - 2.00 (m, 2H), 0.93 (d, *J* = 6.1 Hz, 6H).

Step 2: 3-((tert-butoxycarbonyl)(isopropyl)amino)propanoic acid compound

[00402] To a solution **84-2** (2.1 g, 10.71 mmol, 1 *eq*) and NaOH (642.4 mg, 16.06 mmol, 1.5 *eq*) in THF (10 mL) and water (10 mL) at 0°C was added **84-2a** (2.8 g, 12.85 mmol, 2.95 mL, 1.2 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to remove solvent and then extracted with petroleum ether (20 mL *2) to give the residue. The residue was diluted with water (20 mL), then acidified with 2N HCl at 0°C to pH = 2.5, and then extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **84-3** (920 mg, 3.58 mmol, 33.4% yield). Crude ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.22 (brs, 1H), 4.18 - 3.92 (m, 1H), 3.27 - 3.21 (m, 2H), 2.44 - 2.36 (m, 2H), 1.39 (s, 9H), 1.06 (brd, *J* = 6.8 Hz, 6H).

Step 3: tert-butyl isopropyl(3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propyl)carbamate

[00403] To a solution of **84-3** (188.0 mg, 0.81 mmol, 1.2 *eq*), EDCI (194.8 mg, 1.02 mmol, 1.5 *eq*) and HOBt (137.3 mg, 1.02 mmol, 1.5 *eq*) in DMF (4 mL) at 30°C were added **84-3a** (200 mg, 0.68 mmol, 1 *eq*) and TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give **84-4** (370 mg, 0.51 mmol, 75.2% yield). LCMS (ESI): R = 0.877 min, mass calcd. For C₂₅H₃₁F₃N₄O₄ 508.23 m/z found 531.1 [M+Na]⁺.

Step 4: tert-butyl isopropyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 92)

[00404] To a solution of **84-4** (338 mg, 0.47 mmol, 1 *eq*) in DCM (3 mL) at 30°C were added TEA (141.2 mg, 1.40 mmol, 0.19 mL, 3 *eq*) and TosCl (168.5 mg, 0.88 mmol, 1.9 *eq*). The mixture was stirred at 30°C for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 92** (180 mg, 0.34 mmol, 74.1% yield). LCMS (ESI): RT = 1.017 min, mass calc. for C₂₅H₂₉F₃N₄O₃

490.22, m/z found 491.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.87 (brd, $J = 7.5$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.42 - 7.35 (m, 3H), 6.97 (t, $J = 7.2$ Hz, 1H), 4.45 - 4.08 (m, 1H), 3.57 (brd, $J = 7.0$ Hz, 2H), 3.23 (brd, $J = 8.6$ Hz, 2H), 1.47 (s, 9H), 1.16 (d, $J = 6.9$ Hz, 6H).

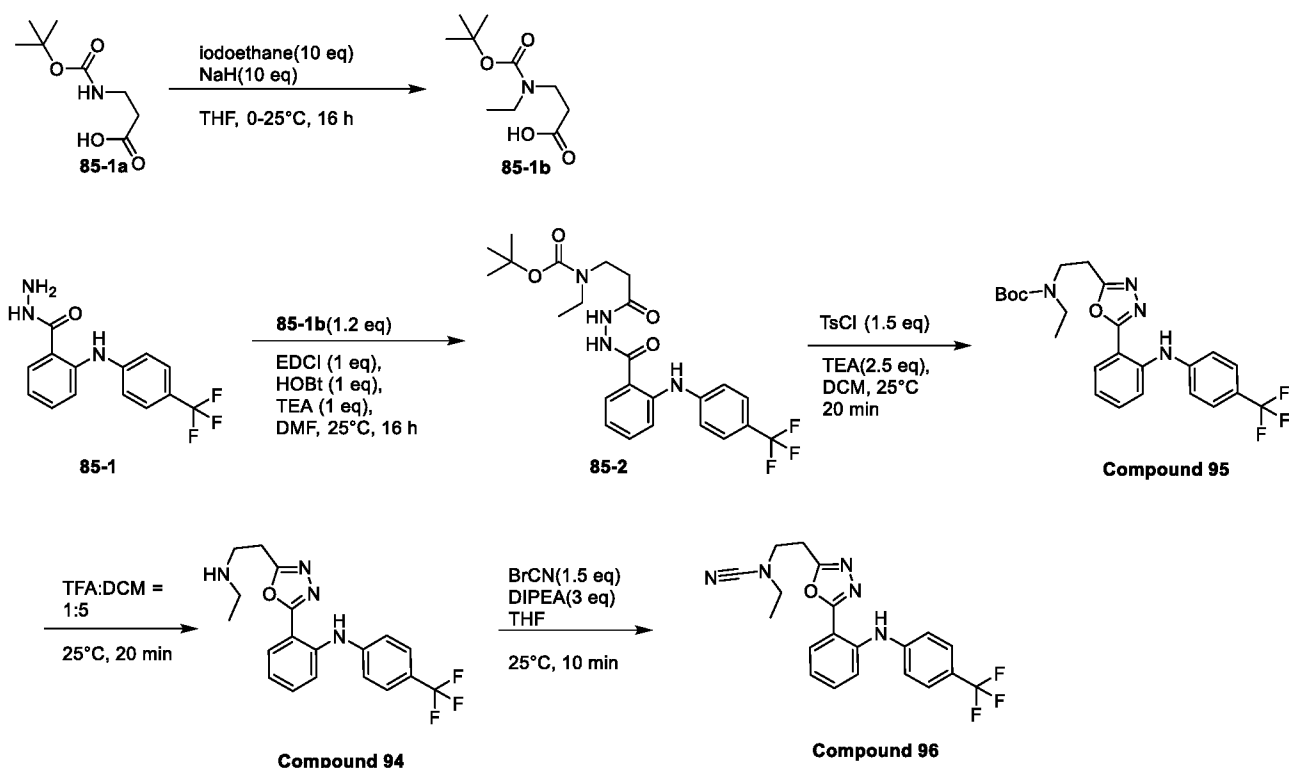
Step 5: 2-(5-(2-(isopropylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 91)

[00405] To a solution of **Compound 92** (160 mg, 0.33 mmol, 1 *eq*) in DCM (3 mL) at 30°C was added TFA (446.3 mg, 3.91 mmol, 0.29 mL, 12 *eq*). The mixture was stirred at 30°C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL), Na_2CO_3 (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purification by prep-HPLC to give **Compound 91** (90 mg, 0.23 mmol, 70.0% yield). LCMS (ESI): RT = 0.750 min, mass calc. for $C_{20}H_{21}F_3N_4O$ 390.17, m/z found 391.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.89 - 7.84 (m, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.42 - 7.35 (m, 3H), 6.97 (t, $J = 7.5$ Hz, 1H), 3.24 (s, 4H), 3.06 - 2.96 (m, 1H), 1.18 (d, $J = 6.3$ Hz, 6H)

Step 6: N-isopropyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 93)

[00406] To a solution of **Compound 91** (40.0 mg, 0.10 mmol, 1 *eq*) and NaOAc (25.2 mg, 0.31 mmol, 3 *eq*) in MeOH (1 mL) at 30°C was added cyanogen bromide (21.7 mg, 0.20 mmol, 15 μ L, 2 *eq*), and the resulting mixture was stirred at 30°C for 2 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 93** (14.9 mg, 36 μ mol, 35.0% yield). LCMS (ESI): RT = 0.896 min, mass calc. for $C_{21}H_{20}F_3N_5O$ 415.16, m/z found 438.0 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.89 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.58 (d, $J = 8.3$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.43 - 7.34 (m, 3H), 6.98 (t, $J = 7.5$ Hz, 1H), 3.60 - 3.55 (m, 2H), 3.33 (t, $J = 7.0$ Hz, 2H), 3.30 - 3.25 (m, 1H), 1.30 (d, $J = 6.5$ Hz, 6H).

Example 85: 2-(5-(2-(ethylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 94), tert-butyl ethyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 95), and N-ethyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 96)



Step 1: 3-((tert-butoxycarbonyl)(ethyl)amino)propanoic acid

[00407] To a solution of 3-(tert-butoxycarbonylamino)propanoic acid **85-1a** (500 mg, 2.64 mmol, 1 eq) and iodoethane (4.12 g, 26.43 mmol, 2.11 mL, 10 eq) in THF (20 mL) was added NaH (1.06 g, 26.43 mmol, 60% purity, 10 eq) slowly in portions (gas evolved) over a period of 1 hr at 0°C. Then the mixture was stirred at 25°C for 16 h. The mixture was quenched with water (20 mL) at 0°C and extracted with EA(20 mL) twice. The separated aqueous layer was cooled in ice-water bath and adjusted to pH~3 with 1 M HCl and then extracted with EA(30 mL) twice. The combined organic layer was washed with brine(15 mL), dried by anhydrous Na₂SO₄, filtered and concentrated to give 3-[tert-butoxycarbonyl(ethyl)amino]propanoic acid **85-1b** (500 mg, 2.30 mmol, 87.1% yield). No purification and used directly for next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.39 - 3.29 (m, 2H), 3.21 - 3.13 (m, 2H), 2.46 - 2.38 (m, 2H), 1.92 (s, 1H), 1.42 - 1.38 (m, 9H), 1.06 - 0.97 (m, 3H).

Step 2: tert-butyl ethyl(3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propyl)carbamate

[00408] To a solution of **85-1** (250 mg, 0.85 mmol, 1 eq) and 3-[tert-butoxycarbonyl(ethyl)amino]propanoic acid (220.7 mg, 1.02 mmol, 1.2 eq), HOBt (114.4 mg, 0.85 mmol, 1 eq) and EDCI (162.3 mg, 0.85 mmol, 1 eq) in DMF (3 mL) was added TEA (85.7 mg, 0.85 mmol, 0.12 mL, 1 eq) at 25°C. Then the mixture was stirred at 25°C for 16 hr. The mixture was diluted with EA(100 mL), washed with saturated aq. NH₄Cl(15 mL*2) and brine(15 mL*2) in

turns, dried by anhydrous Na₂SO₄, filtered and concentrated to give **85-2** (600 mg, crude). No purification and used directly for next step. LCMS (ESI): R = 0.979 min, mass calcd. For C₂₄H₂₉F₃N₄O₄ 494.21 m/z found 517 [M+23]⁺.

Step 3: tert-butyl ethyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 95)

[00409] To a solution of **85-2** (500 mg, 1.01 mmol, 1 *eq*) and TosCl (289.1 mg, 1.52 mmol, 1.5 *eq*) in DCM (15 mL) was added TEA (255.8 mg, 2.53 mmol, 0.35 mL, 2.5 *eq*) at 25°C. Then the mixture was stirred at 25°C for 20 min. The reaction mixture was quenched with water (5 mL) and diluted with DCM (100 mL), washed with saturated aq. NH₄Cl(15 mL*2) and brine(15 mL*2) in turns, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue (500 mg). The residue was purified by prep-HPLC to give **Compound 95** (140 mg, 0.29 mmol, 28.5% yield). LCMS (ESI): R = 1.112 min, mass calcd. For C₂₄H₂₇F₃N₄O₃ 476.20 m/z found 477.1 [M+1]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.24 (br d, *J* = 16.1 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.48 (m, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.19 - 7.10 (m, 1H), 3.56 (t, *J* = 6.5 Hz, 2H), 3.27 - 3.06 (m, 4H), 1.38 - 1.10 (m, 9H), 1.04 (br t, *J* = 6.9 Hz, 3H).

Step 4: 2-(5-(2-(ethylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 94)

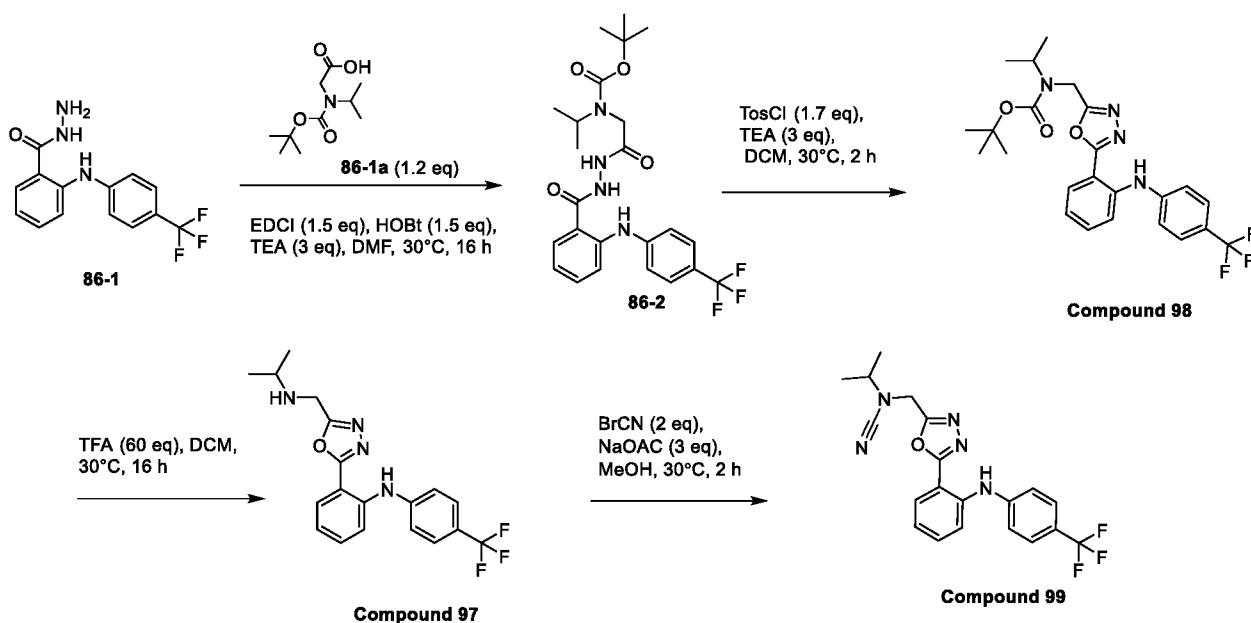
[00410] To a solution of **Compound 95** (130 mg, 0.27 mmol, 1 *eq*) in DCM (3 mL) was added TFA (933.3 mg, 8.18 mmol, 0.61 mL, 30 *eq*) at 25°C. Then the resulting mixture was stirred at 25°C for 20 min. The mixture was concentrated at 25°C to give a residue. The residue was lyophilized to give **Compound 94** (130 mg, 0.26 mmol, 93.9% yield, TFA). LCMS (ESI): R = 0.845 min, mass calcd. For C₁₉H₁₉F₃N₄O 376.15 m/z found 377.1 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.24 (s, 1H), 8.64 (br s, 2H), 7.94 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.62 - 7.51 (m, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.20 - 7.12 (m, 1H), 3.47 - 3.35 (m, 4H), 3.05 (q, *J* = 7.3 Hz, 2H), 1.20 (t, *J* = 7.3 Hz, 3H).

Step 5: N-ethyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 96)

[00411] To a solution of **Compound 94** (50 mg, 0.1 mmol, 1 *eq*, TFA) and DIPEA (39.5 mg, 0.3 mmol, 53 uL, 3 *eq*) in THF (2 mL) was added BrCN (16.2 mg, 0.15 mmol, 11 uL, 1.5 *eq*) at 25°C. Then the resulting mixture was stirred at 25°C for 10 min. The mixture was quenched with water (5 mL) and diluted with EA (100 mL), washed with saturated aq. NH₄Cl(15 mL*2) and brine(15 mL*2) in turns, dried by anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 96** (20.3 mg, 50 umol, 49.3% yield). LCMS (ESI): R = 0.992 min, mass calcd. For C₂₀H₁₈F₃N₅O 401.15 m/z found 402.0 [M+1]⁺; ¹H

NMR (400 MHz, DMSO- d_6) δ 9.24 (s, 1H), 7.95 (br d, J = 7.5 Hz, 1H), 7.64 (br d, J = 8.5 Hz, 2H), 7.60 - 7.45 (m, 2H), 7.38 (br d, J = 8.3 Hz, 2H), 7.14 (br t, J = 7.0 Hz, 1H), 3.54 (br t, J = 6.7 Hz, 2H), 3.27 (br t, J = 6.5 Hz, 2H), 3.10 (q, J = 7.3 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).

Example 86: 2-(5-((isopropylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 97), tert-butyl isopropyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 98), and N-isopropyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 99)



Step 1: tert-butyl isopropyl(2-oxo-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)ethyl)carbamate

[00412] To a solution of **86-1** (200.0 mg, 0.68 mmol, 1.0 eq), EDCI (194.8 mg, 1.02 mmol, 1.5 eq) and HOBT (137.3 mg, 1.02 mmol, 1.5 eq) in DMF (3 mL) at 30°C were added **86-1a** (176.6 mg, 0.81 mmol, 1.2 eq) and TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 eq). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give to give **86-2** (230 mg, 0.39 mmol, 57.7% yield). LCMS (ESI): RT = 0.861 min, mass calc. for C₂₄H₂₉F₃N₄O₄ 494.21, m/z found 517.1 [M+Na]⁺.

Step 2: tert-butyl isopropyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 98)

[00413] To a solution of **86-2** (220 mg, 0.44 mmol, 1 eq) in DCM (3 mL) at 30°C were added TEA (135.1 mg, 1.33 mmol, 0.19 mL, 3 eq) and TosCl (144.2 mg, 0.76 mmol, 1.7 eq), and the mixture was stirred at 30°C for 2 h. The reaction mixture was diluted with water (20 mL), and then

extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 98** (150 mg, 0.31 mmol, 70.8% yield). LCMS (ESI): RT = 1.002 min, mass calc. for C₂₄H₂₇F₃N₄O₃ 476.20, m/z found 499.0 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.50 (s, 1H), 7.84 (brs, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.42 - 7.36 (m, 3H), 6.96 (t, *J* = 7.5 Hz, 1H), 4.58 (brs, 3H), 1.44 (brs, 9H), 1.22 (d, *J* = 6.8 Hz, 6H).

Step 3: 2-(5-((isopropylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 97)

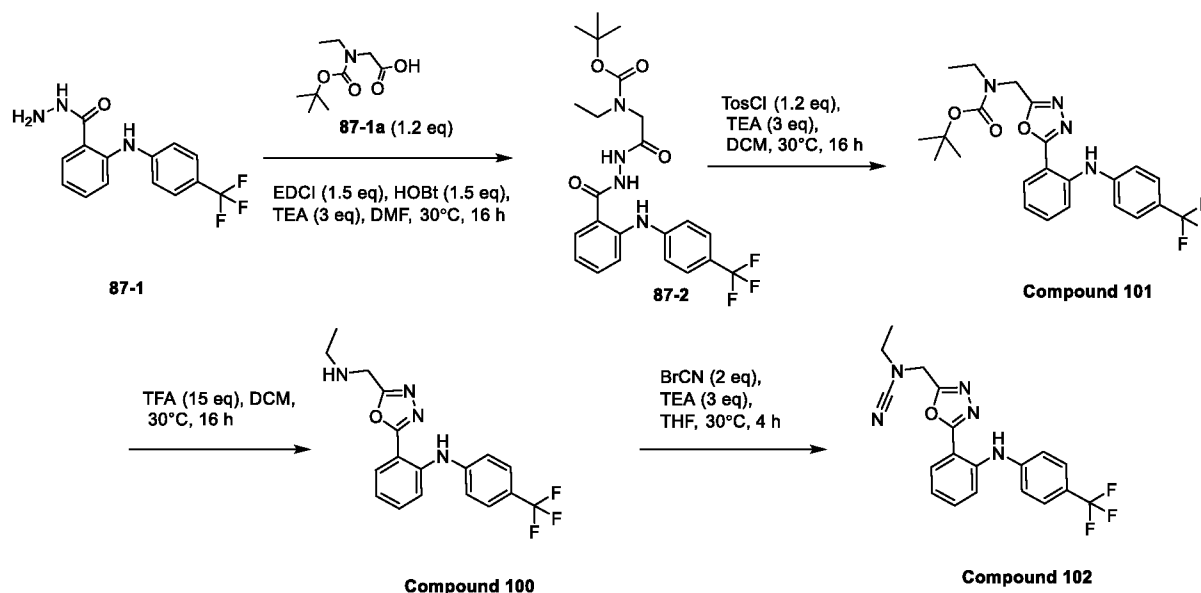
[00414] To a solution of **Compound 98** (140 mg, 0.29 mmol, 1 *eq*) in DCM (3 mL) at 30°C was added TFA (2.0 g, 17.63 mmol, 1.31 mL, 60 *eq*) and the mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with saturation Na₂CO₃ solution (20 mL) and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 97** (70 mg, 0.19 mmol, 63.3% yield). LCMS (ESI): RT = 0.745 min, mass calc. for C₁₈H₁₇F₃N₄O 376.15, m/z found 377 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.91 (dd, *J* = 1.5, 80 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.42 - 7.36 (m, 3H), 6.98 (t, *J* = 7.1 Hz, 1H), 4.16 (s, 2H), 4.16 (s, 2H), 2.96 (quin, *J* = 6.2 Hz, 1H), 1.15 (d, *J* = 6.3 Hz, 6H).

Step 4: N-isopropyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 99)

[00415] To a solution of **Compound 97** (25.0 mg, 66 μmol, 1 *eq*) and NaOAc (16.4 mg, 0.20 mmol, 3 *eq*) in MeOH (1 mL) at 30°C was added cyanogen bromide (14.1 mg, 0.13 mmol, 10 μL, 2 *eq*), and the resulting mixture was stirred at 30°C for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 99** (13.0 mg, 32 μmol, 48.8% yield). LCMS (ESI): RT = 0.888 min, mass calc. for C₂₀H₁₈F₃N₅O 401.15, m/z found 402.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 7.94 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.03 - 6.98 (m, 1H), 4.57 (s, 2H), 3.37 (spt, *J* = 6.5 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 6H).

Example 87: 2-(5-((ethylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 100), and tert-butyl ethyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound

101), and N-ethyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 102)



Step 1: tert-butyl ethyl(2-oxo-2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)ethyl carbamate

[00416] To a solution of **87-1a** (123.9 mg, 0.61 mmol, 1.2 *eq*), EDCI (146.1 mg, 0.76 mmol, 1.5 *eq*) and HOBt (103 mg, 0.76 mmol, 1.5 *eq*) in DMF (3 mL) at 30°C was added **87-1** (150 mg, 0.51 mmol, 1 *eq*) and TEA (154.2 mg, 1.52 mmol, 0.21 mL, 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **87-2** (170 mg, 0.34 mmol, 67.3% yield) was obtained. LCMS (ESI): R = 0.846 min, mass calcd. For C₂₃H₂₇F₃N₄O₄ 480.20 m/z found 503.0 [M+23]⁺.

Step 2: tert-butyl ethyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 101)

[00417] To a solution of **87-2** (170 mg, 0.35 mmol, 1 *eq*) in DCM (3 mL) at 30°C was added TEA (107.4 mg, 1.06 mmol, 0.15 mL, 3 *eq*) and TosCl (80.9 mg, 0.42 mmol, 1.2 *eq*), and the mixture was stirred at 30°C for 2 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 101** (150 mg, 0.32 mmol, 91.7% yield). LCMS (ESI): RT = 0.988 min, mass calc. for C₂₃H₂₅F₃N₄O₃ 462.19, m/z found 485.0 [M+23]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 7.86

(brs, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.43 - 7.34 (m, 3H), 6.97 (t, $J = 7.5$ Hz, 1H), 4.82 - 4.64 (m, 2H), 3.40 (brs, 2H), 1.50 (brs, 9H), 1.18 (brs, 3H).

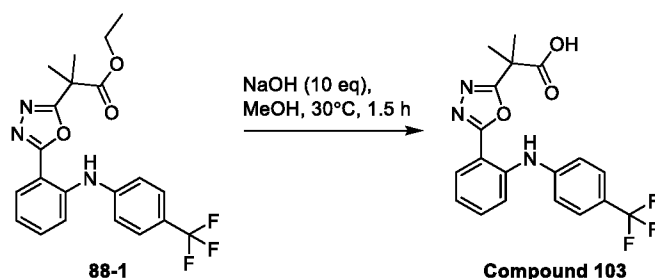
Step 3: 2-(5-((ethylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 100)

[00418] To a solution of **Compound 101** (140 mg, 0.35 mmol, 1 *eq*) in DCM (3 mL) at 30°C was added TFA (517.8 mg, 4.54 mmol, 0.34 mL, 15 *eq*) and the mixture was stirred at 30°C for 1 h. The reaction mixture was diluted with water (20 mL), saturated Na₂CO₃ solution (20 mL) and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 100** (70.0 mg, 0.19 mmol, 61.1% yield). LCMS (ESI): RT = 0.722 min, mass calc. for C₁₈H₁₇F₃N₄O 362.14, m/z found 363 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.91 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.42 - 7.36 (m, 3H), 7.00 - 6.94 (m, 1H), 4.45 (brs, 1H), 4.15 (s, 2H), 2.80 (q, $J = 7.1$ Hz, 2H), 1.18 (t, $J = 7.1$ Hz, 3H).

Step 4: N-ethyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 102)

[00419] To a solution of **Compound 100** (30 mg, 82.8 μ mol, 1 *eq*) and TEA (25.1 mg, 0.25 mmol, 35 μ L, 3 *eq*) in THF (2 mL) at 30°C was added cyanogen bromide (17.5 mg, 0.17 mmol, 12 μ L, 2 *eq*), and the resulting mixture was stirred at 30°C for 4 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 102** (5.0 mg, 12.9 μ mol, 15.6% yield). LCMS (ESI): RT = 0.869 min, mass calc. for C₁₈H₁₇F₃N₄O 387.36, m/z found 388.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 7.94 (dd, $J = 1.3, 7.9$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.04 - 6.97 (m, 1H), 4.56 (s, 2H), 3.22 (q, $J = 7.3$ Hz, 2H), 1.36 (t, $J = 7.3$ Hz, 3H).

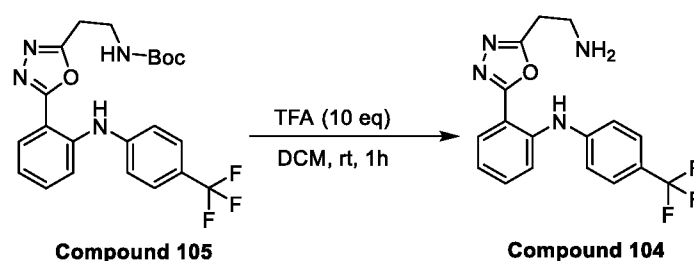
Example 88: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoic acid (Compound 103)



[00420] To a solution of **88-1** (250 mg, 0.60 mmol, 1 *eq*) in MeOH (6 mL) at 30°C was added NaOH (2 M, 2.98 mL, 10 *eq*), and the mixture was stirred at 30°C for 1.5 h. The reaction mixture

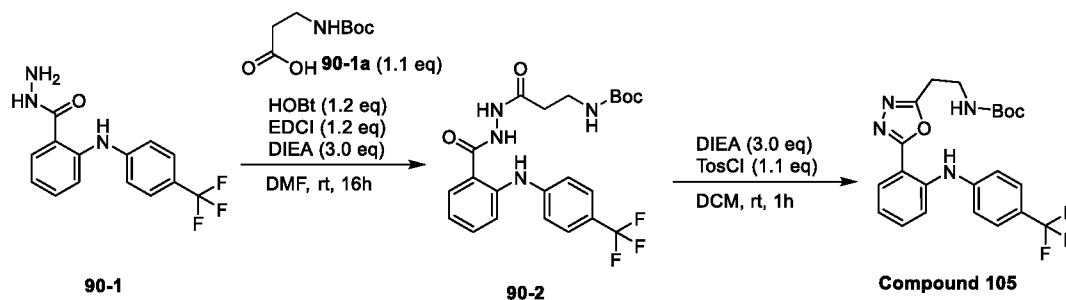
was concentrated under reduced pressure to remove solvent. The residue was diluted with water (20 mL), then acidified with 2N HCl at 0°C to pH = 2-3, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 103** (220 mg, 0.55 mmol, 91.8% yield). LCMS (ESI): RT = 0.988 min, mass calc. for C₁₉H₁₆F₃N₃O₃ 391.11, m/z found 392 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.00 - 6.94 (m, 1H), 1.83 (s, 6H).

Example 89: 2-(5-(2-aminoethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 104)



[00421] To a solution of **Compound 105** (100 mg, 0.22 mmol, 1 eq) in DCM (2 mL) was added TFA (254.2 mg, 2.23 mmol, 0.16 mL, 10 eq). The reaction was stirred at 25°C for 1 hr. The reaction was neutralized with sat. Na₂CO₃ and extracted with DCM (3*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. **Compound 104** (70 mg, 0.19 mmol, 87% yield) was used for next step without further purification. LCMS (ESI): RT = 0.825 min, mass calc. for C₁₇H₁₅F₃N₄O 348.12, m/z found 349.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.88 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.43 - 7.32 (m, 3H), 7.01 - 6.94 (m, 1H), 4.59 (br s, 1H), 3.26 (br s, 2H), 3.13 - 3.06 (m, 2H).

Example 90: tert-butyl (2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 105)



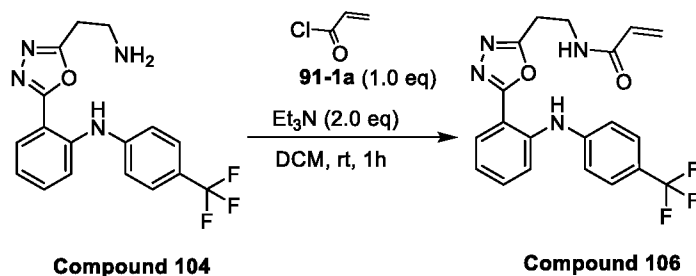
Step 1: tert-butyl N-[3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]carbamate

[00422] To a mixture of compound **90-1** (0.2 g, 0.67 mmol, 1 *eq*), compound **90-1a** (140.9 mg, 0.74 mmol, 1.1 *eq*), HOBt (109.8 mg, 0.81 mmol, 1.2 *eq*) and EDCI (155.8 mg, 0.81 mmol, 1.2 *eq*) in DMF (4 mL) was added DIEA (262.6 mg, 2 mmol, 0.35 mL, 3 *eq*) at 25°C under N₂. The mixture was stirred at 25 °C for 16 hr. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The compound **90-2** (0.3 g, crude) was used for next step directly.

Step 2: tert-butyl (2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate

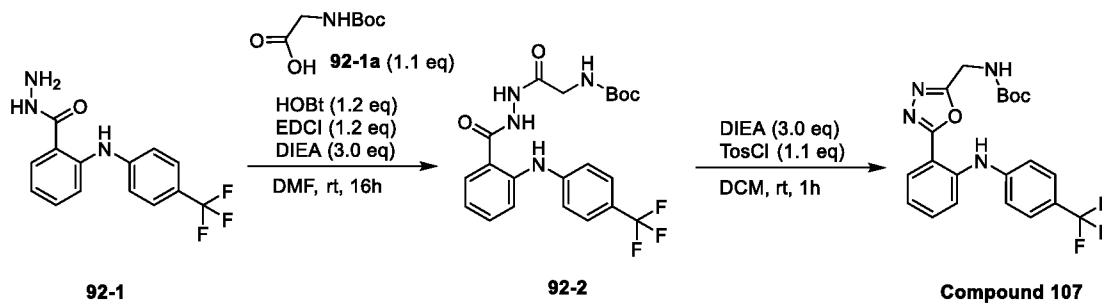
[00423] To a solution of compound **90-2** (0.3 g, 0.64 mmol, 1 *eq*) and DIEA (249.3 mg, 1.9 mmol, 0.33 mL, 3 *eq*) in DCM (4 mL) was added TosCl (134.8 mg, 0.7 mmol, 1.1 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) and washed with water (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give **Compound 105** (130 mg, 0.28 mmol, 45% yield). LCMS (ESI): RT = 1.048 min, mass calc. for C₂₂H₂₃F₃N₄O₃ 448.16, m/z found 449.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.47 (s, 1H), 7.88 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.54 - 7.47 (m, 1H), 7.44 - 7.33 (m, 3H), 7.02 - 6.95 (m, 1H), 3.69 (q, *J* = 6.0 Hz, 2H), 3.16 (t, *J* = 6.3 Hz, 2H), 1.44 (s, 9H).

Example 91: N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)acrylamide (Compound 106)



[00424] To a solution of **Compound 104** (60 mg, 0.17 mmol, 1 *eq*) and Et₃N (34.8 mg, 0.34 mmol, 47.9 uL, 2 *eq*) in DCM (2 mL) was added **91-1a** (15.5 mg, 0.17 mmol, 14 uL, 1 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (20 mL) and washed with H₂O (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 106** (11.2 mg, 27 umol, 16% yield). LCMS (ESI): RT = 0.942 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 403.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.47 - 7.34 (m, 3H), 7.03 - 6.91 (m, 1H), 6.33 (dd, *J* = 1.3, 16.9 Hz, 2H), 6.18 - 6.06 (m, 1H), 5.69 (dd, *J* = 1.3, 10.3 Hz, 1H), 3.93 (q, *J* = 6.1 Hz, 2H), 3.23 (t, *J* = 6.0 Hz, 2H).

Example 92: tert-butyl ((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 107)



Step 1: tert-butyl N-[2-oxo-2-[2-[2-[4-

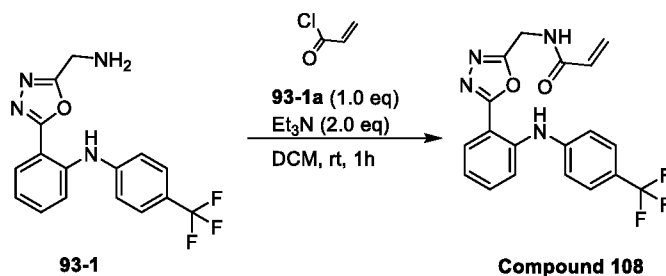
(trifluoromethyl)anilino]benzoyl]hydrazino]ethyl]carbamate

[00425] To a mixture of compound **92-1** (0.2 g, 0.67 mmol, 1 *eq*), compound **92-1a** (130.5 mg, 0.74 mmol, 1.1 *eq*), HOBT (109.8 mg, 0.81 mmol, 1.2 *eq*) and EDCI (155.8 mg, 0.81 mmol, 1.2 *eq*) in DMF (4 mL) was added DIEA (262.6 mg, 2 mmol, 0.35 mL, 3 *eq*) at 25°C under N₂. The mixture was stirred at 25 °C for 16 hr. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The compound **92-2** (0.3 g, crude) was used for next step directly.

Step 2: tert-butyl ((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate

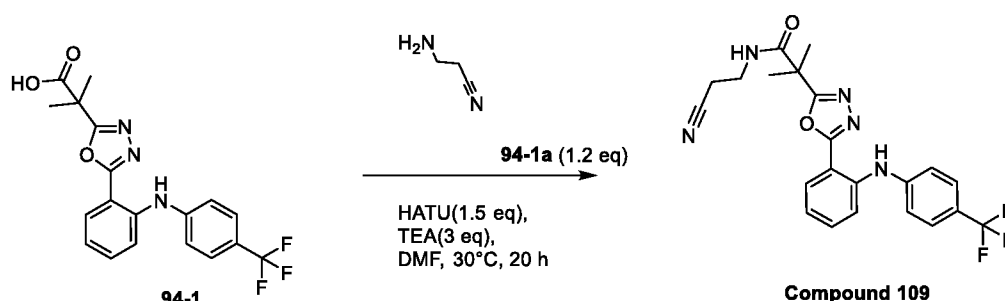
[00426] To a solution of compound **92-2** (0.3 g, 0.66 mmol, 1 *eq*) and DIEA (257 mg, 1.99 mmol, 0.34 mL, 3 *eq*) in DCM (4 mL) was added TosCl (139 mg, 0.72 mmol, 1.1 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) and washed with water (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give **Compound 107** (120 mg, 0.26 mmol, 40.7% yield). LCMS (ESI): RT = 1.040 min, mass calc. for C₂₁H₂₁F₃N₄O₃ 434.16, m/z found 435.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.88 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.43 - 7.33 (m, 3H), 7.01 - 6.93 (m, 1H), 5.24 - 5.12 (m, 1H), 4.67 (d, *J* = 5.8 Hz, 2H), 1.49 (s, 9H).

Example 93: N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)acrylamide (Compound 108)



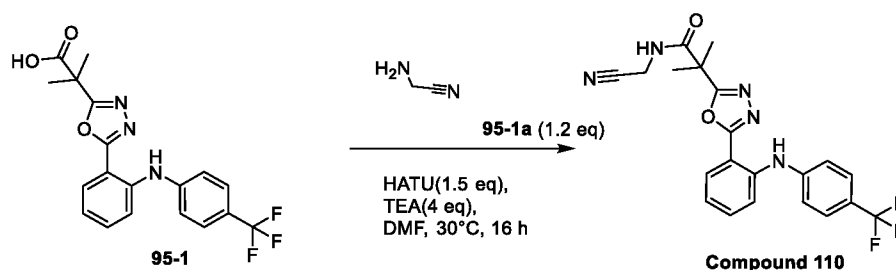
[00427] To a solution of **93-1** (60 mg, 0.17 mmol, 1 *eq*) and Et₃N (36.3 mg, 0.35 mmol, 49.9 uL, 2 *eq*) in DCM (2 mL) was added **93-1a** (16.2 mg, 0.17 mmol, 14.6 uL, 1 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (20 mL) and washed with H₂O (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 108** (17.3 mg, 44 umol, 24.6% yield). LCMS (ESI): RT = 0.942 min, mass calc. for C₁₉H₁₅F₃N₄O₂ 388.11, m/z found 349.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ = 9.42 (s, 1H), 7.90 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.57 - 7.49 (m, 1H), 7.45 - 7.33 (m, 2H), 7.45 - 7.33 (m, 1H), 7.05 - 6.95 (m, 1H), 6.43 (dd, *J* = 1.0, 17.1 Hz, 1H), 6.33 - 6.14 (m, 2H), 5.80 (dd, *J* = 1.3, 10.3 Hz, 1H), 4.90 (d, *J* = 5.8 Hz, 2H).

Example 94: N-(2-cyanoethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 109)



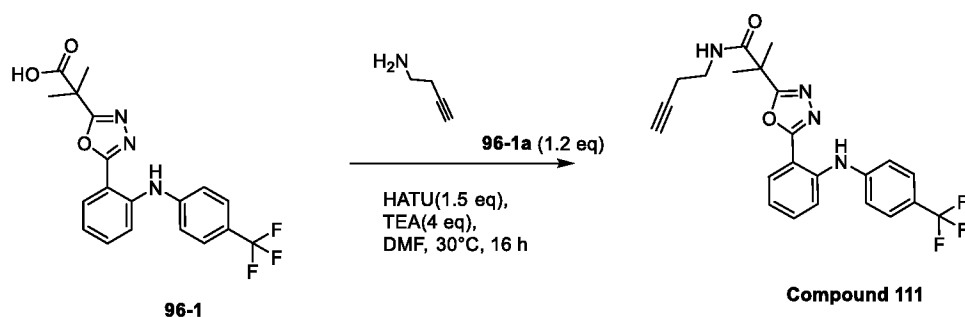
[00428] To a solution of **94-1** (40 mg, 0.10 mmol, 1 *eq*) and HATU (58.3 mg, 0.15 mmol, 1.5 *eq*) in DMF (1 mL) at 30°C were added **94-1a** (8.6 mg, 0.12 mmol, 9 uL, 1.2 *eq*) and TEA (31.0 mg, 0.31 mmol, 43 uL, 3 *eq*). The mixture was stirred at 30°C for 20 h. The reaction mixture was concentrated under reduced pressure to give the residue which was purified by prep-HPLC to give **Compound 109** (20 mg, 45.1 umol, 44.1% yield). LCMS (ESI): RT = 0.853 min, mass calc. for C₂₂H₂₀F₃N₅O₂ 443.16, m/z found 444.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.37 (s, 1H), 7.88 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.52 - 7.48 (m, 1H), 7.43 - 7.38 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.31 (brd, *J* = 5.9 Hz, 1H), 7.01 - 6.95 (m, 1H), 3.54 (q, *J* = 6.3 Hz, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 1.79 (s, 6H).

Example 95: N-(cyanomethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 110)



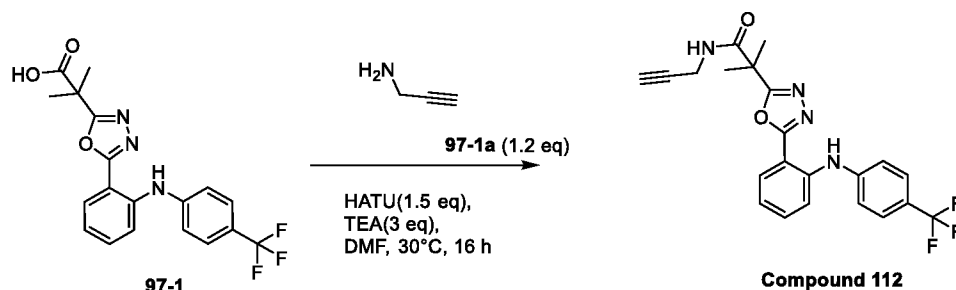
[00429] To a solution of **95-1** (40 mg, 0.1 mmol, 1 *eq*) and HATU (58.3 mg, 0.15 mmol, 1.5 *eq*) in DMF (1 mL) at 30°C were added **95-1a** (15.8 mg, 0.12 mmol, 1.2 *eq*, HCl) and TEA (41.4 mg, 0.41 mmol, 57 μ L, 4 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to give **Compound 110** (13 mg, 30 μ mol, 29.3% yield). LCMS (ESI): RT = 0.860 min, mass calc. for $C_{21}H_{18}F_3N_5O_2$ 429.14, m/z found 430.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.87 (dd, J = 1.4, 7.9 Hz, 1H), 7.74 (brs, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.52 - 7.49 (m, 1H), 7.44 - 7.40 (m, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.02 - 6.97 (m, 1H), 4.22 (d, J = 5.5 Hz, 2H), 1.80 (s, 6H).

Example 96: N-(but-3-yn-1-yl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 111)



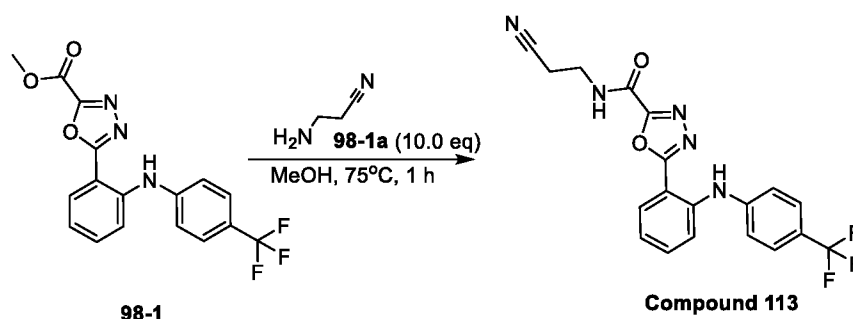
[00430] To a solution of **96-1** (40 mg, 0.10 mmol, 1 *eq*) and HATU (58.3 mg, 0.15 mmol, 1.5 *eq*) in DMF (1 mL) at 30°C were added **96-1a** (17.4 mg, 0.12 mmol, 1.2 *eq*, HCl) and TEA (41.4 mg, 0.41 mmol, 57 μ L, 4 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to give the residue which was purified by prep-HPLC to give **Compound 111** (32 mg, 72.3 μ mol, 70.8% yield). LCMS (ESI): RT = 0.891 min, mass calc. for $C_{23}H_{21}F_3N_4O_2$ 442.16, m/z found 443.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.89 (dd, J = 1.4, 7.9 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.3 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.01 - 6.96 (m, 1H), 6.72 (brs, 1H), 3.42 (q, J = 6.3 Hz, 2H), 2.42 (dt, J = 2.6, 6.4 Hz, 2H), 1.91 (t, J = 2.6 Hz, 1H), 1.79 (s, 6H).

Example 97: 2-methyl-N-(prop-2-yn-1-yl)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 112)



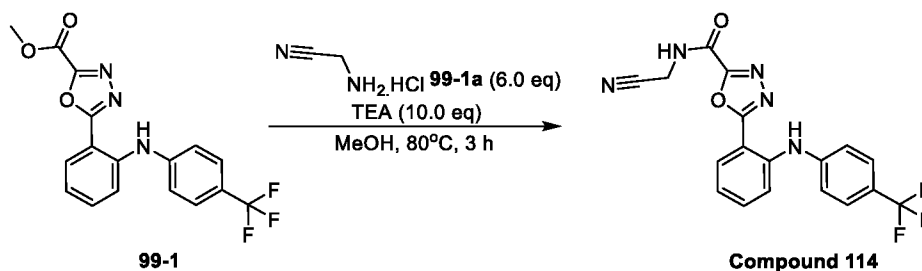
[00431] To a solution of **97-1** (30 mg, 76.7 μmol , 1 *eq*) and HATU (43.7 mg, 0.11 mmol, 1.5 *eq*) in DMF (1 mL) at 30°C were added **97-1a** (5.1 mg, 92.0 μmol , 5.9 μL , 1.2 *eq*) and TEA (23.3 mg, 0.23 mmol, 32 μL , 3 *eq*). The mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to give **Compound 112** (13.0 mg, 30.4 μmol , 39.6% yield). LCMS (ESI): RT = 0.884 min, mass calc. for $\text{C}_{22}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_2$ 428.15, m/z found 429.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ = 9.41 (s, 1H), 7.88 (dd, J = 1.4, 8.0 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.53 - 7.50 (m, 1H), 7.44 - 7.39 (m, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.01 - 6.97 (m, 1H), 6.92 (brs, 1H), 4.07 (dd, J = 2.6, 5.1 Hz, 2H), 2.24 (t, J = 2.6 Hz, 1H), 1.79 (s, 6H)

Example 98: N-(2-cyanoethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 113)



[00432] To a solution of compound **98-1** (50 mg, 0.14 mmol, 1 *eq*) in MeOH (1 mL) was added compound **98-1a** (96.4 mg, 1.38 mmol, 0.1 mL, 10 *eq*). The mixture was stirred at 75°C for 1 hr. The reaction mixture was filtered and the solid was collected to give **Compound 113** (39 mg, 97 μmol , 70.6% yield). LCMS (ESI): RT = 0.841 min, mass calc. For $\text{C}_{19}\text{H}_{14}\text{F}_3\text{N}_5\text{O}_2$, 401.11 m/z found 402.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.64 (t, J = 5.8 Hz, 1H), 9.11 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 3.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.23 - 7.14 (m, 1H), 3.56 (q, J = 6.4 Hz, 2H), 2.82 (t, J = 6.5 Hz, 2H).

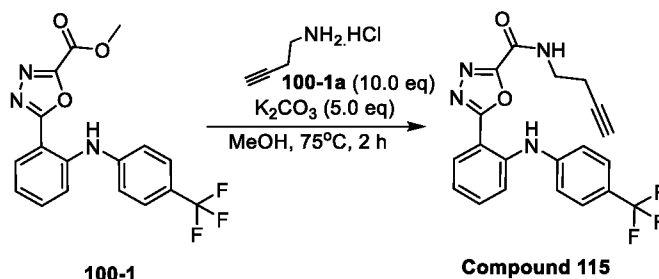
Example 99: N-(cyanomethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 114)



[00433] To a solution of compound **99-1** (50 mg, 0.14 mmol, 1 *eq*) in MeOH (1 mL) were added compound **99-1a** (77.1 mg, 0.83 mmol, 6 *eq*, HCl) and TEA (139.2 mg, 1.38 mmol, 0.19 mL, 10 *eq*). The mixture was stirred at 80°C for 3 hr. The reaction mixture was concentrated in vacuum.

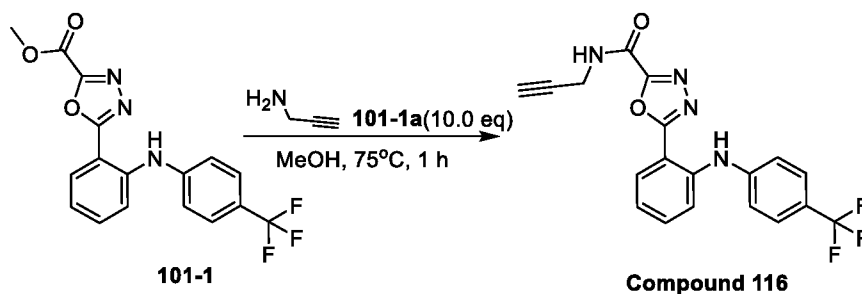
The crude product was purified by prep-HPLC. LCMS and ^1H NMR confirmed that **Compound 114** (24.1 mg, 62.4 μmol , 45.3% yield) was obtained. LCMS (ESI): RT = 0.834 min, mass calcd. For $\text{C}_{18}\text{H}_{12}\text{F}_3\text{N}_5\text{O}_2$, 387.09 m/z found 388.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.27 (s, 1H), 8.05 (d, $J = 7.8$ Hz, 1H), 7.76 (br s, 1H), 7.62 (d, $J = 8.5$ Hz, 2H), 7.52 - 7.42 (m, 2H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.05 - 6.97 (m, 1H), 4.47 (d, $J = 6.0$ Hz, 2H).

Example 100: N-(but-3-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 115)



[00434] To a solution of compound **100-1** (50 mg, 0.14 mmol, 1 *eq*) in MeOH (2 mL) were added K_2CO_3 (95.1 mg, 0.69 mmol, 5 *eq*) and compound **100-1a** (145.2 mg, 1.38 mmol, 10 *eq*). The mixture was stirred at 75°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with H_2O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by prep-TLC. LCMS and ^1H NMR confirmed that **Compound 115** (4.33 mg, 10.8 μmol , 7.8% yield) was obtained. LCMS (ESI): RT = 0.881 min, mass calcd. For $\text{C}_{20}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_2$, 400.11 m/z found 400.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.29 (s, 1H), 7.99 (dd, $J = 1.2, 8.1$ Hz, 1H), 7.53 (d, $J = 8.5$ Hz, 2H), 7.45 - 7.33 (m, 3H), 7.30 (d, $J = 8.5$ Hz, 2H), 6.93 (t, $J = 7.5$ Hz, 1H), 3.62 (q, $J = 6.4$ Hz, 2H), 2.51 (dt, $J = 2.6, 6.4$ Hz, 2H), 2.02 (t, $J = 2.6$ Hz, 1H).

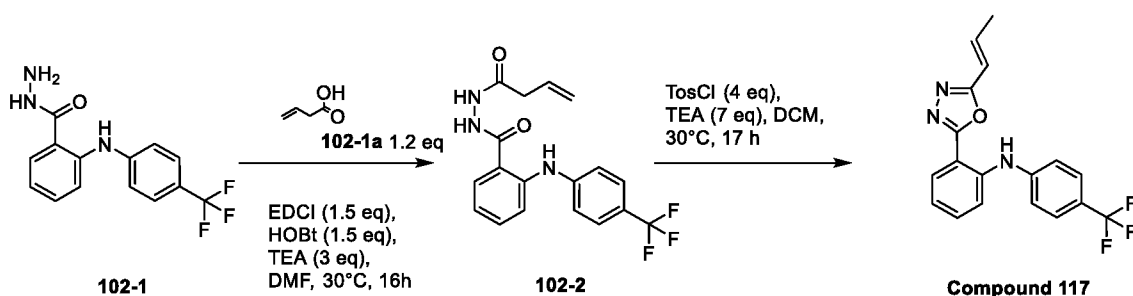
Example 101: N-(prop-2-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 116)



[00435] To a solution of compound **101-1** (50 mg, 0.14 mmol, 1 *eq*) in MeOH (1 mL) was added compound **101-1a** (75.8 mg, 1.38 mmol, 88 μL , 10 *eq*). The mixture was stirred at 75°C for 1 hr. The reaction mixture was filtered and the solid was collected to give **Compound 116** (27 mg, 69

umol, 50.7% yield). LCMS (ESI): RT = 0.862 min, mass calcd. For $C_{19}H_{13}F_3N_4O_2$, 386.10 m/z found 386.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.10 - 8.01 (m, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.52 - 7.47 (m, 1H), 7.47 - 7.42 (m, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.36 - 7.29 (m, 1H), 7.00 (t, J = 7.4 Hz, 1H), 4.33 (dd, J = 2.5, 5.5 Hz, 2H), 2.36 (t, J = 2.5 Hz, 1H).

Example 102: (E)-2-(5-(prop-1-en-1-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 117)



Step 1: N'-(but-3-enoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

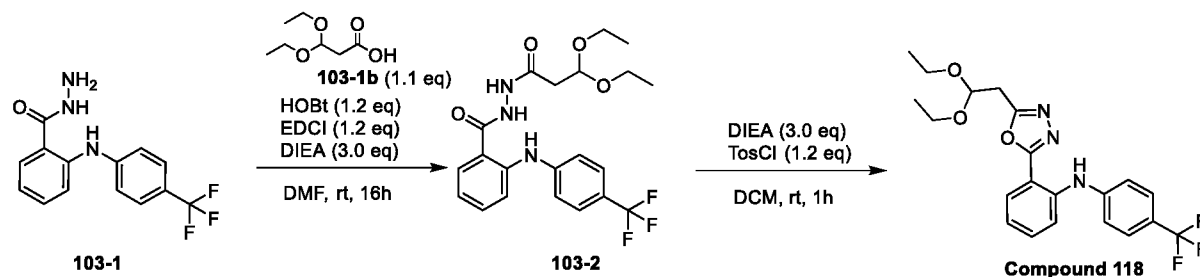
[00436] To a solution of **102-1a** (105 mg, 1.22 mmol, 1.2 eq), EDCI (292.2 mg, 1.52 mmol, 1.5 eq) and HOBt (206 mg, 1.52 mmol, 1.5 eq) in DMF (3 mL) at 30°C were added **102-1** (300 mg, 1.02 mmol, 1 eq) and TEA (308.4 mg, 3.05 mmol, 0.42 mL, 3 eq). The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **102-2** (175 mg, 0.45 mmol, 44.6% yield). LCMS (ESI): RT = 0.775 min, mass calc. for $C_{18}H_{16}F_3N_3O_2$ 363.12, m/z found 363.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.18 (brs, 1H), 7.61 (t, J = 7.1 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.46 - 7.43 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.5 Hz, 3H), 7.07 - 6.95 (m, 1H), 6.92 - 6.89 (m, 1H), 6.03 - 5.92 (m, 1H), 5.36 - 5.31 (m, 1H), 3.17 (d, J = 7.0 Hz, 1H), 1.91 (dd, J = 1.2, 6.9 Hz, 2H).

Step 2: (E)-2-(5-(prop-1-en-1-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00437] To a solution of **102-2** (120 mg, 0.33 mmol, 1 eq) in DCM (2 mL) at 30°C were added TEA (234.0 mg, 2.31 mmol, 0.32 mL, 7 eq) and TosCl (251.9 mg, 1.32 mmol, 4 eq). The mixture was stirred at 30°C for 17 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (20 mL *2) and brine (20 mL *2), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography and prep-HPLC to give **Compound 117** (40 mg, 0.11 mmol, 34.4% yield). LCMS (ESI): RT = 0.968 min, mass calc. for $C_{18}H_{14}F_3N_3O$ 345.11, m/z found 345.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.58

(s, 1H), 7.91 (dd, $J = 1.3$, 7.9 Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.41 - 7.36 (m, 3H), 7.01 - 6.91 (m, 2H), 6.51 (dd, $J = 1.7$, 15.9 Hz, 1H), 2.05 (dd, $J = 1.7$, 6.9 Hz, 3H)

Example 103: 2-(5-(2,2-diethoxyethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 118)



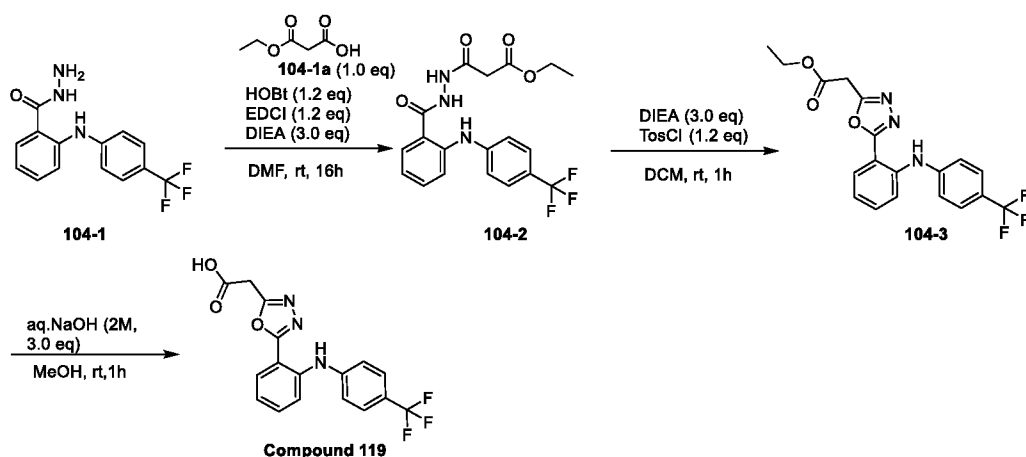
Step 1: N'-(3,3-diethoxypropanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00438] To a solution of **103-1b** (301.5 mg, 1.86 mmol, 1.1 *eq*), EDCI (388.7 mg, 2.03 mmol, 1.2 *eq*) and HOBT (274.0 mg, 2.03 mmol, 1.2 *eq*) in DMF (5 mL) was added compound **103-1** (0.5 g, 1.69 mmol, 1 *eq*) followed by DIEA (655.2 mg, 5.07 mmol, 0.88 mL, 3 *eq*). The reaction mixture was stirred at 25°C for 16 hours. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give compound **103-2** (0.45 g, 0.94 mmol, 55.7% yield).

Step 2: 2-(5-(2,2-diethoxyethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

To a solution of compound **103-2** (0.35 g, 0.79 mmol, 1 *eq*) and DIEA (308.8 mg, 2.39 mmol, 0.41 mL, 3 *eq*) in DCM (6 mL) was added TosCl (182.2 mg, 0.95 mmol, 1.2 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (10 mL) and washed with water (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give **Compound 118** (250 mg, 0.58 mmol, 73.6% yield). LCMS (ESI): RT = 1.075 min, mass calc. for C₂₁H₂₂F₃N₃O₃ 421.16, m/z found 422.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.54 (s, 1H), 7.89 (d, $J = 7.9$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.6$ Hz, 1H), 7.44 - 7.31 (m, 3H), 6.97 (t, $J = 7.6$ Hz, 1H), 5.06 (t, $J = 5.8$ Hz, 1H), 3.81 - 3.72 (m, 2H), 3.66 - 3.55 (m, 2H), 3.31 (d, $J = 5.8$ Hz, 2H), 1.22 (t, $J = 7.0$ Hz, 6H).

Example 104: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetic acid (Compound 119)



Step 1: ethyl 3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propanoate

[00439] To a solution of compound **104-1a** (223.2 mg, 1.6 mmol, 1 *eq*), EDCI (388.7 mg, 2.0 mmol, 1.2 *eq*) and HOBt (274.0 mg, 2.0 mmol, 1.2 *eq*) in DMF (5 mL) was added compound **104-1** (0.5 g, 1.6 mmol, 1 *eq*) followed by DIEA (655.2 mg, 5.0 mmol, 0.88 mL, 3 *eq*). The reaction mixture was stirred at 25°C for 16 hours. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated to give compound **104-2** (700 mg, crude), which was used for next step directly.

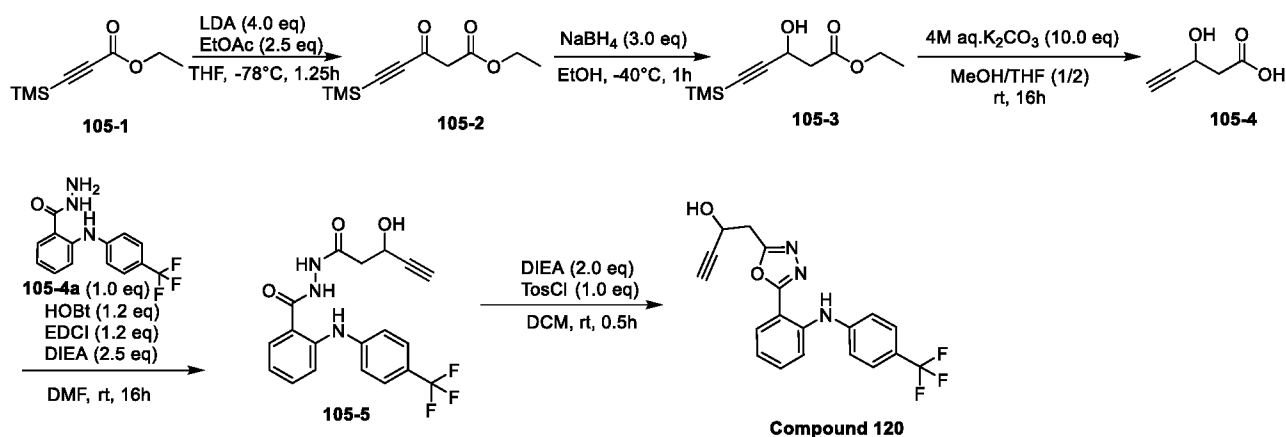
Step 2: ethyl 2-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]acetate

[00440] To a solution of compound **104-2** (700 mg, 1.7 mmol, 1 *eq*) and DIEA (663.0 mg, 5.1 mmol, 0.89 mL, 3 *eq*) in DCM (10 mL) was added TosCl (391.2 mg, 2.0 mmol, 1.2 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) and washed with water (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give compound **104-3** (410 mg, 0.99 mmol, 58.2% yield).

Step 3: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetic acid

[00441] To a solution of compound **104-3** (310 mg, 0.79 mmol, 1 *eq*) in MeOH (1 mL) was added NaOH (2 M, 1.19 mL, 3 *eq*). The reaction was stirred at 25°C for 1 hr. Another batch was combined. The reaction was concentrated. The aqueous layer was adjusted pH to 3-4 with 2N aq. HCl and filtered. **Compound 119** (350 mg, 0.94 mmol, 79.4% yield) was obtained and then used for next step directly. LCMS (ESI): RT = 0.936 min, mass calc. for C₁₇H₁₂F₃N₃O₃ 363.08, m/z found 363.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.44 - 12.87 (m, 1H), 9.22 (s, 1H), 7.89 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.50 (m, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.19 - 7.09 (m, 1H), 4.17 (s, 2H).

Example 105: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-2-ol (Compound 120)



Step 1: Ethyl 3-oxo-5-trimethylsilyl-pent-4-ynoate

[00442] To a solution of EtOAc (1.29 g, 14.6 mmol, 1.4 mL, 2.5 *eq*) in THF (20 mL) was added drop-wise LDA (2 M, 11.7 mL, 4 *eq*) at -78°C . After 15 min, compound **105-1** (1 g, 5.8 mmol, 1.1 mL, 1 *eq*) in THF (5 mL) was added drop-wise at -78°C . The reaction was stirred at -78°C for 1 hr. AcOH (1 mL) was added to the solution. The reaction was poured into ice/water slurry with 2N aq. HCl maintaining aqueous layer at the pH 3 and extracted with EA (2*50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel to give compound **105-2** (100 mg, 0.47 mmol, 8% yield).

Step 2: ethyl 3-hydroxy-5-trimethylsilyl-pent-4-ynoate

[00443] To a solution of compound **105-2** (0.1 g, 0.47 mmol, 1 *eq*) in EtOH (3 mL) was added NaBH_4 (53.4 mg, 1.4 mmol, 3 *eq*) at -40°C and the reaction was stirred at this temperature for 1 hr. The reaction was quenched by 2M aq. HCl (5 mL) and washed with EA (2*20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to give compound **105-3** (20 mg, 93.3 μmol , 19.8% yield).

Step 3: 3-hydroxypent-4-ynoic acid

[00444] A solution of K_2CO_3 (128.9 mg, 0.93 mmol, 10 *eq*) in H_2O (1 mL) was added to the solution of compound **105-3** (20 mg, 93.3 μmol , 1 *eq*) in MeOH (1 mL) and THF (2 mL). The reaction was stirred at 25°C for 16 hr. The reaction was concentrated. EtOH (5 mL) was added and the solution was filtered. The filtrate was concentrated to give compound **105-4** (10 mg, crude), which was used for next step directly.

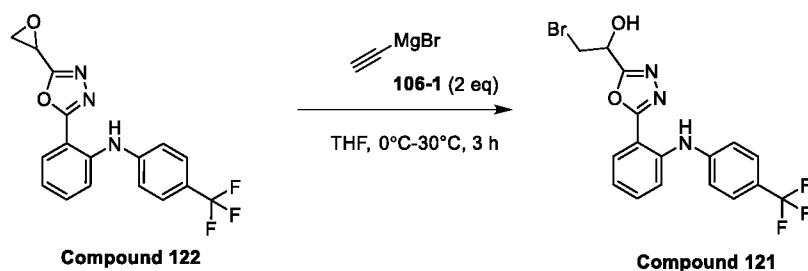
Step 4: N'-(3-hydroxypent-4-ynoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00445] To a solution of compound **105-4** (10 mg, 87.6 μmol , 1 *eq*), HOBt (14.2 mg, 0.1 mmol, 1.2 *eq*) and EDCI (20.1 mg, 0.1 mmol, 1.2 *eq*) in DMF (1 mL) was added compound **105-4a** (25.8 mg, 87.6 μmol , 1 *eq*) followed by DIEA (28.3 mg, 0.21 mmol, 38 μL , 2.5 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was diluted with EA (15 mL) and washed with brine (2*5

mL). The organic layer was dried over Na_2SO_4 and concentrated to give compound **105-5** (25 mg, crude), which was used for next step directly.

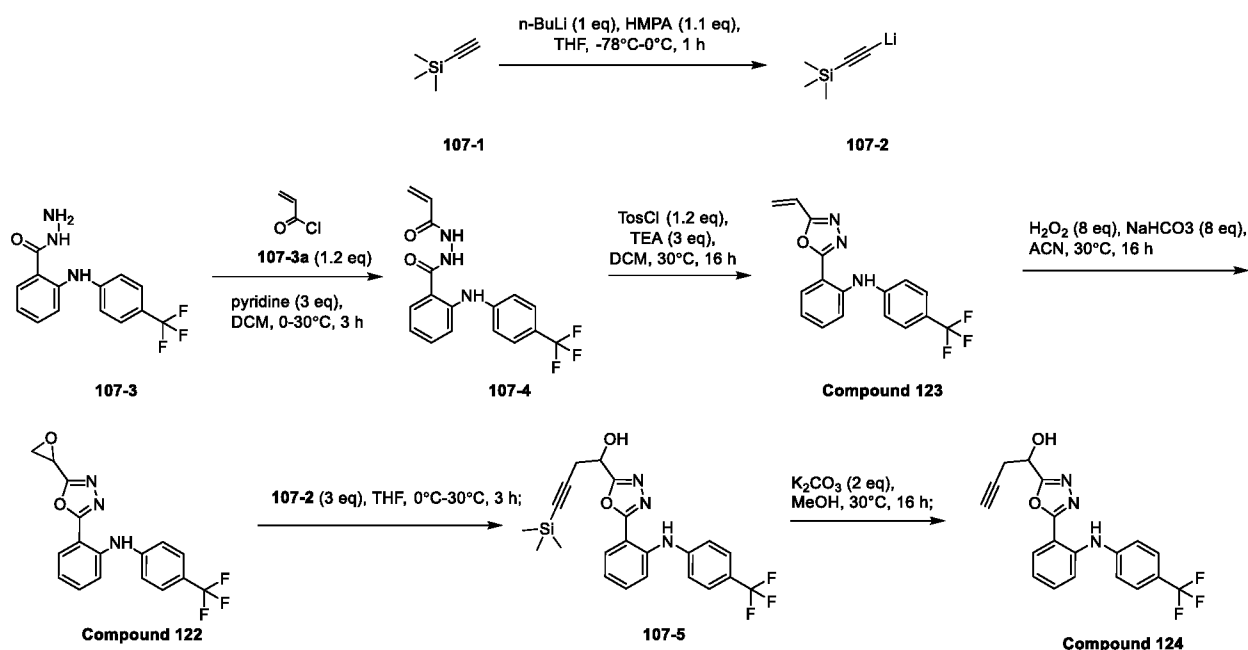
Step 5: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-2-ol [00446] To a solution of compound **105-5** (25 mg, 63.8 μmol , 1 *eq*) and TosCl (12.1 mg, 63.8 μmol , 1.0 *eq*) in DCM (1 mL) was added DIEA (16.5 mg, 0.12 mmol, 22 μL , 2.0 *eq*). The reaction was stirred at 25°C for 30 min. The reaction was diluted with DCM (10 mL) and washed with H_2O (2*5 mL). The organic layer was dried over Na_2SO_4 and concentrated. The reaction was purified by prep-HPLC to give **Compound 120** (1.3 mg, 3.5 μmol , 5.5% yield). LCMS (ESI): RT = 0.961 min, mass calc. for $\text{C}_{19}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$ 373.14, m/z found 374.0 $[\text{M}+1]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.48 (br s, 1H), 7.89 (br d, $J = 8.1$ Hz, 1H), 7.59 (br d, $J = 8.0$ Hz, 2H), 7.52 (br d, $J = 8.3$ Hz, 1H), 7.42 (br d, $J = 7.3$ Hz, 1H), 7.37 (br d, $J = 8.6$ Hz, 2H), 6.98 (t, $J = 7.4$ Hz, 1H), 5.03 - 4.94 (m, 1H), 3.41 (br d, $J = 5.5$ Hz, 2H), 2.57 (s, 1H).

Example 106: 2-bromo-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 121)



[00447] To a solution of **Compound 122** (15.0 mg, 43.2 μmol , 1 *eq*) in THF (1 mL) at 0°C was added **106-1** (0.5 M, 0.17 mL, 2 *eq*), and the mixture was stirred at 30°C for 3 h. The reaction mixture was quenched with saturated NH_4Cl (10 mL), diluted with water (10 mL) and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give **Compound 121** (10.4 mg, 23.7 μmol , 54.8% yield). LCMS (ESI): RT = 0.867 min, mass calc. for $\text{C}_{17}\text{H}_{13}\text{BrF}_3\text{N}_3\text{O}_2$ 427.01, m/z found 429.8 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1H), 7.92 (dd, $J = 1.5, 8.0$ Hz, 1H), 7.60 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.45 - 7.39 (m, 1H), 7.37 (d, $J = 8.5$ Hz, 2H), 7.01 - 6.96 (m, 1H), 5.38 - 5.29 (m, 1H), 3.98 - 3.88 (m, 2H), 3.18 (d, $J = 6.8$ Hz, 1H).

Example 107: 2-(5-(oxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 122), N-(4-(trifluoromethyl)phenyl)-2-(5-vinyl-1,3,4-oxadiazol-2-yl)aniline (Compound 123), and 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-1-ol (Compound 124)



Step 1: ((trimethylsilyl)ethynyl)lithium

[00448] To a solution of **107-1** (1 g, 10.18 mmol, 1.41 mL, 1 *eq*) and HMPA (2.01 g, 11.20 mmol, 1.97 mL, 1.1 *eq*) in THF (20 mL) at -78°C was added *n*-BuLi (2.5 M, 4.07 mL, 1.0 *eq*) drop-wise, and the mixture was stirred at 0°C for 1 h. The mixture was used directly for next step.

Step 2: *N'*-acryloyl-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00449] To a solution of **107-3** (500 mg, 1.69 mmol, 1 *eq*) and pyridine (401.9 mg, 5.08 mmol, 0.41 mL, 3 *eq*) in DCM (10 mL) at 0°C was added **107-3a** (183.9 mg, 2.03 mmol, 0.17 mL, 1.2 *eq*), and the mixture was stirred at 30°C for 3 h. The mixture was quenched with water (1 mL) and concentrated to give a residue. The residue was purified by flash silica gel chromatography to give **107-4** (170 mg, 0.49 mmol, 28.7% yield). LCMS (ESI): RT = 0.762 min, mass calc. for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$ 349.10, m/z found 349.9 $[\text{M}+\text{H}]^{+}$.

Step 3: N-(4-(trifluoromethyl)phenyl)-2-(5-vinyl-1,3,4-oxadiazol-2-yl)aniline (Compound 123)

[00450] To a solution of **107-4** (70.0 mg, 0.20 mmol, 1 *eq*) and TEA (60.8 mg, 0.60 mmol, 84 μL , 3 *eq*) in DCM (3 mL) at 30°C was added TosCl (45.8 mg, 0.24 mmol, 1.2 *eq*), and the mixture was stirred at 30°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 123** (30 mg, 90.6 μmol , 45.2% yield). LCMS (ESI): RT = 0.933 min, mass calc. for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_3\text{O}$ 331.09, m/z found 331.9 $[\text{M}+\text{H}]^{+}$; ^1H NMR (400 MHz, CDCl_3) δ 9.55 (s, 1H), 7.94 (dd, J = 1.5, 8.0 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.44 - 7.35 (m, 3H), 7.02 - 6.96 (m, 1H), 6.81 (dd, J = 11.3, 17.6 Hz, 1H), 6.40 (d, J = 17.8 Hz, 1H), 5.95 - 5.89 (m, 1H), 5.92 (d, J = 11.8 Hz, 1H).

Step 4: 2-(5-(oxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 122)

[00451] To a solution of **Compound 123** (120 mg, 0.36 mmol, 1 *eq*) in ACN (4 mL) at 30°C were added H₂O₂ (328.6 mg, 2.90 mmol, 0.28 mL, 30% purity, 8 *eq*) and NaHCO₃ (243.4 mg, 2.90 mmol, 8 *eq*), and the mixture was stirred at 30°C for 16 h. The reaction mixture was quenched with saturated Na₂SO₃ (30 mL), concentrated under reduced pressure to remove ACN. The residue was extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 122** (19.0 mg, 53.1 umol, 14.7% yield). LCMS (ESI): RT = 0.877 min, mass calc. for C₁₇H₁₂F₃N₃O₂ 347.09, m/z found 347.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 7.86 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 - 7.48 (m, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.00 - 6.94 (m, 1H), 4.26 (dd, *J* = 2.4, 4.1 Hz, 1H), 3.46 (dd, *J* = 2.4, 5.4 Hz, 1H), 3.36 (dd, *J* = 4.1, 5.4 Hz, 1H).

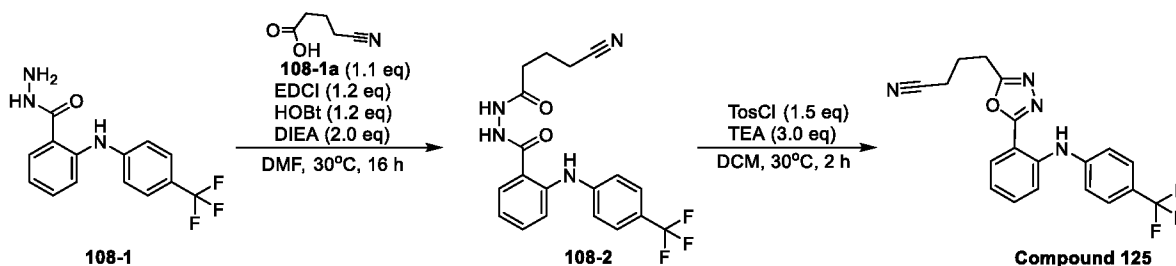
Step 5: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)-4-(trimethylsilyl)but-3-yn-1-ol

[00452] To a solution of **Compound 122** (20 mg, 57.6 umol, 1 *eq*) in THF (0.5 mL) at 0°C was added compound **107-2** (0.37 M, 0.47 mL, 3 *eq*), and the resulting mixture was stirred at 30°C for 3 h. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL), then diluted with water (5 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **107-5** (25.0 mg, 56.1 umol, 97.4% yield) as crude, which was used directly for next step. LCMS (ESI): RT = 0.975 min, mass calc. for C₂₂H₂₂F₃N₃O₂Si 445.14, m/z found 446.2 [M+H]⁺.

Step 6: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-1-ol (Compound 124)

[00453] To a solution of **107-5** (23.0 mg, 51.6 umol, 1 *eq*) in MeOH (1 mL) at 30°C was added K₂CO₃ (14.3 mg, 0.10 mmol, 2 *eq*), and the resulting mixture was stirred at 30°C for 16 h. The reaction mixture was filtered to remove the solid. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 124** (6.5 mg, 17.4 umol, 33.7% yield). LCMS (ESI): RT = 0.855 min, mass calc. for C₁₉H₁₄F₃N₃O₂ 373.10, m/z found 373.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 7.92 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 5.23 (t, *J* = 5.8 Hz, 1H), 3.08 (brs, 1H), 3.04 - 2.97 (m, 2H), 2.16 (t, *J* = 2.6 Hz, 1H).

Example 108: 4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile (Compound 125)



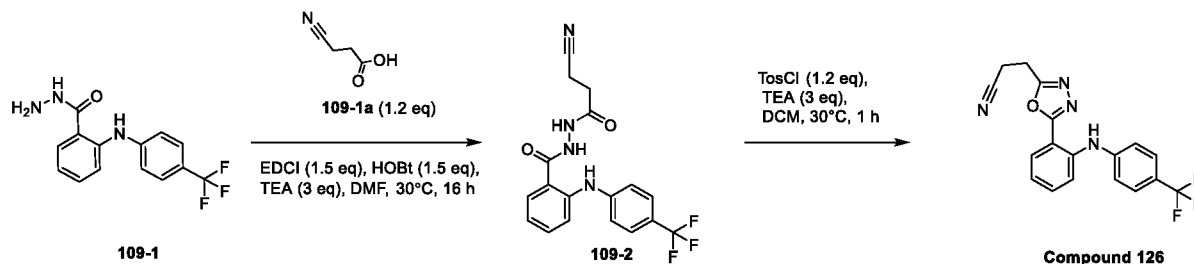
Step 1: N'-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00454] To a solution of compound **108-1** (200 mg, 0.68 mmol, 1 *eq*) and compound **108-1a** (84 mg, 0.75 mmol, 1.1 *eq*) in DMF (3 mL) were added EDCI (155 mg, 0.71 mmol, 1.2 *eq*), HOBt (110 mg, 0.81 mmol, 1.2 *eq*) and DIEA (175 mg, 1.35 mmol, 0.24 mL, 2 *eq*). The mixture was stirred at 30°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL*2) and brine (5 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. Compound **108-2** (165 mg, 0.42 mmol, 62% yield) was obtained.

Step 2: 4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile

[00455] To a solution of compound **108-2** (100 mg, 0.26 mmol, 1 *eq*) in DCM (1 mL) were added TosCl (73 mg, 0.38 mmol, 1.5 *eq*) and TEA (78 mg, 0.77 mmol, 0.1 mL, 3 *eq*). The mixture was stirred at 30°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 125** (47.8 mg, 0.13 mmol, 50% yield) was obtained. LCMS (ESI): RT = 0.879 min, mass calcd. For C₁₉H₁₅F₃N₄O, 372.12 m/z found 372.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.47 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.45 - 7.40 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.06 - 6.94 (m, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.31 (quin, *J* = 7.2 Hz, 2H).

Example 109: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile (Compound 126)



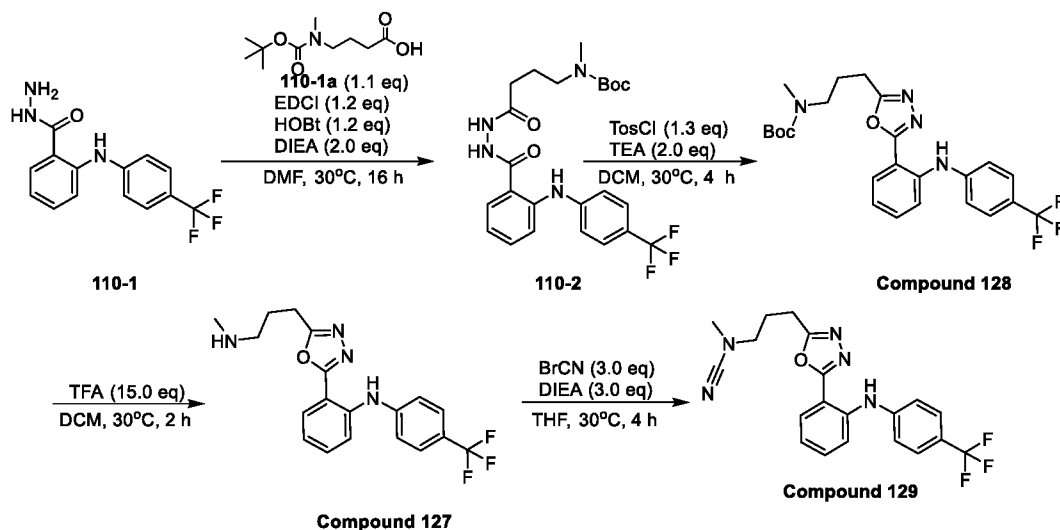
Step 1: N'-((3-cyanopropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00456] To a solution of **109-1a** (40.3 mg, 0.41 mmol, 1.2 *eq*), EDCI (97.4 mg, 0.51 mmol, 1.5 *eq*) and HOBt (68.7 mg, 0.51 mmol, 1.5 *eq*) in DMF (2 mL) at 30°C was added **109-1** (100 mg, 0.34

mmol, 1 *eq*) and then TEA (102.8 mg, 1.02 mmol, 0.14 mL, 3 *eq*), and the resulting mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **109-2** (160 mg, 0.29 mmol, 86.2% yield), which was used directly for next step. LCMS (ESI): RT = 0.749 min, mass calc. for C₁₈H₁₅F₃N₄O₂ 376.11, m/z found 399.0 [M+23]⁺.

Step 2: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile [00457] To a solution of **109-2** (150 mg, 0.27 mmol, 1 *eq*) and TEA (83.1 mg, 0.82 mmol, 0.11 mL, 3 *eq*) in DCM (1 mL) at 30°C was added TosCl (62.7 mg, 0.33 mmol, 1.2 *eq*), and the resulting mixture was stirred at 30°C for 1 h. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give 50 mg sample. The 50 mg sample was purified further by prep-HPLC to give **Compound 126** (14.0 mg, 39.1 μmol, 14.3% yield). LCMS (ESI): RT = 0.862 min, mass calc. for C₁₈H₁₃F₃N₄O 358.10, m/z found 358.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 7.88 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.95 (m, 1H), 3.36 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.4 Hz, 2H).

Example 110: 2-(5-(3-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 127), tert-butyl methyl(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 128), and N-methyl-N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 129)



Step 1: tert-butyl N-methyl-N-[4-oxo-4-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]butyl]carbamate

[00458] To a solution of compound **110-1** (200 mg, 0.68 mmol, 1 *eq*) and compound **110-1a** (161 mg, 0.75 mmol, 1.1 *eq*) in DMF (3 mL) were added EDCI (155 mg, 0.81 mmol, 1.2 *eq*), HOBT (109 mg, 0.81 mmol, 1.2 *eq*) and DIEA (175 mg, 1.35 mmol, 0.24 mL, 2 *eq*). The mixture was stirred at 30°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL*2) and brine (5 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS confirmed that compound **110-2** (260 mg, 0.49 mmol, 72% yield) was obtained.

Step 2: tert-butyl methyl(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 128)

[00459] To a solution of compound **110-2** (260 mg, 0.53 mmol, 1 *eq*) in DCM (3 mL) were added TEA (106 mg, 1.05 mmol, 0.15 mL, 2 *eq*) and TosCl (130 mg, 0.68 mmol, 1.3 *eq*). The mixture was stirred at 30°C for 4 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that **Compound 128** (162 mg, 0.33 mmol, 63% yield) was obtained. LCMS (ESI): RT = 0.973 min, mass calcd. For C₂₄H₂₇F₃N₄O₃, 476.20 m/z found 499.0 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.53 (s, 1H), 7.88 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.42 - 7.33 (m, 3H), 6.97 (t, *J* = 7.2 Hz, 1H), 3.41 (br t, *J* = 6.7 Hz, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.90 (s, 3H), 2.12 (quin, *J* = 7.3 Hz, 2H), 1.45 (s, 9H).

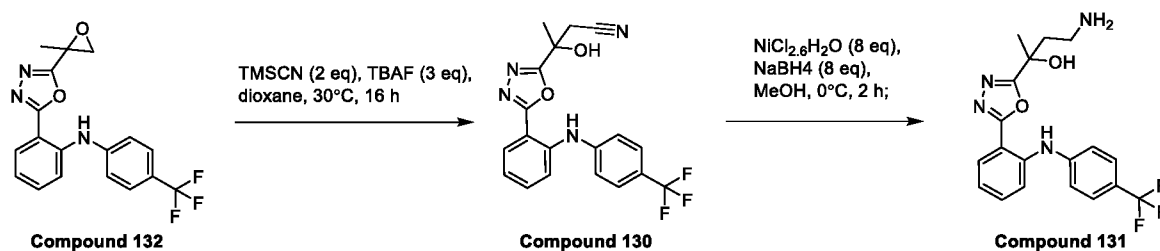
Step 3: 2-(5-(3-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 127)

[00460] To a solution of **Compound 128** (150 mg, 0.31 mmol, 1 *eq*) in DCM (2 mL) was added TFA (538 mg, 4.72 mmol, 0.35 mL, 15 *eq*). The mixture was stirred at 30°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with saturated aq. Na₂CO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. LCMS and ¹H NMR confirmed that **Compound 127** (110 mg, 0.29 mmol, 91% yield) was obtained. LCMS (ESI): RT = 2.008 min, mass calcd. For C₁₉H₁₉F₃N₄O, 376.15 m/z found 377.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.46 (br s, 1H), 7.56 - 7.44 (m, 4H), 7.37 - 7.30 (m, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.90 (t, *J* = 7.2 Hz, 1H), 3.41 (t, *J* = 7.0 Hz, 2H), 2.96 (s, 3H), 2.74 - 2.63 (m, 2H), 2.08 - 1.94 (m, 2H).

Step 4: N-methyl-N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 129)

[00461] To a solution of **Compound 128** (70 mg, 0.19 mmol, 1 *eq*) in THF (1 mL) were added BrCN (59 mg, 0.56 mmol, 41 μ L, 3 *eq*) and DIEA (72 mg, 0.56 mmol, 97 μ L, 3 *eq*). The mixture was stirred at 30°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 129** (4.5 mg, 11 μ mol, 6% yield) was obtained. LCMS (ESI): RT = 2.008 min, mass calcd. For C₂₀H₁₈F₃N₅O, 401.15 m/z found 402.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.47 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.45 - 7.34 (m, 3H), 7.03 - 6.93 (m, 1H), 3.20 (t, *J* = 6.9 Hz, 2H), 3.09 (t, *J* = 7.3 Hz, 2H), 2.93 (s, 3H), 2.27 (quin, *J* = 7.0 Hz, 2H).

Example 111: 3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile (Compound 130) and 4-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol (Compound 131)



Step 1: 3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile (Compound 130)

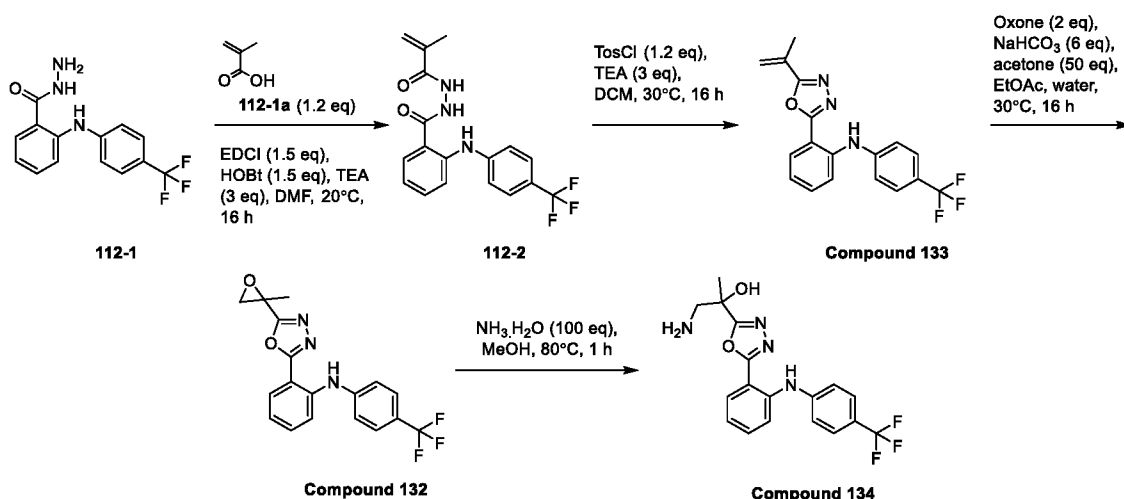
[00462] To a solution of **Compound 132** (25 mg, 69.2 μ mol, 1 *eq*) in dioxane (2 mL) at 30°C was added TMSCN (13.7 mg, 0.14 mmol, 17 μ L, 2 *eq*) and then TBAF (1 M, 0.21 mL, 3 *eq*), and the resulting mixture was stirred at 30°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 130** (20.0 mg, 50.2 μ mol, 72.5% yield). LCMS (ESI): RT = 0.841 min, mass calc. for C₁₉H₁₅F₃N₄O₂ 388.11, m/z found 388.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.36 (s, 1H), 7.91 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 - 7.49 (m, 1H), 7.42 (dt, *J* = 1.4, 7.8 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.97 (m, 1H), 3.44 (brs, 1H), 3.17 (q, *J* = 16.8 Hz, 2H), 1.95 (s, 3H).

Step 2: 4-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol (Compound 131)

[00463] To a solution of **Compound 130** (140 mg, 0.36 mmol, 1 *eq*) in MeOH (3 mL) at 0°C was added NiCl₂·6H₂O (685.5 mg, 2.88 mmol, 8 *eq*) and then NaBH₄ (109.1 mg, 2.88 mmol, 8 *eq*), and the resulting mixture was stirred at 0°C for 2 h. After quenched with saturated NH₄Cl solution (20 mL) at 0°C, it was stirred at 30°C for 16 h. The mixture was concentrated to give a residue. The

residue was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. The collected pure fractions was basified with saturated NaHCO₃ solution to pH = 8-9, then concentrated to remove ACN and then extracted with EA (50 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 131** (45.0 mg, 0.11 mmol, 31.8% yield). LCMS (ESI): RT = 0.705 min, mass calc. for C₁₉H₁₉F₃N₄O₂ 392.15, m/z found 393.0 [M+1]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.73 (d, *J* = 6.9 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.48 - 7.44 (m, 1H), 7.42 - 7.36 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 3.48 (brs, 1H), 3.40 - 3.32 (m, 1H), 2.12 (d, *J* = 6.4 Hz, 2H), 1.50 (s, 3H).

Example 112: 2-(5-(2-methyloxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 132), 2-(5-(prop-1-en-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 133), and 1-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol (Compound 134)



Step 1: *N'*-methacryloyl-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00464] To a solution of **112-1a** (174.9 mg, 2.03 mmol, 0.17 mL, 1.2 eq), EDCI (487.0 mg, 2.54 mmol, 1.5 eq) and HOBt (343.2 mg, 2.54 mmol, 1.5 eq) in DMF (10 mL) at 20°C was added **112-1** (500 mg, 1.69 mmol, 1 eq) and then TEA (514.1 mg, 5.08 mmol, 0.71 mL, 3 eq), and the mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **112-2** (440 mg, 1.17 mmol, 69.2% yield). LCMS (ESI): RT = 0.783 min, mass calc. for C₁₈H₁₆F₃N₃O₂ 363.12, m/z found 363.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.18 (s, 1H), 9.02 (brs, 1H), 8.72 (brs,

1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 2H), 7.48 - 7.44 (m, 1H), 7.43 - 7.38 (m, 1H), 7.24 (d, $J = 8.3$ Hz, 2H), 6.94 (t, $J = 7.5$ Hz, 1H), 5.95 (s, 1H), 5.53 (s, 1H), 2.06 (s, 3H).

Step 2: 2-(5-(prop-1-en-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 133)

[00465] To a solution of **112-2** (200 mg, 0.55 mmol, 1 *eq*) and TEA (167.1 mg, 1.65 mmol, 0.23 mL, 3 *eq*) in DCM (3 mL) at 30°C was added TosCl (125.9 mg, 0.66 mmol, 1.2 *eq*), and the mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 133** (120 mg, 0.34 mmol, 61.2% yield). LCMS (ESI): RT = 0.978 min, mass calc. for C₁₈H₁₄F₃N₃O 345.11, m/z found 345.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.62 (s, 1H), 7.94 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.44 - 7.39 (m, 1H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.03 - 6.95 (m, 1H), 6.13 (s, 1H), 5.63 (d, $J = 0.6$ Hz, 1H), 2.30 (s, 3H).

Step 3: 2-(5-(2-methyloxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 132)

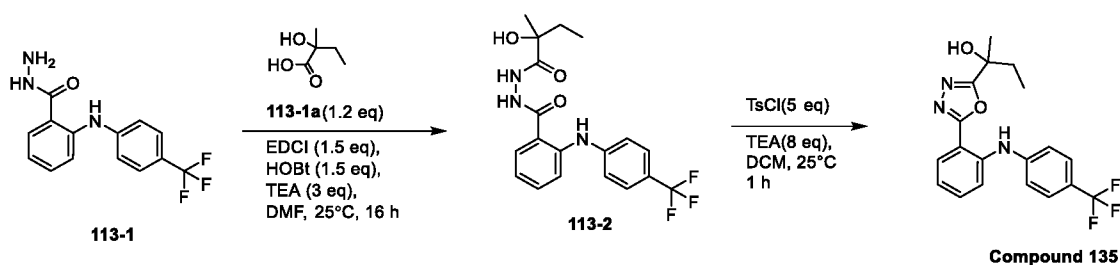
[00466] To a solution of **Compound 133** (120 mg, 0.35 mmol, 1 *eq*) and NaHCO₃ (175.2 mg, 2.09 mmol, 81 μ L, 6 *eq*) in water (2 mL) and EtOAc (2 mL) at 30°C was added acetone (1.01 g, 17.38 mmol, 1.28 mL, 50 *eq*) and then Oxone (427.3 mg, 0.70 mmol, 2 *eq*), and the mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 132** (35.0 mg, 95.3 μ mol, 27.4% yield). LCMS (ESI): RT = 0.914 min, mass calc. for C₁₈H₁₄F₃N₃O₂ 361.10, m/z found 361.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.85 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 7.8$ Hz, 1H), 7.40 (dt, $J = 1.5, 7.9$ Hz, 1H), 7.36 (d, $J = 8.3$ Hz, 2H), 6.97 (ddd, $J = 1.1, 7.2, 8.0$ Hz, 1H), 3.54 (d, $J = 5.5$ Hz, 1H), 3.16 (d, $J = 5.0$ Hz, 1H), 1.94 (s, 3H).

Step 4: 1-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol (Compound 134)

[00467] To a solution of **Compound 132** (30 mg, 83.0 μ mol, 1 *eq*) in MeOH (1 mL) at 30°C was added NH₃·H₂O (1.16 g, 8.30 mmol, 1.28 mL, 25% solution, 100 *eq*), and the mixture was stirred at 80°C for 1 h. The reaction mixture was concentrated under reduced pressure to give **Compound 134** (23.0 mg, 60.8 μ mol, 73.2% yield). LCMS (ESI): RT = 0.718 min, mass calc. for

$C_{18}H_{17}F_3N_4O_2$ 378.13, m/z found 379.0 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.93 (d, $J = 7.0$ Hz, 1H), 7.56 (d, $J = 8.3$ Hz, 2H), 7.49 (d, $J = 8.3$ Hz, 1H), 7.41 - 7.36 (m, 1H), 7.33 (d, $J = 8.5$ Hz, 2H), 6.96 (t, $J = 7.4$ Hz, 1H), 3.59 (d, $J = 12.5$ Hz, 1H), 2.89 (d, $J = 12.5$ Hz, 1H), 2.72 (brs, 3H), 1.66 (s, 3H).

Example 113: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol (Compound 135)



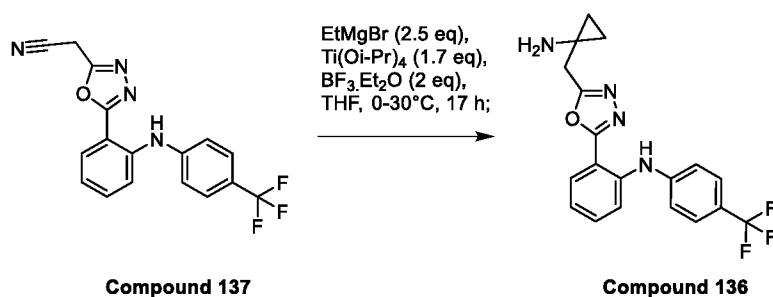
Step 1: N'-(2-hydroxy-2-methylbutanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00468] To a solution of 2-hydroxy-2-methyl-butanoic acid **113-1a** (48.0 mg, 0.41 mmol, 1.2 *eq*), EDCI (97.39 mg, 508.04 μ mol, 1.5 *eq*) and TEA (102.8 mg, 1.02 mmol, 0.14 mL, 3 *eq*) in DMF (1.5 mL) at 25°C were added **113-1** (100 mg, 0.34 mmol, 1 *eq*) and then HOBT (68.6 mg, 0.51 mmol, 1.5 *eq*) and the resulting mixture was stirred at 25°C for 16 h. The mixture was directly purified by prep-HPLC to give **113-2** (30 mg, 75.88 μ mol, 22.40% yield). LCMS (ESI): $R = 0.775$ min, mass calcd. For $C_{19}H_{20}F_3N_3O_3$ 418.0 found $[M+23]^+$.

Step 2: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol

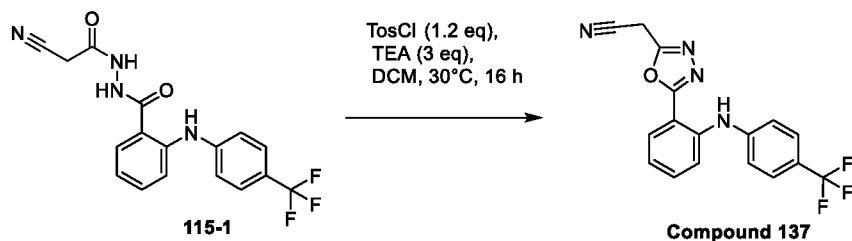
[00469] To a solution of compound **113-2** (25 mg, 63.2 μ mol, 1 *eq*) and TosCl (60.3 mg, 0.32 mmol, 5 *eq*) in DCM (3 mL) was added TEA (51.2 mg, 0.51 mmol, 70 μ L, 8 *eq*) at 25°C and the resulting mixture was stirred at 25°C for 1 h. The mixture was diluted with water (5 mL) and then diluted with EA (30 mL) and separated. The separated organic layer was washed with brine (10 mL) twice, dried by anhydrous Na_2SO_4 , filtered and concentrated under pressure to give a residue. The residue was directly purified by prep-HPLC to give **Compound 135** (7.7 mg, 20.54 μ mol, 32.48% yield). LCMS (ESI): $R = 0.898$ min, mass calcd. For $C_{19}H_{18}F_3N_3O_2$ 377.14 m/z found 377.9 $[M+1]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.24 (s, 1H), 7.94 (d, $J = 7.9$ Hz, 1H), 7.63 (d, $J = 8.6$ Hz, 2H), 7.59 - 7.51 (m, 2H), 7.33 (d, $J = 8.5$ Hz, 2H), 7.22 - 7.11 (m, 1H), 5.97 - 5.79 (m, 1H), 1.96 - 1.80 (m, 2H), 1.63 - 1.45 (m, 3H), 0.83 (t, $J = 7.4$ Hz, 3H).

Example 114: 2-(5-((1-aminocyclopropyl)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 136)



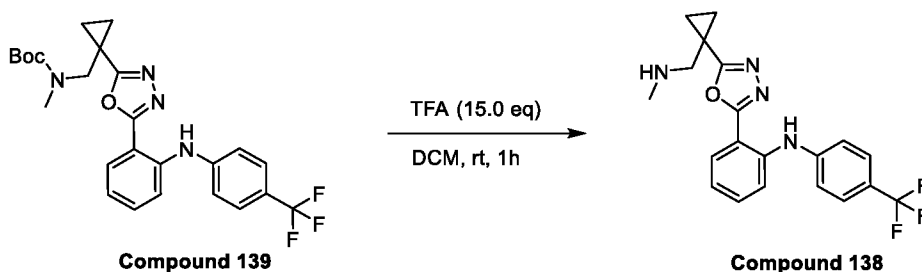
[00470] To a solution of **Compound 137** (50 mg, 0.15 mmol, 1 *eq*) in THF (1 mL) at 0°C were added Ti(*i*-PrO)₄ (70.2 mg, 0.25 mmol, 73 μ L, 1.7 *eq*) and then EtMgBr (3.0 M, 0.12 mL, 2.5 *eq*), and the mixture was stirred at 30°C for 1 h. After BF₃·Et₂O (137.4 mg, 0.29 mmol, 0.12 mL, 30% solution, 2 *eq*) was added at 0°C into the above mixture, the resulting mixture was stirred at 30°C for 16 h. The mixture was quenched with water (1 mL), diluted with saturated Na₂CO₃ solution (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 136** (5.0 mg, 12.6 μ mol, 8.6% yield). LCMS (ESI): RT = 0.739 min, mass calc. for C₁₉H₁₇F₃N₄O 374.14, *m/z* found 375.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H), 7.91 (s, 1H), 7.60 (d, *J* = 7.0 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.45 - 7.36 (m, 3H), 7.02 (s, 1H), 3.08 (brs, 2H), 0.83 (brs, 4H).

Example 115: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetonitrile (Compound 137)



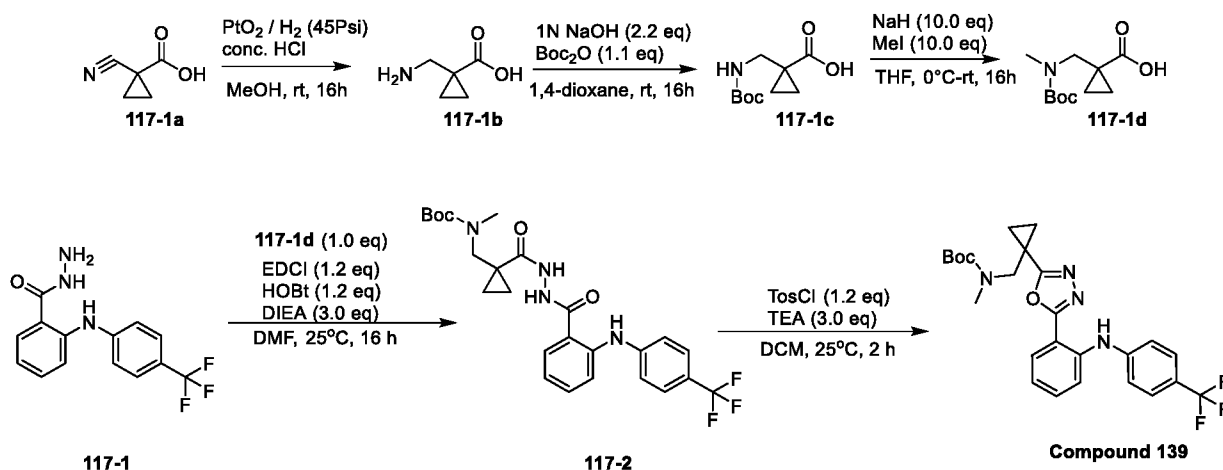
[00471] To a solution of **115-1** (350 mg, 0.97 mmol, 1 *eq*) and TEA (293.3 mg, 2.90 mmol, 0.40 mL, 3 *eq*) in DCM (5 mL) at 30°C was added TosCl (221.0 mg, 1.16 mmol, 1.2 *eq*), and the resulting mixture was stirred at 30°C for 16 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 137** (160 mg, 0.46 mmol, 48.1% yield). LCMS (ESI): RT = 0.857 min, mass calc. for C₁₇H₁₁F₃N₄O 344.09, *m/z* found 344.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.33 (s, 1H), 7.90 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.53 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.03 - 6.97 (m, 1H), 4.17 (s, 2H).

Example 116: 2-(5-(1-((methylamino)methyl)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 138)



[00472] To a solution of **Compound 139** (0.2 g, 0.4 mmol, 1 *eq*) in DCM (2 mL) was added TFA (700 mg, 6.14 mmol, 0.45 mL, 15 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) adjusted pH to 8-9 with Sat. Na₂CO₃ and washed with H₂O (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. **Compound 138** (120 mg, 0.3 mmol, 74% yield) was obtained without further purification. LCMS (ESI): RT = 0.836 min, mass calc. for C₂₀H₁₉F₃N₄O 388.15, m/z found 389.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 7.71 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.34 - 7.24 (m, 3H), 6.88 (t, *J* = 7.6 Hz, 1H), 2.94 (s, 2H), 2.46 - 2.39 (m, 3H), 1.40 - 1.31 (m, 2H), 1.12 - 1.04 (m, 2H).

Example 117: tert-butyl methyl((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)carbamate (Compound 139)



Step 1: 1-(aminomethyl)cyclopropanecarboxylic acid

[00473] To a solution of compound **117-1a** (1 g, 9 mmol, 1 *eq*) and HCl (12 M, 0.5 mL) in MeOH (40 mL) was added PtO₂ (0.3 g, 0.26 mmol, 2.94e-2 *eq*) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (45psi) at 25°C for 16 hours. The reaction was filtered and concentrated. Compound **117-1b** (1.2 g, 7.92 mmol, 87.9% yield, HCl) was used for next step directly. ¹H NMR (400 MHz, CD₃OD) δ 3.33 (td, *J* = 1.6, 3.3 Hz, 2H), 3.04 (s, 3H), 1.32 - 1.25 (m, 3H), 0.93 - 0.84 (m, 3H).

Step 2: 1-[(tert-butoxycarbonylamino)methyl]cyclopropanecarboxylic acid

[00474] A solution of compound **117-1b** (1.2 g, 7.9 mmol, 1 *eq*, HCl) and NaOH (1 M, 17 mL, 2.2 *eq*) in 1,4-dioxane (25 mL) was stirred at 25°C for 15 min. Boc₂O (1.9 g, 8.7 mmol, 2 mL, 1.1 *eq*)

was added to the solution. The reaction was stirred at 25°C for 16 hr. 1,4-dioxane was removed. The aqueous layer was adjusted pH to 3 with Sat. citric acid and extracted with EA (2*40 mL). The organic layer was dried over Na₂SO₄ and concentrated. Compound **117-1c** (1.5 g, 6.97 mmol, 88% yield) was used for next step directly. ¹H NMR (400 MHz, CD₃OD) δ 3.30 (s, 2H), 1.45 (s, 9H), 1.21 - 1.13 (m, 2H), 0.95 - 0.90 (m, 2H).

Step 3: 1-[[tert-butoxycarbonyl(methyl)amino]methyl]cyclopropanecarboxylic acid

[00475] To a solution of compound **117-1c** (0.7 g, 3.2 mmol, 1 *eq*) and MeI (4.6 g, 32.5 mmol, 2 mL, 10 *eq*) in THF (15 mL) was added NaH (1.30 g, 32.52 mmol, 60% purity, 10 *eq*) in portions at 0°C. The reaction was stirred at 25°C for 16 hr. The precipitate was formed. PE (15 mL) was added. The reaction was washed with water (2*20 mL). The aqueous layer was adjusted pH to 4 with Sat. citric acid and extracted with EA (2*30 mL). The organic layer was dried over Na₂SO₄ and concentrated. The compound **117-1d** (0.45 g, 1.9 mmol, 60% yield) was used for next step directly. ¹H NMR (400 MHz, CDCl₃) δ 3.58 (s, 2H), 2.92 (s, 3H), 1.46 (s, 9H), 1.40 - 1.25 (m, 2H), 1.10 - 1.00 (m, 2H).

Step 4: tert-butyl N-methyl-N-[[1-[[[2-[4-

(trifluoromethyl)anilino]benzoyl]amino]carbamoyle]cyclopropyl]methyl]carbamate

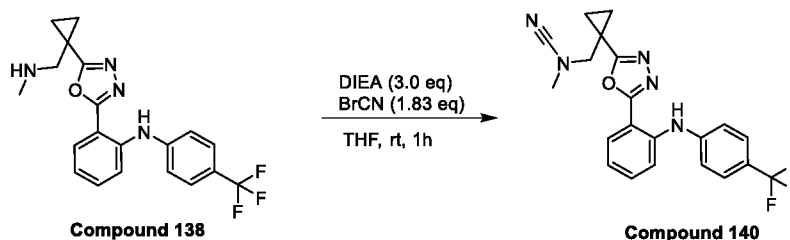
[00476] To a solution of compound **117-1** (300 mg, 1 mmol, 1 *eq*), HOBt (164.7 mg, 1.2 mmol, 1.2 *eq*) and EDCI (233.7 mg, 1.22 mmol, 1.2 *eq*) in DMF (5 mL) was added compound **117-1d** (232.9 mg, 1 mmol, 1 *eq*) followed by DIEA (393.9 mg, 3.05 mmol, 0.53 mL, 3 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was diluted with EA (60 mL) and washed with brine (2*20 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give compound **117-2** (360 mg, 0.68 mmol, 67% yield). LCMS confirmed that desired product was obtained. LCMS (ESI): RT = 1.018 min, mass calc. for C₂₅H₂₉F₃N₄O₄ 506.21, m/z found 507.1 [M+1]⁺.

Step 5: tert-butyl methyl((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)carbamate

[00477] To a solution of compound **117-2** (0.36 g, 0.71 mmol, 1 *eq*) and TosCl (162.6 mg, 0.85 mmol, 1.2 *eq*) in DCM (8 mL) was added DIEA (275.5 mg, 2.13 mmol, 0.37 mL, 3 *eq*). The reaction was stirred at 25°C for 2 hr. The reaction was diluted with DCM (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The reaction was purified by column chromatography on silica gel to give **Compound 139** (0.27 g, 0.55 mmol, 76.9% yield). LCMS (ESI): RT = 1.131 min, mass calc. for C₂₅H₂₇F₃N₄O₃ 488.20, m/z found 489.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (br s, 1H), 7.88 (br s, 1H), 7.59 (d, *J* = 8.5 Hz, 2H),

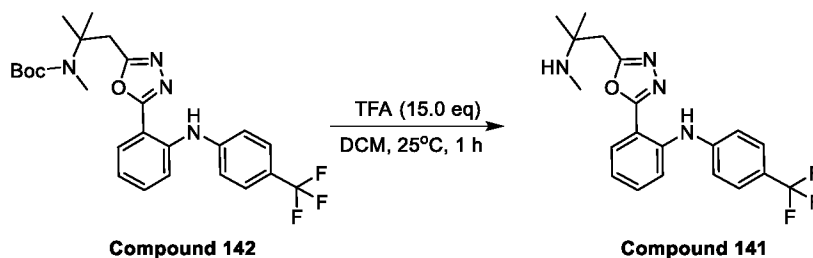
7.55 - 7.50 (m, 1H), 7.44 - 7.33 (m, 3H), 6.98 (t, $J = 7.4$ Hz, 1H), 3.90 - 3.79 (m, 2H), 2.99 (s, 3H), 1.44 (s, 11H), 1.31 - 1.19 (m, 2H).

Example 118: N-methyl-N-((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)cyanamide (Compound 140)



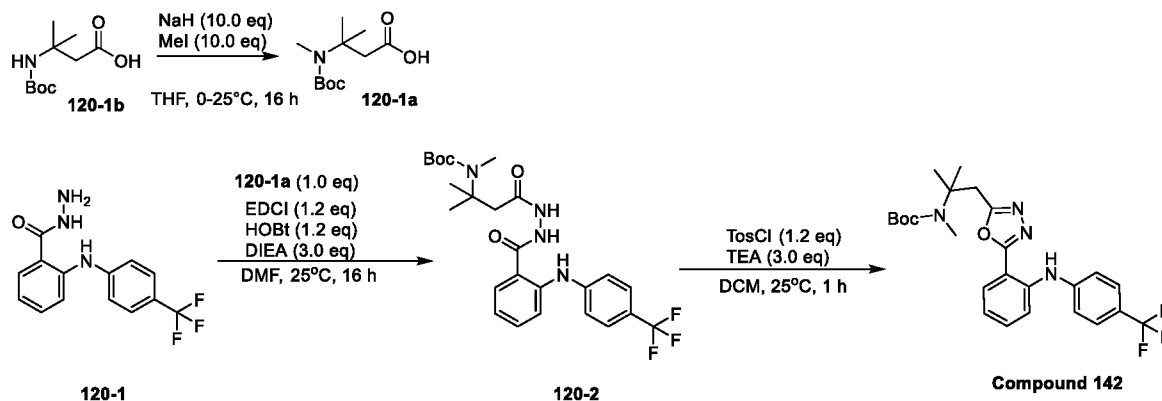
[00478] To a solution of **Compound 138** (0.1 g, 0.25 mmol, 1 *eq*) and DIEA (99.8 mg, 0.77 mmol, 0.13 mL, 3 *eq*) in THF (2 mL) was added BrCN (50 mg, 0.47 mmol, 34 μ L, 1.83 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with EA (30 mL) and washed with brine (3*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was triturated with EA (3 mL) and PE (10 mL), filtered to give **Compound 140** (60.5 mg, 0.14 mmol, 54.5% yield). LCMS (ESI): RT = 1.002 min, mass calc. for C₂₁H₁₈F₃N₅O 413.15, m/z found 414.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.36 (s, 1H), 7.76 (dd, $J = 1.2, 7.9$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 1H), 7.35 - 7.25 (m, 3H), 6.90 (t, $J = 7.4$ Hz, 1H), 3.44 (s, 2H), 2.99 (s, 3H), 1.50 - 1.40 (m, 2H), 1.31 - 1.18 (m, 2H).

Example 119: 2-(5-(2-methyl-2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 141)



[00479] To a solution of **Compound 142** (70 mg, 0.14 mmol, 1 *eq*) in DCM (2 mL) was added TFA (244 mg, 2.1 mmol, 0.15 mL, 15 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (5 mL) and washed with water (10 mL). The aqueous layer was adjusted pH to 8-9 with Sat.Na₂CO₃ and extracted with EA (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. 60 mg of crude **Compound 141** was obtained. 20 mg of crude product was purified by prep-HPLC to give pure **Compound 141** (1.9 mg, 4.8 μ mol, 3% yield). LCMS (ESI): RT = 0.847 min, mass calc. for C₂₀H₂₁F₃N₄O 390.17, m/z found 391.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H), 7.89 (d, $J = 6.8$ Hz, 1H), 7.60 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.44 - 7.36 (m, 3H), 6.99 (t, $J = 7.2$ Hz, 1H), 3.09 (s, 2H), 2.47 (s, 3H), 1.27 (s, 6H). 40 mg of remained crude product was used directly in the synthesis of **Compound 143**.

Example 120: tert-butyl methyl(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate (Compound 142)



Step 1: 3-[tert-butoxycarbonyl(methyl)amino]-3-methyl-butanoic acid

[00480] To a solution of **120-1b** (0.3 g, 1.3 mmol, 1 *eq*) and MeI (1.9 g, 13 mmol, 0.86 mL, 10 *eq*) in THF (8 mL) was added NaH (551.9 mg, 13.8 mmol, 60% purity, 10 *eq*) at 0°C. The reaction was warmed to 25°C and stirred at 25°C for 16 hr. PE (10 mL) was added to the solution. The reaction was washed with water (2*10 mL). The aqueous layer was adjusted pH to 4-5 with Sat. citric acid solution and extracted with EA (2*15 mL). The organic layer was dried over Na₂SO₄ and concentrated. Compound **120-1a** (140 mg, 0.6 mmol, 43% yield) was used for next step directly. ¹H NMR (400 MHz, CDCl₃) δ 2.88 (s, 2H), 2.79 (s, 3H), 1.37 (s, 9H), 1.37 (s, 6H).

Step 2: tert-butyl N-[1,1-dimethyl-3-oxo-3-[2-[2-[4-

(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]-N-methyl-carbamate

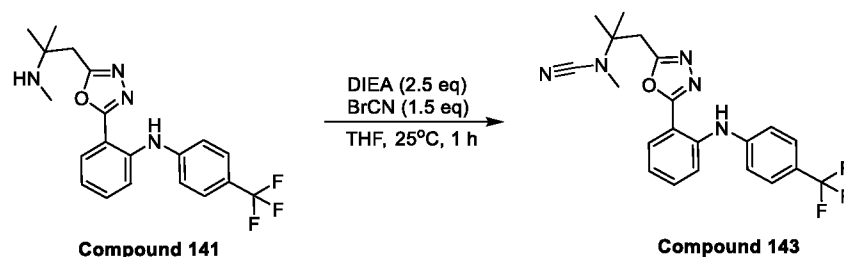
[00481] To a solution of **120-1** (178.7 mg, 0.6 mmol, 1 *eq*), **120-1a** (140 mg, 0.6 mmol, 1 *eq*), EDCI (139.2 mg, 0.72 mmol, 1.2 *eq*) and HOBt (98 mg, 0.72 mmol, 1.2 *eq*) in DMF (5 mL) was added DIEA (234 mg, 1.82 mmol, 0.31 mL, 3 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give **120-2** (170 mg, 0.29 mmol, 49% yield). LCMS (ESI): RT = 1.018 min, mass calc. for C₂₅H₃₁F₃N₄O₄ 508.23, m/z found 509.1 [M+1]⁺.

Step 3: tert-butyl methyl(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate

[00482] To a solution of **120-2** (170 mg, 0.33 mmol, 1 *eq*) and TosCl (76.4 mg, 0.4 mmol, 1.2 *eq*) in DCM (4 mL) was added Et₃N (101 mg, 1 mmol, 0.13 mL, 3 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with DCM (30 mL) and washed with H₂O (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give crude **Compound 142** (90 mg). 20 mg of crude product was re-purified by prep-HPLC to give **Compound 142** (10.2 mg, 20.7 μmol, 6.2% yield). LCMS (ESI):

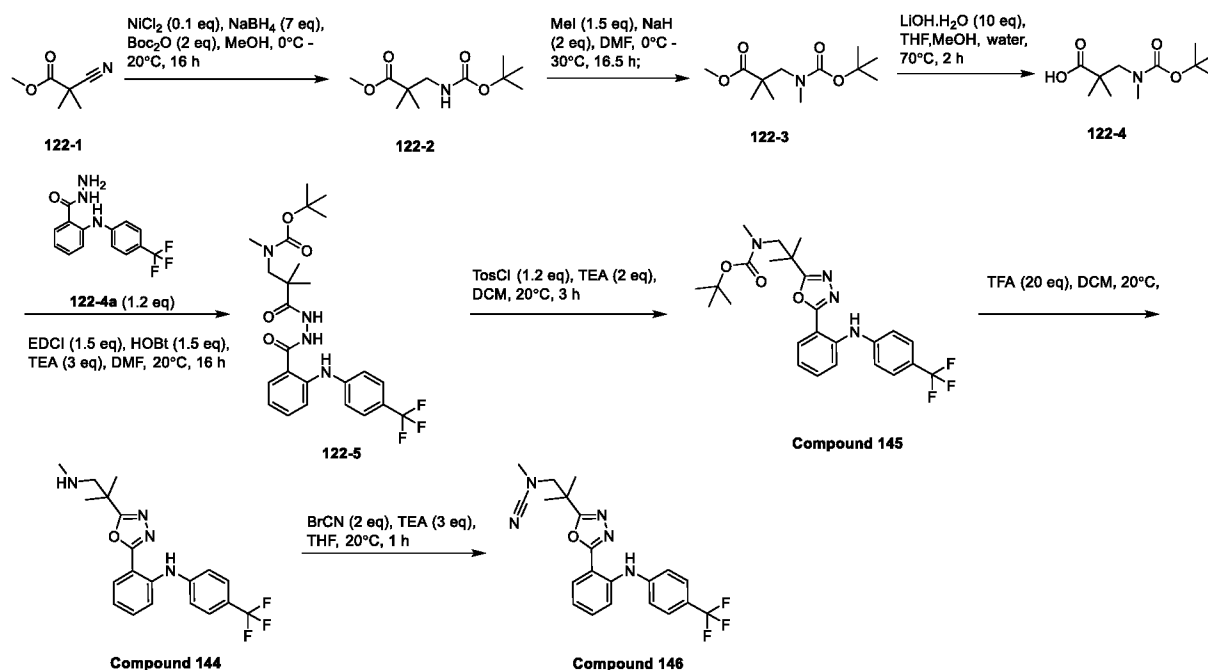
RT = 1.148 min, mass calc. for $C_{25}H_{29}F_3N_4O_3$ 490.22, m/z found 491.1 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.89 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.3$ Hz, 1H), 7.43 - 7.32 (m, 3H), 6.96 (t, $J = 7.2$ Hz, 1H), 3.60 (s, 2H), 2.78 (s, 3H), 1.54 (s, 6H), 1.53 (s, 9H).

Example 121: N-methyl-N-(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide (Compound 143)



[00483] To a solution of **Compound 141** (30 mg, 76 μmol , 1 *eq*) and DIEA (24.8 mg, 0.19 mmol, 33 μL , 2.5 *eq*) in THF (2 mL) was added BrCN (12 mg, 0.11 mmol, 8 μL , 1.5 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with EA (20 mL) and washed with H_2O (2*10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was triturated with MeOH (5 mL) and filtered to give **Compound 143** (16.8 mg, 40 μmol , 52% yield). LCMS (ESI): RT = 0.993 min, mass calc. for $C_{21}H_{20}F_3N_5O$ 415.16, m/z found 416.1 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.3$ Hz, 1H), 7.44 - 7.32 (m, 3H), 6.99 (t, $J = 7.7$ Hz, 1H), 3.24 (s, 2H), 2.95 (s, 3H), 1.50 (s, 6H).

Example 122: 2-(5-(2-methyl-1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 144), tert-butyl methyl(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 145), and N-methyl-N-(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 146)



Step 1: methyl 3-((tert-butoxycarbonyl)amino)-2,2-dimethylpropanoate

[00484] To a solution of **122-1** (2.0 g, 15.73 mmol, 1 *eq*), (Boc)₂O (6.87 g, 31.46 mmol, 7.23 mL, 2 *eq*) and NiCl₂ (203.9 mg, 1.57 mmol, 0.1 *eq*) in MeOH (40 mL) at 0°C was added NaBH₄ (4.17 g, 110.11 mmol, 7 *eq*) slowly portion-wise, and the resulting mixture was stirred at 20°C for 16 h. The reaction mixture was quenched with NH₄.H₂O (10 mL), and then concentrated to remove solvent. And the residue was diluted with water (50 mL), and then extracted with EA (50 mL *3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **122-2** (600 mg, 2.59 mmol, 16.5% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.97 (brs, 1H), 3.69 (s, 3H), 3.24 (d, *J* = 6.6 Hz, 2H), 1.44 (s, 9H), 1.19 (s, 6H).

Step 2: methyl 3-((tert-butoxycarbonyl)(methyl)amino)-2,2-dimethylpropanoate

[00485] To a solution of **122-2** (300 mg, 1.30 mmol, 1 *eq*) in DMF (3 mL) at 0°C was added NaH (103.8 mg, 2.59 mmol, 60% purity, 2 *eq*) slowly portion-wise, and then the mixture was stirred at 0°C for 0.5 h. And then iodomethane (276.2 mg, 1.95 mmol, 0.12 mL, 1.5 *eq*) was added drop-wise into the above mixture at 0°C, and the resulting mixture was stirred at 30°C for 16 h. The reaction mixture was quenched with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **122-3** (120 mg, 0.44 mmol, 33.9% yield). ¹H NMR (400 MHz, CDCl₃) δ 3.69 (s, 3H), 3.45 (s, 2H), 2.80 (s, 3H), 1.45 (s, 9H), 1.19 (s, 6H).

Step 3: 3-((tert-butoxycarbonyl)(methyl)amino)-2,2-dimethylpropanoic acid

[00486] To a solution of **122-3** (120 mg, 0.49 mmol, 1 *eq*) in THF (2 mL) and MeOH (2 mL) at 20°C was added LiOH.H₂O (205.3 mg, 4.89 mmol, 10 *eq*) in water (2 mL), and then the mixture was stirred at 70°C for 2 h. The reaction mixture was quenched with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **122-4** (110 mg, 0.43 mmol, 87.5% yield). ¹H NMR (400 MHz, CDCl₃) δ 3.48 (s, 2H), 2.88 (s, 3H), 1.45 (s, 9H), 1.22 (s, 6H).

Step 4: tert-butyl (2,2-dimethyl-3-oxo-3-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propyl)(methyl)carbamate

[00487] To a solution of **122-4** (100 mg, 0.43 mmol, 1 *eq*), EDCI (124.3 mg, 0.65 mmol, 1.5 *eq*) and HOBt (87.6 mg, 0.65 mmol, 1.5 *eq*) in DMF (2 mL) at 20°C was added **122-4a** (153.2 mg, 0.52 mmol, 1.2 *eq*) and then TEA (131.3 mg, 1.30 mmol, 0.18 mL, 3 *eq*), and the mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **122-5** (310 mg, 0.41 mmol, 95.9% yield), which was used directly for next step. LCMS (ESI): RT = 0.875 min, mass calc. for C₂₅H₃₁F₃N₄O₄ 508.23, m/z found 531.1 [M+23]⁺.

Step 5: tert-butyl methyl(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 145)

[00488] To a solution of **122-5** (300 mg, 0.40 mmol, 1 *eq*) and TEA (81.2 mg, 0.80 mol, 0.11 mL, 2 *eq*) in DCM (1 mL) at 20°C was added TosCl (91.8 mg, 0.48 mmol, 1.2 *eq*), and the mixture was stirred at 20°C for 3 h. The reaction mixture was combined with that of ES8223-478, and then was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EA = 5:1, UV) to give **Compound 145** (140 mg, 0.28 mmol, 70.4% yield). LCMS (ESI): RT = 1.008 min, mass calc. for C₂₅H₂₉F₃N₄O₃ 490.22, m/z found 513.0 [M+23]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.56 (brs, 1H), 7.89 (brs, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.99 (t, *J* = 7.0 Hz, 1H), 3.60 (s, 2H), 2.81 - 2.74 (m, 3H), 1.53 (s, 6H), 1.36 (s, 9H).

Step 6: 2-(5-(2-methyl-1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 144)

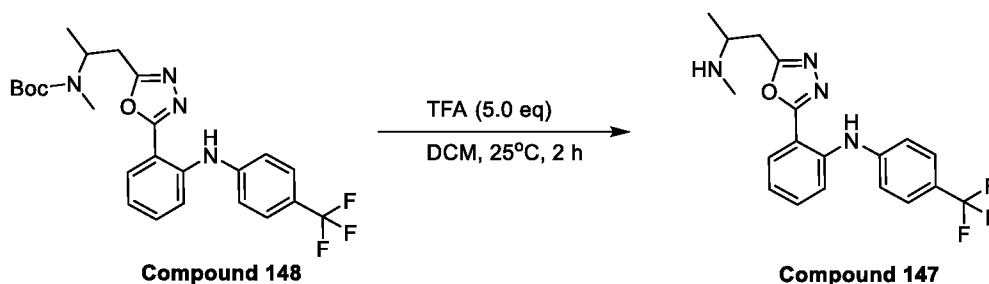
[00489] To a solution of **Compound 145** (130 mg, 0.27 mmol, 1 *eq*) in DCM (2 mL) at 20°C was added TFA (604.4 mg, 5.30 mmol, 0.39 mL, 20 *eq*), and the mixture was stirred at 20°C for 1 h. The mixture was concentrated to remove solvent. The residue was diluted with saturated Na₂CO₃

solution (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 144** (100 mg, 0.25 mmol, 93.9% yield), which was used directly for next step. LCMS (ESI): RT = 0.752 min, mass calc. for C₂₀H₂₁F₃N₄O 390.17, m/z found 391.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.44 (s, 1H), 7.88 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 3.14 (s, 2H), 2.63 (s, 3H), 1.56 (s, 6H).

Step 7: N-methyl-N-(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 146)

[00490] To a solution of **Compound 144** (50 mg, 0.13 mmol, 1 *eq*) and TEA (38.9 mg, 0.38 mmol, 53 uL, 3 *eq*) in THF (2 mL) at 20°C was added BrCN (27.1 mg, 0.26 mmol, 19 uL, 2 *eq*), and the mixture was stirred at 20°C for 1 h. The residue was diluted with water (20 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 146** (13.0 mg, 31.3 umol, 24.4% yield). LCMS (ESI): RT = 0.895 min, mass calc. for C₂₁H₂₀F₃N₅O 415.16, m/z found 437.9 [M+23]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 7.90 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.96 (m, 1H), 3.44 (s, 2H), 2.89 (s, 3H), 1.60 (s, 6H).

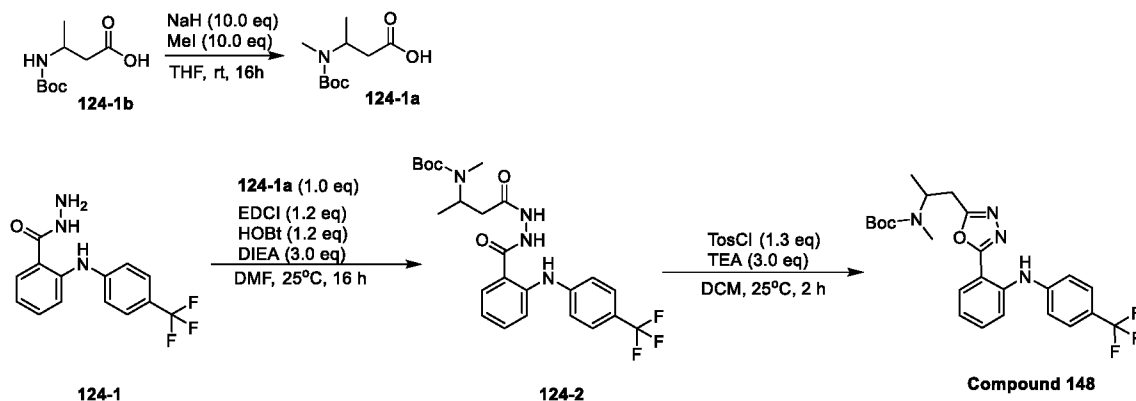
Example 123: 2-(5-(2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 147)



[00491] To a solution of **Compound 148** (130 mg, 0.27 mmol, 1 *eq*) in DCM (3 mL) was added TFA (155.5 mg, 1.36 mmol, 0.1 mL, 5 *eq*). The reaction was stirred at 25°C for 2 hr. The reaction was adjusted pH to 8-9 with sat. Na₂CO₃ and extracted with DCM (2*15 mL). The organic layer was dried over Na₂SO₄ and concentrated. 80 mg of crude product was obtained. Crude **Compound 147** (60 mg, 0.14 mmol, 52% yield) was used for next step directly. 20 mg of crude product was purified by prep-HPLC to give **Compound 147** (4.2 mg, 11 umol, 4% yield). LCMS and ¹H NMR confirmed that desired product was obtained. LCMS (ESI): RT = 0.831 min, mass calc. for C₁₉H₁₉F₃N₄O 376.18, m/z found 377.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.53 (s, 1H), 7.88

(d, $J = 7.03$ Hz, 1H), 7.58 (d, $J = 8.53$ Hz, 2H), 7.52 (d, $J = 8.53$ Hz, 1H), 7.32 - 7.43 (m, 3H), 6.98 (t, $J = 7.40$ Hz, 1H), 3.15 - 3.24 (m, 1H), 2.97 - 3.13 (m, 2H), 1.24 (d, $J = 6.27$ Hz, 3 H).

Example 124: tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate (Compound 148)



Step 1: 3-[tert-butoxycarbonyl(methyl)amino]butanoic acid

[00492] To a solution of compound **124-1b** (0.2 g, 1 mmol, 1 *eq*) and MeI (1.4 g, 10.3 mmol, 0.64 mL, 10 *eq*) in THF (8 mL) was added NaH (411.9 mg, 10.3 mmol, 60% purity, 10 *eq*) at 0°C. The reaction was warmed to 25°C and stirred at 25°C for 16 hr. The reaction was quenched by PE (10 mL). The aqueous layer was adjusted pH to 4-5 with Sat. Citric acid and extracted with EA (2*20 mL). The organic layer was dried over Na₂SO₄ and concentrated to give **124-1a** (0.22 g, 1 mmol, 98% yield), which was used for next step directly. ¹H NMR (400 MHz, CDCl₃) δ 4.44 (br, 1H), 2.66 (s, 3H), 2.51 (dd, $J = 15.06, 8.03$ Hz, 1H), 2.35 (dd, $J = 15.06, 6.53$ Hz, 1H), 1.36 (s, 9H), 1.11 (d, $J = 6.78$ Hz, 3H).

Step 2: tert-butyl N-methyl-N-[1-methyl-3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]carbamate

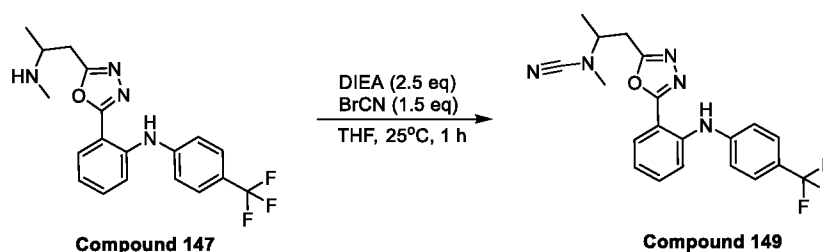
[00493] To a mixture of compound **124-1** (300 mg, 1 mmol, 1 *eq*) and compound **124-1a** (220.7 mg, 1.0 mmol, 1 *eq*) and EDCI (233.7 mg, 1.2 mmol, 1.2 *eq*) in DMF (6 mL) was added HOBt (164.7 mg, 1.2 mmol, 1.2 *eq*), followed by DIEA (393.9 mg, 3 mmol, 0.53 mL, 3 *eq*). The mixture was stirred at 25 °C for 16 hr. The reaction was diluted with EA (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give compound **124-2** (340 mg, 0.6 mmol, 62% yield). LCMS (ESI): RT = 0.962 min, mass calc. for C₂₄H₂₉F₃N₄O₄ 494.21, m/z found 495.1 [M+1]⁺.

Step 3: tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate

[00494] To a solution of compound **124-2** (200 mg, 0.4 mmol, 1 *eq*) in DCM (3 mL) was added TEA (122.7 mg, 1.2 mmol, 0.17 mL, 3 *eq*) followed by TosCl (100 mg, 0.5 mmol, 1.3 *eq*). The reaction was stirred at 25°C for 2 hr. The reaction was diluted with DCM (20 mL) and washed with

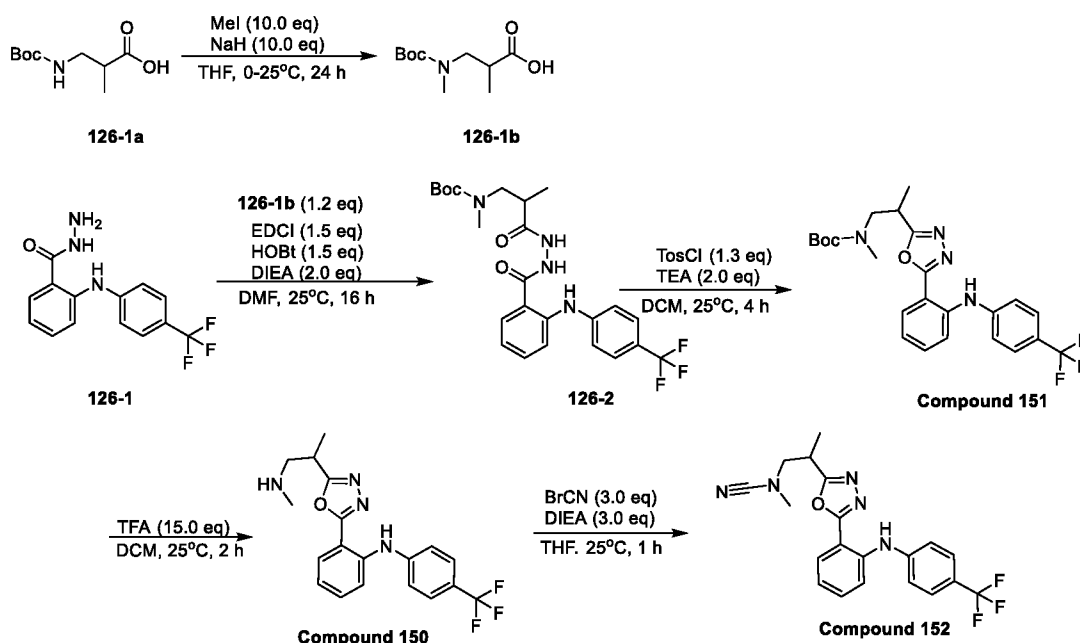
H₂O (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated to give **Compound 148** (130 mg, 0.25 mmol, 62% yield), which was used for next step directly. LCMS (ESI): RT = 1.091 min, mass calc. for C₂₄H₂₇F₃N₄O₃ 476.20, m/z found 477.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.46 (br s, 1H), 7.90 (br s, 1H), 7.58 (d, *J* = 8.53 Hz, 2H), 7.50 (d, *J* = 8.28 Hz, 1H), 7.31 - 7.43 (m, 3H), 6.94 - 7.01 (m, 1H), 4.44 - 4.93 (m, 1H), 3.11 - 3.23 (m, 1H), 3.00 - 3.09 (m, 1H), 2.82 (br d, *J* = 19.58 Hz, 3H), 1.57 (s, 9H), 1.34 - 1.36 (m, 3H).

Example 125: N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide (Compound 149)



[00495] To a solution of **Compound 147** (60 mg, 0.16 mmol, 1 *eq*) and DIEA (51 mg, 0.39 mmol, 69 μ L, 2.5 *eq*) in THF (2 mL) was added BrCN (25.3 mg, 0.23 mmol, 17 μ L, 1.5 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was diluted with EA (10 mL) and washed with H₂O (2*3 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 149** (5.5 mg, 13.5 μ mol, 8.5% yield). LCMS (ESI): RT = 0.991 min, mass calc. for C₂₀H₁₈F₃N₅O 401.15, m/z found 402.1 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.90 (dd, *J* = 7.88, 1.38 Hz, 1H), 7.59 (d, *J* = 8.50 Hz, 2H), 7.51 (d, *J* = 8.13 Hz, 1H), 7.35 - 7.44 (m, 3H), 6.93 - 7.02 (m, 1H), 3.59 - 3.68 (m, 1H), 3.27 - 3.36 (m, 1H), 3.10 - 3.19 (m, 1H), 1.47 (d, *J* = 6.63 Hz, 3H).

Example 126: 2-(5-(1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 150), tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 151), and N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 152)



Step 1: 3-[tert-butoxycarbonyl(methyl)amino]-2-methyl-propanoic acid

[00496] To a solution of compound **126-1a** (200 mg, 0.98 mmol, 1 *eq*) and MeI (1.40 g, 9.84 mmol, 0.6 mL, 10 *eq*) in THF (2 mL) was added NaH (393 mg, 9.84 mmol, 60% purity, 10 *eq*) slowly in portions over a period of 1 hr at 0°C. Then the mixture was stirred at 20°C for 23 hr. The reaction mixture was diluted with petro ether (5 mL). Then the organic phase was removed, the aqueous phase was adjusted pH = 3 with aqueous solution of citric acid and extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹H NMR showed that compound **126-1b** (155 mg, 0.71 mmol, 72.5% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 3.44 - 3.34 (m, 1H), 3.28 (br dd, *J* = 6.9, 13.3 Hz, 1H), 2.83 - 2.69 (m, 4H), 1.41 - 1.35 (m, 9H), 1.11 (d, *J* = 7.1 Hz, 3H).

Step 2: tert-butyl N-methyl-N-[2-methyl-3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]carbamate

[00497] To a solution of compound **126-1** (170 mg, 0.57 mmol, 1 *eq*) and compound **126-1b** (150 mg, 0.69 mmol, 1.2 *eq*) in DMF (2 mL) were added HOBt (116 mg, 0.86 mmol, 1.5 *eq*), EDCI (165 mg, 0.86 mmol, 1.5 *eq*) and DIEA (148 mg, 1.15 mmol, 0.2 mL, 2 *eq*). The mixture was stirred at 25°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. Compound **126-2** (120 mg, 0.22 mmol, 38% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.40 - 8.43 (m, 3H), 7.59 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.45 -

7.41 (m, 1H), 7.39 - 7.33 (m, 1H), 7.21 (d, $J = 8.3$ Hz, 2H), 6.88 (t, $J = 7.4$ Hz, 1H), 3.67 - 3.16 (m, 2H), 2.88 (s, 4H), 1.46 (s, 9H), 1.21 (d, $J = 7.0$ Hz, 3H).

Step 3: tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)carbamate (Compound 151)

[00498] To a solution of compound **126-2** (120 mg, 0.22 mmol, 1 *eq*) in DCM (3 mL) were added TEA (44 mg, 0.44 mmol, 61 μ L, 2 *eq*) and TosCl (54 mg, 0.28 mmol, 1.3 *eq*). The mixture was stirred at 25°C for 4 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. **Compound 151** (95 mg, 0.19 mmol, 88% yield) was obtained. LCMS (ESI): RT = 0.976 min, mass calcd. For C₂₄H₂₇F₃N₄O₃, 476.20 m/z found 499.0 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.52 (br d, $J = 11.4$ Hz, 1H), 7.93 - 7.85 (m, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.43 - 7.33 (m, 3H), 7.01 - 6.95 (m, 1H), 3.73 - 3.46 (m, 3H), 2.98 - 2.84 (m, 3H), 1.46 (br s, 3H), 1.39 (s, 9H).

Step 4: 2-(5-(1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 150)

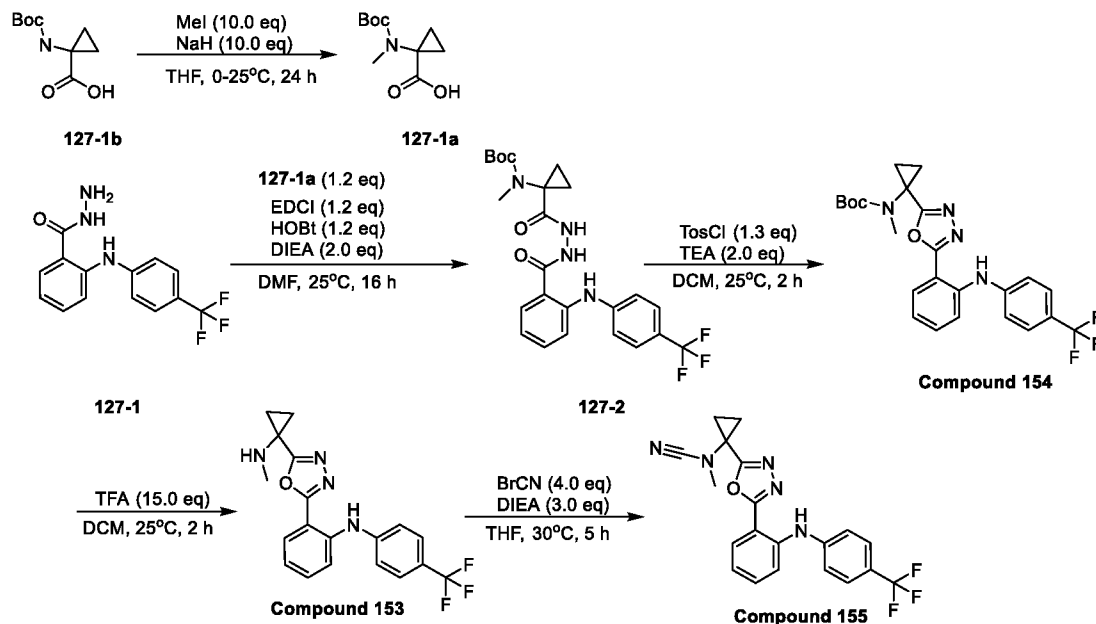
[00499] To a solution of **Compound 151** (90 mg, 0.19 mmol, 1 *eq*) in DCM (2 mL) was added TFA (323 mg, 2.83 mmol, 0.2 mL, 15 *eq*). The mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with saturated aq. Na₂CO₃ (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. LCMS and ¹H NMR confirmed that **Compound 150** (65 mg, 0.16 mmol, 87% yield) was obtained. LCMS (ESI): RT = 0.736 min, mass calcd. For C₁₉H₁₉F₃N₄O, 376.15 m/z found 377.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.54 (s, 1H), 7.89 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.43 - 7.33 (m, 3H), 7.01 - 6.95 (m, 1H), 3.43 (qd, $J = 7.1, 13.9$ Hz, 1H), 3.11 (dd, $J = 8.2, 12.1$ Hz, 1H), 2.93 (dd, $J = 5.6, 12.1$ Hz, 1H), 2.50 (s, 3H), 1.47 (d, $J = 7.0$ Hz, 3H).

Step 5: N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide (Compound 152)

[00500] To a solution of **Compound 150** (60 mg, 0.16 mmol, 1 *eq*) in THF (2 mL) were added DIEA (61 mg, 0.48 mmol, 83 μ L, 3 *eq*) and BrCN (50 mg, 0.48 mmol, 35 μ L, 3 *eq*). The mixture was stirred at 25°C for 1 hr. The reaction mixture was diluted with EA (15 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 152** (19 mg, 47 μ mol, 29% yield) was obtained. LCMS (ESI): RT = 0.875 min, mass calcd. For C₂₀H₁₈F₃N₅O, 401.15 m/z found 401.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 7.92 (dd, $J = 1.4, 7.9$

Hz, 1H), 7.60 (d, $J = 8.3$ Hz, 2H), 7.53 (d, $J = 8.3$ Hz, 1H), 7.45 - 7.36 (m, 3H), 7.01 (t, $J = 7.3$ Hz, 1H), 3.63 - 3.53 (m, 2H), 3.45 - 3.36 (m, 1H), 2.98 (s, 3H), 1.56 (d, $J = 6.8$ Hz, 3H).

Example 127: 2-(5-(1-(methylamino)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 153), tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate (Compound 154), and N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)cyanamide (Compound 155)



Step 1: 1-[tert-butoxycarbonyl(methyl)amino]cyclopropanecarboxylic acid

[00501] To a solution of compound **127-1b** (300 mg, 1.49 mmol, 1 *eq*) and MeI (2.12 g, 14.91 mmol, 0.93 mL, 10 *eq*) in THF (5 mL) was added a mixture of NaH (596 mg, 14.91 mmol, 60% purity, 10 *eq*) in THF (5 mL) slowly at 0°C. Then the mixture was stirred at 25°C for 24 hr. The reaction mixture was diluted with petro ether (5 mL). Then the organic phase was removed, the aqueous phase was adjusted pH = 3 with aqueous solution of citric acid and extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹H NMR confirmed that compound **127-1a** (303 mg, 1.41 mmol, 94% yield) was obtained. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.48 (br s, 1H), 2.75 (s, 3H), 1.35 (s, 8H), 1.37 - 1.34 (m, 1H), 1.28 - 1.07 (m, 4H).

Step 2: tert-butyl N-methyl-N-[1-[[[2-[4-(trifluoromethyl)anilino]benzoyl]amino]carbamoyle]cyclopropyl]carbamate

[00502] To a solution of compound **127-1** (228 mg, 0.77 mmol, 1 *eq*) and compound **127-1a** (200 mg, 0.93 mmol, 1.2 *eq*) in DMF (5 mL) were added HOBt (125 mg, 0.93 mmol, 1.2 *eq*), EDCI (178 mg, 0.93 mmol, 1.2 *eq*) and DIEA (200 mg, 1.55 mmol, 0.3 mL, 2 *eq*). The mixture was stirred at

25°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. Compound **127-2** (235 mg, 0.45 mmol, 58% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.20 (br s, 1H), 8.91 - 8.62 (m, 2H), 7.59 (br d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.47 - 7.43 (m, 1H), 7.41 - 7.35 (m, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 2.99 (s, 3H), 1.69 - 1.64 (m, 2H), 1.51 (s, 9H), 1.22 (br s, 2H).

Step 3: tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate (Compound 154)

[00503] To a solution of compound **127-2** (150 mg, 0.30 mmol, 1 *eq*) in DCM (2 mL) were added TEA (92 mg, 0.91 mmol, 0.13 mL, 3 *eq*) and TosCl (75 mg, 0.4 mmol, 1.3 *eq*). The mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. **Compound 154** (134 mg, 0.27 mmol, 90% yield) was obtained. LCMS (ESI): RT = 0.997 min, mass calcd. For C₂₄H₂₅F₃N₄O₃, 474.19 m/z found 497.1 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.50 (br s, 1H), 7.79 (br s, 1H), 7.57 (br d, *J* = 8.3 Hz, 2H), 7.51 (br d, *J* = 8.3 Hz, 1H), 7.42 - 7.32 (m, 3H), 6.96 (br t, *J* = 7.2 Hz, 1H), 3.08 (s, 3H), 1.73 (br s, 2H), 1.57 - 1.40 (m, 11H).

Step 4: 2-(5-(1-(methylamino)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 153)

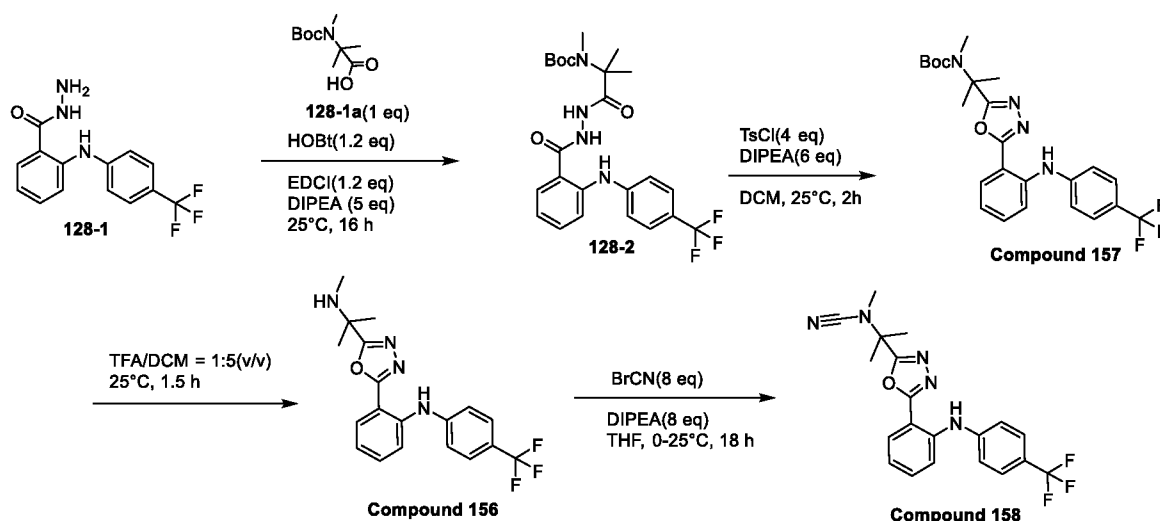
[00504] To a solution of **Compound 154** (120 mg, 0.25 mmol, 1 *eq*) in DCM (2 mL) was added TFA (432 mg, 3.79 mmol, 0.28 mL, 15 *eq*). The mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with saturated aq. Na₂CO₃ (10 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The product was used for the next step directly. LCMS and ¹H NMR showed that **Compound 153** (88 mg, 0.23 mmol, 92% yield) was obtained. LCMS (ESI): RT = 0.736 min, mass calcd. For C₁₉H₁₇F₃N₄O, 374.14 m/z found 374.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.73 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.34 - 7.26 (m, 3H), 6.89 (t, *J* = 7.5 Hz, 1H), 2.56 - 2.53 (m, 1H), 2.55 (s, 2H), 1.35 - 1.30 (m, 2H), 1.25 - 1.19 (m, 2H).

Step 5: N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)cyanamide (Compound 155)

[00505] To a solution of **Compound 153** (80 mg, 0.21 mmol, 1 *eq*) in THF (2 mL) were added DIEA (82 mg, 0.64 mmol, 0.11 mL, 3 *eq*) and BrCN (90 mg, 0.85 mmol, 62 uL, 4 *eq*). The mixture

was stirred at 30°C for 5 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 155** (52 mg, 0.13 mmol, 60% yield) was obtained. LCMS (ESI): RT = 0.897 min, mass calcd. For C₂₀H₁₆F₃N₅O, 399.13 m/z found 399.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.40 (s, 1H), 7.85 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.01 - 6.96 (m, 1H), 3.12 (s, 3H), 1.76 - 1.71 (m, 2H), 1.69 - 1.64 (m, 2H).

Example 128: 2-(5-(2-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 156), tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate (Compound 157), and N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide (Compound 158)



Step 1: tert-butyl methyl(2-methyl-1-oxo-1-(2-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)hydrazinyl)propan-2-yl)carbamate

[00506] To a solution of **128-1a** (200 mg, 0.92 mmol, 1 eq), **128-1** (271.8 mg, 0.92 mmol, 1 eq), HOBt (149.3 mg, 1.10 mmol, 1.2 eq) and EDCI (211.8 mg, 1.10 mmol, 1.2 eq) was added DIPEA (594.9 mg, 4.60 mmol, 0.8 mL, 5 eq) at 25°C. Then the resulting mixture was stirred at 25°C for 16 h. The mixture was directly purified by prep-HPLC to give **128-2** (130 mg, 0.26 mmol, 28.6% yield). LCMS (ESI): RT = 0.852 min, mass calcd. For C₂₄H₂₉F₃N₄O₄ 494.21 m/z found 517.0 [M+23]⁺.

Step 2: tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)carbamate (Compound 157)

[00507] To a solution of **128-2** (125 mg, 0.25 mmol, 1 eq) and TosCl (192.8 mg, 1.01 mmol, 4 eq) in DCM (4 mL) was added DIPEA (196.0 mg, 1.52 mmol, 0.3 mL, 6 eq) at 25°C. Then the

resulting mixture was stirred at 25°C for 2 h. The solution was concentrated to give a residue. The residue was purified by column chromatography to give **Compound 157** (95 mg, 0.20 mmol, 78.5% yield). LCMS (ESI): RT = 0.993 min, mass calcd. For $C_{24}H_{27}F_3N_4O_3$ 476.20 m/z found 477.0 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.87 (dd, J = 1.4, 7.9 Hz, 1H), 7.62 - 7.50 (m, 3H), 7.42 - 7.33 (m, 3H), 7.00 - 6.93 (m, 1H), 3.09 (s, 3H), 1.78 (s, 6H), 1.26 (s, 9H).

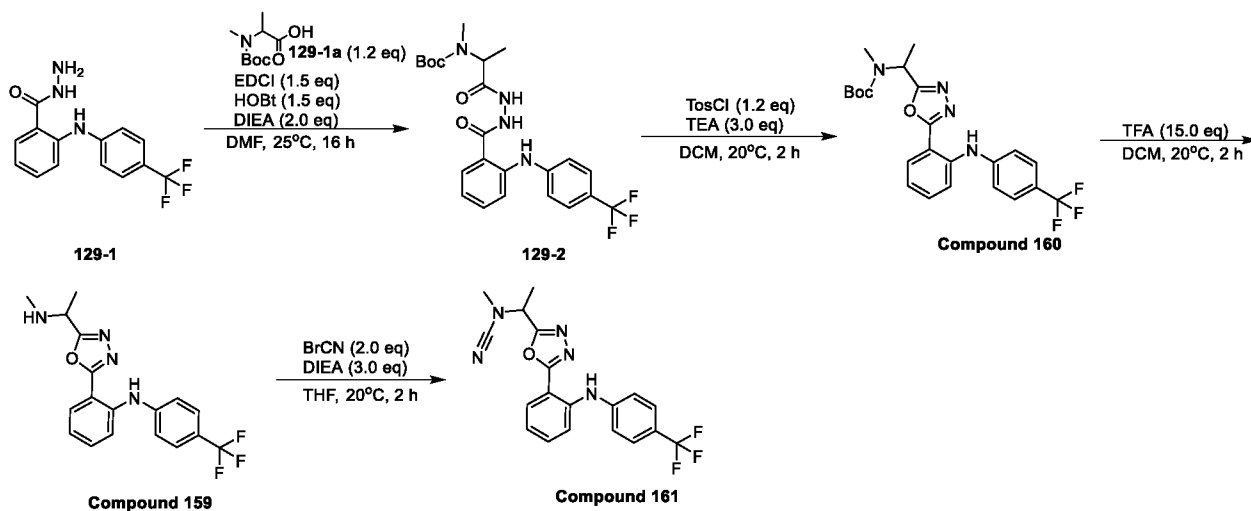
Step 3: 2-(5-(2-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 156)

[00508] To a solution of **Compound 157** (80 mg, 0.17 mmol, 1 *eq*) in DCM (4 mL) was added TFA (0.8 mL) at 25°C. Then the resulting mixture was stirred at 25°C for 1.5 h. The solution was concentrated at 20°C to give a residue. The residue was diluted with 20 mL of water and lyophilized to give **Compound 156** (82 mg, 0.16 mmol, 97.1% yield, TFA). LCMS (ESI): RT = 0.739 min, mass calcd. For $C_{19}H_{19}F_3N_4O$ 376.15 m/z found 376.9 $[M+1]^+$. ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.53 (br s, 1H), 9.03 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.59 - 7.46 (m, 4H), 7.22 (d, J = 8.5 Hz, 2H), 7.15 - 7.07 (m, 1H), 2.48 (s, 3H), 1.64 (s, 6H).

Step 4: N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide (Compound 158)

[00509] To a solution of **Compound 156** (60 mg, 0.16 mmol, 1 *eq*) and DIPEA (82.4 mg, 0.64 mmol, 0.1 mL, 4 *eq*) in THF (3 mL) was added cyanogen bromide (33.8 mg, 0.32 mmol, 24 μ L, 2 *eq*) at 0°C. The mixture was stirred at 25°C for 2 hr. Then another batch of cyanogen bromide (101.3 mg, 0.96 mmol, 70 μ L, 6 *eq*) and DIPEA (82.4 mg, 0.64 mmol, 0.1 mL, 4 *eq*) was added and the resulting mixture was stirred for another 16 h at 25°C. The solution was quenched with water (10 mL) and then diluted with EA (50 mL), washed with brine (15 mL*3). The combined organic layer was dried by anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography to give **Compound 158** (14 mg, 35 μ mol, 21.9% yield). LCMS (ESI): R = 0.885 min, mass calcd. For $C_{20}H_{18}F_3N_5O$ 401.15 m/z found 401.9 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.94 (dd, J = 1.4, 7.9 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.55 - 7.49 (m, 1H), 7.43 (dt, J = 1.5, 7.8 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.05 - 6.98 (m, 1H), 2.86 (s, 3H), 1.94 - 1.84 (m, 6H).

Example 129: 2-(5-(1-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 159), tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 160), and N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 161)



Step 1: tert-butyl N-methyl-N-[1-methyl-2-oxo-2-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]ethyl]carbamate

[00510] To a solution of compound **129-1** (200 mg, 0.67 mmol, 1 eq) and compound **129-1a** (165 mg, 0.81 mmol, 1.2 eq) in DMF (2 mL) were added HOBt (137 mg, 1.02 mmol, 1.5 eq), EDCI (194 mg, 1.02 mmol, 1.5 eq) and DIEA (175 mg, 1.35 mmol, 0.24 mL, 2 eq). The mixture was stirred at 25°C for 16 hr. The reaction mixture was quenched with water (5 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS confirmed that compound **129-2** (120 mg, 0.23 mmol, 34% yield) was obtained.

Step 2: tert-butyl methyl(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 160)

[00511] To a solution of compound **129-2** (120 mg, 0.25 mmol, 1 eq) in DCM (2 mL) were added TEA (75 mg, 0.75 mmol, 0.1 mL, 3 eq) and TosCl (57 mg, 0.3 mmol, 1.2 eq). The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that **Compound 160** (104 mg, 0.22 mmol, 90% yield) was obtained. LCMS (ESI): RT = 0.994 min, mass calcd. For C₂₃H₂₅F₃N₄O₃, 462.19 m/z found 485.0 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H), 7.86 (br d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.43 - 7.34 (m, 3H), 7.00 - 6.95 (m, 1H), 5.94 - 5.34 (m, 1H), 2.81 (br s, 3H), 1.71 (br s, 3H), 1.51 (br s, 9H).

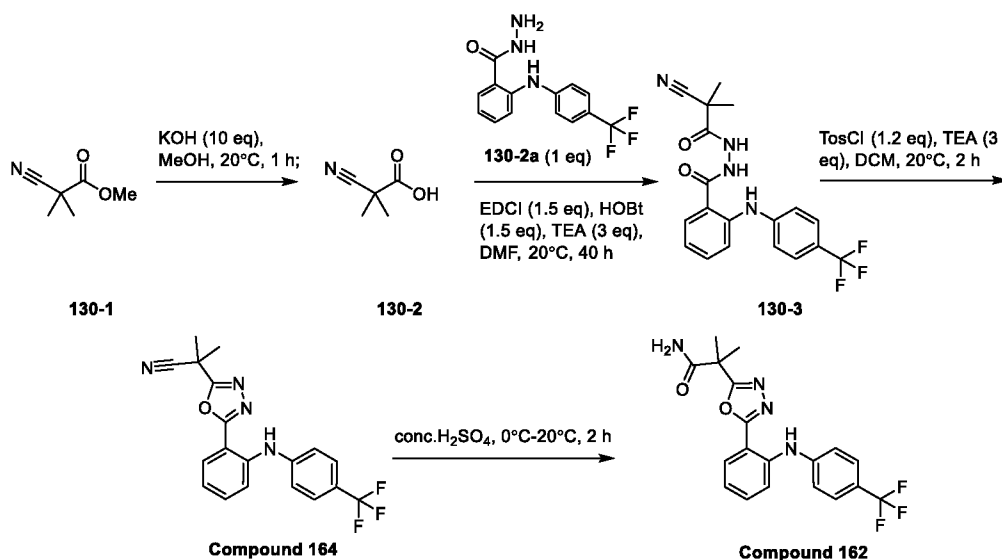
Step 3: 2-(5-(1-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 159)

[00512] To a solution of **Compound 160** (100 mg, 0.22 mmol, 1 *eq*) in DCM (2 mL) was added TFA (369 mg, 3.24 mmol, 0.24 mL, 15 *eq*). The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with saturated aq. Na₂CO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. LCMS and ¹H NMR confirmed that **Compound 159** (65 mg, 0.17 mmol, 80% yield) was obtained. LCMS (ESI): RT = 0.717 min, mass calcd. For C₁₈H₁₇F₃N₄O, 362.14 m/z found 362.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.54 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.44 - 7.35 (m, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 4.15 (q, *J* = 6.9 Hz, 1H), 2.48 (s, 3H), 1.60 (s, 3H).

Step 4: N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 161)

[00513] To a solution of **Compound 159** (60 mg, 0.16 mmol, 1 *eq*) in THF (2 mL) were added DIEA (64 mg, 0.5 mmol, 86 uL, 3 *eq*) and BrCN (35 mg, 0.33 mmol, 24 uL, 2 *eq*). The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 161** (30 mg, 77 umol, 46% yield) was obtained. LCMS (ESI): RT = 0.875 min, mass calcd. For C₁₉H₁₆F₃N₅O, 387.13 m/z found 387.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.86 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.46 - 7.41 (m, 1H), 7.38 - 7.26 (m, 3H), 6.96 - 6.90 (m, 1H), 4.46 (q, *J* = 7.0 Hz, 1H), 2.90 (s, 3H), 1.79 (d, *J* = 7.3 Hz, 3H).

Example 130: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 162)



Step 1: 2-cyano-2-methylpropanoic acid

[00514] To a solution of KOH (2.21 g, 39.33 mmol, 10 *eq*) in MeOH (20 mL) at 20°C was added **130-1** (500 mg, 3.93 mmol, 1 *eq*), and the resulting mixture was stirred at 20°C for 1 h. The reaction mixture was concentrated to remove most of MeOH, and the residue was diluted with water (20 mL), acidified with conc. HCl to pH = 1-2, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue **130-2** (430 mg, 3.80 mmol, 96.7% yield). ¹H NMR (400 MHz, CDCl₃) δ 1.67 (s, 6H).

Step 2: *N'*-(2-cyano-2-methylpropanoyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00515] To a solution of **130-2** (137.9 mg, 1.22 mmol, 1.2 *eq*), EDCI (292.2 mg, 1.52 mmol, 1.5 *eq*) and HOBT (205.9 mg, 1.52 mmol, 1.5 *eq*) in DMF (4 mL) at 20°C was added **130-2a** (300 mg, 1.02 mmol, 1 *eq*) and then TEA (308.4 mg, 3.05 mmol, 0.42 mL, 3 *eq*), and the resulting mixture was stirred at 20°C for 40 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **130-3** (290 mg, 0.71 mmol, 69.5% yield). LCMS (ESI): RT = 0.799 min, mass calc. for C₁₉H₁₇F₃N₄O₂ 390.13, m/z found 390.9 [M+1]⁺.

Step 3: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile (Compound 164)

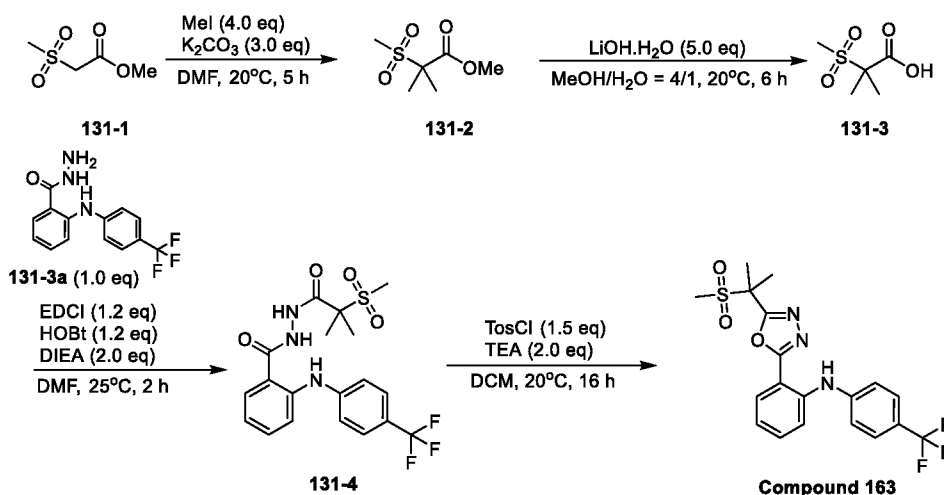
[00516] To a solution of **130-3** (150 mg, 0.38 mmol, 1 *eq*) and TEA (116.7 mg, 1.15 mmol, 0.16 mL, 3 *eq*) in DCM (2 mL) at 20°C was added TosCl (87.9 mg, 0.46 mmol, 1.2 *eq*), and the resulting mixture was stirred at 20°C for 2 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 164** (110 mg, 0.29 mmol, 74.3% yield). LCMS (ESI): RT = 0.924 min, mass calc. for C₁₉H₁₅F₃N₄O 372.12, m/z found 372.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 7.93 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 1.97 (s, 6H).

Step 4: 2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 162)

[00517] The sample of **Compound 164** (50 mg, 0.13 mmol, 1 *eq*) was added slowly to H₂SO₄ (1 mL) at 0°C, and the resulting mixture was stirred at 20°C for 2 h. The reaction mixture was added drop-wise into the ice-water (10 mL) under stirring, then basified with saturated Na₂CO₃ solution to

pH = 8-9, and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 162** (45.3 mg, 0.12 mmol, 86.4% yield). LCMS (ESI): RT = 0.843 min, mass calc. for C₁₉H₁₇F₃N₄O₂ 390.13, m/z found 390.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 7.89 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.42 (dt, *J* = 1.4, 7.8 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.03 - 6.96 (m, 1H), 6.52 (brs, 1H), 5.50 (brs, 1H), 1.80 (s, 6H).

Example 131: 2-(5-(2-(methylsulfonyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 163)



Step 1: methyl 2-methyl-2-methylsulfonyl-propanoate

[00518] To a solution of compound **131-1** (600 mg, 3.94 mmol, 1 *eq*) and MeI (2.24 g, 15.77 mmol, 1 mL, 4 *eq*) in DMF (8 mL) was added K₂CO₃ (1.63 g, 11.83 mmol, 3 *eq*). The mixture was stirred at 20°C for 5 hr. The reaction mixture was quenched with H₂O (10 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL*2), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹HNMR confirmed that compound **131-2** (525 mg, crude) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 3.82 (s, 3H), 3.05 (s, 3H), 1.66 (s, 6H).

Step 2: 2-methyl-2-methylsulfonyl-propanoic acid

[00519] To a solution of compound **131-2** (520 mg, 2.89 mmol, 1 *eq*) in MeOH (2 mL) and H₂O (0.5 mL) was added LiOH.H₂O (605 mg, 14.43 mmol, 5 *eq*). The mixture was stirred at 20°C for 6 hr. The reaction mixture was concentrated in vacuum. The aqueous phase was adjusted pH = 3 with aqueous solution of citric acid and extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹HNMR confirmed that compound **131-3** (230 mg, crude) was obtained. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.09 (s, 3H), 1.50 (s, 6H).

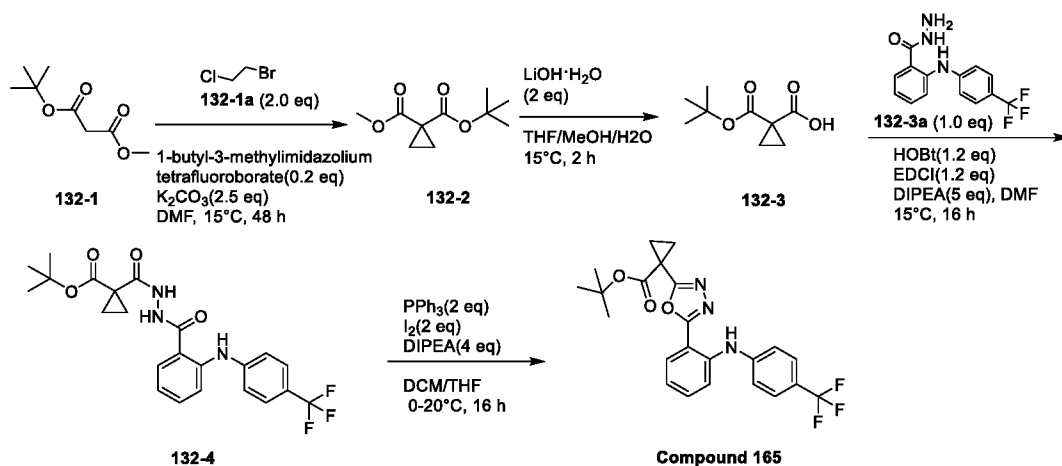
Step 3: N'-(2-methyl-2-methylsulfonyl-propanoyl)-2-[4-(trifluoromethyl)anilino]benzohydrazide

[00520] To a solution of compound **131-3a** (325 mg, 1.10 mmol, 1 eq), compound **131-3** (220 mg, 1.32 mmol, 1.2 eq), EDCI (253 mg, 1.32 mmol, 1.2 eq) and HOBt (178 mg, 1.32 mmol, 1.2 eq) in DMF (4 mL) was added DIEA (285 mg, 2.21 mmol, 0.4 mL, 2 eq). The mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched with H₂O (5 mL), extracted with EA (15 mL*3). The combined organic phase was washed with H₂O (5 mL) and brine (5 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. ¹H NMR confirmed that compound **131-4** (240 mg, 0.54 mmol, 49% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.02 (br d, *J* = 15.1 Hz, 2H), 8.15 (br s, 1H), 7.57 - 7.40 (m, 3H), 7.40 - 7.29 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.85 (t, *J* = 7.4 Hz, 1H), 3.08 (s, 3H), 1.66 (s, 6H).

Step 4: 2-(5-(2-(methylsulfonyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00521] To a solution of compound **131-4** (100 mg, 0.22 mmol, 1 eq) in DCM (2 mL) were added TosCl (64 mg, 0.33 mmol, 1.5 eq) and TEA (45 mg, 0.45 mmol, 62 uL, 2 eq). The mixture was stirred at 20°C for 16 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and NMR confirmed that **Compound 163** (25 mg, 57 umol, 25% yield) was obtained. LCMS (ESI): RT = 0.879 min, mass calcd. For C₁₉H₁₈F₃N₃O₃S, 425.10 m/z found 425.9 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.37 (s, 1H), 7.93 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.54 - 7.48 (m, 1H), 7.46 - 7.40 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.04 - 6.96 (m, 1H), 3.02 (s, 3H), 2.01 (s, 6H).

Example 132: tert-butyl 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylate (Compound 165)



Step 1: O1'-tert-butyl O1-methyl cyclopropane-1,1-dicarboxylate

[00522] To a mixture of compound **132-1** (4 g, 23.0 mmol, 3.9 mL, 1.0 eq) in DMF (35 mL) were added **132-1a** (6.59 g, 45.9 mmol, 3.8 mL, 2.0 eq), 1-butyl-3-methyl-imidazol-3-ium; tetrafluoroborate(1.04 g, 4.59 mmol, 0.9 mL, 0.2 eq) and K₂CO₃ (7.93 g, 57.4 mmol, 2.5 eq). Then the resulting mixture was stirred at 15°C for 48 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with EA(100 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **132-2** (4.1 g, 20.48 mmol, 89.2% yield). ¹H NMR (400 MHz DMSO-*d*₆) δ 3.61-3.69 (m, 3H), 1.37-1.45 (m, 9H), 1.21-1.32 (m, 3H).

Step 2: 1-tert-butoxycarbonylcyclopropanecarboxylic acid

[00523] To a mixture of compound **132-2** (3.1 g, 15.48 mmol, 1 eq) in MeOH (10 mL) and THF (25 mL) was drop-wise added a solution of LiOH.H₂O (1.3 g, 30.96 mmol, 2.0 eq) in H₂O (10 mL) over 2 min at 15°C. The resulting mixture was stirred at 15 °C for 2 h. The solution was concentrated at 15°C to remove most of organic solvent and extracted with EA(10 mL) twice. The separated aqueous layer was adjusted with cold aq 2 M HCl to pH~ 2, along with lots of solid formed. Then the suspension was filtered and washed with water (10 mL). The filter cake was collected to give compound **132-3** (1.1 g, 5.91 mmol, 38.2% yield). The filtrate was extracted with EA (15 mL*4). The combined organic layer was washed with brine (15 mL), dried with Na₂SO₄, filtered and concentrated to give compound **132-3** (500 mg, 2.69 mmol, 17.3% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.43 - 1.36 (m, 9H), 1.26 - 1.18 (m, 4H).

Step 3: tert-butyl 1-[[[2-[4-

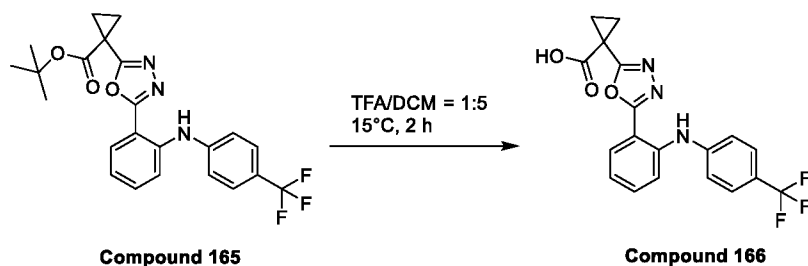
(trifluoromethyl)anilino]benzoyl]amino]carbamoyle]cyclopropanecarboxylate

[00524] To a mixture of compound **132-3a** (800 mg, 2.71 mmol, 1.0 eq), compound **132-3** (605.4 mg, 3.25 mmol, 1.2 eq), HOBt (439.3 mg, 3.25 mmol, 1.2 eq) and EDCI (623.3 mg, 3.25 mmol, 1.2 eq) in DMF (10 mL) was added DIPEA (1.75 g, 13.55 mmol, 2.4 mL, 5 eq) at 15°C. The resulting mixture was stirred at 15 °C for 16 h. The mixture was concentrated at 40°C to remove most of organic solvent, diluted with water (30 mL) and extracted with EA (50 mL) twice. The separated aqueous layer was cooled to 0°C and adjusted with cold aq 2 M HCl to pH~ 2 and then extracted with EA (15 mL*4). The combined organic layer was washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography to give compound **132-4** (780 mg, 1.65 mmol, 60.9% yield). LCMS (ESI): RT = 0.892 min, mass calc. for C₂₃H₂₄F₃N₃O₄ 463.17, m/z found 485.9 [M+23]⁺.

Step 4: tert-butyl 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylate

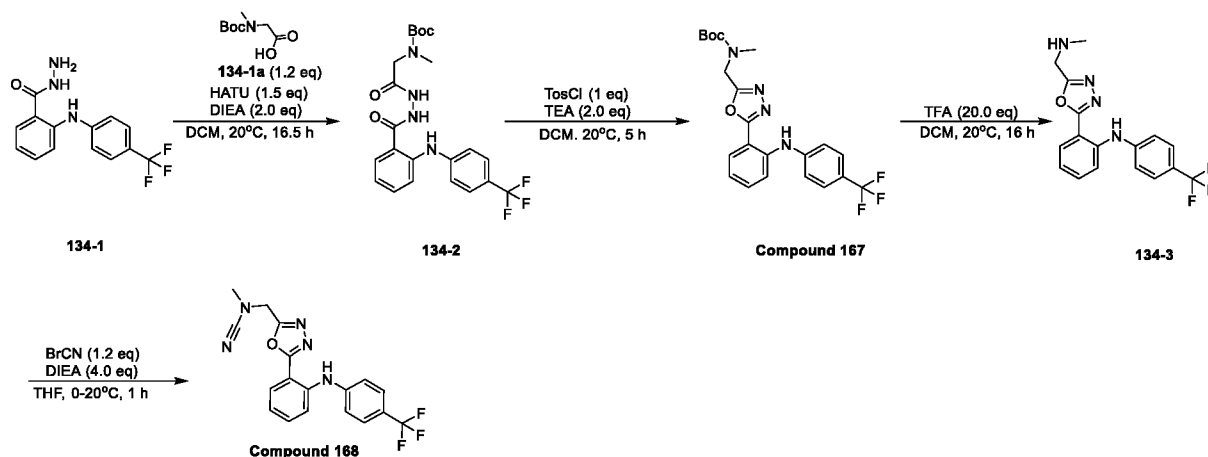
[00525] To a mixture of PPh₃ (860.3 mg, 3.28 mmol, 2.0 eq) in DCM (10 mL) was added iodine (832.5 mg, 3.28 mmol, 0.7 mL, 2.0 eq) in one portion at 0°C. After the iodine was dissolved completely, DIPEA (847.8 mg, 6.6 mmol, 1.2 mL, 4.0 eq) was added, followed by a solution of compound **132-4** (760 mg, 1.64 mmol, 1.0 eq) in THF (10 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EA (50 mL * 2). The combined organic layers were washed with NaHCO₃ (20 mL * 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give **Compound 165** (700 mg, 1.5 mmol, 93.9% yield). LCMS (ESI): RT = 1.018 min, mass calc. for C₂₃H₂₂F₃N₃O₃ 445.16, m/z found 446 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 7.84-8.05 (m, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.52-7.60 (m, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.13-7.21 (m, 1H), 1.55-1.66 (m, 4H), 1.28-1.47 (m, 9H).

Example 133: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylic acid (Compound 166)



[00526] To a mixture of **Compound 165** (300 mg, 0.7 mmol, 1 eq) in DCM (2 mL) was added TFA (0.4 mL) in one portion at 15°C. The mixture was stirred at 15 °C for 2 h. The reaction mixture was concentrated at 15°C to give a residue. The residue was purified by prep-HPLC to give the product (290 mg, 0.75 mmol, 5.5% yield). ¹HNMR and HPLC showed the product was not pure. 30 mg of the product was repurified by prep-HPLC to give **Compound 166** (10.18 mg, 0.03 mmol, 1.94e-1% yield). LCMS (ESI): RT = 0.848 min, mass calc. for C₁₉H₁₄F₃N₃O₃ 389.10, m/z found 389.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.31 (br s, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.63 (br d, *J* = 8.3 Hz, 2H), 7.59 - 7.49 (m, 2H), 7.35 (br d, *J* = 8.5 Hz, 2H), 7.13 (br t, *J* = 7.3 Hz, 1H), 1.39 (br s, 2H), 1.22 (br s, 2H).

Example 134: tert-butyl methyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 167) and N-methyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 168)



Step 1: tert-butyl N-methyl-N-[2-oxo-2-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]ethyl]carbamate

[00527] A solution of compound **134-1a** (153.8 mg, 0.81 mmol, 1.2 *eq*) and HATU (386 mg, 1.02 mmol, 1.5 *eq*) in DCM (2 mL) was stirred at 20°C for 30 min. Then compound **134-1** (200 mg, 0.67 mmol, 1 *eq*) and DIEA (175 mg, 1.35 mmol, 0.24 mL, 2 *eq*) were added to the mixture and stirred at 20°C for 16 hr. The reaction mixture was concentrated in vacuum to give the residue. The residue was diluted with EA (20 mL), washed with H₂O (10 mL*2) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS confirmed that compound **134-2** (105 mg, 0.21 mmol, 30.9% yield) was obtained.

Step 2: tert-butyl methyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate (Compound 167)

[00528] To a solution of compound **134-2** (100 mg, 0.21 mmol, 1 *eq*) in DCM (1 mL) were added TosCl (40.8 mg, 0.21 mmol, 1 *eq*) and TEA (43 mg, 0.43 mmol, 59 μ L, 2 *eq*). The mixture was stirred at 20°C for 5 hr. The reaction mixture was concentrated in vacuum to give a residue. Then the residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that **Compound 167** (35 mg, 78 μ mol, 36.4% yield) was obtained. LCMS (ESI): RT = 0.938 min, mass calcd. For C₂₂H₂₃F₃N₄O₃, 448.17 m/z found 471.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 7.87 (br s, 1H), 7.59 (br d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.44 - 7.34 (m, 3H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.83 - 4.68 (m, 2H), 3.03 (br d, *J* = 11.1 Hz, 3H), 1.51 (br s, 9H).

Step 3: 2-[5-(methylaminomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline

[00529] To a solution of **Compound 167** (30 mg, 66.9 μ mol, 1 *eq*) in DCM (1 mL) was added TFA (152 mg, 1.34 mmol, 99 μ L, 20 *eq*). The mixture was stirred at 20°C for 16 hr. The reaction

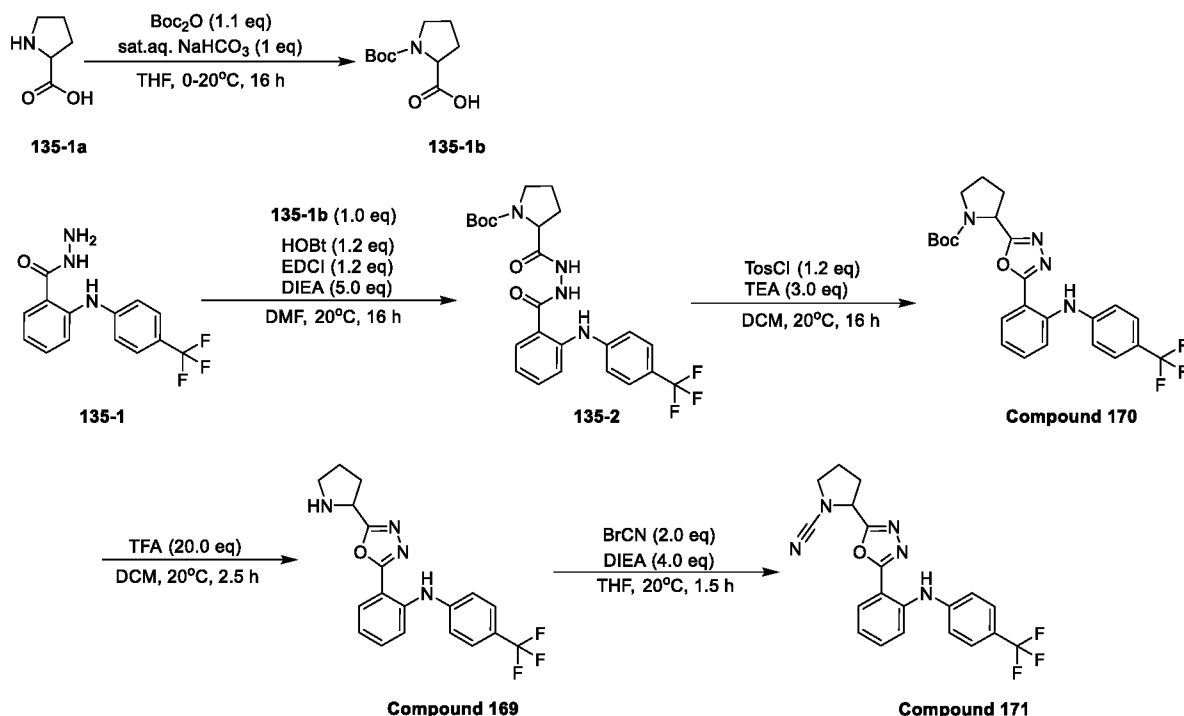
mixture was concentrated in vacuum. The crude product was used for the next step directly.

Compound **134-3** (40 mg, crude) was obtained.

Step 4: N-methyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide (Compound 168)

[00530] To a solution of compound **134-3** (40 mg, 0.11 mmol, 1 *eq*) and DIEA (59 mg, 0.46 mmol, 80 μ L, 4 *eq*) in THF (1 mL) was added BrCN (14.6 mg, 0.14 mmol, 10 μ L, 1.2 *eq*) at 0°C. The mixture was stirred at 20°C for 1 hr. The reaction mixture was concentrated in vacuum to give a residue and the residue was diluted with EA (15 mL), filtered, the filtrate was washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 168** (14 mg, 37 μ mol, 32.3% yield) was obtained. LCMS (ESI): RT = 0.862 min, mass calcd. For C₁₈H₁₄F₃N₅O, 373.12 m/z found 373.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 7.94 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.03 - 6.97 (m, 1H), 4.53 (s, 2H), 3.03 (s, 3H).

Example 135: 2-(5-(pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 169), and tert-butyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate (Compound 170), and 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile (Compound 171)



Step 1: 1-tert-butoxycarbonylpyrrolidine-2-carboxylic acid

[00531] To a solution of compound **135-1a** (1 g, 8.69 mmol, 1 *eq*) in NaHCO₃ (1 M, 8.7 mL, 1 *eq*) was added Boc₂O (2.1 g, 9.55 mmol, 2.2 mL, 1.1 *eq*) in THF (5 mL) at 0°C. Then the mixture was stirred at 20°C for 16 hr. The reaction mixture was concentrated in vacuum to remove THF, then the aqueous phase was adjusted pH = 2 with 1M. aq. HCl. The aqueous phase was extracted with EA (20 mL*3), washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was used for the next step directly. ¹H NMR confirmed that compound **135-1b** (1.8 g, 8.36 mmol, 96.2% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.87 - 7.76 (m, 1H), 4.42 - 4.21 (m, 1H), 3.63 - 3.29 (m, 2H), 2.35 - 2.06 (m, 2H), 2.01 - 1.85 (m, 2H), 1.51 - 1.38 (m, 9H).

Step 2: tert-butyl 2-[[[2-[4-(trifluoromethyl)anilino]benzoyl]amino]carbamoyl]pyrrolidine -1-carboxylate

[00532] To a solution of compound **135-1** (300 mg, 1.02 mmol, 1 *eq*) and compound **135-1b** (218 mg, 1.02 mmol, 1 *eq*) in DMF (3 mL) were added HOBT (164.7 mg, 1.22 mmol, 1.2 *eq*), EDCI (233.7 mg, 1.22 mmol, 1.2 *eq*) and DIEA (656 mg, 5.08 mmol, 0.89 mL, 5 *eq*). The mixture was stirred at 20°C for 16 hr. The reaction mixture was quenched with H₂O (15 mL), extracted with EA (15 mL*3). The combined organic phase was washed with brine (10 mL*3), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that compound **135-2** (300 mg, 0.58 mmol, 56.9% yield) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 9.72 (br s, 1H), 9.22 (br s, 1H), 8.95 - 8.53 (m, 1H), 7.58 (br d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.48 - 7.42 (m, 1H), 7.41 - 7.33 (m, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.90 (br t, *J* = 7.4 Hz, 1H), 4.45 (br s, 1H), 3.64 - 3.32 (m, 2H), 2.50 - 2.15 (m, 1H), 2.05 - 1.87 (m, 3H), 1.50 (s, 9H).

Step 3: tert-butyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate (Compound 170)

[00533] To a solution of compound **135-2** (200 mg, 0.4 mmol, 1 *eq*) in DCM (3 mL) were added TosCl (92.9 mg, 0.48 mmol, 1.2 *eq*) and TEA (123 mg, 1.22 mmol, 0.17 mL, 3 *eq*). The mixture was stirred at 20°C for 16 hr. The reaction mixture was concentrated in vacuum to give a residue and the residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give the crude product (160 mg). Crude **Compound 170** (120 mg, 0.25 mmol, 62% yield) was used for the next step directly. 40 mg of the crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 170** (10 mg, 21 μmol, 5.2% yield) was obtained. LCMS (ESI): RT = 0.969 min, mass calcd. For C₂₄H₂₅F₃N₄O₃, 474.19 m/z found 497.0 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.53 (br s, 1H), 7.86 (br d, *J* = 7.5 Hz, 1H), 7.61 - 7.55 (m, 2H), 7.55 - 7.48 (m, 1H), 7.44 - 7.32 (m, 3H), 7.01 -

6.93 (m, 1H), 5.28 - 5.09 (m, 1H), 3.78 - 3.43 (m, 2H), 2.49 - 2.29 (m, 1H), 2.28 - 2.11 (m, 2H), 2.11 - 2.00 (m, 1H), 1.49 - 1.33 (m, 9H).

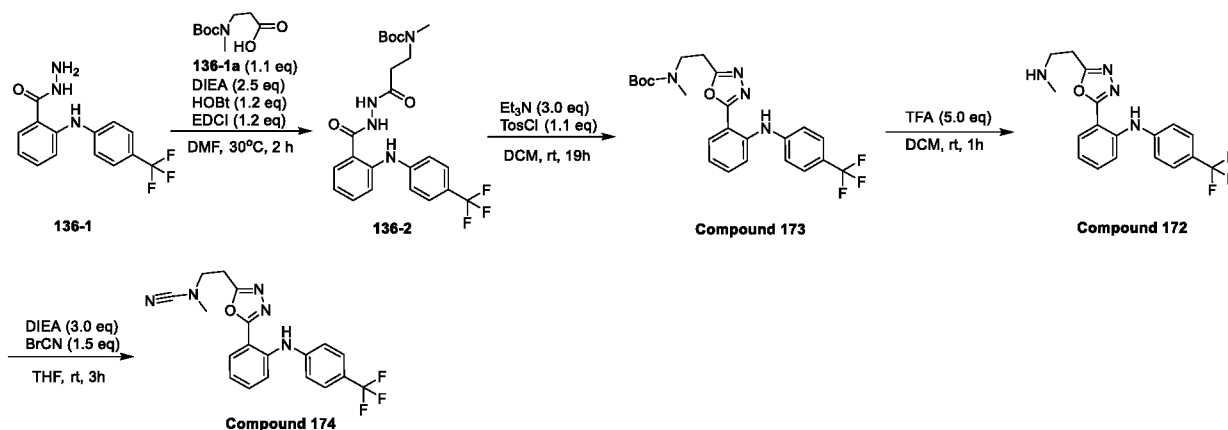
Step 4: 2-(5-(pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 169)

[00534] To a solution of **Compound 170** (120 mg, 0.25 mmol, 1 *eq*) in DCM (3 mL) was added TFA (576.7 mg, 5.06 mmol, 0.4 mL, 20 *eq*). The mixture was stirred at 20°C for 2.5 hr. The reaction mixture was concentrated in vacuum to give a residue and the residue was diluted with EA (10 mL), the precipitate was collected to give **Compound 169** (60 mg, 0.16 mmol, 63.4% yield). The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 169** (7.89 mg, 19.8 umol, 7.8% yield) was obtained. LCMS (ESI): RT = 0.718 min, mass calcd. For C₁₉H₁₇F₃N₄O, 374.14 m/z found 374.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.41 (br s, 1H), 9.09 (s, 1H), 8.03 - 7.95 (m, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.58 - 7.54 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.18 (m, 1H), 5.09 (t, *J* = 7.4 Hz, 1H), 3.36 (t, *J* = 7.3 Hz, 2H), 2.48 - 2.29 (m, 2H), 2.20 - 2.04 (m, 2H).

Step 5: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile (Compound 171)

[00535] To a solution of **Compound 169** (60 mg, 0.16 mmol, 1 *eq*) in THF (2 mL) were added DIEA (82.8 mg, 0.64 mmol, 0.11 mL, 4 *eq*) and BrCN (33.9 mg, 0.32 mmol, 23 uL, 2 *eq*). The mixture was stirred at 20°C for 1.5 hr. The reaction mixture was concentrated in vacuum to give a residue and the residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 171** (31 mg, 76 umol, 47.9% yield) was obtained. LCMS (ESI): RT = 0.874 min, mass calcd. For C₂₀H₁₆F₃N₅O, 399.13 m/z found 421.9 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.41 (s, 1H), 7.92 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.46 - 7.39 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.97 (m, 1H), 5.05 (dd, *J* = 4.3, 7.8 Hz, 1H), 3.74 (dt, *J* = 5.0, 8.4 Hz, 1H), 3.67 - 3.59 (m, 1H), 2.58 - 2.41 (m, 2H), 2.29 - 2.13 (m, 2H).

Example 136: 2-(5-(2-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 172), tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 173), and N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 174)



Step 1: tert-butyl N-methyl-N-[3-oxo-3-[2-[2-[4-(trifluoromethyl)anilino]benzoyl]hydrazino]propyl]carbamate

[00536] To a solution of compound **136-1a** (151 mg, 0.7 mmol, 1.1 *eq*), HOBt (109.8 mg, 0.8 mmol, 1.2 *eq*) and EDCI (155.8 mg, 0.8 mmol, 1.2 *eq*) in DMF (3 mL) was added compound **136-1** (200 mg, 0.6 mmol, 1 *eq*) followed by DIEA (218.8 mg, 1.6 mmol, 0.3 mL, 2.5 *eq*). The reaction was stirred at 30°C for 2 hr. The reaction was diluted with EA (30 mL) and washed with Sat. NaHCO₃ (2*10 mL) and brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude compound **136-2** (0.3 g, 0.5 mmol, 73% yield) was used for next step directly. LCMS confirmed that desired product was obtained.

Step 2: tert-butyl methyl(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)carbamate (Compound 173)

[00537] To a solution of compound **136-2** (0.2 g, 0.3 mmol, 1 *eq*) and Et₃N (101 mg, 0.9 mmol, 0.1 mL, 3 *eq*) in DCM (2 mL) was added TosCl (25.8 mg, 0.4 mmol, 1.1 *eq*). The reaction was stirred at 30°C for 16 hr. Additional TosCl (26 mg) was added. The reaction was continued to stir at 30°C for 3 hr. The reaction was diluted with DCM (30 mL) and washed with brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product (100 mg, crude) was used for next step directly. 60 mg crude product was purified by prep-HPLC to give **Compound 173** (2.88 mg, 6.1 μmol, 1.8% yield). LCMS and ¹H NMR confirmed that desired product was obtained. LCMS (ESI): RT = 1.067 min, mass calc. for C₂₃H₂₅F₃N₄O₃ 462.19, m/z found 463.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.41 (s, 1H), 7.81 (s, 1H), 7.50 (d, *J* = 8.50 Hz, 2H), 7.43 (d, *J* = 8.50 Hz, 1H), 7.25 - 7.35 (m, 3H), 6.87 - 6.93 (m, 1H), 3.65 (s, 2H), 3.13 (s, 2H), 2.86 (d, *J* = 10.76 Hz, 3H), 1.33 (s, 9H).

Step 3: 2-(5-(2-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 172)

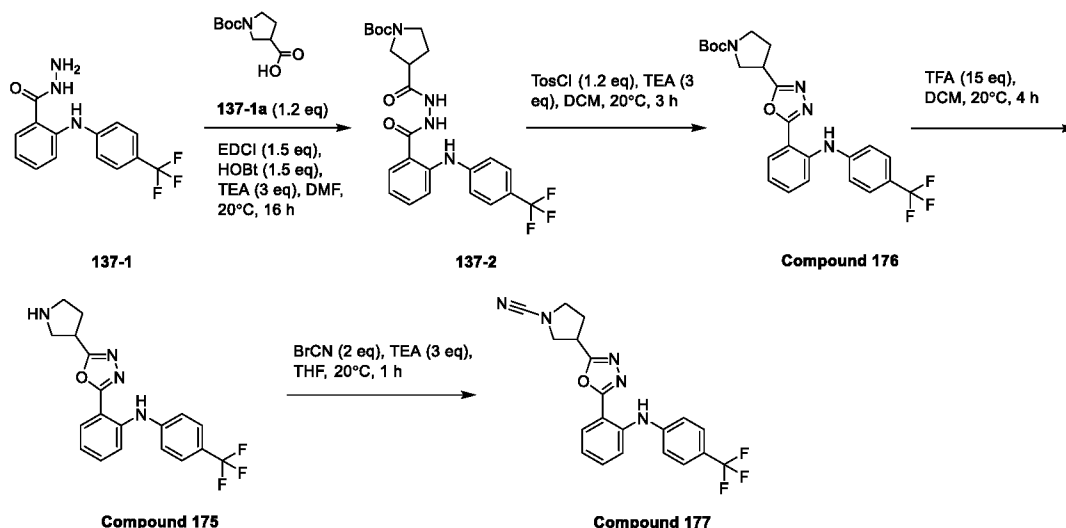
[00538] To a solution of **Compound 173** (70 mg, 0.15 mmol, 1 *eq*) in DCM (1 mL) was added TFA (86 mg, 0.75 mmol, 56 μL, 5 *eq*). The reaction was stirred at 25°C for 1 hr. The reaction was

adjusted pH to 7-8 with Sat. NaHCO₃ and extracted with DCM (3*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. 10 mg crude product was purified by prep-HPLC to give **Compound 172** (4.81 mg, 13.14 μ mol, 8.68% yield). 30 mg **Compound 172** (30 mg, 82 μ mol, 54% yield) was used for next step directly. ¹H NMR and LCMS confirmed that desired product was obtained. LCMS (ESI): RT = 0.892 min, mass calc. for C₂₃H₂₅F₃N₄O₃ 362.19, m/z found 363.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.80 (dd, *J* = 7.91, 1.38 Hz, 1H), 7.50 (d, *J* = 8.53 Hz, 2H), 7.43 (d, *J* = 8.53 Hz, 1H), 7.25 - 7.35 (m, 3H), 6.85 - 6.95 (m, 1H), 2.99 - 3.13 (m, 4H), 2.43 (s, 3H).

Step 4: N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide (Compound 174)

[00539] To a solution of **Compound 172** (30 mg, 82 μ mol, 1 *eq*) and DIEA (32 mg, 0.25 mmol, 43 μ L, 3 *eq*) in THF (2 mL) was added BrCN (13 mg, 0.12 mmol, 9 μ L, 1.5 *eq*). The reaction was stirred at 25°C for 3hr. The reaction was diluted with EA (10 mL) and washed with water (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The reaction was purified by prep-HPLC to give **Compound 174** (14.06 mg, 35 μ mol, 43% yield). LCMS and ¹H NMR confirmed that desired product was obtained. LCMS (ESI): RT = 0.996 min, mass calc. for C₂₃H₂₅F₃N₄O₃ 387.13, m/z found 388.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 7.91 (dd, *J* = 7.91, 1.13 Hz, 1H), 7.60 (d, *J* = 8.53 Hz, 2H), 7.52 (d, *J* = 8.53 Hz, 1H), 7.34 - 7.45 (m, 3H), 7.00 (t, *J* = 7.40 Hz, 1H), 3.54 - 3.65 (m, 2H), 3.30 - 3.39 (m, 2H), 3.00 (s, 3 H).

Example 137: 2-(5-(pyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 175), tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate (Compound 176), and 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile (Compound 177)



Step 1: tert-butyl 3-(2-(2-((4-**(trifluoromethyl)phenyl)amino)benzoyl)hydrazinecarbonyl)pyrrolidine-1-carboxylate**

[00540] To a solution of **137-1a** (175.0 mg, 0.81 mmol, 1.2 eq), EDCI (194.8 mg, 1.02 mmol, 1.5 eq) and HOBt (137.3 mg, 1.02 mmol, 1.5 eq) in DMF (2 mL) at 20°C was added **137-1** (200 mg, 0.68 mmol, 1 eq) and TEA (205.6 mg, 2.03 mmol, 0.28 mL, 3 eq), and the resulting mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (20 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **137-2** (250 mg, 0.49 mmol, 72.7% yield). LCMS (ESI): RT = 0.826 min, mass calc. for C₂₄H₂₇F₃N₄O₄ 492.20, m/z found 515.0 [M+23]⁺.

Step 2: tert-butyl 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate (Compound 176)

[00541] To a solution of **137-2** (250 mg, 0.51 mmol, 1 eq) and TEA (154.1 mg, 1.52 mmol, 0.21 mL, 3 eq) in DCM (2 mL) at 20°C was added TosCl (116.1 mg, 0.61 mmol, 1.2 eq), and the resulting mixture was stirred at 20°C for 3 h. The reaction mixture was quenched with MeOH (0.5 mL) and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Compound 176** (210 mg, 0.44 mmol, 87.2% yield). LCMS (ESI): RT = 0.976 min, mass calc. for C₂₄H₂₅F₃N₄O₃ 474.19, m/z found 475.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 3.89 (brs, 1H), 3.81 - 3.62 (m, 3H), 3.53 (brs, 1H), 2.47 - 2.33 (m, 2H), 1.49 (s, 9H).

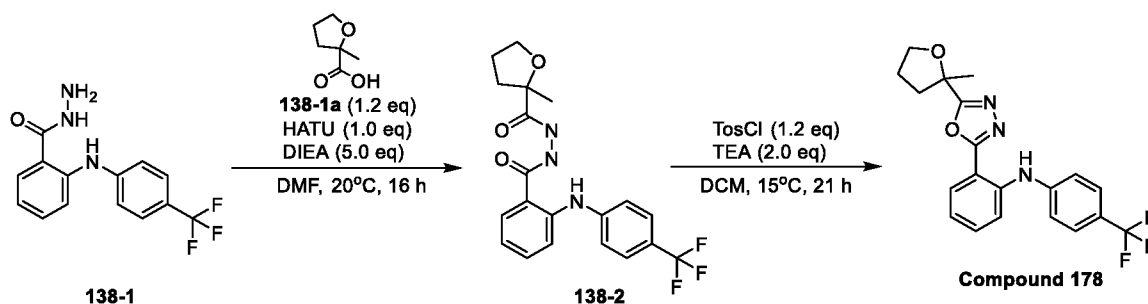
Step 3: 2-(5-(pyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 175)

[00542] To a solution of **Compound 176** (200 mg, 0.42 mmol, 1 eq) in DCM (4 mL) at 20°C was added TFA (720.9 mg, 6.32 mmol, 0.47 mL, 15 eq), and the resulting mixture was stirred at 20°C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with saturated Na₂CO₃ solution (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Compound 175** (150 mg, 0.39 mmol, 93.6% yield). LCMS (ESI): RT = 0.732 min, mass calc. for C₁₉H₁₇F₃N₄O 374.14, m/z found 374.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 7.86 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.02 - 6.95 (m, 1H), 3.95 - 3.78 (m, 3H), 3.76 - 3.60 (m, 2H), 2.54 - 2.43 (m, 2H).

Step 4: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile (Compound 177)

[00543] To a solution of **Compound 175** (70 mg, 0.19 mmol, 1 *eq*) and TEA (56.8 mg, 0.56 mmol, 78 μ L, 3 *eq*) in THF (2 mL) at 20°C was added BrCN (39.6 mg, 0.37 mmol, 27 μ L, 2 *eq*), and the resulting mixture was stirred at 20°C for 1 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL *3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 177** (62.4 mg, 0.16 mmol, 83.6% yield). LCMS (ESI): RT = 0.867 min, mass calc. for C₂₀H₁₆F₃N₅O 399.13, m/z found 399.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H), 7.88 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 3.67 - 3.57 (m, 1H), 3.41 - 3.28 (m, 2H), 3.24 (ddd, *J* = 5.8, 8.1, 11.4 Hz, 1H), 3.12 - 3.04 (m, 1H), 2.38 - 2.19 (m, 2H).

Example 138: 2-(5-(2-methyltetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 178)



Step 1: 2-methyl-N'-[2-[4-(trifluoromethyl)anilino]benzoyl]tetrahydrofuran-2-carbohydrazide

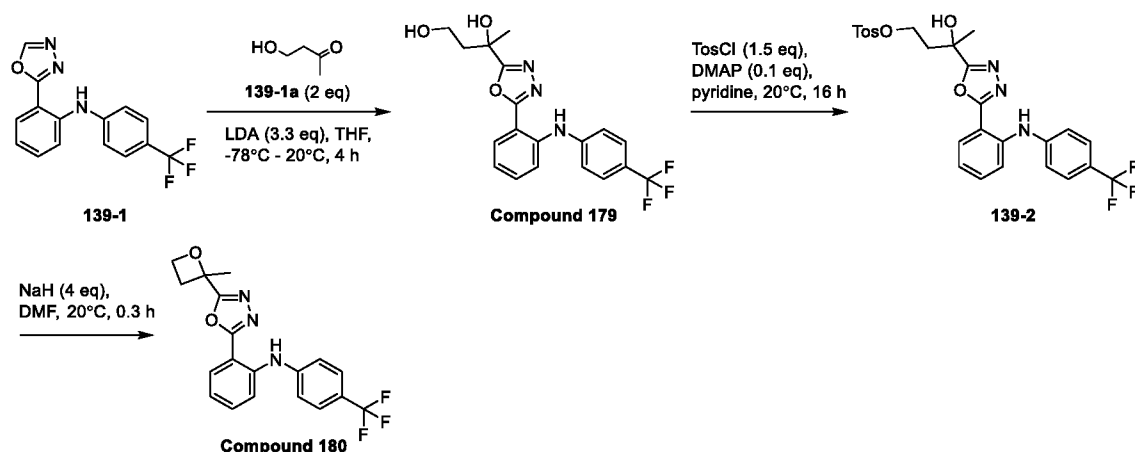
[00544] To a solution of compound **138-1** (113 mg, 0.38 mmol, 1 *eq*), compound **138-1a** (60 mg, 0.46 mmol, 1.2 *eq*) and HATU (146 mg, 0.38 mmol, 1 *eq*) in DMF (1 mL) was added DIEA (248 mg, 1.92 mmol, 0.3 mL, 5 *eq*). The mixture was stirred at 20°C for 16 hr. The reaction mixture was quenched with H₂O (10 mL). Then the precipitate was collected. The crude product was used for the next step directly. LCMS confirmed that compound **138-2** (91 mg, 0.21 mmol, 55.8% yield) was obtained.

Step 2: 2-(5-(2-methyltetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00545] To a mixture of compound **138-2** (60 mg, 0.15 mmol, 1 *eq*) in DCM (1 mL) were added TosCl (33 mg, 0.17 mmol, 1.2 *eq*) and TEA (29 mg, 0.30 mmol, 41 μ L, 2 *eq*). The mixture was stirred at 15°C for 21 hr. The reaction mixture was concentrated in vacuum to give a residue and

then the residue was diluted with EA (20 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC. LCMS and ¹H NMR confirmed that **Compound 178** (26 mg, 67 μ mol, 45.3% yield) was obtained. LCMS (ESI): RT = 0.940 min, mass calcd. For C₂₀H₁₈F₃N₃O₂, 389.14 m/z found 390.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.55 (s, 1H), 7.93 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 7.7 Hz, 1H), 4.16 - 4.06 (m, 1H), 3.99 (q, *J* = 7.6 Hz, 1H), 2.76 (m, 1H), 2.28 - 2.01 (m, 3H), 1.79 (s, 3H).

Example 139: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butane-1,3-diol (Compound 179) and 2-(5-(2-methyloxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 180)



Step 1: 3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butane-1,3-diol (Compound 179)

[00546] To a solution of **139-1** (50 mg, 0.16 mmol, 1 *eq*) in THF (2 mL) at -78°C was added LDA (2 M, 0.3 mL, 3.3 *eq*) drop-wise, and the mixture was stirred at -78°C for 0.5 h. And then the solution of 4-hydroxybutan-2-one (28.9 mg, 0.33 mmol, 28 μ L, 2.0 *eq*) in THF (1 mL) was added at -78°C into the above solution. The resulting mixture was stirred at 20°C for 3.5 h. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL), then diluted with water (5 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EA = 1:1, UV) to give **Compound 179** (10 mg, 24.3 μ mol, 14.8% yield). LCMS (ESI): RT = 0.798 min, mass calc. for C₁₉H₁₈F₃N₃O₃ 393.13, m/z found 394.0 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 7.93 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.02 - 6.94 (m, 1H), 4.53 (s, 1H), 4.09 - 3.93 (m, 2H), 2.41 - 2.25 (m, 3H), 1.78 (s, 3H).

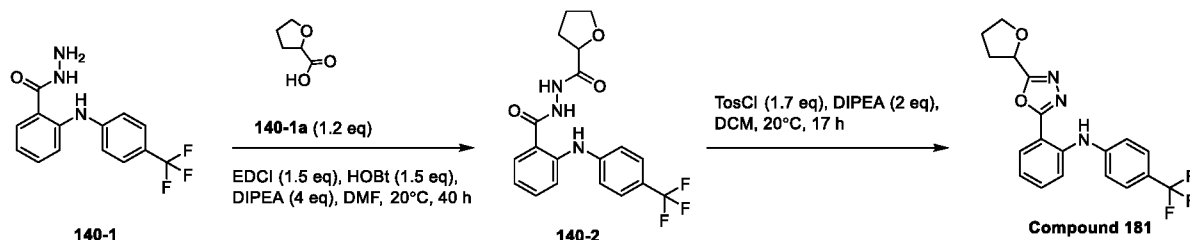
Step 2: 3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butyl 4-methylbenzenesulfonate

[00547] To a solution of **Compound 179** (90 mg, 0.23 mmol, 1 *eq*) in pyridine (2 mL) at 20°C was added TosCl (65.4 mg, 0.34 mmol, 1.5 *eq*) and DMAP (2.8 mg, 23 μ mol, 0.1 *eq*). The resulting mixture was stirred at 20°C for 16 h. The combined mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **139-2** (10 mg, 13 μ mol, 5.6% yield) was obtained. LCMS (ESI): RT = 0.917 min, mass calc. for C₂₆H₂₄F₃N₃O₅S 547.14, m/z found 570.0 [M+23]⁺.

Step 3: 2-(5-(2-methyloxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 180)

[00548] To a solution of **139-2** (22 mg, 40.2 μ mol, 1 *eq*) in DMF (1 mL) at 0°C was added NaH (6.4 mg, 0.16 mmol, 60% purity, 4 *eq*). The resulting mixture was stirred at 20°C for 0.3 h. The reaction mixture was quenched with water (0.5 mL) and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 180** (2.27 mg, 6.1 μ mol, 15.1% yield). LCMS (ESI): RT = 0.897 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 375.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.54 (s, 1H), 7.97 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.00 (t, *J* = 7.6 Hz, 1H), 4.89 - 4.80 (m, 1H), 4.70 (td, *J* = 6.1, 9.0 Hz, 1H), 3.36 (ddd, *J* = 6.3, 8.7, 11.5 Hz, 1H), 2.97 - 2.87 (m, 1H), 2.00 (s, 3H).

Example 140: 2-(5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 181)



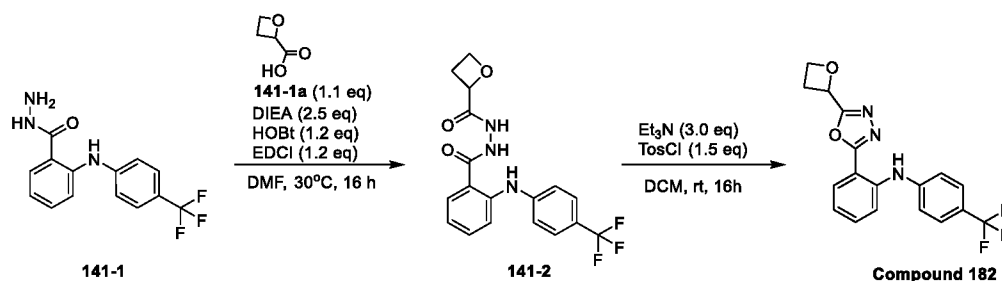
Step 1: N'-(2-((4-(trifluoromethyl)phenyl)amino)benzoyl)tetrahydrofuran-2-carbohydrazide

[00549] To a solution of **140-1a** (94.4 mg, 0.81 mmol, 78.0 μ L, 1.2 *eq*), EDCI (194.8 mg, 1.02 mmol, 1.5 *eq*) and HOBt (137.3 mg, 1.02 mmol, 1.5 *eq*) in DMF (3 mL) at 20°C was added **140-1** (200 mg, 0.68 mmol, 1 *eq*) and then DIPEA (350.2 mg, 2.71 mmol, 0.5 mL, 4 *eq*), and the resulting mixture was stirred at 20°C for 40 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (20 mL *3). The combined organic layers were washed with water (10 mL *2) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **140-2** (340 mg, 0.44 mmol, 66.1% yield) as a crude, which was used directly for next step. LCMS (ESI): RT = 0.768 min, mass calc. for C₁₉H₁₈F₃N₃O₃ 393.13, m/z found 393.9 [M+1]⁺.

Step 2: 2-(5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00550] To a solution of **140-2** (340 mg, 0.45 mmol, 1 *eq*) and DIPEA (115.7 mg, 0.90 mmol, 0.2 mL, 2 *eq*) in DCM (4 mL) at 20°C was added TosCl (102.4 mg, 0.54 mmol, 1.2 *eq*), and the resulting mixture was stirred at 20°C for 16 h. After additional 0.5 *eq* TosCl the reaction was further stirred for 1 h. The mixture was quenched with water (1 mL), and concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 181** (104.96 mg, 0.28 mmol, 62.5% yield). LCMS (ESI): RT = 0.912 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 375.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.20 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 3.0 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.23 - 7.14 (m, 1H), 5.25 (dd, *J* = 5.3, 7.8 Hz, 1H), 3.94 - 3.84 (m, 2H), 2.36 - 2.20 (m, 2H), 2.10 - 1.93 (m, 2H).

Example 141: 2-(5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 182)



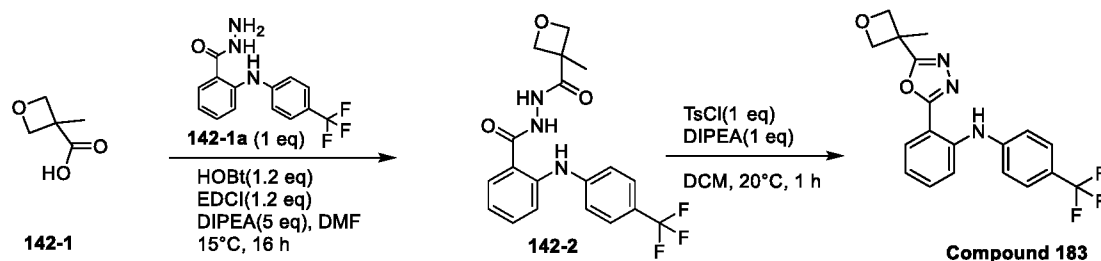
Step 1: N'-[2-[4-(trifluoromethyl)anilino]benzoyl]oxetane-2-carbohydrazide

[00551] To a solution of compound **141-1a** (38 mg, 0.3 mmol, 1.1 *eq*), HOBt (54.9 mg, 0.4 mmol, 1.2 *eq*) and EDCI (77.9 mg, 0.4 mmol, 1.2 *eq*) in DMF (3 mL) was added compound **141-1** (100 mg, 0.3 mmol, 1 *eq*) followed by DIEA (109.4 mg, 0.8 mmol, 0.1 mL, 2.5 *eq*). The reaction was stirred at 30°C for 16 hr. The reaction was diluted with EA (40 mL), washed with Sat. NaHCO₃ (2*10 mL) and brine (2*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give compound **141-2** (70 mg, 0.1 mmol, 47% yield). LCMS confirmed that desired product was obtained.

Step 2: 2-(5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00552] To a solution of compound **141-2** (70 mg, 0.1 mmol, 1 *eq*) and Et₃N (48.7 mg, 0.4 mmol, 67 μ L, 3 *eq*) in DCM (2 mL) was added TosCl (45.9 mg, 0.2 mmol, 1.5 *eq*). The reaction was stirred at 25°C for 16 hr. The reaction was diluted with DCM (20 mL) and washed with brine (10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC to give **Compound 182** (18.07 mg, 49 μ mol, 30% yield). LCMS (ESI): RT = 0.999 min, mass calc. for C₁₈H₁₄F₃N₃O₂ 361.10, m/z found 362.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.44 (s, 1H), 7.91 (dd, *J* = 7.78, 1.51 Hz, 1H), 7.52 (d, *J* = 8.28 Hz, 2H), 7.42 - 7.48 (m, 1H), 7.25 - 7.39 (m, 3H), 6.88 - 6.96 (m, 1H), 5.92 (t, *J* = 7.40 Hz, 1H), 4.75 - 4.90 (m, 2H), 3.15 (q, *J* = 7.78 Hz, 2H).

Example 142: 2-(5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 183)



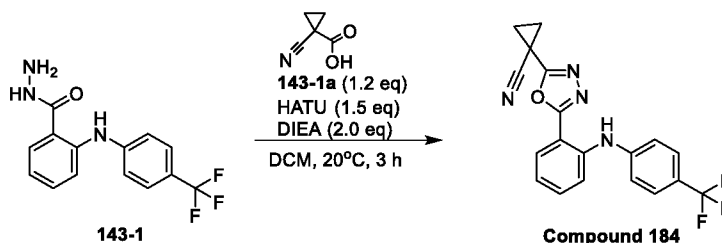
Step 1: 3-methyl-N'-[2-[4-(trifluoromethyl)anilino]benzoyl]oxetane-3-carbohydrazide

[00553] To a mixture of **142-1a** (150 mg, 0.51 mmol, 1.0 eq), compound **142-1** (70.79 mg, 0.61 mmol, 1.2 eq), HOBt (82.4 mg, 0.61 mmol, 1.2 eq) and EDCI (116.9 mg, 0.61 mmol, 1.2 eq) in DMF (3 mL) was added DIPEA (328.3 mg, 2.54 mmol, 0.5 mL, 5 eq) at 15°C. The resulting mixture was stirred at 15 °C for 16 h. The solution was diluted with H₂O (15 mL) and extracted with EA (50 mL) twice. The combined organic layer was washed with Na₂HCO₃ (30 mL), dried with Na₂SO₄, filtered and concentrated to give crude product compound **142-2** (260 mg, crude), which was used directly. LCMS (ESI): RT = 0.751 min, mass calc. for C₁₉H₁₈F₃N₃O₃ 393.13, m/z found 393.9 [M+1]⁺.

Step 2: 2-(5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

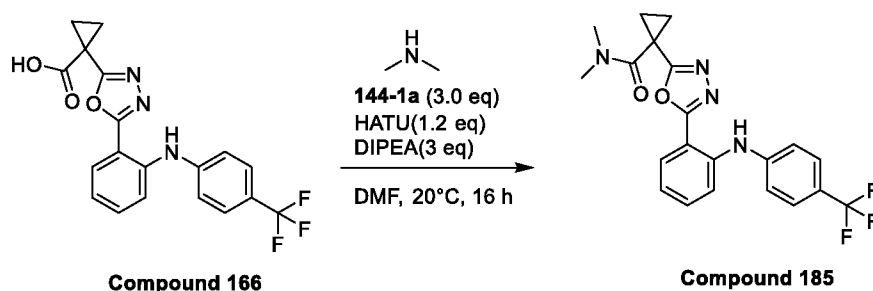
[00554] To a mixture of compound **142-2** (240 mg, 0.61 mmol, 1 eq) and DIPEA (78.8 mg, 0.61 mmol, 0.1 mL, 1 eq) in DCM (10 mL) was added TosCl (116.3 mg, 0.61 mmol, 1 eq) at 20°C. The resulting mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EA (50 mL * 2). The combined organic layers were washed with NaHCO₃ (20 mL * 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 183** (27.31 mg, 70.6 umol, 11.6% yield). LCMS (ESI): RT = 0.889 min, mass calc. for C₁₉H₁₆F₃N₃O₂ 375.12, m/z found 375.9 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃) δ 9.22-9.57 (m, 1H), 7.84 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.29-7.35 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.08 (d, *J* = 6.0 Hz, 2H), 4.60 (d, *J* = 6.0 Hz, 2H), 1.81-1.88 (m, 3H).

Example 143: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carbonitrile (Compound 184)



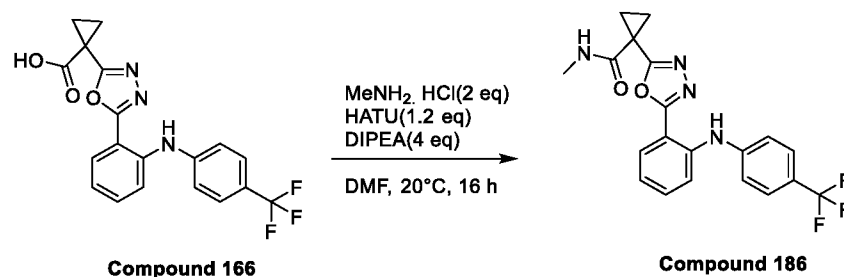
[00555] A solution of compound **143-1a** (90.3 mg, 0.81 mmol, 1.2 *eq*) and HATU (386 mg, 1.02 mmol, 1.5 *eq*) in DCM (6 mL) was stirred at 20°C for 30 min. Then compound **143-1** (200 mg, 0.68 mmol, 1 *eq*) and DIEA (175 mg, 1.35 mmol, 0.23 mL, 2 *eq*) were added to the mixture and stirred at 20°C for 2.5 hr. The reaction mixture was concentrated in vacuum to give a residue. The residue was diluted with EA (30 mL), washed with H₂O (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography. LCMS and ¹H NMR confirmed that **Compound 184** (28 mg, 74.8 μmol, 11% yield) was obtained. LCMS (ESI): RT = 1.022 min, mass calcd. For C₁₉H₁₃F₃N₄O, 370.10 m/z found 371.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.91 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.53 - 7.48 (m, 1H), 7.46 - 7.39 (m, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.03 - 6.96 (m, 1H), 2.03 - 1.98 (m, 4H).

Example 144: N,N-dimethyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (Compound 185)



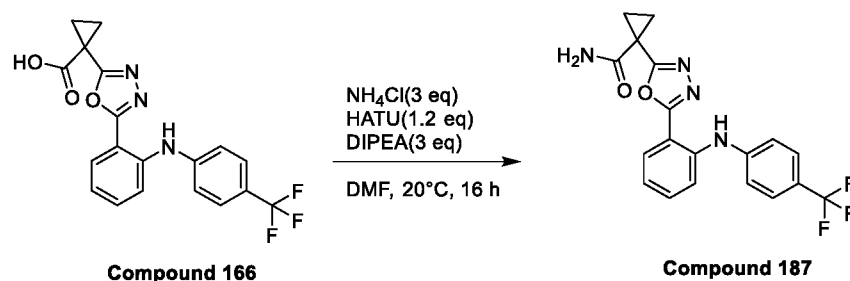
[00556] A mixture of **Compound 166** (40 mg, 0.1 mmol, 1 *eq*), HATU (46.9 mg, 0.12 mmol, 1.2 *eq*), DIPEA (39.8 mg, 0.3 mmol, 0.1 mL, 3 *eq*) and **144-1a** (2 M, 0.15 mL, 3 *eq*) in DMF (1 mL) was stirred at 20 °C for 16 hr under N₂ atmosphere. The mixture was directly purified by prep-HPLC to give **Compound 185** (4.20 mg, 10.1 μmol, 9.8% yield). LCMS (ESI): RT = 0.856 min, mass calc. for C₂₁H₁₉F₃N₄O₂ 416.15, m/z found 438.9 [M+23]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.14 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 3.8 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.12-7.20 (m, 1H), 2.90 (br d, *J* = 14.1 Hz, 6H), 1.47-1.65 (m, 4H).

Example 145: N-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (Compound 186)



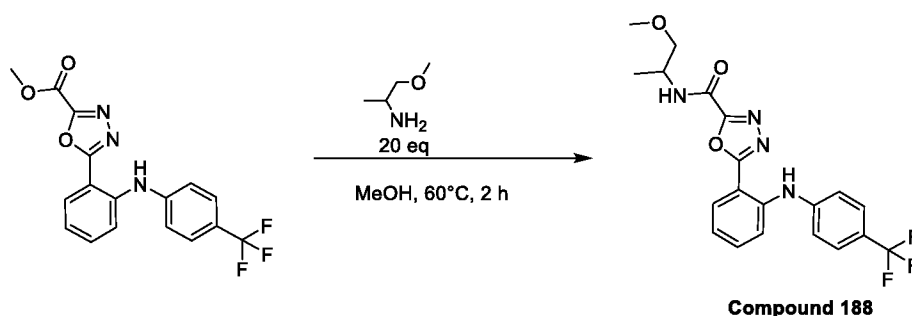
[00557] A mixture of **Compound 166** (40 mg, 0.1 mmol, 1.0 eq), HATU (46.9 mg, 0.12 mmol, 1.2 eq), DIPEA (53.1 mg, 0.4 mmol, 0.1 mL, 4.0 eq) and methanamine hydrochloride (13.9 mg, 0.2 mmol, 2.0 eq) in DMF (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20 °C for 16 hr under N₂ atmosphere. The mixture was directly purified by prep-HPLC to give **Compound 186** (18.19 mg, 0.1 mmol, 44.0% yield). LCMS (ESI): RT = 0.874 min, mass calc. for C₂₀H₁₇F₃N₄O₂ 402.13, m/z found 402.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.25 (s, 1H), 8.08 (br d, *J* = 4.4 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.51 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 2.65 (d, *J* = 4.4 Hz, 3H), 1.58 - 1.51 (m, 2H), 1.47 - 1.40 (m, 2H).

Example 146: 1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (Compound 187)



[00558] A mixture of **Compound 166** (40 mg, 0.1 mmol, 1.0 eq), HATU (46.9 mg, 0.1 mmol, 1.2 eq), DIPEA (39.8 mg, 0.3 mmol, 0.05 mL, 3.0 eq) and NH₄Cl (16.5 mg, 0.3 mmol, 0.01 mL, 3.0 eq) in DMF (1 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20 °C for 16 hr under N₂ atmosphere. The mixture was directly purified by prep-HPLC to give **Compound 187** (28.61 mg, 73.7 μmol, 71.7% yield). LCMS (ESI): RT = 0.843 min, mass calc. for C₁₉H₁₅F₃N₄O₂ 388.11, m/z found 388.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 7.69 (br s, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.60 - 7.47 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 1.61 - 1.52 (m, 2H), 1.49 - 1.42 (m, 2H).

Example 147: N-(1-methoxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 188)

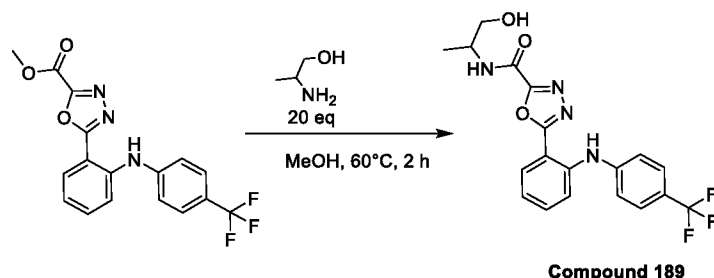


[00559] A mixture of compound methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (50 mg, 0.14 mmol, 1 eq) and 1-methoxypropan-2-amine (245.4 mg,

2.75 mmol, 0.3 mL, 20 eq) in MeOH (0.5 mL) was heated at 60°C for 2 h. The mixture was directly purified by prep-HPLC to give **Compound 188** (24.42 mg, 58.1 μ mol, 42.2% yield).

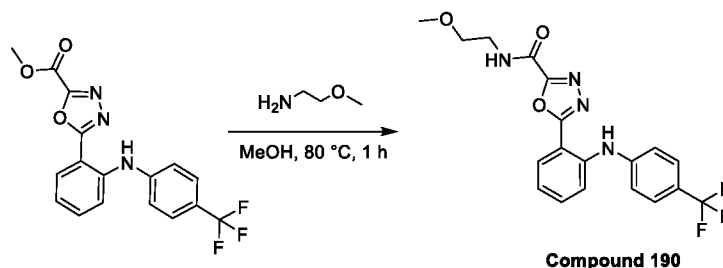
LCMS (ESI): RT = 0.880 min, mass calc. for $C_{20}H_{19}F_3N_4O_3$ 420.14, m/z found 442.9 $[M+23]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.18 (d, J = 8.3 Hz, 1H), 9.13 (s, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 3.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.21 - 7.12 (m, 1H), 4.23 (m, 1H), 3.49 - 3.41 (m, 1H), 3.33 (br d, J = 5.5 Hz, 1H), 3.28 (s, 3H), 1.17 (d, J = 6.8 Hz, 3H).

Example 148: N-(1-hydroxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 189)



[00560] A mixture of methyl compound methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (50 mg, 0.14 mmol, 1.0 eq) and compound **1a** (206.8 mg, 2.6 mmol, 0.22 mL, 20 eq) in MeOH (0.5 mL) was heated at 60°C for 2 h. The residue was directly purified by prep-HPLC to give **Compound 189** (28.39 mg, 0.07 mmol, 50.76% yield). LCMS (ESI): RT = 0.809 min, mass calc. for $C_{19}H_{17}F_3N_4O_3$ 406.13, m/z found 406.9 $[M+1]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.14 (s, 1H), 9.01 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 3.5 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.11-7.24 (m, 1H), 4.85 (t, J = 5.8 Hz, 1H), 3.84-4.26 (m, 1H), 3.41-3.53 (m, 2H), 1.17 (d, J = 6.8 Hz, 3H).

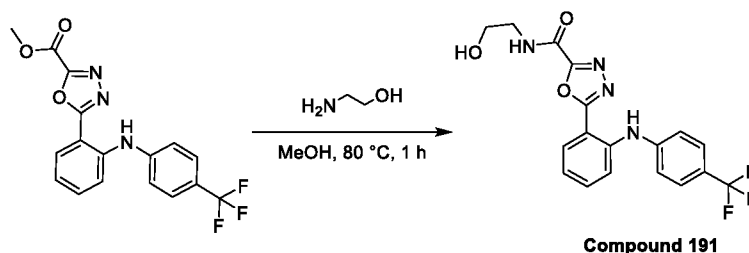
Example 149: N-(2-methoxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 190)



[00561] To a mixture of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60 mg, 0.17 mmol, 1 eq) in MeOH (3 mL) was added 2-methoxyethan-1-amine (62.0 mg, 0.82 mmol, 5 eq). The mixture was stirred at 80 °C for 1 h. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC. **Compound 190** (47.47 mg, 116.82 μ mol, 70.73% yield) was obtained, which was confirmed by LCMS and ^1H NMR. LCMS (ESI): RT = 0.844 min, mass calc. for $C_{19}H_{17}F_3N_4O_3$ 406.13, m/z found 406.9 $[M+H]^+$. ^1H NMR

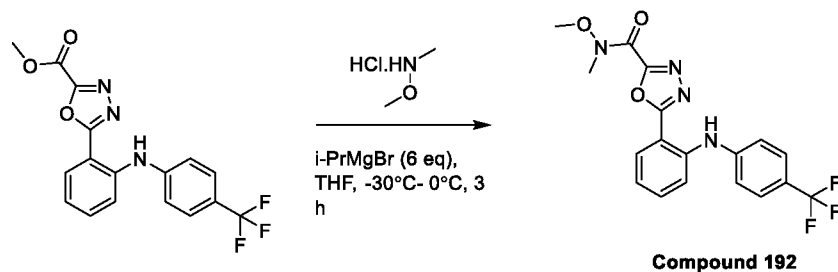
(400MHz, DMSO- d_6) δ 9.38 - 9.33 (m, 1H), 9.13 (s, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.59 - 7.54 (m, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.17 (ddd, J = 3.0, 5.3, 8.0 Hz, 1H), 3.52 - 3.44 (m, 4H), 3.27 (s, 3H).

Example 150: N-(2-hydroxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 191)



[00562] To a mixture of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60 mg, 0.17 mmol, 1 *eq*) in MeOH (3 mL) was added 2-aminoethan-1-ol (50.4 mg, 0.83 mmol, 5 *eq*). The mixture was stirred at 80 °C for 1 h. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC. **Compound 191** (32.95 mg, 83.2 μ mol, 50.3% yield) was obtained, which was confirmed by LCMS and ^1H NMR. LCMS (ESI): RT = 0.787 min, mass calcd. for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_3$ 392.11, m/z found 414.9 $[\text{M}+\text{Na}]^+$. ^1H NMR (400MHz, DMSO- d_6) δ 9.26 (t, J = 5.5 Hz, 1H), 9.14 (s, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.60 - 7.54 (m, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.17 (ddd, J = 2.9, 5.3, 7.9 Hz, 1H), 4.83 (t, J = 5.6 Hz, 1H), 3.54 (q, J = 5.9 Hz, 2H), 3.40 - 3.36 (m, 2H).

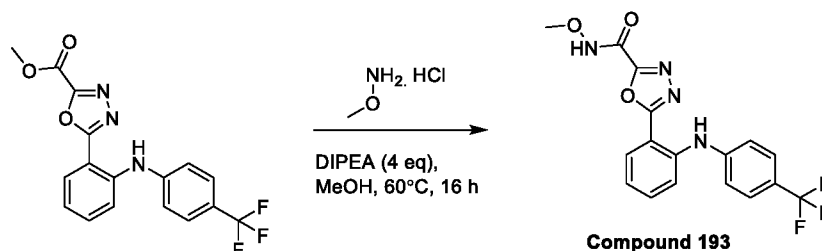
Example 151: N-methoxy-N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 192)



[00563] To a solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and N,O-dimethylhydroxylamine hydrochloride (48.3 mg, 0.50 mmol, 3 *eq*) in THF (2 mL) at -30 °C was added *i*-PrMgBr (0.5 M, 2.0 mL, 6 *eq*) dropwise, and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution (3 mL) at 0 °C, and then diluted with water (20 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give **Compound 192** (6.84 mg, 16.8 μ mol, 10.2% yield). LCMS (ESI): RT = 0.876

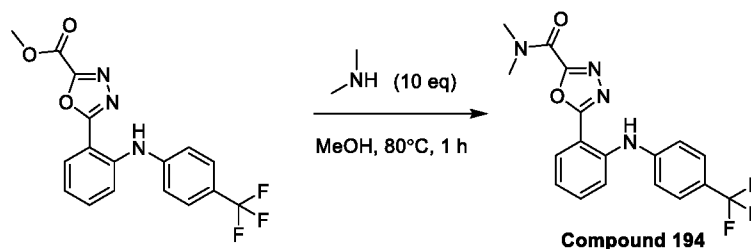
min, mass calc. for $C_{18}H_{15}F_3N_4O_3$ 392.11, m/z found 392.9 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (brs, 1H), 8.02 (d, $J = 7.8$ Hz, 1H), 7.60 (d, $J = 8.3$ Hz, 2H), 7.53 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.02 - 6.97 (m, 1H), 3.97 (s, 3H), 3.45 (s, 3H).

Example 152: N-methoxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 193)



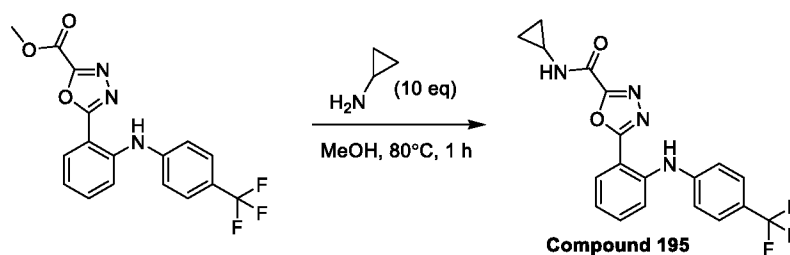
[00564] To a solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and O-methylhydroxylamine hydrochloride (3 *eq*) in MeOH (1 mL) at 20°C was added DIPEA (85.4 mg, 0.66 mmol, 0.1 mL, 4 *eq*), and the mixture was stirred at 60°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 193** (22.02 mg, 58.2 μ mol, 35.2% yield). LCMS (ESI): RT = 0.833 min, mass calc. for $C_{17}H_{13}F_3N_4O_3$ 378.09, m/z found 378.8 $[M+1]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 12.80 (brs, 1H), 9.10 (s, 1H), 7.98 (d, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.57 (d, $J = 3.8$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.17 (td, $J = 4.1, 8.0$ Hz, 1H), 3.76 (s, 3H).

Example 153: N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 194)



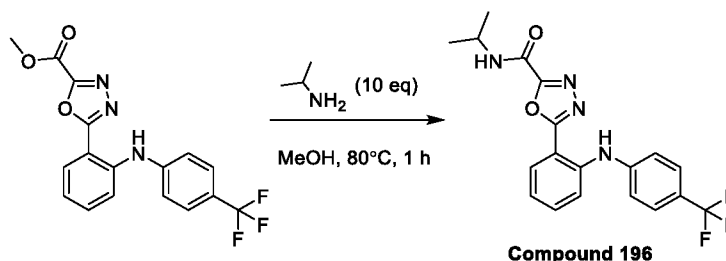
[00565] The solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and dimethylamine (2.0 M, 0.8 mL, 10 *eq*) in MeOH (1 mL) was stirred at 80°C for 1 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 194** (36.42 mg, 96.8 μ mol, 58.6% yield). LCMS (ESI): RT = 0.869 min, mass calc. for $C_{18}H_{15}F_3N_4O_2$ 376.11, m/z found 376.9 $[M+1]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.18 (s, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 8.5$ Hz, 2H), 7.59 - 7.53 (m, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.20 - 7.12 (m, 1H), 3.31 (s, 3H), 3.07 (s, 3H).

Example 154: N-cyclopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 195)



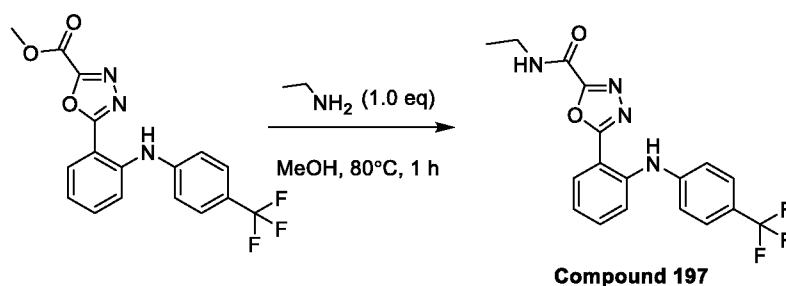
[00566] The solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and cyclopropylamine (94.3 mg, 1.65 mmol, 0.1 mL, 10 *eq*) in MeOH (1 mL) was stirred at 80°C for 1 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 195** (45.52 mg, 0.12 mmol, 71.0% yield). LCMS (ESI): RT = 0.865 min, mass calc. for C₁₉H₁₅F₃N₄O₂ 388.11, m/z found 388.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.42 (d, *J* = 4.5 Hz, 1H), 9.13 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 3.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.20 - 7.14 (m, 1H), 2.93 - 2.88 (m, 1H), 0.79 - 0.73 (m, 2H), 0.72 - 0.66 (m, 2H).

Example 155: N-isopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 196)



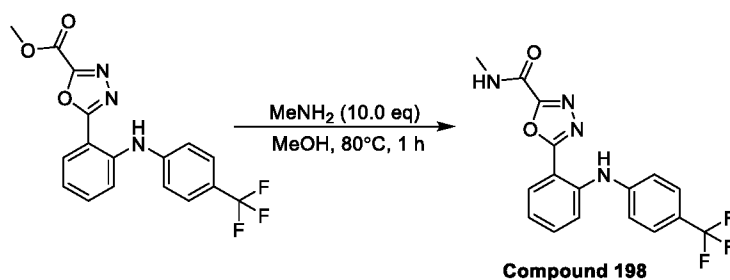
[00567] The solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60.0 mg, 0.17 mmol, 1 *eq*) and *iso*-propylamine (97.6 mg, 1.65 mmol, 0.1 mL, 10 *eq*) in MeOH (1 mL) was stirred at 80°C for 1 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give **Compound 196** (33.33 mg, 85.4 μmol, 51.7% yield). LCMS (ESI): RT = 0.890 min, mass calc. for C₁₉H₁₇F₃N₄O₂ 390.13, m/z found 390.9 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.20 (d, *J* = 8.3 Hz, 1H), 9.14 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.59 - 7.53 (m, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.20 - 7.12 (m, 1H), 4.18 - 4.06 (m, 1H), 1.20 (d, *J* = 6.5 Hz, 6H).

Example 156: N-ethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 197)



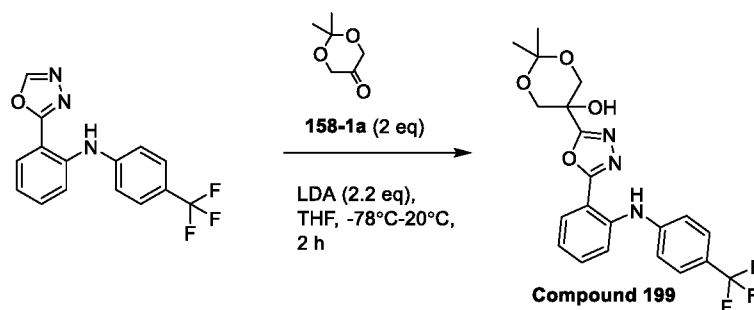
[00568] To a solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60 mg, 0.17 mmol, 1 eq) in MeOH (1 mL) was added ethylamine (7.5 mg, 165.16 μ mol, 10.8 μ L, 1 eq). The mixture was stirred at 80 °C for 1 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 197** (19.53 mg, 51.38 μ mol, 31% yield). LCMS (ESI): RT = 0.986 min, mass calc. for $C_{18}H_{15}F_3N_4O_2$ 376.11, m/z found 377.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.37 (t, J = 5.8 Hz, 1H), 9.14 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 2.8 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.19 - 7.12 (m, 1H), 3.34 - 3.27 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H).

Example 157: N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide (Compound 198)



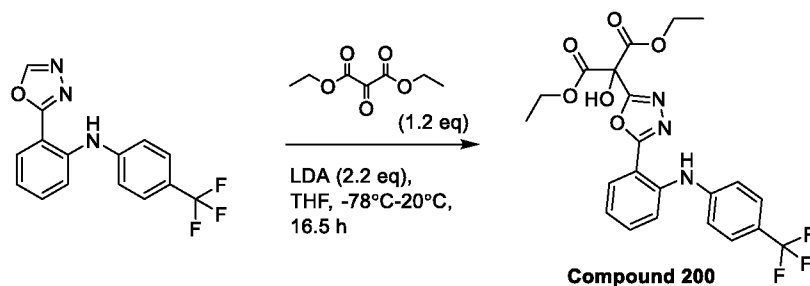
[00569] To a solution of methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate (60 mg, 0.17 mmol, 1 eq) in MeOH (1 mL) was added MeNH₂ (2 M, 0.82 mL, 10 eq). The mixture was stirred at 80 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 198** (5.24 mg, 14.17 μ mol, 8% yield). LCMS (ESI): RT = 0.953 min, mass calc. for $C_{17}H_{13}F_3N_4O_2$ 362.10, m/z found 363.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.28 (d, J = 4.8 Hz, 1H), 9.14 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 2.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.18-7.14 (m, 1H), 2.84 (d, J = 4.8 Hz, 3H).

Example 158: 2,2-dimethyl-5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)-1,3-dioxan-5-ol (Compound 199)



[00570] To a solution of 2-(1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (100 mg, 0.33 mmol, 1 *eq*) in THF (2 mL) at -78°C was added LDA (2 M, 0.4 mL, 2.2 *eq*) drop-wise, and the mixture was stirred at -78°C for 0.5 h. And then the solution of **158-1a** (85.3 mg, 0.66 mmol, 0.2 mL, 2.0 *eq*) in THF (1 mL) was added at -78°C into the above solution. The resulting mixture was stirred at 20°C for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL), then diluted with water (5 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EA = 2:1, UV) to give **Compound 199** (80.13 mg, 0.18 mmol, 56.2% yield). LCMS (ESI): RT = 0.861 min, mass calc. for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_4$ 435.14, m/z found 436.0 $[\text{M}+1]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1H), 7.96 (dd, $J = 1.4, 8.0$ Hz, 1H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, $J = 8.5$ Hz, 2H), 6.99 (t, $J = 7.6$ Hz, 1H), 4.42 (d, $J = 11.9$ Hz, 2H), 4.08 (d, $J = 11.9$ Hz, 2H), 3.70 (s, 1H), 1.57 - 1.55 (m, 6H).

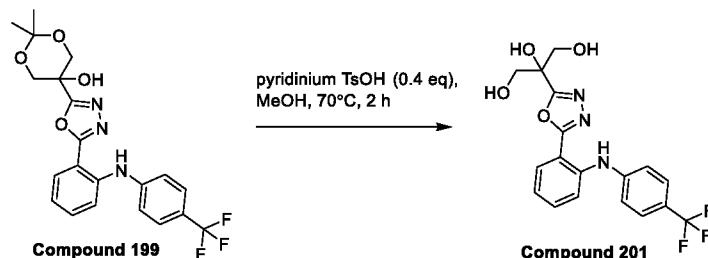
Example 159: diethyl 2-hydroxy-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)malonate (Compound 200)



[00571] To a solution of 2-(1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (50 mg, 0.16 mmol, 1 *eq*) in THF (2 mL) at -78°C was added LDA (2 M, 0.2 mL, 2.2 *eq*) drop-wise, and the mixture was stirred at -78°C for 0.5 h. And then the above solution was added at -78°C into the solution of diethyl 2-oxopropanedioate (34.2 mg, 0.20 mmol, 30 μL , 1.2 *eq*) in THF (1 mL). The resulting mixture was stirred at 20°C for 16 h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL), then diluted with water (5 mL) and extracted with EA (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC

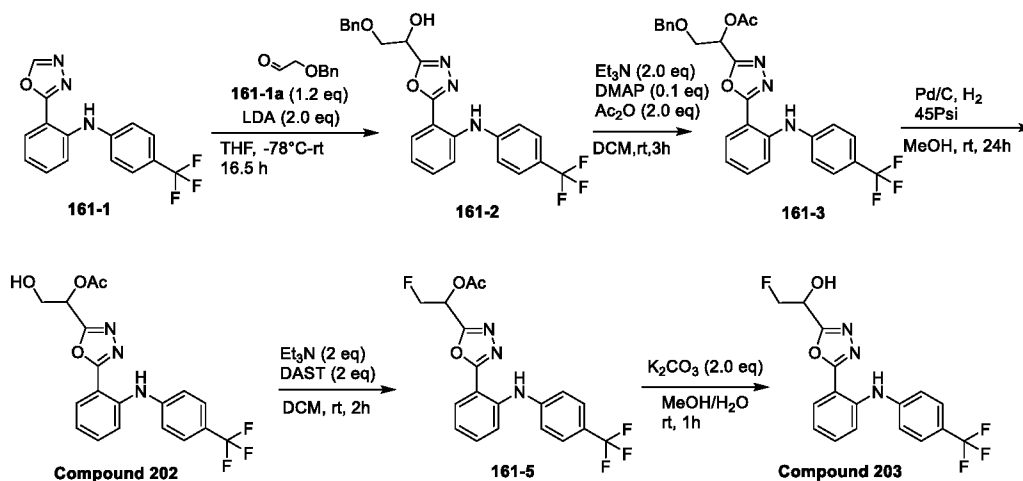
(PE:EA = 2:1, UV) to give **Compound 200** (25.0 mg, 50.1 μ mol, 30.6% yield). LCMS (ESI): RT = 0.902 min, mass calc. for $C_{22}H_{20}F_3N_3O_6$ 479.13, m/z found 480.0 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.54 - 7.49 (m, 1H), 7.45 - 7.39 (m, 1H), 7.36 (d, J = 8.3 Hz, 2H), 6.98 (t, J = 7.0 Hz, 1H), 4.53 (s, 1H), 4.46 (tt, J = 3.6, 7.1, 10.6 Hz, 4H), 1.38 (t, J = 7.0 Hz, 6H).

Example 160: 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propane-1,2,3-triol (Compound 201)



[00572] The solution of **Compound 199** (70.0 mg, 0.16 mmol, 1 *eq*) and pyridinium TsOH (16.2 mg, 64.3 μ mol, 0.4 *eq*) in MeOH (3 mL) was stirred at 70°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 201** (32.41 mg, 82.0 μ mol, 51.0% yield). LCMS (ESI): RT = 0.742 min, mass calc. for $C_{18}H_{16}F_3N_3O_4$ 395.11, m/z found 395.9 $[M+1]^+$; ^1H NMR (400 MHz, $DMSO-d_6$) δ 9.60 - 8.75 (m, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.57 - 7.48 (m, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.14 (dt, J = 1.9, 7.1 Hz, 1H), 3.89 - 3.78 (m, 4H).

Example 161: 2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl acetate (Compound 202) and 2-fluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 203)



Step 1: 2-benzyloxy-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethanol

[00573] To a solution of compound 2-(1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline **161-1** (0.5 g, 1.6 mmol, 1 *eq*) in THF (8 mL) was added LDA (2 M, 1.6 mL, 2 *eq*) at -78°C. The

mixture was stirred at -78°C for 30 min. Compound **161-1a** (295.1 mg, 1.9 mmol, 0.3 mL, 1.2 *eq*) in THF (2 mL) was added drop wise to the solution and the reaction was warmed to 20°C. The reaction was stirred at 20°C for 16 hr. The reaction was quenched by Sat.NH₄Cl (10 mL) and extracted with EA (2*30 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel to give compound **161-2** (207 mg, 0.4 mmol, 27% yield).

Step 2: [2-benzyloxy-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethyl] acetate

[00574] To a solution of compound **161-2** (207 mg, 0.4 mmol, 1 *eq*), DMAP (5.5 mg, 45 μ mol, 0.1 *eq*) and Et₃N (91 mg, 0.9 mmol, 0.1 mL, 2 *eq*) in DCM (5 mL) was added Ac₂O (92.8 mg, 0.9 mmol, 85 μ L, 2 *eq*). The reaction was stirred at 25°C for 3 hr. The reaction was diluted with DCM (30 mL) and washed with brine (3*10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give compound **161-3** (160 mg, 0.2 mmol, 61% yield). LCMS confirmed that desired product was obtained.

Step 3: 2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl acetate (Compound 202)

[00575] To a solution of compound **161-3** (130 mg, 0.2 mmol, 1 *eq*) in MeOH (20 mL) was added Pd/C (30 mg, 10%) under Ar. The suspension was degassed under vacuum and purged with H₂ 3 times. The mixture was stirred under H₂ (50 psi) at 30°C for 16 hours. The reaction was filtered and concentrated. The residue was purified by prep-HPLC to give **Compound 202** (4.63 mg, 10.7 μ mol, 4.1% yield) and compound **3** (20 mg, 40.2 μ mol, 15.4% yield). LCMS (ESI): RT = 0.825 min, mass calc. for C₁₉H₁₆F₃N₃O₄ 407.11, m/z found 407.9 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.99 (dd, *J* = 7.91, 1.38 Hz, 1H), 7.56 - 7.68 (m, 3H), 7.50 (td, *J* = 7.91, 1.51 Hz, 1H), 7.42 (d, *J* = 8.53 Hz, 2H), 7.04 - 7.12 (m, 1H), 2.02 - 2.10 (m, 3H).

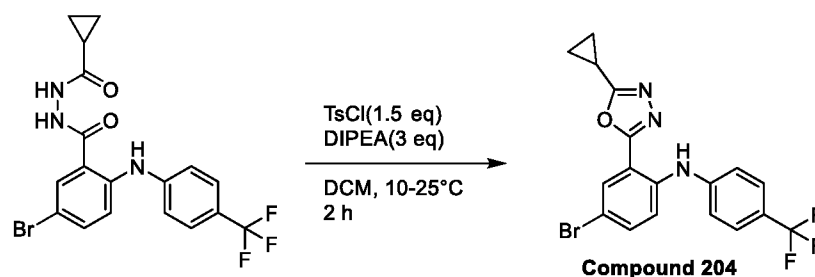
Step 4: [2-fluoro-1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethyl] acetate

[00576] To a solution of **Compound 202** (90 mg, 0.22 mmol, 1 *eq*) and Et₃N (44 mg, 0.44 mmol, 61 μ L, 2 *eq*) in DCM (3 mL) was added DAST (71 mg, 0.44 mmol, 58 μ L, 2 *eq*). The reaction was stirred at 25°C for 2 hr. The reaction was diluted with DCM (15 mL) and washed with water (2*5 mL). The organic layer was dried over Na₂SO₄ and concentrated. The reaction was purified by column chromatography on silica gel to give compound **161-5** (20 mg, 46 μ mol, 21% yield). LCMS confirmed that desired product was obtained. LCMS (ESI): RT = 1.027 min, mass calc. for C₁₉H₁₅F₄N₃O₃ 409.10, m/z found 410.0 [M+H]⁺.

Step 5: 2-fluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol (Compound 203)

[00577] To a solution of compound **161-5** (10 mg, 24 μmol , 1 *eq*) in MeOH (1 mL) was added K_2CO_3 (6.7 mg, 48 μmol , 2 *eq*) in H_2O (0.1 mL). The reaction was stirred at 25°C for 1 hr. The solution was concentrated. The aqueous layer was extracted with EA (2*5 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give **Compound 203** (1.3 mg, 3.4 μmol , 7% yield). LCMS (ESI): RT = 0.946 min, mass calc. for $\text{C}_{17}\text{H}_{13}\text{F}_4\text{N}_3\text{O}_2$ 367.09, m/z found 368.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 9.41 (s, 1H), 7.95 (dd, $J = 7.91, 1.38$ Hz, 1H), 7.61 (d, $J = 8.53$ Hz, 2H), 7.49 - 7.56 (m, 1H), 7.44 (td, $J = 7.84, 1.38$ Hz, 1H), 7.38 (d, $J = 8.53$ Hz, 2H), 6.96 - 7.05 (m, 1H), 5.72 - 5.92 (m, 1H), 4.23 - 4.43 (m, 2H), 2.48 (br s, 1H).

Example 162: 4-bromo-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 204)



[00578] To a mixture of compound 5-bromo-N'-(cyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide (860 mg, 1.94 mmol, 1 *eq*) and DIPEA (754.0 mg, 5.83 mmol, 1.0 mL, 3 *eq*) in DCM (15 mL) was added TsCl (556.1 mg, 2.92 mmol, 1.5 *eq*) at 10°C. Then the mixture was stirred at 25°C for 2 h. The mixture was diluted with DCM (200 mL), washed with 1 M HCl (20 mL) and brine (15 mL*2) in turns, dried with Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography to give the product (800 mg, 1.89 mmol, 97.2% yield). 50 mg of the crude product was purified by TLC to give **Compound 204** (10.64 mg, 24.9 μmol , 1.3% yield). MS: mass calc. for $\text{C}_{18}\text{H}_{13}\text{BrF}_3\text{N}_3\text{O}$ 423.02, m/z found 426.04 $[\text{M}+1]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.21 (s, 1H), 8.01 (d, $J = 2.3$ Hz, 1H), 7.69 - 7.59 (m, 3H), 7.48 (d, $J = 8.8$ Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 2H), 2.38 - 2.27 (m, 1H), 1.21 - 1.09 (m, 4H).

II. Biological Evaluation

Example A1: YAP Reporter Assay

[00579] HEK293T cells stably transfected with 8XTBD luciferase reporter and pRLTK in 384-well plates were treated with the test compounds, starting from 3 μM (final concentration in assay

plate), 1:3 dilution, and 10 points in quadruplicates. Post 24-hr incubation with compounds at 37°C and 5% CO₂, cells were lysed and 8XTBD-driven firefly luciferase and control TK-driven renilla luciferase activities were measured using Promega Dual-Luciferase Reporter Assay System.

[00580] Reagents: The reagents used for this study are: DMEM: Invitrogen# 11960077, Dual-Glo Luciferase Assay System: Promega-E2980, Puromycin Dihydrochloride: Invitrogen-A1113803, 384-well plate: PerkinElmer-6007480, L-GLUTAMINE: Invitrogen-25030164, Hygromycin B: Invitrogen-10687010, and Penicillin-Streptomycin: Merk-TMS-AB2-C

[00581] Media: The media used for this assay were: Culture Medium: DMEM+ 1ug/mL puromycin + 200 ug/mL hygromycin (with 10% FBS + 1mM L-glutamine); and Assay Medium: DMEM (with 10% FBS + 1mM L-glutamine + 1x P/S).

[00582] Cell Plating: The appropriate media was warmed at 37°C by water bath: Culture Medium, Assay Medium, 1* D-PBS, 0.05% trypsin-EDTA. The cells were trypsinized after removing all media, then washed with 1* sterile D-PBS and then with 2 ml 0.05% trypsin-EDTA. The cells were then incubated at RT for one minute. Then 10 ml/75cm² flask Assay Medium was added to each flask. Using a 10 ml pipette, the cells were then gently resuspended in the media, until the clumps completely disappeared. The cells were then transferred into 50 ml centrifuge tubes and were centrifuged at 800 rpm for 5 mins. The medium was removed and the cells were resuspended with Assay Medium. An aliquot of cells was used to count the cell density (cells/ml). The cell suspension was then diluted with Assay Medium to a concentration of 6x10⁴ cells/ml. 50ul cells suspension was then plated to 384-well plate (PerkinElmer-6007480), 3x10³ cells/well and the cells were incubated in an incubator at 37°C, 5% CO₂.

[00583] Compound Treatment: In the afternoon (incubation of the plate with 3-4 hrs), the test compounds were added by Echo, starting from 3uM (final concentration in the assay plate), 1:3 dilution, 10 points, quadruplicates. The plate was placed at 37°C, 5% CO₂ incubator for 24hrs.

[00584] Detection: The Dual-Glo Luciferase Reagent was prepared by transferring the contents of one bottle of Dual-Glo Luciferase Buffer to one bottle of Dual-Glo Luciferase Substrate to create the Dual-Glo Luciferase Reagent. Mixing was performed by inversion until the substrate was thoroughly dissolved. After mixing, the reagent was aliquoted into 15 ml tubes. In the afternoon (24hrs post compound treatment), the DMEM+ medium in the 384 well plates were aspirated by Microplate Washer.

[00585] Measuring firefly luciferase activity: 20ul Dual-Glo Luciferase Reagent was added to the 384-well plates. The plates were protected from light to prevent interference with the assay. The plates were shaken for 1min followed centrifuging plates at 1000rpm for 30 seconds. After waiting at least 10 minutes, the firefly luminescence was measured by Envision.

[00586] Measuring renilla luciferase activity: 20ul Stop-Glo Reagent was added to the 384-well plates. The plates were shaken for 1min and then centrifuged at 1000rpm for 30 seconds. After waiting at least 10 minutes, the renilla luminescence was measured by Envision.

[00587] Compound IC₅₀ and maximum inhibition on the firefly luciferase and renilla luciferase activities were reported separately. IC₅₀ for firefly luciferase activity are shown in the table below.

TABLE 2

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
1	ethyl 2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetate	B
2	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol	A
3	ethyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate	A
4	5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine	B
5	(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol	A
6	N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine	C
8	methyl 5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxylate	B
9	ethyl (5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate	C
10	2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol	B
11	ethyl N-methyl-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)glycinate	B
12	N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-amine	B
13	5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	B
14	N-hydroxy-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
15	5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
16	3-tosyl-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	B
17	4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	A
19	2-(methyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol	B
20	2-(1,3,4-oxadiazol-2-yl)-N-[4-(trifluoromethyl)phenyl]aniline	B
22	5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazole-2-carbonitrile	A
24	2-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)amino)acetamide	B
25	1-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]ethane-1,2-diol	A
26	2-oxo-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidine-3-carboxylate	A
28	2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline	B
29	4-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-1,3-dioxolan-2-one	A
30	2-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol	B
31	2-[5-(azidomethyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline	B
32	N-(2-hydroxyethyl)-N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide	B
34	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)imidazolidin-2-one	B
35	2-(5-(5-methyloxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
36	2-(5-(oxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
37	2-(5-(oxazol-5-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
38	N-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanesulfonamide	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
40	2-(5-(5-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
41	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol	A
42	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol	A
44	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropanol	A
45	2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol	A
46	2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl 4-methylbenzenesulfonate	B
47	(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methanol	A
48	2-[5-(2H-tetrazol-5-yl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline	C
49	cyclopropyl(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methanol	A
50	3-[5-[2-[4-(trifluoromethyl)anilino]phenyl]-1,3,4-oxadiazol-2-yl]-4H-1,2,4-oxadiazol-5-one	C
51	2,2,2-trifluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol	A
52	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopentanol	A
53	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl 4-methylbenzenesulfonate	B
54	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclobutanol	A
55	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxetan-3-ol	A
56	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3-ol	A
57	(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)carbamate	B
58	2-(5-(1-aminocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
59	N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)acetamide	B
60	2,2-difluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethanol	A
62	1-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)urea	B
63	2-(5-(1-fluorocyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
66	2-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-N-[4-(trifluoromethyl)phenyl]aniline	A
67	2-(5-(1-methoxycyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
68	2-(5-(2-methylbut-3-yn-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
69	2-(5-(but-3-yn-2-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
70	2-(5-(but-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
71	2-(5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
72	2-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
73	2-(5-methoxy-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
75	(S)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one	A
76	(R)-3-methyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-2-one	A
77	(R)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	A
78	(S)-4-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidin-2-one	B
79	1-chloro-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol	A
80	3-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol	A

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
81	2-chloro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol	A
82	(E)-2-(5-((3-bromoallyl)oxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
83	2-(5-(prop-2-yn-1-yloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
84	2-(5-(allyloxy)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
85	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-one	A
86	2-(5-(2-methyl-1,3-dioxolan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
87	N-methoxy-N,2-dimethyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide	A
88	1-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyclopropane-1-carbonitrile	B
89	2,2-dimethyl-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile	B
90	2-(5-ethyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
91	2-(5-(2-(isopropylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
93	N-isopropyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide	B
94	2-(5-(2-(ethylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
96	N-ethyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide	A
97	2-(5-((isopropylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
99	N-isopropyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide	B
100	2-(5-((ethylamino)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
102	N-ethyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide	A

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
103	2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanoic acid	B
104	2-(5-(2-aminoethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
108	N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)acrylamide	A
110	N-(cyanomethyl)-2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide	C
112	2-methyl-N-(prop-2-yn-1-yl)-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide	C
113	N-(2-cyanoethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
114	N-(cyanomethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
115	N-(but-3-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
116	N-(prop-2-yn-1-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
117	(E)-2-(5-(prop-1-en-1-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
119	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetic acid	B
120	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-2-ol	A
121	2-bromo-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol	A
122	2-(5-(oxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
123	N-(4-(trifluoromethyl)phenyl)-2-(5-vinyl-1,3,4-oxadiazol-2-yl)aniline	A
124	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)but-3-yn-1-ol	A
126	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
129	N-methyl-N-(3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide	A
130	3-hydroxy-3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butanenitrile	A
132	2-(5-(2-methyloxiran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
133	2-(5-(prop-1-en-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
134	1-amino-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-ol	B
135	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butan-2-ol	A
136	2-(5-((1-aminocyclopropyl)methyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
137	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)acetonitrile	B
140	N-methyl-N-((1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)methyl)cyanamide	A
143	N-methyl-N-(2-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide	C
144	2-(5-(2-methyl-1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
146	N-methyl-N-(2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide	A
147	2-(5-(2-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
149	N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide	A
150	2-(5-(1-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
152	N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propyl)cyanamide	A
153	2-(5-(1-(methylamino)cyclopropyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
155	N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropyl)cyanamide	A
156	2-(5-(2-(methylamino)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
158	N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propan-2-yl)cyanamide	A
159	2-(5-(1-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
161	N-methyl-N-(1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide	A
162	2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanamide	A
163	2-(5-(2-(methylsulfonyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
164	2-methyl-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propanenitrile	A
166	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxylic acid	A
167	tert-butyl methyl((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)carbamate	C
168	N-methyl-N-((5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)cyanamide	A
169	2-(5-(pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
171	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile	A
172	2-(5-(2-(methylamino)ethyl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
174	N-methyl-N-(2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl)cyanamide	A
175	2-(5-(pyrrolidin-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
177	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carbonitrile	B
178	2-(5-(2-methyltetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
179	3-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)butane-1,3-diol	A
180	2-(5-(2-methyloxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
181	2-(5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
182	2-(5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	A
183	2-(5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B
184	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carbonitrile	A
185	N,N-dimethyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide	B
186	N-methyl-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide	B
187	1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide	A
188	N-(1-methoxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B
189	N-(1-hydroxypropan-2-yl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B
190	N-(2-methoxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
191	N-(2-hydroxyethyl)-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
192	N-methoxy-N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B
194	N,N-dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	C
195	N-cyclopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B
196	N-isopropyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	B

Compound No.	Name	Firefly Luciferase IC ₅₀ (μM)
197	N-ethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
198	N-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazole-2-carboxamide	A
199	2,2-dimethyl-5-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)-1,3-dioxan-5-ol	C
200	diethyl 2-hydroxy-2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)malonate	B
201	2-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)propane-1,2,3-triol	A
202	2-hydroxy-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethyl acetate	A
203	2-fluoro-1-(5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)ethan-1-ol	A
204	4-bromo-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline	B

Note: Biochemical assay IC₅₀ data are designated within the following ranges:

A: ≤ 0.100 μM

B: > 0.100 μM to ≤ 1.000 μM

C: > 1.000 μM to ≤ 5.000 μM

D: > 5.000 μM

Example A2: Tumor Suppression Assay

[00588] The procedures described herein for the tumor suppression assay is as described in PCT/US2013/043752 (WO 2013/188138). Mouse procedures are performed according to the guidelines of approved animal protocol and based on the methods. After the cells are grown to 90%> confluence, these cells are harvested by trypsinization, washed in phosphate-buffered saline (PBS), and resuspended in PBS supplemented with 50% matrigel (BD Biosciences). An appropriate amount of cells is prepared for administration, such as 200 μL per injection site. Immuno-compromised mice are injected on the dorsolateral sites subcutaneously. Any one of the compounds described herein is formulated accordingly and is then administered at a suitable dose. Control mice received vehicle alone. The average tumor diameter (two perpendicular axes of the tumor are measured) are recorded. The data are expressed in tumor volume estimated by $(\text{width})^2 \times \text{length} / 2$. Paired, two-tailed Student's t-test is performed to access the statistical significance.

Example A3: Cell Proliferation Assay

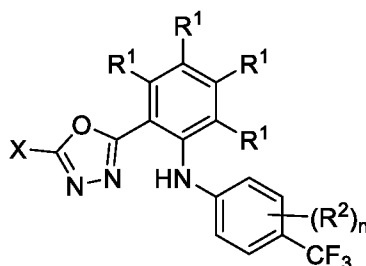
[00589] Cancer cell lines are plated in 384-well plates 24h before drug treatment. Post incubation for various time periods with the test compounds, starting from 3 μ M (final concentration in assay plate), 1:3 dilution, and 10 points in duplicates, the number of viable cells and proliferative cells are determined using CellTiter-Glo® Luminescent Cell Viability Assay Kit (Promega) and Click-iT EdU HCS Assay Kit (Invitrogen) according to the manufacturers' protocols. The IC₅₀ values and maximum % inhibition of the test compounds are calculated using the dose response curves.

[00590] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

X is H, -CN, halogen, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, -L²-L³-Y², -L²-L³-L⁴-Y², -L⁵-L⁶-L³-Y², or -L⁶-L⁵-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y¹ is -N₃, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L² is absent, substituted or unsubstituted C₁-C₆alkylene, substituted or unsubstituted C₃-C₁₀cycloalkylene, or substituted or unsubstituted C₂-C₁₀heterocycloalkylene;

L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-, -O(C=O)-NR³(SO₂)-NR³-, -NR³(SO₂)NR³-(C=O)O-, -O-(SO₂)-, or -(SO₂)-O-;

each R³ is independently H, -CN, -S(=O)₂(C₁-C₄alkyl), or substituted or unsubstituted C₁-C₆alkyl;

L⁴ is substituted or unsubstituted C₁-C₆alkylene;

L⁵ is substituted or unsubstituted C₁-C₆alkylene;

L⁶ is substituted or unsubstituted C₃-C₁₀cycloalkylene;

Y² is H, -CN, -N₃, halogen, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or

unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$;

or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R^6 is independently H or substituted or unsubstituted C_1 - C_6 alkyl;

or two R^6 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R^1 is independently H, halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, or $-\text{L}^7-\text{Y}^3$;

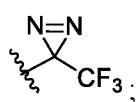
L^7 is substituted or unsubstituted C_1 - C_6 alkylene;

Y^3 is $-\text{Si}(\text{R}^7)_2$;

each R^7 is independently substituted or unsubstituted C_1 - C_6 alkyl;

n is 0, 1, 2, 3, or 4;

each R^2 is independently H, halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R^4 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^4 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

each R^5 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or

unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R⁵ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

2. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:

X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

3. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:

X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

4. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:

X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, or substituted or unsubstituted heteroaryl.

5. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:

X is substituted or unsubstituted C₁-C₄alkyl.

6. The compound, or pharmaceutically acceptable salt thereof, of claim 5, wherein:

X is -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃.

7. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:

X is substituted or unsubstituted C₁-C₄haloalkyl.

8. The compound, or pharmaceutically acceptable salt thereof, of claim 7, wherein:

X is -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.

9. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:

X is substituted or unsubstituted C₃-C₆cycloalkyl.

10. The compound, or pharmaceutically acceptable salt thereof, of claim 9, wherein:

X is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl.

11. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:

X is substituted or unsubstituted C₂-C₆heterocycloalkyl.

12. The compound, or pharmaceutically acceptable salt thereof, of claim 11, wherein:
X is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl.
13. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:
X is substituted or unsubstituted heteroaryl.
14. The compound, or pharmaceutically acceptable salt thereof, of claim 13, wherein:
X is substituted or unsubstituted monocyclic heteroaryl.
15. The compound, or pharmaceutically acceptable salt thereof, of claim 14, wherein:
X is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.
16. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:
X is $-L^1-Y^1$.
17. The compound, or pharmaceutically acceptable salt thereof, of claim 16, wherein:
 L^1 is substituted or unsubstituted C_1-C_4 alkylene; and
 Y^1 is substituted or unsubstituted C_3-C_6 cycloalkyl.
18. The compound, or pharmaceutically acceptable salt thereof, of claim 17, wherein:
 Y^1 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl.
19. The compound, or pharmaceutically acceptable salt thereof, of claim 16, wherein:
 L^1 is substituted or unsubstituted C_1-C_4 alkylene; and

Y¹ is substituted or unsubstituted C₂-C₆ heterocycloalkyl.

20. The compound, or pharmaceutically acceptable salt thereof, of claim 19, wherein:

Y¹ is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl.

21. The compound, or pharmaceutically acceptable salt thereof, of claim 16, wherein:

L¹ is substituted or unsubstituted C₁-C₄alkylene; and

Y¹ is substituted or unsubstituted phenyl.

22. The compound, or pharmaceutically acceptable salt thereof, of claim 16, wherein:

L¹ is substituted or unsubstituted C₁-C₄alkylene; and

Y¹ is substituted or unsubstituted heteroaryl.

23. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein:

Y¹ is substituted or unsubstituted monocyclic heteroaryl.

24. The compound, or pharmaceutically acceptable salt thereof, of claim 23, wherein:

Y¹ is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

25. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:

X is -L²-L³-Y².

26. The compound, or pharmaceutically acceptable salt thereof, of claim 25, wherein:

L² is substituted or unsubstituted C₁-C₄alkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-;

Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂.

27. The compound, or pharmaceutically acceptable salt thereof, of claim 26, wherein:

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-;

Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

28. The compound, or pharmaceutically acceptable salt thereof, of claim 25, wherein:

L^2 is absent;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-;

Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂.

29. The compound, or pharmaceutically acceptable salt thereof, of claim 28, wherein:

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-;

Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or

unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

30. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein: X is -L²-L³-L⁴-Y².

31. The compound, or pharmaceutically acceptable salt thereof, of claim 30, wherein:

L² is substituted or unsubstituted C₁-C₄alkylene;

L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-;

L⁴ is substituted or unsubstituted C₁-C₄alkylene;

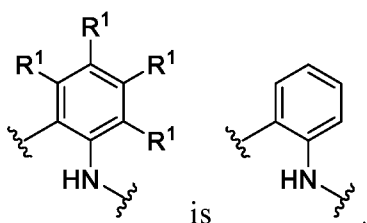
Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂.

32. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein:

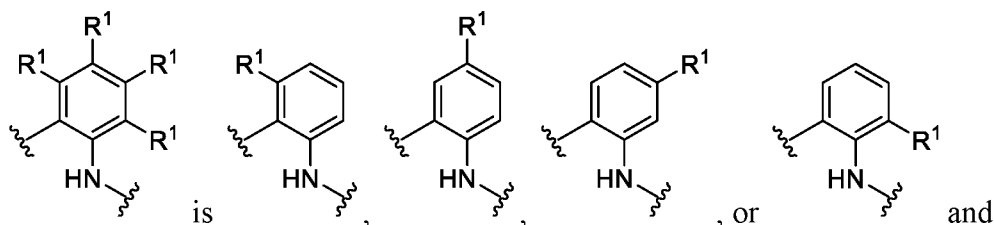
L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-;

Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

33. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-32, wherein:



34. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-32, wherein:



R^1 is halogen, -CN, $-OR^4$, $-SR^4$, $-N(R^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

35. The compound, or pharmaceutically acceptable salt thereof, of claim 34, wherein:

R^1 is halogen, -CN, $-OR^4$, $-SR^4$, $-N(R^4)_2$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

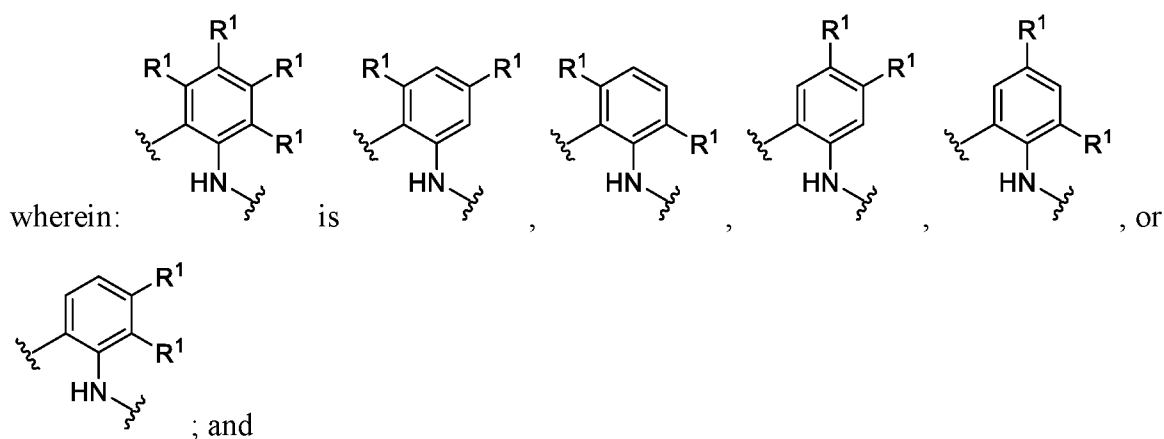
36. The compound, or pharmaceutically acceptable salt thereof, of claim 35, wherein:

R^1 is halogen, substituted or unsubstituted C_1 - C_4 alkyl, or substituted or unsubstituted C_1 - C_4 haloalkyl.

37. The compound, or pharmaceutically acceptable salt thereof, of claim 36, wherein:

R^1 is F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$.

38. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-32,



each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

39. The compound, or pharmaceutically acceptable salt thereof, of claim 38, wherein:

each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

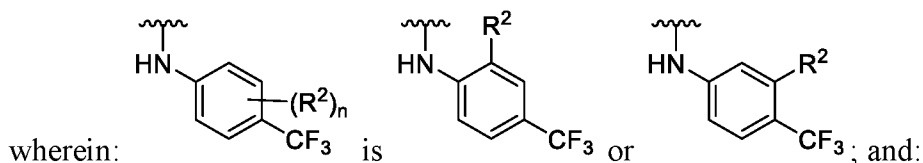
40. The compound, or pharmaceutically acceptable salt thereof, of claim 39, wherein:

each R^1 is independently halogen, substituted or unsubstituted C_1 - C_4 alkyl, or substituted or unsubstituted C_1 - C_4 haloalkyl.

41. The compound, or pharmaceutically acceptable salt thereof, of claim 40, wherein:

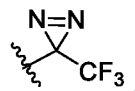
each R^1 is independently F, Cl, Br, I, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$.

42. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-41,



R^2 is halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl,

substituted or unsubstituted heteroaryl, or

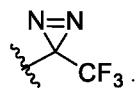


The structure shows a carbon atom double-bonded to a nitrogen atom (N=N), single-bonded to a wavy line, and single-bonded to a CF_3 group.

43. The compound, or pharmaceutically acceptable salt thereof, of claim 42, wherein:

R^2 is halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl,

substituted or unsubstituted monocyclic heteroaryl, or

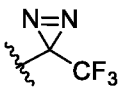


The structure shows a carbon atom double-bonded to a nitrogen atom (N=N), single-bonded to a wavy line, and single-bonded to a CF_3 group.

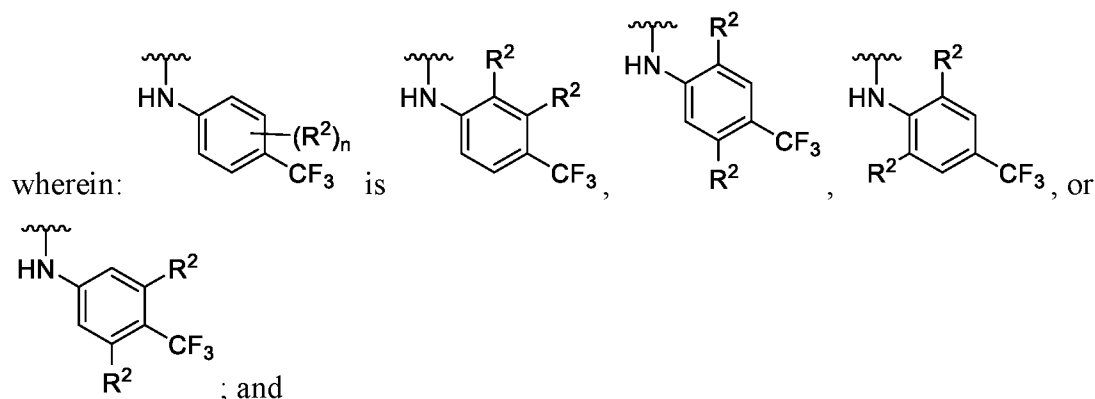
each R^5 is independently H, or substituted or unsubstituted C_1 - C_4 alkyl.

44. The compound, or pharmaceutically acceptable salt thereof, of claim 43, wherein:

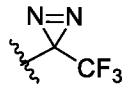
R^2 is halogen, $-N_3$, $-OR^5$, $-(SO_2)R^5$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or

unsubstituted C_1 - C_4 haloalkyl, or .

45. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-41,

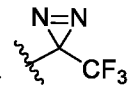


each R^2 is independently halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted aralkyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, or .

46. The compound, or pharmaceutically acceptable salt thereof, of claim 45, wherein:

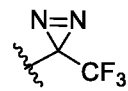
each R^2 is independently halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted benzyl, substituted or

unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and

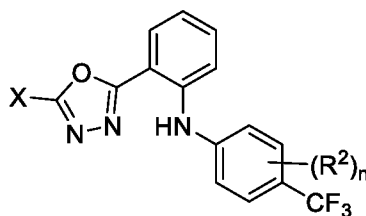
each R^5 is independently H, or substituted or unsubstituted C_1 - C_4 alkyl.

47. The compound, or pharmaceutically acceptable salt thereof, of claim 46, wherein:

each R^2 is independently halogen, $-N_3$, $-OR^5$, $-(SO_2)R^5$, $-CO_2R^5$, substituted or unsubstituted C_1 -

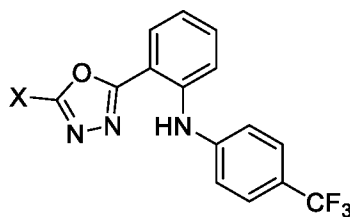
C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, or .

48. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



Formula (Ia).

49. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:



Formula (Ib).

50. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-49, wherein the compound exhibits an IC₅₀ of no more than about 5.000 μ M.

51. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1, or a pharmaceutically acceptable salt thereof.

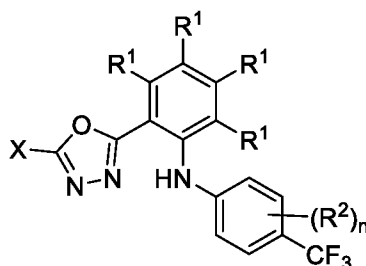
52. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof.

53. A method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

X is H, -CN, halogen, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -L¹-Y¹, -L²-L³-Y², -L²-L³-L⁴-Y², -L⁵-L⁶-L³-Y², or -L⁶-L⁵-L³-Y²;

L¹ is substituted or unsubstituted C₁-C₆alkylene;

Y¹ is -N₃, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L² is absent, substituted or unsubstituted C₁-C₆alkylene, substituted or unsubstituted C₃-C₁₀cycloalkylene, or substituted or unsubstituted C₂-C₁₀heterocycloalkylene;

L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -O-NR³(C=O)-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)-, -(SO₂)NR³-(C=O)O-, -O(C=O)-NR³(SO₂)-, -NR³(SO₂)NR³-(C=O)-, -(C=O)-NR³(SO₂)NR³-, -O(C=O)-NR³(SO₂)-NR³-, -NR³(SO₂)NR³-(C=O)O-, -O-(SO₂)-, or -(SO₂)-O-;

each R³ is independently H, -CN, -S(=O)₂(C₁-C₄alkyl), or substituted or unsubstituted C₁-C₆alkyl;

L⁴ is substituted or unsubstituted C₁-C₆alkylene;

L⁵ is substituted or unsubstituted C₁-C₆alkylene;

L⁶ is substituted or unsubstituted C₃-C₁₀cycloalkylene;

Y² is H, -CN, -N₃, halogen, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or

unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^6$, $-(\text{C}=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)_2$, or $-(\text{C}=\text{O})\text{N}(\text{R}^6)_2$;

or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R^6 is independently H or substituted or unsubstituted C_1 - C_6 alkyl;

or two R^6 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

each R^1 is independently H, halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, or $-\text{L}^7-\text{Y}^3$;

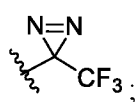
L^7 is substituted or unsubstituted C_1 - C_6 alkylene;

Y^3 is $-\text{Si}(\text{R}^7)_2$;

each R^7 is independently substituted or unsubstituted C_1 - C_6 alkyl;

n is 0, 1, 2, 3, or 4;

each R^2 is independently H, halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, or ;

each R^4 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^4 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

each R^5 is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or

unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R⁵ on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

2. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:

X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₂-C₆alkenyl, substituted or unsubstituted C₂-C₆alkynyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

3. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:

X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

4. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:

X is substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, or substituted or unsubstituted heteroaryl.

5. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:

X is substituted or unsubstituted C₁-C₄alkyl.

6. The compound, or pharmaceutically acceptable salt thereof, of claim 5, wherein:

X is -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, or -C(CH₃)₃.

7. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:

X is substituted or unsubstituted C₁-C₄haloalkyl.

8. The compound, or pharmaceutically acceptable salt thereof, of claim 7, wherein:

X is -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.

9. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:

X is substituted or unsubstituted C₃-C₆cycloalkyl.

10. The compound, or pharmaceutically acceptable salt thereof, of claim 9, wherein:

X is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted cyclohexyl.

11. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:

X is substituted or unsubstituted C₂-C₆heterocycloalkyl.

12. The compound, or pharmaceutically acceptable salt thereof, of claim 11, wherein:
X is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl.
13. The compound, or pharmaceutically acceptable salt thereof, of claim 4, wherein:
X is substituted or unsubstituted heteroaryl.
14. The compound, or pharmaceutically acceptable salt thereof, of claim 13, wherein:
X is substituted or unsubstituted monocyclic heteroaryl.
15. The compound, or pharmaceutically acceptable salt thereof, of claim 14, wherein:
X is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.
16. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:
X is $-L^1-Y^1$.
17. The compound, or pharmaceutically acceptable salt thereof, of claim 16, wherein:
 L^1 is substituted or unsubstituted C_1-C_4 alkylene; and
 Y^1 is substituted or unsubstituted C_3-C_6 cycloalkyl.
18. The compound, or pharmaceutically acceptable salt thereof, of claim 17, wherein:
 Y^1 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl.
19. The compound, or pharmaceutically acceptable salt thereof, of claim 16, wherein:
 L^1 is substituted or unsubstituted C_1-C_4 alkylene; and

Y¹ is substituted or unsubstituted C₂-C₆ heterocycloalkyl.

20. The compound, or pharmaceutically acceptable salt thereof, of claim 19, wherein:

Y¹ is substituted or unsubstituted aziridinyl, substituted or unsubstituted azetidiny, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrothienyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl, substituted or unsubstituted 1,3-dioxolanyl, substituted or unsubstituted 1,3-dioxolan-2-onyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted imidazolidin-2-onyl, or substituted or unsubstituted oxadiazolonyl.

21. The compound, or pharmaceutically acceptable salt thereof, of claim 16, wherein:

L¹ is substituted or unsubstituted C₁-C₄alkylene; and

Y¹ is substituted or unsubstituted phenyl.

22. The compound, or pharmaceutically acceptable salt thereof, of claim 16, wherein:

L¹ is substituted or unsubstituted C₁-C₄alkylene; and

Y¹ is substituted or unsubstituted heteroaryl.

23. The compound, or pharmaceutically acceptable salt thereof, of claim 22, wherein:

Y¹ is substituted or unsubstituted monocyclic heteroaryl.

24. The compound, or pharmaceutically acceptable salt thereof, of claim 23, wherein:

Y¹ is substituted or unsubstituted pyridinyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted furazanyl.

25. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:

X is -L²-L³-Y².

26. The compound, or pharmaceutically acceptable salt thereof, of claim 25, wherein:

L² is substituted or unsubstituted C₁-C₄alkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-;

Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂.

27. The compound, or pharmaceutically acceptable salt thereof, of claim 26, wherein:

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-;

Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

28. The compound, or pharmaceutically acceptable salt thereof, of claim 25, wherein:

L^2 is absent;

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-;

Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂.

29. The compound, or pharmaceutically acceptable salt thereof, of claim 28, wherein:

L^3 is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-;

Y^2 is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or

unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

30. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein: X is -L²-L³-L⁴-Y².

31. The compound, or pharmaceutically acceptable salt thereof, of claim 30, wherein:

L² is substituted or unsubstituted C₁-C₄alkylene;

L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -O(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)NR³-, -NR³(SO₂)-, -(SO₂)NR³-, -(SO₂)NR³-(C=O)-, -(SO₂)NR³-(C=O)O-, -NR³(SO₂)NR³-(C=O)-, -NR³(SO₂)NR³-(C=O)O-, or -O-(SO₂)-;

L⁴ is substituted or unsubstituted C₁-C₄alkylene;

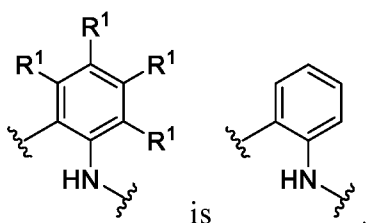
Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂.

32. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein:

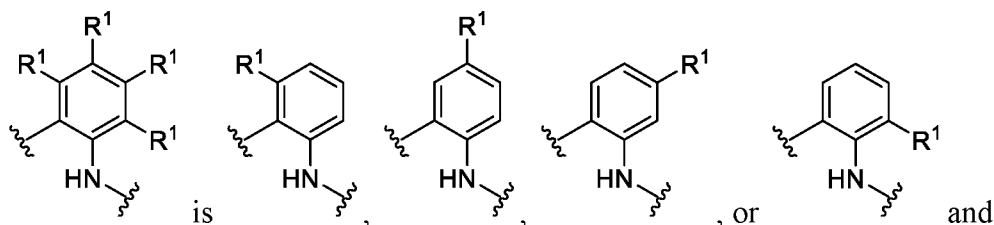
L³ is -O-, -S-, -(S=O)-, -(SO₂)-, -NR³-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR³-, -(C=O)NR³-O-, -NR³(C=O)-, -NR³(C=O)NR³-, -NR³(C=O)O-, -NR³(SO₂)-, -(SO₂)NR³-, or -O-(SO₂)-;

Y² is independently H, -CN, -N₃, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -OR⁶, -(C=O)OR⁶, -N(R⁶)₂, or -(C=O)N(R⁶)₂; and each R⁶ is independently H or substituted or unsubstituted C₁-C₄alkyl.

33. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-32, wherein:



34. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-32, wherein:



R^1 is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆haloalkyl, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₃-C₁₀cycloalkyl, substituted or unsubstituted C₂-C₁₀heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

35. The compound, or pharmaceutically acceptable salt thereof, of claim 34, wherein:

R^1 is halogen, -CN, -OR⁴, -SR⁴, -N(R⁴)₂, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄haloalkyl, substituted or unsubstituted C₁-C₄heteroalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₂-C₆heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

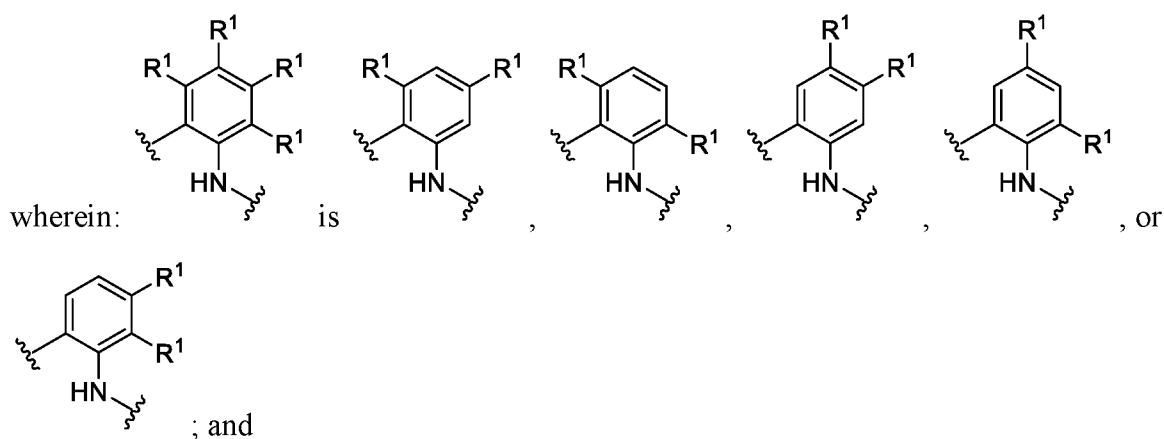
36. The compound, or pharmaceutically acceptable salt thereof, of claim 35, wherein:

R^1 is halogen, substituted or unsubstituted C₁-C₄alkyl, or substituted or unsubstituted C₁-C₄haloalkyl.

37. The compound, or pharmaceutically acceptable salt thereof, of claim 36, wherein:

R^1 is F, Cl, Br, I, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -C(CH₃)₃, -CH₂F, -CHF₂, -CF₃, or -CH₂CF₃.

38. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-32,



each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_2 - C_{10} heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

39. The compound, or pharmaceutically acceptable salt thereof, of claim 38, wherein:

each R^1 is independently halogen, $-\text{CN}$, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{N}(\text{R}^4)_2$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_6 heterocycloalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl.

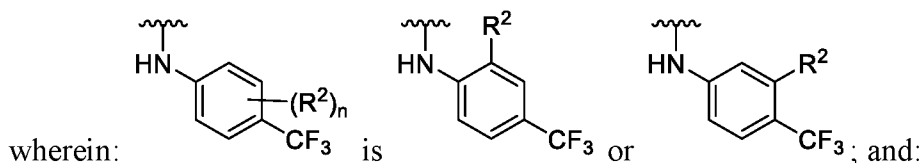
40. The compound, or pharmaceutically acceptable salt thereof, of claim 39, wherein:

each R^1 is independently halogen, substituted or unsubstituted C_1 - C_4 alkyl, or substituted or unsubstituted C_1 - C_4 haloalkyl.

41. The compound, or pharmaceutically acceptable salt thereof, of claim 40, wherein:

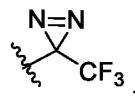
each R^1 is independently F, Cl, Br, I, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, or $-\text{CH}_2\text{CF}_3$.

42. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-41,



R^2 is halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl,

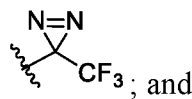
substituted or unsubstituted heteroaryl, or



43. The compound, or pharmaceutically acceptable salt thereof, of claim 42, wherein:

R^2 is halogen, $-\text{N}_3$, $-\text{CN}$, $-\text{OR}^5$, $-\text{SR}^5$, $-(\text{SO}_2)\text{R}^5$, $-\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl,

substituted or unsubstituted monocyclic heteroaryl, or

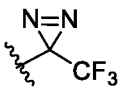


; and

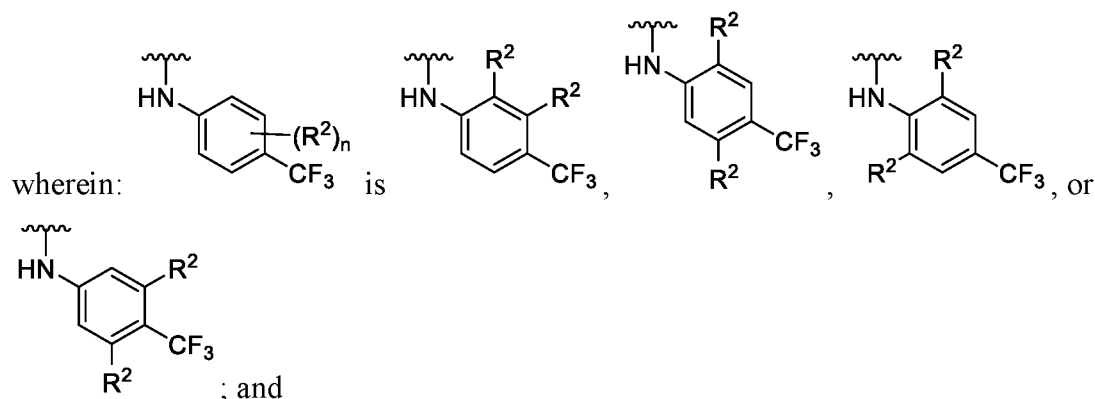
each R^5 is independently H, or substituted or unsubstituted C_1 - C_4 alkyl.

44. The compound, or pharmaceutically acceptable salt thereof, of claim 43, wherein:

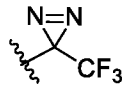
R^2 is halogen, $-N_3$, $-OR^5$, $-(SO_2)R^5$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or

unsubstituted C_1 - C_4 haloalkyl, or .

45. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-41,

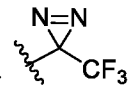


each R^2 is independently halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 haloalkyl, substituted or unsubstituted C_1 - C_6 heteroalkyl, substituted or unsubstituted aralkyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, or .

46. The compound, or pharmaceutically acceptable salt thereof, of claim 45, wherein:

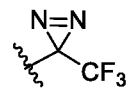
each R^2 is independently halogen, $-N_3$, $-CN$, $-OR^5$, $-SR^5$, $-(SO_2)R^5$, $-N(R^5)_2$, $-CO_2R^5$, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, substituted or unsubstituted benzyl, substituted or

unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or ; and

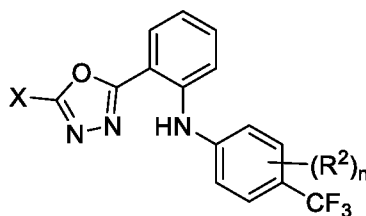
each R^5 is independently H, or substituted or unsubstituted C_1 - C_4 alkyl.

47. The compound, or pharmaceutically acceptable salt thereof, of claim 46, wherein:

each R^2 is independently halogen, $-N_3$, $-OR^5$, $-(SO_2)R^5$, $-CO_2R^5$, substituted or unsubstituted C_1 -

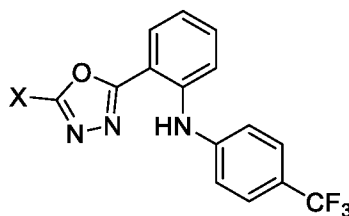
C_4 alkyl, substituted or unsubstituted C_1 - C_4 haloalkyl, or .

48. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



Formula (Ia).

49. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:



Formula (Ib).

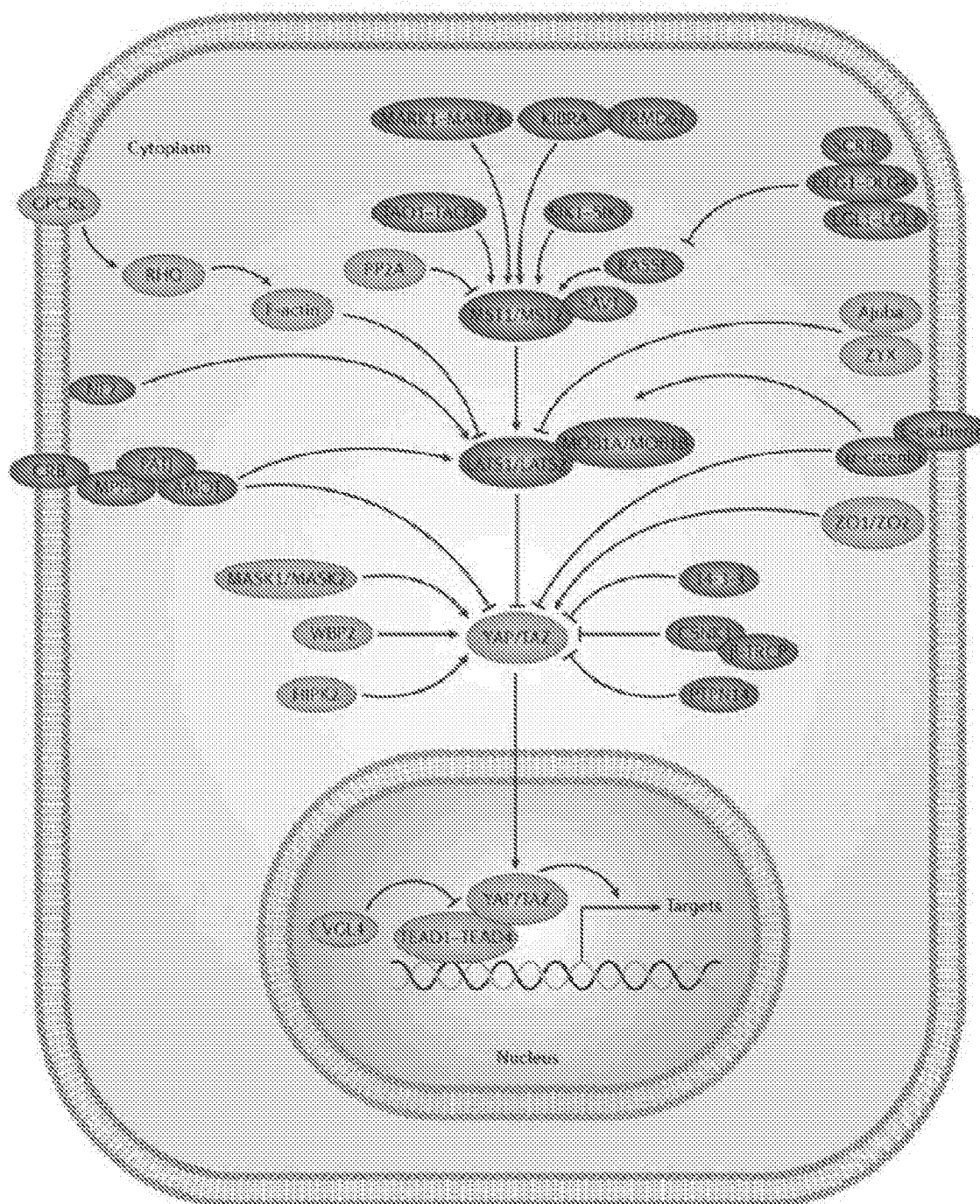
50. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-49, wherein the compound exhibits an IC₅₀ of no more than about 5.000 μ M.

51. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1, or a pharmaceutically acceptable salt thereof.

52. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof.

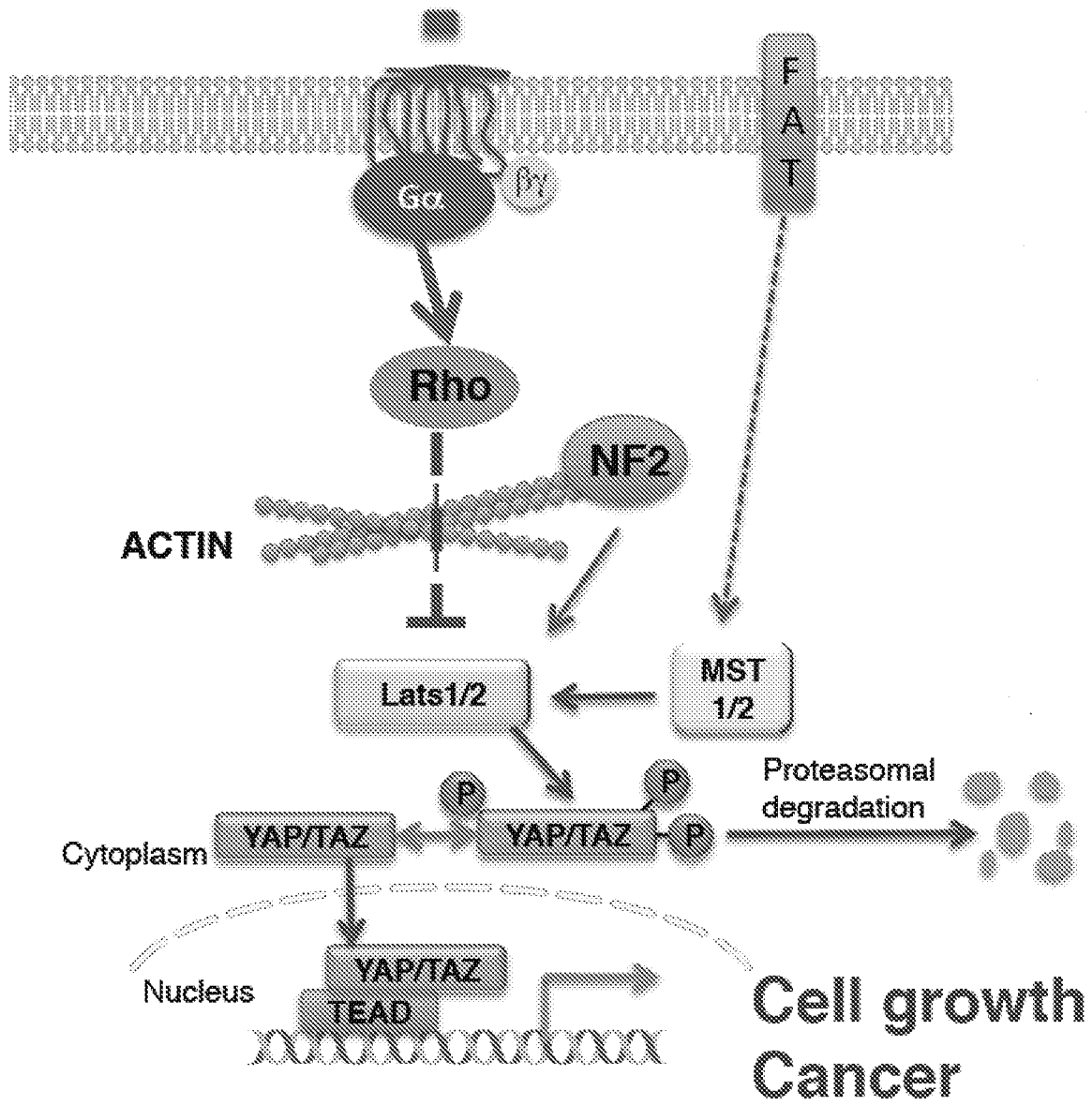
53. A method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof.

FIG.1



2/2

FIG. 2



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/32532

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/42, 31/4245; C07D 271/10 (2019.01)

CPC - A61K 31/42, 31/4245; C07D 271/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,462,952 A (BOSCHELLI, DH et al) 31 October 1995; column 1, lines 40-60; column 2, lines 25-30; column 4, lines 65-67; column 7, lines 1-20	1, 33/1, 48-49, 51
Y	US 9,790,229 B2 (BIOGEN MA INC) 17 October 2017; column 42, lines 35-40; column 131, lines 20-35, 60-65	1, 33/1, 48-49, 51
A	US 2005/0004186 A1 (BARRETT, SD et al) 6 January 2005; paragraphs [0399]-[0400]	1
A	US 2017/0137428A1 (MERCK PATENT GMBH) 18 May 2017; entire publication	1
A	WO 2009/086163 A2 (ABBOTT LABORATORIES) 9 July 2009; entire publication	1



Further documents are listed in the continuation of Box C.



See patent family annex.

*

Special categories of cited documents:

"A"

document defining the general state of the art which is not considered to be of particular relevance

"D"

document cited by the applicant in the international application

"E"

earlier application or patent but published on or after the international filing date

"L"

document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O"

document referring to an oral disclosure, use, exhibition or other means

"P"

document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

8 July 2019 (08.07.2019)

Date of mailing of the international search report

30 AUG 2019

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/32532

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 42-47, 52-53
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-41, 48, 49, 51 and a compound of Formula (I), wherein X is H, each R1 is independently H, and n is 0 [compound 20 of Table 1] (compound) are directed toward compounds having defined structures, or pharmaceutically acceptable salts thereof.

-Continued Within the Next Supplemental Box-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-41 (in-part), 48-49 (in-part), 51 (in-part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US19/32532

-Continued from Box III: Observations where unity of invention is lacking-

The compounds will be searched to the extent they encompass a compound of Formula (I), wherein X is H, each R1 is independently H, and n is 0 [compound 20 of Table 1] (first exemplary compound). Applicant is invited to elect additional compound(s), with fully specified structure(s) thereof (i.e. no optional or variable bonds, atoms, moieties or substituents), and available as an option within at least one searchable claim, to be searched. Additional compound structure(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 33 (in-part), 48 (in-part), 49 (in-part) and 51 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula (I), wherein X is H, each R1 is independently H, and n is 0 [compound 20 of Table 1] (compound). Applicants must specify the claims that encompass any additionally elected compound(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula (I), wherein X is -CN, each R1 is independently H, and n is 0 (compound).

The compounds of Groups I+ share the technical features including: a compound of Formula (I).

However, these shared technical features are previously disclosed by US 5,462,952 A to Boschelli, et al (hereinafter "Boschelli") in view of US 9,790,229 B2 (Biogen MA Inc) (hereinafter "Biogen").

Boschelli discloses a compound similar to the compound of Formula I, as shown (general formula I, in which X is oxygen, A is a bond, R5, R7 and R8 are hydrogens and R6 is trifluoromethyl; column 1, lines 40-60; column 2, lines 25-30) wherein: each R1 is H (in general formula, three of C3, C4, C5 or C6 carbon atoms of the central phenyl ring are unsubstituted and R8 is hydrogen; column 1, lines 40-60; column 2, lines 25-30); n is 0 (in general formula, R5 and R7 are hydrogens; column 1, lines 40-60; column 2, lines 25-30). In the first embodiment Boschelli does not disclose the compound in which X is H, and further does not disclose a motivation to select R1 as H and R2 as H, and trifluoromethyl moiety attached to the C4 carbon atom of the terminal phenyl ring from the list of the useful substituents. However, in a separate embodiment Boschelli discloses the compound in which X is H (Y is H in the fourth compound in table 2; column 7, lines 1-20), and further discloses the motivation to select R1 as H from the list of the useful substituents (the C3, C4, C5 and C6 carbon atoms of the central phenyl ring of the fourth compound in table 2 are unsubstituted; column 7, lines 1-20). Thus, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Boschelli in the first embodiment, in order to have provided for the compound in which X is H, and further to have provided for the motivation to select R1 as H from the list of the useful substituents, as previously disclosed by Boschelli in the second embodiment Boschelli (column 7, lines 1-30), for adjusting the properties of the compound as antiinflammatory agent (column 4, lines 65-67). Further, provided that in both embodiments Boschelli discloses the compounds of similar structures (column 1, lines 40-60; column 2, lines 25-30; column 7, lines 1-30), where the compounds are designed as antiinflammatory agents (column 4, lines 65-67), the modification to Boschelli's structure, of providing for the compound in which X is H, and further to have provided for the motivation to select R1 as H from the list of the useful substituents, would provide the benefit of adjusting the properties of the compound as antiinflammatory agent (column 4, lines 65-67). And further, Biogen discloses the motivation to select R2 as H (C2, C3, C5 and C6 carbon atoms of the terminal phenyl ring are not substituted in (3-(1-(7-H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-3-yl)-N-(4-(trifluoromethyl)phenyl)aniline; column 131, lines 20-35, 60-65), and trifluoromethyl moiety attached to the C4 carbon atom of the terminal phenyl ring from the list of the useful substituents (the trifluoromethyl moiety is attached to the C4 carbon atom of the terminal phenyl ring in the compound 137, which is (3-(1-(7-H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-3-yl)-N-(4-(trifluoromethyl)phenyl)aniline; column 131, lines 20-35, 60-65). Thus, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Boschelli, in order to have provided for the motivation to select R2 as H, and trifluoromethyl moiety attached to the C4 carbon atom of the terminal phenyl ring from the list of the useful substituents, as previously disclosed by Biogen (Biogen; column 131, lines 20-35, 60-65), for adjusting the properties of the compound as antiinflammatory agent (Boschelli; column 4, lines 65-67).

Further, provided that Boschelli and Biogen both disclose the compounds comprising the terminal phenylaniline moiety Boschelli (column 1, lines 40-60; column 2, lines 25-30) (Biogen; column 131, lines 20-35, 60-65), where the compounds are designed as antiinflammatory agents (Boschelli; column 4, lines 65-67) (Biogen; column 42, lines 35-40), the modification to Barrett's structure, of providing for the motivation to select R2 as H, and trifluoromethyl moiety attached to the C4 carbon atom of the terminal phenyl ring from the list of the useful substituents, would provide the benefit adjusting the properties of the compound as antiinflammatory agent (Boschelli; column 4, lines 65-67).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Boschelli and Biogen references, unity of invention is lacking.