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(54) Title: COMPOUNDS AND METHODS OF USE THEREOF

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

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COMPOUNDS AND METHODS OF USE THEREOF

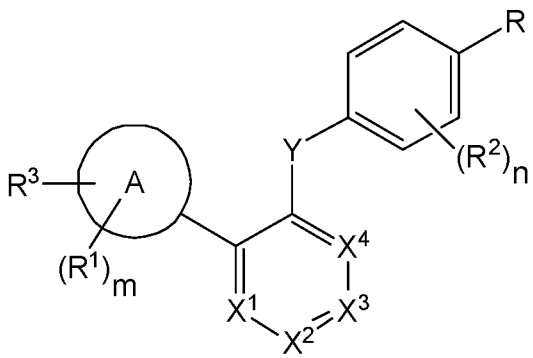
BACKGROUND OF THE DISCLOSURE

[0001] 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

[0002] Provided herein are compounds of Formula (I) and pharmaceutical compositions comprising said compounds. In some embodiments, the subject compounds are useful for the treatment of diseases or disorders. In some embodiments, the disease or disorder is cancer.

[0003] In one aspect, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein,

ring A is monocyclic heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

Y is CR^4R^5, O, S, or NR^6;

each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl,

substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each of R^1 and R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$OC(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)NR^7R^8$, -$S(=NR^7)R^8$, -$S(=NR^7)NR^7R^8$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -$S(=O)(=NR^7)R^7$, -$S(=O)(=NR^7)NR^7R^8$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7S(=O)(=NR^7)R^8$, -$NR^7C(=O)R^8$, -$N[C(=O)R^8]_2$, -$NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, -$NR^7C(=O)OR^8$, -$P(=O)(OR^7)R^8$, -$P(=O)(OR^7)(OR^8)$, -$P(=O)R^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^4, R^5, R^6, R^7, and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^4 and R^5 taken together with the carbon atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or substituted or unsubstituted 3- to 8-membered heterocycloalkyl having 1 or 2 heteroatoms each independently selected from N, O, and S; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N- or P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S;

m is 0, 1, 2, or 3; and

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

[0004] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0005] In another aspect, the present disclosure provides a compound described in Table 1, or a pharmaceutically acceptable salt or solvate thereof.

[0006] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable excipient.

[0007] In another aspect, the present disclosure provides a method of inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway in a subject, comprising administering to a subject in need thereof a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[0008] In another aspect, the present disclosure provides a method of inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP) in a subject comprising administering to a subject in need thereof a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the subject has cancer, polycystic kidney disease, or liver fibrosis. In some embodiments, the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

[0009] In another aspect, the present disclosure provides a method of treating cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

[0010] In another aspect, the present disclosure provides a method of treating polycystic kidney disease or liver fibrosis in a subject in need thereof comprising administering to the subject in need

thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

DETAILED DESCRIPTION OF THE DISCLOSURE

Certain Terminology

[0011] 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.

[0012] 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.

[0013] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0014] 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).

[0015] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0016] "Amino" refers to the $-NH_2$ radical.

[0017] "Cyano" refers to the -CN radical.

[0018] "Nitro" refers to the $-NO_2$ radical.

[0019] "Oxa" refers to the -O- radical.

[0020] "Oxo" refers to the =O radical.

[0021] "Thioxo" refers to the =S radical.

[0022] "Imino" refers to the =N-H radical.

[0023] "Oximo" refers to the =N-OH radical.

[0024] "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.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C_1-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.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C_3-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, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl.

[0025] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl chain as defined above.

[0026] "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 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, 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, cycloalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl.

[0027] "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 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, 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, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl.

[0028] "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.*, C_1 alkylene). In

other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 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, 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, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl.

[0029] "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 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, 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, heterocycloalkyl, heterocycloalkylalkyl, 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.

[0030] "Aryloxy" refers to a radical bonded through an oxygen atom of the formula –O-aryl, where aryl is as defined above.

[0031] "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.

[0032] "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.

[0033] "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.

[0034] "Carbocyclyl" or "carbocycle" refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclyl from "heterocyclyl" rings or "heterocycles" in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, a carbocyclyl is a monocyclic carbocyclyl or a bicyclic carbocyclyl. In some embodiments, a carbocyclyl is a monocyclic carbocyclyl. Carbocyclyls are non-aromatic or aromatic. Non-aromatic carbocyclyls are saturated or partially unsaturated. In some embodiments, a carbocyclyl is a bicyclic carbocyclyl. In some embodiments, at least one of the two rings of a bicyclic carbocyclyl is aromatic. In some embodiments, both rings of a bicyclic carbocyclyl are aromatic. Carbocyclyl include aryls and cycloalkyls.

[0035] "Cycloalkyl" refers to a monocyclic or polycyclic aliphatic, fully saturated non-aromatic carbocyclyl, wherein each of the atoms forming the ring (i.e., skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups include groups having from 3 to 6 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. In some embodiments, a cycloalkyl is a C_3-C_6cycloalkyl.

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.*, C_3-C_8 cycloalkyl). In other embodiments, a cycloalkyl comprises three to seven carbon atoms (*e.g.*, C_3-C_7 cycloalkyl). In other embodiments, a cycloalkyl comprises three to six carbon atoms (*e.g.*, C_3-C_6 cycloalkyl). In other embodiments, a cycloalkyl comprises three to five carbon atoms (*e.g.*, C_3-C_5 cycloalkyl). In other embodiments, a cycloalkyl comprises three to four carbon atoms (*e.g.*, C_3-C_4 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, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term " cycloalkyl" is meant to include cycloalkyl 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 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, 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, heterocycloalkyl, heterocycloalkylalkyl, 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.

[0036] "Carbocycloalkylalkyl" refers to a radical of the formula $-R^c-$ cycloalkyl where R^c is an alkylene chain as defined above. The alkylene chain and the cycloalkyl radical are optionally substituted as defined above.

[0037] "Halo" or "halogen" refers to bromo, chloro, fluoro, or iodo substituents.

[0038] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally substituted as defined above for an alkyl group.

[0039] "Heterocyclyl" or "heterocycle" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 3 to 10 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 10 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 10 atoms in its ring system. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which include fused, spiro, 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).

[0040] "Heterocycloalkyl" refers to a cycloalkyl group in which one or more skeletal atoms of the cycloalkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (e.g. –NH-, -N(alkyl)-, sulfur, or combinations thereof. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. The term heterocycloalkyl 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 another aspect, a heterocycloalkyl is a 5- to 10-membered C_4-C_9heterocycloalkyl. In another aspect, a heterocycloalkyl is a 4- to 7-membered C_3-C_6heterocycloalkyl. 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. Unless stated otherwise specifically in the specification, the term "heterocycloalkyl" is meant to include heterocycloalkyl 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 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, 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)O
R^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-$N(R^a)S(O)_t$
R^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, heterocycloalkyl, heterocycloalkylalkyl, 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.

[0041] "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_6heteroalkyl. In some embodiments, the alkyl part of the heteroalkyl radical is optionally substituted as defined for an alkyl group.

[0042] "Heterocycloalkylalkyl" refers to a radical of the formula –R^c-heterocycloalkyl where R^c is an alkylene chain as defined above. If the heterocycloalkyl is a nitrogen-containing heterocycloalkyl, the heterocycloalkyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocycloalkylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocycloalkyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocycloalkyl group.

[0043] "Heterocycloalkylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R^c- heterocycloalkyl where R^c is an alkylene chain as defined above. If the heterocycloalkyl is a nitrogen-containing heterocycloalkyl, the heterocycloalkyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocycloalkylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocycloalkyl part of the heterocycloalkylalkoxy radical is optionally substituted as defined above for a heterocycloalkyl group.

[0044] "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, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 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, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 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, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 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). 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, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, 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, heterocycloalkyl, heterocycloalkylalkyl, 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.

[0045] "*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.

[0046] "*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.

[0047] "Heteroaryloxy" refers to radical bonded through an oxygen atom of the formula –O-heteroaryl, where heteroaryl is as defined above.

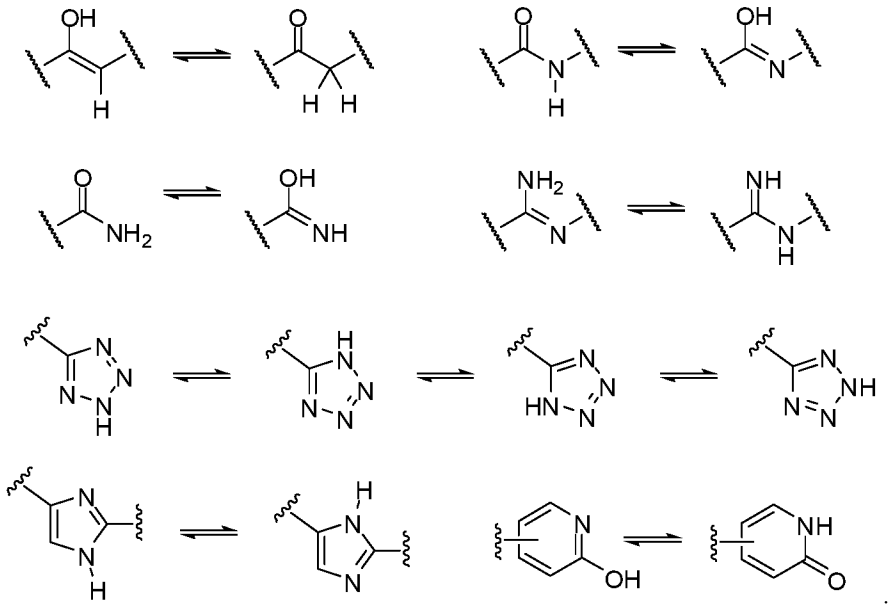
[0048] "Heteroarylalkyl" refers to a radical of the formula –R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl 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.

[0049] "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.

[0050] 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.

[0051] 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:



[0052] "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.

[0053] 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, -NH_2, -NH(alkyl), -$N(alkyl)_2$, -OH, =O, -CO_2H, -CO_2alkyl, -$C(=O)NH_2$, -C(=O)NH(alkyl), -$C(=O)N(alkyl)_2$, -$S(=O)_2NH_2$, -$S(=O)_2$NH(alkyl), -$S(=O)_2N(alkyl)_2$, -CH_2CO_2H, -CH_2CO_2alkyl, -$CH_2C(=O)NH_2$, -$CH_2C(=O)$NH(alkyl), -$CH_2C(=O)N(alkyl)_2$, -$CH_2S(=O)_2NH_2$, -$CH_2S(=O)_2$NH(alkyl), -$CH_2S(=O)_2N(alkyl)_2$, 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, -NH_2, -NH(alkyl), -N(alkyl)$_2$, -OH, -CO_2H, -CO_2alkyl, -C(=O)NH_2, -C(=O)NH(alkyl), -C(=O)N(alkyl)$_2$, -S(=O)$_2NH_2$, -S(=O)$_2$NH(alkyl), -S(=O)$_2$N(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, -NH_2, -NH(CH_3), -N(CH_3)$_2$, -OH, =O, -CO_2H, -CO_2(C_1-C_4alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_4alkyl), -C(=O)N(C_1-C_4alkyl)$_2$, -S(=O)$_2NH_2$, -S(=O)$_2$NH(C_1-C_4alkyl), -S(=O)$_2$N(C_1-C_4alkyl)$_2$, C_1-C_4alkyl, C_3-C_6cycloalkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, -SC_1-C_4alkyl, -S(=O)C_1-C_4alkyl, and -S(=O)$_2C_1$-C_4alkyl. In some embodiments, optional substituents are independently selected from D, halogen, -CN, -NH_2, -OH, =O, -NH(CH_3), -N(CH_3)$_2$, -CH_3, -CH_2CH_3, -CF_3, -OCH_3, and -OCF_3. In some embodiments, optional substituents are independently selected from D, halogen, -CN, -NH_2, -OH, -NH(CH_3), -N(CH_3)$_2$, -CH_3, -CH_2CH_3, -CF_3, -OCH_3, and -OCF_3. In some embodiments, optional substituents are independently selected from D, F, Cl, -CN, -NH_2, -OH, =O, -NH(CH_3), -N(CH_3)$_2$, -CH_3, -CH_2CH_3, -CF_3, -OCH_3, and -OCF_3. In some embodiments, substituted groups are substituted with one to six of the preceding groups. In some embodiments, substituted groups are substituted with one to four of the preceding groups. In some embodiments, substituted groups are substituted with one to three of the preceding groups. 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.

[0054] "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.

[0055] "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 alkanoic acids, hydroxy alkanoic 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, isobutyrates, 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.

[0056] "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, chloroprocaine, 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*.

[0057] 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.

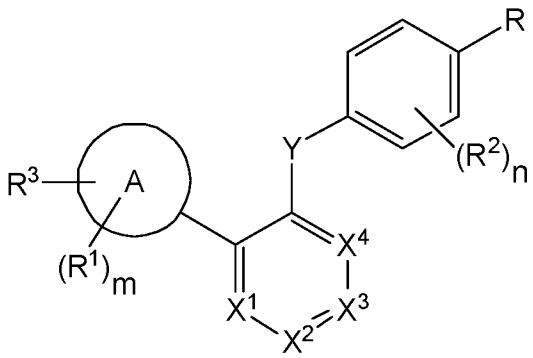
[0058] "Prodrug" is meant to indicate a compound that is converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some embodiments, 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).

[0059] 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.

[0060] 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

[0061] In one aspect, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein,

ring A is monocyclic heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

Y is CR^4R^5, O, S, or NR^6;

each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each of R^1 and R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$OC(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)NR^7R^8$, -$S(=NR^7)R^8$, -$S(=NR^7)NR^7R^8$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -$S(=O)(=NR^7)R^7$, -$S(=O)(=NR^7)NR^7R^8$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7S(=O)(=NR^7)R^8$, -$NR^7C(=O)R^8$, -$N[C(=O)R^8]_2$, -$NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, -$NR^7C(=O)OR^8$, -$P(=O)(OR^7)R^8$, -$P(=O)(OR^7)(OR^8)$, -$P(=O)R^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-

C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^4, R^5, R^6, R^7, and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^4 and R^5 taken together with the carbon atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or substituted or unsubstituted 3- to 8-membered heterocycloalkyl having 1 or 2 heteroatoms each independently selected from N, O, and S; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N- or P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S;

m is 0, 1, 2, or 3; and

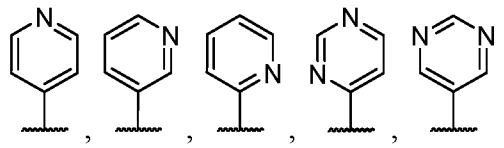
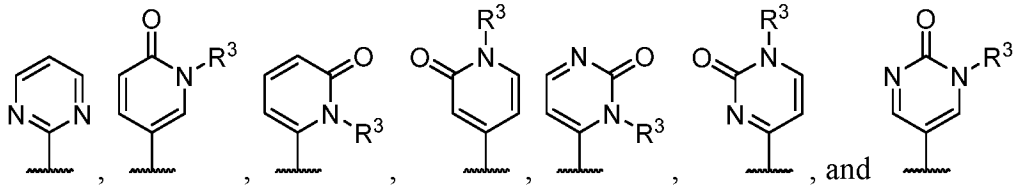
n is 0, 1, 2, 3, or 4.

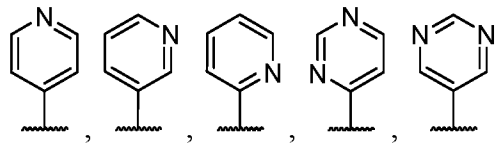
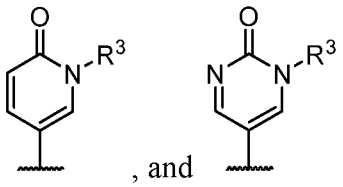
[0062] In some embodiments, ring A is a 5-, 6-, or 7-membered monocyclic heteroaryl. In some embodiments, ring A is a 5- or 6-membered monocyclic heteroaryl. In some embodiments, ring A is a 6- or 7-membered monocyclic heteroaryl. In some embodiments, ring A is a 6-membered monocyclic heteroaryl.

[0063] In some embodiments, ring A is a monocyclic heteroaryl having 1-4 N atoms. In some embodiments, ring A is a monocyclic heteroaryl having 1-3 N atoms. In some embodiments, ring A is a monocyclic heteroaryl having 1-2 N atoms. In some embodiments, ring A is a monocyclic heteroaryl having 1 N atom. In some embodiments, ring A is a monocyclic heteroaryl having 2 N atoms. In some embodiments, ring A is a monocyclic heteroaryl having 3 N atoms. In some embodiments, ring A is a monocyclic heteroaryl having 4 N atoms.

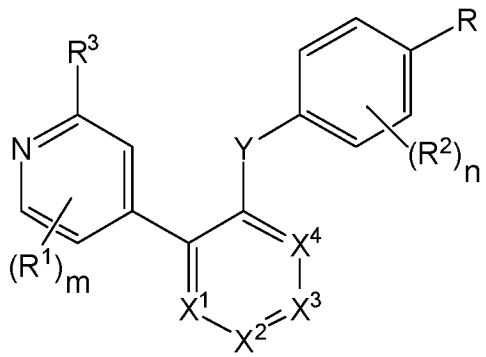
[0064] In some embodiments, ring A is a monocyclic 6-membered heteroaryl having 1-4 N atoms.

[0065] In some embodiments, ring A is pyridinyl, pyrimidinyl, or pyrazinyl.

[0066] In some embodiments, ring A is selected from  ,  , and .

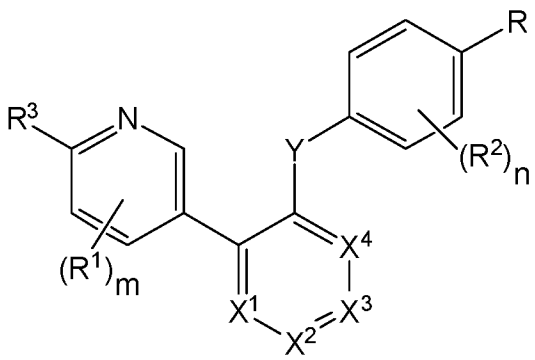
[0067] In some embodiments, ring A is selected from  ,  , and .

[0068] In some embodiments, the compound has a structure of Formula (II-a), or a pharmaceutically acceptable salt or solvate thereof:



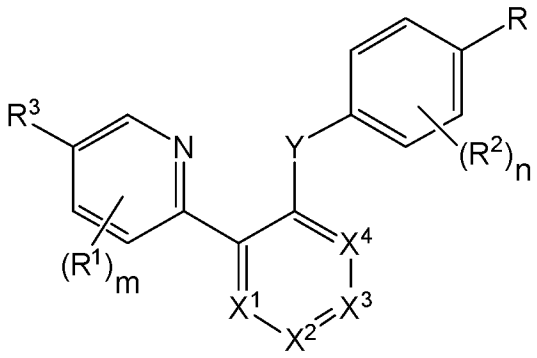
Formula (II-a).

[0069] In some embodiments, the compound has a structure of Formula (II-b), or a pharmaceutically acceptable salt or solvate thereof:



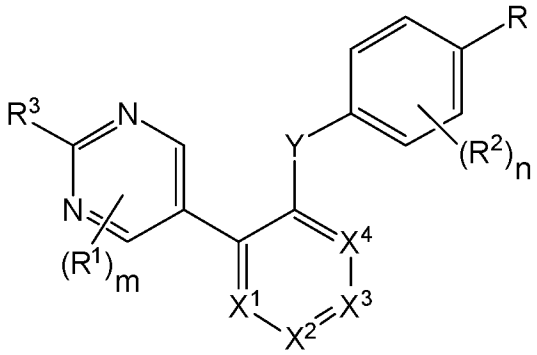
Formula (II-b).

[0070] In some embodiments, the compound has a structure of Formula (II-c), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-c).

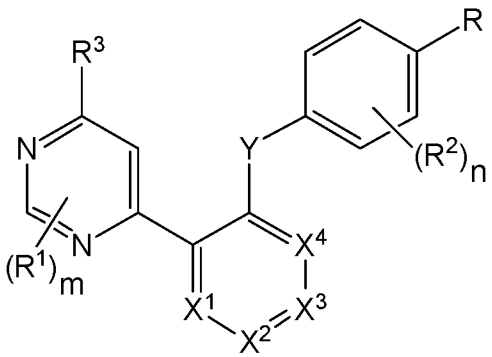
[0071] In some embodiments, the compound has a structure of Formula (II-d), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-d),

wherein m is 0, 1, or 2.

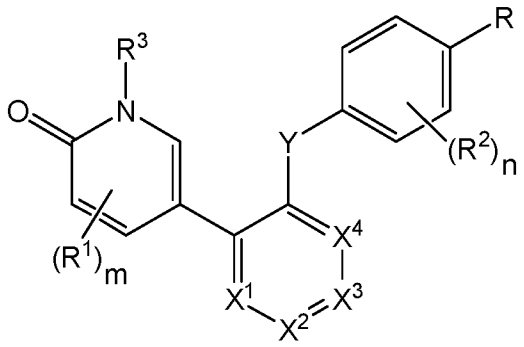
[0072] In some embodiments, the compound has a structure of Formula (II-e), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-e)

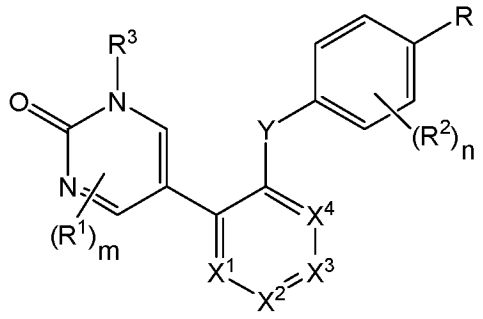
wherein m is 0, 1, or 2.

[0073] In some embodiments, the compound has a structure of Formula (II-f), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-f).

[0074] In some embodiments, the compound has a structure of Formula (II-g), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-g).

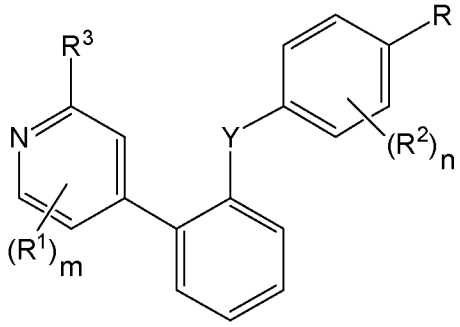
wherein m is 0, 1, or 2.

[0075] In some embodiments, X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is CR^{X4}. In some embodiments, X^1 is N; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is N; X^3 is CR^{X3}; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is N; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is N. In some embodiments, X^1 is N; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is N. In some embodiments, X^1 is N; X^2 is CR^{X2}; X^3 is N; and X^4 is CR^{X4}. In some embodiments, X^1 is N; X^2 is N; X^3 is CR^{X3}; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is N; X^3 is N; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is N; X^3 is X^3 is CR^{X3}; and X^4 is N. In some embodiments, X^1 is N; X^2 is N; X^3 is CR^{X3}; and X^4 is N. In some embodiments, X^1 is N; X^2 is CR^{X2}; X^3 is N; and X^4 is N.

[0076] In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, $-OR^7$, $-SR^7$, -CN, $-NR^7R^8$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, $-OR^7$, $-SR^7$, -CN, $-NR^7R^8$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl.

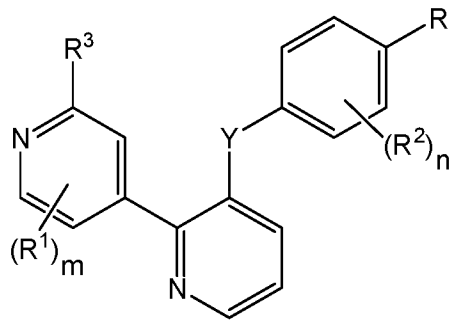
In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH(OH)CH_3$, $-CH_2CN$, $-CH_2C(=O)OH$, $-CH_2C(=O)OCH_3$, $-CH_2C(=O)OCH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHC(=O)OCH_3$, $-N(CH_3)C(=O)OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-NHS(=O)_2CH_3$, or $-N(CH_3)S(=O)_2CH_3$. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-C\equiv CH$, $-OCH_3$, $-NH_2$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHS(=O)_2CH_3$, $-N(CH_3)S(=O)_2CH_3$, $-S(=O)CH_3$, or $-S(=O)_2CH_3$. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-OCH_3$, or $-OCF_3$. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, or $-CH_3$. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen or F. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is hydrogen.

[0077] In some embodiments, the compound has a structure of Formula (III-a), or a pharmaceutically acceptable salt or solvate thereof:



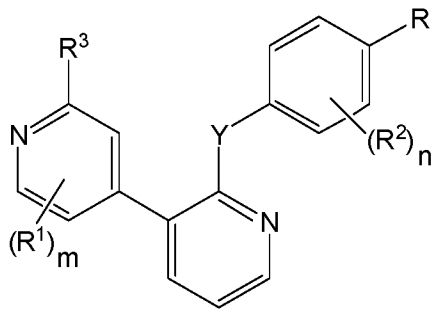
Formula (III-a).

[0078] In some embodiments, the compound has a structure of Formula (III-b), or a pharmaceutically acceptable salt or solvate thereof:



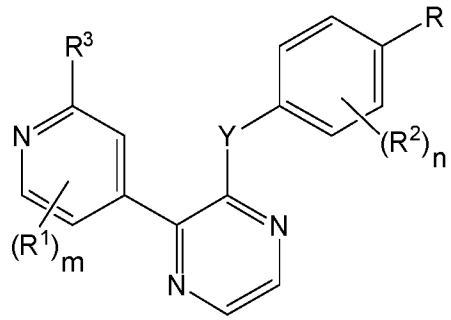
Formula (III-b).

[0079] In some embodiments, the compound has a structure of Formula (III-c), or a pharmaceutically acceptable salt or solvate thereof:



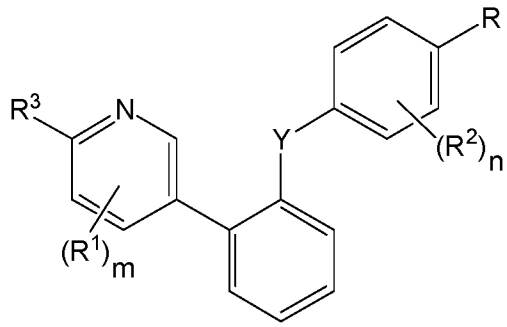
Formula (III-c).

[0080] In some embodiments, the compound has a structure of Formula (III-d), or a pharmaceutically acceptable salt or solvate thereof:



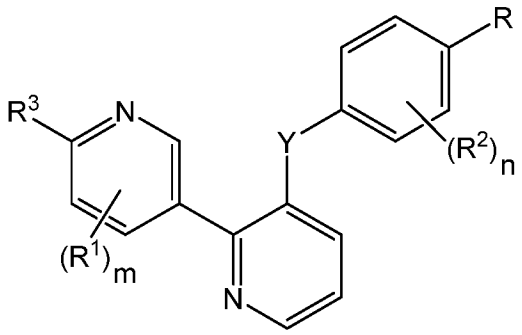
Formula (III-d).

[0081] In some embodiments, the compound has a structure of Formula (III-e), or a pharmaceutically acceptable salt or solvate thereof:



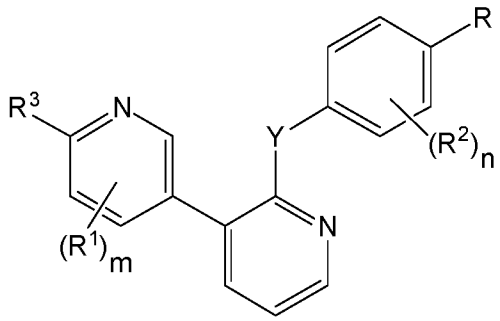
Formula (III-e).

[0082] In some embodiments, the compound has a structure of Formula (III-f), or a pharmaceutically acceptable salt or solvate thereof:



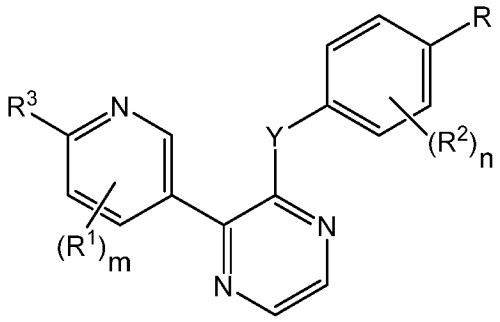
Formula (III-f).

[0083] In some embodiments, the compound has a structure of Formula (III-g), or a pharmaceutically acceptable salt or solvate thereof:



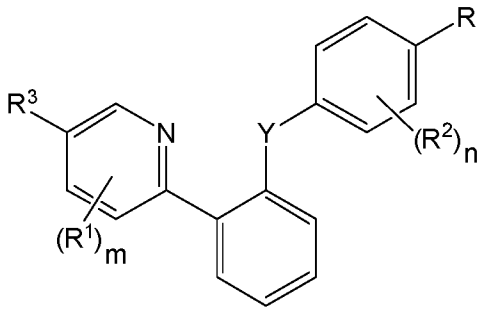
Formula (III-g).

[0084] In some embodiments, the compound has a structure of Formula (III-h), or a pharmaceutically acceptable salt or solvate thereof:



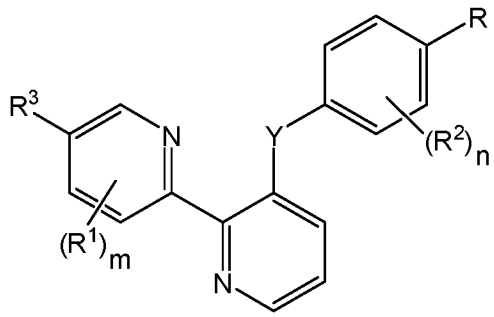
Formula (III-h).

[0085] In some embodiments, the compound has a structure of Formula (III-i), or a pharmaceutically acceptable salt or solvate thereof:



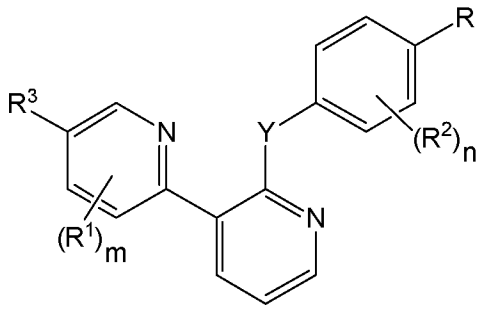
Formula (III-i).

[0086] In some embodiments, the compound has a structure of Formula (III-j), or a pharmaceutically acceptable salt or solvate thereof:



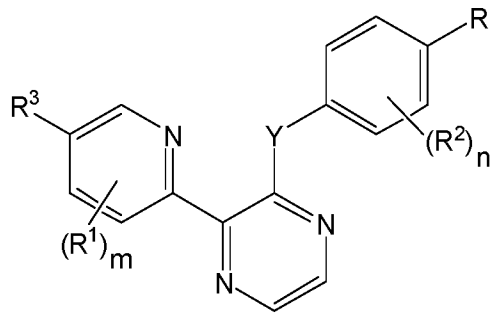
Formula (III-j).

[0087] In some embodiments, the compound has a structure of Formula (III-k), or a pharmaceutically acceptable salt or solvate thereof:



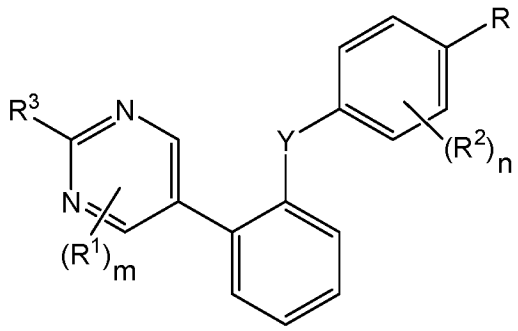
Formula (III-k).

[0088] In some embodiments, the compound has a structure of Formula (III-l), or a pharmaceutically acceptable salt or solvate thereof:



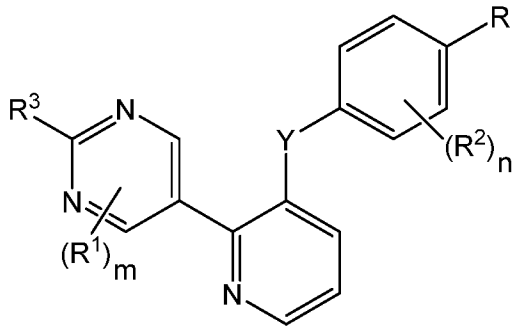
Formula (III-l).

[0089] In some embodiments, the compound has a structure of Formula (III-m), or a pharmaceutically acceptable salt or solvate thereof:



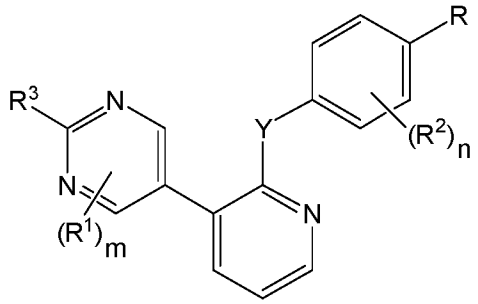
Formula (III-m).

[0090] In some embodiments, the compound has a structure of Formula (III-n), or a pharmaceutically acceptable salt or solvate thereof:



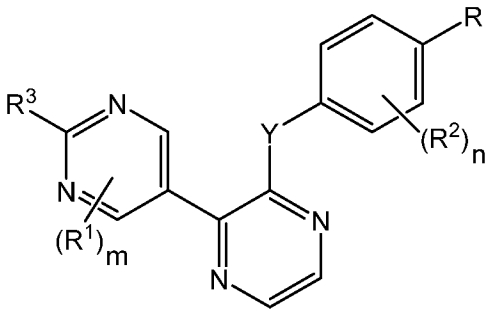
Formula (III-n).

[0091] In some embodiments, the compound has a structure of Formula (III-o), or a pharmaceutically acceptable salt or solvate thereof:



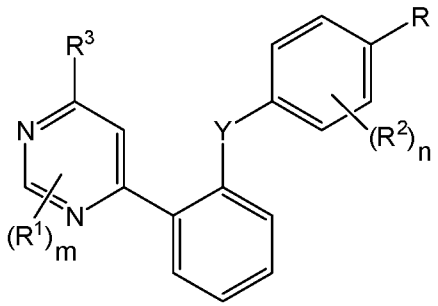
Formula (III-o).

[0092] In some embodiments, the compound has a structure of Formula (III-p), or a pharmaceutically acceptable salt or solvate thereof:



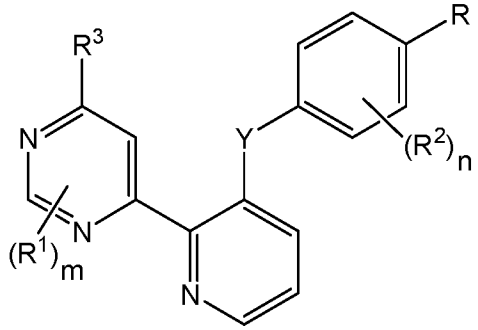
Formula (III-p).

[0093] In some embodiments, the compound has a structure of Formula (III-q), or a pharmaceutically acceptable salt or solvate thereof:



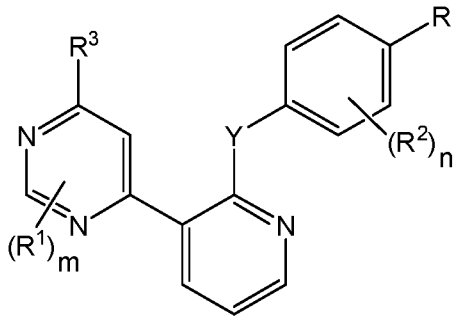
Formula (III-q).

[0094] In some embodiments, the compound has a structure of Formula (III-r), or a pharmaceutically acceptable salt or solvate thereof:



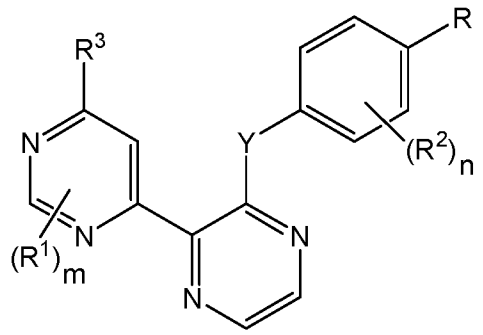
Formula (III-r).

[0095] In some embodiments, the compound has a structure of Formula (III-s), or a pharmaceutically acceptable salt or solvate thereof:



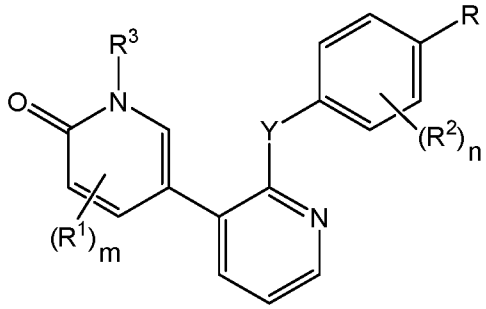
Formula (III-s).

[0096] In some embodiments, the compound has a structure of Formula (III-t), or a pharmaceutically acceptable salt or solvate thereof:



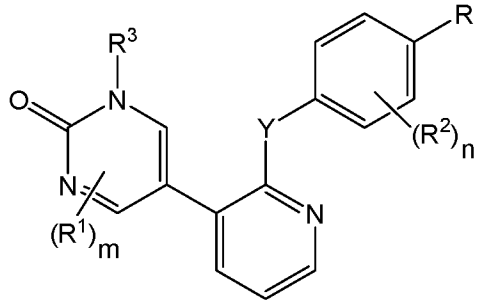
Formula (III-t).

[0097] In some embodiments, the compound has a structure of Formula (III-u), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III-u).

[0098] In some embodiments, the compound has a structure of Formula (III-v), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III-v).

[0099] In some embodiments, the compound of Formula (I) is a compound having a structure selected from Formulas (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (III-h), (III-i), (III-j), (III-k), (III-l), (III-m), (III-n), (III-o), (III-p), (III-q), (III-r), (III-s), (III-t), (III-u), and (III-v).

[00100] In some embodiments, R^3 is halogen, nitro, $-OR^7$, $-SR^7$, -CN, $-OC(=O)R^7$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)NR^7R^8$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-N[C(=O)R^8]_2$, $-NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, $-NR^7C(=O)OR^8$, $-P(=O)(OR^7)R^8$, $-P(=O)(OR^7)(OR^8)$, $-P(=O)R^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or

unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N- or P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

[00101] In some embodiments, R^3 is halogen, $-OR^7$, $-SR^7$, $-C(=O)R^7$, $-OC(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-N[C(=O)R^8]_2$, $NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, $-NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, or substituted or unsubstituted C_1-C_6heteroalkyl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl; or R^7 and R^8 taken together with atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 10-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

[00102] In some embodiments, R^3 is $-OR^7$, $-SR^7$, $-C(=O)R^7$, $-OC(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl.

[00103] In some embodiments, R^3 is $-OR^7$, $-SR^7$, $-C(=O)R^7$, $-OC(=O)R^7$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl.

[00104] In some embodiments, R^3 is $-OR^7$, $-SR^7$, $-C(=O)R^7$, or $-OC(=O)R^7$; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl.

[00105] In some embodiments, R^3 is $-NR^7R^8$, $-NR^7S(=O)_2R^7$, or $-NR^7C(=O)R^7$; and each R^7 and R^8 is independently hydrogen, C_1-C_6alkyl, C_1-C_6fluoroalkyl, or C_3-C_{10}cycloalkyl.

[00106] In some embodiments, R^3 is substituted or unsubstituted C_5-C_{10} aryl. In some embodiments, R^3 is substituted or unsubstituted phenyl. In some embodiments, R^3 is phenyl.

[00107] In some embodiments, R^3 is F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CN$, $-CH=CH_2$, $-CH_2C(=O)OH$, $-CH_2C(=O)OCH_3$, $-CH_2C(=O)OCH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH=CH_2$, $-CH=CHCF_3$, $-C\equiv CH$, $-CH_2C\equiv CH$, cyclopropyl, -CN-cycloprop-1-yl, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, oxetanyloxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, azetidinyl, pyrrolidinyl, tetrazolyl, piperazin-2-one-yl, phenyl, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CH=CH_2$, $-OCH=CHCH_3$, $-OCH_2C\equiv CH$, $-OCH_2CN$, $-OCF_3$, $-C(=O)OH$, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $NHCH_2CH_2OH$, $NCH_3CH_2CH_2OH$, $NHCH_2C(=O)NH_2$, $NHCH_2CH_2C(=O)NH_2$, $N[C(=O)CH=CH_2]_2$, $-N(CH_3)C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NHC(=O)CH=CH_2$, -NHC(=O)O-t-butyl, $-N(CH_3)C(=O)OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NHS(=O)_2CH_3$, or $-N(CH_3)S(=O)_2CH_3$.

[00108] In some embodiments, R^3 is $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2OH$, $-N(CH_3)CH_2CH_2OH$, azetidinyl, pyrrolidinyl, piperazin-2-one-4-yl, phenyl, $-NHCH_2CH_2C(=O)NH_2$, $-NHCH_2C(=O)NH_2$, $-NHC(=O)CH_3$, $-NHC(=O)CH=CH_2$, $-N(C(=O)CH=CH_2)_2$, or $-NHS(=O)_2CH_3$. In some embodiments, R^3 is $-NH_2$. In some embodiments, R^3 is $-NHCH_3$. In some embodiments, R^3 is $-NHCH_2CH_3$. In some embodiments, R^3 is $-N(CH_3)_2$. In some embodiments, R^3 is $-NHCH_2CH_2OH$. In some embodiments, R^3 is $-N(CH_3)CH_2CH_2OH$. In some embodiments, R^3 is azetidinyl. In some embodiments, R^3 is pyrrolidinyl. In some embodiments, R^3 is piperazin-2-one-4-yl. In some embodiments, R^3 is phenyl. In some embodiments, R^3 is $-NHCH_2CH_2C(=O)NH_2$. In some embodiments, R^3 is $-NHCH_2C(=O)NH_2$. In some embodiments, R^3 is $-NHC(=O)CH_3$. In some embodiments, R^3 is $-NHC(=O)CH=CH_2$. In some embodiments, R^3 is $-N(C(=O)CH=CH_2)_2$. In some embodiments, R^3 is $-NHS(=O)_2CH_3$.

[00109] In some embodiments, R^3 is $-CH=CH_2$, $-C\equiv CH$, $-CH=CHCF_3$, cyclopropyl, 1-CN-cycloprop-1-yl, 1-F-cycloprop-1-yl, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, or $-S(=O)_2CH_3$. In some embodiments, R^3 is $-CH=CH_2$. In some embodiments, R^3 is $-C\equiv CH$. In some embodiments, R^3 is $-CH=CHCF_3$. In some embodiments, R^3 is cyclopropyl. In some embodiments, R^3 is 1-CN-cycloprop-1-yl. In some embodiments, R^3 is 1-F-cycloprop-1-yl. In some embodiments, R^3 is -

$C(=O)NHCH_3$. In some embodiments, R^3 is $-C(=O)N(CH_3)_2$. In some embodiments, R^3 is $-S(=O)_2CH_3$.

[00110] In some embodiments, R^3 is -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-OCH=CH_2$, $-OCH_2CH=CH_2$, $-OCH=CHCH_3$, $-OCH_2C\equiv CH$, or $-OC\equiv CCH_3$. In some embodiments, R^3 is -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, or $-OCH(CH_3)_2$. In some embodiments, R^3 is -OH, $-OCH=CH_2$, $-OCH_2CH=CH_2$, $-OCH=CHCH_3$, $-OCH_2C\equiv CH$, or $-OC\equiv CCH_3$. In some embodiments, R^3 is -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH=CH_2$, $-OCH_2CH=CH_2$, $-OCH=CHCH_3$, $-OCH_2C\equiv CH$, or $-OC\equiv CCH_3$. In some embodiments, R^3 is -OH. In some embodiments, R^3 is $-OCH_3$. In some embodiments, R^3 is $-OCH_2CH_3$. In some embodiments, R^3 is $-OCH_2CH_2CH_3$. In some embodiments, R^3 is $-OCH(CH_3)_2$. In some embodiments, R^3 is $-OCH=CH_2$. In some embodiments, R^3 is $-OCH_2CH=CH_2$. In some embodiments, R^3 is $-OCH=CHCH_3$. In some embodiments, R^3 is $-OCH_2C\equiv CH$. In some embodiments, R^3 is $-OC\equiv CCH_3$.

[00111] In some embodiments, R^3 is $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-OCF_2CH_3$, or $-OCH_2CF_3$.

[00112] In some embodiments, R is halogen, nitro, -CN, $-OR^7$, $-SR^7$, $-S(R^7)_5$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7S(=O)_2R^7$, $-NR^7C(=O)R^7$, $-NR^7C(=O)OR^7$, or substituted or unsubstituted C_1-C_6fluoroalkyl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S. In some embodiments, R is F, Cl, Br, I, nitro, -CN, $-SF_5$, $-SCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-C(=O)CH_3$, $-C(=O)OCH_3$ $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-NHS(=O)_2CH_3$, $-N(CH_3)S(=O)_2CH_3$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHC(=O)OCH_3$, $-N(CH_3)C(=O)OCH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, R is F, Cl, -CN, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$. In some embodiments, R is F, Cl, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$. In some embodiments, R is F, Cl, $-SF_5$, $-SCF_3$, or $-CF_3$. In some embodiments, R is F, Cl, $-SF_5$, $-OCF_3$, $-SCF_3$, or $-CF_3$. In some embodiments, R is $-SF_5$, $-SCF_3$, or $-OCF_3$. In some embodiments, R is $-SF_5$, $-SCF_3$, or $-CF_3$. I n some embodiments, R is $-CF_3$, $-SCF_3$, or $-OCF_3$. In some embodiments, R is $-OCF_3$. In some embodiments, R is $-CF_3$. In some embodiments, R is $-SF_5$. In some embodiments, R is $-SCF_3$.

[00113] In some embodiments, each R^1 is independently halogen, -CN, $-OR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-C(=O)R^7$, substituted or unsubstituted C_1-C_6alkyl, substituted

or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted -3 to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S. In some embodiments, each R^1 is independently halogen, -CN, -OR^7, -$S(=O)_2NR^7R^8$, -$C(=O)R^7$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S. In some embodiments, each R^1 is independently F, Cl, -CN, -OH, -OCH_3, -OCH_2CH_3, -$OCH_2CH_2CH_3$, -$OCH(CH_3)_2$, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, -$OCH=CH_2$, -$OCH=CHCH_3$, -$OCH_2CH=CH_2$, -OCH_2CH_2F, -OCH_2CH_2OH, -$OCH_2CH_2CH_2F$, -$OCH_2CH_2CH_2OH$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2NHCH_2CH_3$, -$S(=O)_2NHCH(CH_3)_2$, -$S(=O)_2NCH_3CH_2C{\equiv}CH$, -$S(=O)_2NH$cyclopropyl, -$S(=O)_2NHCH_2CH_2F$, -$S(=O)_2NHCH_2CH_2OH$, or -$S(=O)_2N(CH_3)CH_2CH_3$. In some embodiments, each R^1 is independently F, Cl, -OCH_3, -OCH_2CH_3, -$OCH_2CH_2CH_3$, -$OCH(CH_3)_2$, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, -OCH_2CH_2F, -OCH_2CH_2OH, -$OCH_2CH_2CH_2F$, or -$OCH_2CH_2CH_2OH$. In some embodiments, each R^1 is independently F, Cl, -OH, -OCH_3, or -OCH_2CH_3.

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

[00115] In some embodiments, each R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, each R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)_2R^7$, -NR^7R^8, -$C(=O)OR^7$, substituted or unsubstituted C_1-C_6alkyl, or substituted or

unsubstituted C_1-C_6fluoroalkyl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S. In some embodiments, each R^2 is independently F, Cl, Br, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-S(=O)_2CH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)OCH_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^2 is independently F, Cl, -CN, $-OCH_3$, $-OCF_3$, $-C(=O)OCH_3$, $-CH_3$, or $-CF_3$. In some embodiments, each R^2 is independently F, Cl, $-OCF_3$, or $-CF_3$. In some embodiments, each R^2 is independently F or Cl.

[00116] In some embodiments, n is 0, 1, 2, 3, or 4. In some embodiments, n is 0, 1, 2, or 3. In some embodiments, n is 0, 1, or 2. In some embodiments, n is 1 or 2. In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

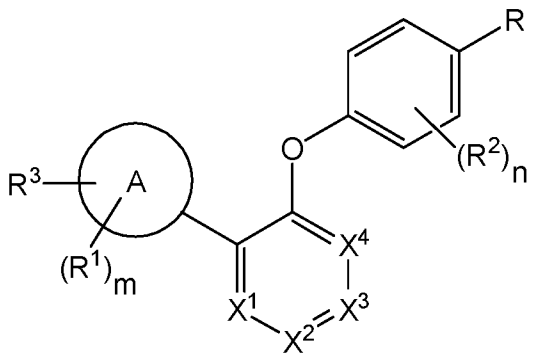
[00117] In some embodiments, Y is CR^4R^5, O, S, or NR^6. In some embodiments, Y is O, S, or NR^6. In some embodiments, Y is CR^4R^5, S, or NR^6. In some embodiments, Y is CR^4R^5, O, or NR^6. In some embodiments, Y is CR^4R^5, O, or S. In some embodiments, Y is CR^4R^5 or O. In some embodiments, Y is CR^4R^5 or S. In some embodiments, Y is CR^4R^5 or NR^6. In some embodiments, Y is O or S. In some embodiments, Y is O or NR^6. In some embodiments, Y is S or NR^6.

[00118] In some embodiments, Y is CR^4R^5. In some embodiments, each R^4 and R^5 is independently hydrogen or C_1-C_4 alkyl. In some embodiments, each R^4 and R^5 is hydrogen. In some embodiments, each R^4 is hydrogen and R^5 is $-CH_3$. In some embodiments, each R^4 and R^5 is $-CH_3$.

[00119] In some embodiments, Y is O or S. In some embodiments, Y is O. In some embodiments, Y is S.

[00120] In some embodiments, Y is NR^6. In some embodiments, R^6 is hydrogen or C_1-C_4 alkyl. In some embodiments, R^6 is hydrogen or $-CH_3$. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is $-CH_3$. In some embodiments, R^6 is $-OCH_3$. In some embodiments, R^6 is $-OCH_2CH_3$.

[00121] In another aspect, provided herein are compounds having a structure of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV)

wherein,

ring A is monocyclic 6-membered heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each of R^1 and R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$OC(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)NR^7R^8$, -$S(=NR^7)R^8$, -$S(=NR^7)NR^7R^8$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -$S(=O)(=NR^7)R^7$, -$S(=O)(=NR^7)NR^7R^8$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7S(=O)(=NR^7)R^8$, -$NR^7C(=O)R^8$, -$N[C(=O)R^8]_2$, -$NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, -$NR^7C(=O)OR^8$, -$P(=O)(OR^7)R^8$, -$P(=O)(OR^7)(OR^8)$, -$P(=O)R^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

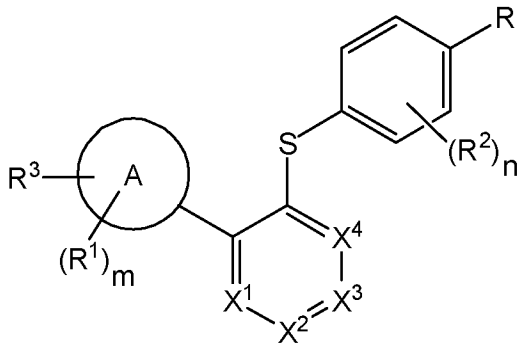
each R^7 and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N- or P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S;

m is 0, 1, 2, or 3; and

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

[00122] In another aspect, the present disclosure provides a compound of Formula (V), or a pharmaceutically acceptable salt or solvate thereof:



Formula (V)

wherein,

ring A is monocyclic 6-membered heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, -OR^7, -SR^7, -CN, -C(=O)R^7, -C(=O)NR^7R^8, -C(=O)OR^7, -S(=O)R^7, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -C(=O)R^7, -C(=O)NR^7R^8, -C(=O)OR^7, -S(=O)R^7, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each of R^1 and R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -S(=O)R^7, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -C(=O)R^7, -C(=O)OR^7, -C(=O)NR^7R^8, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or

unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is halogen, nitro, $-OR^7$, $-SR^7$, -CN, $-C(=O)R^7$, $-OC(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)NR^7R^8$, $-S(=NR^7)R^8$, $-S(=NR^7)NR^7R^8$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-S(=O)(=NR^7)R^7$, $-S(=O)(=NR^7)NR^7R^8$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7S(=O)(=NR^7)R^8$, $-NR^7C(=O)R^8$, $-N[C(=O)R^8]_2$, $-NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, $-NR^7C(=O)OR^8$, $-P(=O)(OR^7)R^8$, $-P(=O)(OR^7)(OR^8)$, $-P(=O)R^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

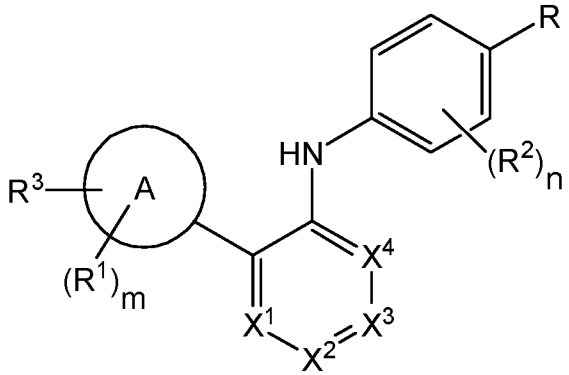
each R^7 and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N- or P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S;

m is 0, 1, 2, or 3; and

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

[00123] In another aspect, the present disclosure provides a compound of Formula (VI), or a pharmaceutically acceptable salt or solvate thereof:



Formula (VI)

wherein,

ring A is monocyclic 6-membered heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each of R^1 and R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$OC(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)NR^7R^8$, -$S(=NR^7)R^8$, -$S(=NR^7)NR^7R^8$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -$S(=O)(=NR^7)R^7$, -$S(=O)(=NR^7)NR^7R^8$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7S(=O)(=NR^7)R^8$, -$NR^7C(=O)R^8$, -$N[C(=O)R^8]_2$, -$NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, -$NR^7C(=O)OR^8$, -$P(=O)(OR^7)R^8$, -$P(=O)(OR^7)(OR^8)$, -$P(=O)R^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

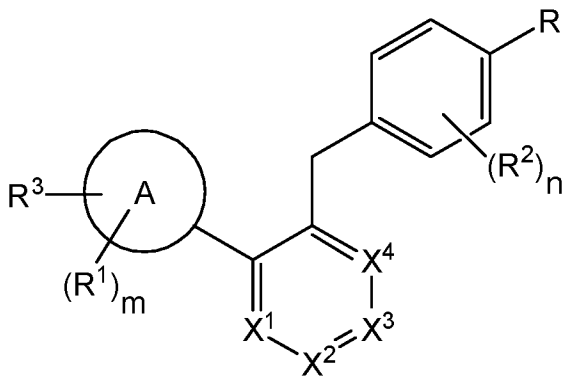
each R^7 and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N- or P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S;

m is 0, 1, 2, or 3; and

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

[00124] In another aspect, the present disclosure provides a compound of Formula (VII), or a pharmaceutically acceptable salt or solvate thereof:



Formula (VII)

wherein,

ring A is monocyclic 6-membered heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each of R^1 and R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$OC(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)NR^7R^8$, -$S(=NR^7)R^8$, -$S(=NR^7)NR^7R^8$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -$S(=O)(=NR^7)R^7$, -$S(=O)(=NR^7)NR^7R^8$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7S(=O)(=NR^7)R^8$, -$NR^7C(=O)R^8$, -$N[C(=O)R^8]_2$, -$NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, -$NR^7C(=O)OR^8$, -$P(=O)(OR^7)R^8$, -$P(=O)(OR^7)(OR^8)$, -

$P(=O)R^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

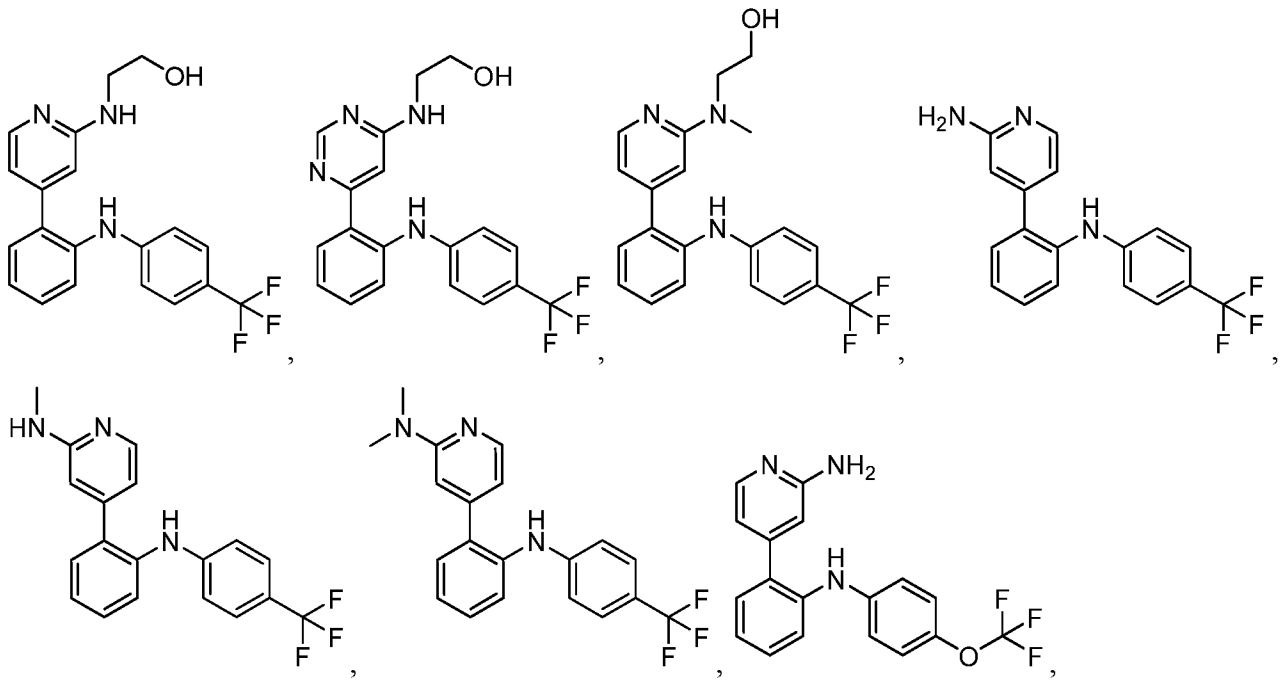
each R^7 and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

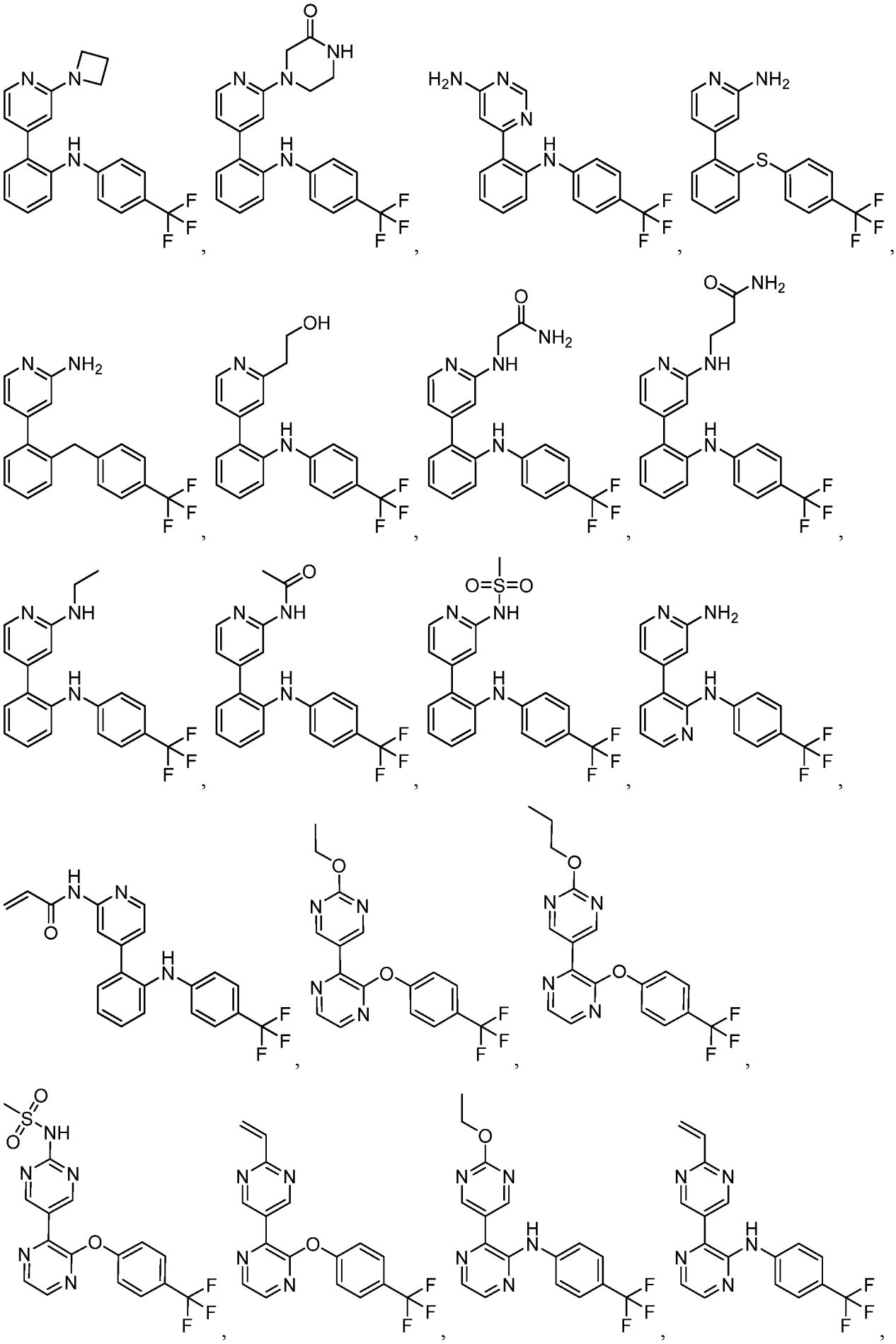
R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N- or P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S;

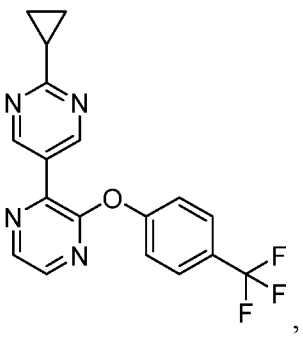
m is 0, 1, 2, or 3; and

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

[00125] In some embodiments, the compound of Formula (I) is selected from the group consisting of:



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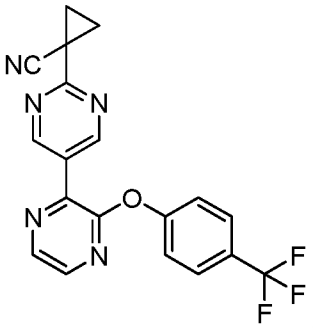
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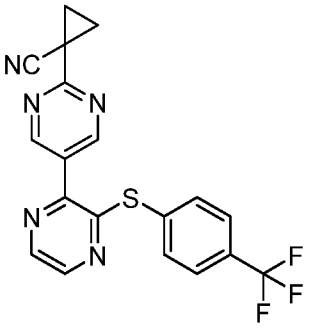
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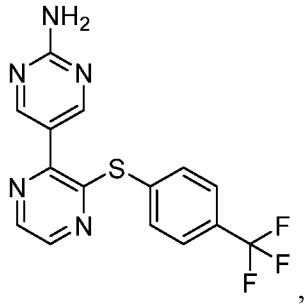
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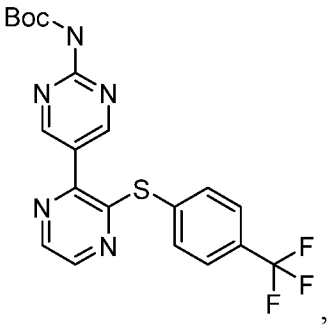
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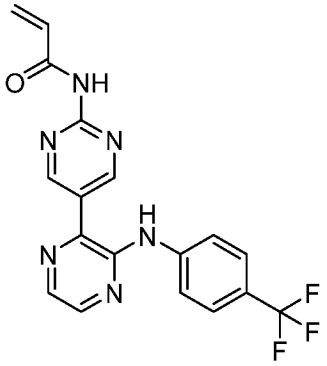
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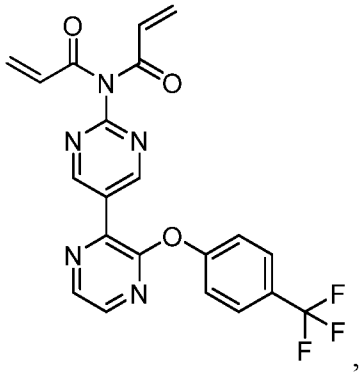
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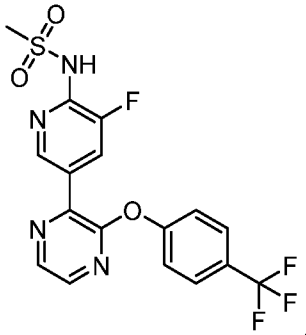
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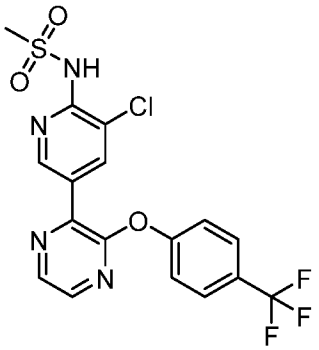
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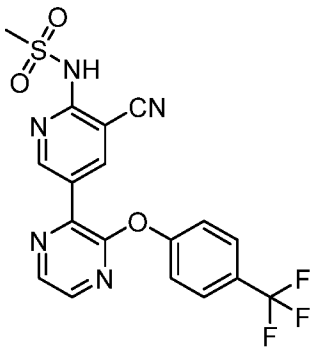
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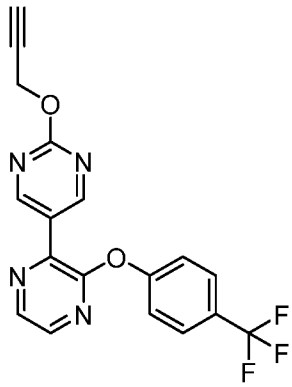
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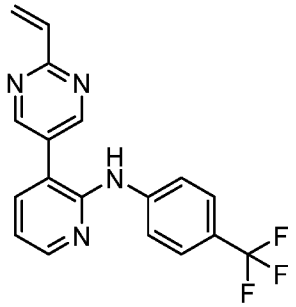
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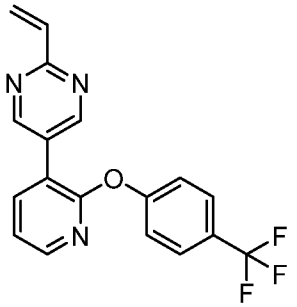
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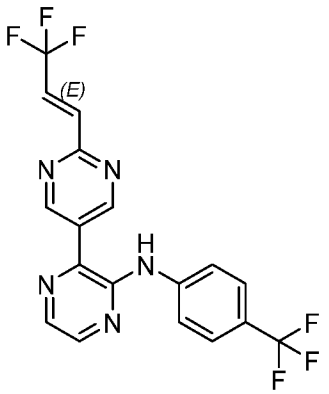
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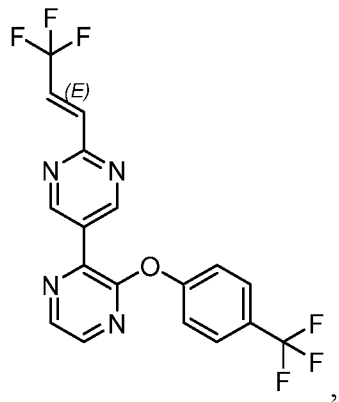
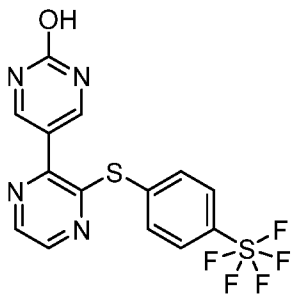
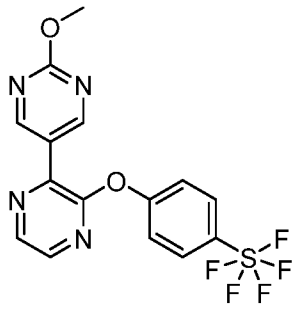
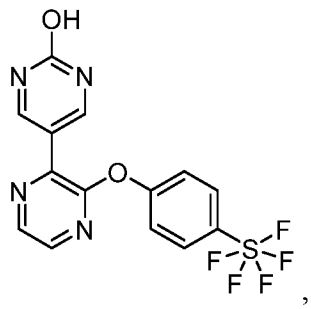
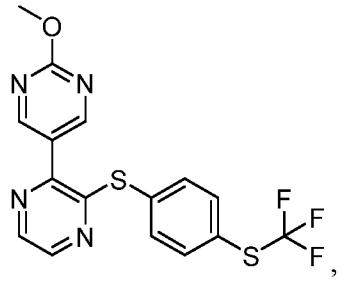
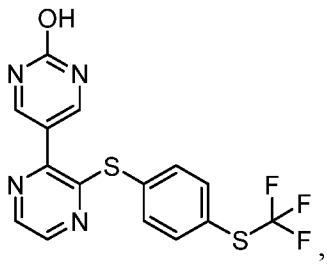
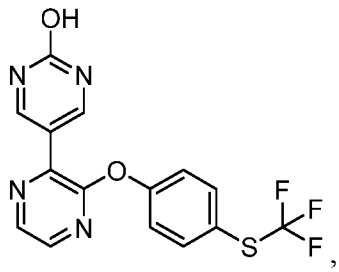
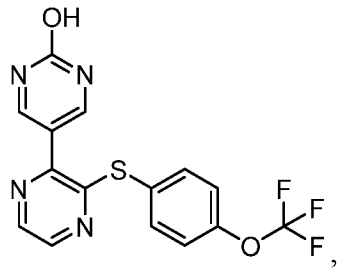
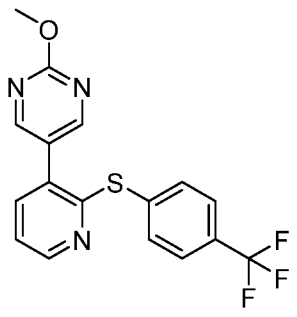
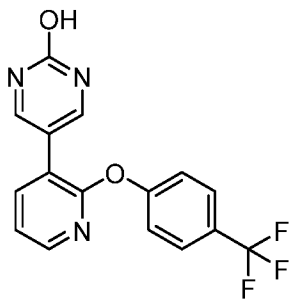
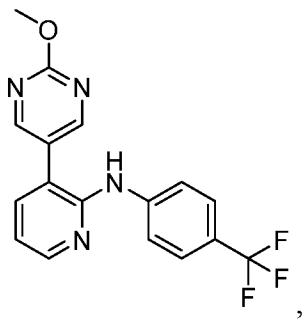
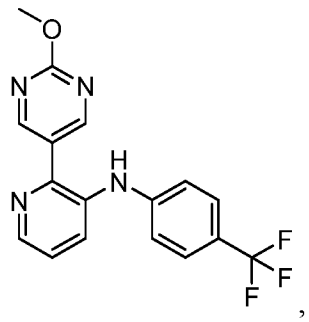
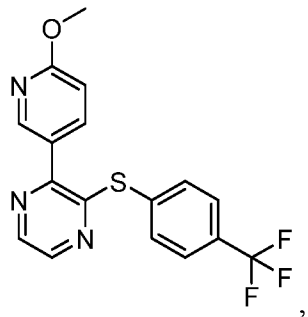
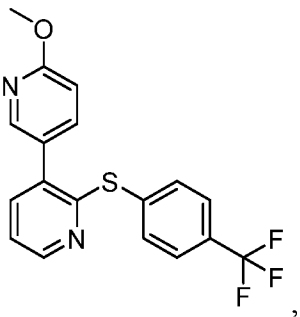
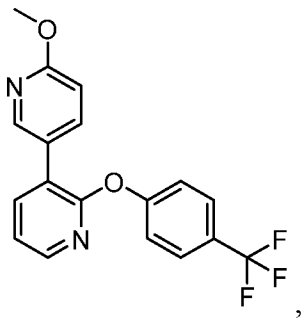
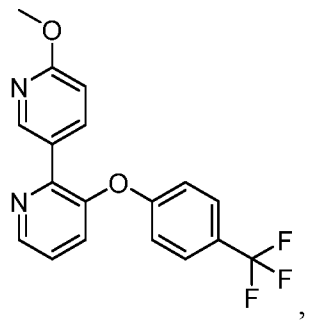
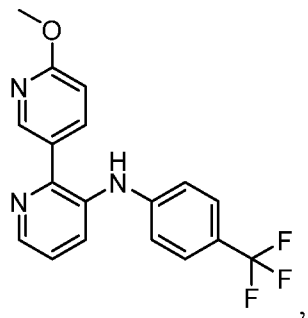
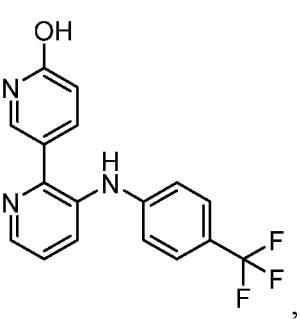
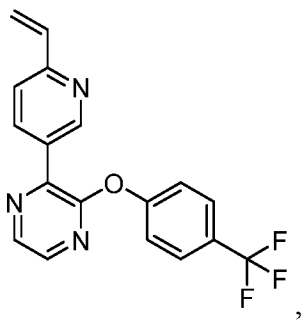

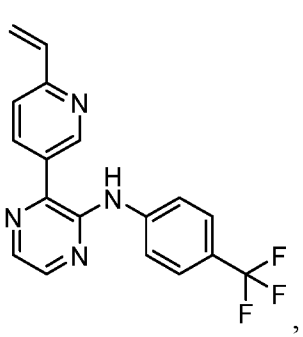
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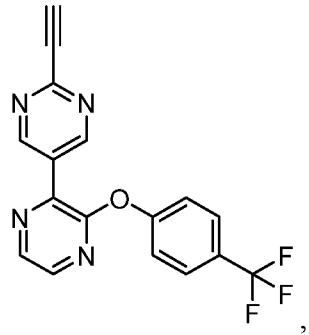
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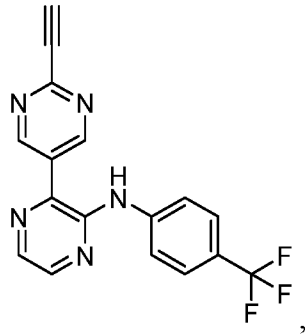
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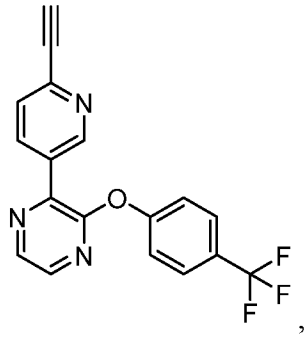
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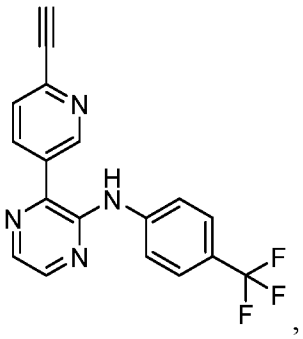
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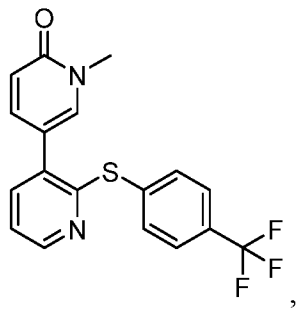
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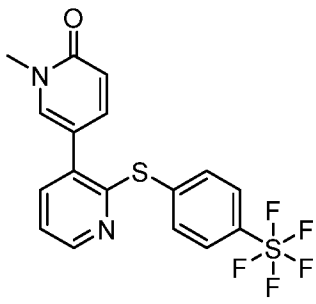
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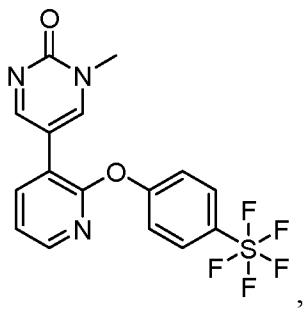
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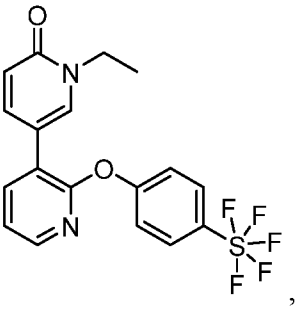
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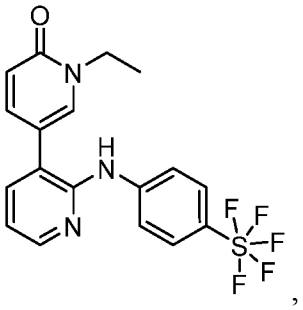
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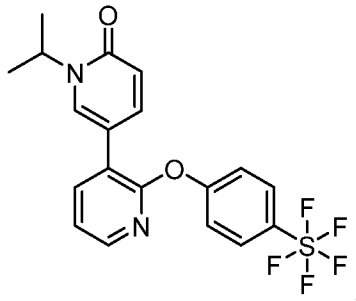
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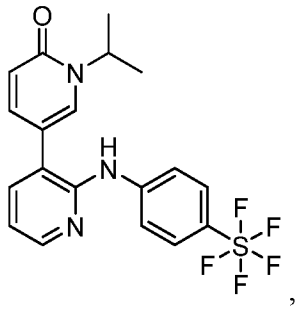
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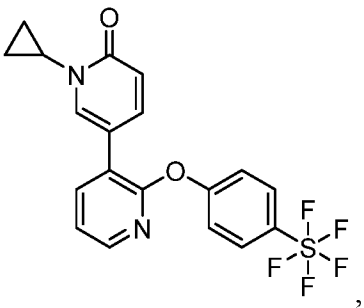
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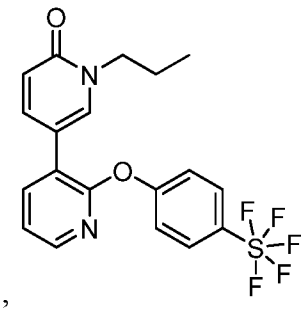
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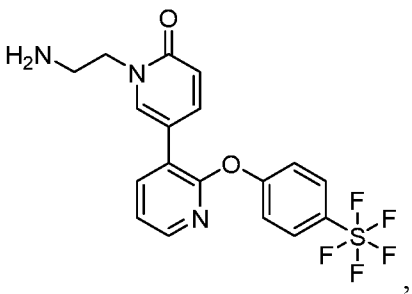
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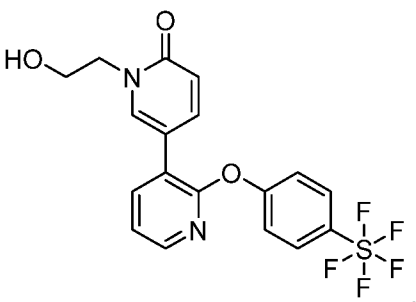
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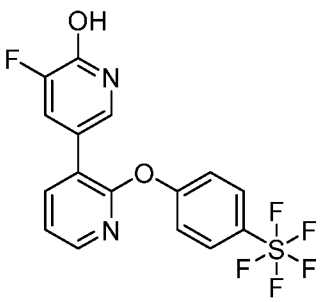
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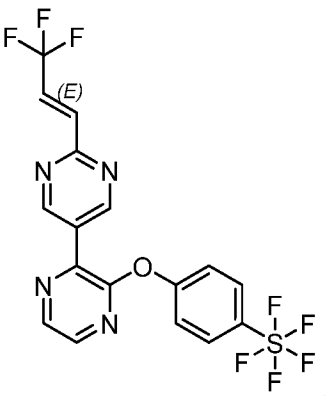
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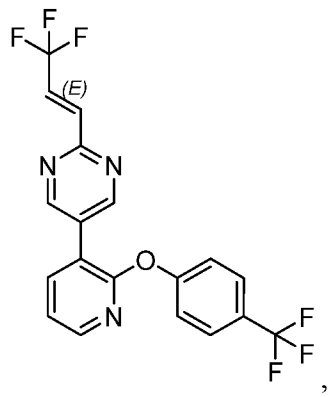
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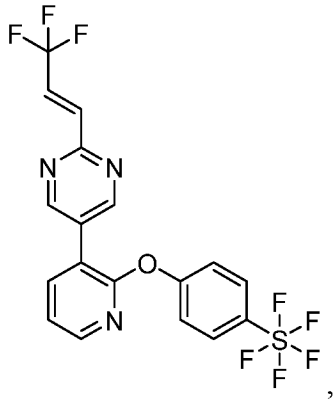
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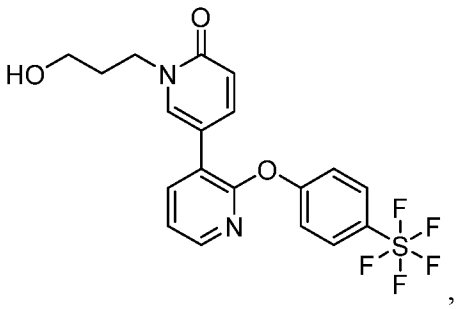
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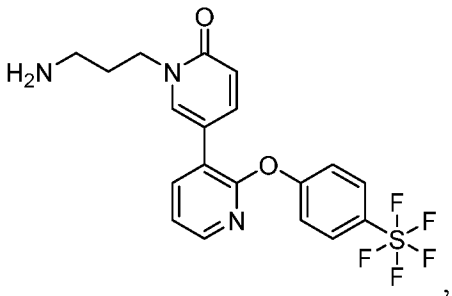
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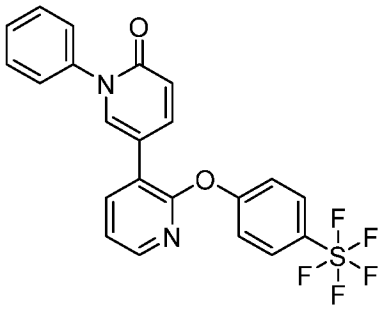
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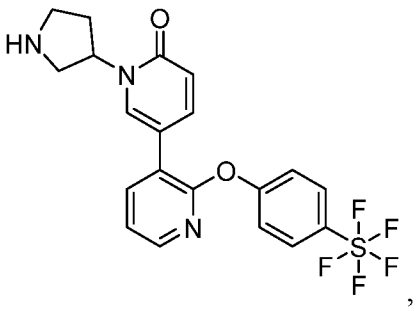
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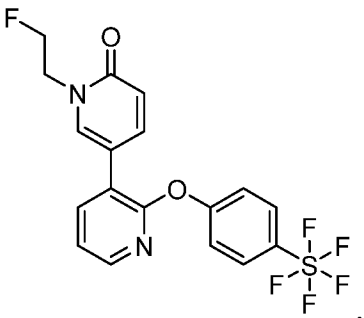
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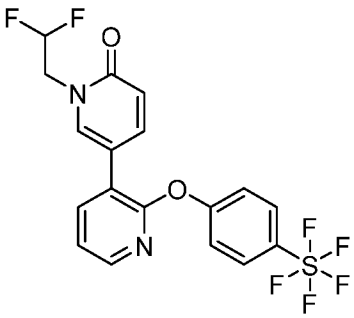
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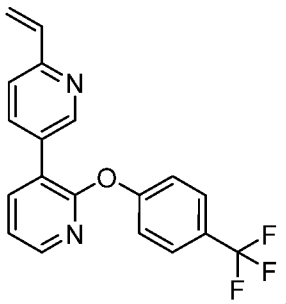
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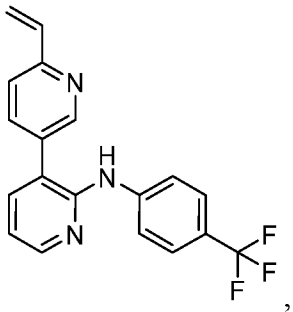
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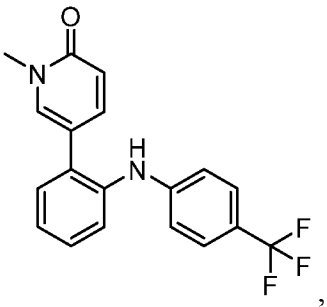
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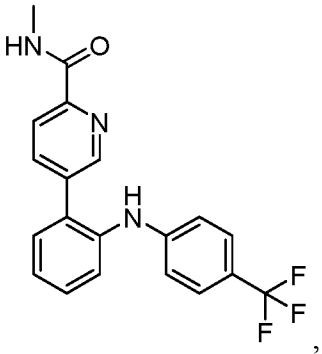
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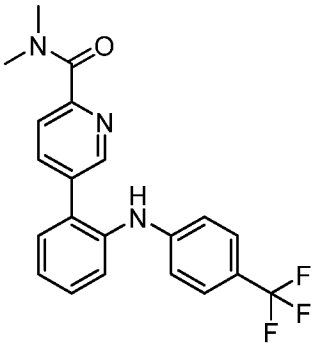
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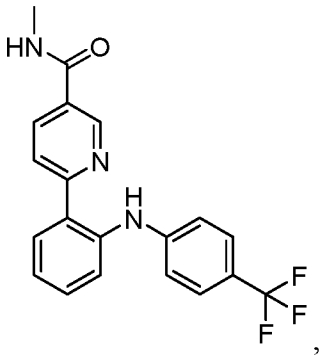
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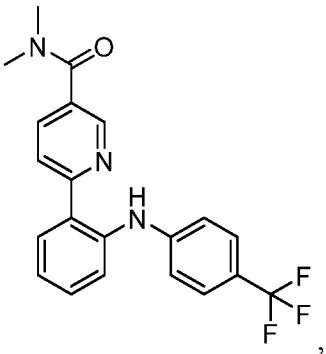
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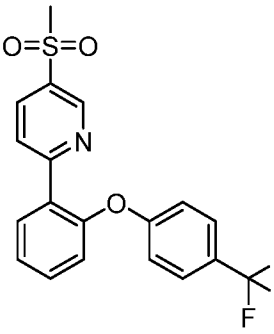
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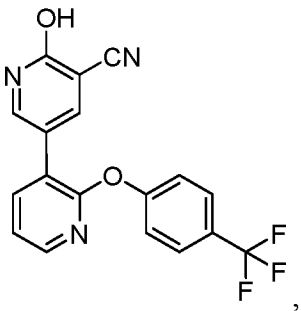
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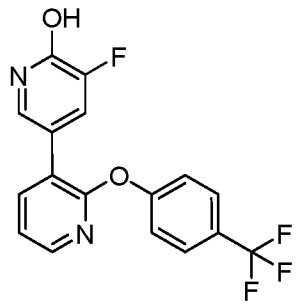
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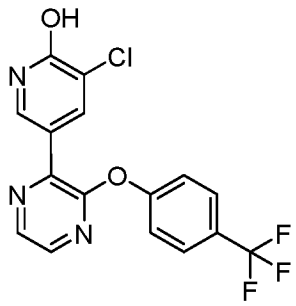
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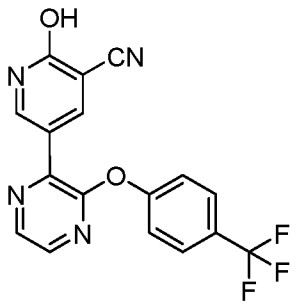
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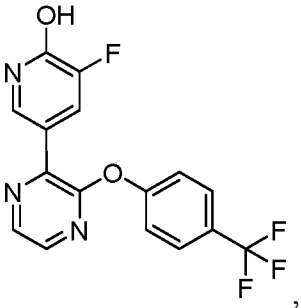
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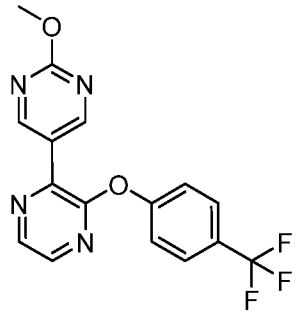
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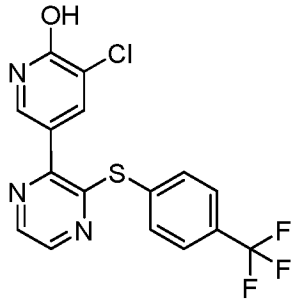
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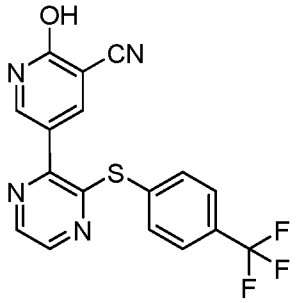
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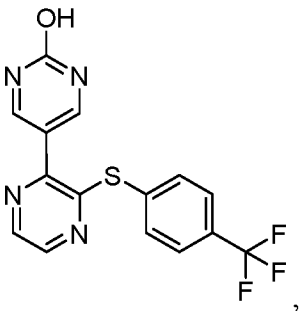
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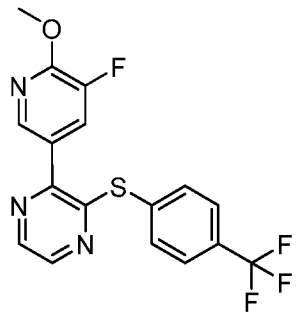
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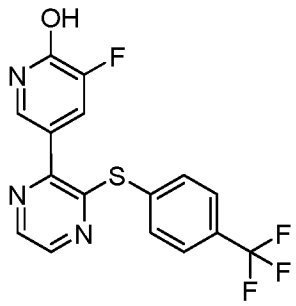
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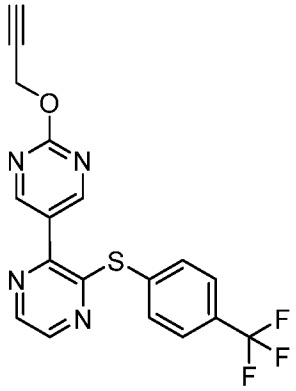
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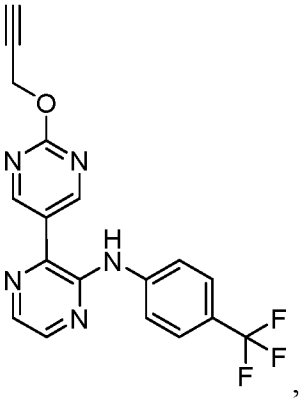
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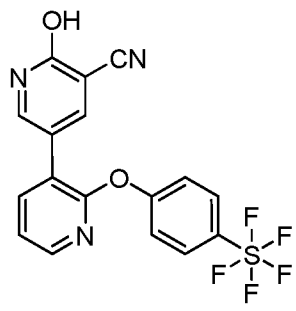
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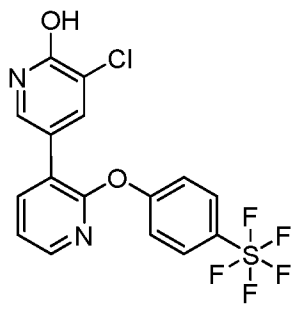
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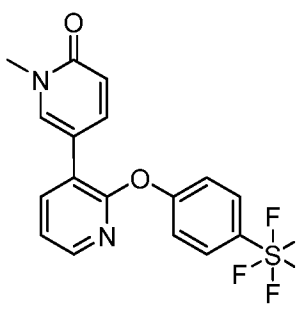
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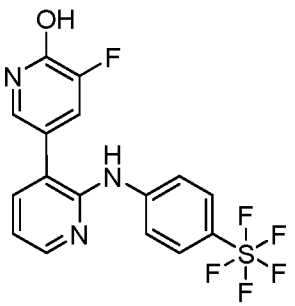
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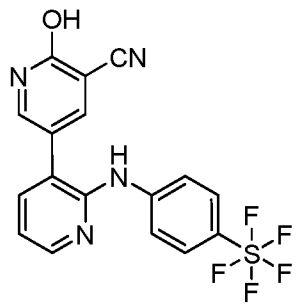
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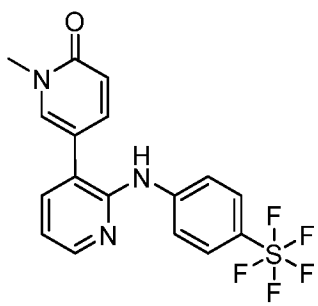
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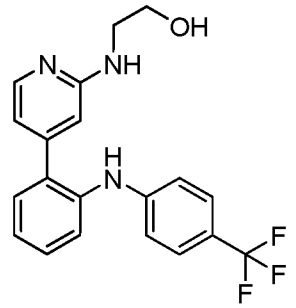
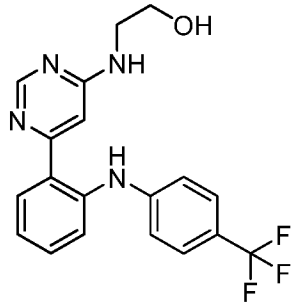
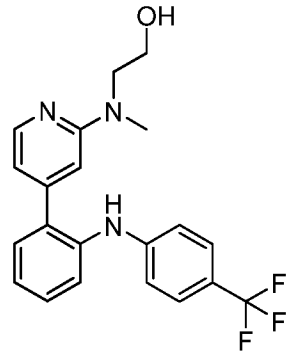
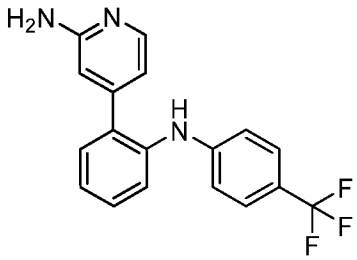
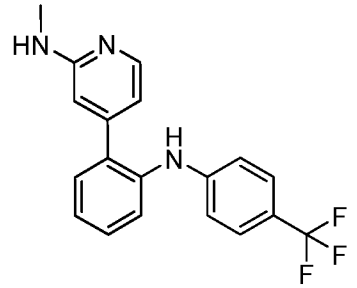
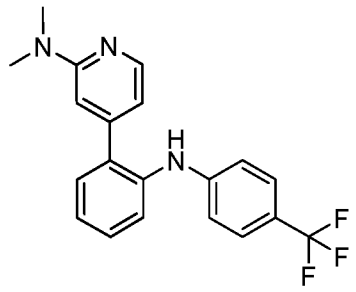
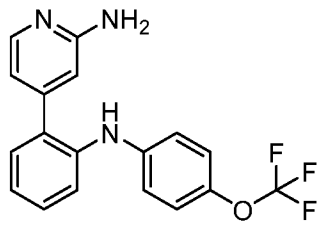
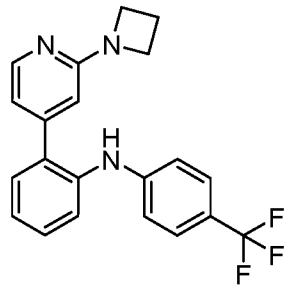
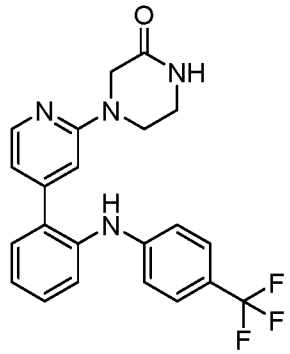
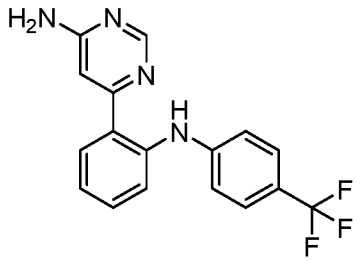
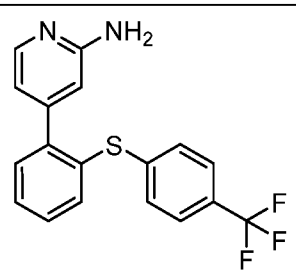
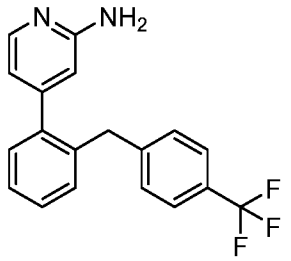
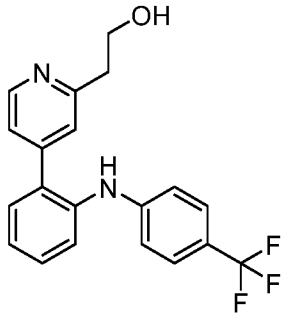
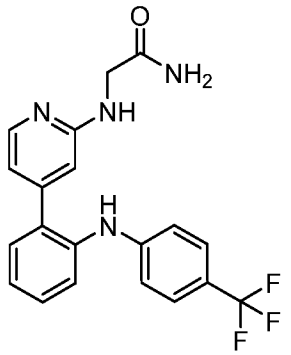
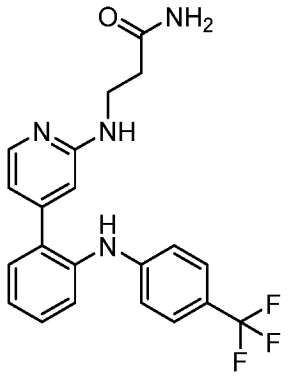
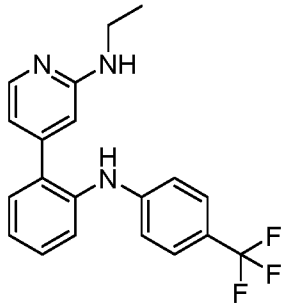
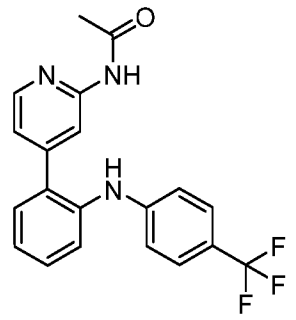
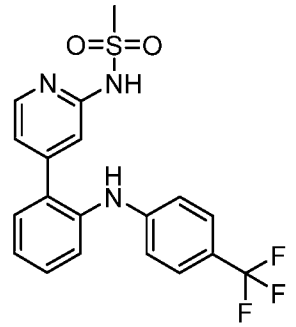
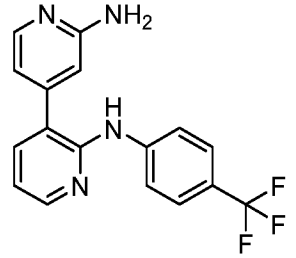
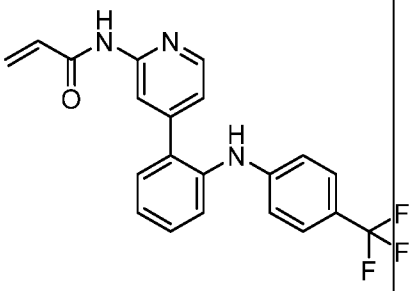
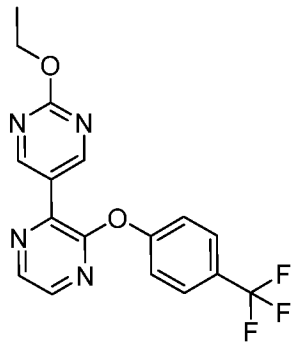
[00126] In another aspect, the present disclosure provides a compound or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1.

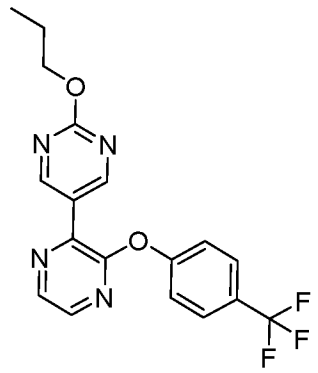
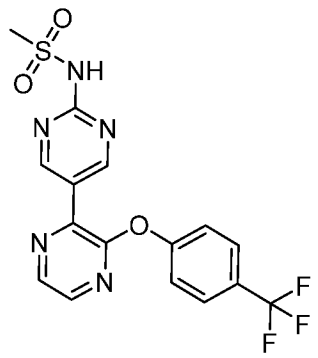
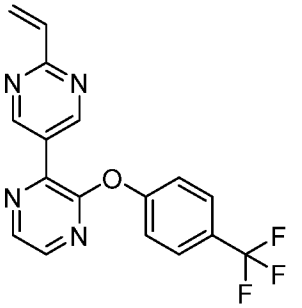
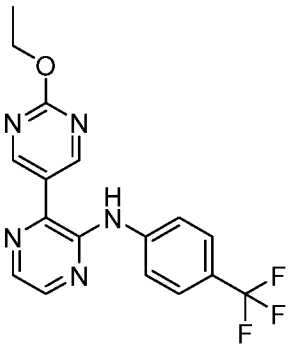
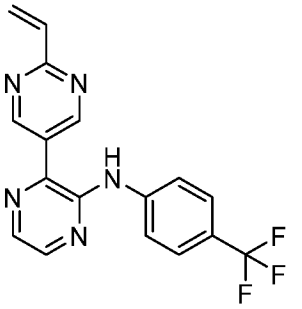
TABLE 1

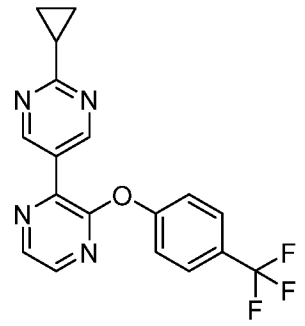
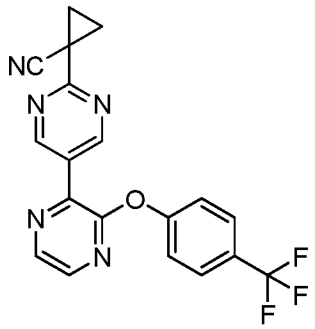
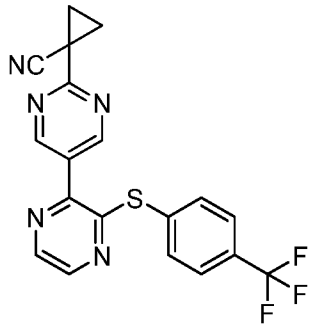
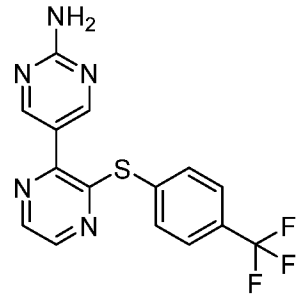
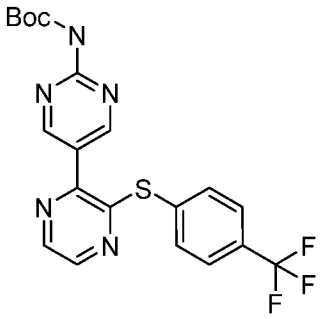
Compound #	**Structure**	Name
1		2-[[4-[2-[4-(trifluoromethyl)anilino]phenyl]-2-pyridyl]amino]ethanol
2		2-((6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyrimidin-4-yl)amino)ethanol
3		2-(methyl(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)amino)ethan-1-ol
4		4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine
5		N-methyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine

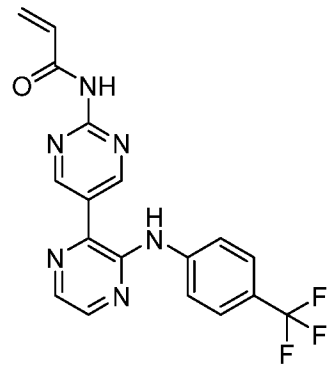
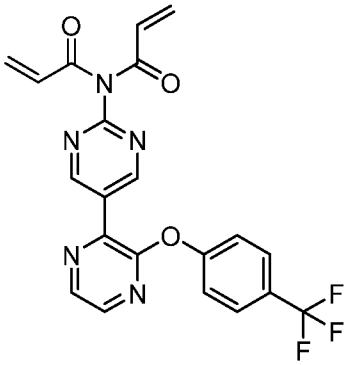
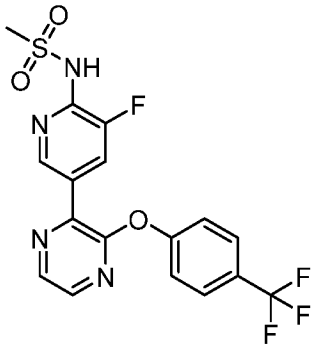
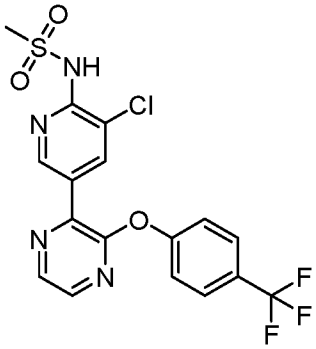
Compound #	Structure	Name
6		N,N-dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine
7		4-(2-((4-(trifluoromethoxy)phenyl)amino)phenyl)pyridin-2-amine
8		2-(2-(azetidin-1-yl)pyridin-4-yl)-N-(4-(trifluoromethyl)phenyl)aniline
9		4-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)piperazin-2-one
10		6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyrimidin-4-amine
11		4-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)pyridin-2-amine

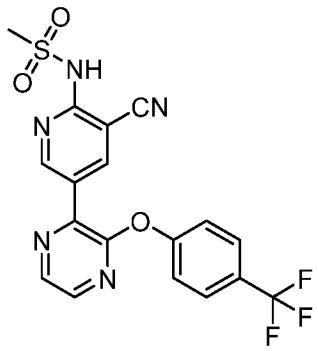
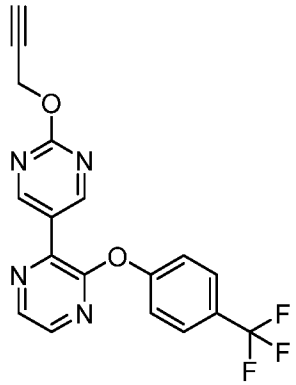
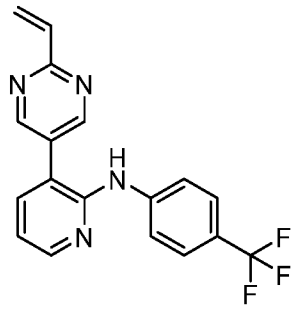
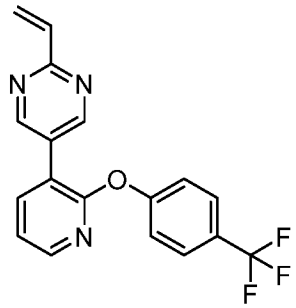
Compound #	Structure	Name
12		4-(2-(4-(trifluoromethyl)benzyl)phenyl)pyridin-2-amine
13		2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)ethan-1-ol
14		2-((4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)amino)acetamide
15		3-((4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)amino)propanamide
16		N-ethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine

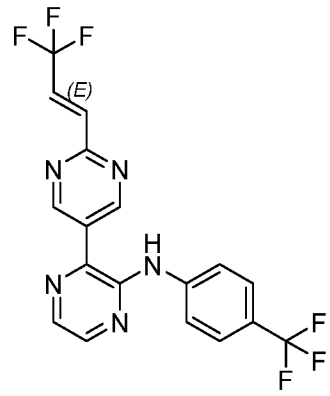
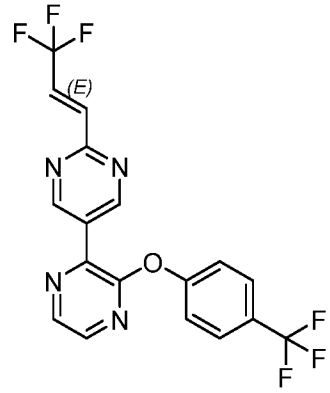
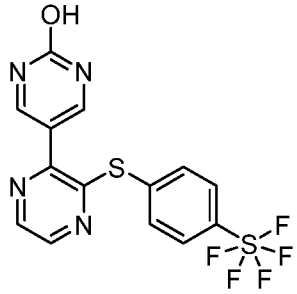
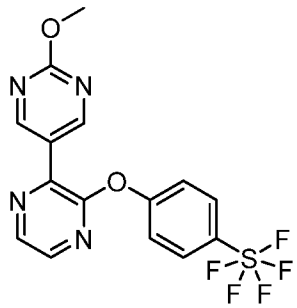
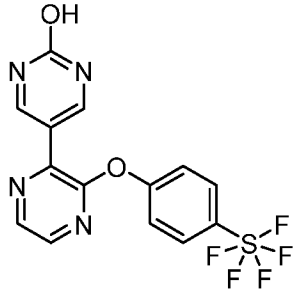
Compound #	Structure	Name
17		N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)acetamide
18		N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)methanesulfonamide
19		N2-(4-(trifluoromethyl)phenyl)-[3,4'-bipyridine]-2,2'-diamine
20		N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)acrylamide
21		2-ethoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine

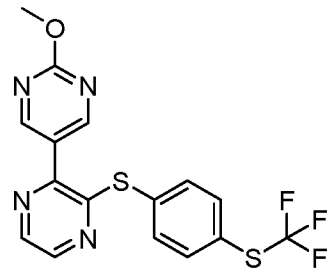
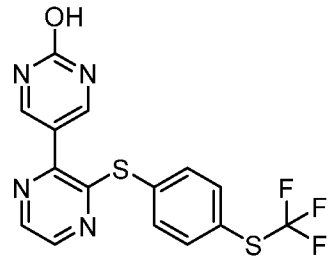
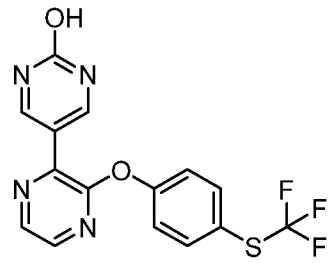
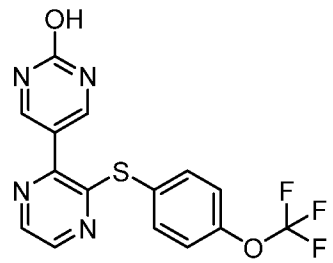
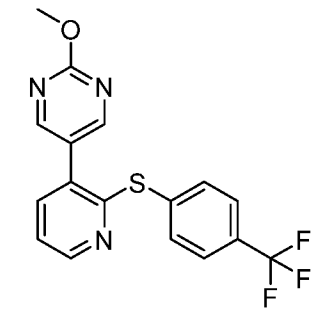
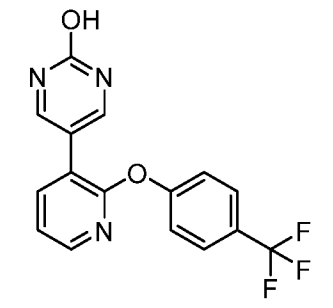
Compound #	Structure	Name
22		2-propoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine
23		N-(5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-yl)methanesulfonamide
24		5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-2-vinylpyrimidine
25		3-(2-ethoxypyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine
26		N-(4-(trifluoromethyl)phenyl)-3-(2-vinylpyrimidin-5-yl)pyrazin-2-amine

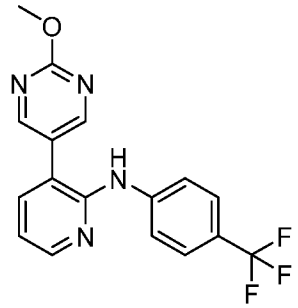
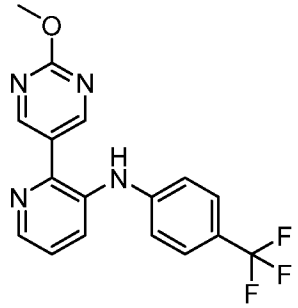
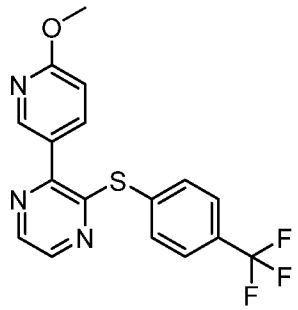
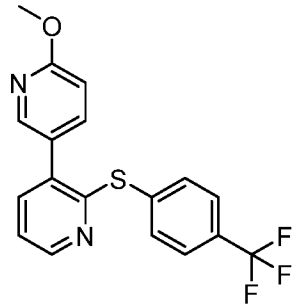
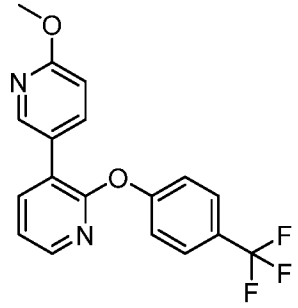
Compound #	Structure	Name
27		2-cyclopropyl-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine
28		1-(5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-yl)cyclopropane-1-carbonitrile
29		1-(5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-yl)cyclopropane-1-carbonitrile
30		5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-amine
30a		tert-butyl (5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-yl)carbamate

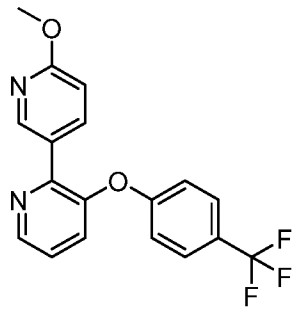
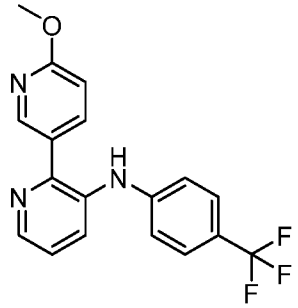
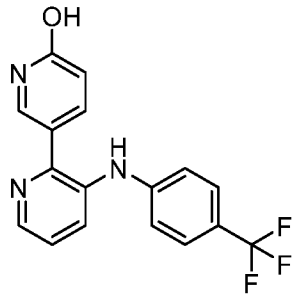
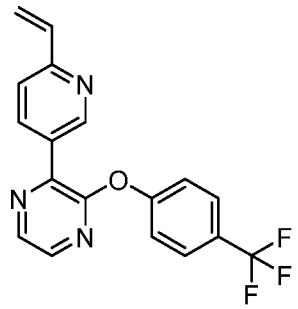
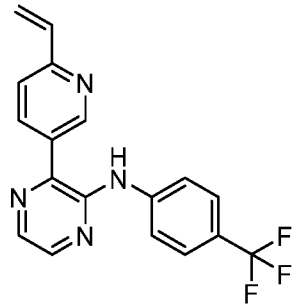
Compound #	Structure	Name
31		N-(5-(3-((4-(trifluoromethyl)phenyl)amino)pyrazin-2-yl)pyrimidin-2-yl)acrylamide
32		N-acryloyl-N-(5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-yl)acrylamide
33		N-(3-fluoro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-yl)methanesulfonamide
34		N-(3-chloro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-yl)methanesulfonamide

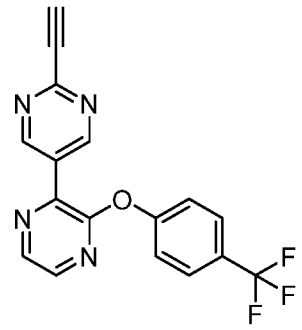
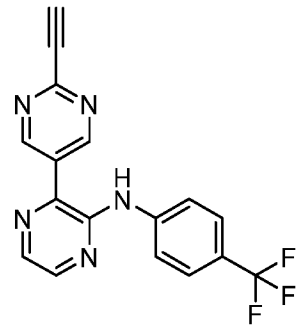
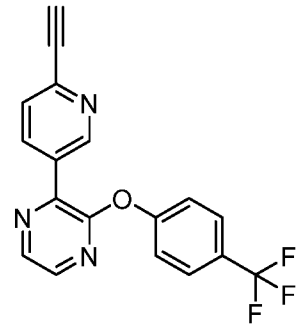
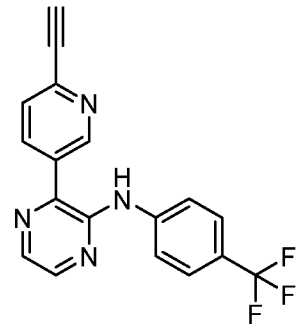
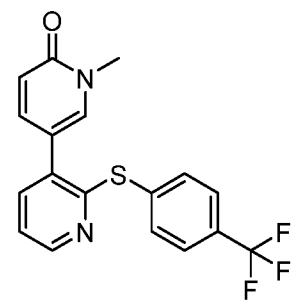
Compound #	Structure	Name
35		N-(3-cyano-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-yl)methanesulfonamide
36		2-(prop-2-yn-1-yloxy)-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine
37		N-(4-(trifluoromethyl)phenyl)-3-(2-vinylpyrimidin-5-yl)pyridin-2-amine
38		5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-2-vinylpyrimidine

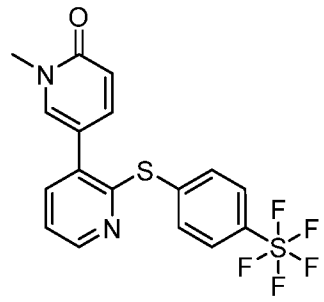
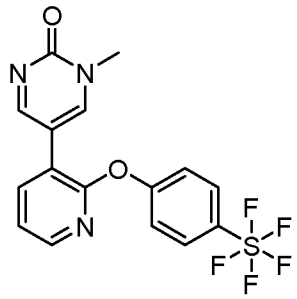
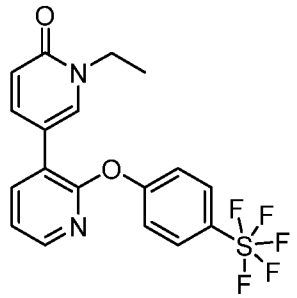
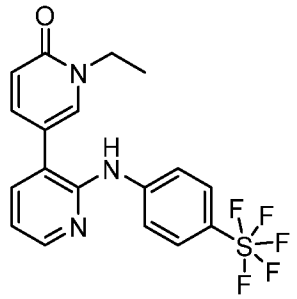
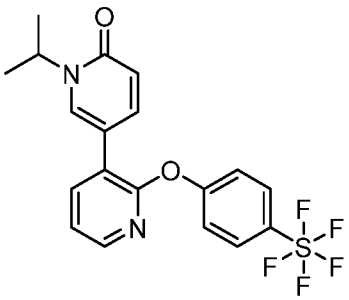
Compound #	Structure	Name
39		(*E*)-N-(4-(trifluoromethyl)phenyl)-3-(2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidin-5-yl)pyrazin-2-amine
40		(*E*)-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine
41		5-(3-((4-(pentafluoro-λ6-sulfaneyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol
42		2-methoxy-5-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)pyrimidine
43		5-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)pyrimidin-2-ol

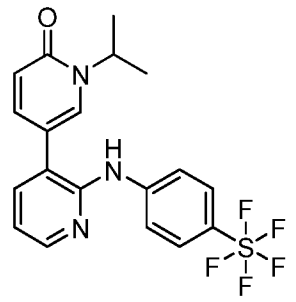
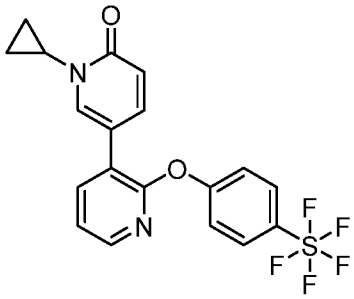
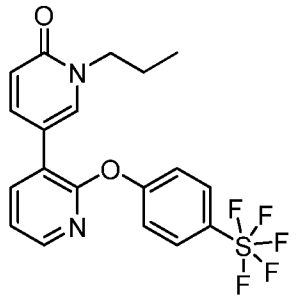
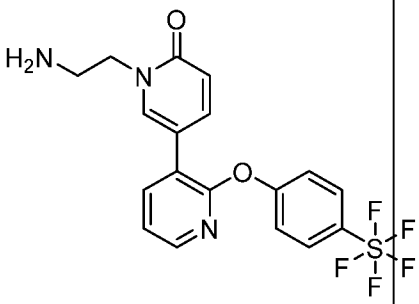
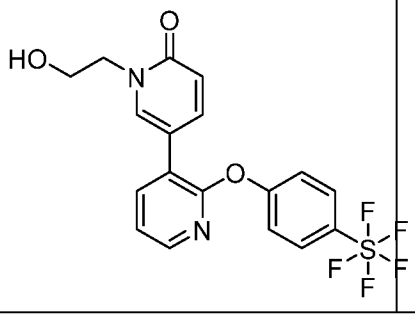
Compound #	Structure	Name
44		2-methoxy-5-(3-((4-((trifluoromethyl)thio)phenyl)thio)pyrazin-2-yl)pyrimidine
44a		5-(3-((4-((trifluoromethyl)thio)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol
45		5-(3-(4-((trifluoromethyl)thio)phenoxy)pyrazin-2-yl)pyrimidin-2-ol
46		5-(3-((4-(trifluoromethoxy)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol
47		5-(2-((4-(trifluoromethyl)phenyl)thio)pyridin-3-yl)pyrimidin-2-ol
48		5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)pyrimidin-2-ol

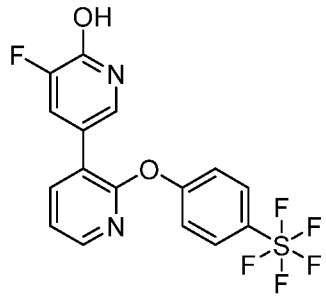
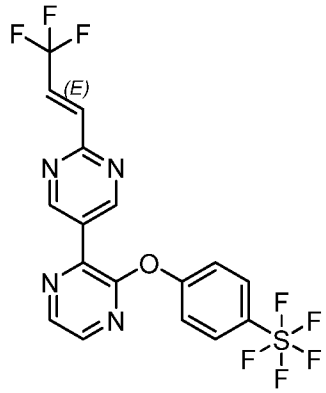
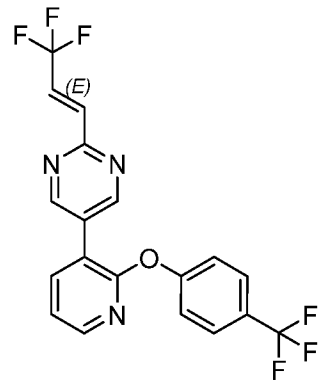
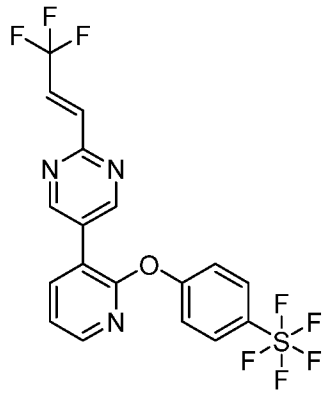
Compound #	Structure	Name
49		3-(2-methoxypyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine
50		2-(2-methoxypyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine
51		2-(6-methoxypyridin-3-yl)-3-((4-(trifluoromethyl)phenyl)thio)pyrazine
52		6'-methoxy-2-((4-(trifluoromethyl)phenyl)thio)-3,3'-bipyridine
53		6'-methoxy-2-(4-(trifluoromethyl)phenoxy)-3,3'-bipyridine

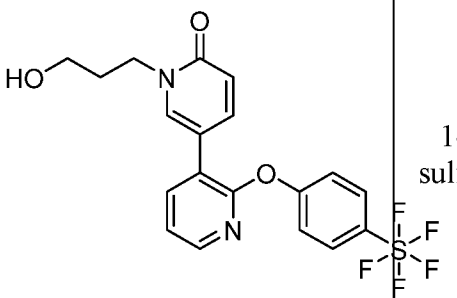
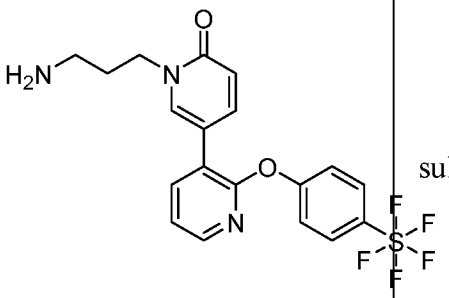
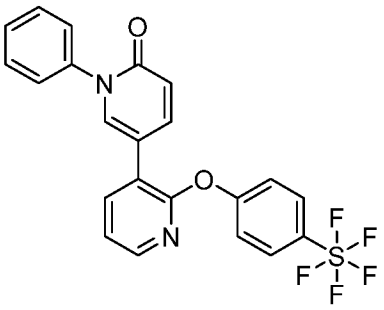
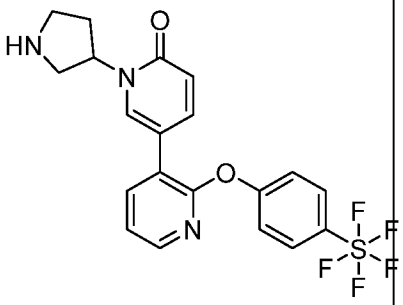
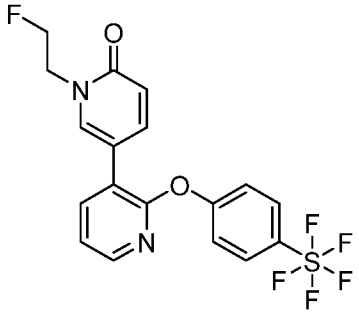
Compound #	Structure	Name
54		6'-methoxy-3-(4-(trifluoromethyl)phenoxy)-2,3'-bipyridine
55		6'-methoxy-N-(4-(trifluoromethyl)phenyl)-[2,3'-bipyridin]-3-amine
55a		3-((4-(trifluoromethyl)phenyl)amino)-[2,3'-bipyridin]-6'-ol
56		2-(4-(trifluoromethyl)phenoxy)-3-(6-vinylpyridin-3-yl)pyrazine
57		N-(4-(trifluoromethyl)phenyl)-3-(6-vinylpyridin-3-yl)pyrazin-2-amine

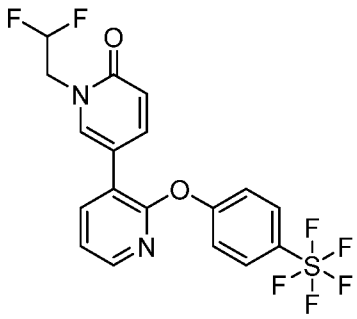
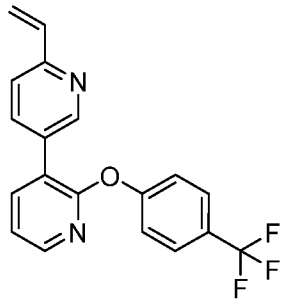
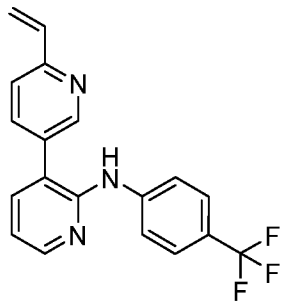
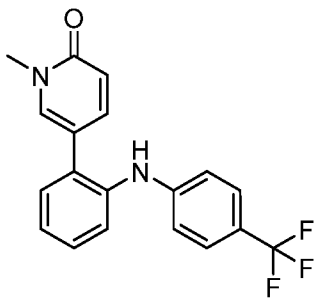
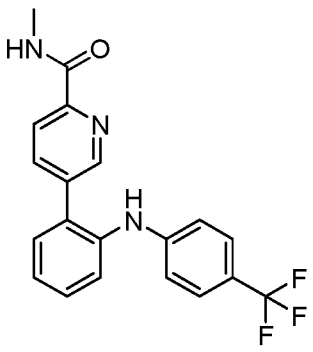
Compound #	Structure	Name
58		2-ethynyl-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine
59		3-(2-ethynylpyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine
60		2-(6-ethynylpyridin-3-yl)-3-(4-(trifluoromethyl)phenoxy)pyrazine
61		3-(6-ethynylpyridin-3-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine
62		1-methyl-2'-((4-(trifluoromethyl)phenyl)thio)-[3,3'-bipyridin]-6(1H)-one

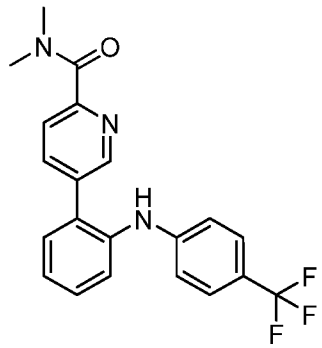
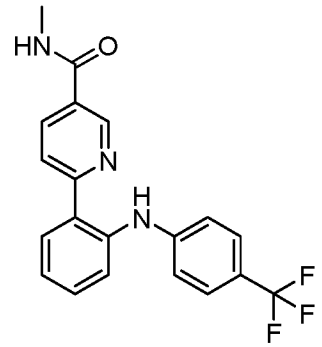
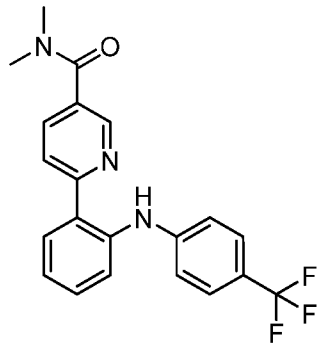
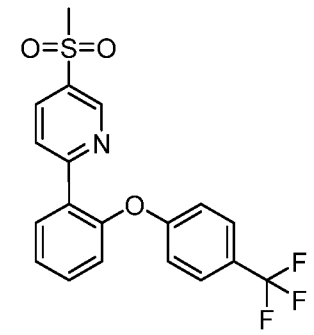
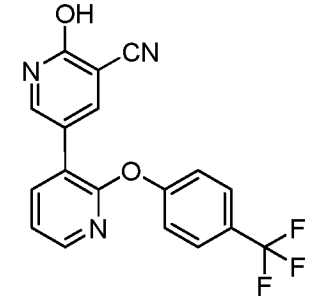
Compound #	Structure	Name
63		1-methyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)thio)-[3,3'-bipyridin]-6(1H)-one
64		1-methyl-5-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)pyrimidin-2(1H)-one
65		1-ethyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one
66		1-ethyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6(1H)-one
67		1-isopropyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one

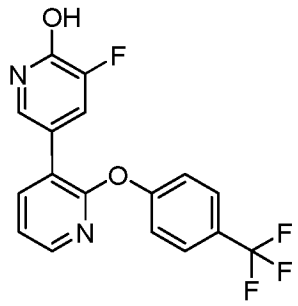
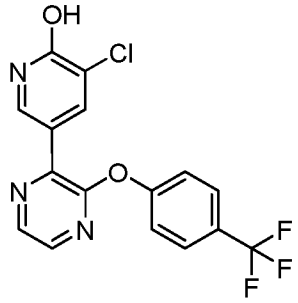
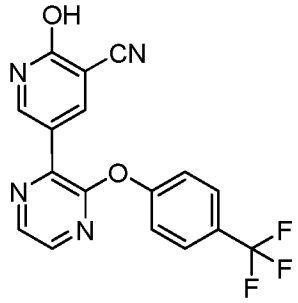
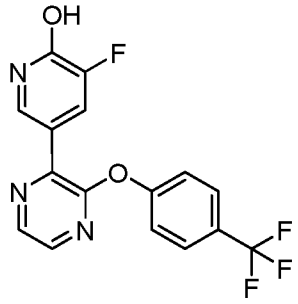
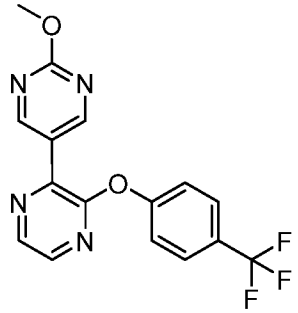
Compound #	Structure	Name
68		1-isopropyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6(1H)-one
69		1-cyclopropyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one
70		2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-1-propyl-[3,3'-bipyridin]-6(1H)-one
71		1-(2-aminoethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one
72		1-(2-hydroxyethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one

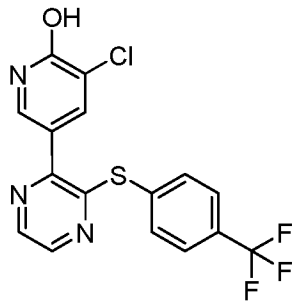
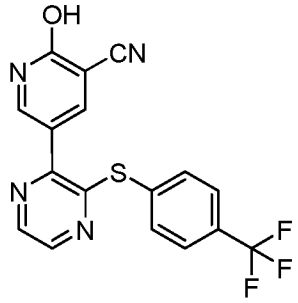
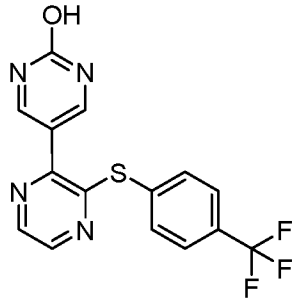
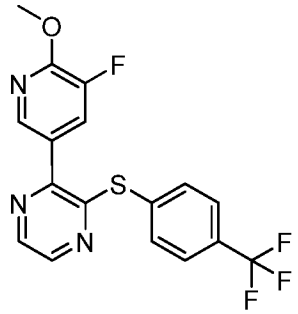
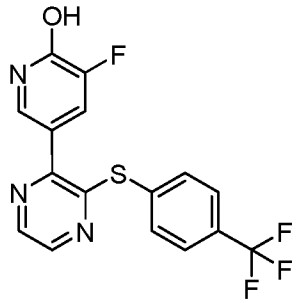
Compound #	Structure	Name
73		5-fluoro-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6-ol
74		(E)-5-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine
75		(E)-5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine
76		(E)-5-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine

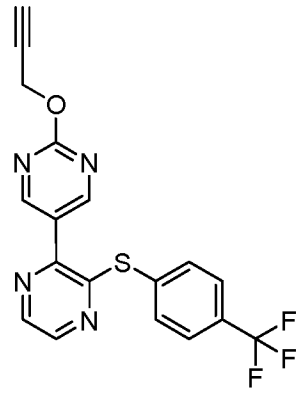
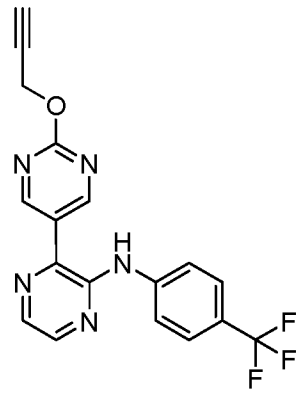
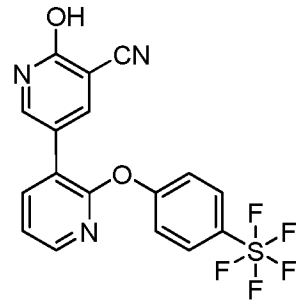
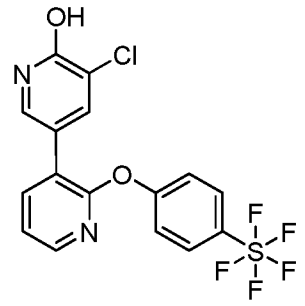
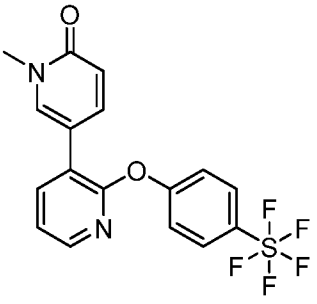
Compound #	Structure	Name
77		1-(3-hydroxypropyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one
78		1-(3-aminopropyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one
79		2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-1-phenyl-[3,3'-bipyridin]-6(1H)-one
80		2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-1-(pyrrolidin-3-yl)-[3,3'-bipyridin]-6(1H)-one
81		1-(2-fluoroethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one

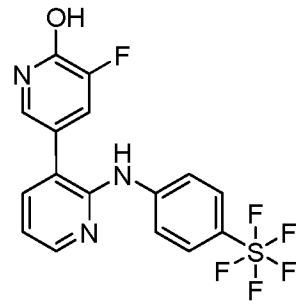
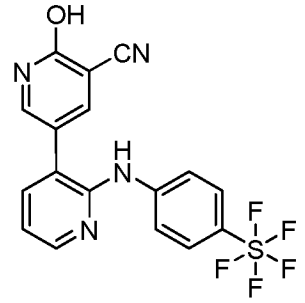
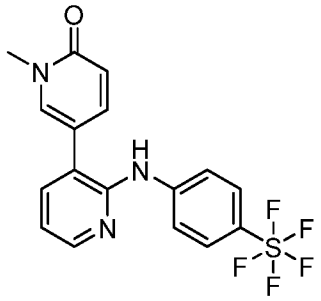
Compound #	Structure	Name
82		1-(2,2-difluoroethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one
83		2-(4-(trifluoromethyl)phenoxy)-6'-vinyl-3,3'-bipyridine
84		N-(4-(trifluoromethyl)phenyl)-6'-vinyl-[3,3'-bipyridin]-2-amine
85		1-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2(1H)-one
86		N-Methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)picolinamide

Compound #	Structure	Name
87		N,N-Dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)picolinamide
88		N-Methyl-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)nicotinamide
89		N,N-Dimethyl-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)nicotinamide
90		5-(methylsulfonyl)-2-(2-(4-(trifluoromethyl)phenoxy)phenyl)pyridine
91		6-Hydroxy-2'-(4-(trifluoromethyl)phenoxy)-[3,3'-bipyridine]-5-carbonitrile

Compound #	Structure	Name
92		5-Fluoro-2'-(4-(trifluoromethyl)phenoxy)-[3,3'-bipyridin]-6-ol
93		3-Chloro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-ol
94		2-Hydroxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)nicotinonitrile
95		3-Fluoro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-ol
96		2-Methoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine

Compound #	Structure	Name
97		3-Chloro-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyridin-2-ol
98		2-Hydroxy-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)nicotinonitrile
99		5-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol
100		2-Methoxy-5-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidine
101		3-Fluoro-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyridin-2-ol

Compound #	Structure	Name
102		2-(Prop-2-yn-1-yloxy)-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidine
103		3-(2-(Prop-2-yn-1-yloxy)pyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine
104		6-Hydroxy-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridine]-5-carbonitrile
105		5-Chloro-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6-ol
106		1-Methyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one

Compound #	Structure	Name
107		5-Fluoro-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6-ol
108		6-Hydroxy-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridine]-5-carbonitrile
109		1-Methyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6(1H)-one

[00127] In some embodiments, provided is a pharmaceutically acceptable salt or solvate thereof of a compound described in Table 1.

Further Forms of Compounds

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, disclosed herein are dissociable complexes (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 does 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 ^{2}H, ^{3}H, ^{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 ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^{3}H 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.*, ^{2}H, 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

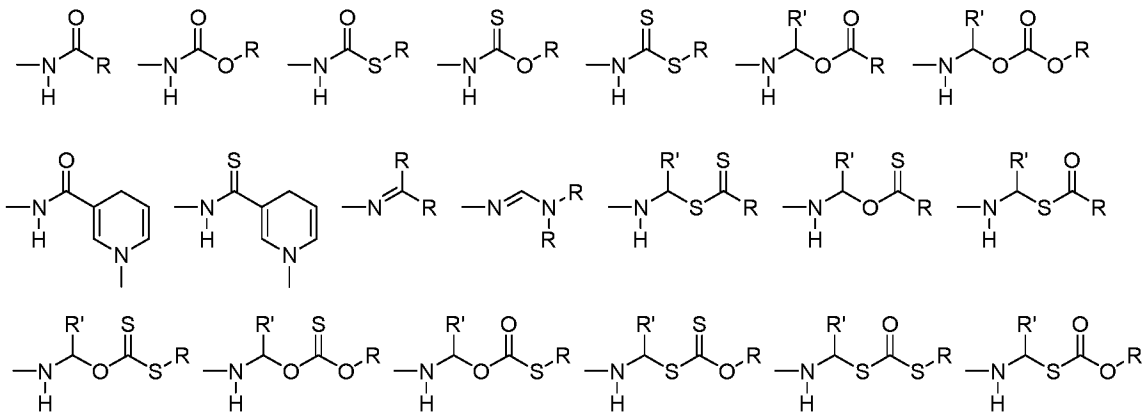
further provides for methods of treating diseases by administering such prodrugs as pharmaceutical compositions.

[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.

Preparation of the Compounds

[00143] 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).

[00144] 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.

[00145] 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.

[00146] In some embodiments, the compounds disclosed herein are prepared as described in the Examples section.

Pharmaceutical Compositions

[00147] 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.

[00148] 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.

[00149] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (III-h), (III-i), (III-j), (III-k), (III-l), (III-m), (III-n), (III-o), (III-p), (III-q), (III-r), (III-s), (III-t), (III-u), (III-v), (IV), (V), (VI), or (VII), or a pharmaceutically acceptable salt or solvate thereof.

[00150] Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (III-h), (III-i), (III-j), (III-k), (III-l), (III-m), (III-n), (III-o), (III-p), (III-q), (III-r), (III-s), (III-t), (III-u), (III-v), (IV), (V), (VI), or (VII), or a pharmaceutically acceptable salt or solvate thereof.

[00151] 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.

[00152] 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.

[00153] 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.

[00154] 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.

[00155] 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 a 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.

[00156] 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.

[00157] 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.

[00158] In some embodiments, the doses 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.

[00159] 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.

[00160] 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

[00161] 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). 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.

[00162] 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. 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.

[00163] 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.

[00164] 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 CK1δ/ε in the degradation motif, which then signals for interaction with the β-TRCP E3 ubiquitin ligase, leading to polyubiquitination and degradation of YAP.

[00165] 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.

[00166] In some embodiments, phosphorylated YAP/TAZ accumulates in the cytoplasm, and undergoes $SCF^{\beta\text{-}TRCP}$-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, βTrCP1, Fbxw1, hsSlimb, plkappaBalpha-E3 receptor subunit) and S-phase kinase-associated proteins 2 (SKP2). In some embodiments, the SCF complex (e.g. $SCF^{\beta TrCP1}$) 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.

[00167] In some embodiments, the Hippo pathway is regulated upstream by several different families of regulators. 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

[00168] 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*.

[00169] 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

[00170] 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. 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).

[00171] 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.

[00172] 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

[00173] $G_q\alpha$ (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.

[00174] 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-HT_2 and 5-HT_3; 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 M_1, M_3, and M_5; and trace amine-associated receptor 1.

[00175] In some instances, there are several types of $G_q\alpha$: 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 *GNA11*. $G_{q/14}$ is encoded by *GNA14*. $G_{q/15}$ is encoded by *GNA15*.

[00176] In some instances, mutations or modifications of the $G_q\alpha$ genes have been associated with cancer. Indeed, studies have shown that mutations in $G_q\alpha$ promote uveal melanoma (UM) tumorigenesis. In some instances, about 80% of UM cases have been detected to contain a mutation in *GNAQ* and/or *GNA11*.

[00177] In some instances, mutations or modifications of the $G_q\alpha$ genes have been associated with congenital diseases. In some instances, mutations of $G_q\alpha$ 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

[00178] $G_{12/13}\alpha$ 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.

[00179] In some embodiments, the GPCRs that interact with $G_{12/13}\alpha$ include, but are not limited to, purinergic receptors (e.g. $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$); muscarinic acetylcholine receptors M1 and M3; receptors for thrombin [protease-activated receptor (PAR)-1, PAR-2]; thromboxane (TXA2); sphingosine 1-phosphate (e.g. $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$); lysophosphatidic acid (e.g. LPA_1, LPA_2, LPA_3); angiotensin II (AT1); serotonin ($5\text{-}HT_{2c}$ and $5\text{-}HT_4$); somatostatin (sst_5); endothelin (ET_A and ET_B); cholecystokinin (CCK_1); V_{1a} vasopressin receptors; D_5 dopamine receptors; fMLP formyl peptide receptors; GAL_2 galanin receptors; EP_3 prostanoid receptors; A_1 adenosine receptors; α_1 adrenergic receptors; BB_2 bombesin receptors; B_2 bradykinin receptors; calcium-sensing receptors; KSHV-ORF74 chemokine receptors; NK_1 tachykinin receptors; and thyroid-stimulating hormone (TSH) receptors.

[00180] In some instances, $G_{12/13}\alpha$ is further subdivided into G_{12} and G_{13} types which are encoded by *GNA12* and *GNA13*, respectively.

$G_{i/o}$ Family

[00181] $G_{i/o}\alpha$ (G inhibitory, G other) (also known as G_i/G_0 or G_i protein) 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.

[00182] In some embodiments, the GPCRs that interact with $G_i\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types $5\text{-}HT_1$ and $5\text{-}HT_5$; muscarinic acetylcholine receptors such as M_2 and M_4; adenosine receptors such as A_1 and A_3; 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 D_2, D_3, and D_4; $GABA_B$ 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 H_3 and H_4 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 (EP_1), prostaglandin E receptor 3 (EP_3), prostaglandin F receptor (FP), and thromboxane receptor (TP); somatostatin receptors sst1, sst2, sst3, sst4, and sst5; and trace amine-associated receptor 8.

[00183] In some instances, there are several types of $G_i\alpha$: $G_i\alpha1$, $G_i\alpha2$, $G_i\alpha3$, $G_i\alpha4$, $G_o\alpha$, G_t, G_{gust}, and G_z. $G_i\alpha1$ is encoded by *GNAI1*. $G_i\alpha2$ is encoded by *GNAI2*. $G_i\alpha3$ 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

[00184] $G_s\alpha$ (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 convers 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-HT_4, 5-HT_6, and 5-HT_7; adrenocorticotropic 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 D_1-like family receptors such as D_1 and D_5; follicle-stimulating hormone receptor (FSH-receptor); gastric inhibitory polypeptide receptor; glucagon receptor; histamine H_2 receptor; luteinizing hormone/choriogonadotropin receptor; melanocortin receptors such as MC1R, MC2R, MC3R, MC4R, and MC5R; parathyroid hormone receptor 1; prostaglandin receptor types D_2 and I_2; secretin receptor; thyrotropin receptor; trace amine-associated receptor 1; and box jellyfish opsin.

[00185] In some instances, there are two types of $G_s\alpha$: G_s and G_{olf}. G_s is encoded by *GNAS*. G_{olf} is encoded by *GNAL*.

Additional Regulators of the Hippo signaling network

[00186] 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.

[00187] 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.

[00188] 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.

[00189] 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.

[00190] 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).

[00191] 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 described above. 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.

[00192] 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.

[00193] 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).

[00194] 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.

[00195] 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.

[00196] 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.

[00197] Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

[00198] In another aspect, the present disclosure provides a method of inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway in a subject, comprising administering to a subject a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[00199] In another aspect, the present disclosure provides a method of inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP) in a subject comprising administering to a subject in need thereof a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the subject has cancer, polycystic kidney disease, or liver fibrosis. In some embodiments, the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

[00200] In another aspect, the present disclosure provides a method of treating cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

[00201] In another aspect, the present disclosure provides a method of treating polycystic kidney disease or liver fibrosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[00202] In yet another aspect, the present disclosure provides a method of treating or preventing a disease or disorder amenable to treatment with a compound that inhibits the activity of one or more of proteins encompassed by, or related to, the Hippo pathway in a subject, comprising administering to a subject in need thereof a therapeutically acceptable amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[00203] In yet another aspect, the present disclosure provides a method of treating or preventing a disease or disorder amenable to treatment with a compound that inhibits transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP) in a subject comprising administering to a subject in need thereof a therapeutically acceptable amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[00204] In yet another aspect, provided herein are uses of a compound of Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (III-h), (III-i), (III-j), (III-k), (III-l), (III-m), (III-n), (III-o), (III-p), (III-q), (III-r), (III-s), (III-t), (III-u), (III-v), (IV), (V), (VI), or (VII), as disclosed herein or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof as described herein, in the preparation of a medicament for treating a disease or disorder (e.g., a disease or disorder conducive to treatment to prevention by inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway; or a disease or disorder conducive to treatment to prevention by inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP)) in a subject in need thereof.

[00205] In another aspect, a compound disclosed herein is for use in a method of treating a disease or disorder (e.g., a disease or disorder amenable to treatment with a compound that inhibits one or more of proteins encompassed by, or related to, the Hippo pathway; or a disease or disorder conducive to treatment to prevention by inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP)) in a subject in need thereof, such cancer. Such a compound is, for example, a compound of Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (III-h), (III-i), (III-j), (III-k), (III-l), (III-m), (III-n), (III-o), (III-p), (III-q), (III-r), (III-s), (III-t), (III-u), (III-v), (IV), (V), (VI), or (VII), as disclosed herein, or a pharmaceutical composition comprising the compound disclosed herein, and a pharmaceutically acceptable excipient, as disclosed herein.

[00206] In another aspect, provided herein are pharmaceutical compositions comprising a compound Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), (III-g), (III-h), (III-i), (III-j), (III-k), (III-l), (III-m), (III-n), (III-o), (III-p), (III-q), (III-r), (III-s), (III-t), (III-u), (III-v), (IV), (V), (VI), or (VII), as disclosed herein or a pharmaceutically acceptable salt thereof, for use in treating a disease or disorder (e.g., a disease or disorder amenable to treatment with a compound that inhibits one or more of proteins encompassed by, or related to, the Hippo pathway; or a disease or disorder conducive to treatment to prevention

by inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP)) in a subject in need thereof.

Diseases

Cancer

[00207] In some embodiments, the compounds disclosed herein are useful for treating cancer. In some embodiments, disclosed herein is a method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, disclosed herein is a compound for use in treating a cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt or solvate thereof. 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 Gα-protein. In some embodiments, the mutant Gα-protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant Gα-protein is G12. In some embodiments, the mutant Gα-protein is G13. In some embodiments, the mutant Gα-protein is Gq. In some embodiments, the mutant Gα-protein is G11. In some embodiments, the mutant Gα-protein is Gi. In some embodiments, the mutant Gα-protein is Go. In some embodiments, the mutant Gα-protein is Gs.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] 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.

[00212] 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.

[00213] 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.

[00214] 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.

[00215] 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, and 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, or 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.

[00216] 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.

[00217] 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.

[00218] 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.

[00219] 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

[00220] 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 Gα-protein. In some embodiments, the mutant Gα-protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant Gα-protein is G12. In some embodiments, the mutant Gα-protein is G13. In some embodiments, the mutant Gα-protein is Gq. In some embodiments, the mutant Gα-protein is G11. In some embodiments, the mutant Gα-protein is Gi. In some embodiments, the mutant Gα-protein is Go. In some embodiments, the mutant Gα-protein is Gs.

[00221] 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

[00222] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

List of abbreviations

[00223] 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
Ac	acetyl
BOC or Boc	*tert*-butyl carbamate

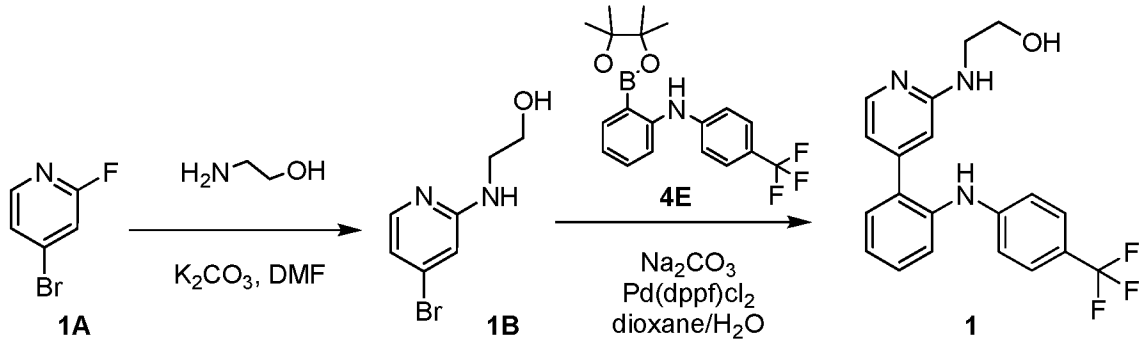
t-Bu	*tert*-butyl
°C	degrees Celsius
DBA or dba	dibenzylideneacetone
DCE	dichloroethane ($ClCH_2CH_2Cl$)
DCM	dichloromethane (CH_2Cl_2)
DIPEtOAc or DIEtOAc	diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc or EtOAc	ethyl acetate
Et	ethyl
EtOH	ethanol
g	gram(s)
h, hr, hrs	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz
LCMS	liquid chromatography mass spectrometry
m/z	mass-to-charge ratio
M	molar
Me	methyl
MeOH	methanol
mg	milligram(s)
MHz	megahertz
µmol	micromole(s)
uL	microliter(s)
mL	milliliter(s)
mmol	millimole(s)
MS	mass spectroscopy
NMR	nuclear magnetic resonance
PE	petroleum ether
Ph	phenyl
prep-HPLC	preparative high pressure liquid chromatography
prep-TLC	preparative thin layer chromatography
Py	pyridine
RT	retention time

TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

I. Chemical Synthesis

[00224] 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.

Example 1: 2-[[4-[2-[4-(trifluoromethyl)anilino]phenyl]-2-pyridyl]amino]ethanol (Compound 1)



2-[(4-bromo-2-pyridyl)amino]ethanol

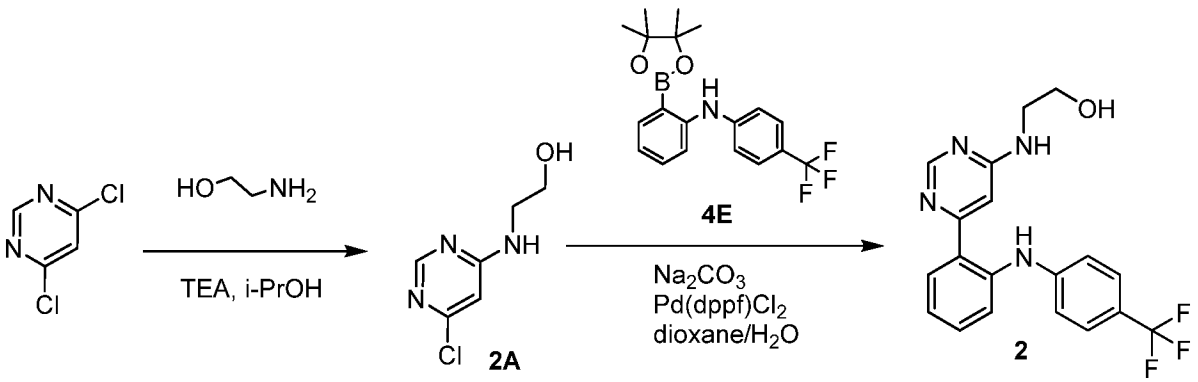
[00225] To a solution of 4-bromo-2-fluoropyridine (**1A**, 200.0 mg, 1.1 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K_2CO_3 (315.1 mg, 2.3 mmol, 2.0 *eq*) and 2-aminoethan-1-ol (6 9.6 mg, 1.1 mmol, 68.9 uL, 1.0 *eq*). The reaction mixture was stirred at 80 °C for 16 hrs under N_2 atmosphere. The reaction was filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography over silica gel and eluted with petroleum ether/ethyl acetate=1/0 to 10/1 to give intermediate **1B** (100.0 mg, 0.46 mmol, 40.4% yield) as a colorless oil. LCMS (ESI): RT = 0.627 min, mass calc. for $C_7H_9BrN_2O$ 215.99m/z found 218.9 $[M+H+2]^+$; ^{1}HNMR (400 MHz, $CDCl_3$-*d*) δ 7.87 (d, *J* = 5.5 Hz, 1H), 6.75 (dd, *J* = 1.5, 5.5 Hz, 1H), 6.64 (d, *J* = 1.5 Hz, 1H), 3.83 - 3.78 (m, 2H), 3.54 - 3.50 (m, 2H).

2-[[4-[2-[4-(trifluoromethyl)anilino]phenyl]-2-pyridyl]amino]ethanol

[00226] To a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (intermediate **4E**, 100.0 mg, 0.14 mmol, 1.0 *eq*) and intermediate

1B (35.9 mg, 0.17 mmol, 1.2 *eq*) in dioxane (5.0 mL) was added H_2O (0.5 mL), $Pd(dppf)Cl_2$ (10.1 mg, 13.8 µmol, 0.1 *eq*) and Na_2CO_3 (29.2 mg, 0.28 mmol, 2.0 *eq*). The reaction mixture was stirred at 100 °C for 16 hrs under N_2 atmosphere. The reaction was filtered through celite and concentrated under reduced pressure to give a residue. The crude product was purified by preparative HPLC (Condition: water(0.05%HCl)-ACN. Column:Phenomenex Gemini 150x25mmx10um. Begin B:25. End B:55) to afford **Compound 1** as a white solid (14.73 mg, 28.37% yield). LCMS (ESI): RT = 0.702 min, mass calc. for $C_{20}H_{18}F_3N_3O$ 373.14, m/z found 374.0 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.33 (s, 1H), 7.85 (d, J = 6.8 Hz, 1H), 7.54 - 7.40 (m, 5H), 7.33 - 7.25 (m, 1H), 7.13 (s, 1H), 6.94 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 5.8 Hz, 1H), 3.65 - 3.55 (m, 2H), 3.44 (d, J = 4.3 Hz, 2H).

Example 2: 2-((6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyrimidin-4-yl)amino)ethanol (Compound 2)



2-((6-chloropyrimidin-4-yl)amino)ethanol

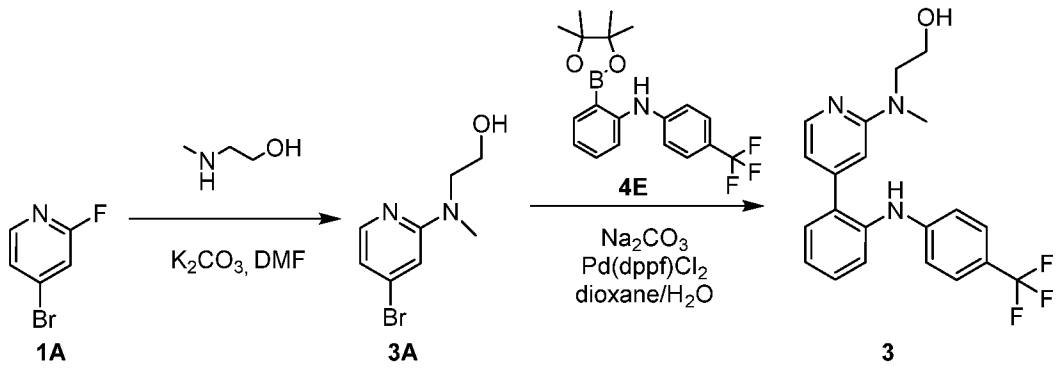
[00227] To a mixture of 2-aminoethan-1-ol (98.2 mg, 1.6 mmol, 97 uL, 1.20 *eq*) and TEA (176.3 mg, 1.7 mmol, 0.2 mL, 1.3 *eq*) in *i*-PrOH (3.0 mL), was added 4,6-dichloropyrimidine (200.0 mg, 1.3 mmol, 1.0 *eq*). The resulted mixture was stirred at 85 °C for 2 h. The reaction mixture was concentrated in vacuum. The residue was diluted with water (20 mL), extracted with DCM (20 mL x2). The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuum. Intermediate **2A** was obtained as light yellow solid (200.0 mg, 1.2 mmol, 86.0% yield), which was confirmed by ^{1}H NMR. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.77 (s, 1H), 6.55 (s, 1H), 4.79 (s, 1H), 3.50 (q, J = 5.4 Hz, 2H), 3.35 - 3.38 (m, 2H).

2-((6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyrimidin-4-yl)amino)ethanol

[00228] To a mixture of intermediate **2A** (35.9 mg, 0.2 mmol, 1.50 *eq*), intermediate **4E** (50.0 mg, 0.1 mmol, 1.00 *eq*) and Na_2CO_3 (29.2 mg, 0.3 mmol, 2.00 *eq*) in dioxane (3.0 mL) and H_2O (1.0 mL), was added $Pd(dppf)Cl_2$ (10.1 mg, 13.8 µmol, 0.10 *eq*). The reaction mixture was

degassed under vacuum and purged with N_2 for 3 times. The resulted mixture was stirred at 100 °C under N_2 for 17 h. The reaction mixture was filtered, and the solid was washed with DCM (10 mL x2). The filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (acidic HCl condition). **Compound 2** was obtained as brown oil (0.65 mg, 1.2% yield, HCl), which was combined with the previous batch (1.69 mg, HCl), and confirmed by LC-MS and ^{1}HNMR. LCMS (ESI): RT = 0.681 min, mass calcd. for $C_{19}H_{17}F_3N_4O$ 374.14, m/z found 375.0 $[M+H]^+$. ^{1}HNMR (400MHz, DMSO-d_6) δ 8.81 (s, 1H), 7.58 - 7.47 (m, 6H), 7.26 - 7.18 (m, 1H), 7.13 - 7.06 (m, 2H), 6.84 (s, 1H), 3.60 - 3.51 (m, 4H).

Example 3: 2-(Methyl(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)amino)ethan-1-ol (Compound 3)



2-[(4-bromo-2-pyridyl)-methyl-amino]ethanol

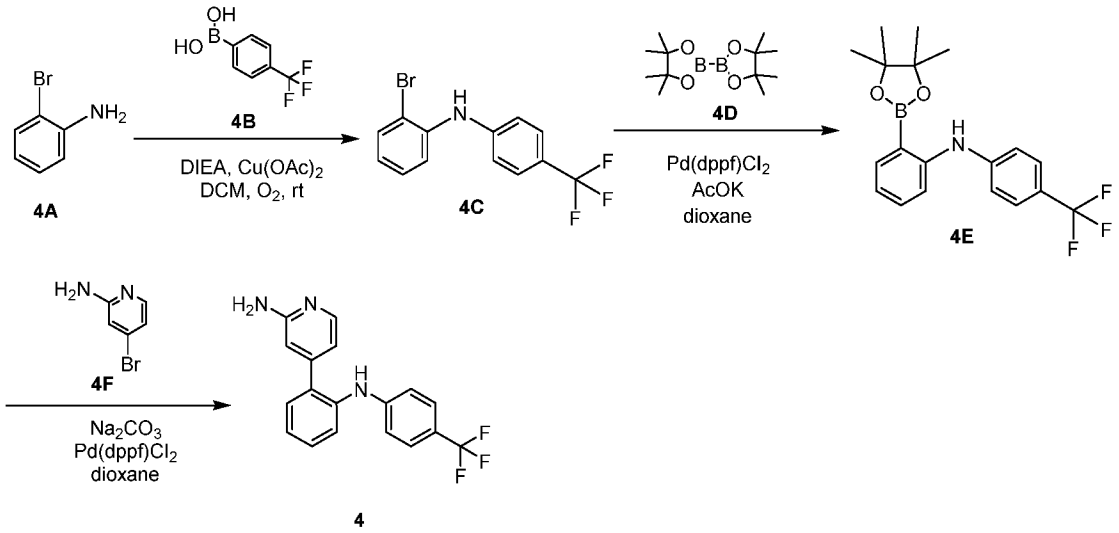
[00229] To a solution of 4-bromo-2-fluoropyridine (**1A**, 200.0 mg, 1.1 mmol, 1.0 *eq*) in DMF (5.0 mL) was added K_2CO_3 (315.1 mg, 2.3 mmol, 2.0 *eq*) and 2-(methylamino)ethan-1-ol. The reaction mixture was stirred at 80 °C for 16 hrs under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate=1/0 to 10/1 to give intermediate **3A** (100.0 mg, 0.46 mmol, 40.4% yield) as a colorless oil. LCMS (ESI): RT = 0.792 min, mass calc. for $C_8H_{11}BrN_2O$ 230.01m/z found 232.9 $[M+H+2]^+$; ^{1}HNMR (400 MHz, $CDCl_3$-*d*) δ 7.88 (d, *J* = 5.5 Hz, 1H), 6.75 - 6.68 (m, 2H), 3.87 - 3.81 (m, 2H), 3.75 - 3.70 (m, 2H), 3.06 (s, 3H).

2-[methyl-[4-[2-[4-(trifluoromethyl)anilino]phenyl]-2-pyridyl]amino]ethanol

[00230] To a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (intermediate **4E**, 100.0 mg, 0.14mmol, 1.0 *eq*) and intermediate **3A** (38.2 mg, 0.16 mmol, 1.2 *eq*) in dioxane (5.0 mL) was added H_2O (0.5 mL) $Pd(dppf)Cl_2$ (10.1

mg, 13.8 μmol, 0.1 *eq*) and Na_2CO_3 (29.2 mg, 0.28 mmol, 2.0 *eq*). The reaction mixture was stirred at 100 °C for 16 hrs under N_2 atmosphere. The reaction was filtered through celite and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (Condition: water(0.05%HCl)-ACN. Column:Phenomenex Gemini 150x25mmx10um. Begin B:26. End B:56) to give **Compound 3** (21.18 mg, 39.32% yield) as a white solid. LCMS (ESI): RT = 0.714 min, mass calc. for $C_{21}H_{20}F_3N_3O$ 387.16, m/z found 388.1 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 7.89 (d, J = 6.5 Hz, 1H), 7.56 - 7.49 (m, 2H), 7.43 (d, J = 8.5 Hz, 3H), 7.32 (t, J = 7.3 Hz, 1H), 7.27 (s, 1H), 6.92 - 6.85 (m, 3H), 3.73 (d, J = 4.3 Hz, 2H), 3.63 (d, J = 4.3 Hz, 2H), 3.22 (s, 3H).

Example 4: 4-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine (Compound 4)



2-bromo-N-[4-(trifluoromethyl)phenyl]aniline

[00231] To a solution of 2-bromoaniline (**4A**, 1.5 g, 8.72 mmol, 1 *eq*) and (4-(trifluoromethyl)phenyl)boronic acid (**4B**, 2.48 g, 13.08 mmol, 1.5 *eq*) in DCM (30.0 mL) was added DIEtOAc (4.5 g, 34.9 mmol, 6.1 mL, 4.0 *eq*) and $Cu(OAc)_2$ (2.38 g, 13.1 mmol, 1.5 *eq*). The reaction mixture was stirred at 20 °C for 16 hrs under O_2 atmosphere. The reaction mixture was filtered to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate=1/0 to 10/1 to give 2-bromo-N-[4-(trifluoromethyl)phenyl]aniline (0.5 g, 1.58 mmol, 18.14% yield) as a yellow oil. LCMS (ESI): RT = 0.844 min, mass calc. for $C_{13}H_9BrF_3N$ 314.99 m/z found 315.8 $[M+H]^+$.

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-[4-(trifluoromethyl)phenyl]aniline

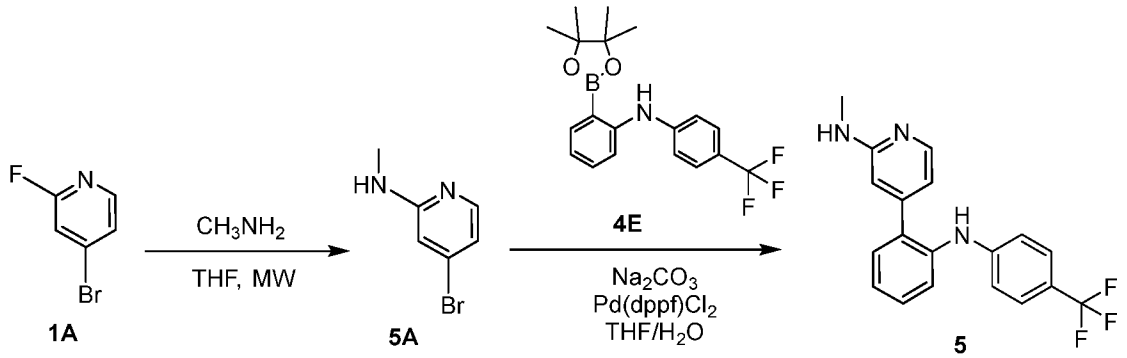
[00232] To a solution of 2compound **4C** (0.5 g, 1.58 mmol, 1 *eq*) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (**4D**, 0.44 g, 1.74 mmol, 1.1 *eq*) in dioxane (20 mL) was

added $Pd(dppf)Cl_2$ (0.12 g, 0.16 mmol, 0.1 *eq*) and AcOK (0.31 g, 3.16 mmol, 2.0 *eq*). The reaction mixture was stirred at 100 °C for 16 hrs under N_2 atmosphere. The reaction mixture was filtered through celite and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate=1/0 to 10/1 to give crude compound **4E** (0.34 g, 936.17 µmol, 59.19% yield) as a yellow solid. The residue was directly used without further purification. LCMS (ESI): RT = 0.957 min, mass calc. for $C_{19}H_{21}BF_3NO_2$ 363.16 m/z found 364.0 $[M+H]^+$.

4-[2-[4-(trifluoromethyl)anilino]phenyl]pyridin-2-amine

[00233] To a solution of compound **4E** (50 mg, 0.14 mmol, 1.0 *eq*) and 4-bromopyridin-2-amine (**4F**, 35.7 mg, 0.21 mmol, 1.5 *eq*) in dioxane (5.0 mL) was added H_2O (0.5 mL), $Pd(dppf)Cl_2$ (10.1 mg, 13.8 µmol, 0.1 *eq*) and Na_2CO_3 (29.2 mg, 0.28 mmol, 2.0 *eq*). The reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The reaction mixture was filtered through celite and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (Condition: water (0.05% ammonia hydroxide v/v)-ACN. Column: Waters Xbridge 150x25 5u. Begin B:45. End B:75) to give the **Compound 4** (6 .51 mg, 13.64% yield) was obtained as a white solid. LCMS (ESI): RT = 0.678 min, mass calc. for $C_{18}H_{14}F_3N_3$ 329.11, m/z found 329.9 $[M+H]^+$; ^{1}HNMR (400 MHz, $CDCl_3$-*d*) δ 8.12 (d, *J* = 5.0 Hz, 1H), 7.50 - 7.43 (m, 3H), 7.39 - 7.33 (m, 1H), 7.31 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.17 - 7.12 (m, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.69 (dd, *J* = 1.3, 5.3 Hz, 1H), 6.53 (s, 1H), 5.72 (s, 1H), 4.50 (s, 2H).

Example 5: *N*-methyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine (Compound 5)



4-bromo-N-methyl-pyridin-2-amine

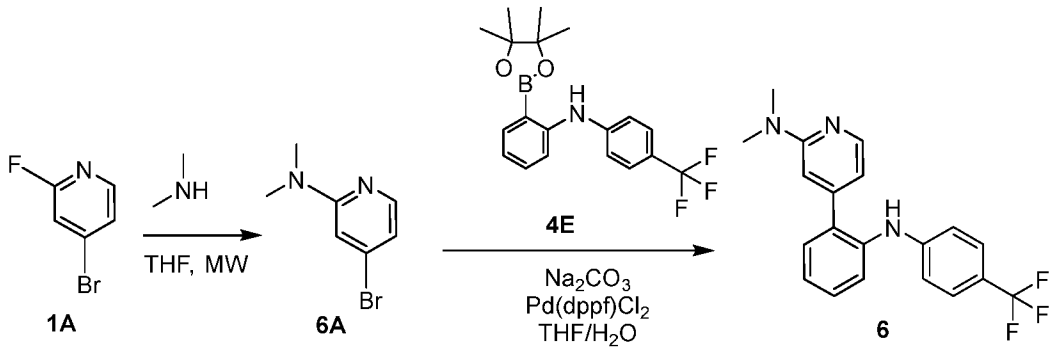
[00234] 4-Bromo-2-fluoropyridine (**1A**, 0.1 g, 0.5 mmol, 1.0 *eq*) and methylamine (2 M, 1.14 mL, 4.0 *eq*) were taken up into a microwave tube in THF (1.0 mL). The sealed tube was heated at 70 °C for 0.5 hr under microwave. The reaction mixture was filtered to give a crude

product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate=1/0 to 10/1 to give intermediate **5A** (6 0 mg, 0.32 mmol, 56.5% yield) as a white solid. LCMS (ESI): RT = 2.482 min, mass calc. for $C_6H_7BrN_2$ 185.98 m/z found 188.9 $[M+H+2]^+$.

N-methyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyridin-2-amine

[00235] To a solution of intermediate **4E** (50 mg, 0.14 mmol, 1.0 *eq*) and intermediate **5A** (38.6 mg, 0.21 mmol, 1.5 *eq*) in dioxane (5.0 mL) was added H_2O (0.5 mL), $Pd(dppf)Cl_2$ (10.1 mg, 13.8 µmol, 0.1 *eq*) and Na_2CO_3 (29.2 mg, 0.28 mmol, 2.0 *eq*). The reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The crude product was purified by prep-HPLC (Condition: water (0.05% ammonia hydroxide v/v)-acetonitrile. Column: Waters Xbridge 150x25 5u. Begin B:48. End B:78) to give **Compound 5** (1.94 mg, 4.10% yield) as a white solid. LCMS (ESI): RT = 0.685 min, mass calc. for $C_{19}H_{16}F_3N_3$ 343.13, m/z found 343.9 $[M+H]^+$; ^{1}HNMR (400 MHz, $CDCl_3$-*d*) δ 8.13 (d, *J* = 5.3 Hz, 1H), 7.50 - 7.42 (m, 3H), 7.40 - 7.31 (m, 2H), 7.17 - 7.11 (m, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.61 (dd, *J* = 1.4, 5.1 Hz, 1H), 6.38 (s, 1H), 5.75 (s, 1H), 4.62 (d, *J* = 4.0 Hz, 1H), 2.89 (d, *J* = 5.3 Hz, 3H).

Example 6: *N,N*-Dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine (Compound 6)



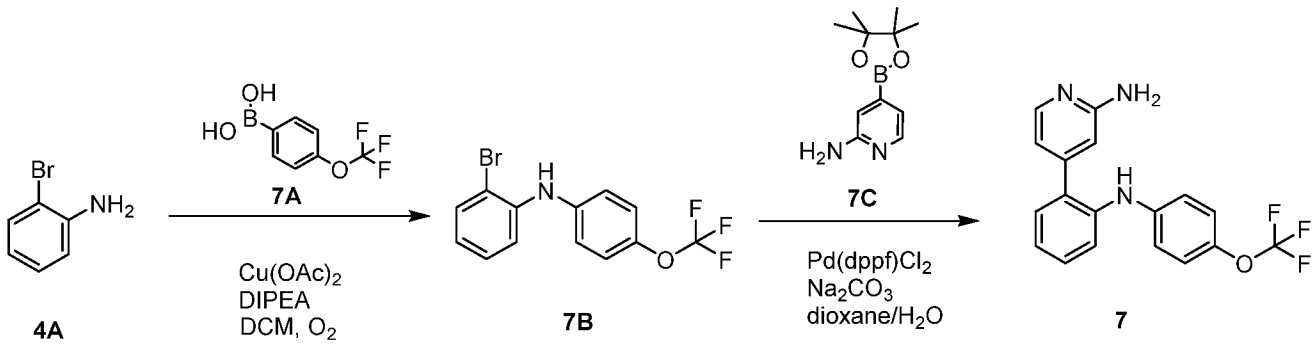
4-bromo-N,N-dimethyl-pyridin-2-amine

[00236] 4-Bromo-2-fluoropyridine (**1A**, 0.1 g, 0.57 mmol, 1.0 *eq*) and dimethylamine (0.31 g, 2.3 mmol, 4.0 *eq*) were taken up into a microwave tube in THF (1 mL) and H_2O (1 mL). The sealed tube was heated at 70 °C for 0.5 hr under microwave. The reaction mixture was filtered to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate=1/0 to 10/1 to give intermediate **6A** (6 0 mg, 0.32 mmol, 56.5% yield) as a white solid. LC-MS (ESI): RT = 0.991 min, mass calc. for C_7H9BrN_2 199.99 m/z found 202.9 $[M+H+2]^+$.

N,N-dimethyl-4-[2-[4-(trifluoromethyl)anilino]phenyl]pyridin-2-amine

[00237] To a solution of compound **4E** (50 mg, 0.14 mmol, 1.0 *eq*) and intermediate **6A** (41.5 mg, 0.21 mmol, 1.5 *eq*) in dioxane (5.0 mL) was added H_2O (500.00 uL), $Pd(dppf)Cl_2$ (10.1 mg, 13.8 µmol, 0.1 *eq*), and Na_2CO_3 (29.2 mg, 0.28 mmol, 2.0 *eq*). The reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The crude product was purified by prep-HPLC (Condition: water (0.05% ammonia hydroxide v/v)-ACN. Column: Waters Xbridge 150x25 5u. Begin B: 55. End B: 75) to give **Compound 6** (8.90 mg, 17.91% yield) as a white solid. LCMS (ESI): RT = 0.683 min, mass calc. for $C_{20}H_{18}F_3N_3$ 357.15, m/z found 358.0 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.12 - 7.98 (m, 2H), 7.48 - 7.34 (m, 5H), 7.32 - 7.24 (m, 1H), 6.83 (br d, *J*=8.3 Hz, 2H), 6.57 (s, 2H), 2.93 (s, 6H).

Example 7: 4-(2-((4-(Trifluoromethoxy)phenyl)amino)phenyl)pyridin-2-amine (Compound 7)



2-bromo-N-(4-(trifluoromethoxy)phenyl)aniline

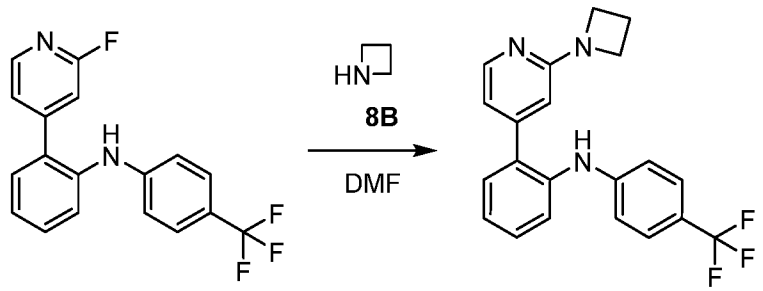
[00238] To a solution of compound **4A** (1 g, 5.81 mmol, 1 *eq*) in DCM (10 mL) were added $Cu(OAc)_2$ (1.58 g, 8.72 mmol, 1.5 *eq*), DIPEtOAc (1.50 g, 11.63 mmol, 2.0 mL, 2 *eq*) and (4-(trifluoromethoxy)phenyl)boronic acid (**7A**, 1.80 g, 8.72 mmol, 1.5 *eq*). The reaction mixture was stirred at 25 °C for 16 hrs under O_2 (15 psi) atmosphere. The reaction mixture was filtered, and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient). Intermediate **7B** (900 mg, 2.2 mmol, 38.2% yield) was obtained as a light yellow oil. LCMS (ESI): RT = 0.943 min, mass calcd. for $C_{13}H_9BrF_3NO$ 330.98, m/z found 333.9 $[M+H]^+$.

4-(2-((4-(trifluoromethoxy)phenyl)amino)phenyl)pyridin-2-amine

[00239] To a solution of intermedaite **7B** (80 mg, 0.24 mmol, 1 *eq*) in dioxane (5 mL) and H_2O (1 mL) were added $Pd(dppf)Cl_2$ (8.8 mg, 12.0 µmol, 0.05 *eq*), Na_2CO_3 (51.0 mg, 0.48 mmol, 2 *eq*) and 4-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (**7C**, 79.5 mg, 0.36 mmol, 1.5 *eq*). The reaction mixture was stirred at 90 °C for 2 hrs. The reaction mixture was filtered, and the filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (column: Waters

Xbridge 150x25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 55%-85%, 6.5min). **Compound 7** was obtained as a yellow solid (7.28 mg, 21.1 µmol, 8.8% yield). LCMS (ESI): RT = 0.722 min, mass calcd. for $C_{18}H_{14}F_3N_3O$ 345.11, m/z found 345.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 5.8 Hz, 1H), 7.35 (d, *J* = 3.8 Hz, 2H), 7.29 - 7.28 (m, 1H), 7.27 - 7.25 (m, 1H), 7.14 - 7.11 (m, 1H), 7.15 - 7.10 (m, 1H), 7.10 - 7.06 (m, 1H), 7.10 - 7.06 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 4.8 Hz, 1H), 6.75 (s, 1H), 5.67 (s, 2H).

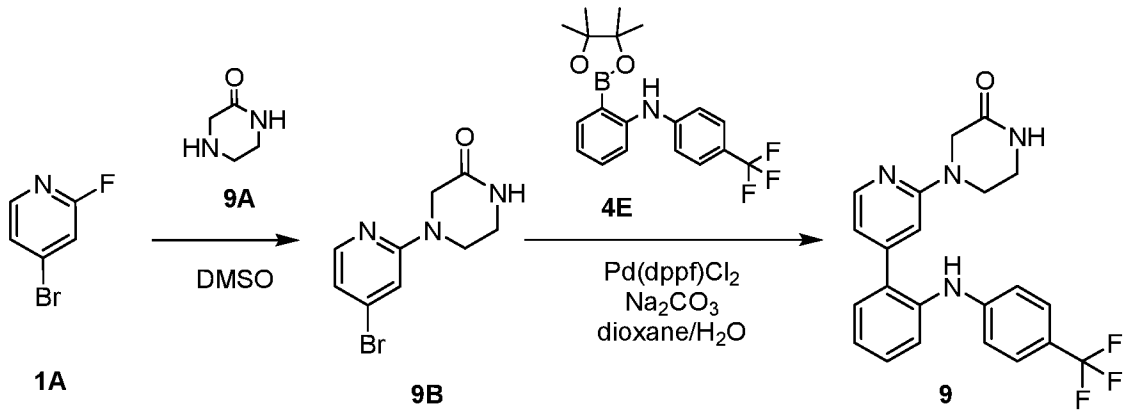
Example 8: 2-(2-(Azetidin-1-yl)pyridin-4-yl)-N-(4-(trifluoromethyl)phenyl)aniline (Compound 8)



8A **8**

[00240] A solution of 2-(2-fluoropyridin-4-yl)-N-(4-(trifluoromethyl)phenyl)aniline (**8A**, 30 mg, 90 µmol, 1.0 *eq*) and azetidine (**8B**, 26 mg, 0.45 mmol, 5 *eq*) in DMF (1 mL) was stirred at 100 °C for 6 hrs. The reaction mixture was concentrated under reduced pressure. The reaction mixture was diluted with water (30 mL) and the resultant mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge 150x25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 60%-90%, 9.5min) to obtain a crude product. The crude product **Compound 8** was purified by prep-HPLC (column: Xtimate C18 150x25mmx5um; mobile phase: [water (0.05%HCl)-ACN]; B%: 30%-60%, 6.5min) to obtain **Compound 8** (5.40 mg, 14% yield) as a yellow solid. LCMS (ESI): RT = 0.878 min, mass calcd. For $C_{21}H_{18}F_3N_3$ 369.15, m/z found 370.4 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.91 - 7.86 (m, 1H), 7.57 - 7.50 (m, 2H), 7.48 - 7.42 (m, 3H), 7.36 - 7.29 (m, 1H), 6.91 - 6.81 (m, 4H), 4.24 (t, *J*=7.7 Hz, 4H), 2.47 - 2.39 (m, 2H).

Example 9: 4-(4-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)piperazin-2-one (Compound 9)



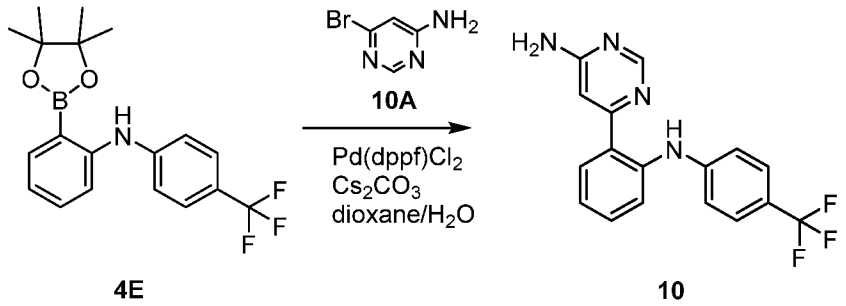
4-(4-Bromopyridin-2-yl)piperazin-2-one

[00241] A solution of compound **1A** (100 mg, 0.568 mmol, 1.0 *eq*) and piperazin-2-one (**9A**, 171 mg, 1.70 mmol, 3.0 *eq*) in DMSO (1 mL) was stirred at 120 °C for 2 hrs. The reaction mixture was diluted with water (20 mL) and the resulting mixture was extracted with EtOAc (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure to affording intermediate **9B** (110 mg, 76% yield) as a light yellow solid.

4-(4-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)piperazin-2-one

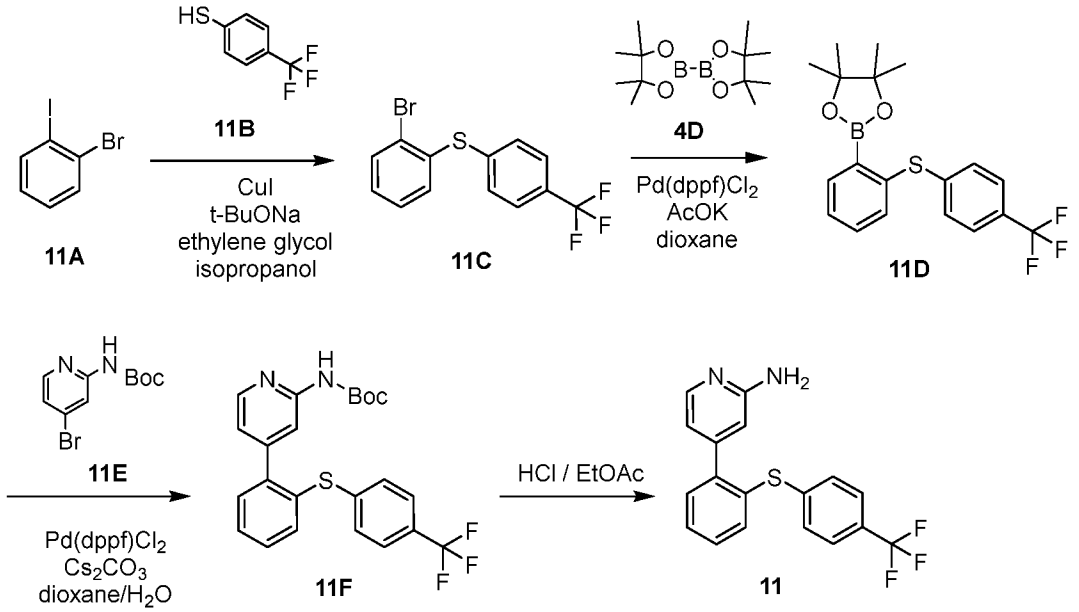
[00242] To a solution of intermediate **4E** (50 mg, 0.14 μmol, 1.0 *eq*), intermediate **9B** (35 mg, 0.14 mmol, 1.0 *eq*), Na_2CO_3 (29 mg, 0.28 mmol, 2.0 *eq*) in dioxane (2 mL) and H_2O (0.4 mL) was added Pd(dppf)Cl_2 (5.0 mg, 6.9 μmol, 0.05 *eq*) under N_2. The reaction suspension was degassed under vacuum and purged with N_2 several times. The reaction mixture was stirred under N_2 at 90°C for 3 hrs. The reaction mixture was concentrated under reduced pressure. The reaction mixture was diluted with water (10 mL) and the resultant mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge 150x25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 45%-75%, 7.8 min) to afford **Compound 9** as a white solid (17.13 mg, 30% yield). LC-MS (ESI): RT = 0.701 min, mass calcd. For $C_{22}H_{19}F_3N_4O$ 412.15, m/z found 413.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.0 Hz, 1H), 7.52 - 7.43 (m, 3H), 7.43 - 7.37 (m, 1H), 7.34 (dd, *J* = 1.3, 7.5 Hz, 1H), 7.22 - 7.16 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.77 - 6.72 (m, 1H), 6.59 (s, 1H), 6.35 (s, 1H), 5.73 (s, 1H), 4.14 (s, 2H), 3.87 (t, *J* = 5.3 Hz, 2H), 3.53 - 3.47 (m, 2H).

Example 10: 6-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)pyrimidin-4-amine (Compound 10)



[00243] To a solution of intermediate **4E** (100 mg, 0.27 mmol, 1.0 eq) in dioxane (5 mL) and H_2O (1 mL) were added $Pd(dppf)Cl_2$ (10.0 mg, 13.7 μmol, 0.05 eq), Cs_2CO_3 (179.4 mg, 0.55 mmol, 2.0 eq) and 6-bromopyrimidin-4-amine (**10A**, 71.8 mg, 0.41 mmol, 1.5 eq). The reaction mixture was stirred at 90 °C for 16 hrs. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (column: Waters Xbridge 150x25 5u;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 50%-80%,9.5min). **Compound 10** was obtained as a yellow solid (14.86 mg, 16.34% yield). LC-MS (ESI): RT = 0.679 min, mass calcd. for $C_{17}H_{13}F_3N_4$ 330.11, m/z found 330.9 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 10.44 (br s, 1H), 8.66 (s, 1H), 7.59 (d, *J* = 6.5 Hz, 1H), 7.50 (dd, *J* = 8.5, 11.5 Hz, 4H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.03 - 6.98 (m, 1H), 6.77 (s, 1H), 4.95 (br s, 2H).

Example 11: 4-(2-((4-(Trifluoromethyl)phenyl)thio)phenyl)pyridin-2-amine (Compound 11)



(2-bromophenyl)(4-(trifluoromethyl)phenyl)sulfane

[00244] The mixture of 1-bromo-2-iodo-benzene (**11A**, 2 g, 7.07 mmol, 0.90 mL, 1 *eq*), 4-(trifluoromethyl)benzenethiol (**11B**, 1.26 g, 7.07 mmol, 1 *eq*), ethylene glycol (877.6 mg, 14.14 mmol, 0.79 mL, 2 *eq*), CuI (134.6 mg, 0.70 mmol, 0.1 *eq*) and t-BuONa (1.36 g, 14.14 mmol, 2

eq) in isopropanol (2 mL) was stirred at 90 °C under N_2 for 16 hrs. The reaction mixture was diluted with H_2O (6 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0). Intermediate **11C** (was obtained as colorless oil 2 g, 6.00 mmol, 84.9% yield) .

4,4,5,5-tetramethyl-2-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)-1,3,2-dioxaborolane

[00245] A mixture of intermediate **11C** (1 g, 3.00 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 1.14 g, 4.50 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (109.8 mg, 0.15 mmol, 0.05 *eq*) and AcOK (589.1 mg, 6.00 mmol, 2 *eq*) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 3 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (15 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 5:1). Intermediate **11D** was obtained as yellow oil (6 00 mg, 1.58 mmol, 52.5% yield) .

tert-butyl (4-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)pyridin-2-yl)carbamate

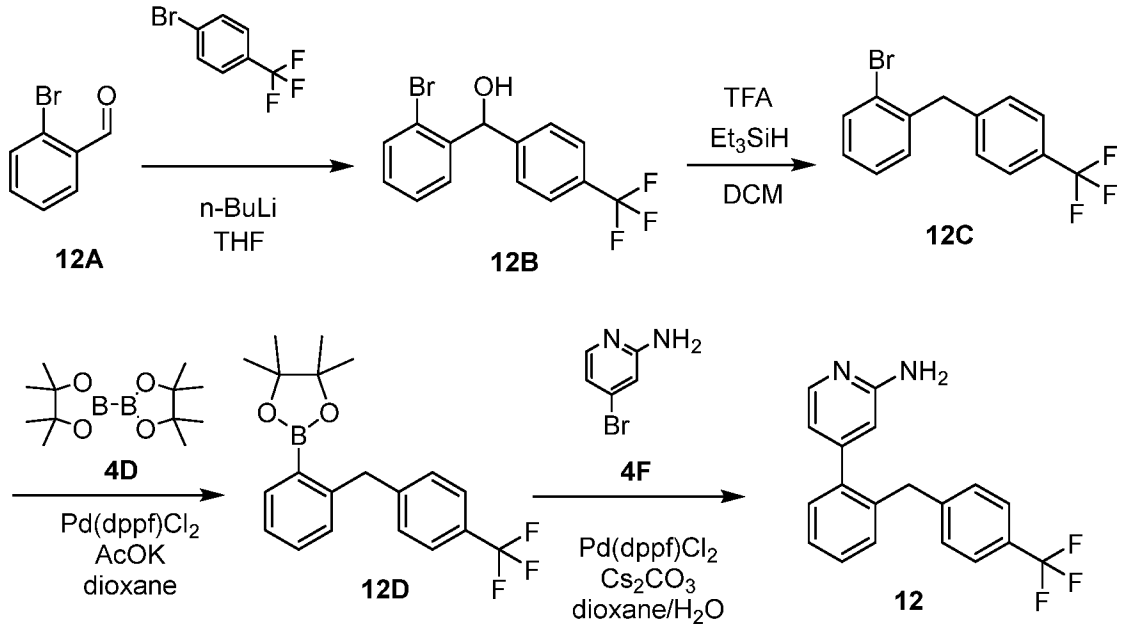
[00246] The mixture of intermediate **11D** (50 mg, 0.13 mmol, 1 *eq*), tert-butyl N-(4-bromo-2-pyridyl)carbamate (**11E**, 35.9 mg, 0.13 mmol, 1 *eq*), Cs_2CO_3 (85.6 mg, 0.26 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (4.8 mg, 6.5 μmol, 0.05 *eq*) in dioxane (1 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 80 °C for 2 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (6 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 5:1). Intermediate **11F** was obtained as yellow oil (40 mg, 89.5 μmol, 68.1% yield).

4-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)pyridin-2-amine

[00247] The mixture of intermediate **11F** (40 mg, 89.5 μmol, 1 *eq*) in HCl/dioxane (2 mL) was stirred at 50 °C for 1 hr. The reaction mixture was diluted with H_2O (5 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The

residue was purified by prep-HPLC (column: Xtimate C18 150x25mmx5um;mobile phase: [water(0.05%HCl)-ACN];B%: 28%-58%,7.8min). **Compound 11** (8 mg, 25.5% yield) was obtained as a yellow solid. LC-MS (ESI): RT = 0.828 min, mass calc. for $C_{18}H_{13}F_3N_2S$ 346.37, m/z found 347.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ = 8.08 - 8.04 (m, 1H), 8.06 (br s, 1H), 7.94 (d, *J* = 6.5 Hz, 1H), 7.64 - 7.59 (m, 1H), 7.65 - 7.59 (m, 4H), 7.55 - 7.49 (m, 1H), 7.25 (br d, *J* = 8.1 Hz, 2H), 6.89 - 6.80 (m, 2H).

Example 12: 4-(2-(4-(trifluoromethyl)benzyl)phenyl)pyridin-2-amine (Compound 12)



(2-bromophenyl)-[4-(trifluoromethyl)phenyl]methanol

[00248] To a solution of 2-bromobenzaldehyde (**12A**, 10.9 g, 48.6 mmol, 6.7 mL, 1 *eq*) in THF (200 mL) was added drop-wise n-BuLi (2.5 M, 17.5 mL, 0.9 *eq*) at -78°C. After addition, the reaction mixture was stirred at this temperature for 1 hr, and then 1-bromo-4-(trifluoromethyl)benzene (9 g, 48.6 mmol, 5.6 mL, 1 *eq*) in THF (30 mL) was added dropwise at -78 °C. And the reaction mixture was allowed to warm to 20 °C was stirred for 2 hrs. The residue was poured into NH_4Cl (300 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (150 mL x 3). The combined organic phase was washed with brine (250 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (120 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~10%) to afford intermediate **12B** as a colorless oil (23.8 g, 71.9 mmol, 73.9% yield).

1-bromo-2-[[4-(trifluoromethyl)phenyl]methyl]benzene

[00249] To a solution of intermediate **12B** (10 g, 30.2 mmol, 1 *eq*) in DCM (200 mL) was added dropwise TFA (13.8 g, 120.8 mmol, 8.94 mL, 4 *eq*) at 0 °C under N_2. After addition, the reaction mixture was stirred at this temperature for 0.5 hr, and then Et_3SiH (7.02 g, 60.4 mmol, 9.6 mL, 2 *eq*) was added dropwise at 0 °C. The resulting mixture was stirred at 50 °C for 15.5 hrs. The residue was poured into H_2O (300 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (150 mL x 3). The combined organic phase was washed with brine (250 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (120 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~1%) to give intermediate **12C** (15.2 g, 48.2 mmol, 79.8% yield) as a colorless oil.

4,4,5,5-tetramethyl-2-[2-[[4-(trifluoromethyl)phenyl]methyl]phenyl]-1,3,2-dioxaborolane

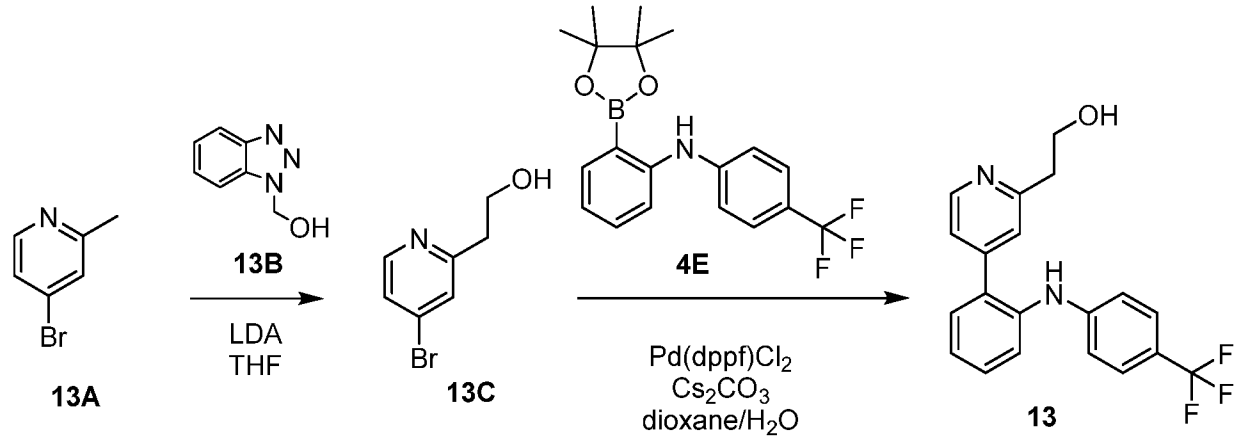
[00250] A mixture of intermediate **12C** (3 g, 9.5 mmol, 1 *eq*), compound **4D** (3.6 g, 14.3 mmol, 1.5 *eq*) , KOAc (1.9 g, 19.0 mmol, 2 *eq*) , $Pd(dppf)Cl_2$ (348.3 mg, 0.5 mmol, 0.05 *eq*) in dioxane (30 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 3 hr under N_2 atmosphere. The reaction mixture was poured into H_2O (50 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (40 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~5%) to give intermediate **12D** (1.85 g, 5.1 mmol, 53.6% yield) as a yellow oil.

4-[2-[[4-(trifluoromethyl)phenyl]methyl]phenyl]pyridin-2-amine

[00251] A mixture of intermediate **12D** (180 mg, 0.5 mmol, 1 *eq*), compound **4F** (90.3 mg, 0.5 mmol, 1.05 *eq*), Cs_2CO_3 (161.9 mg, 0.5 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (18.2 mg, 24.9 μmol, 0.05 *eq*) in dioxane (10 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 110 °C for 3 hr under N_2 atmosphere. The reaction mixture was poured into H_2O (100 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Xtimate C18 150x25mmx5um; mobile phase: [water (0.05%HCl)-ACN]; B%: 25%-55%, 7.8 min) to give **Compound 12** as a white solid (48.3 mg, 26.1% yield, HCl). LC-MS (ESI): RT = 0.72 min, mass calc. for $C_{19}H_{15}F_3N_2$ 328.1, m/z found 328.9 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.15 (s, 2H), 7.96 (d, J = 6.5 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.50 - 7.44

(m, 1H), 7.44 - 7.38 (m, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.29 (dd, *J* = 1.3, 7.5 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.83 (s, 1H), 6.78 (dd, *J* = 1.4, 6.7 Hz, 1H), 4.11 (s, 2H).

Example 13: 2-(4-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)ethan-1-ol (Compound 13)



2-(4-bromopyridin-2-yl)ethanol

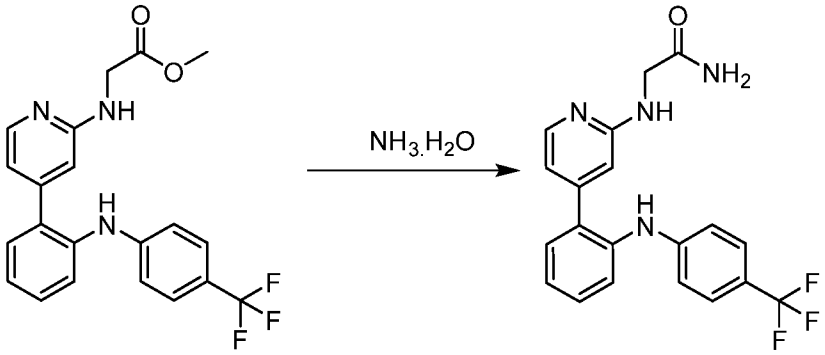
[00252] To a solution of 4-bromo-2-methyl-pyridine (**13A**, 1.8 g, 10.46 mmol, 1 *eq*) in THF (20 mL) was added dropwise LDA (2 M, 6.28 mL, 1.2 *eq*) at -78 °C under N_2. After addition, the reaction mixture was stirred at this temperature for 1 hr, and then benzotriazol-1-ylmethanol (**13B**, 1.87 g, 12.56 mmol, 1.2 *eq*) was added at -78 °C. The resulting reaction mixture was stirred at -78 °C for 2 hrs and the reaction mixture was warmed to 0 °C was stirred for 1 hr. The residue was poured into H_2O (60 mL) and stirred for 5 min. The aqueous phase was extracted with EtAOc (30 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (20 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~50%). Intermediate **13C** (0.65 g, 3.22 mmol, 30.7% yield) was obtained as a yellow solid.

2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)ethanol

[00253] A mixture of intermediate **4E** (200 mg, 0.55 mmol, 1 *eq*), intermediate **13C** (133.5 mg, 0.66 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (20.1 mg, 27.5 μmol, 0.05 *eq*), Cs_2CO_3 (358.85 mg, 1.10 mmol, 2 *eq*) in dioxane (5 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 110 °C for 3 hr under N_2 atmosphere. The reaction mixture was poured into H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (10 mL x 3).The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Xtimate C18 150x25mmx5um;mobile phase: [water(0.05%HCl)-ACN];B%: 18%-48%,5.5min).

Compound 13 was obtained as a yellow solid (53.2 mg, 24.0% yield, HCl). LC-MS (ESI): RT = 0.696 min, mass calcd for $C_{20}H_{17}F_3N_2O$ 358.36, m/z found 359.0 $[M+H]^+$, ^1H NMR (400MHz, METHANOL-d_4) δ = 8.62 (d, *J* = 6.3 Hz, 1H), 8.12 (d, *J* = 1.8 Hz, 1H), 8.03 (dd, *J* = 1.8, 6.3 Hz, 1H), 7.61 (ddd, *J* = 1.4, 7.7, 14.1 Hz, 2H), 7.55 - 7.50 (m, 1H), 7.44 - 7.35 (m, 3H), 6.90 (d, *J* = 8.5 Hz, 2H), 3.92 (t, *J* = 5.9 Hz, 2H), 3.19 (t, *J* = 5.9 Hz, 2H).

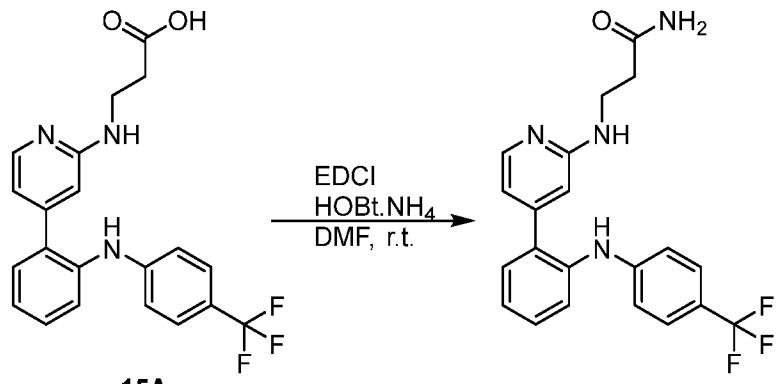
Example 14: 2-((4-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)amino)acetamide (Compound 14)



14A **14**

[00254] To a solution of methyl 2-[[4-[2-[4-(trifluoromethyl)anilino]phenyl]-2-pyridyl]amino]acetate (**14A**, 20 mg, 49.8 μmol, 1 *eq*) in $NH_3.H_2O$ (1 mL) was stirred at 80 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Xtimate C18 150x25mmx5um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 45%-75%,7.8min). **Compound 14** was obtained as a white solid (1.1 mg, 5.7% yield). LC-MS (ESI): RT = 0.701 min, mass calc. for $C_{20}H_{17}F_3N_4O$ 386.37, m/z found 386.9 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d_4) δ = 7.95 (d, *J* = 5.5 Hz, 1H), 7.44 - 7.35 (m, 5H), 7.27 - 7.21 (m, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.69 (dd, *J* = 1.4, 5.4 Hz, 1H), 6.66 (s, 1H), 3.94 (s, 2H).

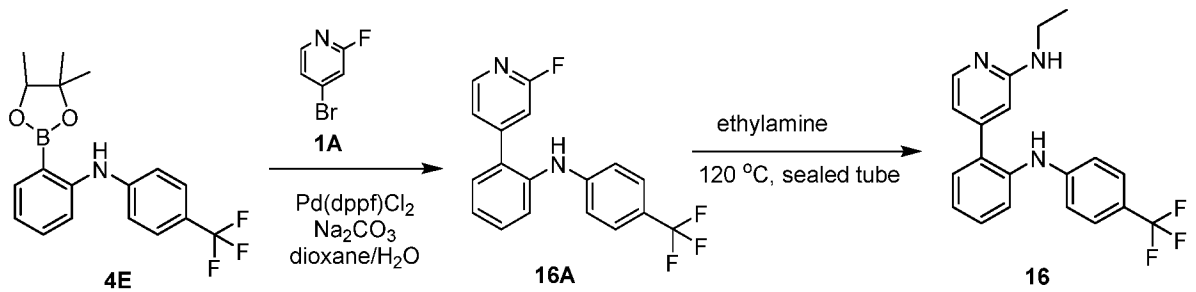
Example 15: 3-((4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)amino)propanamide (Compound 15)



15A 15

[00255] To a solution of 3-[[4-[2-[4-(trifluoromethyl)anilino]phenyl]-2-pyridyl]amino]propanoic acid (**15A**, 10 mg, 24.9 µmol, 1 *eq*) in DMF (1 mL) was added ammonium;1-oxidobenzotriazole (HOBt.NH4) (7.5 mg, 49.8 µmol, 2 *eq*) and EDCI (14.3 mg, 74.7 µmol, 3 *eq*). The reaction mixture was stirred at 25 °C for 1 hr. The reaction mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (7 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Xtimate C18 150 x 25mm x 5um; mobile phase: [water(0.05%HCl)-ACN]; B%: 20%-50%,7min). The residue was re-purified by prep-HPLC (column: Waters Xbridge 150x25 5u;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 45%-85%,7.8min). **Compound 15** was obtained as a white solid (1.8 mg, 18.4% yield). LC-MS (ESI): RT = 0.704 min, mass calc. for $C_{21}H_{19}F_3N_4O$ 400.40, m/z found 400.9 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d_4) δ = 7.91 (d, *J* = 5.4 Hz, 1H), 7.44 - 7.34 (m, 4H), 7.44 - 7.34 (m, 1H), 7.28 - 7.21 (m, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.66 - 6.59 (m, 2H), 3.53 (t, *J* = 6.8 Hz, 2H), 2.48 (t, *J* = 6.8 Hz, 2H).

Example 16: N-ethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine (Compound 16)



4E 16A 16

2-(2-fluoropyridin-4-yl)-N-(4-(trifluoromethyl)phenyl)aniline

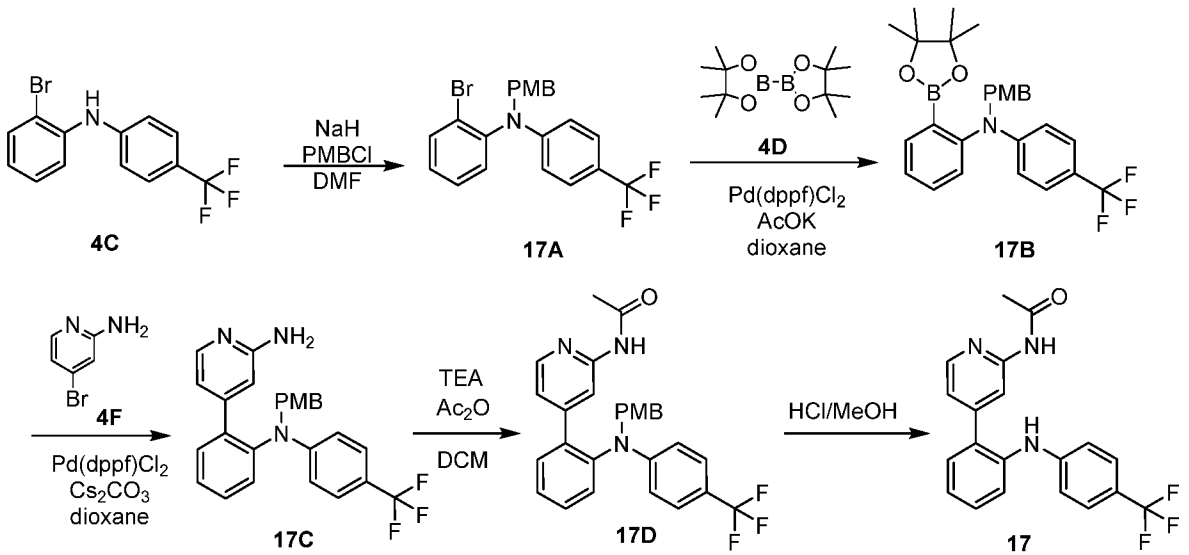
[00256] A mixture of intermediate **4E** (12 g, 33.04 mmol, 1 *eq*), 4-bromo-2-fluoro-pyridine (**1A**, 8.72 g, 49.56 mmol, 1.5 *eq*), Na_2CO_3 (7.00 g, 66.08 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (1.21 g, 1.65 mmol, 0.05 *eq*) in dioxane (150 mL) and H_2O (30 mL) was degassed and purged with N_2 for 3

times, and then the reaction mixture was stirred at 110 °C for 16 hr under N_2 atmosphere. The reaction mixture was poured into H_2O (150 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (80 mL x 3). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (330 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~20%). Intermediate **16A** (3.8 g, 11.44 mmol, 34.61% yield) was obtained as a yellow solid.

N-ethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine

[00257] To a solution of intermediate **16A** (150 mg, 0.45 mmol, 1 *eq*) in dioxane (0.5 mL) was added ethanamine (203.5 mg, 4.51 mmol, 0.29 mL, 10 *eq*) in a sealed tube. The reaction mixture was stirred at 120 °C for 16 hrs. The reaction mixture was poured into H_2O (20 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Xtimate C18 150 x 25mm x 5um; mobile phase: [water(0.05%HCl)-ACN]; B%: 30%-55.5%,9.5min). **Compound 16** was obtained as a yellow solid (34.6 mg, 19.5% yield, HCl). LC-MS (ESI): RT = 0.753 min, mass calcd for $C_{20}H_{18}F_3N_3$ 357.37, m/z found 358.0 $[M+H]^+$, ^1H NMR (400MHz, METHANOL-d_4) δ = 7.74 (d, J = 6.8 Hz, 1H), 7.56 - 7.44 (m, 3H), 7.40 (d, J = 8.5 Hz, 2H), 7.36 - 7.30 (m, 1H), 7.08 (d, J = 1.0 Hz, 1H), 6.96 (dd, J = 1.6, 6.8 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 3.40 - 3.35 (m, 2H), 1.32 (t, J = 7.3 Hz, 3H).

Example 17: N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)acetamide (Compound 17)



2-bromo-N-(4-methoxybenzyl)-N-(4-(trifluoromethyl)phenyl)aniline

[00258] To a solution of intermediate **4C** (1 g, 3.16 mmol, 1 *eq*) in DMF (10 mL) was added NaH (151.8 mg, 3.80 mmol, 60%, 1.2 *eq*) at 0 °C under N_2. After addition, the reaction mixture was stirred at 0°C for 1 hr, and then PMB-Cl (594.5 mg, 3.80 mmol, 0.51 mL, 1.2 *eq*) in DMF (5 mL) was added dropwise at 0°C. The resulting mixture was stirred at 20 °C for 2 hrs. The reaction mixture was poured into NH_4Cl (50 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (40 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~20%). Intermediate **17A** (920 mg, 2.11 mmol, 66.6% yield) was obtained as a colorless oil.

N-(4-methoxybenzyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00259] A mixture of intermediate **17A** (700 mg, 1.60 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 11.1 mg, 2.41 mmol, 1.5 *eq*), Pd(dppf)Cl_2 (58.7 mg, 80.2 μmol, 0.05 *eq*), AcOK (314.9 mg, 3.21 mmol, 2 *eq*) in dioxane (6 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 3 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mLx2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 20/1). Intermediate **17B** (300 mg, 0.62 mmol, 38.6% yield) was obtained as yellow oil.

4-(2-((4-methoxybenzyl)(4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine

[00260] The mixture of intermediate **17B** (300 mg, 0.62 mmol, 1 *eq*), 4-bromopyridin-2-amine (**4F**, 128.8 mg, 0.74 mmol, 1.2 *eq*), Cs_2CO_3 (404.4 mg, 1.24 mmol, 2 *eq*) and Pd(dppf)Cl_2 (22.7 mg, 31.0 μmol, 0.05 *eq*) in dioxane (3 mL) was stirred at 90 °C for 2 hrs. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (15 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 0/1). Intermediate **17C** (200 mg, 0.20 ,mmol, 32.2% yield) was obtained as yellow solid.

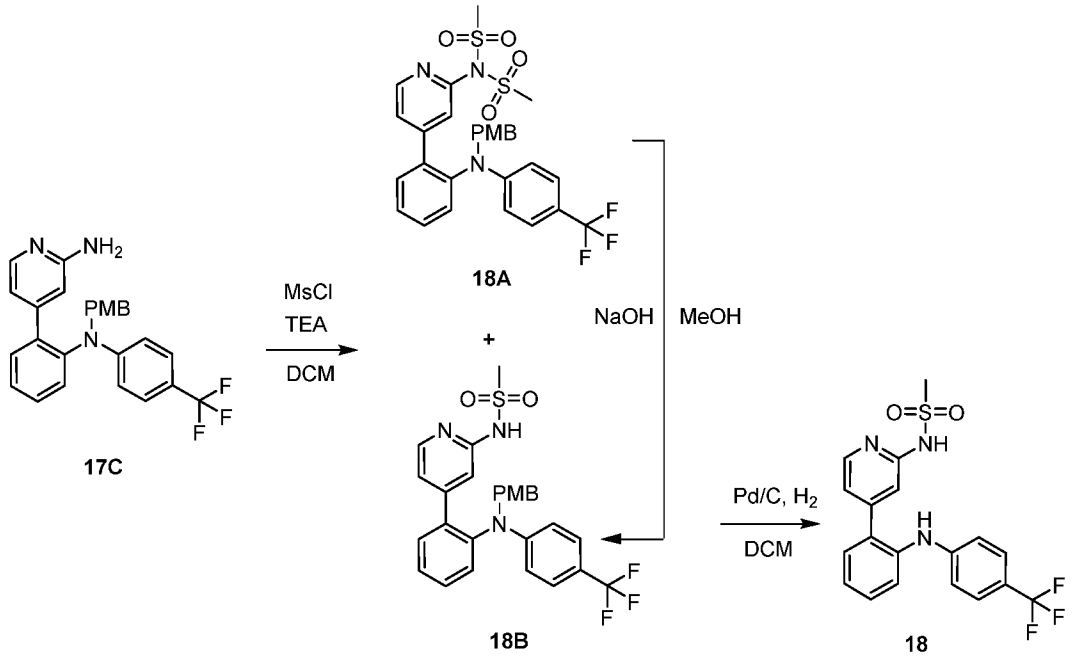
N-(4-(2-((4-methoxybenzyl)(4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)acetamide

[00261] The mixture of intermediate **17C** (100 mg, 0.22 mmol, 1 *eq*), TEA (67.5 mg, 0.66 mmol, 92.9 uL, 3 *eq*) and Ac_2O (34.0 mg, 0.33 mmol, 31.2 uL, 1.5 *eq*) in DCM (2 mL) was stirred at 50 °C for 2 hrs. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Intermediate **17D** (100 mg, crude) was obtained as yellow oil, which was used into the next step without further purification.

N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)acetamide

[00262] The mixture of crude intermediate **17D** (100 mg, 0.20 mmol, 1 *eq*) and HCl/MeOH (4 M, 50.8 uL, 1 *eq*) was stirred at 50 °C for 2 hrs. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was adjusted to pH of 9 with NaOH (4 M). The reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Xtimate C18 150 x 25mm x 5um; mobile phase: [water(0.225%FA)-ACN];B%: 47%-77%,7min). **Compound 17** was obtained as a white solid (10 mg, 11.6% yield, HCOOH). LC-MS (ESI): RT = 0.859 min, mass calcd for $C_{20}H_{16}F_3N_3O$ 371.36, m/z found 372.1 $[M+H]^+$, ^1H NMR (400MHz, METHANOL-d_4) δ = 8.23 - 8.17 (m, 2H), 7.45 - 7.42 (m, 3H), 7.33 (d, J = 8.5 Hz, 2H), 7.31 - 7.25 (m, 1H), 7.17 (dd, J = 1.5, 5.3 Hz, 1H), 6.83 (d, J = 8.5 Hz, 2H), 2.17 (s, 3H).

Example 18: N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)methanesulfonamide (Compound 18)



[00263] Methanesulfonyl chloride (0.34 g, 2.97 mmol, 0.22 mL, 13.34 *eq*) was added at the reaction mixture of intermediate **17C** (100 mg, 0.22 mmol, 1 *eq*) and TEA (6 7.5 mg, 0.66 mmol, 92.9 uL, 3 *eq*) in DCM (3 mL) was stirred at 0 °C. Then the reaction mixture was stirred at 25 °C for 16 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate= 1:1). A mixture of intermediates **18A** and **18B** (50 mg, 82.5 µmol, 37.1% yield) was obtained as yellow solid.

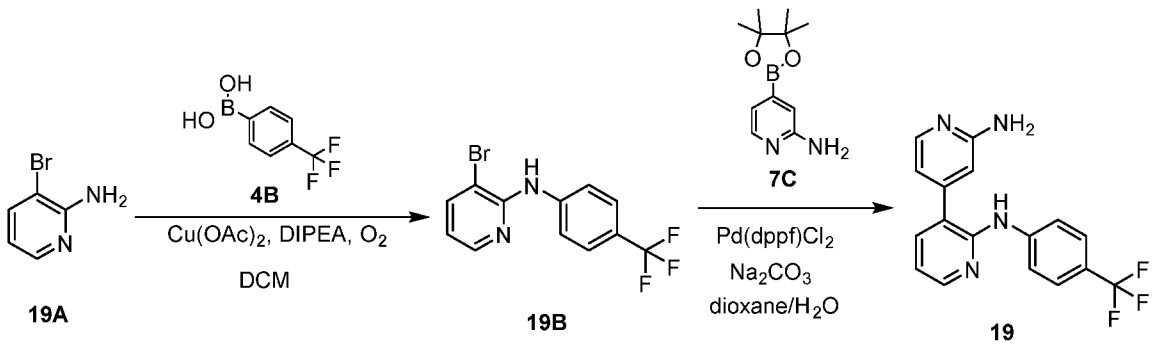
N-(4-(2-((4-methoxybenzyl)(4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)methanesulfonamide

[00264] The mixture of intermediates **18A** and **18B** (50 mg, 82.5 µmol, 1 *eq*) and NaOH (4 M, 20.64 uL, 1 *eq*) in MeOH (3 mL) was stirred at 40 °C for 20 min. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mLx3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Intermediate **18B** (50 mg, crude) was obtained as yellow solid, which was used into the next step without further purification.

N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)methanesulfonamide

[00265] The mixture of intermediate **18B** (80 mg, 0.15 mmol, 1 *eq*) and Pd/C (0.15 mmol, 40%, 1 *eq*) in DCM (5 mL) was degassed and purged with H_2 for 3 times, and then the reaction mixture was stirred at 25°C for 16 hr under H_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Xtimate C18 150 x 25mm x 5um;mobile phase: [water(0.05%HCl)-ACN];B%: 50%-80%,7.8min). **Compound 18** (8 mg, 11.7% yield, HCl) was obtained as a white solid. LCMS (ESI): RT = 0.913 min, mass calcd for $C_{19}H_{16}F_3N_3O_2S$ 407.41, m/z found 308.0 $[M+H]^+$, ^1H NMR (400MHz, METHANOL-d_4) δ = 8.13 (d, *J* = 5.9 Hz, 1H), 7.54 - 7.42 (m, 3H), 7.41 - 7.35 (m, 3H), 7.35 - 7.30 (m, 1H), 7.24 (dd, *J* = 1.4, 6.0 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.20 - 3.14 (m, 3H).

Example 19: N^2-(4-(trifluoromethyl)phenyl)-[3,4'-bipyridine]-2,2'-diamine (Compound 19)



3-bromo-*N*-(4-(trifluoromethyl)phenyl)pyridin-2-amine

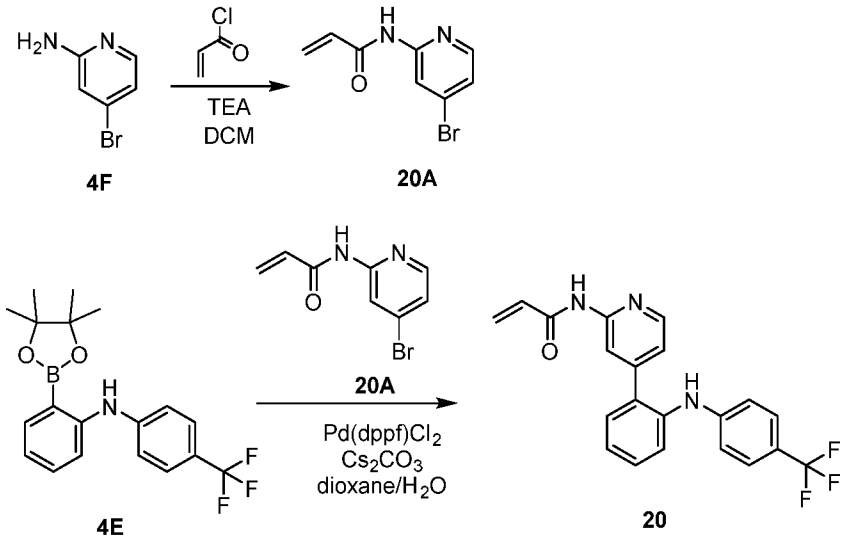
[00266] To a solution of intermediate **4B**, (8.2 g, 43.3 mmol, 1.5 eq) in DCM (20 mL) were added $Cu(OAc)_2$ (7.8 g, 43.3 mmol, 1.5 eq), DIPEtOAc (7.4 g, 57.8 mmol, 10.0 mL, 2.0 eq) and 3-bromopyridin-2-amine (**19A**, 5.0 g, 28.9 mmol, 1.0 eq). The reaction mixture was stirred at 25 °C for 16 hr under O_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient) to give intermediate **19B** (1.5 g, 2.8 mmol, 9.8% yield) as a light yellow oil. LCMS (ESI): RT = 1.012 min, mass calcd. for $C_{12}H_8BrF_3N_2$ 315.98, m/z found 317 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 1.5, 4.8 Hz, 1H), 7.80 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 6.74 (dd, *J* = 5.0, 7.8 Hz, 1H).

N^2-(4-(trifluoromethyl)phenyl)-[3,4'-bipyridine]-2,2'-diamine

[00267] To a solution of intermediate **19B** (100 mg, 0.3 mmol, 1.0 eq) in dioxane (5 mL) and H_2O (1 mL) were added $Pd(dppf)Cl_2$ (11.5 mg, 15.7 μmol, 0.05 eq), Na_2CO_3 (6 6.8 mg, 0.6 mmol,

2.0 eq) and 4-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (intermediate **7C**, 83.2 mg, 0.4 mmol, 1.2 eq). The reaction mixture was stirred at 90 °C for 2 hrs. The reaction mixture was filtered, and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient) to give **Compound 19** (10.82 mg, 9.87% yield) as a light yellow solid. LC-MS (ESI): RT = 0.773 min, mass calcd. for $C_{17}H_{13}F_3N_4$ 330.11, m/z found 331.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.24 (dd, J = 1.8, 4.8 Hz, 1H), 7.98 (d, J = 5.3 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.59 (dd, J = 1.9, 7.4 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.03 (dd, J = 4.8, 7.5 Hz, 1H), 6.58 (dd, J = 1.5, 5.3 Hz, 1H), 6.55 (s, 1H), 6.02 (s, 2H).

Example 20: N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)acrylamide (Compound 20)



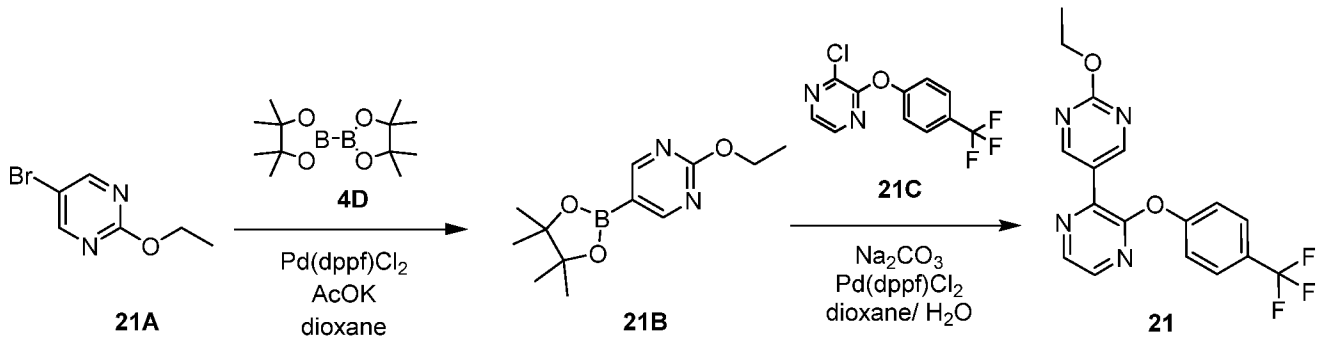
N-(4-bromo-2-pyridyl)prop-2-enamide

[00268] To a solution of compound **4F** (300 mg, 1.73 mmol, 1 eq) in THF (3 mL) were added TEA (701.8 mg, 6.94 mmol, 0.96 mL, 4.0 eq) and acryloyl chloride (313.8 mg, 3.4 mmol, 0.28 mL, 2.0 eq). The reaction mixture was stirred at 25 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 5/1) to give intermediate **20A** (250 mg, 0.85 mmol, 49% yield) as a light yellow solid. LC-MS (ESI): RT = 0.940 min, mass calcd. for $C_8H_7BrN_2O$ 225.97, m/z found 226.9 $[M+H]^+$.

N-[4-[2-[4-(trifluoromethyl)anilino]phenyl]-2-pyridyl]prop-2-enamide

[00269] To a solution of intermediate **4E** (100 mg, 0.27 mmol, 1 eq) in H_2O (1 mL) and dioxane (5 mL) were added $Pd(dppf)Cl_2$ (20.1 mg, 27.5 µmol, 0.1 eq), intermediate **20A** (93.7 mg, 0.41 mmol, 1.5 eq) and Cs_2CO_3 (269.1 mg, 0.82 mmol, 3.0 eq). The reaction mixture was stirred at 90 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150x25 5u;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 65%-95%,7.8min) to give **Compound 20** (5.2 mg, 4% yield) as a white solid. LC-MS (ESI): RT = 0.904 min, mass calcd. for $C_{21}H_{16}F_3N_3O$ 383.12, m/z found 383.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.29 (d, *J* = 5.1 Hz, 1H), 8.26 - 8.20 (m, 1H), 7.45 (d, *J* = 8.6 Hz, 3H), 7.41 - 7.35 (m, 2H), 7.18 (dt, *J* = 1.1, 7.4 Hz, 1H), 7.11 (dd, *J* = 1.5, 5.1 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.52 - 6.43 (m, 1H), 6.35 - 6.20 (m, 1H), 5.89 - 5.80 (m, 2H).

Example 21: 2-Ethoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine (Compound 21)



2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine

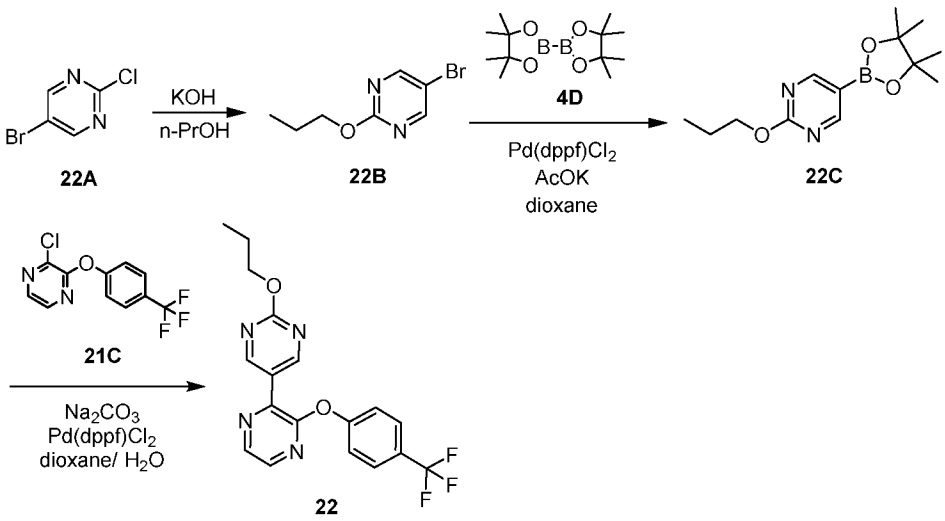
[00270] A solution of 5-bromo-2-ethoxypyrimidine (**20A**, 50.0 mg, 0.25 mmol, 1 *eq*), compound **4D** (75.0 mg, 0.30 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (18.0 mg, 25 µmol, 0.1 *eq*) and potassium acetate (48.3 mg, 0.49 mmol, 2 *eq*) in 1,4-dioxane (2 mL) at 20°C was purged and degassed with N_2 and then stirred at 100 °C for 6 hrs. The crude intermediate **20B** (61.6 mg) was obtained as black oil.

2-ethoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine

[00271] A solution of 2-chloro-3-(4-(trifluoromethyl)phenoxy)pyrazine (**21C**, 79.1 mg, 0.29 mmol, 1.2 *eq*), intermediate **20B** (60.0 mg, 0.24 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (17.6 mg, 24 µmol, 0.1 *eq*) and Na_2CO_3 (50.9 mg, 0.48 mmol, 2 *eq*) in 1,4-dioxane (2 mL) and H_2O (0.2 mL) at 20 °C was purged and degassed with N_2 and then stirred at 100 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~42% Ethyl

acetate/Petroleum ether gradient @20 mL/min) and prep-HPLC (column: Xtimate C18 100x30mmx3um; mobile phase: [water(0.05%HCl)-ACN]; B%: 50%-80%, 8.5 min) to give **Compound 20** (2.1 mg, 2.4% yield) as a yellow solid. LC-MS (ESI): RT = 0.954 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, $CDCl_3$) δ 9.37 (s, 2H), 8.44 (d, *J* = 2.4 Hz, 1H), 8.08 (d, *J* = 2.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 4.54 (q, *J* = 7.0 Hz, 2H), 1.49 (t, *J* = 7.0 Hz, 3H).

Example 22: 2-propoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine (Compound 22)



5-Bromo-2-propoxypyrimidine

[00272] A mixture of 5-bromo-2-chloropyrimidine (**22A**, 200.0 mg, 1.03 mmol, 1 *eq*) and KOH (116.0 mg, 2.07 mmol, 2 *eq*) in *n*-PrOH (2 mL) was stirred at 20 °C for 3 hrs. The residue was filtered and diluted with water (10 mL), and then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with water (10 mL x 2) and brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate **22B** (320.0 mg, 1.46 mmol, 94.1% yield) as colorless oil. LC-MS (ESI): RT = 0.845 min, mass calc. for $C_7H_9BrN_2O$ 215.99, m/z found 218.8 $[M+H]^+$.

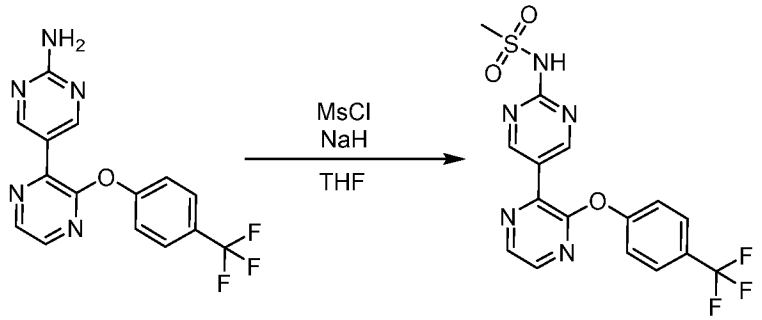
2-Propoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine

[00273] A solution of intermediate **22B** (100.0 mg, 0.46 mmol, 1 *eq*), compound **4D** (140.4 mg, 0.55 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (33.7 mg, 46 μmol, 0.1 *eq*) and AcOK (90.4 mg, 0.92 mmol, 2 *eq*) in dioxane (1 mL) at 20°C was purged and degassed with N_2 and then stirred at 90 °C for 5 hrs. The crude intermediate **22C** was obtained (121.0 mg, 0.46 mmol, 99.4% yield) as black oil.

2-propoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine

[00274] A solution of 2-chloro-3-(4-(trifluoromethyl)phenoxy)pyrazine (**21C**, 121.0 mg, 0.46 mmol, 1.2 *eq*), intermediate **22C** (104.8 mg, 0.38 mmol, 1 *eq*), Pd(dppf)Cl_2 (27.9 mg, 38 μmol, 0.1 *eq*) and Na_2CO_3 (80.9 mg, 0.76 mmol, 2.0 *eq*) in dioxane (1 mL) and H_2O (0.1 mL) at 20 °C was purged and degassed with N_2 and then stirred at 90 °C for 16 hrs. The residue was concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~35% Ethyl acetate/Petroleum ether gradient @ 20/min), prep-HPLC :(column: Xtimate C18 100x30mmx3um; mobile phase: [water(0.05%HCl)-ACN]; B%: 55%-85%, 8.5min) and prep-TLC (SiO_2, PE:EtOAc = 3:1, UV) to give **Compound 22** (12.7 mg, 8.8% yield) as a white solid. LC-MS (ESI): RT = 1.007 min, mass calc. for $C_{18}H_{15}F_3N_4O_2$ 376.11, m/z found 376.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 2H), 8.44 (d, *J* = 2.5 Hz, 1H), 8.08 (d, *J* = 2.5 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 4.42 (t, *J* = 6.8 Hz, 2H), 1.94 - 1.85 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

Example 23: N-(5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-yl)methanesulfonamide (Compound 23)



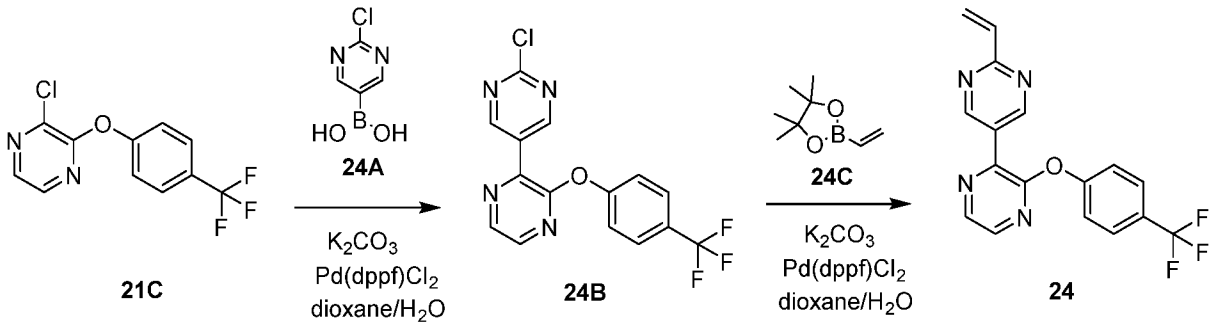
23A **23**

***N*-[5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]pyrimidin-2-yl]methanesulfonamide**

[00275] To a solution of compound **23A** (40 mg, 0.12 mmol, 1 *eq*) in THF (0.5 mL) at 0°C was added MsCl (27.5 mg, 0.24 mmol, 18 uL, 2.0 *eq*) and NaH (7.2 mg, 0.18 mmol, 60%, 1.5 *eq*). The reaction mixture was stirred at 25°C for 4 h. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xtimate C18 100x30mmx3um; mobile phase: [water (0.05% HCl)-ACN]; B%: 40%-70%, 8.5min) to give **Compound 23** (1.5 mg, 3.0% yield) as a white solid. LC-MS (ESI): RT = 0.807 min, mass calc. for $C_{16}H_{12}F_3N_5O_3S$ 411.06, m/z found 411.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 2H), 8.54 (d, *J* = 2.5 Hz, 1H), 8.20 (d, *J* = 2.6 Hz, 1H),

7.81 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 6.15 (br s, 1H), 6.16 - 6.13 (m, 1H), 3.44 - 3.31 (m, 3H).

Example 24: 5-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)-2-vinylpyrimidine (Compound 24)



2-chloro-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]pyrimidine

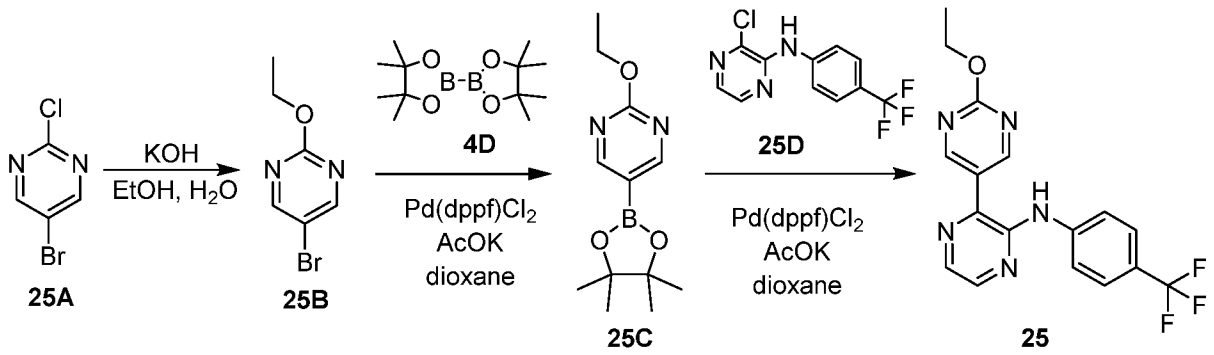
[00276] To a solution of intermediate **21C** (200 mg, 0.73 mmol, 1 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) were added $Pd(dppf)Cl_2$ (53.2 mg, 72.8 µmol, 0.1 *eq*), Na_2CO_3 (154.3 mg, 1.46 mmol, 2 *eq*) and compound (2-chloropyrimidin-5-yl)boronic acid (**1a**, 115.3 mg, 0.73 mmol, 1 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 110°C for 1 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EtOAc (20 mL), filtered and the filtrate was washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 30 mL/min). Intermediate **24B** (80 mg, 0.21 mmol, 29.2% yield) was obtained as a yellow solid.

2-[4-(trifluoromethyl)phenoxy]-3-(2-vinylpyrimidin-5-yl)pyrazine

[00277] To a solution of intermediate **24B** (50 mg, 0.14 mmol, 1 *eq*) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (**24C**, 26.2 mg, 0.17 mmol, 28 uL, 1.2 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) were added $Pd(dppf)Cl_2$ (10.3 mg, 14.1 µmol, 0.1 *eq*) and Na_2CO_3 (30.0 mg, 0.28 mmol, 2 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 110°C for 1 hr. The residue was filtered, and the filtrate was concentrated in vacuum. The crude product was checked by HPLC and purified by prep-HPLC (column: Waters Xbridge C18 150x50mmx 10um;mobile phase: [water(0.04%NH3H2O+10mM NH4HCO3)-ACN];B%: 51%-81%,9.3min). to afford **Compound 24** (20.1 mg, 40.9% yield) was obtained as a white solid. LCMS (ESI): RT = 0.910 min, mass calc. for $C_{17}H_{11}F_3N_4O$ 344.09, m/z found 344.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 2H), 8.49 (d, *J* = 2.5 Hz, 1H), 8.13 (d, *J* = 2.3 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H),

7.32 (d, *J* = 8.3 Hz, 2H), 6.98 (dd, *J* = 10.5, 17.3 Hz, 1H), 6.75 (dd, *J* = 1.5, 17.3 Hz, 1H), 5.85 (dd, *J* = 1.8, 10.5 Hz, 1H).

Example 25: 3-(2-Ethoxypyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (Compound 25)



5-bromo-2-ethoxypyrimidine

[00278] To a solution of 5-bromo-2-chloro-pyrimidine (**25A**, 1 g, 5.17 mmol, 1 *eq*) in EtOH (10 mL) was added KOH (580.1 mg, 10.34 mmol, 2 *eq*) in H_2O (2 mL). The reaction mixture was stirred at 25 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to remove EtOH**.** Then the residue was diluted with H_2O (5 mL) and neutralized to pH = 6-7 with 2M HCl, then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. It was used into next step without further purification. Compound 5-bromo-2-ethoxy-pyrimidine (intermediate **25B**, 800 mg, 3.94 mmol, 76.2% yield) was obtained as a yellow solid.

2-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine

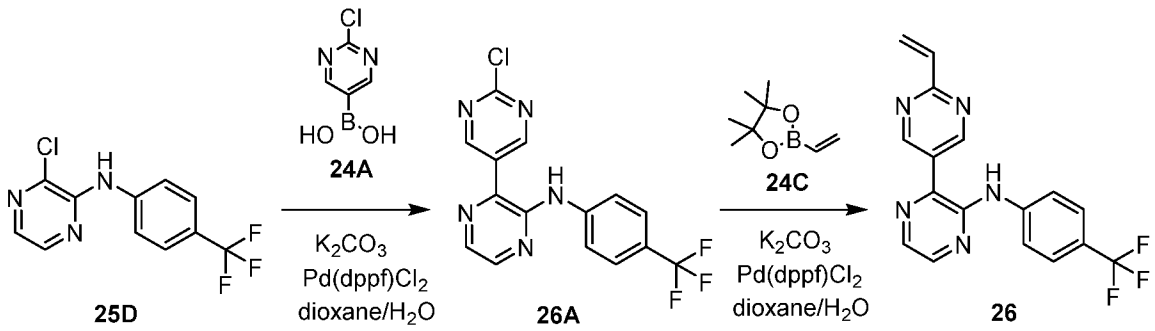
[00279] A mixture of intermediate **25B** (100 mg, 0.49 mmol, 1 *eq*), intermediate **4D** (125.0 mg, 0.49 mmol, 1 *eq*), KOAc (96.6 mg, 0.98 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (36.0 mg, 49.2 µmol, 0.1 *eq*) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 4 hr under N_2 atmosphere. After removing solvent *in vacuo*, crude intermediate **25C** (123 mg, 0.49 mmol, 99.8% yield) was obtained as a black oil, and was used for the next step without further purification.

3-(2-ethoxypyrimidin-5-yl)-N-[4-(trifluoromethyl)phenyl]pyrazin-2-amine

[00280] A mixture of 3-chloro-N-[4-(trifluoromethyl)phenyl]pyrazin-2-amine (**25D**, 110 mg, 0.40 mmol, 1 *eq*), intermediate **25C** (120.6 mg, 0.48 mmol, 1.2 *eq*), KOAc (78.9 mg, 0.80 mmol, 2

eq), $Pd(dppf)Cl_2$ (29.4 mg, 40.2 μmol, 0.1 *eq*) in dioxane (5 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was filtered and added H_2O (10 mL), then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xtimate C18 100x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 45%-75%,8.5min). **Compound 25** (5.4 mg, 3.5% yield) was obtained as a yellow solid. LC-MS (ESI): RT = 0.930 min, mass calcd for $C_{17}H_{14}F_3N_5O$ 361.32 m/z found 380.9$[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ 8.95 (s, 2H), 8.22 (dd, *J* = 2.6, 12.8 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 4.56 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H).

Example 26: *N*-(4-(Trifluoromethyl)phenyl)-3-(2-vinylpyrimidin-5-yl)pyrazin-2-amine (Compound 26)



3-(2-chloropyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine

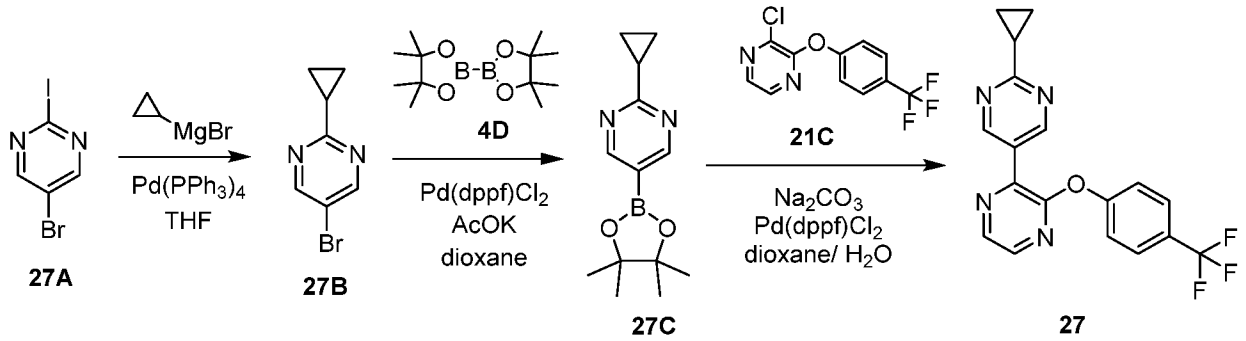
[00281] A mixture of 3-chloro-N-[4-(trifluoromethyl)phenyl]pyrazin-2-amine (**25D**, 100 mg, 0.36 mmol, 1 *eq*), (2-chloropyrimidin-5-yl)boronic acid (**24A**, 6 3.6 mg, 0.40 mmol, 1.1 *eq*), $Pd(dppf)Cl_2$ (26.7 mg, 36.5 μmol, 0.1 *eq*) and K_2CO_3 (101.0 mg, 0.73 mmol, 2 *eq*) in dioxane (3 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 110 °C for 4 hrs under N_2 atmosphere. The reaction mixture was added H_2O (10 mL) and extracted with EtOAc (10 mL x 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 chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 25 mL/min**).** Intermediate **26A** (70 mg, 0.19 mmol, 52.8% yield) was obtained as a yellow solid.

N-(4-(trifluoromethyl)phenyl)-3-(2-vinylpyrimidin-5-yl)pyrazin-2-amine

[00282] A mixture of intermediate **26A** (70 mg, 0.19 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (**24C**, 33.7 mg, 0.21 mmol, 37 uL, 1.1 *eq*), K_2CO_3 (55.0 mg, 0.39 mmol,

2 *eq*) and $Pd(dppf)Cl_2$ (14.5 mg, 19.9 µmol, 0.1 *eq*) in dioxane (3 mL) and H_2O (0.3 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 4 hrs under N_2 atmosphere. The reaction mixture was added H_2O (10 mL) and extracted with EtOAc (10 mL x 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 (column: Xtimate C18 100x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 42%-72%,8.5min) to give 13 mg crude product. Then the residue was purified by prep-HPLC (column: Welch Xtimate C18 150x25mmx5um;mobile phase: [water(0.05%HCl)-ACN];B%: 42%-72%,8.5min). **Compound 26** (3.3 mg, 4.9% yield) was obtained as a yellow solid. LC-MS (ESI): RT = 0.928 min, mass calcd for $C_{17}H_{12}F_3N_5$ 343.31 m/z found 344.0$[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 2H), 8.29 - 8.24 (m, 2H), 7.65 - 7.57 (m, 4H), 6.99 (dd, *J* = 10.6, 17.3 Hz, 1H), 6.82 - 6.73 (m, 2H), 5.88 (dd, *J* = 1.4, 10.6 Hz, 1H).

Example 27: 2-cyclopropyl-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine (Compound 27)



5-bromo-2-cyclopropylpyrimidine

[00283] To a solution of 5-bromo-2-iodopyrimidine (**27A**, 200 mg, 0.70 mmol, 1 *eq*) and $Pd(PPh_3)_4$ (162.3 mg, 0.14 mmol, 0.2 *eq*) in THF (2 mL) at 20°C was added cyclopropylmagnesium bromide (0.5 M, 2.81 mL, 2 *eq*), and the reaction mixture was purged and degassed with N_2 for 3 times and then stirred at 70°C under N_2 for 16 hrs. The reaction mixture was quenched with water (0.5 mL) and then concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **27B** (80 mg, 0.39 mmol, 56.1% yield) as colorless oil. LCMS (ESI): RT = 0.752 min, mass calc. for $C_7H_7BrN_2$ 197.98, m/z found 200.8 $[M+H]^+$.

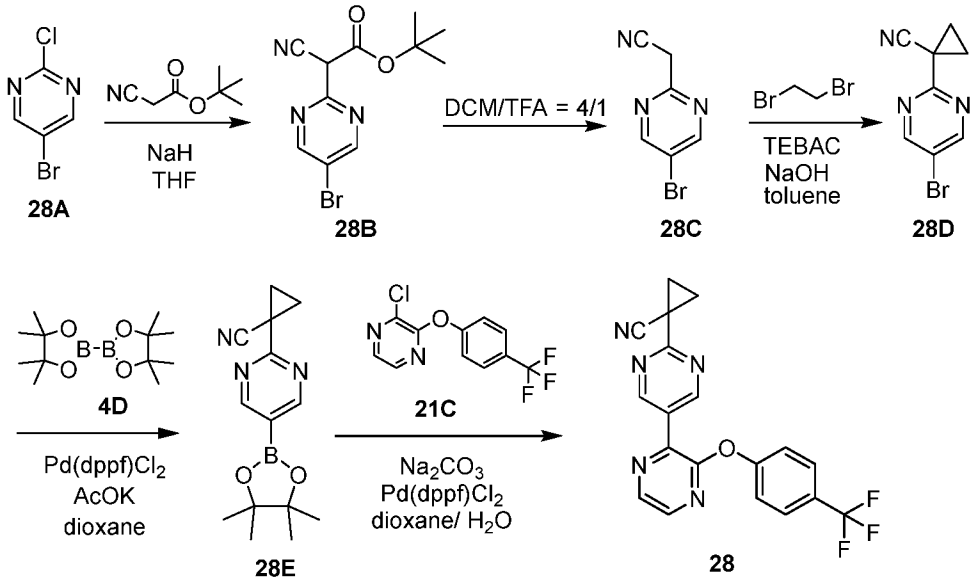
2-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine

[00284] The mixture of intermediate **27B** (40 mg, 0.20 mmol, 1 *eq*), **4D** (6 6.3 mg, 0.26 mmol, 1.3 *eq*), $Pd(dppf)Cl_2$ (7.4 mg, 10.1 µmol, 0.05 *eq*) and AcOK (39.4 mg, 0.40 mmol, 2 *eq*) in dioxane (2 mL) at 20°C was purged and degassed with N_2 for 3 times and then stirred at 100°C under N_2 for 2 hrs. The reaction mixture was concentrated under reduced pressure to give intermediate **27C** (49 mg, 0.20 mmol, 99.1% yield) as black oil, which was used directly for next step without further purification.

2-cyclopropyl-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine

[00285] The mixture of intermediate **21C** (40 mg, 0.15 mmol, 1 *eq*), intermediate **27C** (43.0 mg, 0.17 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (5.3 mg, 7.3 µmol, 0.05 *eq*) and Na_2CO_3 (30.9 mg, 0.29 mmol, 2 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) at 20°C was purged and degassed with N_2 for 3 times and then stirred at 100°C under N_2 for 16 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give 50 mg crude product, which was purified further by prep-HPLC (column: Xtimate C18 100x30mmx3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 45%-75%, 8.5min) to give the title compound (23.7 mg, 45.5% yield) as a white solid. LC-MS (ESI): RT = 0.925 min, mass calc. for $C_{18}H_{13}F_3N4O$ 358.10, m/z found 358.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 2H), 8.47 (d, *J* = 2.5 Hz, 1H), 8.11 (d, *J* = 2.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 2.43 - 2.35 (m, 1H), 1.31 - 1.24 (m, 2H), 1.23 - 1.16 (m, 2H).

Example 28: 1-(5-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-yl)cyclopropane-1-carbonitrile (Compound 28)



tert-butyl 2-(5-bromopyrimidin-2-yl)-2-cyano-acetate

[00286] To a solution of NaH (413.5 mg, 10.34 mmol, 60%, 2 *eq*) in THF (20 mL) were added 5-bromo-2-chloropyrimidine (**28A**, 802.8 mg, 5.69 mmol, 0.81 mL, 1.1 *eq*) at 0°C and stirred for 1 hr. Then tert-butyl 2-cyanoacetate (1.00 g, 5.17 mmol, 1 *eq*) was added to the reaction mixture and stirred at 20 °C for 16 hrs. The reaction mixture was quenched with H_2O (20 mL), extracted with EtOAc (20 mL). The aqueous phase was adjusted pH = 4 with 1N.aq.HCl and extracted with EtOAc (20 mL x 3). Then the combined organic phase was washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was used for the next step directly. Intermediate **28B** (1.50 g, 3.27 mmol, 63.2% yield) was obtained as a yellow solid.

2-(5-bromopyrimidin-2-yl)acetonitrile

[00287] To a solution of intermediate **28B** (1.50 g, 3.27 mmol, 1 *eq*) in DCM (20 mL) was added TFA (4 mL). The reaction mixture was stirred at 20 °C for 1 hr. LCMS showed that the starting material was consumed completely and 67% of the desired product was detected. The reaction mixture was concentrated in vacuum. The residue was diluted with H_2O (10 mL), adjusted pH = 7 with saturated aq.$NaHCO_3$ and extracted with EtOAc (15 mL x 3). The combined organic phase was washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 40 mL/min). Intermediate **28C** (300.0 mg, 1.51 mmol, 46.3% yield) was obtained as a yellow solid.

1-(5-bromopyrimidin-2-yl)cyclopropanecarbonitrile

[00288] To a solution of Intermediate **28C** (300.0 mg, 1.51 mmol, 1 *eq*), 1,2-dibromoethane (1.14 g, 6.06 mmol, 0.45 mL, 4 *eq*) and benzyl(triethyl)ammonium chloride (TEBAC, 34.5 mg, 0.15 mmol, 0.1 *eq*) in toluene (6 mL) was added NaOH (1.62 g, 12.12 mmol, 1.5 mL, 30%, 8 *eq*) at 20°C. Then the reaction mixture was stirred at 25°C for 16 hr. The colorless solution had turn into a red one. Then the reaction mixture was stirred at 25°C for 24 hr. The reaction mixture was poured into ice water (20 mL), extracted with EtOAc (15 mL x 3). The combined organic phase was washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 40

mL/min). Intermediate **28D** (110.0 mg, 0.48 mmol, 32.0% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 2H), 1.90 - 1.82 (m, 4H).

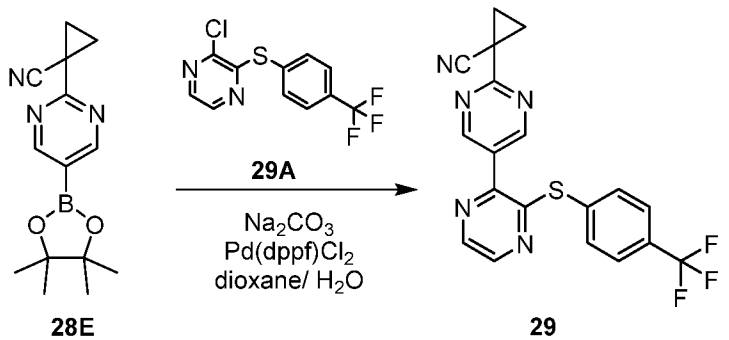
1-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]cyclopropanecarbonitrile

[00289] To a solution of intermediate **28D** (30.0 mg, 0.13 mmol, 1 *eq*) and intermediate **4D** (51.0 mg, 0.2 mmol, 1.5 *eq*) in dioxane (1 mL) were added $Pd(dppf)Cl_2$ (9.8 mg, 13.3 μmol, 0.1 *eq*) and AcOK (26.2 mg, 0.27 mmol, 2 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 100 °C for 2 hr. The reaction mixture was concentrated in vacuum and diluted with EtOAc (20 mL), filtered and the filtrate was concentrated in vacuum. The crude product was used for the next step directly. Crude intermediate **28E** (36.0 mg, crude) was obtained as a yellow oil, and used for the next step without further purification.

1-[5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]pyrimidin-2-yl]cyclopropanecarbonitrile

[00290] To a solution of intermediate **21C** (43.7 mg, 0.16 mmol, 1.2 *eq*) and intermediate **28E** (36.0 mg, 0.13 mmol, 1 *eq*) in dioxane (1 mL) were added $Pd(dppf)Cl_2$ (9.7 mg, 13.2 μmol, 0.1 *eq*), Na_2CO_3 (28.1 mg, 0.26 mmol, 2 *eq*) and H_2O (0.2 mL). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 100 °C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was checked by HPLC and purified by prep-HPLC (column: Xtimate C18 100x30mmx3um; mobile phase: [water (0.225%FA)-ACN]; B%: 55%-85%, 7.8min). **Compound 28** (16.7 mg, 32.9% yield) was obtained as a white solid. LC-MS (ESI): RT = 0.907 min, mass calc. for $C_{19}H_{12}F_3N_5O$ 383.10, m/z found 383.9 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 2H), 8.49 (d, *J* = 2.5 Hz, 1H), 8.14 (d, *J* = 2.4 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 2.03 - 1.87 (m, 4H).

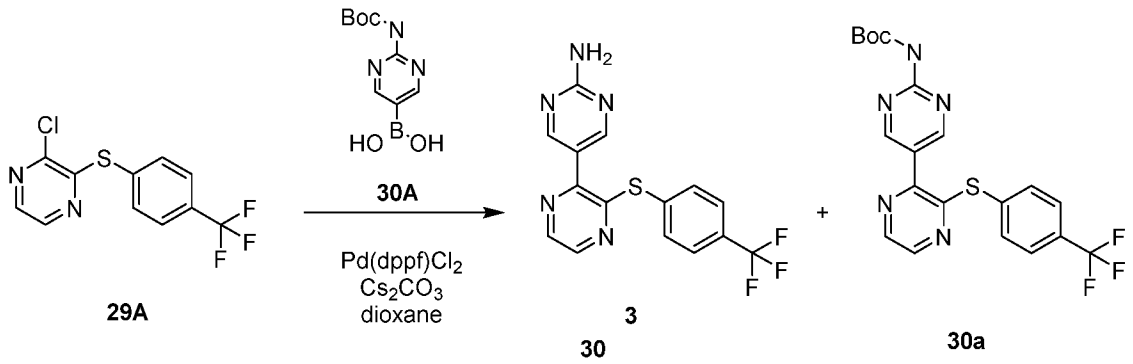
Example 29: 1-(5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-yl)cyclopropane-1-carbonitrile (Compound 29)



1-[5-[3-[4-(trifluoromethyl)phenyl]sulfanylpyrazin-2-yl]pyrimidin-2-yl]cyclopropanecarbonitrile

[00291] To a solution of intermediate **28E** (47.1 mg, 0.16 mmol, 1.1 *eq*) and 2-chloro-3-((4-(trifluoromethyl)phenyl)thio)pyrazine (**29A**, 40 mg, 0.15 mmol, 1 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) were added Pd(dppf)Cl_2 (10.8 mg, 14.7 µmol, 0.1 *eq*) and Na_2CO_3 (31.2 mg, 0.29 mmol, 2 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 100 °C for 2 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EtOAc (20 mL), filtered and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 20 mL/min). **Compound 29** (8.3 mg, 14.1% yield) was obtained as a white solid. LC-MS (ESI): RT = 0.909 min, mass calc. for $C_{19}H_{12}F_3N_5S$ 399.08, m/z found 399.9 $[M-H]^-$; 1H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 2H), 8.46 (d, *J* = 2.4 Hz, 1H), 8.35 (d, *J* = 2.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 2.01 - 1.92 (m, 4H).

Example 30: 5-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-amine (Compound 30) and tert-butyl (5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-yl)carbamate Compound 30a)

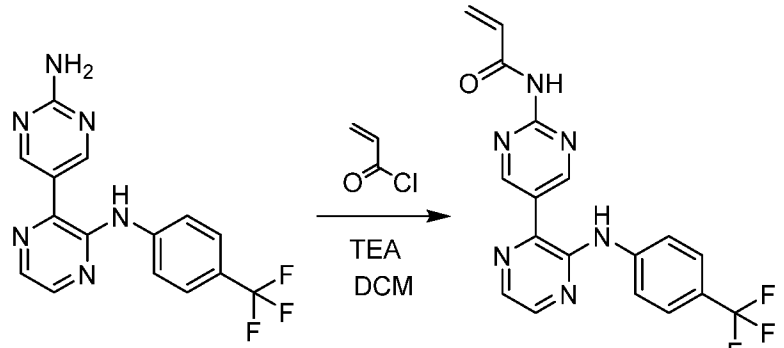


5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-amine

[00292] To a solution of 2-chloro-3-[4-(trifluoromethyl)phenyl]sulfanyl-pyrazine (**29A**, 100 mg, 0.34 mmol, 1 *eq*) and [2-(tert-butoxycarbonylamino)pyrimidin-5-yl]boronic acid (**30A**, 82.2 mg, 0.34 mmol, 1 *eq*) in dioxane (3 mL) were added Pd(dppf)Cl_2 (25.1 mg, 34.4 µmol, 0.1 *eq*) and Cs_2CO_3 (168.1 mg, 0.51 mmol, 1.5 *eq*). The reaction mixture was stirred at 110 °C for 16 hr under N_2 atmosphere. The reaction mixture was added H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was

purified by prep-HPLC (column: Waters Xbridge C18 150x50mmx 10um;mobile phase: [water(0.04%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 43%-73%,11min). **Compound 30** (6 .8 mg, 5.7% yield) was obtained as a white solid. LC-MS (ESI): RT = 0.833 min, mass calcd for $C_{15}H_{10}F_3N_5S$ 349.33 m/z found 350.0$[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 2H), 8.40 (d, *J* = 2.5 Hz, 1H), 8.26 (d, *J* = 2.5 Hz, 1H), 7.68 - 7.60 (m, 4H), 5.31 (br s, 2H). **Compound 30a** (8.9 mg, 5.7% yield) was obtained as a white solid. LCMS (ESI): RT = 0.954 min, mass calcd for $C_{20}H_{18}F_3N_5O_2S$ 449.45 m/z found 450.0$[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 2H), 8.43 (d, *J* = 2.3 Hz, 1H), 8.31 (d, *J* = 2.5 Hz, 1H), 7.71 (s, 1H), 7.68 - 7.60 (m, 4H), 1.58 (s, 9H).

Example 31: *N*-(5-(3-((4-(Trifluoromethyl)phenyl)amino)pyrazin-2-yl)pyrimidin-2-yl)acrylamide (Compound 31)

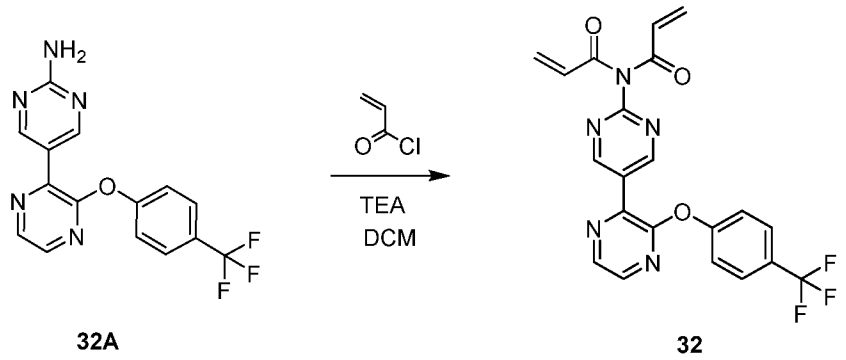


31A **31**

N-(5-(3-((4-(trifluoromethyl)phenyl)amino)pyrazin-2-yl)pyrimidin-2-yl)acrylamide

[00293] To a solution of 3-(2-aminopyrimidin-5-yl)-N-[4-(trifluoromethyl)phenyl]pyrazin-2-amine (**31A**, 80 mg, 0.24 mmol, 1 *eq*) and TEA (73.0mg, 0.72 mmol, 0.1 mL, 3 *eq*) in DCM (2 mL) was added prop-2-enoyl chloride (32.6 mg, 0.36 mmol, 29 uL, 1.5 *eq*) under N_2. Then the reaction mixture was stirred at 25 °C for 16 hrs. The reaction mixture was added H_2O (10 mL) and extracted with EtOAc (10 mL x 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 (column: Waters Xbridge C18 150x50mmx 10um;mobile phase: [water(0.04%NH3H2O)-ACN];B%: 46%-46%,9.5min) to afford **Compound 31** (2.8 mg, 2.9% yield) as a yellow solid. LCMS (ESI): RT = 0.789 min, mass calcd for $C_{18}H_{13}F_3N_6O$ 386.33 m/z found 386.9$[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ 8.95 - 8.85 (m, 2H), 8.12 (q, *J* = 2.6 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 6.57 - 6.35 (m, 2H), 5.83 - 5.74 (m, 1H).

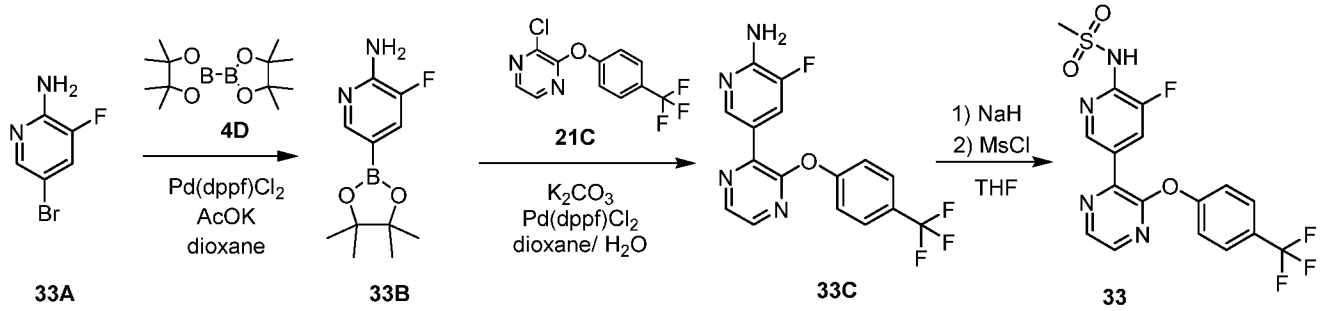
Example 32: *N*-Acryloyl-N-(5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-yl)acrylamide (Compound 32)



32A 32

[00294] To a solution of 5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-amine (**32A**, 20 mg, 60.0 µmol, 1 *eq*) in DCM (0.5 mL) was added prop-2-enoyl chloride (6 .5 mg, 72.0 µmol, 5 uL, 1.2 *eq*) and TEA (18.2 mg, 0.18 mmol, 25 uL, 3.0 *eq*). The solution was stirred at 25°C for 16 hrs. The residue was purified by prep-HPLC (column: Xtimate C18 100x30mmx3um; mobile phase: [water (0.05% HCl) -ACN]; B%: 45%-75%, 8.5min) to give **Compound 32** (4.7 mg, 17.3% yield) as a yellow solid. LCMS (ESI): RT = 0.896 min, mass calc. for $C_{21}H_{14}F_3N_5O_3$ 441.10, m/z found 441.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 2H), 8.52 (d, *J* = 2.5 Hz, 1H), 8.18 (d, *J* = 2.5 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 6.60 - 6.53 (m, 2H), 6.52 - 6.42 (m, 2H), 5.86 (dd, *J* = 1.6, 9.9 Hz, 2H).

Example 33: N-(3-fluoro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-yl)methanesulfonamide (Compound 33)



33A 33B 33C 33

3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine

[00295] A mixture of 5-bromo-3-fluoro-pyridin-2-amine (**33A**, 650 mg, 3.40 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 1.30 g, 5.10 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (124.51 mg, 0.17mmol, 0.05 *eq*), AcOK (1.00 g, 10.21 mmol, 3 *eq*) in dioxane (10 mL)was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 10 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 20 g

SepaFlash® Silica Flash Column, Eluent of 0~30% PE/EtOAc@ 35 mL/min). Intermediate **33B** (500 mg, 2.10 mmol, 61.7% yield) was obtained as white solid.

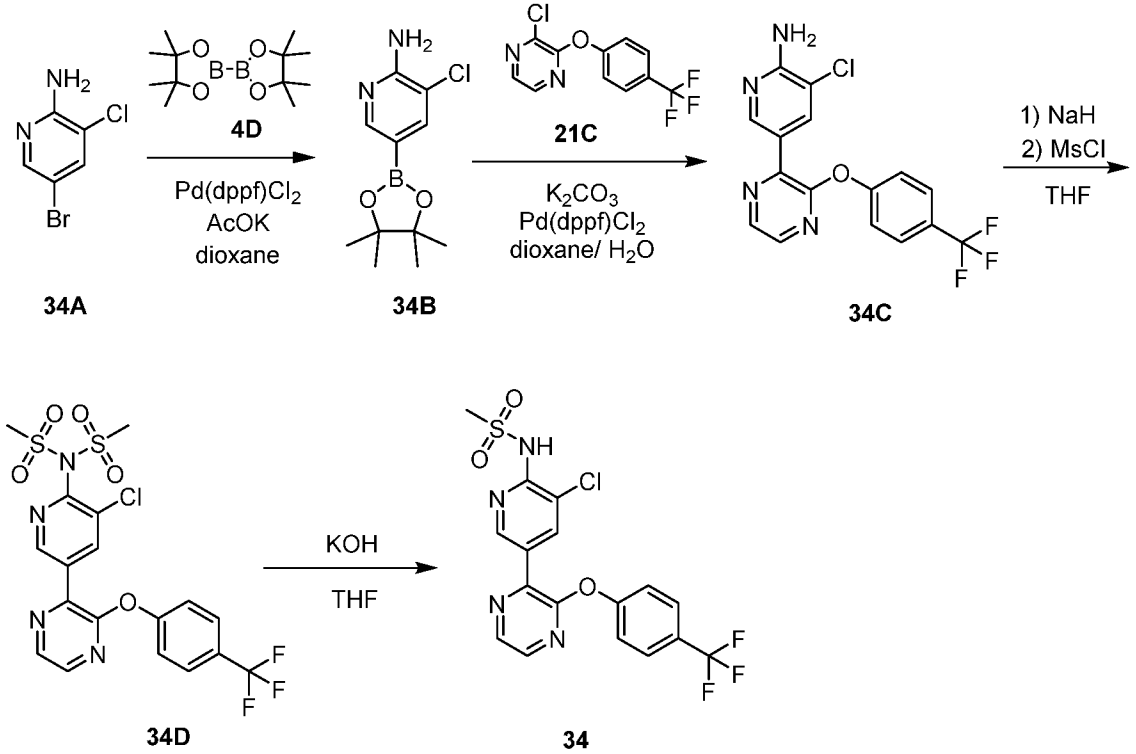
3-fluoro-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]pyridin-2-amine

[00296] A mixture of intermediate **33B** (208.0 mg, 0.87 mmol, 1.2 *eq*), intermediate **21C** (200 mg, 0.72 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (26.6 mg, 36.4 μmol, 0.05 *eq*), K_2CO_3 (301.9 mg, 2.18 mmol, 3 *eq*) in dioxane (2 mL)and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 10 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 25 mL/min). Intermediate **33C** (170 mg, 0.45 mmol, 61.9% yield) was obtained as a yellow solid.

N-[3-fluoro-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]-2-pyridyl]methanesulfonamide

[00297] NaH (137.04 mg, 0.57mmol, 10%, 2 *eq*) was added at the reaction mixture of Intermediate **33C** (100 mg, 0.28mmol, 1 *eq*) in THF (3 mL) at 25°C. The reaction mixture was stirred at 70°C for 1 hr. MsCl (32.70 mg, 0.28 mmol, 22.1 uL, 1 *eq*) was added at the reaction mixture at 25°C. Then the reaction mixture was stirred at 70°C for another 16 hrs. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 45%-75%,6.5min) to afford **Compound 33** (7.31 mg, 5.9% yield) was obtained as yellow solid. LC-MS (ESI): RT = 0.891 min, mass calcd for $C_{17}H_{12}F_4N_4O_3S$ 428.36 m/z found 429.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 3.45 (s, 3 H) 7.43 (d, J = 8.50 Hz, 2 H) 7.77 (d, J = 8.63 Hz, 2 H) 8.12 (d, J = 2.50 Hz, 1 H) 8.36 (dd, J = 11.63, 1.88 Hz, 1 H) 8.47 (d, J = 2.63 Hz, 1 H) 8.98 (d, J = 1.38 Hz, 1 H).

Example 34: *N*-(3-Chloro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-yl)methanesulfonamide (Compound 34)



3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine

[00298] A mixture of 5-bromo-3-chloro-pyridin-2-amine (**34A**, 1 g, 4.82 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 1.84 g, 7.23 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (176.3 mg, 0.24 mmol, 0.05 *eq*), AcOK (1.42 g, 14.4 mmol, 3 *eq*) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 10 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®;20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @35 mL/min). Intermediate **34B** (1.2 g, 4.71 mmol, 97.8% yield) was obtained as yellow oil.

3-chloro-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]pyridin-2-amine

[00299] A mixture of intermediate **34B** (400 mg, 1.46 mmol, 1 *eq*), intermediate **21C** (556.0 mg, 2.18 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (53.2 mg, 72.8 μmol, 0.05 *eq*), K_2CO_3 (6 03.9 mg, 4.37 mmol, 3 *eq*) in dioxane (3 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 10 hr under N_2 atmosphere. The reaction mixture was

diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% PE/EtOAc@ 35 mL/min). Intermediate 34C (300 mg, 0.81 mmol, 56.1% yield) was obtained as a yellow solid.

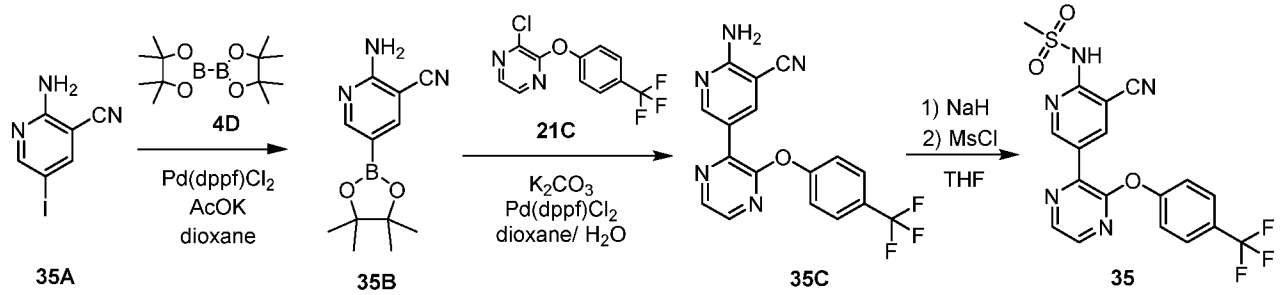
N-[3-chloro-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]-2-pyridyl]-N-methylsulfonyl-methanesulfonamide

[00300] NaH (261.7 mg, 1.09 mmol, 10%, 2 *eq*) was added at the reaction mixture of Intermediate **34C** (200 mg, 0.54 mmol, 1 *eq*) in THF (3 mL) at 25°C. The reaction mixture was stirred at 70 °C for 1 hr. MsCl (6 2.4 mg, 0.54 mmol, 42.2 uL, 1 *eq*) was added at the reaction mixture at 25 °C. Then the reaction mixture was stirred at 70 °C for another 16 hr. LC-MS showed the desired compound was detected. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with **EtOAc** (**20** mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Crude intermediate **34D** (200 mg, crude) was obtained as yellow solid which was used into the next step without further purification.

N-[3-chloro-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]-2-pyridyl]methanesulfonamide

[00301] The mixture intermediate **34D** (200 mg, 0.38 mmol, 1 *eq*) and KOH (2 M, 0.19 mL, 1 *eq*) in THF (2 mL) was stirred at 25°C for 15 min. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 50%-80%,6.5min) to afford **Compound 34** (29.1 mg, 16.7% yield) was obtained white solid. LC-MS (ESI): RT = 0.918 min, mass calcd for $C_{17}H_{12}ClF_3N_4O_3S$ 444.82 m/z found 445.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 1 H) 3.43 (br s, 3 H) 7.54 (d, J = 8.53 Hz, 2 H) 7.85 (d, J = 8.53 Hz, 2 H) 8.22 (d, J = 2.51 Hz, 1 H) 8.55 (d, J = 2.51 Hz, 2 H) 9.00 (br s, 1 H) 10.59 (br s, 1 H).

Example 35: *N*-(3-Cyano-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-yl)methanesulfonamide (Compound 35)



2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carbonitrile

[00302] A mixture of 2-amino-5-bromo-pyridine-3-carbonitrile (**35A**, 6 00 mg, 3.03 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 1.15 g, 4.54 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (110.8 mg, 0.15 mmol, 0.05 *eq*), AcOK (892.0 mg, 9.09 mmol, 3 *eq*) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 10 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~55% PE/EtOAc@ 35 mL/min). Intermediate **35B** (580 mg, 2.30 mmol, 75.76% yield) was obtained as a white solid.

2-amino-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]pyridine-3-carbonitrile

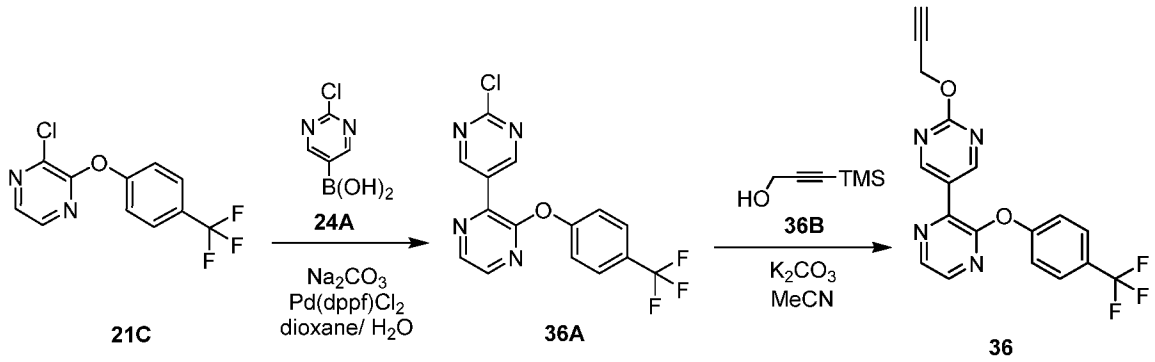
[00303] A mixture of intermediate **35B** (214.1 mg, 0.87mmol, 1.2 *eq*), intermediate **21C** (200 mg, 0.72mmol, 1 *eq*), $Pd(dppf)Cl_2$ (26.6 mg, 36.4 μmol, 0.05 *eq*), K_2CO_3 (301.9 mg, 2.18 mmol, 3 *eq*) in dioxane (2 mL)and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 10 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 25 mL/min). Intermediate **35C** (200 mg, 548.58 μmol, 75.33% yield) was obtained as a yellow solid.

N-[3-cyano-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]-2-pyridyl]methanesulfonamide

[00304] NaH (134.3 mg, 0.55 mmol, 10%, 2 *eq*) was added at the reaction mixture of intermediate **35C** (100.0 mg, 0.27 mmol, 1 *eq*) in THF (3 mL) at 25 °C. The reaction mixture was stirred at 70°C for 1 hr. MsCl (32.0 mg, 0.27 mmol, 21.6 uL, 1 *eq*) was added at the reaction

mixture at 25 °C. Then the reaction mixture was stirred at 70°C for another 16 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 40%-70%,6.5min) to afford **Compound 35** (9.2 mg, 7.5% yield) was obtained as a white solid. LC-MS (ESI): RT = 0.883 min, mass calcd for $C_{18}H_{12}F_3N_5O_3S$ 435.38 m/z found 436.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 3.44 (s, 3 H) 7.46 (d, *J* = 8.53 Hz, 2 H) 7.79 (d, *J* = 8.78 Hz, 2 H) 8.16 (d, *J* = 2.51 Hz, 1 H) 8.50 (d, *J* = 2.51 Hz, 1 H) 8.94 (d, *J* = 2.01 Hz, 1 H) 9.30 (s, 1 H).

Example 36: 2-(Prop-2-yn-1-yloxy)-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine (Compound 36)



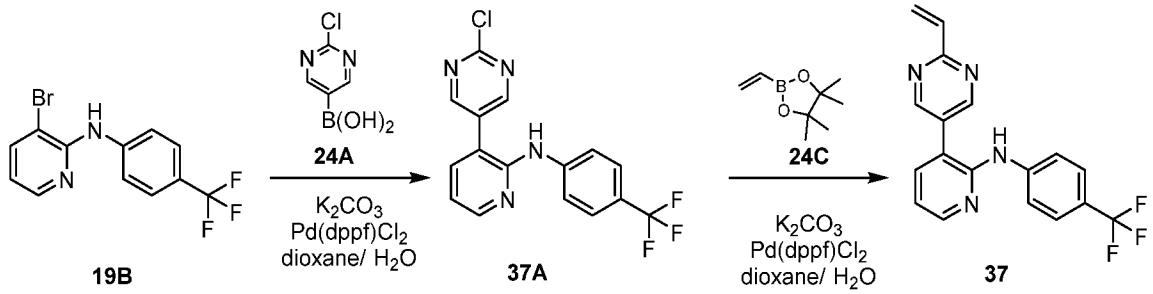
2-chloro-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]pyrimidine

[00305] To a solution of intermediate **21C** (5 g, 18.21 mmol, 1 *eq*) in dioxane (40 mL) and H_2O (0.4 mL) was added (2-chloropyrimidin-5-yl)boronic acid (**24A**, 2.88 g, 18.21 mmol, 1.2 *eq*), Na_2CO_3 (3.86 g, 36.41 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (6 66.1 mg, 0.91 mmol, 0.05 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times. The solution was stirred at 110°C for 3 hr under N_2. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) to give intermediate **36A** (1.7 g, 4.48 mmol, 24.6% yield) as a yellow solid. LCMS (ESI): RT = 0.914 min, mass calc. for $C_{15}H_8ClF_3N_4O$ 352.03, m/z found 352.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.58 - 9.41 (m, 1H), 9.53 - 9.41 (m, 1H), 8.50 (d, *J* = 2.4 Hz, 1H), 8.17 (d, *J* = 2.4 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H).

2-prop-2-ynoxy-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]pyrimidine

[00306] To a solution of intermediate **36A** (350 mg, 0.99 mmol, 1 *eq*) in MeCN (3 mL) was added 3-(trimethylsilyl)prop-2-yn-1-ol (**36B**, 127.3 mg, 0.99 mmol, 0.1 mL, 1 *eq*) and K_2CO_3 (411.5 mg, 2.98 mmol, 3.0 *eq*). The solution was stirred at 80°C for 16 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (40 mL) and extracted with EtOAc (45 mL x 3). The combined organic layers were washed with brine (45 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to afford **Compound 36** (97.4 mg, 25.3% yield) as a white solid. LC-MS (ESI): RT = 0.946 min, mass calc. for $C_{18}H_{11}F_3N_4O_2$ 372.08, m/z found 373.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 - 9.43 (m, 1H), 9.42 (s, 1H), 8.45 (d, *J* = 2.5 Hz, 1H), 8.10 (d, *J* = 2.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.13 (d, *J* = 2.3 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H).

Example 37: *N*-(4-(Trifluoromethyl)phenyl)-3-(2-vinylpyrimidin-5-yl)pyridin-2-amine (Compound 37)



3-(2-chloropyrimidin-5-yl)-*N*-[4-(trifluoromethyl)phenyl]pyridin-2-amine

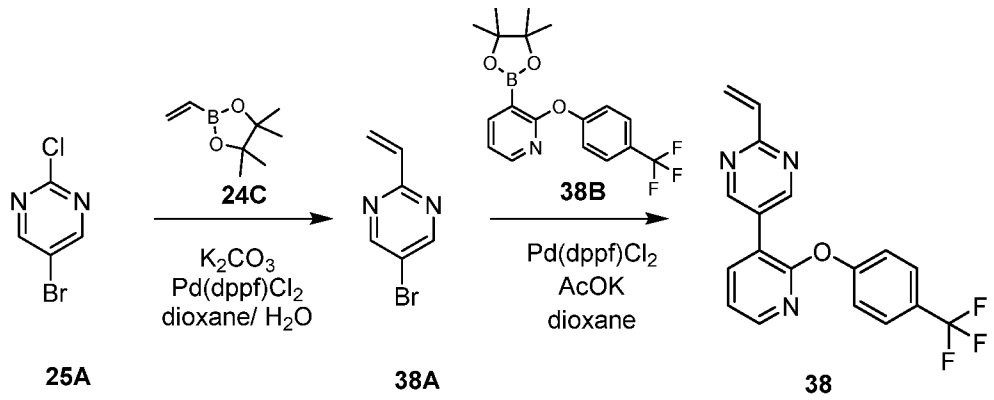
[00307] To a solution of intermediate **19B** (300.0 mg, 0.95 mmol, 1.0 *eq*), (2-chloropyrimidin-5-yl)boronic acid (**24A**, 179.8 mg, 1.14 mmol, 1.2 *eq*) and K_2CO_3 (261.5 mg, 1.89 mmol, 2.0 *eq*) in dioxane (3 mL) and H_2O (0.3 mL) was added $Pd(dppf)Cl_2$ (6 9.2 mg, 94.6 µmol, 0.1 *eq*). The reaction mixture was degassed and purged with N_2 for three times. The reaction mixture was stirred at 90 °C for 3 hr under N_2 atmosphere. Crude intermediate **37A** (330.0 mg, crude) was obtained as black oil, which was used for the next step without further purification.

***N*-[4-(trifluoromethyl)phenyl]-3-(2-vinylpyrimidin-5-yl)pyridin-2-amine**

[00308] To a solution of intermediate **37A** (330.0 mg, 0.33 mmol, 1.0 *eq*), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (**24C**, 60.8 mg, 0.40 mmol, 67 uL, 1.2 *eq*) and K_2CO_3 (91.0 mg, 0.66 mmol, 2.0 *eq*) in dioxane (1 mL) and H_2O (0.1 mL) was added $Pd(dppf)Cl_2$ (12.0 mg, 16 µmol, 0.05 *eq*). The reaction mixture was degassed and purged with N_2 for three times. The

reaction mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 150x25mmx5um; mobile phase: [water (0.05% NH_3H_2O+10mM NH_4HCO_3) - ACN]; B%: 55 %-85 %, 9.5 min) to afford **Compound 37** (12.9 mg, 37.2 µmol, 11.2 % yield) as a yellow solid. LC-MS (ESI): RT = 0.849 min, mass calc. for $C_{18}H_{13}F_3N_4$ 342.11, m/z found 343.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.95 - 8.80 (m, 2H), 8.67 (s, 1H), 8.30 (dd, J = 1.5, 4.8 Hz, 1H), 7.76 - 7.67 (m, 3H), 7.55 (d, J = 8.8 Hz, 2H), 7.09 (dd, J = 4.9, 7.4 Hz, 1H), 6.91 (dd, J = 10.4, 17.4 Hz, 1H), 6.61 (dd, J = 1.8, 17.6 Hz, 1H), 5.80 (dd, J = 1.8, 10.5 Hz, 1H).

Example 38: 5-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-2-vinylpyrimidine (Compound 38)



5-bromo-2-vinyl-pyrimidine

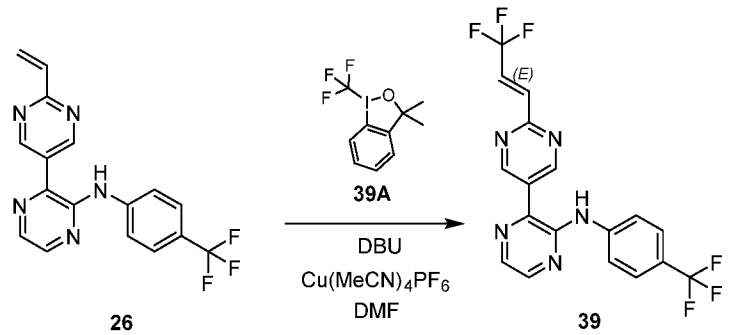
[00309] To a solution of 5-bromo-2-chloropyrimidine (**25A**, 320 mg, 1.12 mmol, 1 *eq*) in dioxane (3 mL) and H_2O (0.3 mL) was added intermediate **24C** (207.6 mg, 1.35 mmol, 0.3 mL, 1.2 *eq*), $Pd(dppf)Cl_2$ (41.1 mg, 56.2 µmol, 0.05 *eq*) and K_2CO_3 (310.5 mg, 2.25 mmol, 2.0 *eq*). The reaction mixture was degassed and purged with N_2 for three times. The reaction mixture was stirred at 80°C for 16 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 100% Petroleum ether gradient @ 30 mL/min) to give intermediate **38A** (110 mg, 0.56 mmol, 49.7% yield) as a colorless oil. LC-MS (ESI): RT = 0.699 min, mass calc. for $C_6H_5BrN_2$ 183.96, m/z found 186.7 $[M+H]^+$.

5-[2-[4-(trifluoromethyl)phenoxy]-3-pyridyl]-2-vinyl-pyrimidine

[00310] To a solution of intermediate **38A** (98.7 mg, 0.27 mmol, 1 *eq*) in dioxane (1 mL) and H_2O (0.1 mL) was added 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-(trifluoromethyl)phenoxy)pyridine (**38B**, 50 mg, 0.27 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (19.8 mg, 27 µmol, 0.1 *eq*) and K_2CO_3 (74.7 mg, 0.54 mmol, 2.0 *eq*). The reaction mixture was degassed and purged

with N_2 for three times. The reaction mixture was stirred at 90°C for 16 hrs under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (15 mL x3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 150x25mmx5um; mobile phase: [water (0.05% HCl)-ACN]; B%: 50%-80%, 8.5min) to afford **Compound 38** (17.7 mg, 17.1% yield, HCl) as a yellow solid. LC-MS (ESI): RT = 0.968 min, mass calc. for $C_{18}H_{12}F_3N_3O$ 343.09, m/z found 344.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 2H), 8.26 (d, *J* = 4.0 Hz, 1H), 7.87 (br d, *J* = 6.8 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.26 - 7.21 (m, 2H), 7.03 (dd, *J* = 10.5, 17.3 Hz, 1H), 6.77 (dd, *J* = 1.4, 17.2 Hz, 1H), 5.88 (dd, *J* = 1.3, 10.5 Hz, 1H), 4.93 (br s, 1H).

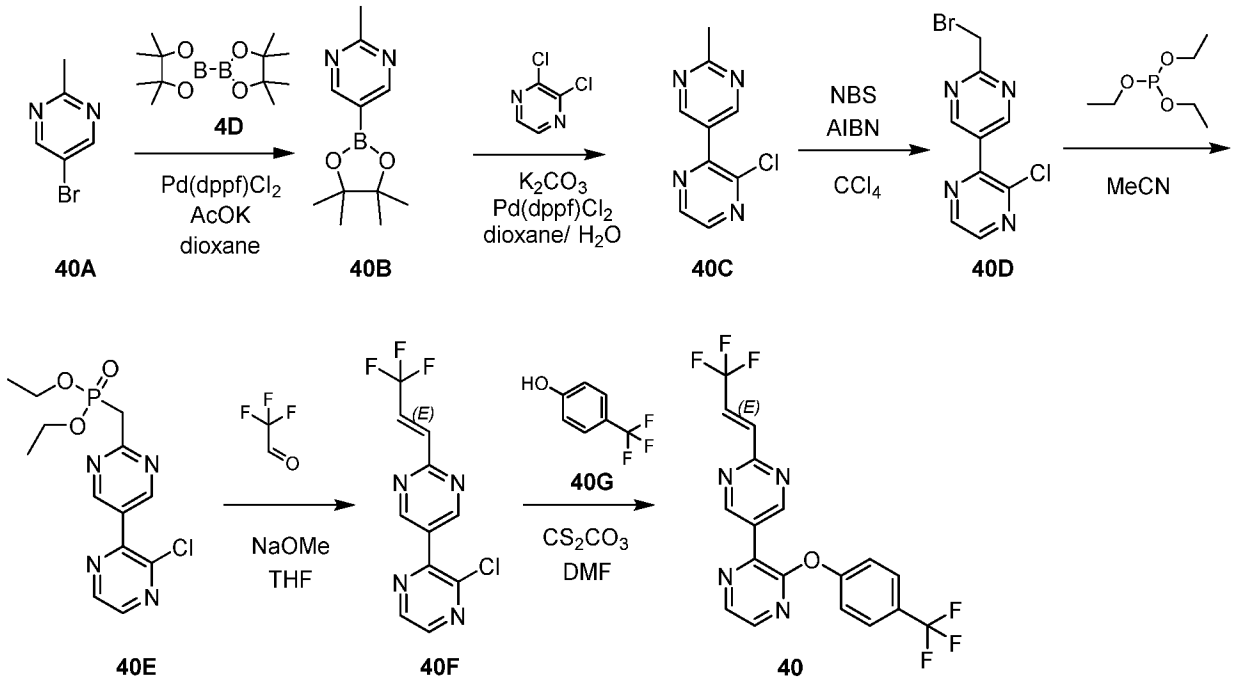
Example 39: (*E*)-*N*-(4-(Trifluoromethyl)phenyl)-3-(2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidin-5-yl)pyrazin-2-amine (Compound 39)



26 39

[00311] To a solution of Compound **26** (120 mg, 0.35 mmol, 1 *eq*) and 3,3-dimethyl-1-(trifluoromethyl)-1,3-dihydro-1l3-benzo[d][1,2]iodaoxole (**39A**, 288.5 mg, 0.87 mmol, 2.5 *eq*) in DMF (0.5 mL) were added DBU (106.4 mg, 0.70 mmol, 0.11 mL, 2 *eq*) and $Cu(MeCN)_4PF_6$ (26.1 mg, 69.9 µmol, 0.2 *eq*). The reaction mixture was stirred at 60 °C for 6 hrs. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL x 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, which was purified by prep-HPLC (column: Waters Xbridge 150x25mmx 5um; mobile phase: [water (0.05%NH_3H_2O)-ACN]; B%: 57%-87%, 9.5 min) to give the title compound (12 mg, yellow solid) to afford **Compound 39**(5.9 mg, 4.1% yield) as a yellow solid. LC-MS (ESI): RT = 1.009 min, mass calc. for $C_{18}H_{11}F_6N_5$ 411.09, m/z found 412.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 2H), 8.29 (d, *J* = 6.3 Hz, 2H), 7.59 (s, 4H), 7.39 - 7.31 (m, 1H), 7.25 - 7.14 (m, 1H), 6.67 (s, 1H)

Example 40: (*E*)-5-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine (Compound 40)



2-methyl-5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) pyrimidine

[00312] A mixture of 5-bromo-2-methylpyrimidine (**40A**, 5 g, 28.90 mmol, 1 *eq*), **4D** (8.81 g, 34.68 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (2.11 g, 2.89 mmol, 0.1 *eq*), KOAc (4.25 g, 43.35 mmol, 1.5 *eq*) in dioxane (50 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The residue was poured into H_2O (50 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give intermediate **40B** (6 .2 g, crude) as a yellow solid. The crude intermediate **40B** was used for next step without further purification.

2-chloro-3-(2-methylpyrimidin-5-yl) pyrazine

[00313] A mixture of intermediate **40B** (6 .1 g, 27.72 mmol, 1 *eq*), 2,3-dichloropyrazine (4.96 g, 33.26 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (1.01 g, 1.39 mmol, 0.05 *eq*), K_2CO_3 (5.75 g, 41.58 mmol, 1.5 *eq*) in dioxane (50 mL) and H_2O (10 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 3 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (80 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (40 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~30%) to give intermediate **40C** (4.8 g, 21.37 mmol, 77% yield) as a yellow solid.

2-(bromomethyl)-5-(3-chloropyrazin-2-yl) pyrimidine

[00314] A mixture of intermediate **40C** (1.5 g, 7.26 mmol, 1 *eq*), NBS (1.55 g, 8.71 mmol, 1.2 *eq*), AIBN (238.4 mg, 1.45 mmol, 0.2 *eq*) in CCl_4 (10 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 70 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (50 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (20 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~30%) to give intermediate **40D** (318 mg, 1.08 mmol, 15% yield) as a yellow solid.

2-chloro-3-[2-(diethoxyphosphorylmethyl) pyrimidin-5-yl] pyrazine

[00315] To a solution of intermediate **40D** (280 mg, 0.98 mmol, 1 *eq*) and triethyl phosphite (195.5 mg, 1.18 mmol, 0.20 mL, 1.2 *eq*) in MeCN (3 mL) and the reaction mixture was stirred at 100 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent to give intermediate **40E** (318 mg, crude) as a yellow oil. The crude intermediate **40E** was used for next step without further purification.

2-chloro-3-[2-[(E)-3, 3, 3-trifluoroprop-1-enyl] pyrimidin-5-yl] pyrazine

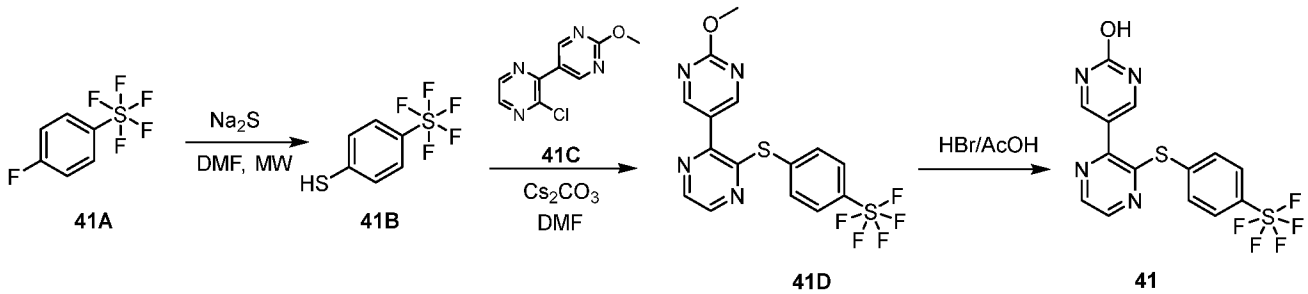
[00316] To a solution of intermediate **40E** (285 mg, 0.83 mmol, 1 *eq*) in THF (3 mL) was added NaOMe (6 7.4 mg, 1.25 mmol, 1.5 *eq*). After addition, the reaction mixture was stirred at this temperature for 0.5 hr, and then 2,2,2-trifluoroacetaldehyde (174.7 mg, 1.25 mmol, 1.5 *eq*) was added. The resulting mixture was stirred at 25 °C for 2.5 hr. The reaction mixture was diluted with H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (15 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (12 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~20%) to give intermediate **40F** (156 mg, 0.54 mmol, 65.5% yield) as a yellow solid.

2-chloro-3-[2-[(E)-3, 3, 3-trifluoroprop-1-enyl] pyrimidin-5-yl] pyrazine

[00317] To a solution of intermediate **40F** (120 mg, 0.42 mmol, 1 *eq*) in DMF (2 mL) were added 4-(trifluoromethyl)phenol (**40G**, 74.7 mg, 0.46 mmol, 1.1 *eq*), Cs_2CO_3 (204.6 mg, 0.63 mmol, 1.5 *eq*). The reaction mixture was stirred at 110 °C for 3 hr. The reaction mixture was diluted with H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (15

mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Waters Xbridge 150x25mmx 5um; mobile phase: [water (0.04%NH3H2O+10mM NH4HCO3)-ACN]; B%: 63%-73%, 9.5min) to afford **Compound 40** (36.7 mg, 21.3% yield) as a white solid. LC-MS (ESI): RT = 0.981 min, mass calcd for $C_{18}H_{10}F_6N_4O$ 412.08, m/z found 412.9 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.59 (s, 2H), 8.53 (d, *J* = 2.5 Hz, 1H), 8.20 (d, *J* = 2.3 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.38 - 7.20 (m, 2H).

Example 41: 5-(3-((4-(pentafluoro-λ6-sulfaneyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol (Compound 41)



4-(pentafluoro-sulfanyl)benzenethiol

[00318] To a solution of pentafluoro(4-fluorophenyl)-λ6-sulfane (**41A**, 0.15 g, 0.67 mmol, 1 eq) in DMF (4 mL) was added Na_2S (131.7 mg, 1.6 mmol, 70.8 uL, 2.5 eq). The reaction mixture was stirred at 120 °C for 0.5 hr under the microwave. The reaction mixture was quenched by addition NaOH (2 M, 15 mL), and then washed with EtOAc (20 mL). The pH of the aqueous phase was adjusted with HCl (2M) to 2-3, and then extracted with DCM (15 x 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude intermediate **41B** was used into the next step without further purification.

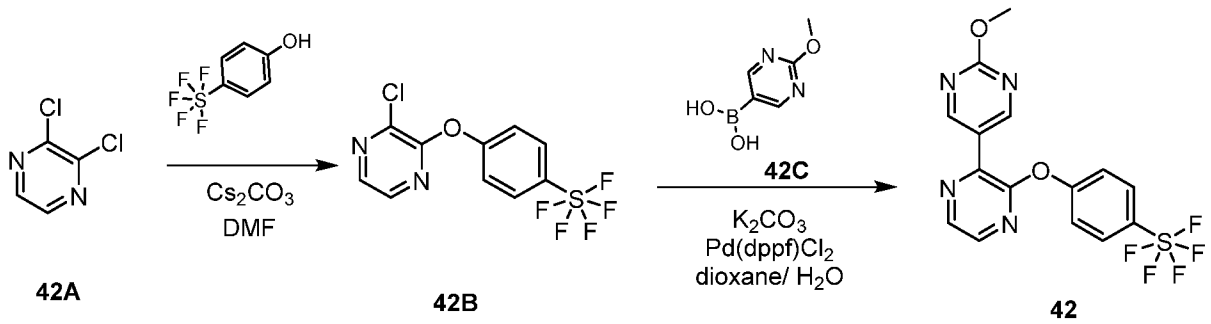
pentafluoro-[4-[3-(2-methoxypyrimidin-5-yl)pyrazin-2-yl]sulfanylphenyl]-sulfane

[00319] To a solution of intermediate **41B** (56.5 mg, 0.25 mmol, 1 eq) in DMF (6 mL) was added Cs_2CO_3 (165.5 mg, 0.5 mmol, 2.0 eq) and 5-(3-chloropyrazin-2-yl)-2-methoxypyrimidine (**41C**, 60 mg, 0.25 mmol, 1.0 eq). The reaction mixture was stirred at 100 °C for 1 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 5/1) to give intermediate **41D** (6 0 mg, 0.14 mmol, 55.9% yield) as a white solid. LCMS (ESI): RT = 0.950 min, mass calcd for $C_{15}H_{11}F_5N_4OS_2$ 422.03 m/z found 423.2 $[M+H]^+$.

5-[3-[4-(pentafluoro-sulfanyl)phenyl]sulfanylpyrazin-2-yl]pyrimidin-2-ol

[00320] A solution of intermediate **41D** (6 0 mg, 0.14 mmol, 1 eq) in HBr/AcOH (0.24 mmol, 3 mL) was stirred at 25 °C for 16 hrs. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 30%-60%, 6.5min) to afford **Compound 41** (4.3 mg, 7.3% yield) as a white solid. LC-MS (ESI): RT = 0.817 min, mass calcd for: $C_{14}H_9F_5N_4OS_2$ 408.01 m/z found 409.2$[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 8.69 (s, 2H), 8.56 (d, J = 2.5 Hz, 1H), 8.45 (d, J = 2.5 Hz, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H).

Example 42: 2-Methoxy-5-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)pyrimidine (Compound 42)



[4-(3-chloropyrazin-2-yl)oxyphenyl]-pentafluoro-sulfane

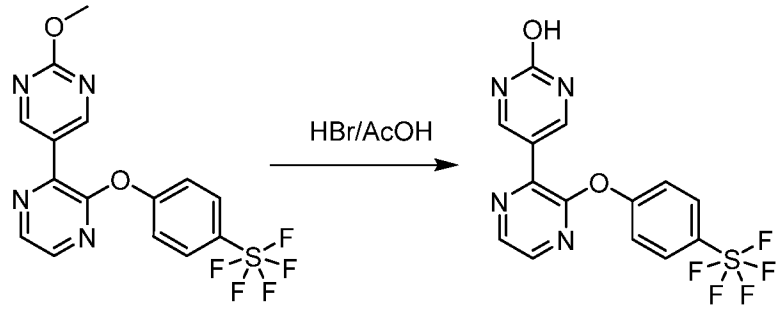
[00321] To a solution of 2,3-dichloropyrazine (**42A**, 500 mg, 3.3 mmol, 1 eq) in DMF (6 mL) was added K_2CO_3 (927.6 mg, 6.7 mmol, 2.0 eq) and 4-(pentafluoro-λ6-sulfaneyl)phenol (738.9 mg, 3.3 mmol, 1.0 eq). The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 1/1) to give intermediate **42B** (0.6 g, 1.80 mmol, 53.74% yield) as a white solid.

pentafluoro-[4-[3-(2-methoxypyrimidin-5-yl)pyrazin-2-yl]oxyphenyl]-sulfane

[00322] To a solution of intermediate **42B** (300 mg, 0.90 mmol, 1 eq) and (2-methoxypyrimidin-5-yl)boronic acid (**42C**, 152.6 mg, 0.99 mmol, 1.1 eq) in dioxane (4 mL) and H_2O (1 mL) was added $Pd(dppf)Cl_2$ (6 5.9 mg, 90.1 µmol, 0.1 eq) and Na_2CO_3 (286.7 mg, 2.71 mmol, 3.0 eq). The reaction mixture was stirred at 90 °C for 16 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 1/1) to afford **Compound 42** (250 mg, 68.2% yield) as a white solid. 50 mg of the compound was additionally purified by

prep-HPLC (column: Welch Xtimate C18 150x25mmx5um;mobile phase: [water(0.05%HCl)-ACN];B%: 50%-80%,8.5min) to afford the desired **Compound 42** (9.91 mg) as a white solid. LC-MS (ESI): RT = 0.955 min, mass calcd for $C_{15}H_{11}F_5N_4O_2S$ 406.05 m/z found 407.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 2H), 8.46 (d, *J* = 2.3 Hz, 1H), 8.09 (d, *J* = 2.5 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 4.14 - 4.05 (m, 3H).

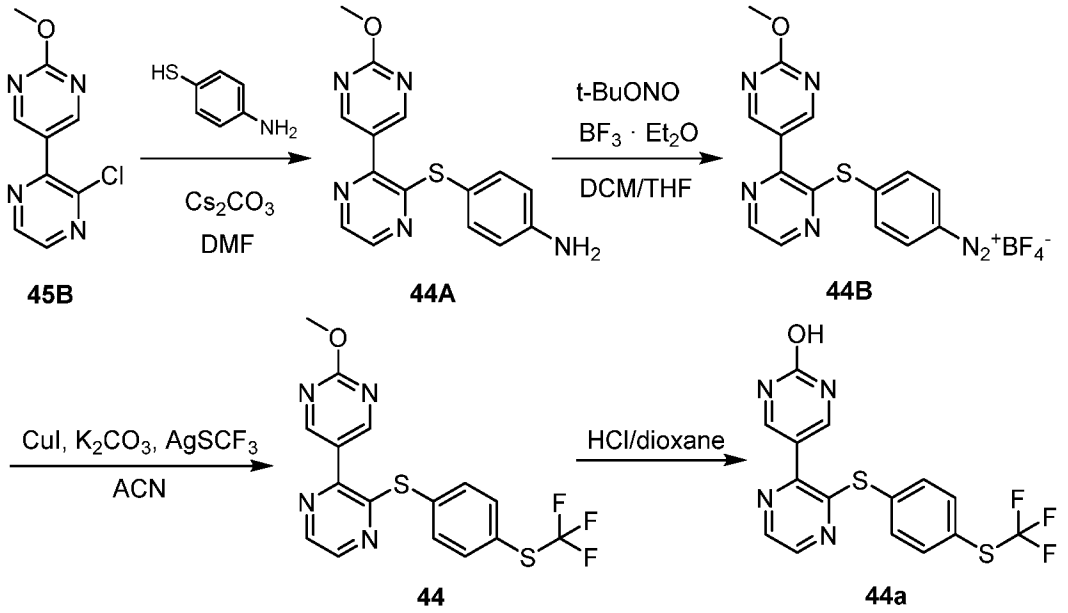
Example 43: 5-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)pyrimidin-2-ol (Compound 43)



42 **43**

[00323] A solution of **Compound 42**(100 mg, 0.24 mmol, 1 eq) in HBr/AcOH (0.24 mmol, 3 mL) was stirred at 25 °C for 16 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 150x25mmx5um;mobile phase: [water(0.05%HCl)-ACN];B%: 40%-70%,8.5min) to afford **Compound 43** (29.7 mg, 30.8% yield) as a white solid. LC-MS (ESI): RT = 0.824 min, mass calcd for $C_{14}H_9F_5N_4O_2S$ 392.04 m/z found 393.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 2H), 8.48 (d, *J* = 2.8 Hz, 1H), 8.14 (d, *J* = 2.5 Hz, 1H), 8.05 - 7.99 (m, 2H), 7.53 (d, *J* = 9.0 Hz, 2H).

Example 44: 2-Methoxy-5-(3-((4-((trifluoromethyl)thio)phenyl)thio)pyrazin-2-yl)pyrimidine (Compound 44) and 5-(3-((4-((trifluoromethyl)thio)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol (Compound 44a)



4-[3-(2-Methoxypyrimidin-5-yl)pyrazin-2-yl]sulfanylaniline

[00324] To a solution of 5-(3-chloropyrazin-2-yl)-2-methoxypyrimidine (**45B**, 200 mg, 0.90 mmol, 1 *eq*) and 4-aminobenzenethiol (168.7 mg, 1.35 mmol, 1.5 *eq*) in DMF (2 mL) was added Cs_2CO_3 (585.4 mg, 1.80 mmol, 2 *eq*). The reaction mixture was stirred at 100 °C for 2 hrs. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (30 mL x 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, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 35 mL/min) to give intermediate **44A** (240 mg, 0.74 mmol, 82.3% yield) as a red solid. LC-MS (ESI): RT = 0.714 min, mass calc. for $C_{15}H_{13}N_5OS$ 311.08, m/z found 312.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 2H), 8.31 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 2.5 Hz, 1H), 7.29 (s, 2H), 6.74 - 6.68 (m, 2H), 4.12 (s, 3H), 3.89 (br s, 2H).

Tetrafluoro-[4-[3-(2-methoxypyrimidin-5-yl)pyrazin-2-yl]sulfanylphenyl]iminoiminio-boron

[00325] To a solution of intermediate **44A** (120 mg, 0.39 mmol, 1 *eq*) in DCM (1.5 mL) was added $BF_3{\cdot}Et_2O$ (114.9 mg, 0.81 mmol, 99.9 µL, 2.1 *eq*). The reaction mixture was stirred at 25 °C for 5 min. THF (1 mL) was added into the reaction mixture. The reaction mixture was cooled to -20 °C and *tert*-butyl nitrite (39.7 mg, 0.39 mmol, 46 uL, 1 *eq*) in DCM (0.5 mL) was added into the reaction mixture. The reaction mixture was stirred at 0 °C for 0.5 hr. Brown solid formed. The reaction mixture was filtered, and the filter cake was washed with DCM give intermediate **44B** (120 mg, crude) as a brown solid. The crude intermediate **44B** was used into the next step without further purification.

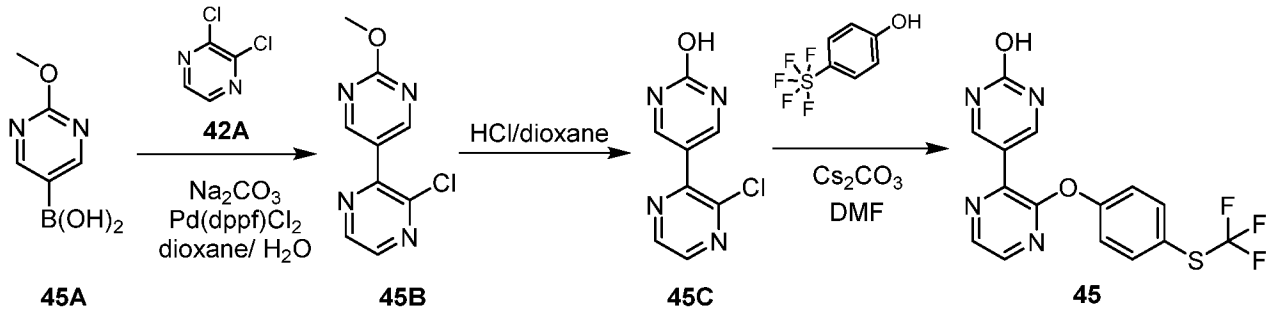
2-Methoxy-5-[3-[4-(trifluoromethylsulfanyl)phenyl]sulfanylpyrazin-2-yl]pyrimidine

[00326] To a mixture of intermediate **44B** (120 mg, 0.29 mmol, 1 *eq*) and (trifluoromethylthio) silver (91.7 mg, 0.44 mmol, 1.5 *eq*) in acetonitrile (2 mL) were added CuI (55.7 mg, 0.29 mmol, 1 *eq*) and K_2CO_3 (80.9 mg, 0.59 mmol, 2 *eq*). The reaction mixture was stirred at 25 °C for 16 hr. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL x 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, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 45%-75%, 8.5 min) to afford **Compound 44** (25 mg, 21.3% yield) as a white solid. LC-MS (ESI): RT = 0.714 min, mass calc. for $C_{16}H_{11}F_3N_4OS_2$ 396.03, m/z found 397.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 2H), 8.44 (d, *J*=2.5 Hz, 1H), 8.32 (d, *J*=2.5 Hz, 1H), 7.68 (d, *J*=8.3 Hz, 2H), 7.54 (d, *J*=8.5 Hz, 2H), 4.13 (s, 3H).

5-[3-[4-(Trifluoromethylsulfanyl)phenyl]sulfanylpyrazin-2-yl]pyrimidin-2-ol

[00327] A solution of **Compound 44** (20 mg, 50.5 µmol, 1 *eq*) in HCl/dioxane (1 mL) was stirred at 70 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 30%-60%, 6.5 min) to give **Compound 44a** (3.6 mg, 18.4% yield) as a white solid. LC-MS (ESI): RT = 0.818 min, mass calc. for $C_{15}H_9F_3N_4OS_2$ 382.02, m/z found 383.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 2H), 8.55 (d, *J* = 2.3 Hz, 1H), 8.44 (d, *J* = 2.3 Hz, 1H), 7.74 (br d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H).

Example 45: 5-(3-(4-((Trifluoromethyl)thio)phenoxy)pyrazin-2-yl)pyrimidin-2-ol (Compound 45)



45A 45B 45C 45

5-(3-Chloropyrazin-2-yl)-2-methoxypyrimidine

[00328] A solution of 2,3-dichloropyrazine (**42A**, 5.8 g, 38.98 mmol, 1.2 *eq*), (2-methoxypyrimidin-5-yl)boronic acid (**45A**, 5.0 g, 32.48 mmol, 1.0 *eq*), $Pd(dppf)Cl_2$ (2.4 g, 3.25 mmol, 0.1 *eq*) and Na_2CO_3 (6 .9 g, 64.96 mmol, 2.0 *eq*) in dioxane (50 mL) and H_2O (5 mL) at

30 °C was purged and degassed with N_2 for 3 times and then stirred at 90 °C under N_2 for 16 hrs. The reaction mixture was quenched with water (200 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate **45B** (2.8 g, 11.81 mmol, 36.4% yield) as a white solid. LC-MS (ESI): RT = 0.712 min, mass calc. for $C_9H_7ClN_4O$ 222.03, m/z found 223.1 $[M+H]^+$.

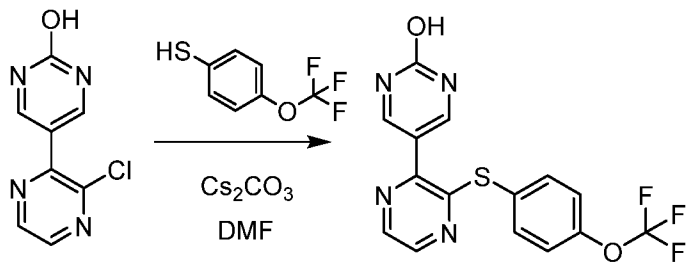
5-(3-Chloropyrazin-2-yl)pyrimidin-2-ol

[00329] A solution of intermediate **45B** (1.0 g, 4.49 mmol, 1 *eq*) in HCl/dioxane (4 M, 10.0 mL, 8.91 *eq*) was stirred at 80 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to give intermediate **45C** (930.0 mg, 4.41 mmol, 98.3% yield) as a brown solid.

5-(3-(4-((Trifluoromethyl)thio)phenoxy)pyrazin-2-yl)pyrimidin-2-ol

[00330] To a solution of 4-(pentafluoro-λ6-sulfaneyl)phenol (51.2 mg, 0.26 mmol, 1.1 *eq*) in DMSO (1 mL) was added intermediate **45C** (50.0 mg, 0.24 mmol, 1.0 *eq*) and Cs_2CO_3 (117.1 mg, 0.36 mmol, 1.5 *eq*). The reaction mixture was stirred at 110 °C for 4 hrs. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by prep-HPLC: (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water(0.05%HCl)-ACN];B%: 30%-60%, 6.5 min) to afford **Compound 55** (270.0 mg, 46.8% yield) as a yellow oil. LCMS (ESI): RT = 0.827 min, mass calc. for $C_{15}H_9F_3N_4O_2S$ 366.04, m/z found 367.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.03 (brs, 2H), 8.47 (brs, 1H), 8.15 (brd, J = 1.8 Hz, 1H), 7.82 (brd, J = 8.3 Hz, 2H), 7.47 (brd, J = 8.4 Hz, 2H).

Example 46: 5-(3-((4-(Trifluoromethoxy)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol (Compound 46)

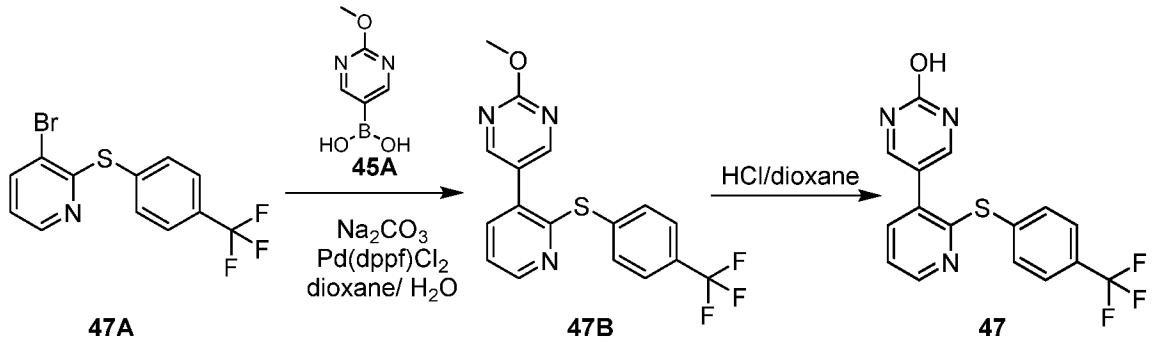


45C 46

5-(3-((4-(trifluoromethoxy)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol

[00331] To a solution of 4-(trifluoromethoxy)benzenethiol (69.8 mg, 0.36 mmol, 1.5 *eq*) in DMSO (1 mL) was added intermediate **45C** (50.0 mg, 0.24 mmol, 1.0 *eq*) and Cs_2CO_3 (117.1 mg, 0.36 mmol, 1.5 *eq*). The solution was stirred at 110 °C for 4 hrs. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water(0.05%HCl)-ACN]; B%: 25%-55%, 6.5 min) to afford **Compound 46** (17.55 mg, 19.8% yield) as a white solid. LC-MS (ESI): RT = 0.797 min, mass calc. for $C_{15}H_9F_3N_4O_2S$ 366.04, m/z found 367.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 2H), 8.50 (d, J = 2.5 Hz, 1H), 8.39 (d, J = 2.5 Hz, 1H), 7.66 - 7.62 (m, 2H), 7.44 (d, J = 8.0 Hz, 2H).

Example 47: 5-(2-((4-(Trifluoromethyl)phenyl)thio)pyridin-3-yl)pyrimidin-2-ol (Compound 47)



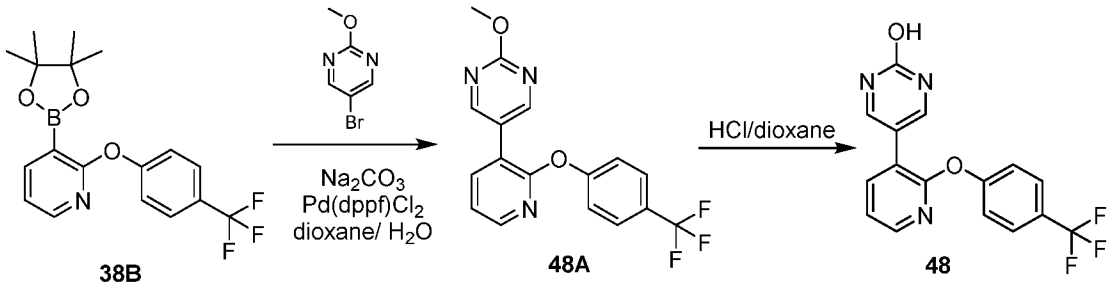
2-methoxy-5-[2-[4-(trifluoromethyl)phenyl]sulfanyl-3-pyridyl]pyrimidine

[00332] To a solution of 3-bromo-2-((4-(trifluoromethyl)phenyl)thio)pyridine (**47A**, 100 mg, 0.30 mmol, 1 *eq*) and (2-methoxypyrimidin-5-yl)boronic acid (**45A**, 55.3 mg, 0.36 mmol, 1.2 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) were added $Pd(dppf)Cl_2$ (21.9 mg, 29.93 µmol, 0.1 *eq*) and Na_2CO_3 (6 3.4 mg, 0.60 mmol, 2.0 *eq*) in one portion with N_2 for 3 times. The reaction mixture was stirred at 100 °C for 5 hr under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (6 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-TLC (PE:EtOAc = 5:1) to give intermediate **47B** (21 mg, 36.9 µmol, 12.3% yield) as a yellow solid. LC-MS (ESI): RT = 0.877 min, mass calcd. For $C_{17}H_{12}F_3N_3OS$, 363.07 m/z found 363.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 3H) 7.21 - 7.26 (m, 2H) 7.48 - 7.56 (m, 3H) 7.57 - 7.63 (m, 2H) 8.45 (dd, J = 4.77, 1.76 Hz, 1H) 8.62 (s, 2 H) 8.94 (s, 1H).

5-[2-[4-(trifluoromethyl)phenyl]sulfanyl-3-pyridyl]pyrimidin-2-ol

[00333] To a solution of intermediate **47B** (21 mg, 57.7 µmol, 1 *eq*) was added HCl/dioxane (2 mL) in one portion at 25 °C for 18 hrs, and at 60 °C for 19 hr. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 25%-55%, 6.5 min) to afford **Compound 47** (3.7 mg, 18.3% yield). LC-MS (ESI): RT = 0.723 min, mass calcd. For $C_{16}H_{10}F_3N_3OS$, 349.05 m/z found 349.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.44 (dd, *J* = 7.65, 4.89 Hz, 1H) 7.56 (d, *J* = 8.03 Hz, 2H) 7.63 - 7.68 (m, 2 H) 7.86 (dd, *J* = 7.78, 1.76 Hz, 1H) 8.48 (br d, *J* = 3.26 Hz, 1H) 8.81 (br s, 2H).

Example 48: 5-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)pyrimidin-2-ol (Compound 48)



2-methoxy-5-[2-[4-(trifluoromethyl)phenoxy]-3-pyridyl]pyrimidine

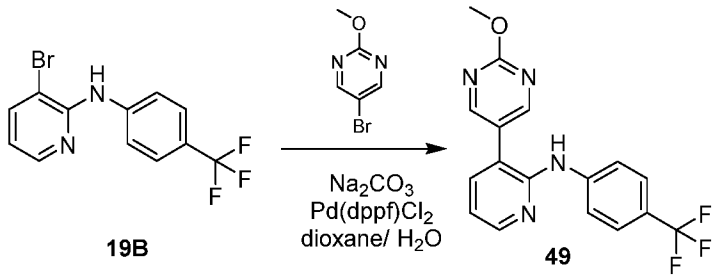
[00334] To a solution of 5-bromo-2-methoxypyrimidine (124.2 mg, 0.66 mmol, 1.2 *eq*) and intermediate **38B** (200 mg, 0.55 mmol, 1 *eq*) in dioxane (4 mL) and H_2O (0.4 mL) were added $Pd(dppf)Cl_2$ (80.1 mg, 0.11 mmol, 0.2 *eq*) and Na_2CO_3 (116.1 mg, 1.10 mmol, 2.0 *eq*) in one portion with N_2 for 3 times and the reaction mixture was stirred at 100 °C for 4 hr under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **48A** (95 mg, 0.26 mmol, 48.4% yield) as a white solid. LCMS (ESI): RT = 0.869 min, mass calcd. For $C_{17}H_{12}F_3N_3O_2$, 347.09 m/z found 347.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3 H) 4.08 (s, 3 H) 7.26 (s, 3 H) 7.67 (d, *J* = 8.53 Hz, 2 H) 7.81 (dd, *J* = 7.53, 1.76 Hz, 1 H) 8.21 (dd, *J* = 5.02, 1.76 Hz, 1 H) 8.82 (s, 2 H).

5-[2-[4-(trifluoromethyl)phenoxy]-3-pyridyl]pyrimidin-2-ol

[00335] To a solution of intermediate **48A** (50 mg, 143.97 µmol, 1 *eq*) was added HCl/dioxane (2 mL) in one portion at 60°C for 17 hr. The reaction mixture was concentrated under

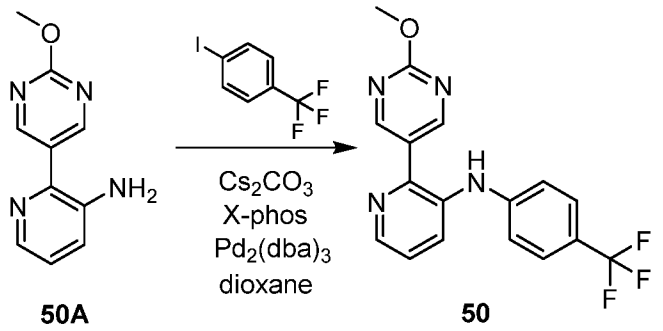
reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl) -ACN]; B%: 25%-55%, 6.5min) to afford **Compound 48** (5.1 mg, 10.7% yield). LC-MS (ESI): RT = 0.728 min, mass calcd. For $C_{16}H_{10}F_3N_3O_2$, 333.07 m/z found 333.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.30 (dd, *J* = 7.53, 5.02 Hz, 1H) 7.36 (d, *J* = 8.53 Hz, 2H) 7.74 (d, *J* = 8.53 Hz, 2H) 8.05 (br d, *J* = 7.53 Hz, 1H) 8.16 (br d, *J* = 3.76 Hz, 1H) 9.02 (br s, 2H).

Example 49: 3-(2-Methoxypyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine (Compound 49)



[00336] To a solution of intermediate **19B** (100 mg, 0.31 mmol, 1 *eq*) and 5-bromo-2-methoxypyrimidine (58.2 mg, 0.38 mmol, 1.2 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) were added $Pd(dppf)Cl_2$ (46.1 mg, 63 μmol, 0.2 *eq*) and Na_2CO_3 (6 6.8 mg, 0.63 mmol, 2.0 *eq*) in one portion with N_2 for 3 times. And the reaction mixture was stirred at 100 °C for 2 hr under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (6 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to afford **Compound 49** (42 mg, 37.6% yield) was obtained as a white solid. LC-MS (ESI): RT = 0.816 min, mass calcd. For $C_{17}H_{13}F_3N_4O$, 346.10 m/z found 346.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 3H) 6.41 (s, 1H) 6.92 - 7.02 (m, 1H) 6.99 (dd, *J* = 7.40, 4.89 Hz, 1H) 7.46 (dd, *J* = 7.28, 1.76 Hz, 1H) 7.51 - 7.57 (m, 2H) 7.57 - 7.65 (m, 2H) 8.35 (dd, *J* = 4.89, 1.63 Hz, 1H) 8.64 (s, 2H).

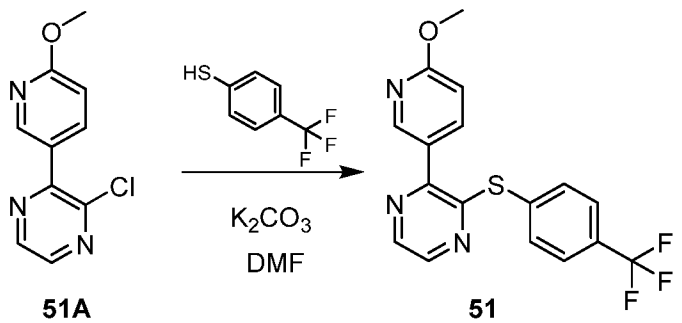
Example 50: 2-(2-Methoxypyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 50)



50A **50**

[00337] To a solution of 2-(2-methoxypyrimidin-5-yl)pyridin-3-amine (**50A**, 35 mg, 0.17 mmol, 1 *eq*), 1-iodo-4-(trifluoromethyl)benzene (70.6 mg, 0.26 mmol, 38 uL, 1.5 *eq*) and Cs_2CO_3 (169.2 mg, 0.52 mmol, 3 *eq*) in dioxane (1 mL) at 20°C was added $Pd_2(dba)_3$ (7.9 mg, 8.7 µmol, 0.05 *eq*) and X-Phos (8.3 mg, 17.3 µmol, 0.1 *eq*), and the reaction mixture was purged and degassed with N_2 for 3 times and then stirred at 100°C under N_2 for 16 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL) and EtOAc (10 mL), and then filtered to remove the solid. The filtrate was extracted with EtOAc (20 mL x 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, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to afford **Compound 50** (50 mg, 83.4% yield) as a yellow solid. LC-MS (ESI): RT = 0.775 min, mass calc. for $C_{17}H_{13}F_3N_4O$ 346.10, m/z found 346.9 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 2H), 8.49 (dd, *J* = 1.3, 4.6 Hz, 1H), 7.75 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.32 (dd, *J* = 4.6, 8.3 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.73 (s, 1H), 4.06 (s, 3H).

Example 51: 2-(6-methoxypyridin-3-yl)-3-((4-(trifluoromethyl)phenyl)thio)pyrazine (Compound 51)

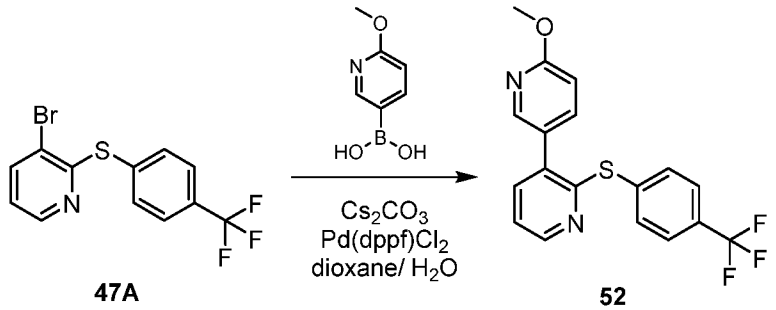


51A **51**

[00338] To a mixture of 2-chloro-3-(6-methoxypyridin-3-yl)pyrazine (**51A**, 100 mg, 0.45 mmol, 1 *eq*) and 4-(trifluoromethyl)benzenethiol (96.5 mg, 0.54 mmol, 1.2 *eq*) in DMF (2 mL) at 30°C was added K_2CO_3 (187.1 mg, 1.35 mmol, 3 *eq*). And the reaction mixture was degassed and purged with N_2 for 3 times, and the reaction mixture was stirred at 80°C for 2 h under N_2. The

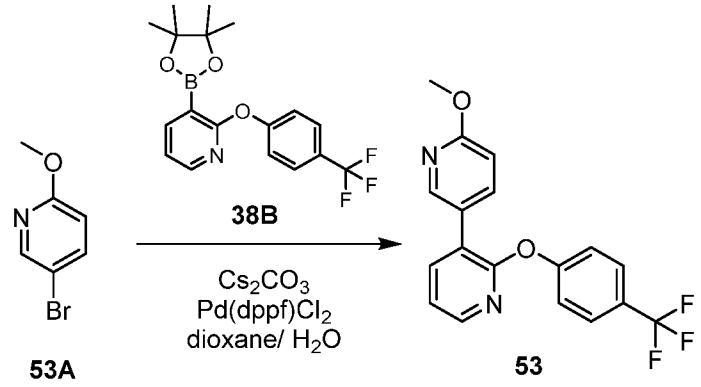
reaction mixture was diluted with water (10 mL), and then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to afford **Compound 51** (120 mg, 71.7% yield) as a white solid. LC-MS (ESI): RT = 0.928 min, mass calc. for $C_{17}H_{12}F_3N_3OS$ 363.07, m/z found 364.0 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 2.5 Hz, 1H), 8.40 (d, *J* = 2.5 Hz, 1H), 8.25 (d, *J* = 2.5 Hz, 1H), 8.01 (dd, *J* = 2.5, 8.8 Hz, 1H), 7.63 (q, *J* = 8.4 Hz, 4H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.04 (s, 3H).

Example 52: 6'-Methoxy-2-((4-(trifluoromethyl)phenyl)thio)-3,3'-bipyridine (Compound 52)



[00339] A mixture of (6-methoxy-3-pyridyl)boronic acid (95.0 mg, 0.62 mmol, 1.2 *eq*), intermediate **47A** (173.0 mg, 0.51 mmol, 1 *eq*), Cs_2CO_3 (506.1 mg, 1.55 mmol, 3 *eq*), $Pd(dppf)Cl_2$ (37.8 mg, 51.7 μmol, 0.1 *eq*) in dioxane (2 mL) and H_2O (0.1 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% PE/EtOAc@ 35 mL/min) to afford **Compound 52** (7.1 mg, 17% yield) was obtained as white solid. LC-MS (ESI): RT = 1.026 min, mass calcd for $C_{18}H_{13}F_3N_2OS$ 362.37 m/z found 363.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 3.96 (s, 3 H) 6.90 (d, *J* = 8.28 Hz, 1 H) 7.36 (dd, *J* = 7.65, 4.89 Hz, 1 H) 7.49 (d, *J* = 8.03 Hz, 2 H) 7.60 (d, *J* = 8.28 Hz, 2 H) 7.71 (dd, *J* = 7.53, 1.76 Hz, 1 H) 7.81 (dd, *J* = 8.66, 2.38 Hz, 1 H) 8.17 (d, *J* = 2.26 Hz, 1 H) 8.39 (dd, *J* = 4.89, 1.63 Hz, 1 H).

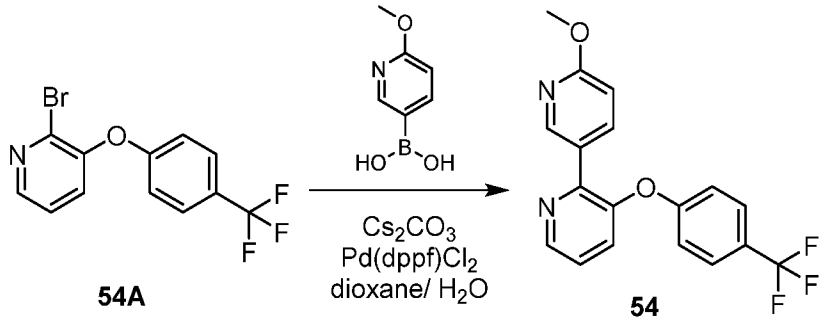
Example 53: 6'-Methoxy-2-(4-(trifluoromethyl)phenoxy)-3,3'-bipyridine (Compound 53)



2-methoxy-5-[2-[4-(trifluoromethyl)phenoxy]-3-pyridyl]pyridine

[00340] A mixture of 5-bromo-2-methoxy-pyridine (**53A**, 100 mg, 0.53 mmol, 68.9 uL, 1 *eq*), intermediate **38B** (213.6 mg, 0.58 mmol, 1.1 *eq*), $Pd(dppf)Cl_2$ (19.4 mg, 26.5 µmol, 0.05 *eq*), Cs_2CO_3 (519.8 mg, 1.60 mmol, 3 *eq*) in dioxane (1 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% PE/EtOAc @ 35mL/min) to afford **Compound 53** (9.83 mg, 19% yield) as a white solid. LC-MS (ESI): RT = 0.827 min, mass calcd for $C_{17}H_{11}F_3N_2O_2$ 332.28 m/z found 333.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.44 - 6.49 (m, 1 H) 7.26 (dd, J = 7.53, 4.77 Hz, 1 H) 7.37 (d, J = 8.28 Hz, 2 H) 7.78 (br d, J = 8.53 Hz, 3 H) 7.84 (dd, J = 9.41, 2.89 Hz, 1 H) 7.97 (dd, J = 7.53, 1.76 Hz, 1 H) 8.09 (dd, J = 4.89, 1.88 Hz, 1 H).

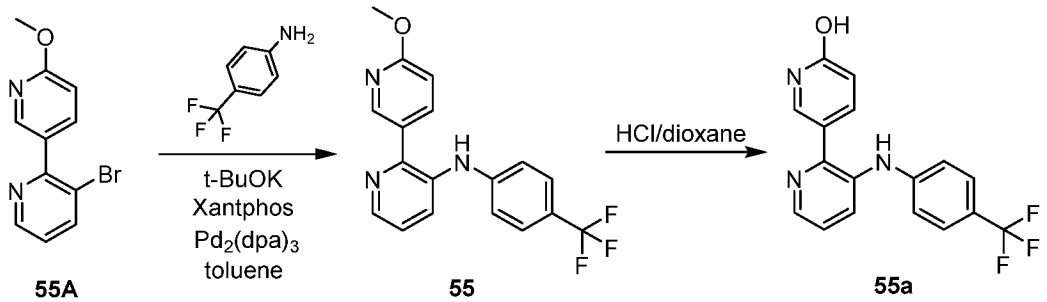
Example 54: 6'-Methoxy-3-(4-(trifluoromethyl)phenoxy)-2,3'-bipyridine (Compound 54)



[00341] A mixture of 2-bromo-3-[4-(trifluoromethyl)phenoxy]pyridine (**54A**, 100 mg, 0.31 mmol, 1 *eq*), (6-methoxy-3-pyridyl)boronic acid (72.1 mg, 0.47 mmol, 1.5 *eq*), Cs_2CO_3 (307.2 mg, 0.94 mmol, 3 *eq*), $Pd(dppf)Cl_2$ (11.5 mg, 15.7 µmol, 0.05 *eq*) in dioxane (2 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2

atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~20% PE/EtOAc@ 35 mL/min) to afford **Compound 54** (7.6 mg, 6.2% yield, HCl) was obtained as a white solid. LC-MS (ESI): RT = 0.941 min, mass calcd for $C_{18}H_{13}F_3N_2O_2$ 346.30 m/z found 347.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 3.98 (s, 3 H) 6.98 (d, *J* = 8.78 Hz, 1 H) 7.25 (d, *J* = 8.53 Hz, 2 H) 7.30 (dd, *J* = 7.40, 4.89 Hz, 1 H) 7.68 (d, *J* = 8.53 Hz, 2 H) 7.97 (dd, *J* = 7.53, 1.76 Hz, 1 H) 8.08 (dd, *J* = 8.66, 2.38 Hz, 1 H) 8.14 (dd, *J* = 4.89, 1.88 Hz, 1 H) 8.42 (d, *J* = 2.26 Hz, 1 H).

Example 55: 6'-methoxy-N-(4-(trifluoromethyl)phenyl)-[2,3'-bipyridin]-3-amine (Compound 55) and 3-((4-(trifluoromethyl)phenyl)amino)-[2,3'-bipyridin]-6'-ol (Compound 55a)



55A 55 55a

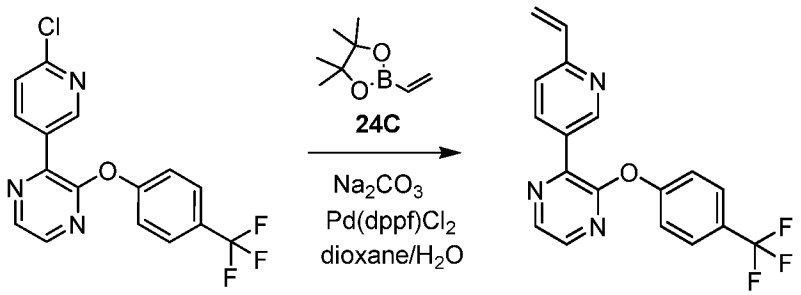
2-(6-Methoxy-3-pyridyl)-N-[4-(trifluoromethyl)phenyl]pyridin-3-amine (Compound 55)

[00342] A mixture of 3-bromo-2-(6-methoxy-3-pyridyl)pyridine (**55A**, 200 mg, 0.75mmol, 1 *eq*) , 4-(trifluoromethyl)aniline (145.8 mg, 0.90mmol, 0.1mL, 1.2 *eq*), $Pd_2(dba)_3$ (34.5 mg, 37.7 µmol, 0.05 *eq*), Xantphos (43.6 mg, 75.4 µmol, 0.1 *eq*) and t-BuOK (253.9 mg, 2.26 mmol, 3 *eq*) in toluene (2 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 110 °C for 10 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (5 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 40 g SepaFlash ® Silica Flash Column, Eluent of 0~50% PE/EtOAc@ 35 mL/min) to afford **Compound 55** (150 mg, 52.9% yield) as a yellow solid. LC-MS (ESI): RT = 0.818 min, mass calcd for $C_{18}H_{14}F_3N_3O$ 345.32 m/z found 346.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 - 3.94 (m, 1H) 3.92 (s, 2H) 5.97 (br s, 1H) 6.83 (br s, 1H) 7.03 (br s, 2H) 7.34 (br s, 1H) 7.49 (br d, *J* = 5.38 Hz, 2H) 7.78 - 7.98 (m, 2H) 8.36 (br s, 1H) 8.50 (br s, 1H).

5-[3-[4-(Trifluoromethyl)phenyl]sulfanyl-2-pyridyl]pyridin-2-ol (Compound 55a)

[00343] The mixture of **Compound 55** (80 mg, 231.67 µmol, 1 *eq*) and HCl/dioxane (4 M, 3 mL, 51.80 *eq*) was stirred at 70 °C for 4 hr. The reaction mixture was diluted with H_2O (3 mL) and the reaction mixture was adjusted pH to 8 with NaOH (4 M).The reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl)-ACN];B%: 20%-50%,6.5min) to afford **Compound 55a** as a yellow solid. LC-MS (ESI): RT = 0.753 min, mass calcd for $C_{17}H_{12}F_3N_3O$ 331.29 m/z found 332.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.64 (d, *J* = 9.54 Hz, 1H) 7.20 (d, *J* = 8.28 Hz, 2H) 7.58 (d, *J* = 8.53 Hz, 2H) 7.76 (dd, *J* = 8.53, 5.52 Hz, 1H) 7.84 (dd, *J* = 9.66, 2.64 Hz, 1H) 7.98 (d, *J* = 2.01 Hz, 1H) 8.28 (dd, *J* = 8.53, 1.25 Hz, 1H) 8.36 (dd, *J* = 5.27, 1.26 Hz, 1H).

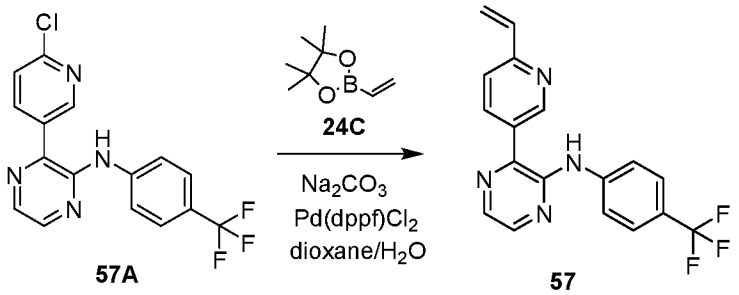
Example 56: 2-(4-(Trifluoromethyl)phenoxy)-3-(6-vinylpyridin-3-yl)pyrazine (Compound 56)



56A **56**

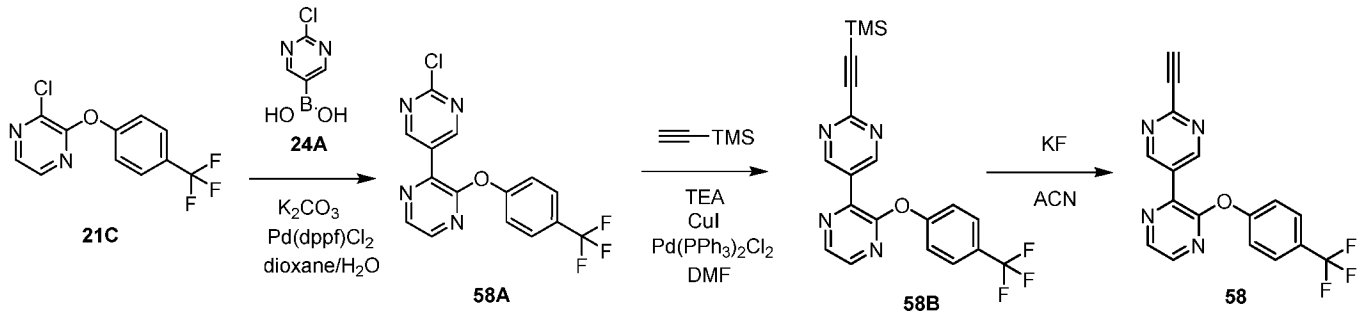
[00344] A solution of 2-(6-chloropyridin-3-yl)-3-(4-(trifluoromethyl)phenoxy)pyrazine (**56A**, 150.0 mg, 0.43 mmol, 1.0 eq), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (**24C**, 92.0 mg, 0.60 mmol, 0.1 mL, 1.4 eq), $Pd(dppf)Cl_2$ (31.2 mg, 43 µmol, 0.1 eq) and Na_2CO_3 (90.4 mg, 0.85 mmol, 2.0 eq) in dioxane (1.5 mL) and H_2O (0.15 mL) at 20 °C was purged and degassed with N_2 purged for 3 times and then stirred under N_2 at 90 °C for 16 hrs. The residue was concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) and purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN]; B%: 40%-70%, 6.5 min) to afford **Compound 56** (6.0 mg, 3.5% yield, HCl) as a white solid. LC-MS (ESI): RT = 0.872 min, mass calc. for $C_{18}H_{12}F_3N_3O$ 343.09, m/z found 344.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.47 (d, *J* = 1.5 Hz, 1H), 9.33 (dd, *J* = 1.8, 8.5 Hz, 1H), 8.58 (d, *J* = 2.5 Hz, 1H), 8.39 (d, *J* = 8.8 Hz, 1H), 8.27 (d, *J* = 2.3 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.49 (brd, *J* = 8.5 Hz, 2H), 7.09 (dd, *J* = 11.2, 17.7 Hz, 1H), 6.67 (d, *J* = 17.6 Hz, 1H), 6.15 (d, *J* = 11.3 Hz, 1H).

Example 57: *N*-(4-(Trifluoromethyl)phenyl)-3-(6-vinylpyridin-3-yl)pyrazin-2-amine (Compound 57)



[00345] To a solution of 3-(6-chloropyridin-3-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (**57A**, 50 mg, 0.14 mmol, 1 *eq*), Na_2CO_3 (30.2 mg, 0.29 mmol, 2 *eq*) and $Pd(PPh_3)_4$ (8.2 mg, 7.1 µmol, 0.05 *eq*) in dioxane (2 mL) and Water (0.2 mL) at 20°C was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolaner (**24C**, 32.9 mg, 0.21 mmol, 36 uL, 1.5 *eq*), and the resulting mixture was purged and degassed with N_2 for 3 times and then stirred at 90°C under N_2 for 16 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 20 mL/min), and was further purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water(0.05%HCl)-ACN];B%: 40%-70%,6.5min) to afford **Compound 57** (19.3 mg, 35.9% yield, HCl) as a yellow solid. LC-MS (ESI): RT = 0.781 min, mass calc. for $C_{18}H_{13}F_3N_4$ 342.11, m/z found 342.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 9.01 (d, J = 1.5 Hz, 1H), 8.45 - 8.39 (m, 1H), 8.34 - 8.27 (m, 2H), 7.97 (br d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.02 (dd, J = 11.0, 17.3 Hz, 1H), 6.52 (d, J = 17.6 Hz, 1H), 5.79 (d, J = 10.8 Hz, 1H).

Example 58: 2-Ethynyl-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine (Compound 58)



2-chloro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine

[00346] A solution of 2-chloro-3-(4-(trifluoromethyl)phenoxy)pyrazine (**21C**, 1 g, 3.64 mmol, 1 *eq*), (2-chloropyrimidin-5-yl)boronic acid (**24A**, 691.9 mg, 4.37 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (266.4 mg, 0.36 mmol, 0.1 *eq*) and Na_2CO_3 (771.9 mg, 7.28 mmol, 2 *eq*) in dioxane (10 mL) and H_2O (1 mL) at 20°C was purged and degassed with N_2 purged for 3 times and then stirred under N_2 at 90°C for 16 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **58A** (220 mg, 0.59 mmol, 16.2% yield) as a yellow solid. LCMS (ESI): RT = 0.963 min, mass calc. for $C_{15}H_8ClF_3N_4O$ 352.03, m/z found 353.1 $[M+1]^+$.

5-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)-2-((trimethylsilyl)ethynyl)pyrimidine

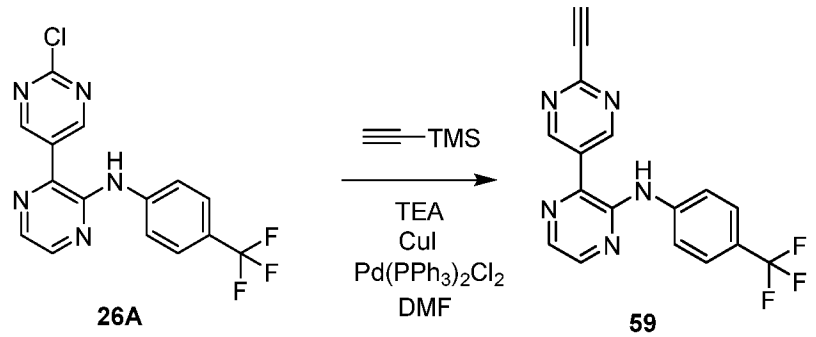
[00347] To a solution of intermediate **58A** (90 mg, 0.26 mmol, 1 *eq*) and ethynyltrimethylsilane (50.1 mg, 0.51 mmol, 71 uL, 2 *eq*) in DMF (1 mL) was added TEA (90.4 mg, 0.89 mmol, 0.12 mL, 3.5 *eq*). The reaction mixture was degassed with N_2 for 3 times and CuI (2.4 mg, 12.8 µmol, 0.05 *eq*) and $Pd(PPh_3)_2Cl_2$ (17.9 mg, 25.5 µmol, 0.1 *eq*) were added. The reaction mixture was further degassed with N_2 for 3 times and then was stirred and heated to 120 °C for 1 h under N_2. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give intermediate **58B** (65 mg, 0.12 mmol, 47.9% yield) as a yellow solid. LCMS (ESI): RT = 1.070 min, mass calc. for $C_{20}H_{17}F_3N_4OSi$ 414.11, m/z found 415.1 $[M+1]^+$.

2-Ethynyl-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine

[00348] To a solution of intermediate **58B** (40 mg, 96.5 µmol, 1 *eq*) in ACN (1 mL)at 20°C was added KF (11.2 mg, 0.19 mmol, 5 uL, 2 *eq*), and the reaction mixture was stirred at 20°C for 16 hrs. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to afford **Compound 58** (10.2 mg, 30.6% yield) as a yellow solid. LCMS (ESI): RT = 0.848 min, mass calc. for $C_{17}H_9F_3N_4O$ 342.07, m/z

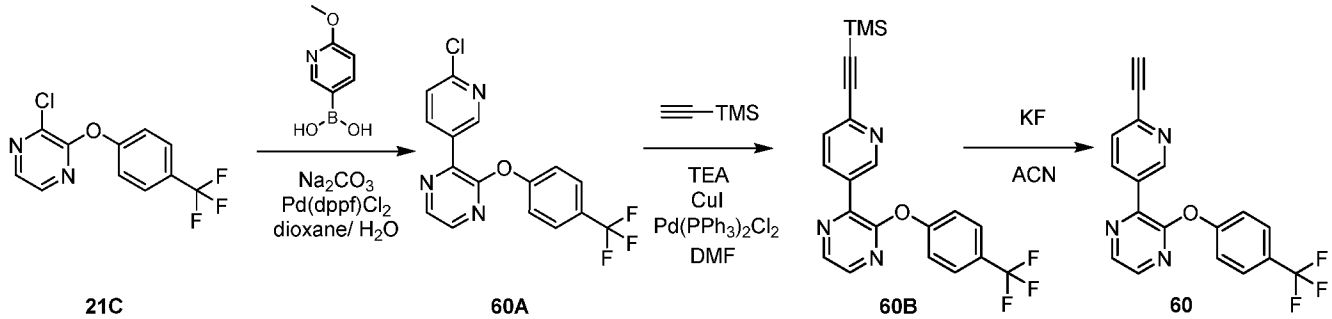
found 342.9 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 2H), 8.51 (d, *J* = 2.3 Hz, 1H), 8.16 (d, *J* = 2.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 3.26 (s, 1H).

Example 59: 3-(2-Ethynylpyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (Compound 59)



[00349] To a solution of 3-(2-chloropyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (**26A**, 100.0 mg, 0.28 mmol, 1.0 eq) and ethynyltrimethylsilane (55.9 mg, 0.57 mmol, 79 uL, 2.0 eq) in DMF (1 mL) was added TEA (100.7 mg, 1.0 mmol, 0.1 mL, 3.5 eq). The reaction mixture was degassed with N_2 for 3 times and CuI (2.7 mg, 14 μmol, 0.05 eq) and $Pd(PPh_3)_2Cl_2$ (20.0 mg, 28 μmol, 0.1 eq) were added. The reaction mixture was further degassed with N_2 for 3 times and then was stirred and heated to 120 °C for 0.5 hr under N_2. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 20 mL/min), and was further purified by prep-HPLC: (column: Welch Xtimate C18 150x25mmx5um; mobile phase: [water (0.05%NH_3H_2O)-ACN]; B%: 51%-81%, 9.5 min) to afford **Compound 59** (11.2 mg, 10.7% yield) as a yellow solid. LC-MS (ESI): RT = 0.896 min, mass calc. for $C_{17}H_{10}F_3N_5$ 341.09, m/z found 342.1 $[M+H]^+$; ^1H NMR (400 Hz, $CDCl_3$) δ 9.15 (s, 2H), 8.30 - 8.27 (m, 2H), 7.60 (d, J .3 Hz, 4H), 6.94 (s, 1H), 3.25 (s, 1H).

Example 60: 2-(6-Ethynylpyridin-3-yl)-3-(4-(trifluoromethyl)phenoxy)pyrazine (Compound 60)



2-(6-Chloropyridin-3-yl)-3-(4-(trifluoromethyl)phenoxy)pyrazine

[00350] A solution of 2-chloro-3-(4-(trifluoromethyl)phenoxy)pyrazine (**21C**, 1 g, 3.64 mmol, 1 *eq*), (6-methoxy-3-pyridyl)boronic acid (6 87.6 mg, 4.37 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (266.4 mg, 0.36 mmol, 0.1 *eq*) and Na_2CO_3 (771.9 mg, 7.28 mmol, 2 *eq*) in dioxane (10 mL) and H_2O (1 mL) was degassed with N_2 for 3 times and then was stirred and heated to 90 °C for 16 hrs under N_2. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **60A** (330 mg, 0.90 mmol, 24.7% yield) as a yellow solid. LCMS (ESI): RT = 0.982 min, mass calc. for $C_{16}H_9ClF_3N_3O$ 351.04, m/z found 352.0 $[M+H]^+$.

2-(4-(Trifluoromethyl)phenoxy)-3-(6-((trimethylsilyl)ethynyl)pyridin-3-yl)pyrazine

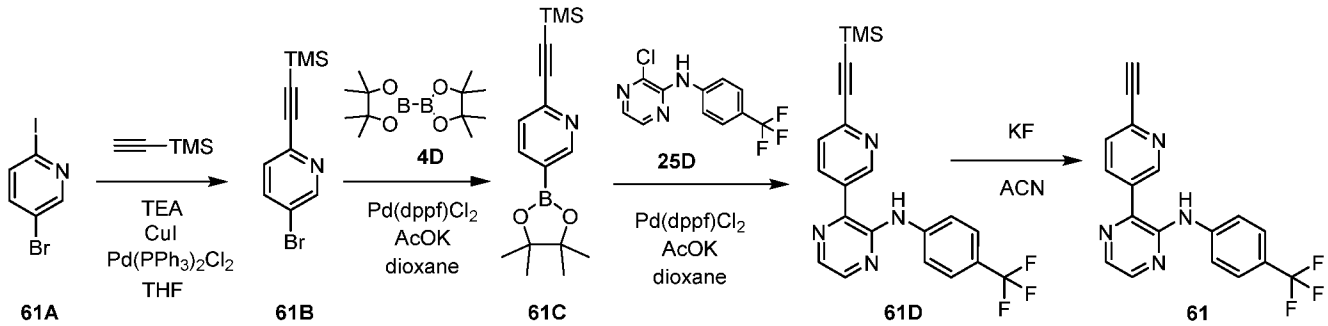
[00351] To a solution of intermediate **60A** (100 mg, 0.28 mmol, 1 *eq*) and ethynyltrimethylsilane (55.85 mg, 0.57 mmol, 79 uL, 2 *eq*) in DMF (1 mL) was added TEA (100.7 mg, 1.00 mmol, 0.14 mL, 3.5 *eq*). The reaction mixture was degassed with N_2 for 3 times and CuI (2.7 mg, 14.2 µmol, 0.05 *eq*) and $Pd(PPh_3)_2Cl_2$ (20.0 mg, 28.4 µmol, 0.1 *eq*) were added. The reaction mixture was further degassed with N_2 for 3 times and then was stirred and heated to 120 °C for 1 h under N_2. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give intermediate **60B**(70 mg, 83.0 µmol, 29.2% yield) as a yellow solid. LCMS (ESI): RT = 1.087 min, mass calc. for $C_{21}H_{18}F_3N_3OSi$ 413.12, m/z found 414.1 $[M+H]^+$.

2-(6-ethynylpyridin-3-yl)-3-(4-(trifluoromethyl)phenoxy)pyrazine

[00352] To a solution of intermediate **60B** (30 mg, 72.6 µmol, 1 *eq*) in ACN (1 mL) at 20°C was added KF (8.4 mg, 0.15 mmol, 3.4 uL, 2 *eq*), and the reaction mixture was stirred at 20°C for

16 hrs. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to afford **Compound 60** (9.0 mg, 36.4% yield) as a white solid. LC-MS (ESI): RT = 0.864 min, mass calc. for $C_{18}H_{10}F_3N_3O$ 341.08, m/z found 341.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.52 - 8.45 (m, 2H), 8.12 (s, 1H), 7.73 (br d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.31 (br d, *J* = 8.8 Hz, 2H), 3.28 (s, 1H).

Example 61: 3-(6-ethynylpyridin-3-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (Compound 61)



5-Bromo-2-((trimethylsilyl)ethynyl)pyridine

[00353] To a solution of 5-bromo-2-iodopyridine (**61A**, 1 g, 3.52 mmol, 1 *eq*), CuI (6 7.1 mg, 0.35 mmol, 0.1 *eq*) and $Pd(PPh_3)_2Cl_2$ (247.2 mg, 0.35 mmol, 0.1 *eq*) in THF (10 mL) at 20°C were added TEA (1.07 g, 10.57 mmol, 1.47 mL, 3 *eq*) and ethynyltrimethylsilane (415.2 mg, 4.23 mmol, 0.59 mL, 1.2 *eq*). And the resulting mixture was purged and degassed with N_2 for 3 times, and then stirred at 20°C under N_2 for 16 hrs. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **61B** (6 50 mg, 2.40 mmol, 68.1% yield) as a gray solid. LCMS (ESI): RT = 0.932 min, mass calc. for $C_{10}H_{12}BrNSi$ 252.99, m/z found 253.8 $[M+H]^+$.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-((trimethylsilyl)ethynyl)pyridine

[00354] The mixture of intermediate **61B** (200 mg, 0.79 mmol, 1 *eq*), **4D** (299.7 mg, 1.18 mmol, 1.5 *eq*), KOAc (154.4 mg, 1.57 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (28.8 mg, 39.3 μmol, 0.05 *eq*) in dioxane (2 mL) at 20°C was purged and degassed with N_2 for 3 times, and then stirred at 100°C

under N_2 for 3 hrs. The reaction mixture was concentrated under reduced pressure to give crude intermediate **61C** (237 mg, 0.79 mmol, 100 % yield) as black oil, which was used directly for next step.

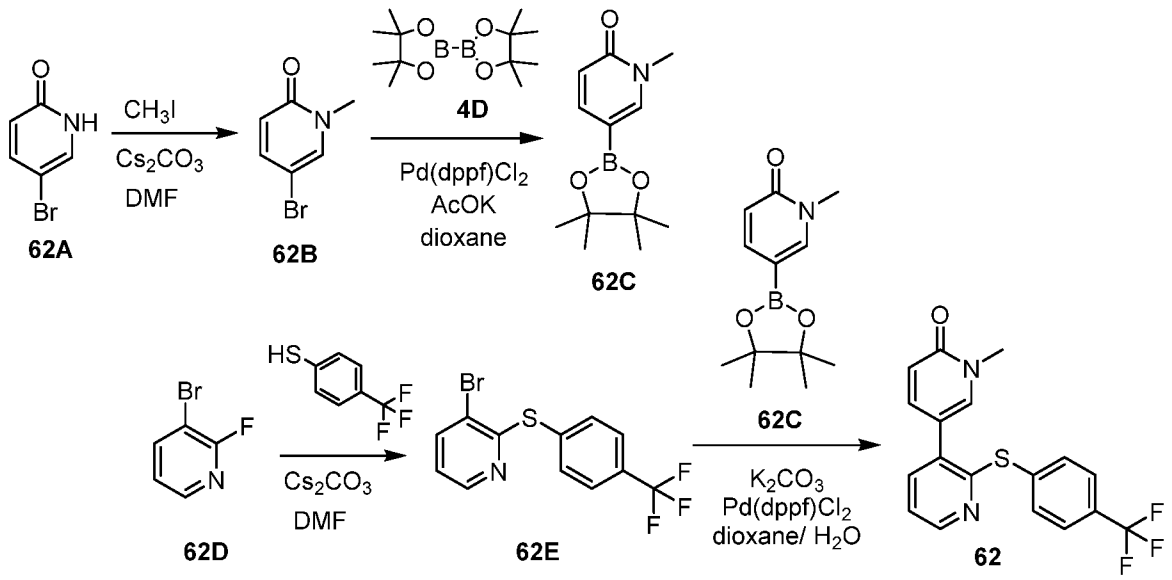
***N*-(4-(Trifluoromethyl)phenyl)-3-(6-((trimethylsilyl)ethynyl)pyridin-3-yl)pyrazin-2-amine**

[00355] The mixture of intermediate **61C** (170 mg, 0.62 mmol, 1 *eq*), intermediate **25D** (224.6 mg, 0.75 mmol, 1.2 *eq*), Na_2CO_3 (131.7 mg, 1.24 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (22.7 mg, 31.1 µmol, 0.05 *eq*) in dioxane (4 mL) and Water (0.4 mL) at 20°C was purged and degassed with N_2 for 3 times, and then stirred at 100°C under N_2 for 2 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **61D** (60 mg, 0.12 mmol, 19.0% yield) as a yellow oil. LC-MS (ESI): RT = 0.990 min, mass calc. for $C_{21}H_{19}F_3N_4Si$ 412.13, m/z found 413.0 $[M+H]^+$.

3-(6-Ethynylpyridin-3-yl)-*N*-(4-(trifluoromethyl)phenyl)pyrazin-2-amine

[00356] To a solution of intermediate **61D** (6 0 mg, 0.15 mmol, 1 *eq*) in ACN (1 mL) at 20°C was added KF (16.9 mg, 0.29 mmol, 7 uL, 2 *eq*), and the reaction mixture was stirred at 20°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL) and extracted with EtOAc (20 mL x 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, which was purified by prep-TLC (SiO_2, PE: EtOAc = 2:1, UV) to afford **Compound 61** (15.4 mg, 29.7% yield) as a yellow solid. LC-MS (ESI): RT = 0.854 min, mass calc. for $C_{18}H_{11}F_3N_4$ 340.09, m/z found 340.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 2.0 Hz, 1H), 8.24 (q, *J* = 2.5 Hz, 2H), 8.08 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.74 - 7.62 (m, 3H), 7.62 - 7.54 (m, 2H), 6.88 (brs, 1H), 3.29 (s, 1H).

Example 62: 1-Methyl-2'-((4-(trifluoromethyl)phenyl)thio)-[3,3'-bipyridin]-6(1H)-one (Compound 62)



5-Bromo-1-methyl-pyridin-2-one

[00357] The mixture of 5-bromo-1H-pyridin-2-one (**62A**, 1 g, 5.75 mmol, 1 *eq*), MeI (815.7 mg, 5.75 mmol, 0.35 mL, 1 *eq*) and Cs_2CO_3 (3.75 g, 11.49 mmol, 2 *eq*) in DMF (1 mL) was stirred at 25°C for 2 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®;12 g SepaFlash® Silica Flash Column, Eluent of 0~100% PE/EtOAc@ 35 mL/min**)** to give intermediate **62B** as a white solid.

1-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one

[00358] A mixture of intermediate **62B** (520 mg, 2.77 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 1.40 g, 5.53 mmol, 2 *eq*), AcOK (814.2 mg, 8.30 mmol, 3 *eq*), $Pd(dppf)Cl_2$ (101.1 mg, 0.13 mmol, 0.05 *eq*) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 4 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~65%PE/EtOAc@ 35 mL/min) to give intermediate **62C**, 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (781 mg, 1.89 mmol, 68.4% yield) as a yellow oil.

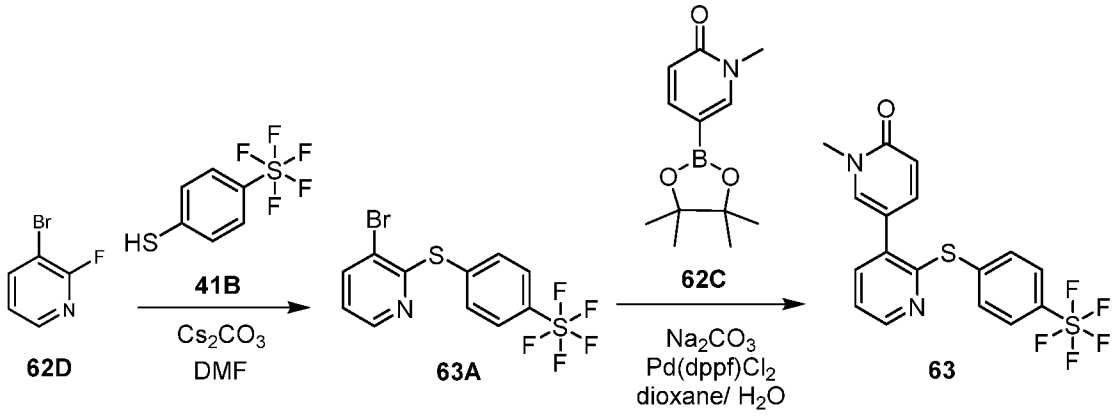
3-bromo-2-[4-(trifluoromethyl)phenyl]sulfanyl-pyridine

[00359] The mixture of 3-bromo-2-fluoro-pyridine (**62D**, 200 mg, 1.14 mmol, 1 *eq*), 4-(trifluoromethyl)benzenethiol (202.4 mg, 1.14 mmol, 1 *eq*) and Cs_2CO_3 (740.5 mg, 2.27 mmol, 2 *eq*) in DMF (2 mL) was stirred at 100°C for 1 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®;12 g SepaFlash® Silica Flash Column, Eluent of 0~10% PE/EtOAc@ 35mL/min) to give intermediate **62E** (293 mg, 0.87 mmol, 77.1% yield) as a yellow oil.

1-methyl-5-[2-[4-(trifluoromethyl)phenyl]sulfanyl-3-pyridyl]pyridin-2-one

[00360] A mixture of intermediate **62C** (296.2 mg, 0.71 mmol, 0.29 mL, 1.2 *eq*), intermediate **62E** (200 mg, 0.59 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (21.9 mg, 29.9 μmol, 0.05 *eq*), K_2CO_3 (248.1 mg, 1.80 mmol, 3 *eq*) in dioxane (2 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 35%-65%,6.5min) to afford **Compound 62** (8.3 mg, 3.8% yield) as a yellow solid. LC-MS (ESI): RT = 0.842 min, mass calcd for $C_{18}H_{13}F_3N_2OS$ 362.37 m/z found 363.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.40 - 8.33 (m, 1H), 7.90 (d, *J* = 2.3 Hz, 1H), 7.76 - 7.69 (m, 3H), 7.61 (br d, *J* = 7.8 Hz, 3H), 7.34 (dd, *J* = 4.8, 7.5 Hz, 1H), 6.48 (d, *J* = 9.3 Hz, 1H), 5.19 (br s, 5H), 5.25 - 5.09 (m, 1H), 3.50 - 3.42 (m, 3H), 2.50 (br s, 4H)

Example 63: 1-Methyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)thio)-[3,3'-bipyridin]-6(1H)-one (Compound 63)



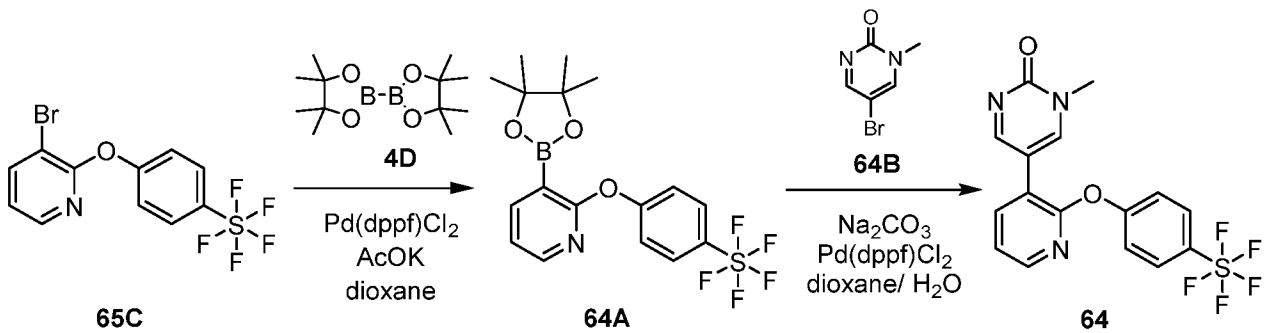
[4-[(3-bromo-2-pyridyl)sulfanyl]phenyl]-pentafluoro-sulfane

[00361] A mixture of 3-bromo-2-fluoro-pyridine (**62D**, 374.7 mg, 2.13 mmol, 1 *eq*), 4-(pentafluoro-sulfanyl)benzenethiol (**41B**, 503 mg, 2.13 mmol, 1 *eq*), Cs_2CO_3 (1.39 g, 4.2 mmol, 2 *eq*) in DMF (5 mL) was stirred at 100 °C for 1 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% PE/EtOAc@ 30mL/min) to give intermediate **63A** (237 mg, 0.60 mmol, 28.3% yield) as a yellow oil.

1-Methyl-5-[2-[4-(pentafluoro-sulfanyl)phenyl]sulfanyl-3-pyridyl]pyridin-2-one

[00362] A mixture of intermediate **62C** (89.9 mg, 0.38 mmol, 89 uL, 1.5 *eq*), intermediate **63A** (100 mg, 0.25 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (55.9 mg, 76.4 μmol, 0.3 *eq*), Na_2CO_3 (54.0 mg, 0.50 mmol, 2 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 34%-64%,8.5min) to afford **Compound 63** (3.2 mg, 3.0% yield) as white solid. LC-MS (ESI): RT = 0.865 min, mass calcd for $C_{17}H_{13}F_5N_2OS_2$ 420.42 m/z found 421.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.77 (d, *J* = 4.5 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.88 - 7.79 (m, 4H), 7.48 (br d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 9.5 Hz, 1H), 3.61 (s, 3H).

Example 64: 1-Methyl-5-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)pyrimidin-2(1H)-one (Compound 64)



pentafluoro-[4-[[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]phenyl]-sulfane

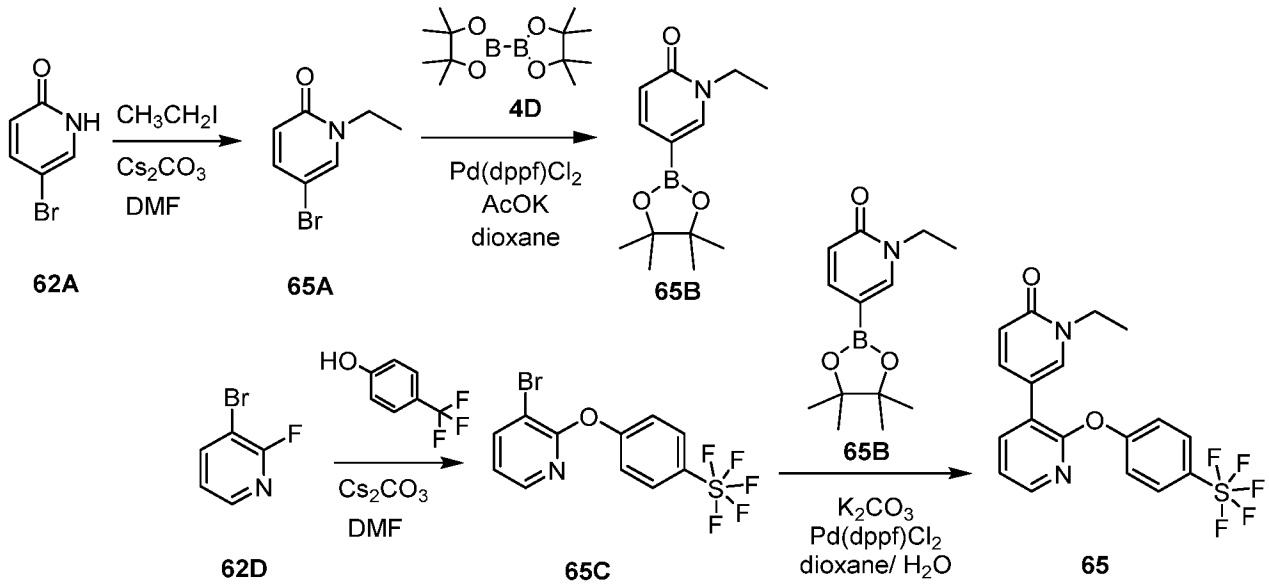
[00363] To a solution of 3-bromo-2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridine (**65C**, 150 mg, 0.39 mmol, 1 eq) and **4D** (121.5 mg, 0.47 mmol, 1.2 eq) in dioxane (3 mL) was added AcOK (78.2 mg, 0.79 mmol, 2.0 eq) and $Pd(dppf)Cl_2$ (29.1 mg, 39.8 µmol, 0.1 eq). The reaction mixture was stirred at 90 °C for 1 hr under N_2. The reaction mixture was filtered and concentrated under reduced pressure to give crude intermediate **64A** (170 mg, crude) as a black solid, which was used in the next step without further purification.

1-Methyl-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]pyrimidin-2-one

[00364] To a solution of intermediate **64A** (50 mg, 0.11 mmol, 1 eq) and 5-bromo-1-methylpyrimidin-2(1H)-one (**64B**, 24.5 mg, 0.12 mmol, 1.1 eq) in dioxane (3.0 mL) and H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (8.6 mg, 11.8 µmol, 0.1 eq) and Na_2CO_3 (25.0 mg, 0.23 mmol, 2.0 eq). The reaction mixture was stirred at 90 °C for 1 hr under N_2. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 35%-65%, 6.5 min) to afford **Compound 64** (4.2 mg, 8.6% yield as a white solid. LC-MS (ESI): RT = 0.823 min, mass calcd for: $C_{16}H_{12}F_5N_3O_2S$ 405.06 m/z found 406.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, J = 3.1 Hz, 1H), 8.93 (d, J = 3.0 Hz, 1H), 8.17 (dd, J = 1.6, 4.8 Hz, 1H), 8.07 (dd, J = 1.6, 7.4 Hz, 1H), 7.98 (d, J = 9.1 Hz, 2H), 7.44 (d, J = 8.9 Hz, 2H), 7.34 (dd, J = 4.9, 7.4 Hz, 1H), 3.68 - 3.63 (m, 1H), 3.59 (s, 2H).

h

Example 65: 1-ethyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 65)



5-Bromo-1-ethyl-pyridin-2-one

[00365] The mixture of 5-bromo-1H-pyridin-2-one (**62A**, 500.0 mg, 2.87 mmol, 1 *eq*) and iodoethane (448.1 mg, 2.87 mmol, 0.22 mL, 1 *eq*), Cs_2CO_3 (1.87 g, 5.75 mmol, 2 *eq*) in DMF (2 mL) was stirred at 25°C for 1 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% PE/EtOAc @ 35 mL/min) to give intermediate **65A** (304.0 mg, 1.50 mmol, 52.3% yield) was obtained as a yellow solid.

1-Ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one

[00366] A mixture of intermediate **65A** (304.0 mg, 1.50 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 573.1 mg, 2.26 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (55.0 mg, 75.2 µmol, 0.05 *eq*), AcOK (442.9 mg, 4.51 mmol, 3 *eq*) in dioxane (2 mL) was degassed and purged with N_2 for 3 times and then the reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 35mL/min) to give intermediate **65B** (295 mg, 1.18 mmol, 78.7% yield) was obtained as a yellow oil.

[4-[(3-Bromo-2-pyridyl)oxy]phenyl]-pentafluoro-sulfane

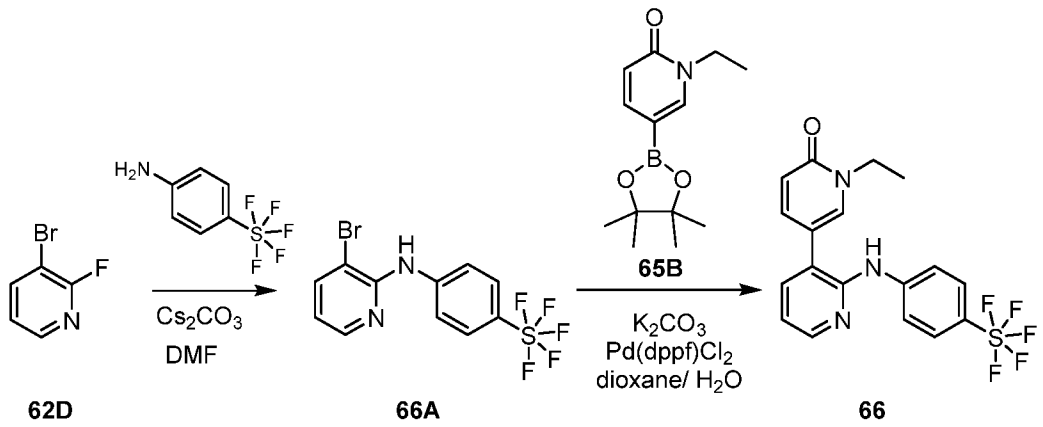
[00367] The mixture of 4-(pentafluoro-sulfanyl)phenol (1 g, 4.54 mmol, 1 *eq*), 3-bromo-2-fluoro-pyridine (**62D**, 799.3 mg, 4.54 mmol, 1 *eq*) and Cs_2CO_3 (2.96 g, 9.08 mmol, 2 *eq*) in DMF (6 mL) was stirred at 100°C for 1 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% PE/EtOAc@ 35 mL/min) to give intermediate **65C** (1.26 g, 3.35 mmol, 73.7% yield) as a white solid.

1-Ethyl-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]pyridin-2-one

[00368] A mixture of intermediate **65B** (6 6.2 mg, 0.26 mmol, 1 *eq*), intermediate **65C** (100 mg, 0.26mmol, 1 *eq*), $Pd(dppf)Cl_2$ (9.7 mg, 13.2 µmol, 0.05 *eq*), K_2CO_3 (110.2 mg, 0.79 mmol, 3

eq) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 5 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water(0.05%HCl)-ACN];B%: 50%-80%,6.5min) to afford **Compound 65** (6.7 mg, 16.2 µmol, 6.1% yield) as a white solid. LC-MS (ESI): RT = 0.906 min, mass calcd for $C_{18}H_{15}F_5N_2O_2S$ 418.38 m/z found 419.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.16 (dd, *J* = 1.5, 4.8 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.98 (dd, *J* = 1.6, 7.4 Hz, 1H), 7.93 - 7.85 (m, 3H), 7.35 - 7.25 (m, 3H), 6.66 (d, *J* = 9.3 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

Example 66: 1-Ethyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6(1H)-one (Compound 66)



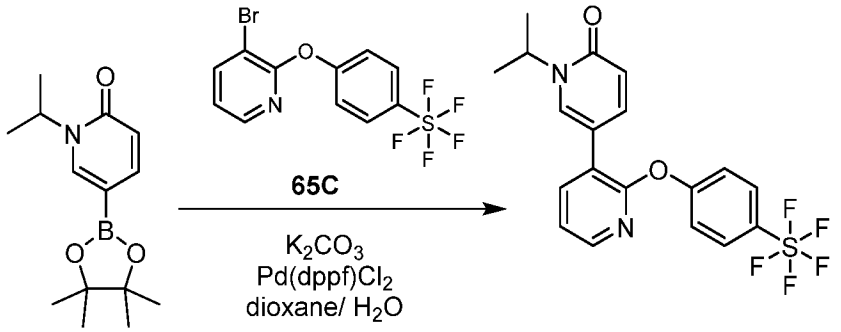
3-bromo-N-[4-(pentafluoro-sulfanyl)phenyl]pyridin-2-amine

[00369] The mixture of 4-(pentafluoro-sulfanyl)aniline (1 g, 4.56 mmol, 1 *eq*), 3-bromo-2-fluoro-pyridine (**62D**, 802.9 mg, 4.56 mmol, 1 *eq*) and Cs_2CO_3 (2.97 g, 9.13 mmol, 2 *eq*) in DMF (6 mL) was stirred at 100 °C for 1 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~40% PE/EtOAc@35 mL/min) to give intermediate **66A** (1 g, 2.45 mmol, 53.7% yield) as a white solid.

1-Ethyl-5-[2-[4-(pentafluoro-sulfanyl)anilino]-3-pyridyl]pyridin-2-one

[00370] A mixture of intermediate **65B** (6 6.4 mg, 0.26 mmol, 1 *eq*), intermediate **66A** (100 mg, 0.26 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (9.75 mg, 13.3 µmol, 0.05 *eq*), K_2CO_3 (110.5 mg, 0.79 mmol, 3 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 5 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water(0.05%HCl)-ACN];B%: 40%-70%,6.5min) to afford **Compound 66** (15.2 mg, 13.5% yield) as a white solid. LC-MS (ESI): RT = 0.864 min, mass calcd for $C_{18}H_{16}F_5N_3OS$ 417.40 m/z found 418.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.09 (d, *J* = 5.3 Hz, 1H), 8.02 - 7.95 (m, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.67 (br d, *J* = 9.0 Hz, 1H), 7.59 (br d, *J* = 8.8 Hz, 2H), 7.25 (t, *J* = 6.5 Hz, 1H), 6.66 (d, *J* = 9.0 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H).

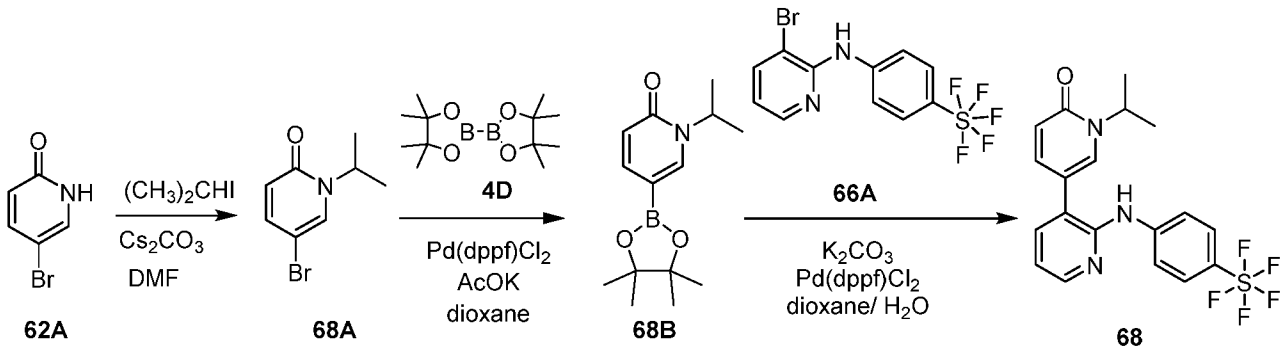
Example 67: 1-Isopropyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 67)



[00371] A mixture of 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (**68B**, 83.9 mg, 0.31 mmol, 1.2 *eq*), intermediate **65C** (100 mg, 0.26 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (9.7 mg, 13.2 µmol, 0.05 *eq*), K_2CO_3 (110.2 mg, 0.79 mmol, 3 *eq*) in dioxane (2 mL)and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 50%-80%,6.5min) to afford **Compound 67** (16.2 mg, 14.0% yield) as a white solid. LC-MS (ESI): RT = 0.926 min, mass calcd for $C_{19}H_{17}F_5N_2O_2S$ 432.41 m/z

found 433.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (br d, J = 5.3 Hz, 1H), 8.02 - 7.94 (m, 2H), 7.89 - 7.78 (m, 3H), 7.34 - 7.24 (m, 3H), 6.63 (d, J=9.5 Hz, 1H), 5.23 (quin, J = 6.8 Hz, 1H), 1.41 (d, J = 6.8 Hz, 6H).

Example 68: 1-Isopropyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6(1H)-one (Compound 68)



5-Bromo-1-isopropyl-pyridin-2-one

[00372] The mixture of 5-bromo-1H-pyridin-2-one (**62A**, 1 g, 5.75 mmol, 1 *eq*) and 2-iodopropane (976.9 mg, 5.75 mmol, 0.5 mL, 1 *eq*), Cs_2CO_3 (3.75 g, 11.49 mmol, 2 *eq*) in DMF (6 mL) was stirred at 25°C for 1 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®;12 g SepaFlash® Silica Flash Column, Eluent of 0~65%PE/EtOAc@30 mL/min) to give intermediate **68A** (259 mg, 1.17 mmol, 20.4% yield) as a white solid.

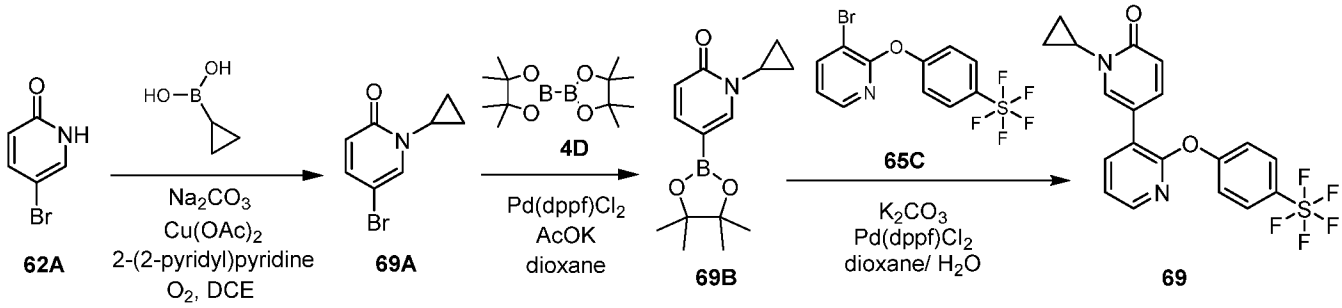
1-Isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one

[00373] A mixture of intermediate **68A** (259 mg, 1.20 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 365.2 mg, 1.44 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (43.8 mg, 59.9 µmol, 0.05 *eq*), AcOK (352.9 mg, 3.60 mmol, 3 *eq*) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 5 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; X g SepaFlash® Silica Flash Column, Eluent of 0~65% PE/EtOAc@ 35 mL/min) to give intermediate **68B** (231 mg, 0.82 mmol, 68.8% yield) was obtained as yellow solid.

1-Isopropyl-5-[2-[4-(pentafluoro-sulfanyl)anilino]-3-pyridyl]pyridin-2-one

[00374] A mixture of intermediate **68B** (84.1 mg, 0.31 mmol, 1.2 *eq*), intermediate **66A** (100 mg, 0.26 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (9.7 mg, 13.3 μmol, 0.05 *eq*), K_2CO_3 (110.5 mg, 0.79 mmol, 3 *eq*) in dioxane (2 mL)and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 40%-70%,6.5min) to afford **Compound 68** (18.3 mg, 15.9% yield) as a white solid. LC-MS (ESI): RT = 0.896 min, mass calcd for $C_{19}H_{18}F_5N_3OS$ 431.42 m/z found 432.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.03 (br s, 1H), 8.22 (dd, *J* = 1.4, 5.1 Hz, 1H), 7.89 (d, *J* = 2.5 Hz, 1H), 7.80 - 7.73 (m, 3H), 7.64 (d, *J* = 9.0 Hz, 2H), 7.48 (dd, *J* = 2.5, 9.3 Hz, 1H), 7.14 (dd, *J* = 5.3, 7.3 Hz, 1H), 6.48 (d, *J* = 9.3 Hz, 1H), 5.12 - 5.02 (m, 1H), 1.32 (d, *J* = 7.0 Hz, 6H).

Example 69: 1-Cyclopropyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 69)



5-Bromo-1-cyclopropyl-pyridin-2-one

[00375] A mixture of 5-bromo-1H-pyridin-2-one (**62A**, 500 mg, 2.87 mmol, 1 *eq*), cyclopropylboronic acid (493.6 mg, 5.75 mmol, 2 *eq*), $Cu(OAc)_2$ (6 26.3 mg, 3.45 mmol, 1.2 *eq*) and Na_2CO_3 (6 70.0 mg, 6.32 mmol, 2.2 *eq*) , 2-(2-pyridyl)pyridine (538.5 mg, 3.45 mmol, 1.2 *eq*) in DCE (5 mL)was degassed and purged with O_2 for 3 times, and then the reaction mixture was stirred at 70 °C for 16 hr under O_2 atmosphere. The reaction mixture was filtered to remove the insoluble. The filter liquor was concentrated *in vacuo*, and was purified by flash chromatography on silica gel (ISCO®;12 g SepaFlash® Silica Flash Column, Eluent of 0~80%PE/EtOAc@35 mL/min) to give intermediate **69A** (393 mg, 1.84 mmol, 63.8% yield) as a yellow oil.

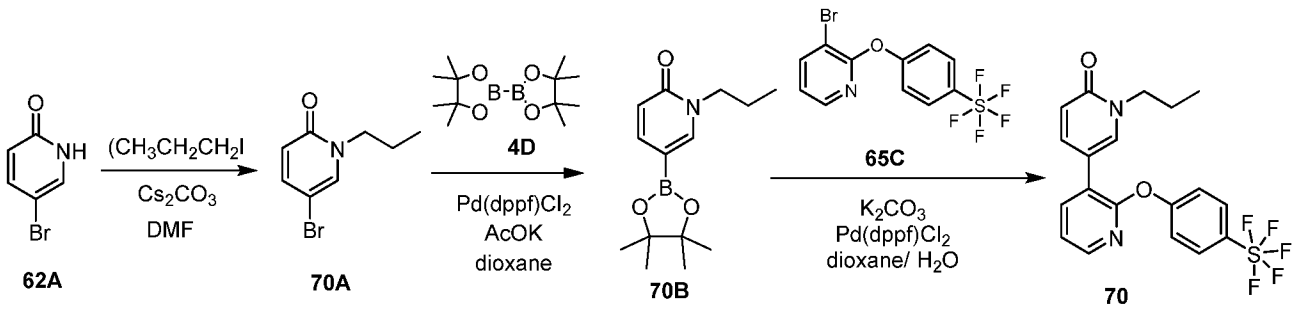
Cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one

[00376] A mixture of intermediate **69A** (393 mg, 1.84 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 559.4 mg, 2.20 mmol, 1.2 *eq*), AcOK (540.5 mg, 5.51 mmol, 3 *eq*), $Pd(dppf)Cl_2$ (6 7.1 mg, 91.8 μmol, 0.05 *eq*) in dioxane (15 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 4 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude intermediate **69B** (515 mg, crude) as a yellow oil, which was used in the next step without further purification.

1-Cyclopropyl-5-[2-[4-(pentafluoro-λ^6-sulfanyl)phenoxy]-3-pyridyl]pyridin-2-one

[00377] A mixture of intermediate **69B** (104.1 mg, 0.39 mmol, 1.5 *eq*), intermediate **65C** (100 mg, 0.26 mmol, 1 *eq*), Cs_2CO_3 (259.8 mg, 0.79 mmol, 3 *eq*), $Pd(dppf)Cl_2$ (9.7 mg, 13.2 μmol, 0.05 *eq*) in dioxane (5 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 40%-70%,8.5min) to afford **Compound 69** (10.0 mg, 8.6% yield) as a white solid. LC-MS (ESI): RT = 0.902 min, mass calcd for $C_{19}H_{15}F_5N_2O_2S$ 430.39 m/z found 431.0$[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.17 (dd, *J* = 1.8, 5.0 Hz, 1H), 8.10 (d, *J* = 1.8 Hz, 1H), 8.05 - 7.99 (m, 2H), 7.91 - 7.87 (m, 2H), 7.35 - 7.27 (m, 3H), 6.79 (d, *J* = 9.3 Hz, 1H), 3.52 (td, *J* = 3.5, 7.2 Hz, 1H), 1.24 - 1.17 (m, 2H), 1.07 - 0.99 (m, 2H).

Example 70: 2'-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)-1-propyl-[3,3'-bipyridin]-6(1H)-one (Compound 70)



5-Bromo-1-propyl-pyridin-2-one

[00378] A mixture of 5-bromo-1H-pyridin-2-one (**62A**, 500.0 mg, 2.87 mmol, 1 *eq*), 1-iodopropane (488.5 mg, 2.87 mmol, 0.28 mL, 1 *eq*), Cs_2CO_3 (1.87 g, 5.75 mmol, 2 *eq*) in DMF (2 mL) was stirred at 25°C for 1 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 35 mL/min) to give intermediate **70A** (226 mg, 0.99 mmol, 34.5% yield) as a yellow oil.

1-Propyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one

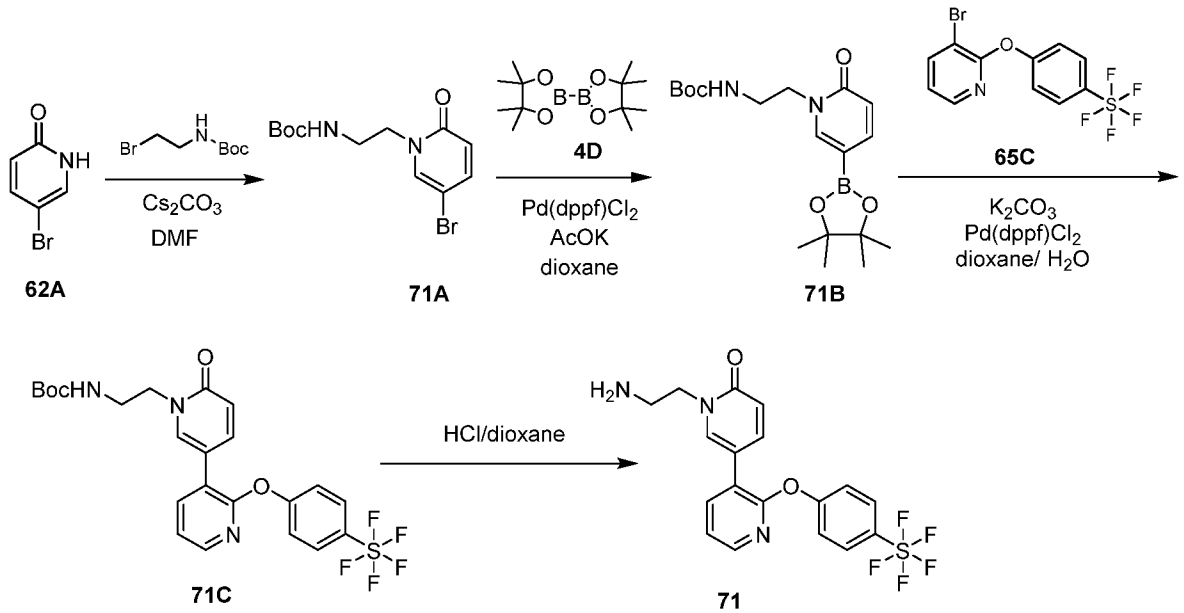
[00379] A mixture of intermediate **70A** (226 mg, 1.0 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 398.4 mg, 1.5 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (38.2 mg, 52.3 μmol, 0.05 *eq*), AcOK (307.9 mg, 3.14 mmol, 3 *eq*) in dioxane (2 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 35mL/min) to give intermediate **70B** (182 mg, 0.69 mmol, 66.1% yield) as a yellow oil.

5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]-1-propyl-pyridin-2-one

[00380] A mixture of intermediate **65C** (100.2 mg, 0.26 mmol, 1 *eq*), intermediate **70B** (98.2 mg, 0.37 mmol, 1.4 *eq*), $Pd(dppf)Cl_2$ (9.7 mg, 13.3 μmol, 0.05 *eq*), K_2CO_3 (110.5 mg, 0.79 mmol, 3 *eq*) in dioxane (10 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times and then the reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0% PE/EtOAc@ 35 mL/min) to afford **Compound 70** (11.0 mg, 9.4% yield) as a white solid. LC-MS (ESI): RT = 0.922 min, mass calcd for $C_{19}H_{17}F_5N_2O_2S$ 432.41 m/z found 433.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.16 (dd, J = 1.9, 4.9 Hz, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.97 (dd, J = 1.8, 7.5 Hz, 1H), 7.90 - 7.84 (m, 3H), 7.34 -

7.26 (m, 3H), 6.64 (d, J = 9.3 Hz, 1H), 4.04 (t, J = 7.3 Hz, 2H), 1.81 (sxt, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H).

Example 71: 1-(2-Aminoethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 71)



tert-Butyl N-[2-(5-bromo-2-oxo-1-pyridyl)ethyl]carbamate

[00381] The mixture of 5-bromo-1H-pyridin-2-one (**62A**, 1 g, 5.75 mmol, 1 *eq*), tert-butyl N-(2-bromoethyl)carbamate (1.67 g, 7.47 mmol, 1.3 *eq*) and Cs_2CO_3 (3.75 g, 11.49 mmol, 2 *eq*) in DMF (6 mL) was stirred at 25°C for 2 hrs. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®;12 g SepaFlash® Silica Flash Column, Eluent of 0~100% PE/EtOAc@35 mL/min) to give intermediate **71A** (725 mg, 1.90 mmol, 33.0% yield) as a white solid.

tert-Butyl N-[2-[2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-pyridyl]ethyl]carbamate

[00382] A mixture of intermediate **71A** (725 mg, 1.90 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 579.9 mg, 2.28 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (6 9.6 mg, 95.1 μmol, 0.05 *eq*), AcOK (560.3 mg, 5.71 mmol, 3 *eq*) in dioxane (7 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 10 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed

with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12g SepaFlash® Silica Flash Column, Eluent of 0~80%PE/EtOAc@30 mL/min) to give intermediate **71B** (343 mg, 0.81 mmol, 43.0% yield) as a white solid.

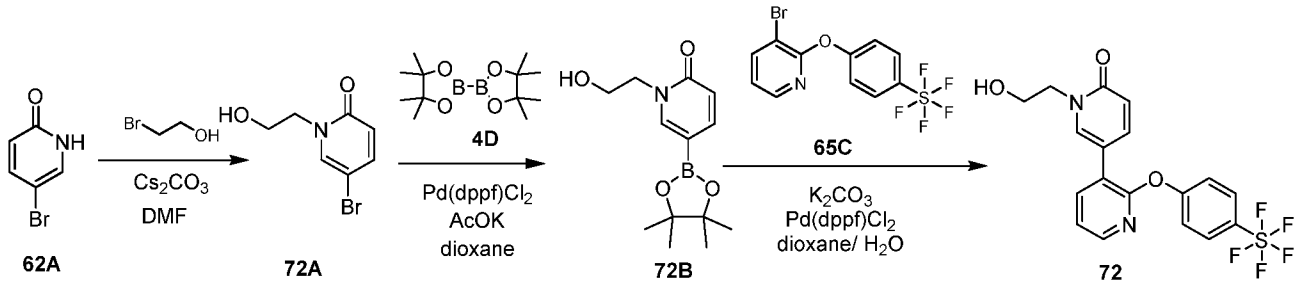
tert-Butyl N-[2-[2-oxo-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]-1-pyridyl]ethyl]carbamate

[00383] A mixture of intermediate **71B** (139.4 mg, 0.38 mmol, 1.2 *eq*), intermediate **65C** (120 mg, 0.31 mmol, 1 *eq*), K_2CO_3 (132.2 mg, 0.95 mmol, 3 *eq*), $Pd(dppf)Cl_2$ (11.6 mg, 15.9 µmol, 0.05 *eq*) in dioxane (2 mL) and H_2O (0.05 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Crude intermediate **71C** (159 mg, crude) was obtained as yellow oil, which was used in the next step without further purification.

1-(2-Aminoethyl)-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]pyridin-2-one

[00384] Intermediate **71C** (159 mg, 0.29 mmol, 1 *eq*) in HCl/dioxane (4 M, 3 mL, 40.26 *eq*) was stirred at 25°C for 1 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was adjusted pH to 8 with NaOH (4 M). The reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mLx3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150x25mmx5um;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 45%-75%,7.8min) to afford **Compound 71** (48.9 mg, 36.5% yield) as a white solid. LC-MS (ESI): RT = 0.789 min, mass calcd for $C_{18}H_{17}F_5N_4OS$ 432.41 m/z found 434.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, *J* = 5.0 Hz, 1H), 8.05 (br s, 1H), 8.02 - 7.93 (m, 3H), 7.83 (dd, *J* = 2.5, 9.5 Hz, 1H), 7.40 (br d, *J* = 8.5 Hz, 2H), 7.32 (dd, *J* = 4.8, 7.3 Hz, 1H), 6.50 (d, *J* = 9.3 Hz, 1H), 4.07 - 3.97 (m, 2H), 2.95 (br t, *J* = 6.0 Hz, 1H), 2.99 - 2.90 (m, 1H).

Example 72: 1-(2-Hydroxyethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 72)



5-Bromo-1-(2-hydroxyethyl)pyridin-2-one

[00385] A mixture of 5-bromo-1H-pyridin-2-one (**62A**, 500 mg, 2.87 mmol, 1 *eq*), 2-bromoethanol (359.1 mg, 2.87 mmol, 0.20 mL, 1 *eq*) Cs_2CO_3 (1.87 g, 5.75 mmol, 2 *eq*) in DMF (6 mL) was stirred at 25 °C for 1 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®;4 g SepaFlash® Silica Flash Column, Eluent of 0~100%PE/EtOAc@ 30 mL/min) to give intermediate **72A** (312 mg, 1.39 mmol, 48.3% yield) as a yellow solid.

1-(2-hydroxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one

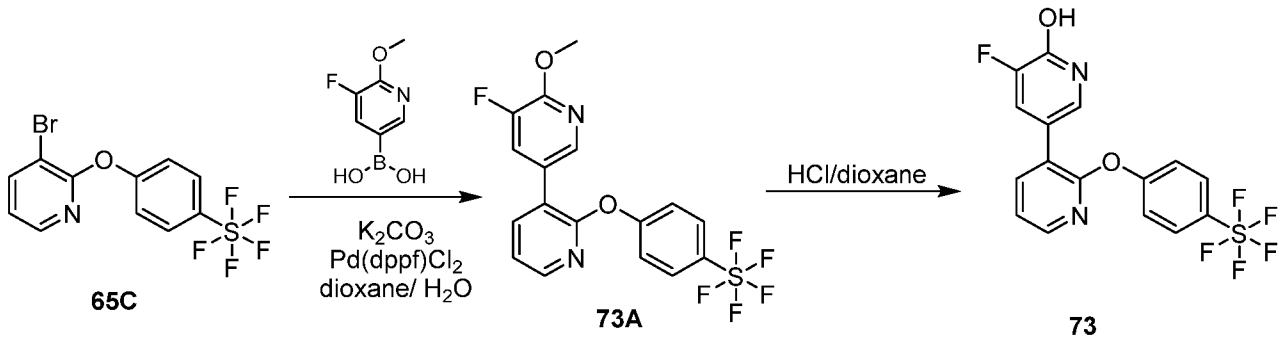
[00386] A mixture of intermediate **72A** (312 mg, 1.43 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 545.0 mg, 2.15 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (52.3 mg, 71.5 µmol, 0.05 *eq*), AcOK (421.2 mg, 4.29 mmol, 3 *eq*) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100%PE/EtOAc@30 mL/min) to give intermediate **72B** (66 mg, 0.24 mmol, 17.4% yield) as a white solid.

1-(2-Hydroxyethyl)-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]pyridin-2-one

[00387] A mixture of intermediate **72B** (6 2.0 mg, 0.23mmol, 1.1 *eq*), intermediate **65C** (80 mg, 0.21mmol, 1 *eq*), K_2CO_3 (88.1 mg, 0.63mmol, 3 *eq*), $Pd(dppf)Cl_2$ (7.7 mg, 10.6 µmol, 0.05 *eq*) in dioxane (2 mL) and H_2O (0.05 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 5 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered

and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®;4 g SepaFlash® Silica Flash Column, Eluent of 0~100% PE/EtOAc@ 20 mL/min) and was further separated by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 35%-65%,6.5min) to afford **Compound 72** (10.8 mg, 11.7% yield) as a white solid. LC-MS (ESI): RT = 0.844 min, mass calcd for $C_{18}H_{15}F_5N_2O_3S$ 434.38 m/z found 435.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.20 (d, *J* = 2.0 Hz, 1H), 8.16 (dd, *J* = 1.6, 4.9 Hz, 1H), 8.10 (dd, *J* = 2.3, 9.3 Hz, 1H), 8.00 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.88 - 7.84 (m, 2H), 7.34 - 7.28 (m, 3H), 6.86 (d, *J* = 9.3 Hz, 1H), 4.29 (t, *J* = 5.0 Hz, 2H), 3.89 (t, *J* = 5.0 Hz, 2H).

Example 73: 5-Fluoro-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6-ol (Compound 73)



pentafluoro-[4-[[3-(5-fluoro-6-methoxy-3-pyridyl)-2-pyridyl]oxy]phenyl]-sulfane

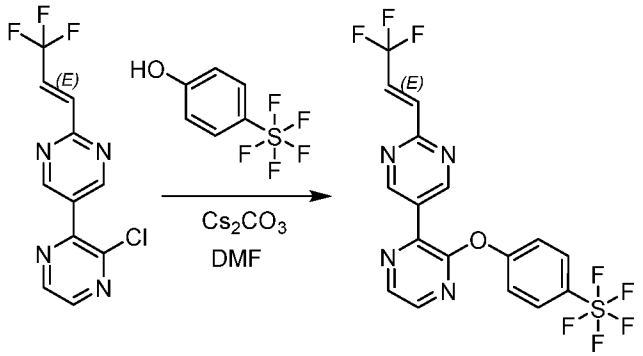
[00388] To a solution of intermediate **65C** (350 mg, 0.93 mmol, 1 *eq*) and (5-fluoro-6-methoxypyridin-3-yl)boronic acid (159.1 mg, 0.93 mmol, 1 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added K_2CO_3 (385.8 mg, 2.79 mmol, 3 *eq*) and $Pd(dppf)Cl_2$ (6 8.1 mg, 93.1 μmol, 0.1 *eq*). The reaction mixture was degassed under vacuum and purged with N_2 3 times. The reaction mixture was stirred at 90 °C for 6 hrs. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (30 mL x 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 chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give intermediate **73A** (300 mg, 0.69 mmol, 74.4% yield) as a yellow oil. LC-MS (ESI): RT = 1.043 min, mass calc. for $C_{17}H_{12}F_6N_2O_2S$ 422.05, m/z found 423.1 $[M+H]^+$.

3-fluoro-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]pyridin-2-ol

[00389] A solution of intermediate **73A** (250 mg, 0.59 mmol, 1 *eq*) in HCl/dioxane (1 mL) was stirred at 70 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;

mobile phase: [water (0.05%HCl)-ACN]; B%: 40%-70%, 6.5 min) to afford **Compound 73** (172.4 mg, 69.3% yield) as a white solid. LC-MS (ESI): RT = 0.863 min, mass calc. for $C_{16}H_{10}F_6N_2O_2S$ 408.04, m/z found 409.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-*d6*) δ 12.46 (br s, 1H), 8.10 (dd, *J* = 1.8, 5.0 Hz, 1H), 8.00 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.98 - 7.93 (m, 2H), 7.84 (dd, *J* = 2.3, 12.3 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.28 (dd, *J* = 5.0, 7.5 Hz, 1H).

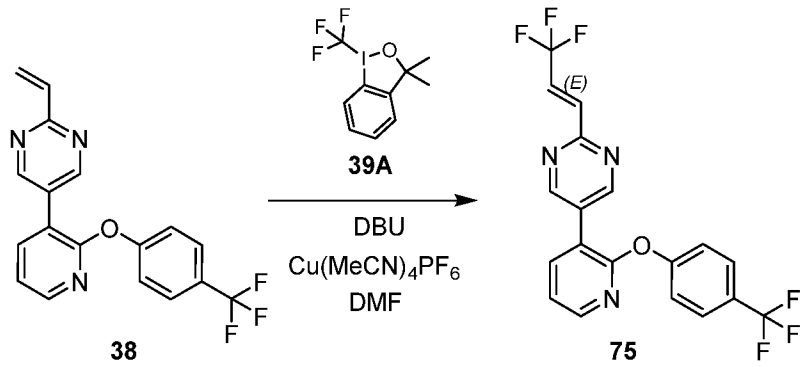
Example 74: (*E*)-5-(3-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine (Compound 74)



40F **74**

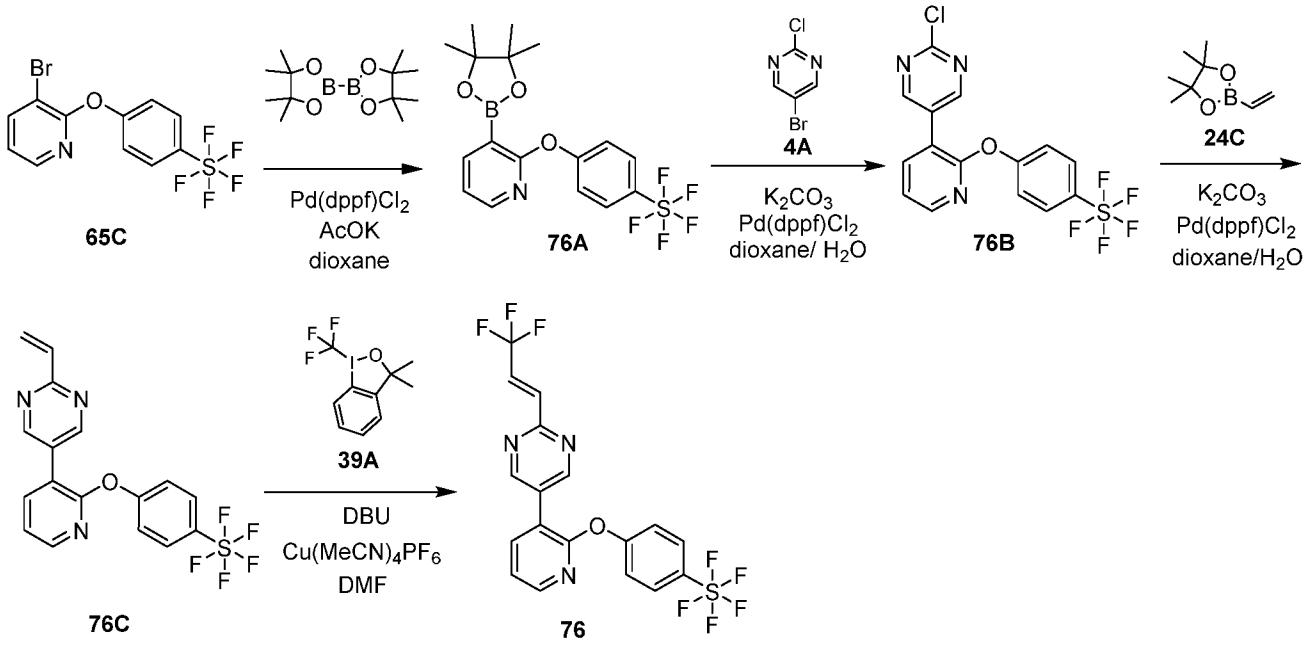
[00390] To a solution of intermediate **40F** (120 mg, 0.42 mmol, 1 *eq*) in DMF (1.5 mL) were added 4-(pentafluoro-λ6-sulfaneyl)phenol (101.4 mg, 0.46 mmol, 1.1 *eq*), Cs_2CO_3 (204.6 mg, 0.63 mmol, 1.5 *eq*). The reaction mixture was stirred at 110 °C for 3 hrs. The reaction mixture was diluted with H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (15 mLx3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150x25mmx5um; mobile phase: [water (0.04%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 60%-90%, 7.8min) to afford **Compound 74** (58.7 mg, 29.8% yield) as a yellow solid. LCMS (ESI): RT = 1.000 min, mass calcd for $C_{17}H_{10}F_8N_4OS$ 470.04, m/z found470.9 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.58 (s, 2H), 8.55 (d, *J* = 2.5 Hz, 1H), 8.22 (d, *J* = 2.5 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.38 - 7.20 (m, 2H).

Example 75: (*E*)-5-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine (Compound 75)



[00391] To a solution of **Compound 38** (150 mg, 0.44 mmol, 1 *eq*) and **39A** (360.6 mg, 1.09 mmol, 2.5 *eq*) in DMF (1 mL) were added DBU (133.0 mg, 0.87 mmol, 0.13 mL, 2 *eq*) and $Cu(MeCN)_4PF_6$ (32.6 mg, 87.4 µmol, 0.2 *eq*). The reaction mixture was stirred at 60 °C for 6 hrs. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 60%-90%, 6.5 min) to **Compound 75** (18.7 mg, 10.4% yield) as a white solid. LC-MS (ESI): RT = 0.967 min, mass calc. for $C_{19}H_{11}F_6N_3O$ 411.08 found 412.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 2H), 8.33 - 8.26 (m, 1H), 7.90 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.36 (dd, *J* = 1.6, 15.9 Hz, 1H), 7.32 - 7.27 (m, 3H), 7.23 - 7.12 (m, 1H).

Example 76: (E)-5-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine (Compound 76)



pentafluoro-[4-[[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]phenyl]-sulfane

[00392] To a solution of intermediate **65C** (0.5 g, 1.33 mmol, 1 *eq*) and **4D** (337.6 mg, 1.33 mmol, 1 *eq*) in dioxane (5 mL) were added AcOK (260.9 mg, 2.66 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (97.3 mg, 0.13 mmol, 0.1 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times, then the reaction mixture was stirred at 100 °C for 2 hr under N_2. Crude intermediate **76A** (562 mg, crude, black oil) was obtained and used in the next step without further purification.

[4-[[3-(2-chloropyrimidin-5-yl)-2-pyridyl]oxy]phenyl]-pentafluoro-sulfane

[00393] To a solution of intermediate **76A** (560 mg, 1.32 mmol, 1 *eq*) and 5-bromo-2-methylpyrimidine (**40A**, 256.0 mg, 1.32 mmol, 1 *eq*) in dioxane (3 mL) and H_2O (1 mL) were added $Pd(dppf)Cl_2$ (96.8 mg, 0.13 mmol, 0.1 *eq*) and K_2CO_3 (365.8 mg, 2.65 mmol, 2 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times, then the reaction mixture was stirred at 100 °C for 2 hrs under N_2. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~35% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **76B** (290 mg, 0.68 mmol, 51.3% yield) as a white solid. LC-MS (ESI): RT = 0.978 min, mass calc. for $C_{15}H_9ClF_5N_3OS$ 409.01 found 410.0 $[M+H]^+$.

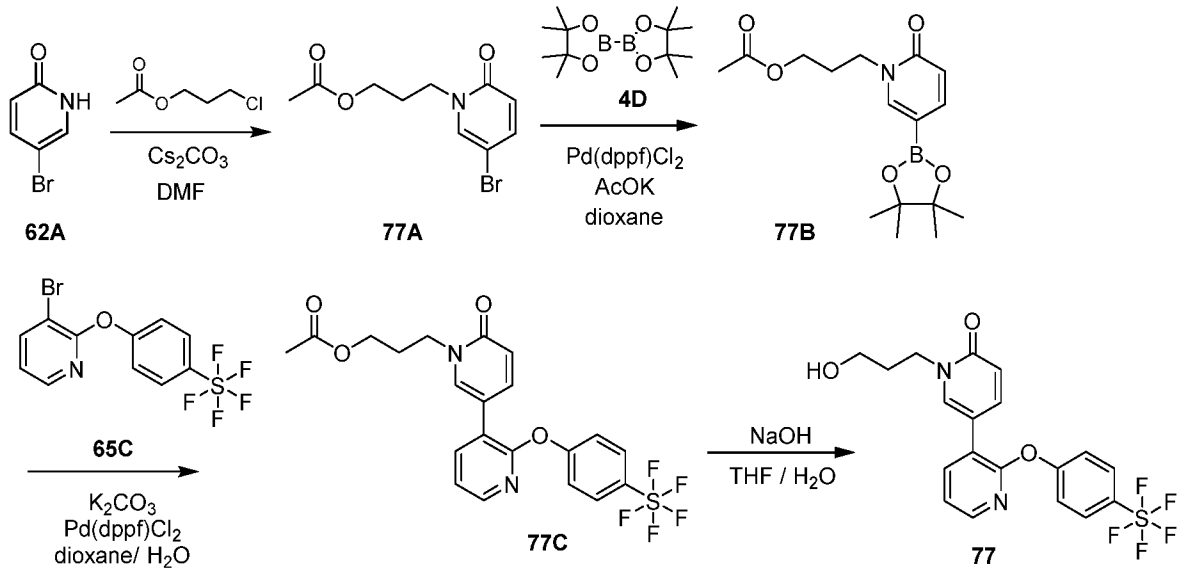
pentafluoro-[4-[[3-(2-vinylpyrimidin-5-yl)-2-pyridyl]oxy]phenyl]-sulfane

[00394] To a solution of intermediate **76B** (290 mg, 0.71 mmol, 1 *eq*) and **24C** (119.9 mg, 0.78 mmol, 0.13 mL, 1.1 *eq*) in dioxane (3 mL) and HO (0.3 mL) were added $Pd(dppf)Cl_2$ (51.8 mg, 70.8 µmol, 0.1 *eq*) and K_2CO_3 (195.6 mg, 1.42 mmol, 2 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times, then the reaction mixture was stirred at 100 °C for 3 hrs under N_2. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **76C** (220 mg, 0.50 mmol, 70.5% yield) as a yellow solid. LC-MS (ESI): RT = 0.970 min, mass calc. for $C_{15}H_8ClF_3N_4O$ 401.06 found 402.0 $[M+H]^+$.

Pentafluoro-[4-[[3-[2-[(E)-3,3,3-trifluoroprop-1-enyl]pyrimidin-5-yl]-2-pyridyl]oxy]phenyl]-sulfane

[00395] To a solution of intermediate **76C** (180 mg, 0.45 mmol, 1 *eq*) and **39A** (370.1 mg, 1.12 mmol, 2.5 *eq*) in DMF (3 mL) were added DBU (136.6 mg, 0.90 mmol, 0.14 mL, 2 *eq*) and $Cu(MeCN)_4PF_6$ (33.4 mg, 89.7 µmol, 0.2 *eq*). The reaction mixture was stirred at 60 °C for 3.5 hrs. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 65%-95%, 6.5 min) to afford **Compound 76** (16.8 mg, 8.0% yield) as a yellow solid. LC-MS (ESI): RT = 1.064 min, mass calc. for $C_{18}H_{11}F_8N_3OS$ 469.05 found 470.1 $[M+H]^+$; ^1H NMR (40 0MHz, $CDCl_3$) δ 9.06 (s, 2H), 8.28 (dd, *J* = 1.8, 4.8 Hz, 1H), 7.88 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 2H), 7.36 - 7.27 (m, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.20 - 7.09 (m, 1H).

Example 77: 1-(3-Hydroxypropyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 77)



3-(5-bromo-2-oxo-1-pyridyl)propyl acetate

[00396] To a solution of 5-bromo-1H-pyridin-2-one (**62A**, 1 g, 5.75 mmol, 1 *eq*) and 3-chloropropyl acetate (1.1 g, 8.63 mmol, 1.06 mL, 1.5 *eq*) in DMF (5 mL) was added Cs_2CO_3 (3.7 g, 11.50 mmol, 2 *eq*). The reaction mixture was stirred at 25 °C for 16 hr. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 30% Ethyl acetate/Petroleum ether

gradient @ 30 mL/min) to give intermediate **77A** (6 84 mg, 2.38 mmol, 41.3% yield) as a white solid.

3-[2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-pyridyl]propyl acetate

[00397] A mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 236.1 mg, 0.92 mmol, 1.2 *eq*), intermediate **77A** (212.4 mg, 0.77 mmol, 1 *eq*), KOAc (152.0 mg, 1.55 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (28.3 mg, 38.7 μmol, 0.05 *eq*) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90°C for 16 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x3). The combined organic layers were washed with brine (50 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude intermediate **77B** (200 mg, crude) as a white solid.

3-[2-oxo-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]-1-pyridyl]propyl acetate

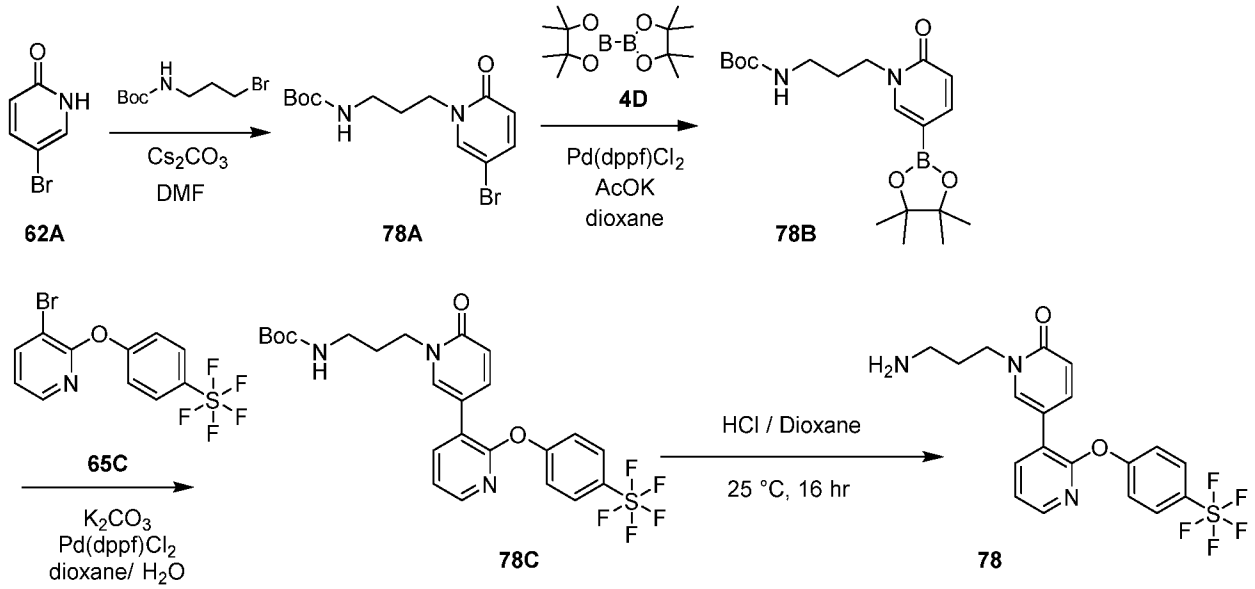
[00398] A mixture of intermediate **65C** (150 mg, 0.39 mmol, 1 *eq*), intermediate **77B** (153.7 mg, 0.47 mmol, 1.2 *eq*), K_2CO_3 (165.3 mg, 1.20 mmol, 3 *eq*), $Pd(dppf)Cl_2$ (29.1 mg, 39.8 μmol, 0.1 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 6 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 90% Ethyl acetate/Petroleum ether gradient @ 35 mL/min) to give intermediate **77C** (139 mg, 0.27 mmol, 68.2% yield) as a yellow solid.

1-(3-hydroxypropyl)-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]pyridin-2-one

[00399] To a solution of intermediate **77C** (70 mg, 0.14 mmol, 1 *eq*) in THF (2 mL) and H_2O (0.2 mL) was added NaOH (28.5 mg, 0.71 mmol, 5 *eq*). The reaction mixture was stirred at 25 °C for 16 hr. The reaction mixture was diluted with H_2O (30 mL) and HCl (2 mL, 2 M) extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 150x25mmx5um;mobile phase: [water(0.05%HCl)-ACN];B%: 35%-65%,6.5min) to afford **Compound 77** (11.20 mg, 17.4% yield) as a white solid. LC-MS (ESI): RT = 0.858 min, mass calcd for $C_{19}H_{17}F_5N_2O_3S$

448.41 m/z, found 449.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 (quin, J = 6.53 Hz, 2 H) 3.42 (t, J = 6.15 Hz, 2 H) 4.00 (t, J = 6.90 Hz, 2 H) 6.47 (d, J = 9.29 Hz, 1 H) 7.30 (dd, J = 7.40, 4.89 Hz, 1 H) 7.39 (br d, J = 8.78 Hz, 2 H) 7.79 (dd, J = 9.29, 2.51 Hz, 1 H) 7.95 (d, J = 9.29 Hz, 2 H) 7.98 (dd, J = 7.53, 1.51 Hz, 1 H) 8.04 (d, J = 2.26 Hz, 1 H) 8.12 (dd, J = 4.77, 1.51 Hz, 1 H).

Example 78: 1-(3-Aminopropyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 78)



Tert-butyl N-[3-(5-bromo-2-oxo-1-pyridyl)propyl]carbamate

[00400] To a solution of 5-bromo-1H-pyridin-2-one (**62A**, 3 g, 17.24 mmol, 1 *eq*) and tert-butyl N-(3-bromopropyl)carbamate (6 .1 g, 25.86 mmol, 1.5 *eq*) in DMF (5 mL) was added Cs_2CO_3 (11.2 g, 34.48 mmol, 2 *eq*). The reaction mixture was stirred at 25 °C for 16 hrs. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 30% Ethyl acetate/Petroleum ether gradient @ 35 mL/min) to give intermediate **78A** (2.7 g, 8.11 mmol, 47.0% yield) as a white solid.

tert-butyl N-[3-[2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-pyridyl]propyl]carbamate

[00401] A mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4D**, 184.0 mg, 0.72 mmol, 1.2 eq), intermediate **78A** (200 mg, 0.60 mmol, 1 eq), KOAc (118.5 mg, 1.21 mmol, 2 eq), $Pd(dppf)Cl_2$ (22.0 mg, 30.1 µmol, 0.05 eq) in dioxane (10

mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x3). The combined organic layers were washed with brine (50 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude intermediate **78B** (200 mg, crude) as a white solid.

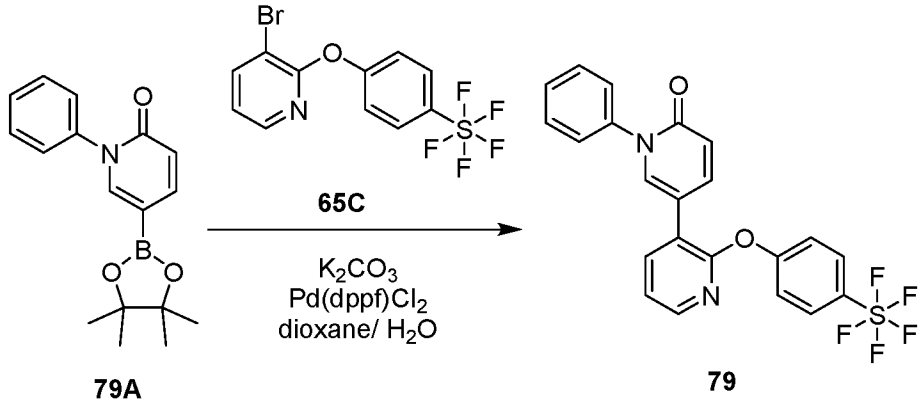
tert-butyl N-[3-[2-oxo-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]-1-pyridyl]propyl]carbamate

[00402] A mixture of intermediate **65C** (150 mg, 398.79 µmol, 1 eq), intermediate **78B** (181.0 mg, 0.47 mmol, 1.2 eq), K_2CO_3 (165.3 mg, 1.20 mmol, 3 eq), $Pd(dppf)Cl_2$ (29.1 mg, 39.8 µmol, 0.1 eq) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 6 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 80% Ethyl acetate/Petroleum ether gradient @ 35 mL/min) to give intermediate **78C** (150 mg, 0.21 mmol, 54.6% yield) as a white solid.

1-(3-aminopropyl)-5-[2-[4-(pentafluoro-sulfanyl)phenoxy]-3-pyridyl]pyridin-2-one

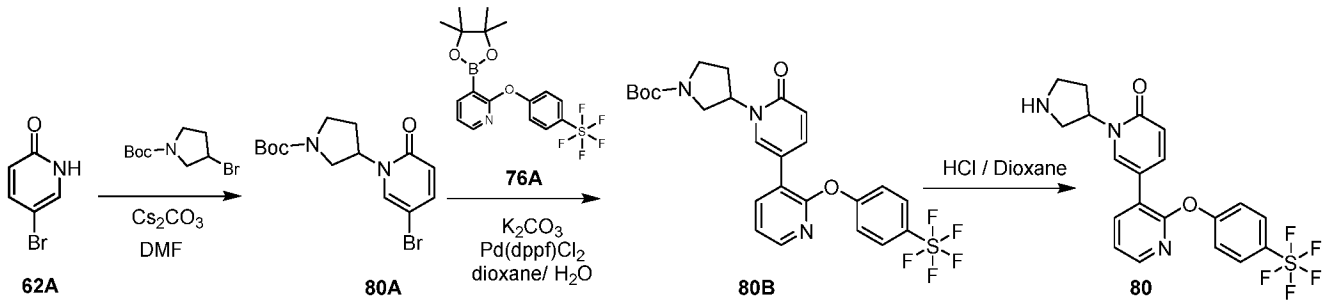
[00403] To a solution of intermediate **78C** (70 mg, 0.12 mmol, 1 eq) was added HCl/dioxane (4 M, 4.20 mL, 131.4 eq). The reaction mixture was stirred at 25 °C for 16 hrs. The reaction mixture was diluted with H_2O (30 mL) and HCl (2 mL, 2 M) extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 150x25mmx5um;mobile phase: [water(0.05%HCl)-ACN];B%: 20%-50%,6.5min) to afford **Compound 78** (35.88 mg, 57.8% yield, HCl) as a white solid. LC-MS (ESI): RT = 0.795 min, mass calcd for $C_{19}H_{18}F_5N_3O_2S$ 447.42 m/z, found 448.1 $[M+H]^+$, ^{1}HNMR (400 MHz, $CDCl_3$) ppm 2.42 (br s, 1 H) 3.22 (br s, 1 H) 4.44 (br s, 1 H) 7.03 - 7.23 (m, 2 H) 7.74 (br d, J = 7.78 Hz, 1 H) 8.09 (br s, 1 H) 8.47 (br s, 2 H).

Example 79: 2'-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)-1-phenyl-[3,3'-bipyridin]-6(1H)-one (Compound 79)



[00404] A mixture of [4-[(3-bromo-2-pyridyl)oxy]phenyl]-pentafluoro-λ^6-sulfane (**65C**, 83.1 mg, 0.22 mmol, 1 *eq*), 1-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (**79A**, 90 mg, 0.22 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (8.0 mg, 11.0 μmol, 0.05 *eq*), Na_2CO_3 (70.3 mg, 0.66 mmol, 3 *eq*)and H_2O (0.2 mL) in dioxane (1 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 3 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with saturated brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (4 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~60%) to afford **Compound 79** (9.2 mg, 8.8 % yield) as a white solid. LC-MS (ESI): RT = 0.873 min, mass calcd for $C_{22}H_{15}F_5N_2O_2S$ 466.42 m/z, found 467.1$[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.72 (dd, *J* = 9.51, 0.63 Hz, 1 H) 7.23 - 7.32 (m, 3 H) 7.41 - 7.59 (m, 6 H) 7.82 - 7.88 (m, 2 H) 7.93 - 8.02 (m, 3 H) 8.14 (dd, *J* = 4.88, 1.88 Hz, 1 H).

Example 80: 2'-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)-1-(pyrrolidin-3-yl)-[3,3'-bipyridin]-6(1H)-one (Compound 80)



Tert-butyl 3-(5-bromo-2-oxo-1-pyridyl)pyrrolidine-1-carboxylate

[00405] The mixture of 5-bromo-1H-pyridin-2-one (**62A**, 347.8 mg, 2.00 mmol, 1 *eq*), tert-butyl 3-bromopyrrolidine-1-carboxylate (500 mg, 2.00 mmol, 1 *eq*) and Cs_2CO_3 (6 51.3 mg, 2.00 mmol, 1 *eq*) in DMF (3 mL) was stirred at 60 °C for 16 hr. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and

concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50 % Ethyl acetate/Petroleum ether gradient @20 mL/min) to give intermediate **80A** (45 mg, 0.12 mmol, 6.4% yield) as a white solid.

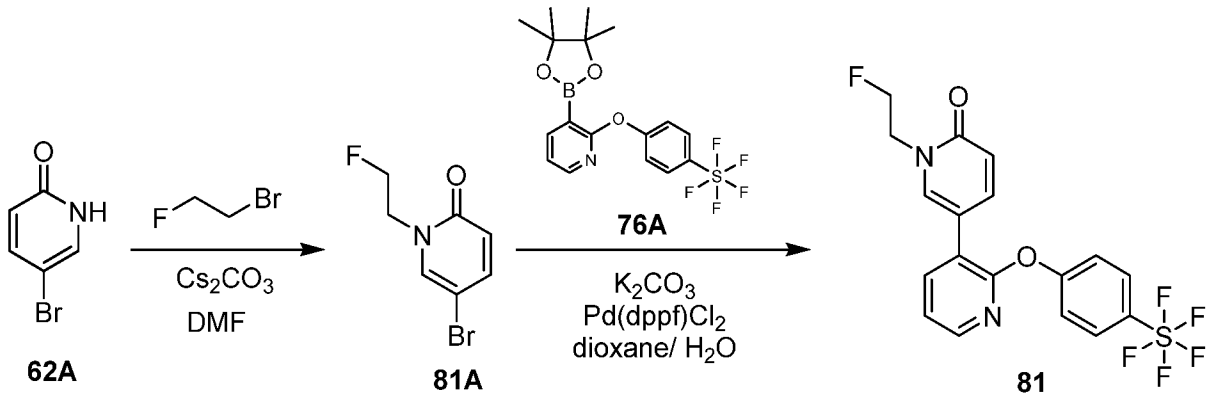
Cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one

[00406] A mixture of intermediate **80A** (42.0 mg, 0.12 mmol, 1 *eq*), intermediate **76A** (77.6 mg, 0.18 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (4.48 mg, 6.1 μmol, 0.05 *eq*), K_2CO_3 (50.7 mg, 0.36 mmol, 3.0 *eq*) in dioxane (1 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 8 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude intermediate **80B** (68 mg, crude) as a yellow oil, which was used into next step without further purification.

5-[2-[4-(pentafluoro-λ^6-sulfanyl)phenoxy]-3-pyridyl]-1-pyrrolidin-3-yl-pyridin-2-one

[00407] intermediate **80B** (68 mg, 0.12 mmol, 1 *eq*) in HCl/dioxane (4 M, 30 uL, 1 *eq*) was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 25%-55%, 6.5 min) to afford **Compound 80** (7.2 mg, 12.0 % yield, HCl) as a white solid. LC-MS (ESI): RT = 0.787 min, mass calcd for $C_{20}H_{18}F_5N_3O_2S$ 459.4 m/z found 460.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.17 (d, *J* = 4.0 Hz, 1H), 8.08 - 8.02 (m, 2H), 7.94 (br d, *J* = 9.3 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 2H), 7.37 - 7.28 (m, 3H), 6.68 (d, *J*=9.3 Hz, 1H), 5.18 (br s, 1H), 3.89 - 3.76 (m, 2H), 3.74 - 3.63 (m, 1H), 3.41 - 3.34 (m, 1H), 2.75 - 2.64 (m, 1H), 2.54 - 2.43 (m, 1H).

Example 81: 1-(2-Fluoroethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 81)



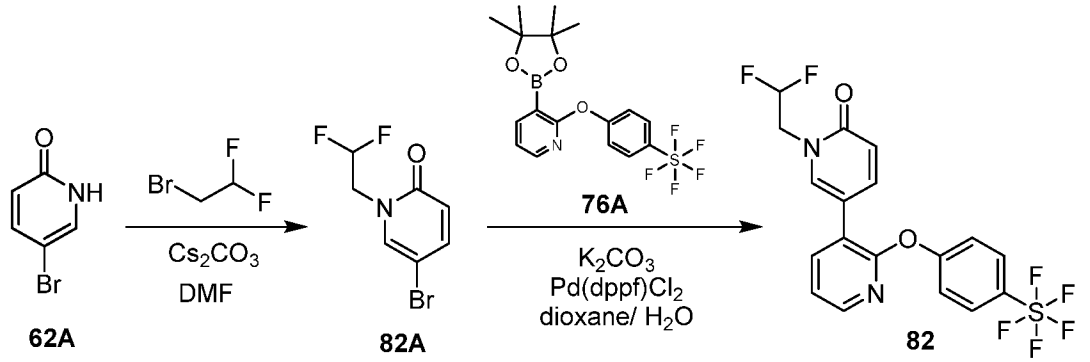
5-bromo-1-(2-fluoroethyl)pyridin-2-one

[00408] To a solution of 5-bromo-1H-pyridin-2-one (**62A**, 500 mg, 2.87 mmol, 1 *eq*) and 1-bromo-2-fluoro-ethane (364.8 mg, 2.87 mmol, 1 *eq*) in DMF (5 mL) was added Cs_2CO_3 (1.8 g, 5.75 mmol, 2 *eq*). The reaction mixture was stirred at 25 °C for 16 hr. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 45% Ethyl acetate/Petroleum ether gradient @ 35mL/min) to give intermediate **81A** (334 mg, 1.50 mmol, 52.2% yield) as a white solid.

1-(2-fluoroethyl)-5-[2-[4-(pentafluoro-λ6-sulfanyl)phenoxy]-3-pyridyl]pyridin-2-one

[00409] A mixture of intermediate **81A** (50 mg, 0.22 mmol, 1 eq), intermediate **76A** (115.4 mg, 0.27 mmol, 1.2 eq), K_2CO_3 (6 2.8 mg, 0.45 mmol, 2 eq), $Pd(dppf)Cl_2$ (8.3 mg, 11.3 μmol, 0.05 eq) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 6 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 40%-70%,6.5min) to afford **Compound 81** (45.11 mg, 22.5% yield) as a white solid. LC-MS (ESI): RT = 0.898 min, mass calcd for $C_{18}H_{14}F_6N_2O_2S$ 436.37 m/z, found 437.0 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) ppm 4.33 - 4.47 (m, 2 H) 4.67 (t, *J* = 4.52 Hz, 1 H) 4.79 (t, *J* = 4.52 Hz, 1 H) 6.68 (d, *J* = 9.29 Hz, 1 H) 7.22 - 7.32 (m, 3 H) 7.84 (d, *J* = 9.29 Hz, 2 H) 7.93 (td, *J* = 8.22, 1.63 Hz, 2 H) 8.01 (s, 1 H) 8.13 (dd, *J* = 4.77, 1.51 Hz, 1 H).

Example 82: 1-(2,2-difluoroethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 82)



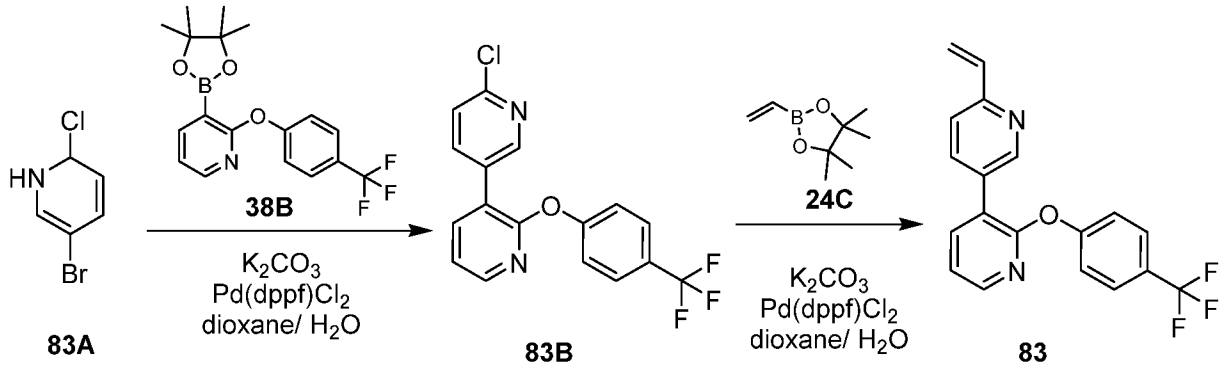
5-bromo-1-(2,2-difluoroethyl)pyridin-2-one

[00410] To a solution of 5-bromo-1H-pyridin-2-one (**62A**, 500 mg, 2.87 mmol, 1 *eq*) and 2-bromo-1,1-difluoro-ethane (416.5 mg, 2.87 mmol, 1 *eq*) in DMF (5 mL) was added Cs_2CO_3 (1.87 g, 5.75 mmol, 2 *eq*). The reaction mixture was stirred at 25 °C for 16 hrs. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 35% Ethyl acetate/Petroleum ether gradient @ 35 mL/min) to give intermediate **82A** (248 mg, 1.03 mmol, 35.8% yield) as a white solid.

1-(2,2-difluoroethyl)-5-[2-[4-(pentafluoro-λ6-sulfanyl)phenoxy]-3-pyridyl]pyridin-2-one

[00411] A mixture of intermediate **82A** (50 mg, 0.21 mmol, 1 *eq*), intermediate **76A** (106.6 mg, 0.25 mmol, 1.2 *eq*), K_2CO_3 (58.0 mg, 0.42 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (7.6 mg, 10.5 µmol, 0.05 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 6 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 40%-70%,6.5min) to afford **Compound 82** (13.37 mg, 13.9% yield) as a white solid. LC-MS (ESI): RT = 0.919 min, mass calcd for $C_{18}H_{14}F_7N_3OS$ 454.36 m/z, found 455.0 $[M+H]^+$, ^1H NMR (400 MHz,CD_3OD) δ ppm 4.47 (td, *J* = 14.18, 4.02 Hz, 2 H) 6.04 - 6.37 (m, 1 H) 6.65 (d, *J* = 9.29 Hz, 1 H) 7.23 - 7.32 (m, 3 H) 7.82 - 7.88 (m, 2 H) 7.88 - 7.95 (m, 2 H) 7.98 (d, *J* = 2.26 Hz, 1 H) 8.13 (dd, *J* = 4.89, 1.88 Hz, 1 H).

Example 83: 2-(4-(Trifluoromethyl)phenoxy)-6'-vinyl-3,3'-bipyridine (Compound 83)



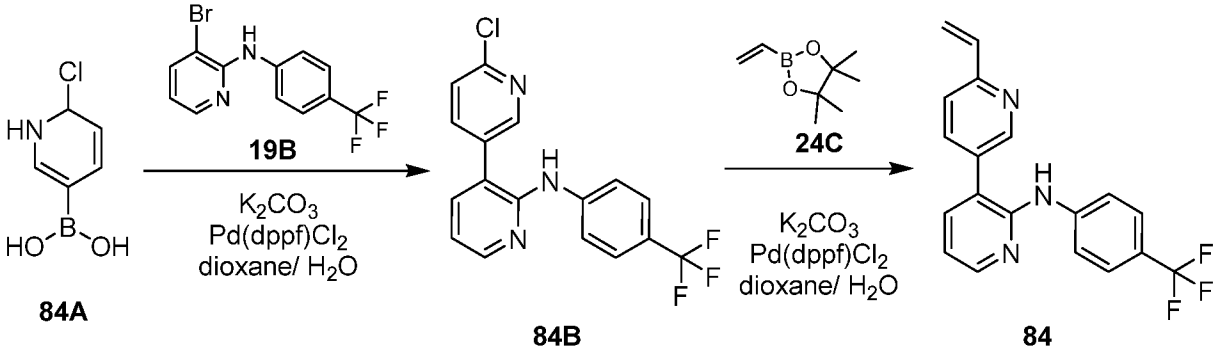
2-chloro-5-[2-[4-(trifluoromethyl)phenoxy]-3-pyridyl]pyridine

[00412] A mixture of 5-bromo-2-chloro-pyridine (**62A**, 200 mg, 1.04 mmol, 1 *eq*), intermediate **38B** (455.4 mg, 1.25 mmol, 1.2 *eq*), K_2CO_3 (287.2 mg, 2.08 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (38.0 mg, 51.9 µmol, 0.05 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 6 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give intermediate **83B** (234 mg, 0.61 mmol, 59.0% yield) as a white solid.

2-[4-(trifluoromethyl)phenoxy]-3-(6-vinyl-3-pyridyl)pyridine

[00413] A mixture of intermediate **83B** (50 mg, 0.14 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (**24C**, 26.3 mg, 0.17 mmol, 29.0 µL, 1.2 *eq*), K_2CO_3 (39.4 mg, 0.28 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (5.2 mg, 7.1 µmol, 0.05 *eq*) in dioxane (2 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 6 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 37%-67%,8.5min) to afford **Compound 83** (3.52 mg, 7.1% yield) as a white solid. LC-MS (ESI): RT = 0.873 min, mass calcd for $C_{19}H_{13}F_3N_2O$ 342.31 m/z, found 343.1 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) ppm 6.12 (d, *J* = 11.13 Hz, 1 H) 6.62 (d, *J* = 17.64 Hz, 1 H) 7.05 (dd, *J* = 17.64, 11.26 Hz, 1 H) 7.34 - 7.40 (m, 3 H) 7.74 (d, *J* = 8.50 Hz, 2 H) 8.17 (dd, *J* = 7.63, 1.88 Hz, 1 H) 8.26 (dd, *J* = 4.94, 1.81 Hz, 1 H) 8.34 (d, *J* = 8.63 Hz, 1 H) 8.87 (dd, *J* = 8.63, 2.13 Hz, 1 H) 9.09 (d, *J* = 1.63 Hz, 1 H).

Example 84: *N*-(4-(Trifluoromethyl)phenyl)-6'-vinyl-[3,3'-bipyridin]-2-amine (Compound 84)



3-(6-chloro-3-pyridyl)-N-[4-(trifluoromethyl)phenyl]pyridin-2-amine

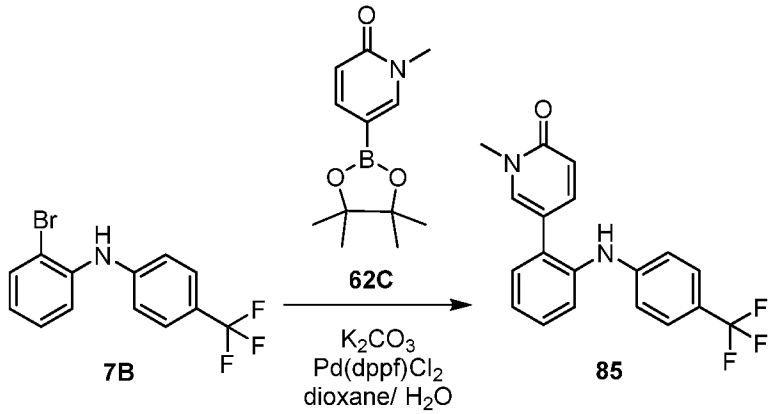
[00414] A mixture of (6-chloro-3-pyridyl)boronic acid (**84A**, 300 mg, 1.91 mmol, 1 *eq*), intermediate **19B** (6 04.5 mg, 1.91 mmol, 1 *eq*), K_2CO_3 (526.9 mg, 3.81 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (6 9.7 mg, 95.3 µmol, 0.05 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 6 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 30% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **84B** (402 mg, 0.87 mmol, 45.8% yield) as a white solid.

N-[4-(trifluoromethyl)phenyl]-3-(6-vinyl-3-pyridyl)pyridin-2-amine

[00415] A mixture of intermediate **84B** (100 mg, 0.28 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (**24C**, 52.8 mg, 0.34 mmol, 58.2 µL, 1.2 *eq*), K_2CO_3 (79.0 mg, 0.57 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (10.4 mg, 14.3 µmol, 0.05 *eq*) in dioxane (2 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 6 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x3). The combined organic layers were washed with brine (30 mL x2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75x30mmx3um;mobile phase: [water(0.05%HCl)-ACN];B%: 30%-60%,6.5min) to afford **Compound 84** (25.31 mg, 25.9% yield) as a yellow solid. LC-MS (ESI): RT = 0.776 min, mass calcd for $C_{19}H_{14}F_3N_3$ 341.33 m/z, found 341.9 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) ppm 6.15 (d, *J* = 11.04 Hz, 1 H) 6.67 (d, *J* = 17.57 Hz, 1 H) 7.09 (dd, *J*

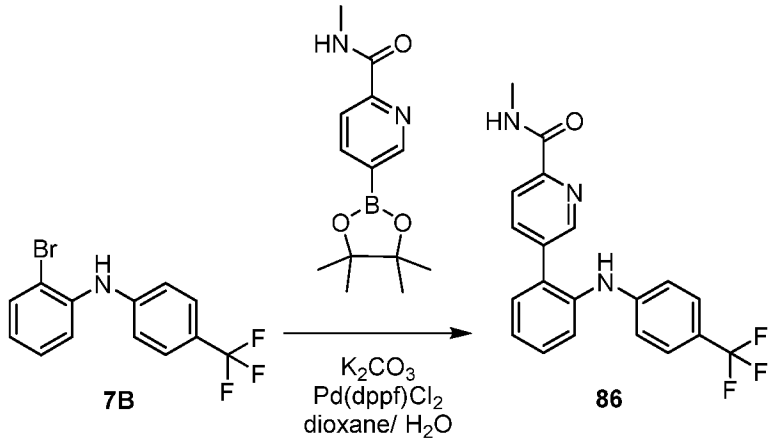
= 17.57, 11.29 Hz, 1 H) 7.33 (dd, *J* = 7.28, 6.02 Hz, 1 H) 7.63 (d, *J* = 8.53 Hz, 2 H) 7.79 (d, *J* = 8.53 Hz, 2 H) 8.15 (ddd, *J* = 13.87, 6.71, 1.51 Hz, 2 H) 8.38 (d, *J* = 8.53 Hz, 1 H) 8.69 (dd, *J* = 8.41, 1.63 Hz, 1 H) 9.03 (d, *J* = 1.26 Hz, 1 H).

[00416] Example 85: 1-Methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2(1H)-one (Compound 85)



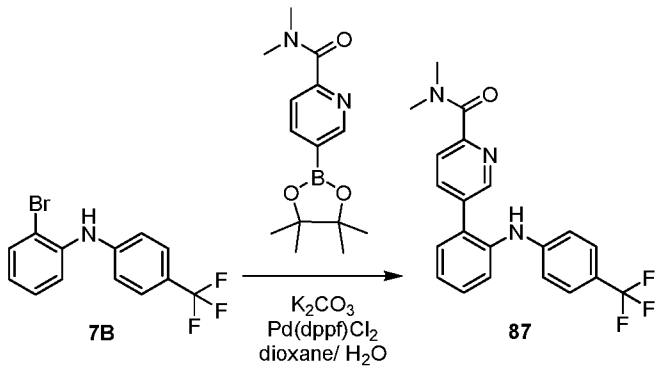
[00417] 2-Bromo-N-(4-(trifluoromethyl)phenyl)aniline (**7B**, 1 eq) and (1-methylpyridin-2(1H)-one-5-yl)boronic acid (**62C**, 1.2 eq) were suspended in 1:4 2M K_2CO_3 /dioxane, and the reaction mixture was purged with N_2 for 10 min. To this reaction mixture was added Pd(dppf)Cl_2 (0.1 eq), and the reaction mixture was heated to 100 °C until LCMS indicated starting materials were consumed. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford **Compound 85** (84% yield). LCMS Calcd.: 344.1, m/z found: 345.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm: 3.41 (s, 3 H) 6.32 (d, *J*=9.35 Hz, 1 H) 6.85 (d, *J*=8.62 Hz, 2 H) 7.17 - 7.22 (m, 1 H) 7.31 - 7.41 (m, 6 H) 7.77 (d, *J*=2.48 Hz, 1 H) 8.09 (s, 1 H).

Example 86: *N*-Methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)picolinamide (Compound 86)



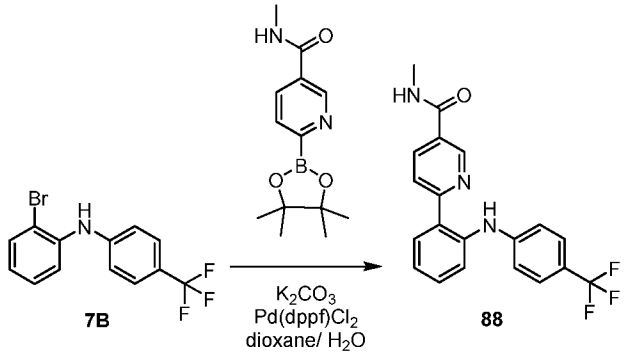
[00418] **Compound 86** was prepared by employing the procedure for **Compound 85** using N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide in lieu of 1-methylpyridin-2(1H)-one-5-yl)boronic acid (**62C**). LC-MS Calcd.: 371.1 m/z found: 372.1 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 2.81 (d, *J*=4.77 Hz, 3 H) 6.83 (d, *J*=8.44 Hz, 2 H) 7.34 (t, *J*=7.40 Hz, 1 H) 7.39 - 7.44 (m, 3 H) 7.45 - 7.54 (m, 2 H) 7.99 - 8.04 (m, 2 H) 8.25 (s, 1 H) 8.61 (s, 1 H) 8.77 (q, *J*=4.40 Hz, 1 H).

Example 87: *N*,*N*-Dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)picolinamide (Compound 87)



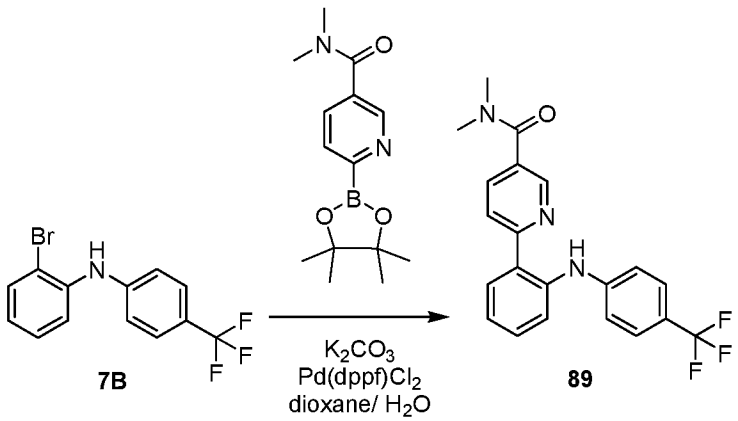
[00419] **Compound 87** was prepared by employing the procedure for **Compound 85** using *N*,*N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide in lieu of 1-methylpyridin-2(1H)-one-5-yl)boronic acid (**62C**). LC-MS Calcd.: 385.1 m/z found: 386.1 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 2.70 (s, 5 H) 2.82 (s, 3 H) 2.99 (s, 3 H) 6.76 (d, *J*=8.44 Hz, 2 H) 7.31 - 7.37 (m, 3 H) 7.40 (d, *J*=8.07 Hz, 1 H) 7.46 - 7.51 (m, 3 H) 7.90 (dd, *J*=8.07, 2.20 Hz, 1 H) 8.34 (s, 1 H) 8.58 (s, 1 H).

Example 88: *N*-Methyl-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)nicotinamide (Compound 88)



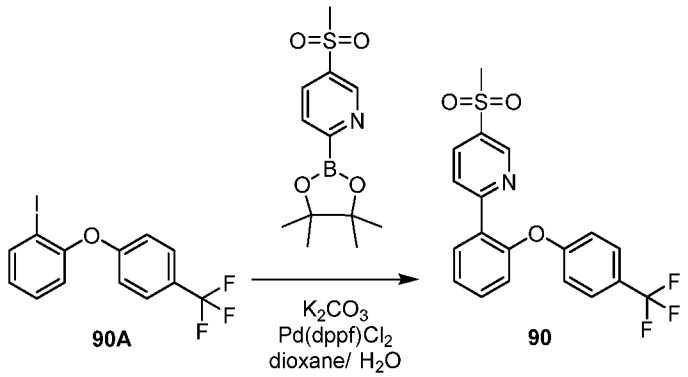
[00420] **Compound 88** was prepared by employing the procedure for **Compound 85** using N-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide in lieu of 1-methylpyridin-2(1H)-one-5-yl)boronic acid (**62C**). LC-MS Calcd.: 371.1 m/z found: 372.1 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 2.83 (d, *J*=4.40 Hz, 3 H) 7.12 (d, *J*=8.44 Hz, 2 H) 7.20 (t, *J*=7.51 Hz, 1 H) 7.43 - 7.51 (m, 4 H) 7.81 (dd, *J*=7.89, 1.28 Hz, 1 H) 7.89 (d, *J*=8.07 Hz, 1 H) 8.24 (dd, *J*=8.44, 2.20 Hz, 1 H) 8.65 - 8.70 (m, 1 H) 9.11 (d, *J*=1.83 Hz, 1 H) 9.86 (s, 1 H).

Example 89: *N,N*-Dimethyl-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)nicotinamide (Compound 89)



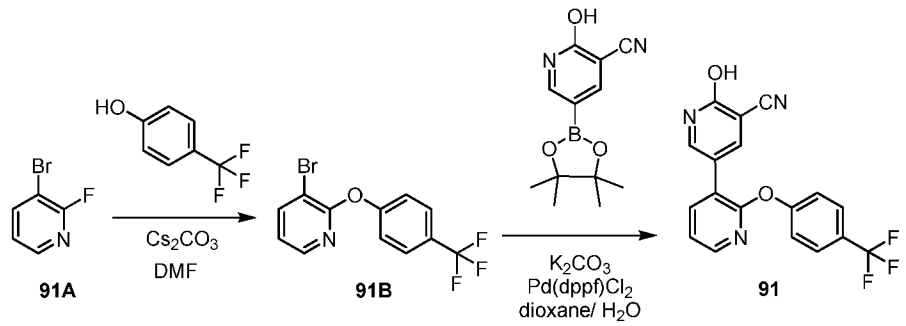
[00421] **Compound 89** was prepared by employing the procedure for **Compound 85** using *N,N*-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide in lieu of 1-methylpyridin-2(1H)-one-5-yl)boronic acid (**62C**). LC-MS Calcd.: 385.1 m/z found: 386.1 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 2.94 (s, 3 H) 3.02 (s, 3 H) 7.07 (d, *J*=8.80 Hz, 2 H) 7.21 (t, *J*=7.36 Hz, 1 H) 7.43 - 7.49 (m, 4 H) 7.77 - 7.82 (m, 2 H) 7.90 (dd, *J*=8.07, 2.20 Hz, 1 H) 8.72 (s, 1 H) 9.69 (s, 1 H).

Example 90: 5-(Methylsulfonyl)-2-(2-(4-(trifluoromethyl)phenoxy)phenyl)pyridine (Compound 90)



[00422] 1-Iodo-2-(4-(trifluoromethyl)phenoxy)benzene (**90A**, 36 mg, 0.1 mmol, 1 eq) and (5-(methylsulfonyl)pyridine-2-yl)boronic acid (24 mg, 0.12 mmol, 1.2 eq.) were suspended in 1:4 2M K_2CO_3 /dioxane, and the reaction mixture was purged with N_2 for 10 min. To the reaction mixture was added $Pd(dppf)Cl_2$ (0.1 eq), and the reaction mixture was heated to 100 °C until LCMS indicated starting materials were consumed. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography (DCM/EtOAc gradient) to afford **Compound 90** (34 mg, 87%). LCMS Calcd.: 393.1 m/z found: 394.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 3.33 - 3.35 (m, 3 H) 7.15 (m, *J*=8.80 Hz, 2 H) 7.22 (d, *J*=8.15 Hz, 1 H) 7.46 (td, *J*=7.52, 1.10 Hz, 1 H) 7.60 (td, *J*=7.70, 1.83 Hz, 1 H) 7.72 (m, *J*=8.80 Hz, 2 H) 7.97 (dd, *J*=7.89, 1.65 Hz, 1 H) 8.05 (d, *J*=8.44 Hz, 1 H) 8.33 (dd, *J*=8.44, 2.57 Hz, 1 H) 9.12 (d, *J*=2.20 Hz, 1 H).

Example 91: 6-Hydroxy-2'-(4-(trifluoromethyl)phenoxy)-[3,3'-bipyridine]-5-carbonitrile (Compound 91)



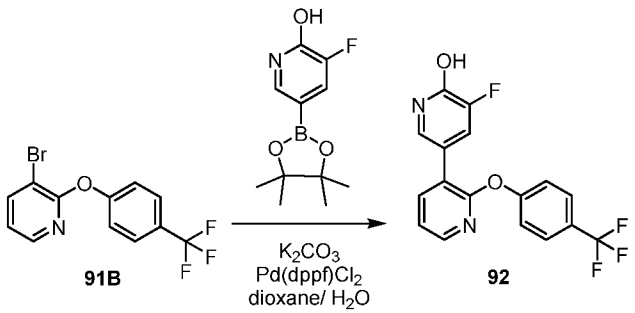
3-Bromo-2-(4-(trifluoromethyl)phenoxy)pyridine

[00423] 3-Bromo-2-fluoropyridine (**91A**, 20.6 g, 117 mmol, 1 eq.), 4-(trifluoromethyl)phenol (19.02 g, 117 mmol, 1 eq.), Cs_2CO_3 (45.8 g, 141 mmol, 1.2 eq.), and DMF (292 mL) were heated to 100 °C for 6 hrs until LC-MS indicated the completion of reaction. The reaction mixture was added to rapidly stirring water, and the solid was filtered to give intermediate **91B** (26.3g, 71%). LC-MS Calcd.: 318 ($[M+H]^+$), m/z found: 318.

6-Hydroxy-2'-(4-(trifluoromethyl)phenoxy)-[3,3'-bipyridine]-5-carbonitrile

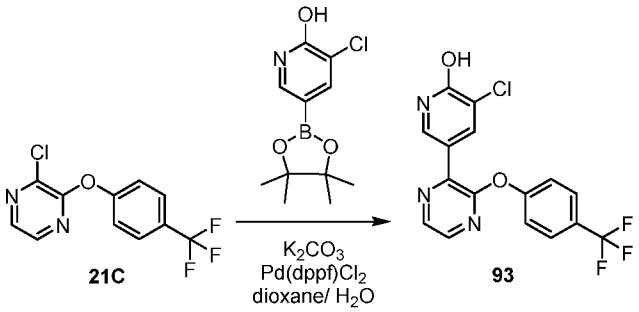
[00424] Intermediate **91B** (1 eq.) and (2-hydroxy-3-cyanopyridin-5-yl)boronic acid (1.1 eq.) were suspended in 1:4 2M K_2CO_3 /dioxane, and the reaction mixture was purged with N_2 for 10 min. To the reaction mixture was added Pd(dppf)Cl_2 (0.1 eq), and the reaction mixture was heated to 100 °C until LCMS indicated reaction completion. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford **Compound 91**. LCMS mass calcd., C*18*H*10*F*3*N*3*O*2*, 357. m/z found, 358 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 7.29 (dd, *J*=7.52, 4.95 Hz, 1 H) 7.43 (d, *J*=8.44 Hz, 2 H) 7.81 (d, *J*=8.44 Hz, 2 H) 8.03 (dd, *J*=7.34, 1.83 Hz, 1 H) 8.12 (dd, *J*=4.77, 1.83 Hz, 1 H) 8.17 (d, *J*=2.20 Hz, 1 H) 8.57 (d, *J*=2.93 Hz, 1 H) 12.90 (br d, *J*=1.83 Hz, 1 H).

Example 92: 5-Fluoro-2'-(4-(trifluoromethyl)phenoxy)-[3,3'-bipyridin]-6-ol (Compound 92)



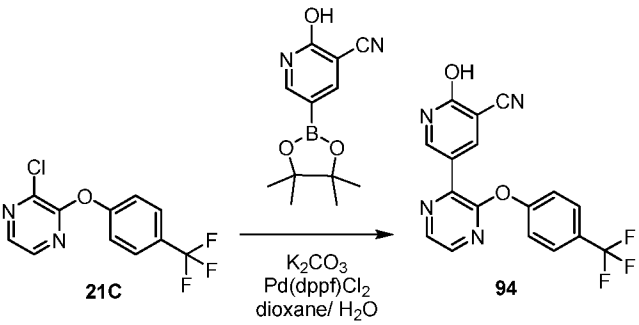
[00425] **Compound 92** was prepared by employing the procedure for **Compound 91** using (2-hydroxy-3-fluoropyridin-5-yl)boronic acid in lieu of (2-hydroxy-3-cyanopyridin-5-yl)boronic acid. LC-MS Calcd.: 351 ([M+H]+), m/z found: 351.0. ^1H NMR (600 MHz, DMSO-*d*6) δ ppm: 7.27 (dd, *J*=7.34, 4.77 Hz, 1 H) 7.41 (m, *J*=8.44 Hz, 2 H) 7.64 (s, 1 H) 7.79 (m, *J*=8.44 Hz, 2 H) 7.85 (dd, *J*=12.10, 2.20 Hz, 1 H) 8.00 (dd, *J*=7.34, 1.83 Hz, 1 H) 8.10 (dd, *J*=4.77, 1.83 Hz, 1 H) 12.44 (br s, 1 H).

Example 93: 3-Chloro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-ol (Compound 93)



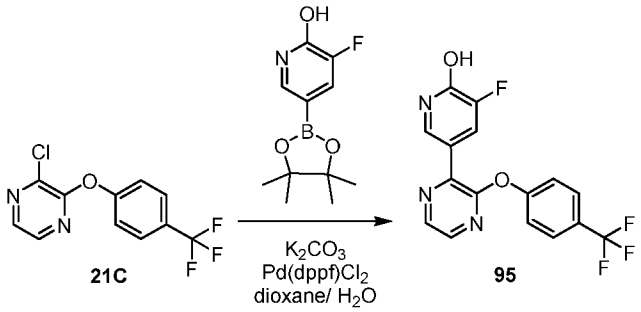
[00426] Intermediate **21C** (20 mg, 0.07 mmol, 1 eq.) and (2-hydroxy-3-chloropyridin-5-yl)boronic acid (23 mg, 0.087 mmol, 1.2 equiv.) were suspended in 1:4 2M K_2CO_3 /dioxane, and this mixture was purged with N_2 for 10 min. To this mixture was added $Pd(dppf)Cl_2$ (0.1 eq), and the reaction mixture was heated to 100 °C until LCMS indicated starting materials were consumed. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford **Compound 93** (5 mg). LCMS mass calcd. $C_{16}H_9ClF_3N_3O2$, 367. m/z found, 368 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 7.54 (d, J=8.44 Hz, 2 H) 7.86 (d, J=8.80 Hz, 2 H) 8.11 (d, J=2.57 Hz, 1 H) 8.30 - 8.33 (m, 1 H) 8.47 (d, J=2.57 Hz, 1 H) 8.50 (d, J=2.57 Hz, 1 H) 12.57 (br s, 1 H).

Example 94: 2-Hydroxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)nicotinonitrile (Compound 94)



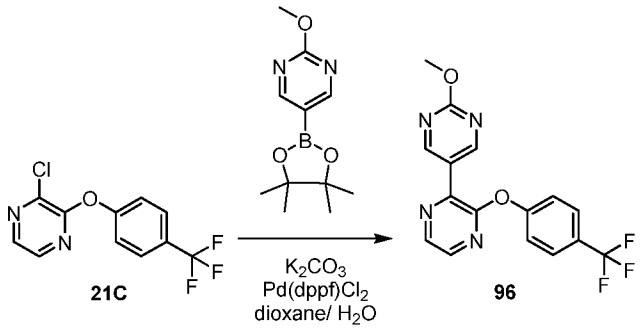
[00427] **Compound 94** was prepared by employing the procedure for **Compound 93** using (2-hydroxy-3-cyanopyridin-5-yl)boronic acid in lieu of (2-hydroxy-3-chloropyridin-5-yl)boronic acid. LC-MS mass calcd., $C_{17}H_9F_3N_4O_2$, 358. m/z found, 359 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) $^{\delta}$ ppm 7.54 (d, ^{J}=8.44 Hz, 2 H) 7.87 (d, ^{J}=8.80 Hz, 2 H) 8.14 (d, ^{J}=2.57 Hz, 1 H) 8.48 (d, ^{J}=2.57 Hz, 1 H) 8.57 (d, ^{J}=2.57 Hz, 1 H) 8.84 (d, ^{J}=2.57 Hz, 1 H) 13.00 (br s, 1 H).

Example 95: 3-Fluoro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-ol (Compound 95)



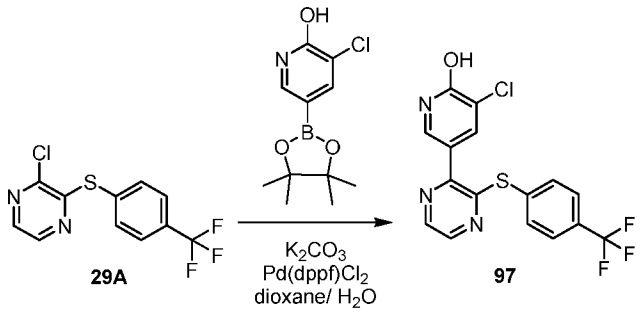
[00428] **Compound 95** was prepared by employing the procedure for **Compound 93** using (2-hydroxy-3-fluoropyridin-5-yl)boronic acid in lieu of (2-hydroxy-3-chloropyridin-5-yl)boronic acid. LC-MS mass calcd., $C_{16}H_9F_4N_3O_2$, 351. m/z found, 352 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 7.54 (d, J=8.44 Hz, 2 H) 7.86 (d, J=8.44 Hz, 2 H) 8.09 - 8.20 (m, 3 H) 8.47 (d, J=2.57 Hz, 1 H) 12.55 (br s, 1 H).

Example 96: 2-Methoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine (Compound 96)



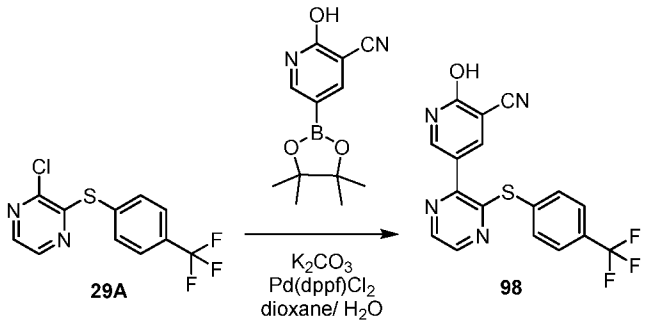
[00429] **Compound 96** was prepared by employing the procedure for **Compound 93** using (2-methoxy-pyrimidin-5-yl)boronic acid in lieu of (2-hydroxy-3-chloropyridin-5-yl)boronic acid. LC-MS calcd.: 348.1, m/z found: 349.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 3.95 - 4.05 (m, 3 H) 7.56 (d, J=8.44 Hz, 2 H) 7.86 (d, J=8.80 Hz, 2 H) 8.24 (d, J=2.57 Hz, 1 H) 8.57 (d, J=2.57 Hz, 1 H) 9.29 (s, 2 H).

Example 97: 3-Chloro-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyridin-2-ol (Compound 97)



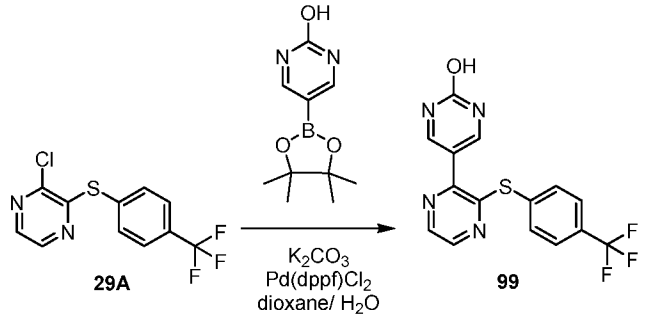
[00430] Intermediate **29A** (2.35 g, 8 mmol, 1 eq.) and (2-hydroxy-3-chloropyridin-5-yl)boronic acid (1.81 g, 9.6 mmol, 1.2 equiv.) were suspended in 1:4 2M K_2CO_3 /dioxane, and this reaction mixture was purged with N_2 for 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (0.1 eq), and the reaction mixture was heated to 100 °C until LCMS indicated starting materials were consumed. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford **Compound 97**. LC-MS mass calcd., $C_{16}H_9ClF_3N_3OS$, 383. m/z found, 384 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 7.71 (m ,*J*=8.44 Hz, 2 H) 7.80 (m, *J*=8.44 Hz, 2 H) 7.95 (br s, 1 H) 8.14 (d, *J*=2.57 Hz, 1 H) 8.40 (d, *J*=2.20 Hz, 1 H) 8.52 (d, *J*=2.57 Hz, 1 H) 12.62 (br s, 1 H).

Example 98: 2-Hydroxy-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)nicotinonitrile (Compound 98)



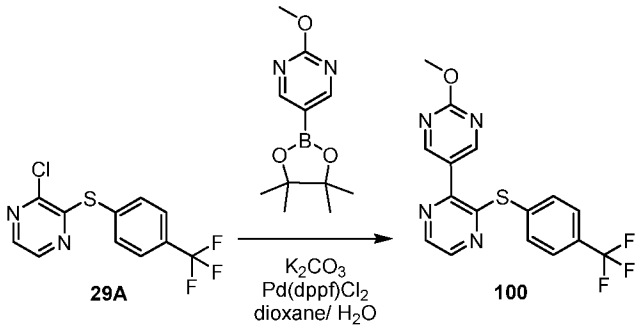
[00431] **Compound 98** was prepared by employing the procedure for **Compound 97** using (2-hydroxy-3-cyanopyridin-5-yl)boronic acid in lieu of (2-hydroxy-3-chloropyridin-5-yl)boronic acid. LC-MS mass calcd., $C_{17}H_9F_3N_4OS$, 374. m/z found, 375 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 7.70 (d, *J*=8.07 Hz, 2 H) 7.79 (d, *J*=8.44 Hz, 2 H) 8.30 (d, *J*=2.57 Hz, 1 H) 8.41 (d, *J*=2.57 Hz, 1 H) 8.47 (d, *J*=2.57 Hz, 1 H) 8.53 (d, *J*=2.57 Hz, 1 H).

Example 99: 5-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol (Compound 99)



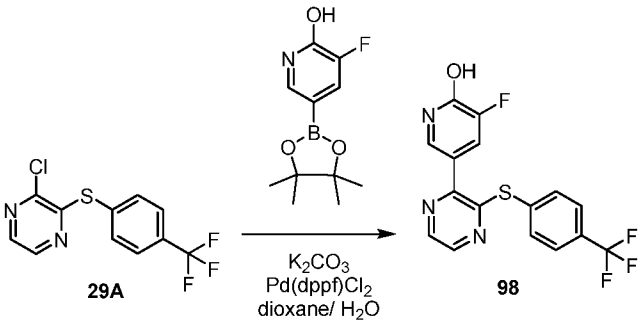
[00432] **Compound 99** was prepared by employing the procedure for **Compound 97** using (2-hydroxy-pyrimidin-5-yl)boronic acid in lieu of (2-hydroxy-3-chloropyridin-5-yl)boronic acid. LC-MS Calcd.: 351 ([M+H]+), m/z found: 351.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 7.71 (m, *J*=8.07 Hz, 2 H) 7.79 (m, *J*=8.07 Hz, 2 H) 8.44 (d, *J*=2.57 Hz, 1 H) 8.56 (d, *J*=2.57 Hz, 1 H) 8.71 (br s, 2 H).

Example 100: 2-Methoxy-5-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidine (Compound 100)



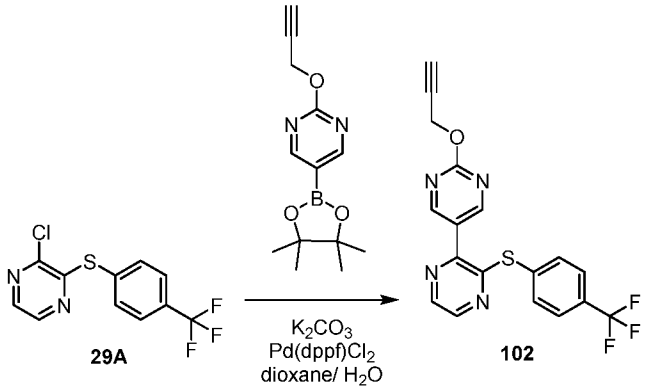
[00433] **Compound 100** was prepared by employing the procedure for **Compound 97** using (2-methoxy-pyrimidin-5-yl)boronic acid in lieu of (2-hydroxy-3-chloropyridin-5-yl)boronic acid. LC-MS Calcd.: 364.1 m/z found: 365.0 ([M+H]$^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 4.03 (s, 3 H) 7.71 (m, *J*=8.07 Hz, 2 H) 7.79 (m, *J*=8.07 Hz, 2 H) 8.51 (d, *J*=2.57 Hz, 1 H) 8.62 (d, *J*=2.20 Hz, 1 H) 9.01 (s, 2 H).

Example 101: 3-Fluoro-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyridin-2-ol (Compound 101)



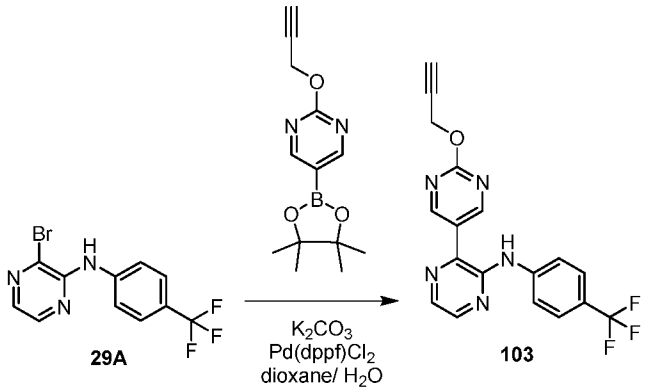
[00434] **Compound 101** was prepared by employing the procedure for **Compound 97** using (2-hydroxy-3-fluoropyridin-5-yl)boronic acid in lieu of (2-hydroxy-3-chloropyridin-5-yl)boronic acid. LC-MS Calcd.: 368 ([M+H]+), m/z found: 368.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 7.71 (d, *J*=8.07 Hz, 2 H) 7.78 - 7.84 (m, 4 H) 8.39 (d, *J*=2.57 Hz, 1 H) 8.51 (d, *J*=2.57 Hz, 1 H) 12.59 (br s, 1 H).

Example 102: 2-(Prop-2-yn-1-yloxy)-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidine (Compound 102)



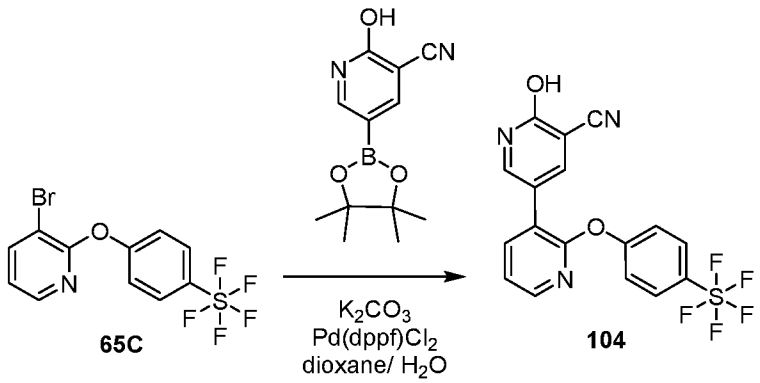
[00435] **Compound 102** was prepared by employing the procedure for **Compound 97** using 2-(prop-2-yn-1-yloxy)pyrimidin-5-yl)boronic acid in lieu of (2-hydroxy-3-chloropyridin-5-yl)boronic acid. LC-MS Calcd.: 389 ([M+H]+), m/z found: 389.

Example 103: 3-(2-(Prop-2-yn-1-yloxy)pyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (Compound 103)



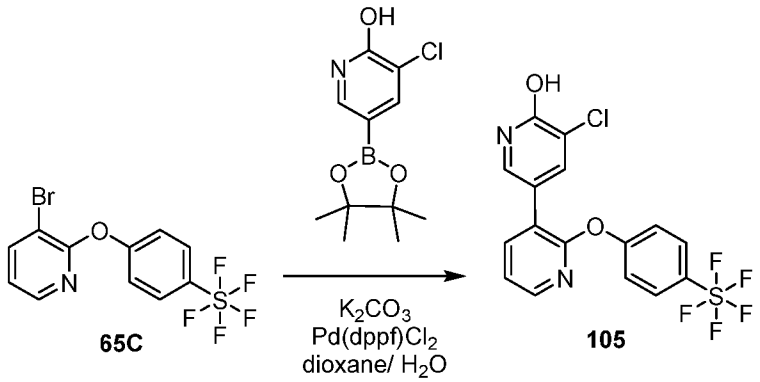
[00436] Intermediate **19B** (1 eq.) and 2-(prop-2-yn-1-yloxy)pyrimidin-5-yl)boronic acid (1.2 equiv.) were suspended in 1:4 2M K_2CO_3 /dioxane, and this mixture was purged with N_2 for 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (0.1 eq), and the reaction mixture was heated to 100 °C until LCMS indicated starting materials were consumed. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford **Compound 103**. LC-MS Calcd.: 371.1, m/z found: 372.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 3.61 (t, *J*=2.38 Hz, 1 H) 5.12 (d, *J*=2.40 Hz, 2 H) 7.63 (m, *J*=8.71 Hz, 2 H) 7.74 - 7.78 (m, 2 H) 8.27 (s, 2 H) 8.97 (s, 2 H) 9.12 (s, 1 H).

Example 104: 6-Hydroxy-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridine]-5-carbonitrile (Compound 104)



[00437] Intermediate **65C** (1 eq.) and (2-hydroxy-3-cyanopyridin-5-yl)boronic acid (1.2 equiv.), were suspended in 1:4 2M K_2CO_3 /dioxane, and this mixture was purged with N_2 for 10 min. To this mixture was added $Pd(dppf)Cl_2$ (0.1 eq), and the reaction mixture was heated to 100 °C until LCMS indicated starting materials were consumed. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford Compound 104. LC-MS Calcd.: 416 ([M+H]+), m/z found: 416. ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 7.28 - 7.31 (m, 1 H) 7.43 (d, J=9.17 Hz, 2 H) 7.95 - 8.00 (m, 2 H) 8.04 (dd, J=7.34, 1.83 Hz, 1 H) 8.13 (dd, J=4.77, 1.83 Hz, 1 H) 8.17 (d, J=2.57 Hz, 1 H) 8.56 (d, J=2.57 Hz, 1 H) 12.71 - 13.08 (m, 1 H).

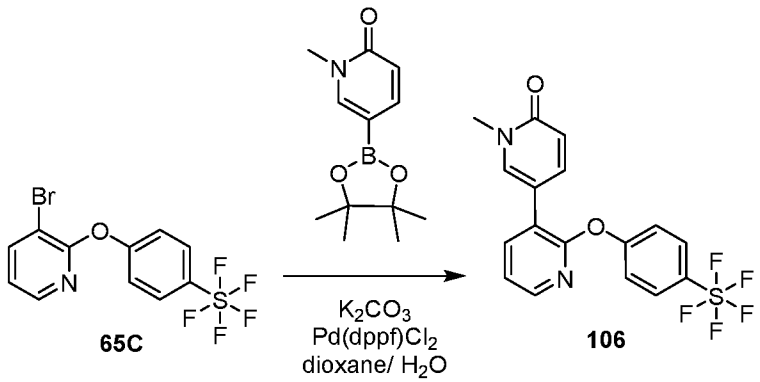
Example 105: 5-Chloro-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6-ol (Compound 105)



[00438] **Compound 105** was prepared by employing the procedure for **Compound 104** using (2-hydroxy-3-chloropyridin-5-yl)boronic acid in lieu of (2-hydroxy-3-cyanopyridin-5-yl)boronic acid. LC-MS Calcd.: 425 ([M+H]+), m/z found: 425. ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 7.26 - 7.30 (m, 1 H) 7.41 (d, J=8.80 Hz, 2 H) 7.79 (d, J=2.20 Hz, 1 H) 7.95 - 7.99 (m, 2 H)

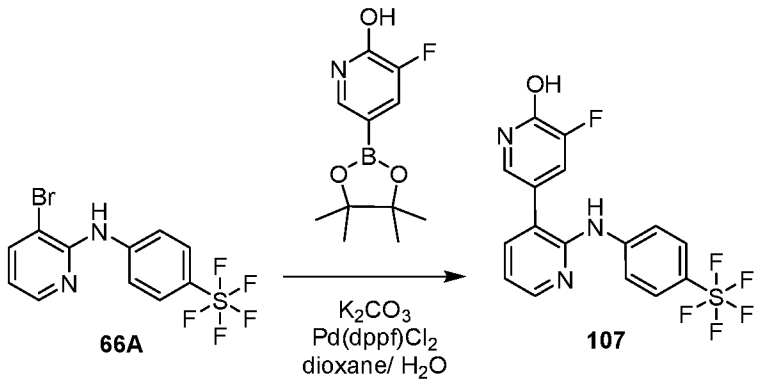
8.02 (dd, J=7.34, 1.83 Hz, 1 H) 8.11 (dd, J=5.13, 1.83 Hz, 1 H) 8.15 (d, J=2.20 Hz, 1 H) 12.47 (br s, 1 H).

Example 106: 1-Methyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one (Compound 106)



[00439] **Compound 106** was prepared by employing the procedure for **Compound 104** using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one in lieu of (2-hydroxy-3-cyanopyridin-5-yl)boronic acid. LC-MS Calcd.: 405 ([M+H]+), m/z found: 405. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 3.50 (s, 3 H) 6.48 (d, J=9.54 Hz, 1 H) 7.30 (dd, J=7.34, 4.77 Hz, 1 H) 7.39 (d, J=9.17 Hz, 2 H) 7.80 (dd, J=9.35, 2.75 Hz, 1 H) 7.94 - 7.99 (m, 4 H) 8.09 (d, J=2.57 Hz, 1 H) 8.12 (dd, J=4.77, 1.83 Hz, 1 H).

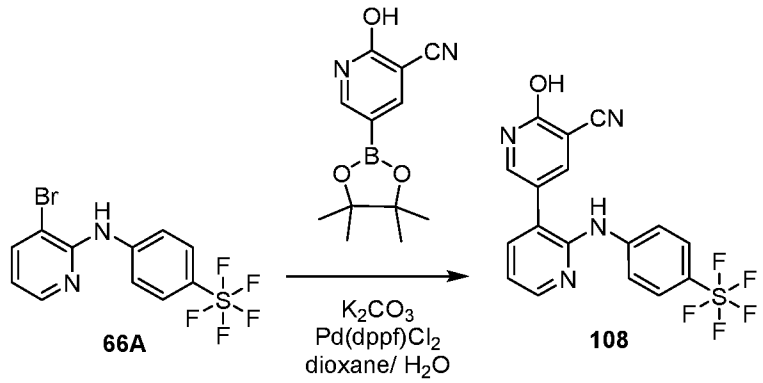
Example 107: 5-Fluoro-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6-ol (Compound 107)



[00440] Intermediate **66A** (1 eq.) and (2-hydroxy-3-fluoropyridin-5-yl)boronic acid (1.2 equiv.) were suspended in 1:4 2M K_2CO_3 /dioxane, and this mixture was purged with N_2 for 10 min. To this mixture was added $Pd(dppf)Cl_2$ (0.1 eq), and the reaction mixture was heated to 100 °C until LCMS indicated starting materials were consumed. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford

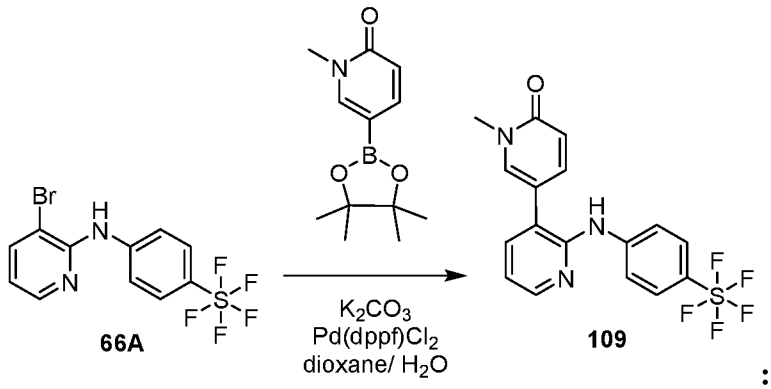
Compound 107. LCMS Calcd.: 408 ([M+H]+), m/z found: 408.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 7.03 (dd, *J*=7.52, 4.95 Hz, 1 H) 7.36 (s, 1 H) 7.50 (dd, *J*=11.74, 2.20 Hz, 1 H) 7.62 (dd, *J*=7.34, 1.83 Hz, 1H) 7.69 - 7.75 (m, 4 H) 8.22 (dd, *J*=4.77, 1.83 Hz, 1 H) 8.55 (s, 1 H) 12.35 (br s, 1 H).

Example 108: 6-Hydroxy-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridine]-5-carbonitrile (Compound 108)



[00441] **Compound 108** was prepared by employing the procedure for **Compound 107** using (2-hydroxy-3-cyanopyridin-5-yl)boronic acid in lieu of (2-hydroxy-3-fluoropyridin-5-yl)boronic acid. LCMS Calcd.: 415 ([M+H]+), m/z found: 415.0.

Example 109: 1-Methyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6(1H)-one (Compound 109)



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[00442] **Compound 109** was prepared by employing the procedure for **Compound 107** using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one in lieu of (2-hydroxy-3-fluoropyridin-5-yl)boronic acid. LCMS Calcd.: 435 ([M+H]+), m/z found: 435.0.

II. Biological Evaluation

Example A1: YAP Reporter Assay

[00443] 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% CO_2, cells were lysed, and 8XTBD-driven firefly luciferase and control TK-driven renilla luciferase activities were measured using Promega Dual-Luciferase Reporter Assay System.

[00444] Reagents: The reagents used for this study were: 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.

[00445] 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).

[00446] Cell Plating: The appropriate media was warmed at 37 °C by water bath: Culture Medium, Assay Medium, 1x D-PBS, 0.05% trypsin-EDTA. The cells were trypsinized after removing all media, then washed with 1x 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/75 cm^2 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 $6x10^4$ cells/mL. 50 μL cells suspension was then plated to 384-well plate (PerkinElmer-6007480), $3x10^3$ cells/well and the cells were incubated in an incubator at 37 °C, 5% CO_2.

[00447] Compound Treatment: In the afternoon (incubation of the plate with 3-4 hrs), the test compounds were added by Echo, starting from 3 μM (final concentration in the assay plate), 1:3 dilution, 10 points, quadruplicates. The plate was placed at 37°C, 5% CO2 incubator for 24hrs.

[00448] 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 (24 hrs post-compound treatment), the DMEM+ medium in the 384 well plates were aspirated by Microplate Washer.

[00449] Measuring firefly luciferase activity: 20 μL 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 1 min followed centrifuging plates at 1000 rpm for 30 seconds. After waiting at least 10 minutes, the firefly luminescence was measured by Envision.

[00450] Measuring renilla luciferase activity: 20 µL Stop-Glo Reagent was added to the 384-well plates. The plates were shaken for 1 min and then centrifuged at 1000rpm for 30 seconds. After waiting at least 10 minutes, the renilla luminescence was measured by Envision.

[00451] Compounds' IC_{50} and maximum inhibition on the firefly luciferase and renilla luciferase activities were reported separately. IC_{50}'s for firefly luciferase activity of the tested compounds are shown in Table 2.

TABLE 2

Compound #	Name	Firefly Luciferase IC_{50} (µM)
1	2-[[4-[2-[4-(trifluoromethyl)anilino]phenyl]-2-pyridyl]amino]ethanol	B
2	2-((6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyrimidin-4-yl)amino)ethanol	C
3	2-(methyl(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)amino)ethan-1-ol	B
4	4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine	B
5	N-methyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine	B
6	N,N-dimethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine	C
7	4-(2-((4-(trifluoromethoxy)phenyl)amino)phenyl)pyridin-2-amine	C
8	2-(2-(azetidin-1-yl)pyridin-4-yl)-N-(4-(trifluoromethyl)phenyl)aniline	C
9	4-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)piperazin-2-one	C
10	6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyrimidin-4-amine	C
11	4-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)pyridin-2-amine	B
12	4-(2-(4-(trifluoromethyl)benzyl)phenyl)pyridin-2-amine	C

Compound #	Name	Firefly Luciferase IC_{50} (μM)
13	2-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)ethan-1-ol	C
14	2-((4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)amino)acetamide	C
15	3-((4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)amino)propanamide	C
16	N-ethyl-4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-amine	C
17	N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)acetamide	C
18	N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)methanesulfonamide	B
19	N2-(4-(trifluoromethyl)phenyl)-[3,4'-bipyridine]-2,2'-diamine	C
20	N-(4-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2-yl)acrylamide	A
21	2-ethoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine	C
22	2-propoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine	D
23	N-(5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-yl)methanesulfonamide	A
24	5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-2-vinylpyrimidine	A
25	3-(2-ethoxypyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine	D
26	N-(4-(trifluoromethyl)phenyl)-3-(2-vinylpyrimidin-5-yl)pyrazin-2-amine	A
27	2-cyclopropyl-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine	C
28	1-(5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-yl)cyclopropane-1-carbonitrile	B
29	1-(5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-yl)cyclopropane-1-carbonitrile	B

Compound #	Name	Firefly Luciferase IC_{50} (μM)
30	5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-amine	C
30a	tert-butyl (5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-yl)carbamate	N.D.
31	N-(5-(3-((4-(trifluoromethyl)phenyl)amino)pyrazin-2-yl)pyrimidin-2-yl)acrylamide	C
32	N-acryloyl-N-(5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidin-2-yl)acrylamide	D
33	N-(3-fluoro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-yl)methanesulfonamide	A
34	N-(3-chloro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-yl)methanesulfonamide	A
35	N-(3-cyano-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-yl)methanesulfonamide	A
36	2-(prop-2-yn-1-yloxy)-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine	A
37	N-(4-(trifluoromethyl)phenyl)-3-(2-vinylpyrimidin-5-yl)pyridin-2-amine	A
38	5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-2-vinylpyrimidine	A
39	(*E*)-N-(4-(trifluoromethyl)phenyl)-3-(2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidin-5-yl)pyrazin-2-amine	B
40	(*E*)-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine	A
41	5-(3-((4-(pentafluoro-λ6-sulfaneyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol	A
42	2-methoxy-5-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)pyrimidine	C
43	5-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)pyrimidin-2-ol	A
44	2-methoxy-5-(3-((4-((trifluoromethyl)thio)phenyl)thio)pyrazin-2-yl)pyrimidine	N.D.
44a	5-(3-((4-((trifluoromethyl)thio)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol	A
45	5-(3-(4-((trifluoromethyl)thio)phenoxy)pyrazin-2-yl)pyrimidin-2-ol	A

Compound #	Name	Firefly Luciferase IC_{50} (μM)
46	5-(3-((4-(trifluoromethoxy)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol	A
47	5-(2-((4-(trifluoromethyl)phenyl)thio)pyridin-3-yl)pyrimidin-2-ol	A
48	5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)pyrimidin-2-ol	A
49	3-(2-methoxypyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine	D
50	2-(2-methoxypyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine	C
51	2-(6-methoxypyridin-3-yl)-3-((4-(trifluoromethyl)phenyl)thio)pyrazine	D
52	6'-methoxy-2-((4-(trifluoromethyl)phenyl)thio)-3,3'-bipyridine	B
53	6'-methoxy-2-(4-(trifluoromethyl)phenoxy)-3,3'-bipyridine	C
54	6'-methoxy-3-(4-(trifluoromethyl)phenoxy)-2,3'-bipyridine	C
55	6'-methoxy-N-(4-(trifluoromethyl)phenyl)-[2,3'-bipyridin]-3-amine	D
55a	3-((4-(trifluoromethyl)phenyl)amino)-[2,3'-bipyridin]-6'-ol	N.D.
56	2-(4-(trifluoromethyl)phenoxy)-3-(6-vinylpyridin-3-yl)pyrazine	A
57	N-(4-(trifluoromethyl)phenyl)-3-(6-vinylpyridin-3-yl)pyrazin-2-amine	A
58	2-ethynyl-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine	A
59	3-(2-ethynylpyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine	A
60	2-(6-ethynylpyridin-3-yl)-3-(4-(trifluoromethyl)phenoxy)pyrazine	A
61	3-(6-ethynylpyridin-3-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine	A
62	1-methyl-2'-((4-(trifluoromethyl)phenyl)thio)-[3,3'-bipyridin]-6(1H)-one	B
63	1-methyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)thio)-[3,3'-bipyridin]-6(1H)-one	C

Compound #	Name	Firefly Luciferase IC_{50} (μM)
64	1-methyl-5-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)pyrimidin-2(1H)-one	B
65	1-ethyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	A
66	1-ethyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6(1H)-one	B
67	1-isopropyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	A
68	1-isopropyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6(1H)-one	B
69	1-cyclopropyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	A
70	2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-1-propyl-[3,3'-bipyridin]-6(1H)-one	A
71	1-(2-aminoethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	B
72	1-(2-hydroxyethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	A
73	5-fluoro-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6-ol	A
74	(E)-5-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine	A
75	(E)-5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine	A
76	(E)-5-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrimidine	A
77	1-(3-hydroxypropyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	A
78	1-(3-aminopropyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	B
79	2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-1-phenyl-[3,3'-bipyridin]-6(1H)-one	C
80	2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-1-(pyrrolidin-3-yl)-[3,3'-bipyridin]-6(1H)-one	B
81	1-(2-fluoroethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	A
82	1-(2,2-difluoroethyl)-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	B
83	2-(4-(trifluoromethyl)phenoxy)-6'-vinyl-3,3'-bipyridine	A

Compound #	Name	Firefly Luciferase IC_{50} (μM)
84	N-(4-(trifluoromethyl)phenyl)-6'-vinyl-[3,3'-bipyridin]-2-amine	A
85	1-methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)pyridin-2(1H)-one	B
86	N-Methyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)picolinamide	C
87	N,N-Dimethyl-5-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)picolinamide	D
88	N-Methyl-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)nicotinamide	B
89	N,N-Dimethyl-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)nicotinamide	C
90	5-(methylsulfonyl)-2-(2-(4-(trifluoromethyl)phenoxy)phenyl)pyridine	B
91	6-Hydroxy-2'-(4-(trifluoromethyl)phenoxy)-[3,3'-bipyridine]-5-carbonitrile	A
92	5-Fluoro-2'-(4-(trifluoromethyl)phenoxy)-[3,3'-bipyridin]-6-ol	A
93	3-Chloro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-ol	A
94	2-Hydroxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)nicotinonitrile	A
95	3-Fluoro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyridin-2-ol	A
96	2-Methoxy-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)pyrimidine	D
97	3-Chloro-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyridin-2-ol	A
98	2-Hydroxy-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)nicotinonitrile	A
99	5-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidin-2-ol	A
100	2-Methoxy-5-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidine	D
101	3-Fluoro-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyridin-2-ol	A
102	2-(Prop-2-yn-1-yloxy)-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)pyrimidine	A

Compound #	Name	Firefly Luciferase IC_{50} (μM)
103	3-(2-(Prop-2-yn-1-yloxy)pyrimidin-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine	B
104	6-Hydroxy-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridine]-5-carbonitrile	A
105	5-Chloro-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6-ol	A
106	1-Methyl-2'-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)-[3,3'-bipyridin]-6(1H)-one	A
107	5-Fluoro-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6-ol	A
108	6-Hydroxy-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridine]-5-carbonitrile	A
109	1-Methyl-2'-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)-[3,3'-bipyridin]-6(1H)-one	A

Note: Biochemical assay IC_{50} data are designated within the following ranges:

A: ≤ 0.1 μM

B: > 0.1 μM to ≤ 0.2 μM

C: > 0.2 μM to ≤ 1.0 μM

D: > 1.0 μM ≤ 10 μM

N.D.: Not determined

Example A2: Tumor Suppression Assay

[00452] 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 ([width]2 x length/2). Paired, two-tailed Student's t-test is performed to access the statistical significance.

Example A3: Cell Proliferation Assay

[00453] Cancer cell lines are plated in 384-well plates 24 hrs before drug treatment. Post incubation for various time periods with the test compounds, starting from 3 μM (final

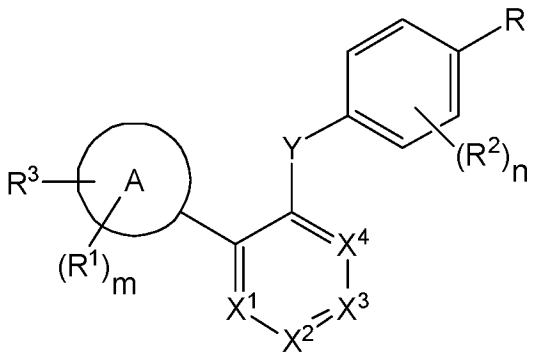
concentration in assay plate), 1:3 dilution, and 10 points in duplicates, the number of viable cells and proliferative cells are determined using CellTiter-Glo® Luminescent Cell Viability Assay Kit (Promega) and Click-iT EdU HCS Assay Kit (Invitrogen) according to the manufacturers' protocols. The IC_{50} values and maximum % inhibition of the test compounds are calculated using the dose response curves.

[00454] 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 or solvate thereof:



Formula (I)

wherein,

ring A is monocyclic heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

Y is CR^4R^5, O, S, or NR^6;

each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each of R^1 and R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$OC(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)NR^7R^8$, -$S(=NR^7)R^8$, -$S(=NR^7)NR^7R^8$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -$S(=O)(=NR^7)R^7$, -$S(=O)(=NR^7)NR^7R^8$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7S(=O)(=NR^7)R^8$, -$NR^7C(=O)R^8$, -$N[C(=O)R^8]_2$, -$NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$,

$NR^7CH_2CH_2C(=O)NR^7R^8$, $-NR^7C(=O)OR^8$, $-P(=O)(OR^7)R^8$, $-P(=O)(OR^7)(OR^8)$, $-P(=O)R^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^4, R^5, R^6, R^7, and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^4 and R^5 taken together with the carbon atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or substituted or unsubstituted 3- to 8-membered heterocycloalkyl having 1 or 2 heteroatoms each independently selected from N, O, and S; or

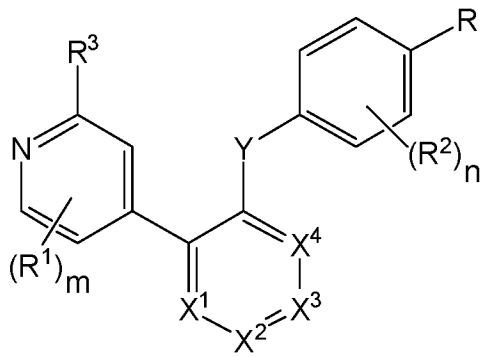
R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N- or P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S;

m is 0, 1, 2, or 3; and

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

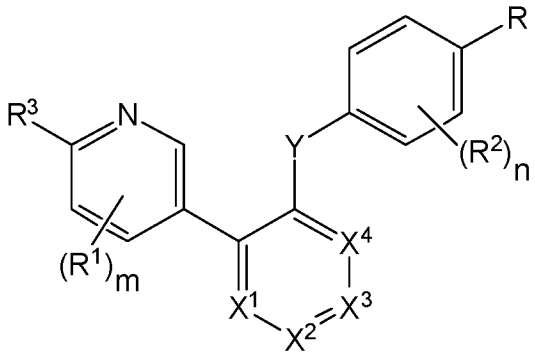
2. The compound of claim 1, wherein ring A is a monocyclic 6-membered heteroaryl having 1-4 N atoms.

3. The compound of claim 1 or claim 2, wherein the compound has a structure of Formula (II-a), or a pharmaceutically acceptable salt or solvate thereof:



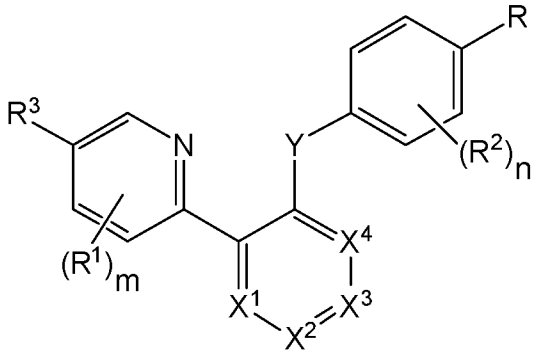
Formula (II-a).

4. The compound of claim 1 or claim 2, wherein the compound has a structure of Formula (II-b), or a pharmaceutically acceptable salt or solvate thereof:



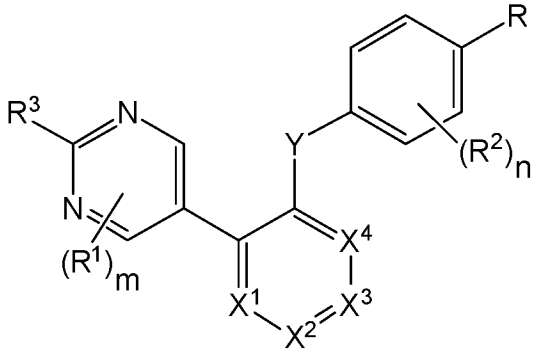
Formula (II-b).

5. The compound of claim 1 or claim 2, wherein the compound has a structure of Formula (II-c), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-c).

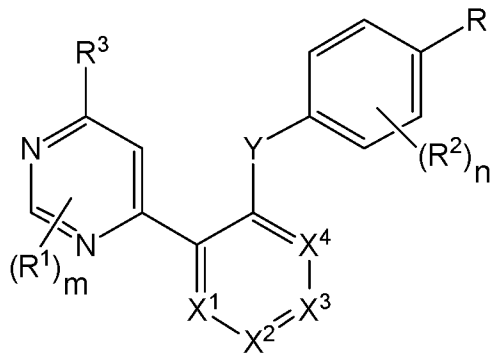
6. The compound of claim 1 or claim 2, wherein the compound has a structure of Formula (II-d), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-d),

wherein m is 0, 1, or 2.

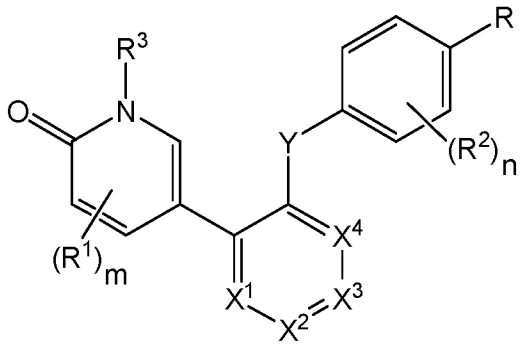
7. The compound of claim 1 or claim 2, wherein the compound has a structure of Formula (II-e), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-e)

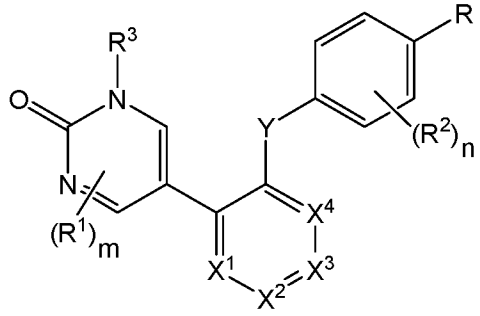
wherein m is 0, 1, or 2.

8. The compound of claim 1 or claim 2, wherein the compound has a structure of Formula (II-f), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-f).

9. The compound of claim 1 or claim 2, wherein the compound has a structure of Formula (II-g), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-g)

wherein m is 0, 1, or 2.

10. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is CR^{X4}.

11. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is CR^{X4}.

12. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is N; X^3 is CR^{X3}; and X^4 is CR^{X4}.

13. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is N; and X^4 is CR^{X4}.
14. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is N.
15. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is N.
16. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is N; X^3 is N; and X^4 is CR^{X4}.
17. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N; X^2 is N; X^3 is CR^{X3}; and X^4 is N.
18. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N; X^2 is CR^{X2}; X^3 is N; and X^4 is N.
19. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, $-OR^7$, $-SR^7$, -CN, $-NR^7R^8$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl.
20. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, $-OR^7$, $-SR^7$, -CN, $-NR^7R^8$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl.
21. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH(OH)CH_3$, $-CH_2CN$, $-CH_2C(=O)OH$, $-CH_2C(=O)OCH_3$, $-CH_2C(=O)OCH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHC(=O)OCH_3$, $-N(CH_3)C(=O)OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-NHS(=O)_2CH_3$, or $-N(CH_3)S(=O)_2CH_3$.
22. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl,

Br, I, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-C\equiv CH$, $-OCH_3$, $-NH_2$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHS(=O)_2CH_3$, $-N(CH_3)S(=O)_2CH_3$, $-S(=O)CH_3$, or $-S(=O)_2CH_3$.

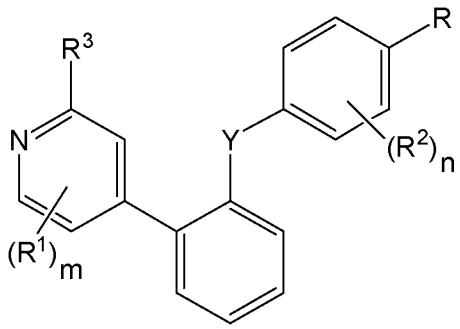
23. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-OCH_3$, or $-OCF_3$.

24. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, or $-CH_3$.

25. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen or F.

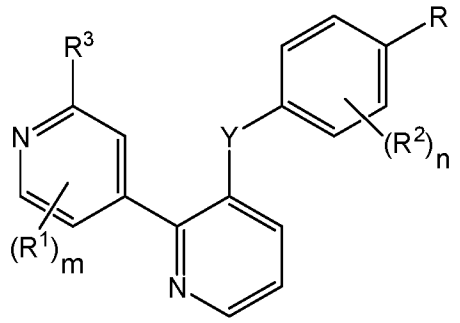
26. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is hydrogen.

27. The compound of any one of claims 1-3 or 10, wherein the compound has a structure of Formula (III-a), or a pharmaceutically acceptable salt or solvate thereof:



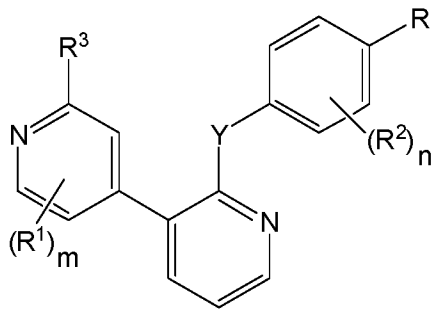
Formula (III-a).

28. The compound of any one of claims 1-3 or 11, wherein the compound has a structure of Formula (III-b), or a pharmaceutically acceptable salt or solvate thereof:



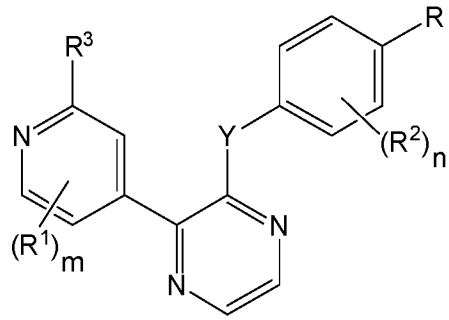
Formula (III-b).

29. The compound of any one of claims 1-3 or 14, wherein the compound has a structure of Formula (III-c), or a pharmaceutically acceptable salt or solvate thereof:



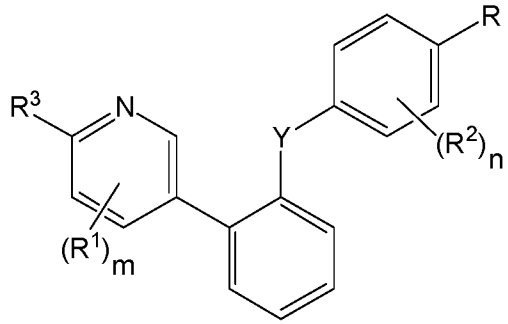
Formula (III-c).

30. The compound of any one of claims 1-3 or 15, wherein the compound has a structure of Formula (III-d), or a pharmaceutically acceptable salt or solvate thereof:



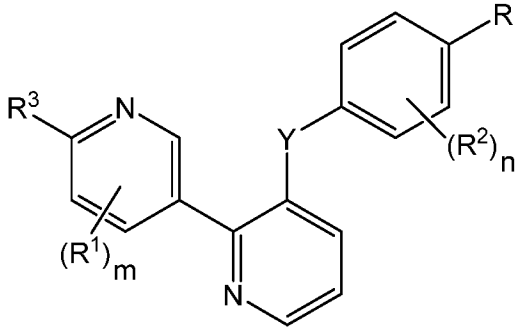
Formula (III-d).

31. The compound of any one of claims 1, 2, 4, or 10, wherein the compound has a structure of Formula (III-e), or a pharmaceutically acceptable salt or solvate thereof:



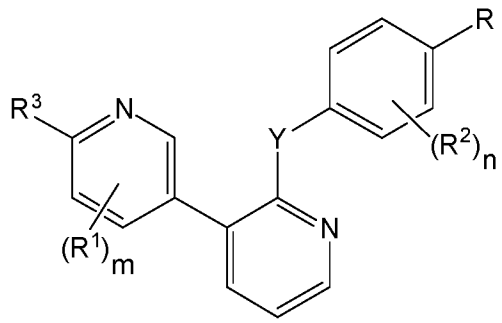
Formula (III-e).

32. The compound of any one of claims 1, 2, 4, or 11, wherein the compound has a structure of Formula (III-f), or a pharmaceutically acceptable salt or solvate thereof:



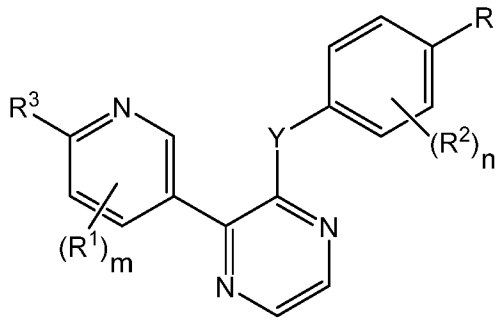
Formula (III-f).

33. The compound of any one of claims 1, 2, 4, or 14, wherein the compound has a structure of Formula (III-g), or a pharmaceutically acceptable salt or solvate thereof:



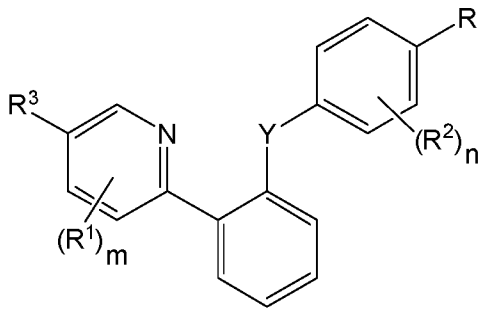
Formula (III-g).

34. The compound of any one of claims 1, 2, 4, or 15, wherein the compound has a structure of Formula (III-h), or a pharmaceutically acceptable salt or solvate thereof:



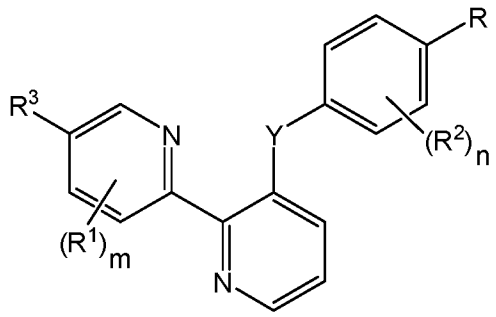
Formula (III-h).

35. The compound of any one of claims 1, 2, 5, or 10, wherein the compound has a structure of Formula (III-i), or a pharmaceutically acceptable salt or solvate thereof:



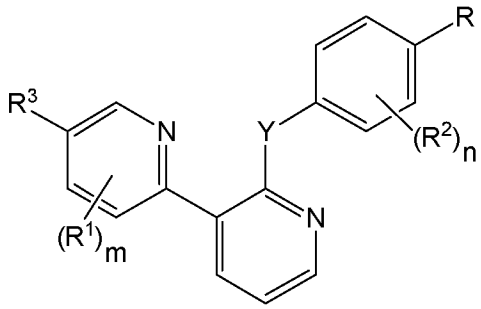
Formula (III-i).

36. The compound of any one of claims 1, 2, 5, or 11, wherein the compound has a structure of Formula (III-j), or a pharmaceutically acceptable salt or solvate thereof:



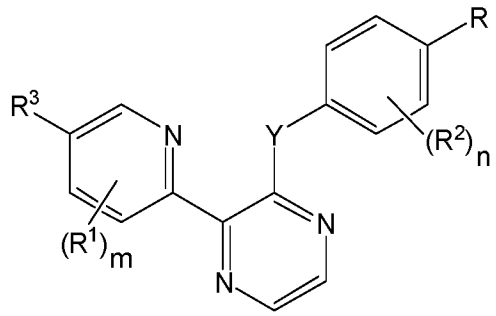
Formula (III-j).

37. The compound of any one of claims 1, 2, 5, or 14, wherein the compound has a structure of Formula (III-k), or a pharmaceutically acceptable salt or solvate thereof:



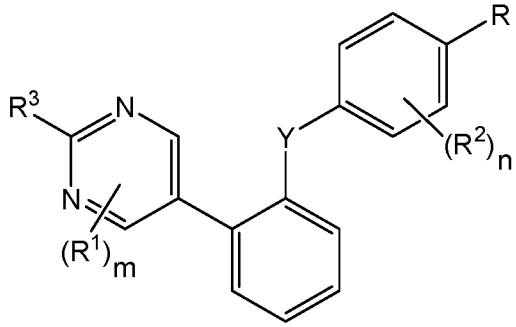
Formula (III-k).

38. The compound of any one of claims 1, 2, 5, or 15, wherein the compound has a structure of Formula (III-l), or a pharmaceutically acceptable salt or solvate thereof:



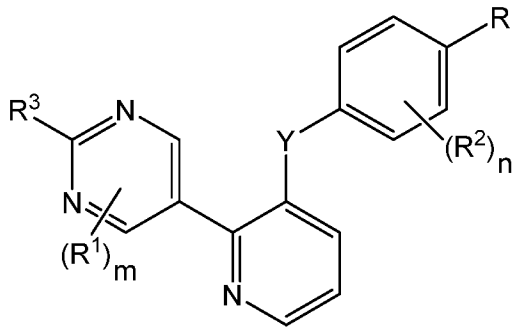
Formula (III-l).

39. The compound of any one of claims 1, 2, 6, or 10, wherein the compound has a structure of Formula (III-m), or a pharmaceutically acceptable salt or solvate thereof:



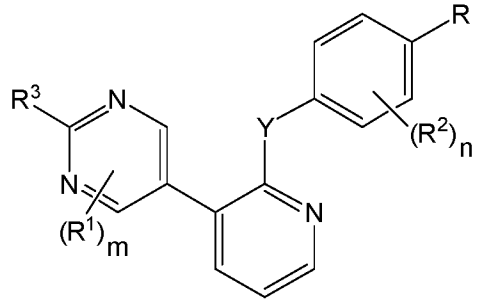
Formula (III-m).

40. The compound of any one of claims 1, 2, 6, or 11, wherein the compound has a structure of Formula (III-n), or a pharmaceutically acceptable salt or solvate thereof:



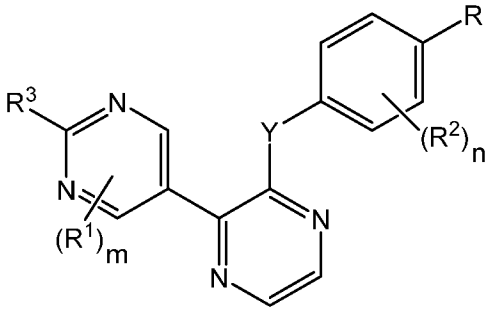
Formula (III-n).

41. The compound of any one of claims 1, 2, 6, or 14, wherein the compound has a structure of Formula (III-o), or a pharmaceutically acceptable salt or solvate thereof:



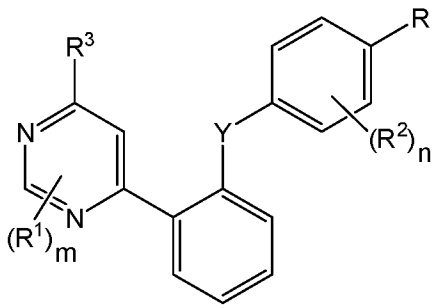
Formula (III-o).

42. The compound of any one of claims 1, 2, 6, or 15, wherein the compound has a structure of Formula (III-p), or a pharmaceutically acceptable salt or solvate thereof:



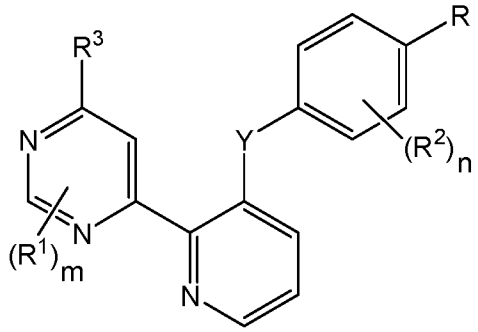
Formula (III-p).

43. The compound of any one of claims 1, 2, 7, or 10, wherein the compound has a structure of Formula (III-q), or a pharmaceutically acceptable salt or solvate thereof:



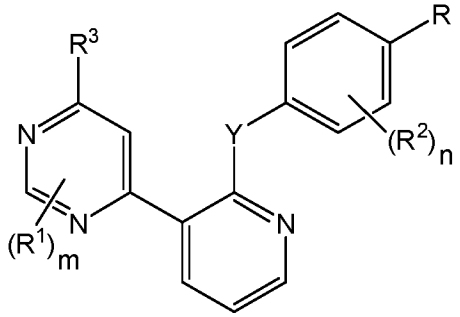
Formula (III-q).

44. The compound of any one of claims 1, 2, 7, or 11, wherein the compound has a structure of Formula (III-r), or a pharmaceutically acceptable salt or solvate thereof:



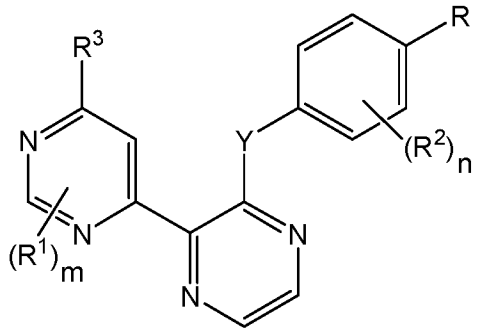
Formula (III-r).

45. The compound of any one of claims 1, 2, 7, or 14, wherein the compound has a structure of Formula (III-s), or a pharmaceutically acceptable salt or solvate thereof:



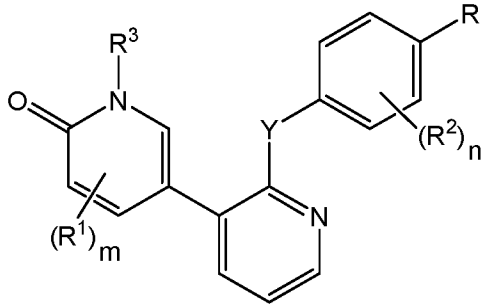
Formula (III-s).

46. The compound of any one of claims 1, 2, 7, or 15, wherein the compound has a structure of Formula (III-t), or a pharmaceutically acceptable salt or solvate thereof:



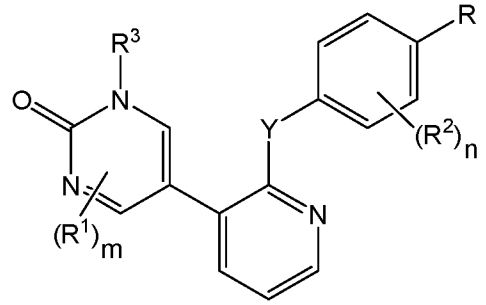
Formula (III-t).

47. The compound of any one of claims 1, 2, 8, or 14, wherein the compound has a structure of Formula (III-u), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III-u).

48. The compound of any one of claims 1, 2, 9, or 14, wherein the compound has a structure of Formula (III-v), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III-v).

49. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is halogen, nitro, $-OR^7$, $-SR^7$, -CN, $-OC(=O)R^7$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)NR^7R^8$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-N[C(=O)R^8]_2$, $-NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, $-NR^7C(=O)OR^8$, $-P(=O)(OR^7)R^8$, $-P(=O)(OR^7)(OR^8)$, $-P(=O)R^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted C_5-C_{10} aryl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl; and

each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N- or P-containing

3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

50. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is halogen, $-OR^7$, $-SR^7$, $-C(=O)R^7$, $-OC(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-N[C(=O)R^8]_2$, $NR^7C(=O)NR^7R^8$, $NR^7CH_2C(=O)NR^7R^8$, $NR^7CH_2CH_2C(=O)NR^7R^8$, $-NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, or substituted or unsubstituted C_1-C_6heteroalkyl; and
each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl; or R^7 and R^8 taken together with atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

51. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-OR^7$, $-SR^7$, $-C(=O)R^7$, $-OC(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; and
each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl.

52. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-OR^7$, $-SR^7$, $-C(=O)R^7$, $-OC(=O)R^7$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; and
each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl.

53. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-OR^7$, $-SR^7$, $-C(=O)R^7$, or $-OC(=O)R^7$; and
each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl.

54. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-NR^7R^8$, $-NR^7S(=O)_2R^7$, or $-NR^7C(=O)R^7$; and each R^7 and R^8 is independently hydrogen, C_1-C_6alkyl, C_1-C_6fluoroalkyl, or C_3-C_{10}cycloalkyl.

55. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CN$, $-CH=CH_2$, $-CH_2C(=O)OH$, $-CH_2C(=O)OCH_3$, $-CH_2C(=O)OCH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH=CH_2$, $-CH=CHCF_3$, $-C\equiv CH$, $-CH_2C\equiv CH$, cyclopropyl, -CN-cycloprop-1-yl, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, oxetanyloxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, azetidinyl, pyrrolidinyl, tetrazolyl, piperazin-2-one-yl, phenyl, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CH=CH_2$, $-OCH=CHCH_3$, $-OCH_2C\equiv CH$, $-OCH_2CN$, $-OCF_3$, $-C(=O)OH$, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $NHCH_2CH_2OH$, $NCH_3CH_2CH_2OH$, $NHCH_2C(=O)NH_2$, $NHCH_2CH_2C(=O)NH_2$, $N[C(=O)CH=CH_2]_2$, $-N(CH_3)C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NHC(=O)CH=CH_2$, -NHC(=O)O-t-butyl, $-N(CH_3)C(=O)OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NHS(=O)_2CH_3$, or $-N(CH_3)S(=O)_2CH_3$.

56. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2OH$, $-N(CH_3)CH_2CH_2OH$, azetidinyl, pyrrolidinyl, piperazin-2-one-4-yl, phenyl, $-NHCH_2CH_2C(=O)NH_2$, $-NHCH_2C(=O)NH_2$, $-NHC(=O)CH_3$, $-NHC(=O)CH=CH_2$, $-N(C(=O)CH=CH_2)_2$, or $-NHS(=O)_2CH_3$.

57. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-CH=CH_2$, $-C\equiv CH$, $-CH=CHCF_3$, cyclopropyl, 1-CN-cycloprop-1-yl, 1-F-cycloprop-1-yl, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, or $-S(=O)_2CH_3$.

58. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-OCH=CH_2$, $-OCH_2CH=CH_2$, $-OCH=CHCH_3$, $-OCH_2C\equiv CH$, or $-OC\equiv CCH_3$.

59. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-OCF_2CH_3$, or $-OCH_2CF_3$.

60. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is halogen, nitro, -CN, $-OR^7$, $-SR^7$, $-S(R^7)_5$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, -

$C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl; and

each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

61. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, Br, I, nitro, -CN, $-CF_3$, $-SF_5$, $-SCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-C(=O)CH_3$, $-C(=O)OCH_3$ $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-NHS(=O)_2CH_3$, $-N(CH_3)S(=O)_2CH_3$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHC(=O)OCH_3$, $-N(CH_3)C(=O)OCH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$.

62. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, -CN, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$.

63. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$.

64. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, $-SF_5$, $-SCF_3$, or $-CF_3$.

65. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, $-SF_5$, $-OCF_3$, $-SCF_3$, or $-CF_3$.

66. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is $-CF_3$.

67. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is $-OCF_3$.

68. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is $-SF_5$.

69. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt or solvate thereof, wherein R is $-SCF_3$.

70. The compound of any one of claims 1-69, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^1 is independently halogen, -CN, $-OR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-C(=O)R^7$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted

C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

71. The compound of any one of claims 1-69, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^1 is independently halogen, -CN, -OR^7, -$S(=O)_2NR^7R^8$, -$C(=O)R^7$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; and

each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

72. The compound of any one of claims 1-69, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^1 is independently F, Cl, Br, -CN, -OH, -OCH_3, -OCH_2CH_3, -$OCH_2CH_2CH_3$, -$OCH(CH_3)_2$, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, -$OCH=CH_2$, -$OCH=CHCH_3$, -$OCH_2CH=CH_2$, -OCH_2CH_2F, -OCH_2CH_2OH, -$OCH_2CH_2CH_2F$, -$OCH_2CH_2CH_2OH$.

73. The compound of any one of claims 1-69, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^1 is independently F, Cl, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, cyclopropyl, cyclobutyl, or cyclopentyl.

74. The compound of any one of claims 1-69, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^1 is independently F, Cl, -OCH_3, -OCH_2CH_3, -$OCH_2CH_2CH_3$, -$OCH(CH_3)_2$, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, -OCH_2CH_2F, -OCH_2CH_2OH, -$OCH_2CH_2CH_2F$, or -$OCH_2CH_2CH_2OH$.

75. The compound of any one of claims 1-69, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^1 is independently -CH_2F, -CHF_2, -CF_3, -CF_2CH_3, -CH_2CF_3, -OCH_2F, -$OCHF_2$, -OCF_3, -OCF_2CH_3, or -OCH_2CF_3.

76. The compound of any one of claims 1-75, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 0, 1, or 2.
77. compound of any one of claims 1-76, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 0 or 1.
78. The compound of any one of claims 1-77, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1.
79. The compound of any one of claims 1-77, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 0.
80. The compound of any one of claims 1-79, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)_2R^7$, -NR^7R^8, -$C(=O)OR^7$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6fluoroalkyl; and

each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.
81. The compound of any one of claims 1-79, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently F, Cl, Br, -CN, -OH, -OCH_3, -OCH_2CH_3, -OCH_2CH_2OH, -OCH_2CN, -OCF_3, -$S(=O)_2CH_3$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)OCH_3$, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, or -CF_3.
82. The compound of any one of claims 1-79, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently F, Cl, -CN, -OCH_3, -OCF_3, -$C(=O)OCH_3$, -CH_3, or -CF_3.
83. The compound of any one of claims 1-79, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently F, Cl, -OCF_3, or -CF_3.
84. The compound of any one of claims 1-79, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently F or Cl.
85. The compound of any one of claims 1-84, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0, 1, or 2.
86. The compound of any one of claims 1-85, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0 or 1.

87. The compound of any one of claims 1-86, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.
88. The compound of any one of claims 1-86, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1.
89. The compound of any one of claims 1-88, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is CR^4R^5.
90. The compound of claim 89, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 and R^5 is independently hydrogen or C_1-C_4 alkyl.
91. The compound of claim 89, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 and R^5 is hydrogen.
92. The compound of any one of claims 1-88, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is O.
93. The compound of any one of claims 1-88, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is S.
94. The compound of any one of claims 1-88, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is NR^6.
95. The compound of claim 94, or a pharmaceutically acceptable salt or solvate thereof, wherein R^6 is hydrogen or C_1-C_4 alkyl.
96. The compound of claim 94, or a pharmaceutically acceptable salt or solvate thereof, wherein R^6 is hydrogen.
97. A compound or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is a compound from Table 1.
98. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-97, and a pharmaceutically acceptable excipient.
99. A method of inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway in a subject, comprising administering to the subject the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-97, or a pharmaceutical composition of claim 98.
100. A method of inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP) in a subject comprising administering to the subject the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-97, or the pharmaceutical composition of claim 98.
101. The method of claim 99 or claim 100, wherein the subject has cancer, polycystic kidney disease or liver fibrosis.

102. The method of claim 101, wherein the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.
103. A method of treating cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-97, or the pharmaceutical composition of claim 98.
104. The method of claim 103, wherein the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.
105. A method of treating polycystic kidney disease or liver fibrosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-97, or the pharmaceutical composition of claim 98.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/013749

A. CLASSIFICATION OF SUBJECT MATTER

C07D 213/74(2006.01)i; **C07D 239/42**(2006.01)i; **C07D 401/04**(2006.01)i; **C07D 213/83**(2006.01)i; **C07D 239/34**(2006.01)i; **A61K 31/4418**(2006.01)i; **A61K 31/505**(2006.01)i; **A61P 35/00**(2006.01)i; **A61P 13/12**(2006.01)i; **A61P 1/16**(2006.01)i

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)

C07D 213/74(2006.01); A61K 31/196(2006.01); A61K 31/235(2006.01); A61K 31/4425(2006.01); A61K 31/444(2006.01); A61K 31/50(2006.01); A61K 31/541(2006.01); C07D 213/64(2006.01); C07D 213/65(2006.01); C07D 491/056(2006.01); C07D 491/22(2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN(Registry, CAplus) & Keywords: phenyl, monocyclic heteroaryl, YAP, TAZ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019-113236 A1 (VIVACE THERAPEUTICS, INC.) 13 June 2019 (2019-06-13) claims 1, 13, 135; table 1	1-7,97
A		8,9
X	US 2013-0331382 A1 (ABBVIE INC.) 12 December 2013 (2013-12-12) claims 27, 31; example 231	1,2,8,9
X	US 9994581 B2 (ABBVIE INC.) 12 June 2018 (2018-06-12) examples A-29a, A-29b, A-29c	1,2,8
X	WO 2017-047602 A1 (KAKEN PHARMACEUTICAL CO., LTD.) 23 March 2017 (2017-03-23) example 203	1,2

☑ 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	Date of mailing of the international search report
21 October 2022	**24 October 2022**
Name and mailing address of the ISA/KR **Korean Intellectual Property Office** **189 Cheongsa-ro, Seo-gu, Daejeon** **35208, Republic of Korea** Facsimile No. **+82-42-481-8578**	Authorized officer **HEO, Joo Hyung** Telephone No. **+82-42-481-5373**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/013749

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2018-145180 A (KAKEN PHARMACEUTICAL CO., LTD.) 20 September 2018 (2018-09-20) example 207	1,2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/013749

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.: **99-105**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 99-105 pertain to methods for treatment of the human body by surgery or therapy as well as diagnostic methods (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. ☑ Claims Nos.: **90, 91, 95, 96, 102, 104**
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:

Claims 90, 91, 95, 96, 102 and 104 are regarded to be unclear because they refer to claims which do not comply with PCT Rule 6.4(a).

3. ☑ Claims Nos.: **10-89, 92-94, 98-101, 103, 105**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/013749

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Information on patent family members

International application No.
PCT/US2022/013749

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