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(54) **Title:** PHENYL PHOSPHINE OXIDE COMPOUNDS AND METHODS OF USE THEREOF

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

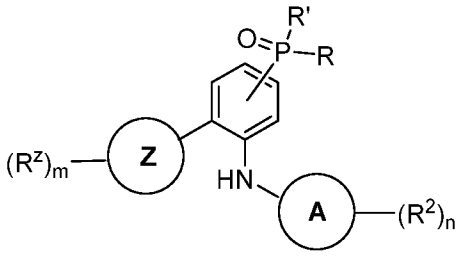
PHENYL PHOSPHINE OXIDE COMPOUNDS AND METHODS OF USE THEREOF

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.

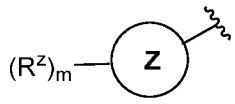
SUMMARY OF THE DISCLOSURE

[0002] In one aspect, provided herein are compounds of Formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein,



is a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl ring containing at least one N atom, or a substituted or unsubstituted monocyclic heteroaryl ring containing at least one N atom;

each R^z 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, $-L^1-Y^1$, or $-L^2-L^3-Y^2$;

m is 0, 1, 2, 3, 4, or 5;

L^1 is substituted or unsubstituted C_1-C_6alkylene, substituted or unsubstituted C_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2- C_{10}heterocycloalkylene;

Y^1 is 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;

L^2 is absent, substituted or unsubstituted C_1-C_6alkylene, substituted or unsubstituted C_3-C_{10}cyclolalkylene, or substituted or unsubstituted 3- to 10-membered heterocycloalkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -O-NR^3(C=O)-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -NR^3(SO_2)-,-(SO_2)NR^3-, -(SO_2)NR^3-(C=O)-, -(C=O)-NR^3(SO_2)-, -(SO_2)NR^3-(C=O)O-, -O(C=O)-NR^3(SO_2)-, -NR^3(SO_2)NR^3-(C=O)-, -(C=O)-NR^3(SO_2)NR^3-, -O(C=O)-NR^3(SO_2)-NR^3-, or -NR^3(SO_2)NR^3-(C=O)O-;

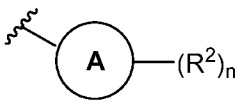
each R^3 is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl;

Y^2 is hydrogen, substituted or unsubstituted C_1-C_6alkyl, 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;

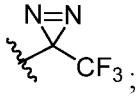
or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

R and R' are each independently 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_1-C_6alkoxy, 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 and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.



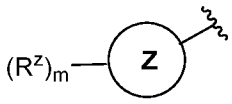
is substituted or unsubstituted phenyl or substituted or unsubstituted cyclohexyl;

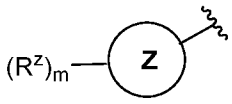
each R^2 is independently hydrogen, halogen, -N_3, -CN, -OR^4, -SR^4, -(SO_2)R^4, -S(R^4)$_5$, -(S=O)R^4, -(SO_2)R^4, -N(R^4)$_2$, -CO_2R^4, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or 

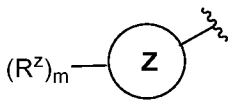
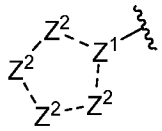
;

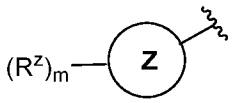
n is 0, 1, 2, 3, 4, or 5; and

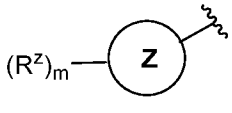
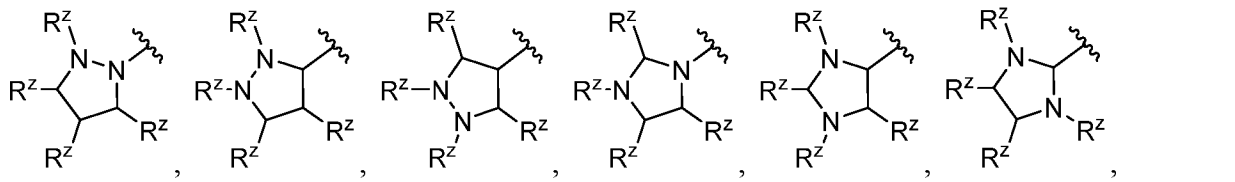
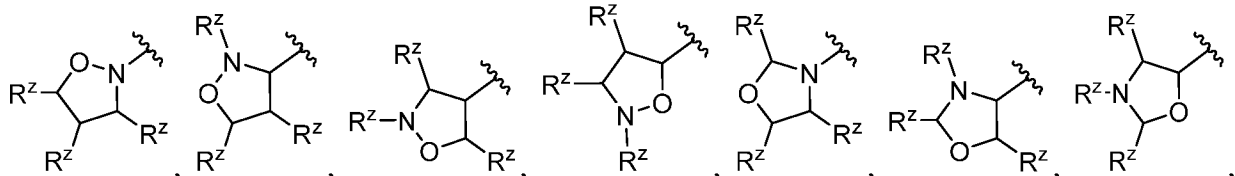
each R^4 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

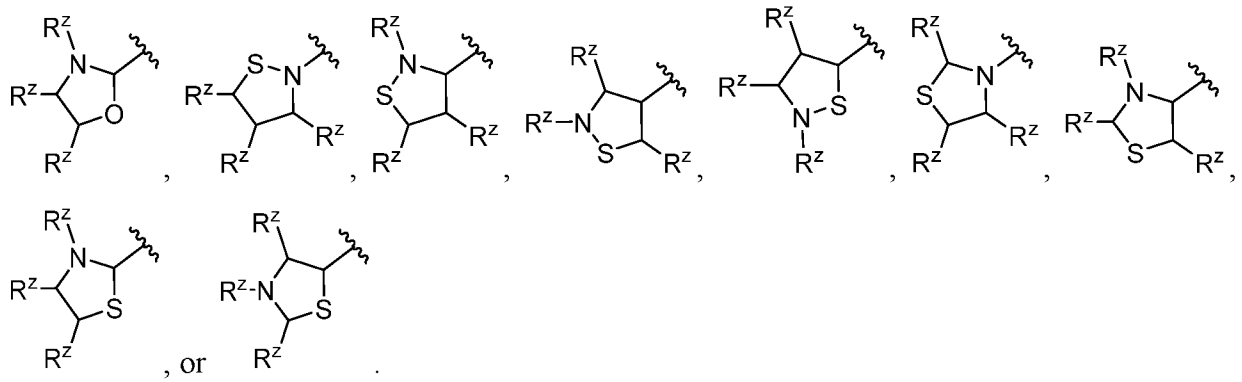
[0003] In certain embodiments,  is a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl ring containing at least one N atom.

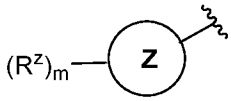
[0004] In certain embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocycloalkyl ring containing 1-4 N atoms, 0-2 O atoms, and 0-2 S atoms.

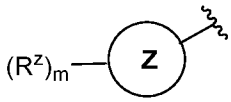
[0005] In certain embodiments,  is  ; Z^1 is –N-, –CH-, or -C-; each Z^2 is independently -CR^z, -CHR^z-, -$C(R^z)_2$-, -NR^z-, -N-, -O-, or –S-; and each - - is independently a single or double bond.

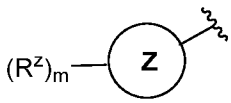
[0006] In certain embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

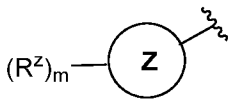
[0007] In certain embodiments,  is  ,  ,  ,

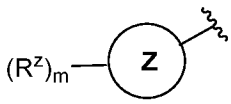


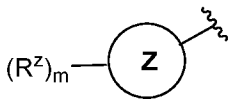
[0008] In certain embodiments,  is a substituted or unsubstituted monocyclic heteroaryl ring containing at least one N atom.

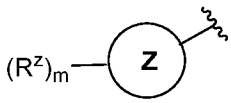
[0009] In certain embodiments,  is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing at least one N atom.

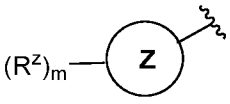
[0010] In certain embodiments,  is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 1 N atom.

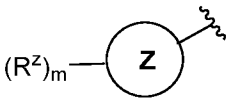
[0011] In certain embodiments,  is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 2 N atoms.

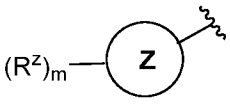
[0012] In certain embodiments,  is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 3 N atoms.

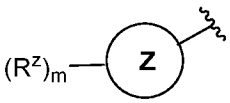
[0013] In certain embodiments,  is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 4 N atoms.

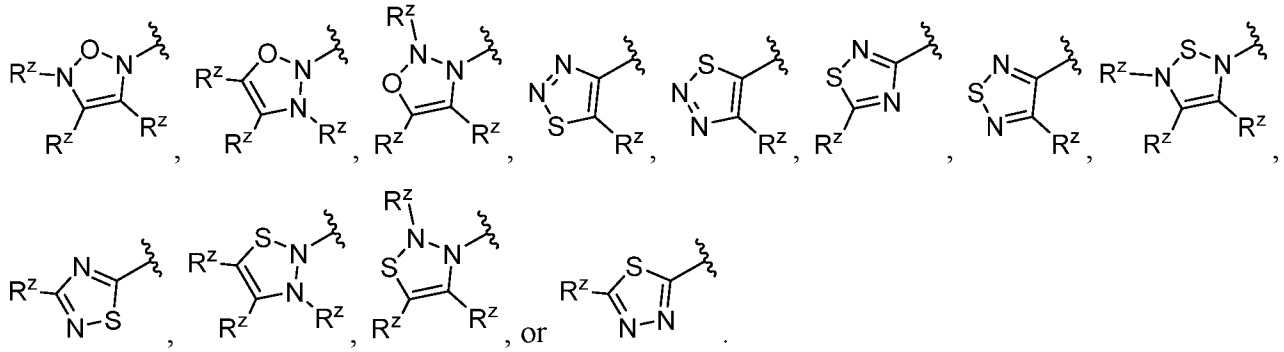
[0014] In certain embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazoyl, substituted or unsubstituted tetrazoyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

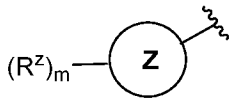
[0015] In certain embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, or substituted or unsubstituted isoxazolyl.

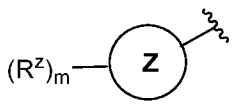
[0016] In certain embodiments,  is substituted or unsubstituted imidazolyl or substituted or unsubstituted pyrazolyl.

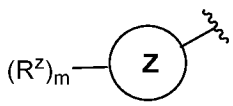
[0017] In certain embodiments,  is substituted or unsubstituted imidazolyl.

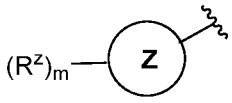
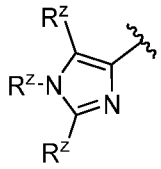
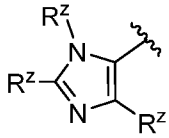
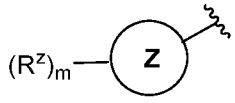
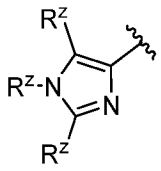
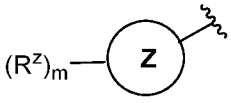
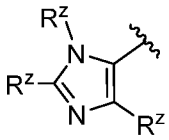
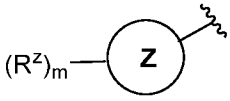
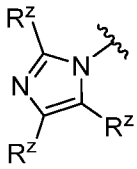
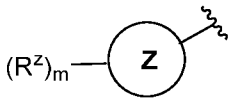
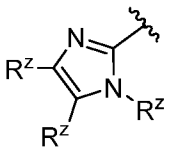
[0018] In certain embodiments,  is



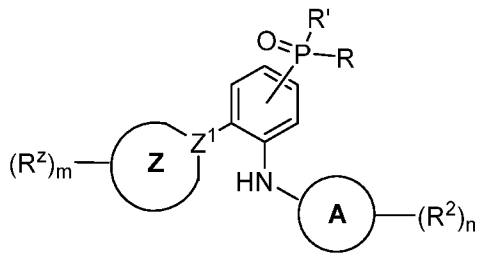
[0019] In certain embodiments,  is

[0020] In certain embodiments,  is

[0021] In certain embodiments,  is

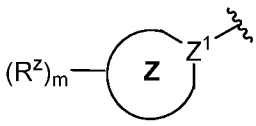
[0022] In certain embodiments,  is  or  . In certain embodiments,  is  . In certain embodiments,  is  . In certain embodiments,  is  . In certain embodiments,  is  .

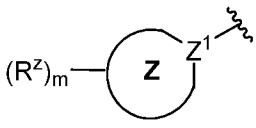
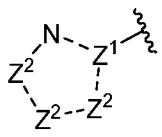
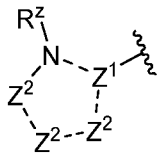
[0023] In certain embodiments, the compound has the structure of Formula (Ia)

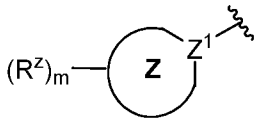


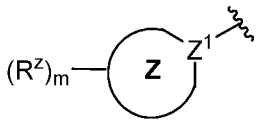
Formula (Ia)

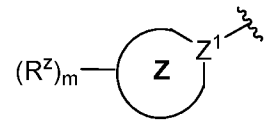
wherein: Z^1 is –N-, –CH-, or -C-.

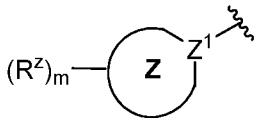
[0024] In certain embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom, and the at least one N atom is adjacent to Z^1.

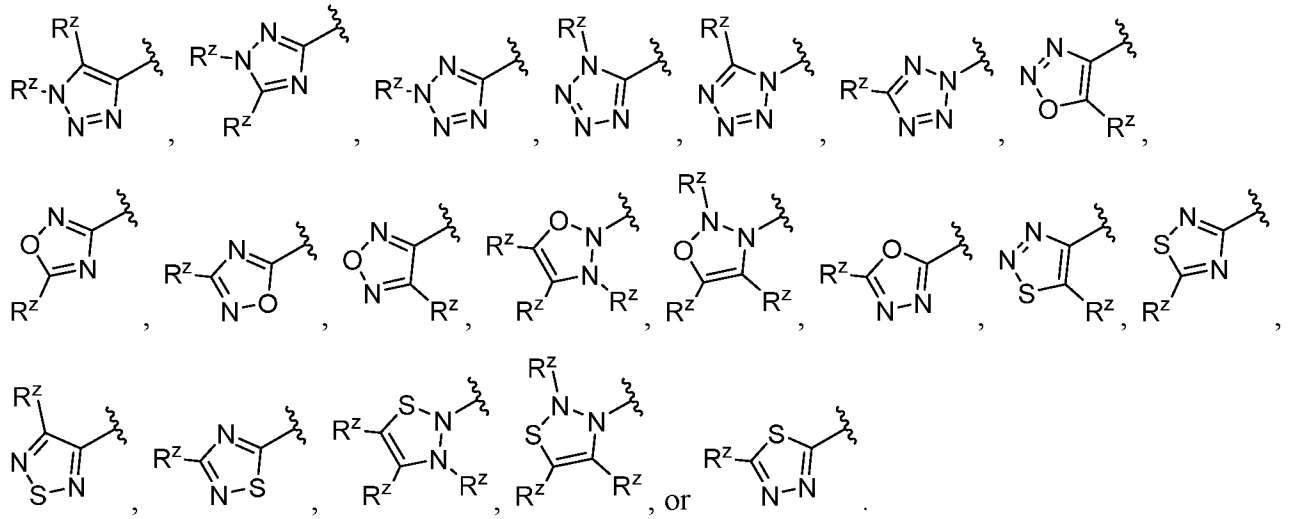
[0025] In certain embodiments,  is  or  ; Z^1 is –N-, –CH-, or -C-; each Z^2 is independently CR^z, NR^z, N, O, or S; each -- is independently a single or double bond; and with the provision that the 5-membered heterocyclic ring contains at least one N atom.

[0026] In certain embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

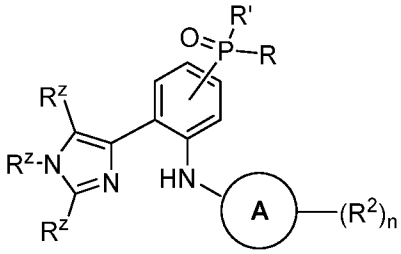
[0027] In certain embodiments,  is .

[0028] In certain embodiments, wherein:  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazoyl, substituted or unsubstituted tetrazoyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

[0029] In certain embodiments,  is .

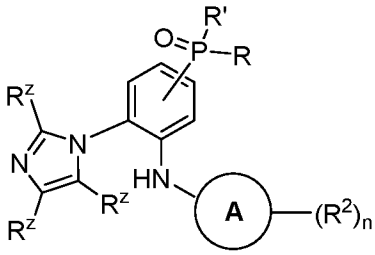


[0030] In certain embodiments, the compound has a structure of Formula (II-a):



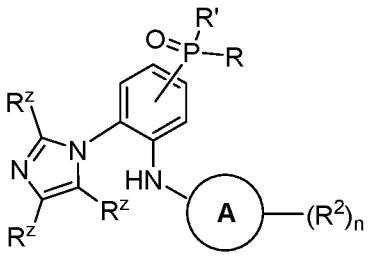
Formula (II-a).

[0031] In certain embodiments, the compound has a structure of Formula (II-b):



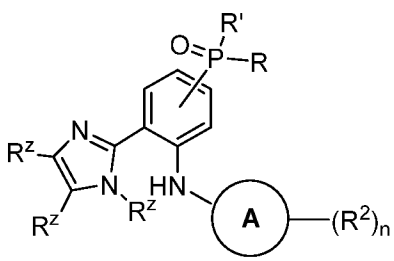
Formula (II-b).

[0032] In certain embodiments, the compound has a structure of Formula (II-c):



Formula (II-c).

[0033] In certain embodiments, the compound has a structure of Formula (II-d):



Formula (II-d).

[0034] In certain embodiments, each R^z 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 aryl, or substituted or unsubstituted heteroaryl.

[0035] In certain embodiments, each R^z is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted aryl.

In certain embodiments, each R^z is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl.

[0036] In certain embodiments, each R^z is independently hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[0037] In certain embodiments, each R^z is independently hydrogen, -F, -Cl, - methyl, ethyl, n-propyl, iso-propyl, or cyclopropyl.

[0038] In certain embodiments, each R^z is methyl.

[0039] In certain embodiments, R^z is $-L^1-Y^1$.

[0040] In certain embodiments, L^1 is substituted or unsubstituted C_1-C_4alkylene; and Y^1 is substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0041] In certain embodiments, R^z is $-L^2-L^3-Y^2$.

[0042] In certain embodiments, L^2 is substituted or unsubstituted C_1-C_6alkylene; L^3 is -O-, -S-, -(S=O)-, $-(SO_2)-$, $-NR^3-$, -(C=O)-, -(C=O)O-, -O(C=O)-, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(SO_2)NR^3-(C=O)O-$, $-NR^3(SO_2)NR^3-(C=O)-$, or $-NR^3(SO_2)NR^3-(C=O)O-$; each R^3 is independently H or substituted or unsubstituted C_1-C_6alkyl; and Y^2 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

In certain embodiments, L^2 is absent; L^3 is -O-, -S-, -(S=O)-, $-(SO_2)-$, $-NR^3-$, -(C=O)-, -(C=O)O-, -O(C=O)-, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(SO_2)NR^3-(C=O)O-$, $-NR^3(SO_2)NR^3-(C=O)-$, or $-NR^3(SO_2)NR^3-(C=O)O-$; each R^3 is independently H or substituted or unsubstituted C_1-C_6alkyl; and Y^2 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or

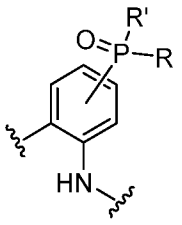
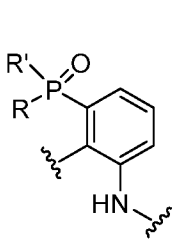
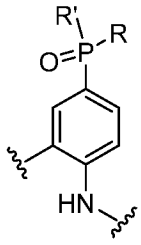
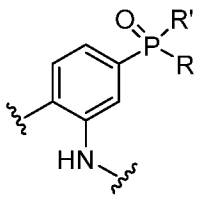
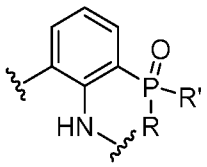
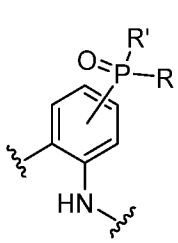
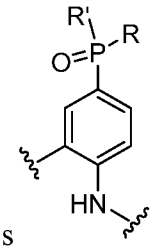
unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0043] In certain embodiments, m is 1, 2, or 3.

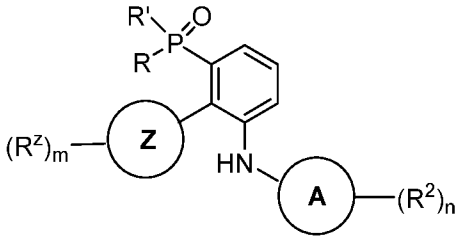
[0044] In certain embodiments, m is 1 or 2.

[0045] In certain embodiments, m is 1.

[0046] In certain embodiments, m is 1 and R^z is methyl.

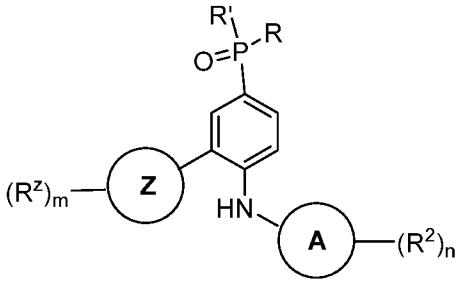
[0047] In certain embodiments,  is  ,  ,  , or  . In certain embodiments,  is  .

[0048] In certain embodiments, the compound has a structure of Formula (III-a):



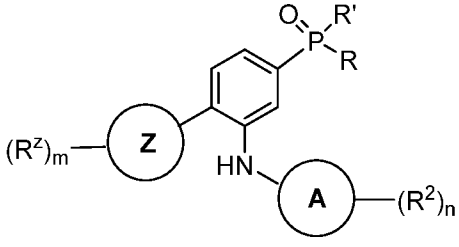
Formula (III-a).

[0049] In certain embodiments, the compound has a structure of Formula (III-b):



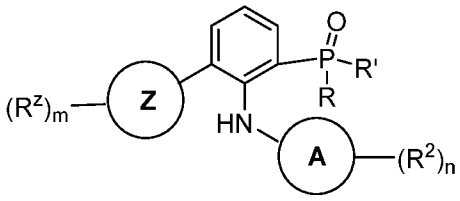
Formula (III-b).

[0050] In certain embodiments, the compound has a structure of Formula (III-c):



Formula (III-c).

[0051] In certain embodiments, the compound has a structure of Formula (III-d):



Formula (III-d).

[0052] In certain embodiments, R and R' are each independently 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_1-C_6alkoxy, 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.

[0053] In certain embodiments, R and R' are each independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0054] In certain embodiments, R and R' are each independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted aryl.

[0055] In certain embodiments, R and R' are each independently substituted or unsubstituted C_1-C_6alkyl or substituted or unsubstituted C_1-C_6alkoxy.

[0056] In certain embodiments, R and R' are each independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, or phenyl.

[0057] In certain embodiments, R and R' are each independently methyl, ethyl, n-propyl, methoxy, ethoxy, n-propoxy, or iso-propoxy.

[0058] In certain embodiments, R and R' are each methyl.

[0059] In certain embodiments, R and R' are each ethyl.

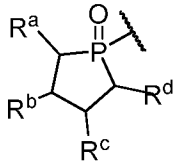
[0060] In certain embodiments, R and R' are each methoxy.

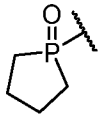
[0061] In certain embodiments, R and R' are each ethoxy.

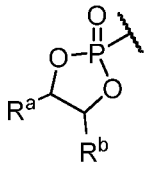
[0062] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

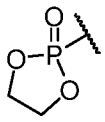
[0063] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 5- or 6-membered heterocycloalkyl.

[0064] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 5-membered heterocycloalkyl.

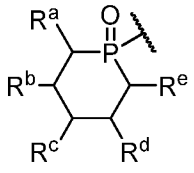
[0065] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  ; wherein R^a, R^b, R^c, and R^d are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

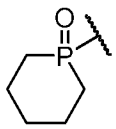
[0066] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  .

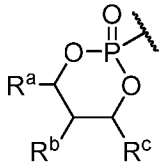
[0067] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  ; wherein R^a and R^b are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

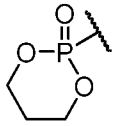
[0068] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  .

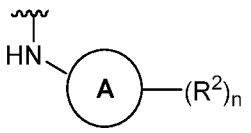
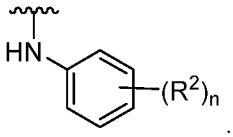
[0069] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 6-membered heterocycloalkyl.

[0070] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  ; wherein R^a, R^b, R^c, R^d and R^e are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

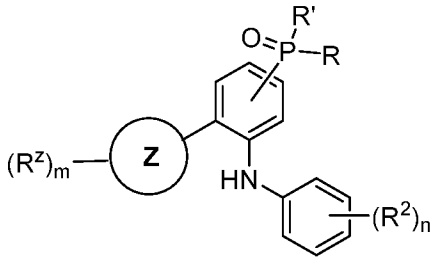
[0071] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  .

[0072] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  ; wherein R^a, R^b, and R^c are each independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl.

[0073] In certain embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  .

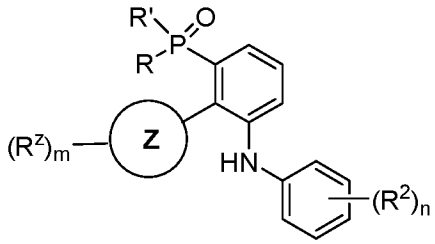
[0074] In certain embodiments,  is  .

[0075] In certain embodiments, the compound has the structure of Formula (IV):



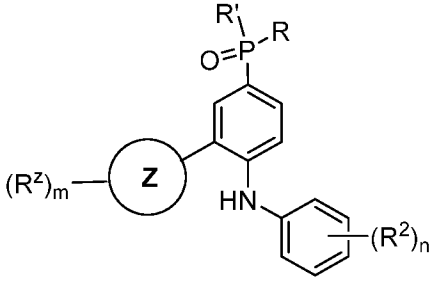
Formula (IV).

[0076] In certain embodiments, the compound has the structure of Formula (IV-a):



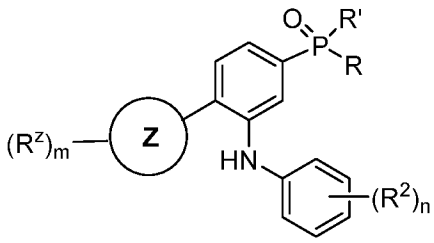
Formula (IV-a).

[0077] In certain embodiments, the compound has the structure of Formula (IV-b):



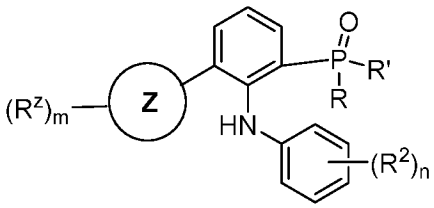
Formula (IV-b).

[0078] In certain embodiments, the compound has the structure of Formula (IV-c), or a pharmaceutically acceptable salt thereof:

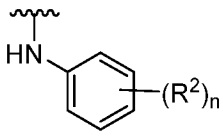
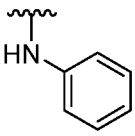
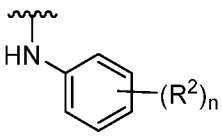
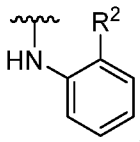
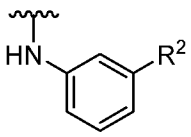
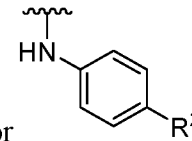
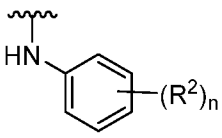
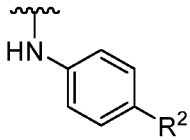
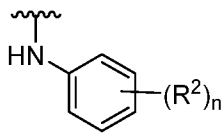
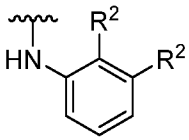
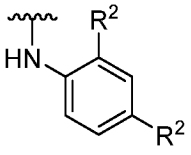
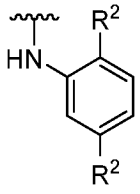
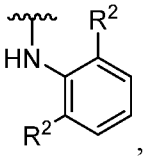
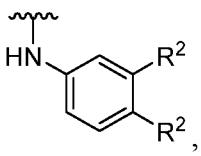
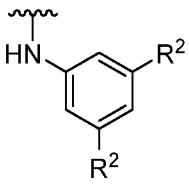
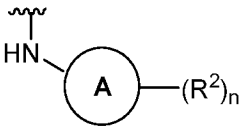
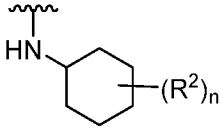


Formula (IV-c).

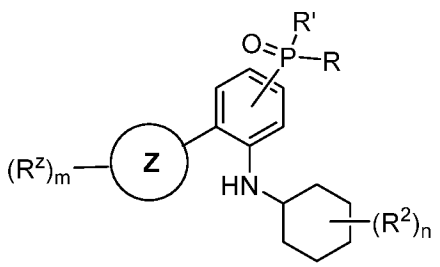
[0079] In certain embodiments, the compound has the structure of Formula (IV-d), or a pharmaceutically acceptable salt thereof:



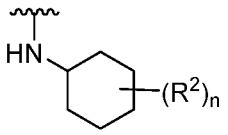
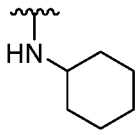
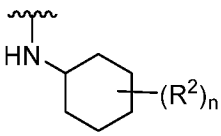
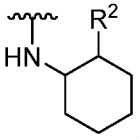
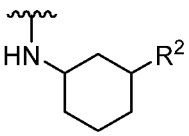
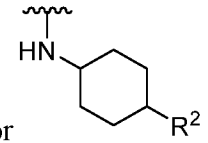
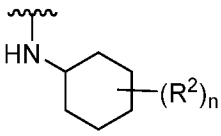
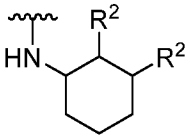
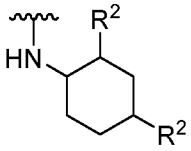
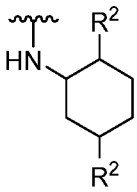
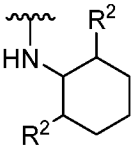
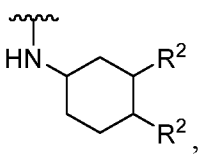
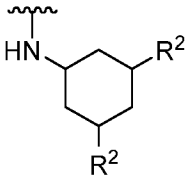
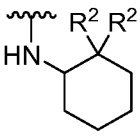
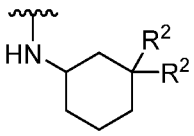
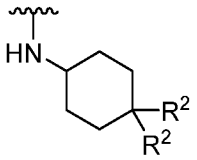
Formula (IV-d).

[0080] In certain embodiments,  is  . In certain embodiments,  is  ,  , or  . In certain embodiments,  is  . In certain embodiments,  is  ,  ,  ,  ,  , or  . In certain embodiments,  is  .

[0081] In certain embodiments, the compound has the structure of Formula (V):



Formula (V).

[0082] In certain embodiments,  is  . In certain embodiments,  is  ,  , or  . In certain embodiments,  is  ,  ,  ,  ,  ,  ,  ,  , or  .

[0083] In certain embodiments, each R^2 is independently hydrogen, halogen, nitro, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-S(R^4)_5$, $-(S{=}O)R^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl; each R^4 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl.

[0084] In certain embodiments, each R^2 is independently F, Cl, Br, I, nitro, -CN, $-SF_5$, $-SCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-C(=O)OCH_3$ $-S(=O)_2CH_3$, $-N(CH_3)_2$, $-NH(CH_3)$, $-CH_2F$, $-CHF_2$, or $-CF_3$.

[0085] In certain embodiments, each R^2 is independently F, Cl, -CN, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$.

[0086] In certain embodiments, each R^2 is independently F, Cl, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$.

[0087] In certain embodiments, each R^2 is independently F, Cl, $-SF_5$, $-SCF_3$, or $-CF_3$.

[0088] In certain embodiments, each R^2 is independently F, Cl, $-SF_5$, $-OCF_3$, $-SCF_3$, or $-CF_3$.

[0089] In certain embodiments, each R^2 is $-CF_3$.

[0090] In certain embodiments, each R^2 is $-SF_5$.

[0091] In certain embodiments, each R^2 is $-SCF_3$.

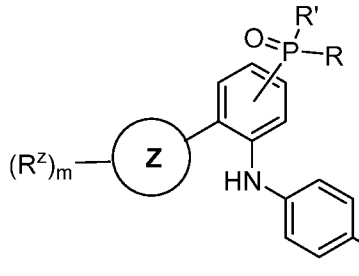
[0092] In certain embodiments, each R^2 is $-OCF_3$.

[0093] In certain embodiments, n is 0, 1, or 2.

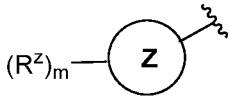
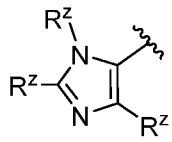
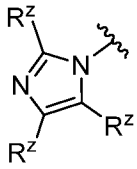
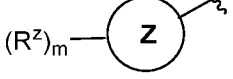
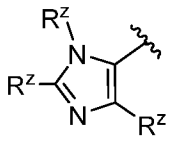
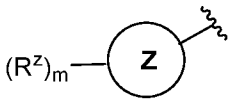
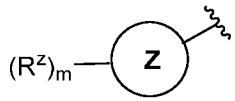
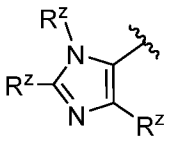
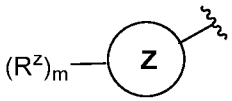
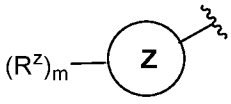
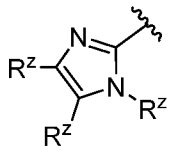
[0094] In certain embodiments, n is 1 or 2.

[0095] In certain embodiments, n is 1.

[0096] In certain embodiments, the compound has the structure of Formula (VI):



Formula (VI).

[0097] In certain embodiments,  is  ,  ,  , or  . In certain embodiments,  is  or  . In certain embodiments,  is  . In certain embodiments,  is  . In certain embodiments,  is  . In certain embodiments,  is  .

[0098] In certain embodiments, the compound provided herein is a compound from Table 1.

[0099] In another aspect, also provided herein are pharmaceutical compositions comprising the compound or pharmaceutically acceptable salt thereof provided herein, and a pharmaceutically acceptable excipient.

[00100] In yet another aspect, also provided herein are methods of inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway in a subject, comprising administering to a subject the compound or pharmaceutically acceptable salt thereof provided herein or pharmaceutical compositions provided herein.

[00101] In yet another aspect, also provided herein are methods of inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP) in a subject comprising administering to a subject the compound or pharmaceutically acceptable salt thereof provided herein, or the pharmaceutical composition provided herein.

[00102] In certain embodiments, the subject has cancer, polycystic kidney disease or liver fibrosis.

[00103] In certain 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.

[00104] In yet another aspect, also provided herein are methods 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 thereof provided herein, or the pharmaceutical composition provided herein.

[00105] In certain 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.

[00106] In yet another aspect, also provided herein are methods 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 thereof provided herein, or the pharmaceutical composition provided herein.

INCORPORATION BY REFERENCE

[00107] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE DISCLOSURE

Certain Terminology

[00108] 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.

[00109] 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.

[00110] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00111] 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).

[00112] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[00113] "Amino" refers to the $-NH_2$ radical.

[00114] "Cyano" refers to the -CN radical.

[00115] "Nitro" refers to the $-NO_2$ radical.

[00116] "Oxa" refers to the -O- radical.

[00117] "Oxo" refers to the =O radical.

[00118] "Thioxo" refers to the =S radical.

[00119] "Imino" refers to the =N-H radical.

[00120] "Oximo" refers to the =N-OH radical.

[00121] "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.

[00122] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl chain as defined above.

[00123] "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.

[00124] "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.

[00125] "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.

[00126] "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.

[00127] "Aryloxy" refers to a radical bonded through an oxygen atom of the formula –O-aryl, where aryl is as defined above.

[00128] "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.

[00129] "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.

[00130] "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.

[00131] "Carbocyclyl" or "carbocycle" refers 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-aromatice 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.

[00132] "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.

[00133] "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.

[00134] "Halo" or "halogen" refers to bromo, chloro, fluoro, or iodo substituents.

[00135] "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.

[00136] "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).

[00137] "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, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (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.

[00138] "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.

[00139] "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.

[00140] "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.

[00141] "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.

[00142] "*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.

[00143] "*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.

[00144] "Heteroaryloxy" refers to radical bonded through an oxygen atom of the formula –O-heteroaryl, where heteroaryl is as defined above.

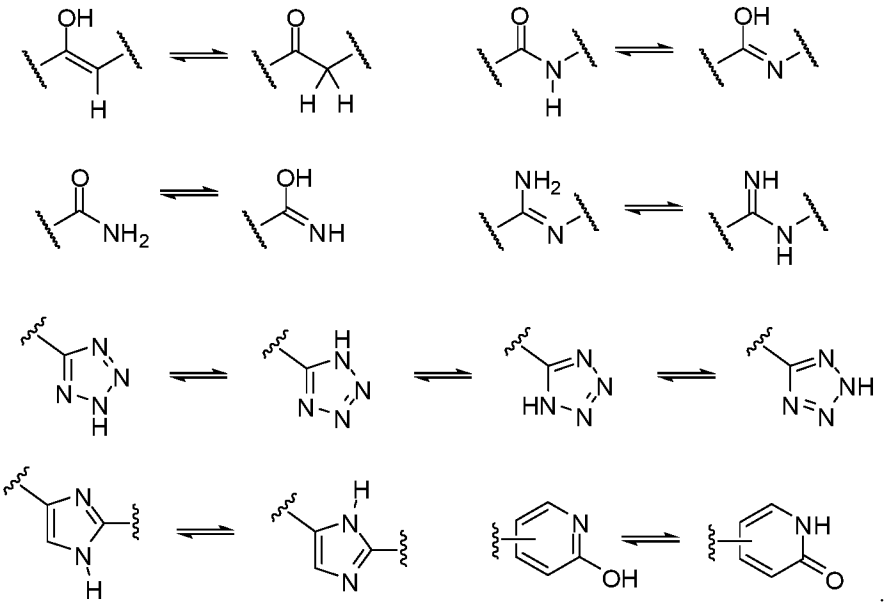
[00145] "Heteroarylalkyl" refers to a radical of the formula $–R^c$-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl 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.

[00146] "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.

[00147] 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.

[00148] 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:



[00149] "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.

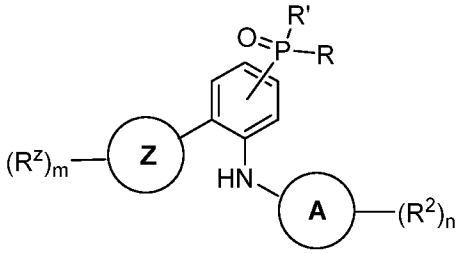
[00150] The term “optionally substituted” or “substituted” means that the referenced group is optionally substituted with one or more additional group(s). In some other embodiments, optional substituents are individually and independently selected from D, halogen, -CN, -NH_2, -NH(alkyl), -$N(alkyl)_2$, -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.

[00151] 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.

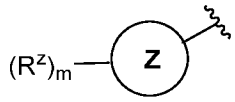
Compounds

[00152] In one aspect, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein,



is a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl ring containing at least one N atom, or a substituted or unsubstituted monocyclic heteroaryl ring containing at least one N atom;

each R^z 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, -L^1-Y^1, or -L^2-L^3-Y^2;

m is 0, 1, 2, 3, 4, or 5;

L^1 is substituted or unsubstituted C_1-C_6alkylene, substituted or unsubstituted C_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2- C_{10}heterocycloalkylene;

Y^1 is 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;

L^2 is absent, substituted or unsubstituted C_1-C_6alkylene, substituted or unsubstituted C_3-C_{10}cyclolalkylene, or substituted or unsubstituted 3- to 10-membered heterocycloalkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -O-NR^3(C=O)-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -NR^3(SO_2)-,-(SO_2)NR^3-, -(SO_2)NR^3-(C=O)-, -(C=O)-NR^3(SO_2)-, -(SO_2)NR^3-(C=O)O-, -O(C=O)-NR^3(SO_2)-, -NR^3(SO_2)NR^3-(C=O)-, -(C=O)-NR^3(SO_2)NR^3-, -O(C=O)-NR^3(SO_2)-NR^3-, or -NR^3(SO_2)NR^3-(C=O)O-;

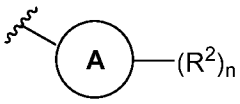
each R^3 is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl;

Y^2 is hydrogen, substituted or unsubstituted C_1-C_6alkyl, 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;

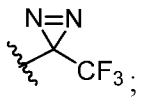
or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

R and R' are each independently 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_1-C_6alkoxy, 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 and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.



is substituted or unsubstituted phenyl or substituted or unsubstituted cyclohexyl;

each R^2 is independently hydrogen, halogen, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-S(R^4)_5$, $-(S{=}O)R^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6haloalkyl, 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, substituted or unsubstituted heteroaryl, or 

;

n is 0, 1, 2, 3, 4, or 5; and

each R^4 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

[00153] In some embodiments, ring Z is monocyclic 3- to 8-membered heterocycloalkyl ring.

[00154] In some embodiments, ring Z is monocyclic 4- to 7-membered heterocycloalkyl ring.

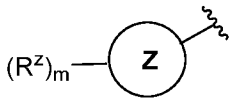
[00155] In some embodiments, ring Z is monocyclic 4- to 6-membered heterocycloalkyl ring.

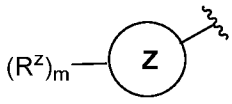
[00156] In some embodiments, ring Z is monocyclic 4- to 5-membered heterocycloalkyl ring.

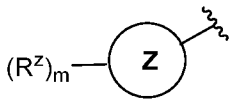
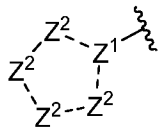
[00157] In some embodiments, ring Z is monocyclic 5- to 6-membered heterocycloalkyl ring.

[00158] In some embodiments, ring Z is monocyclic 5-membered heterocycloalkyl ring.

[00159] In some embodiments, ring Z is monocyclic 6-membered heterocycloalkyl ring.

[00160] In some embodiments,  is a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl ring containing at least one N atom.

[00161] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocycloalkyl ring containing 1-4 N atoms, 0-2 O atoms, and 0-2 S atoms.

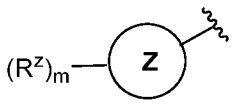
[00162] In some embodiments,  is  ;

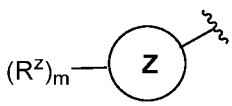
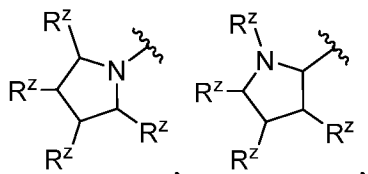
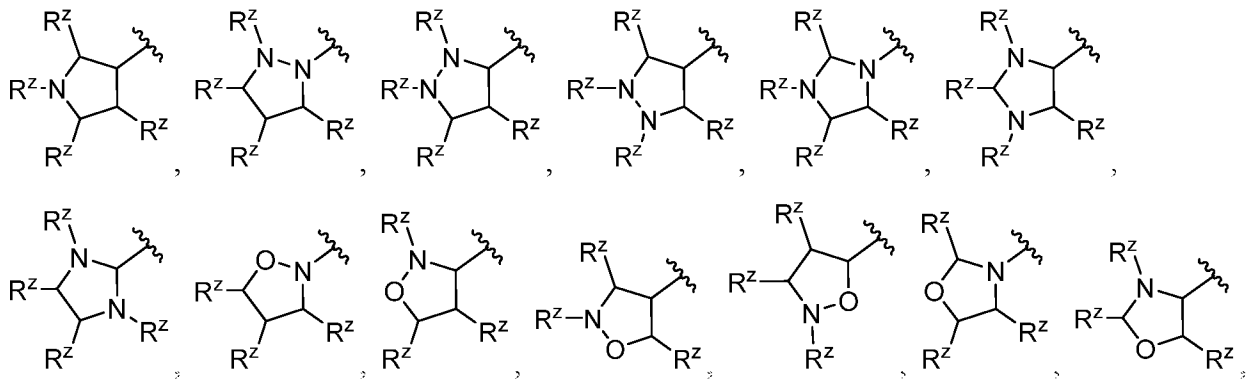
Z^1 is –N-, –CH-, or -C-;

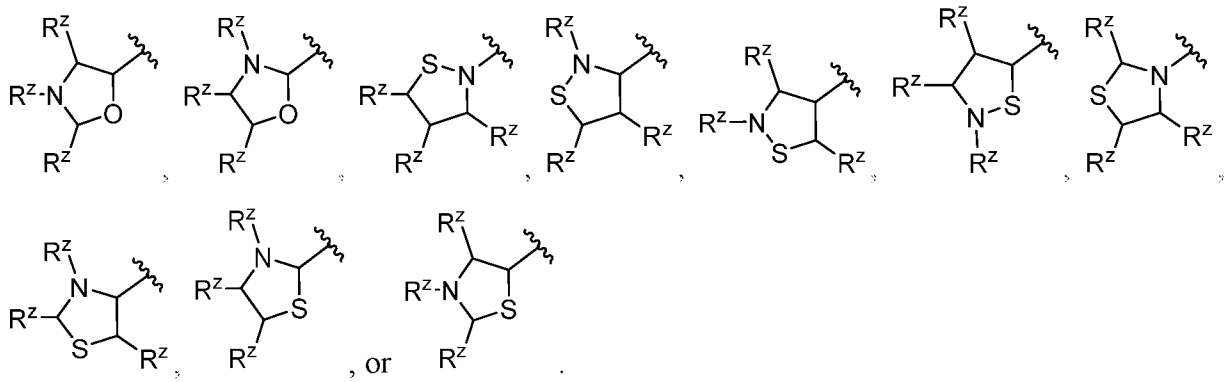
each Z^2 is independently -CR^z, -CHR^z-, -$C(R^z)_2$-, -NR^z-, -N-, -O-, or –S-;

[00163] each - - is independently a single or double bond

.

[00164] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

[00165] In some embodiments,  is  , 



[00166] In some embodiments, ring Z is monocyclic heteroaryl ring.

[00167] In some embodiments, ring Z is monocyclic 5- to 12- membered heteroaryl ring.

[00168] In some embodiments, ring Z is monocyclic 5- to 10- membered heteroaryl ring.

[00169] In some embodiments, ring Z is monocyclic 5- to 8- membered heteroaryl ring.

[00170] In some embodiments, ring Z is monocyclic 5- to 7- membered heteroaryl ring.

[00171] In some embodiments, ring Z is monocyclic 5- to 6- membered heteroaryl ring.

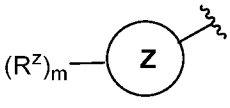
[00172] In some embodiments, ring Z is monocyclic 5-membered heteroaryl ring.

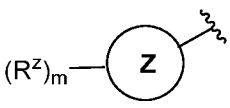
[00173] In some embodiments, ring Z is monocyclic 6-membered heteroaryl ring.

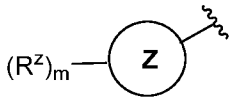
[00174] In some embodiments, ring Z is a 5-, 6-, or 7-membered monocyclic heteroaryl. In some embodiments, ring Z is a 5- or 6-membered monocyclic heteroaryl. In some embodiments, ring Z is a 6- or 7-membered monocyclic heteroaryl. In some embodiments, ring Z is a 6-membered monocyclic heteroaryl.

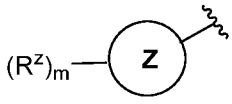
[00175] In some embodiments, ring Z is a monocyclic heteroaryl having 1-4 N atoms. In some embodiments, ring Z is a monocyclic heteroaryl having 1-3 N atoms. In some embodiments, ring Z is a monocyclic heteroaryl having 1-2 N atoms. In some embodiments, ring Z is a monocyclic heteroaryl having 1 N atom. In some embodiments, ring Z is a monocyclic heteroaryl having 2 N atoms. In some embodiments, ring Z is a monocyclic heteroaryl having 3 N atoms. In some embodiments, ring Z is a monocyclic heteroaryl having 4 N atoms.

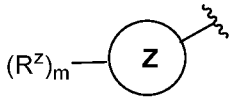
[00176] In some embodiments, ring Z is a monocyclic 5-membered heteroaryl having 1-4 N atoms.

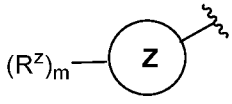
[00177] In some embodiments,  is a substituted or unsubstituted monocyclic heteroaryl ring containing at least one N atom.

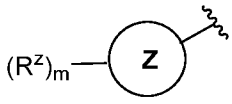
[00178] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 1 N atom.

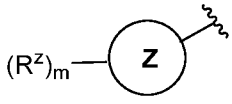
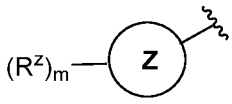
[00179] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 2 N atoms.

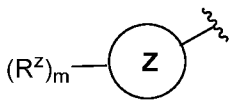
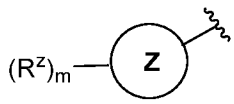
[00180] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 3 N atoms.

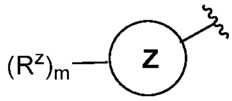
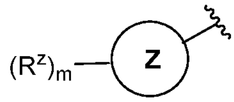
[00181] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 4 N atoms.

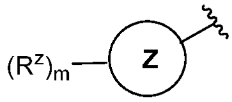
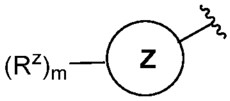
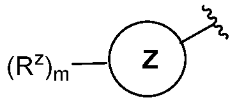
[00182] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazoyl, substituted or unsubstituted tetrazoyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

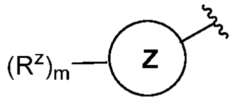
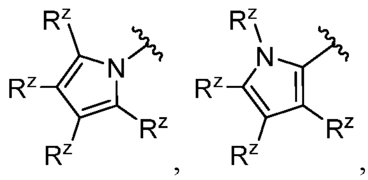
[00183] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, or substituted or unsubstituted isoxazolyl.

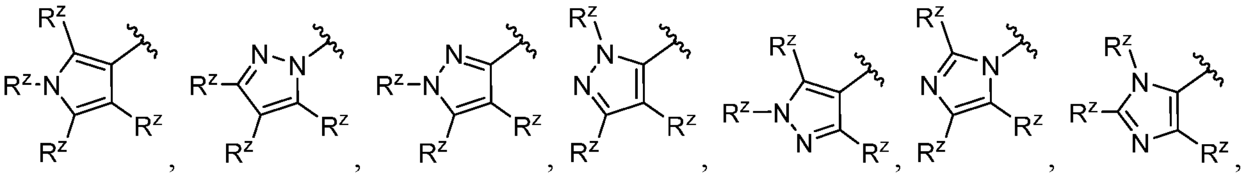
[00184] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, or substituted or unsubstituted oxazolyl. In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, or substituted or unsubstituted isoxazolyl.

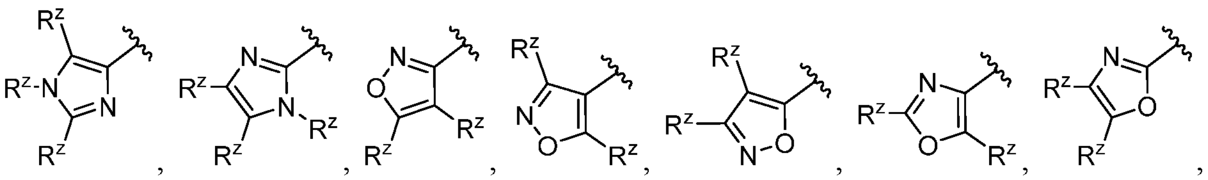
[00185] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, or substituted or unsubstituted pyrazolyl. In some embodiments,  is substituted or unsubstituted imidazolyl or substituted or

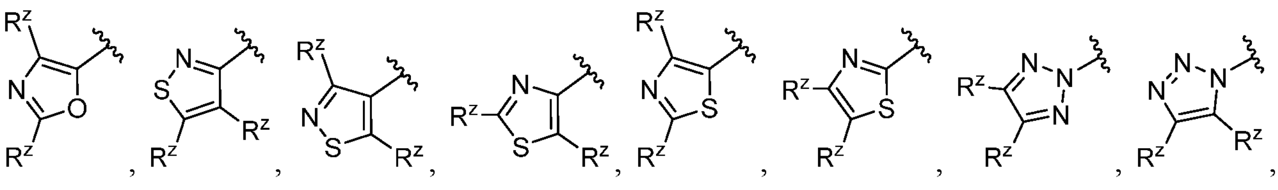
unsubstituted pyrazolyl. In some embodiments,  is substituted or unsubstituted pyrrolyl or substituted or unsubstituted imidazolyl. In some embodiments,  is substituted or unsubstituted pyrrolyl or substituted or unsubstituted pyrazolyl.

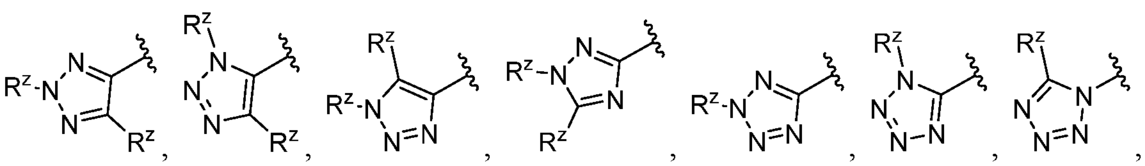
[00186] In some embodiments,  is substituted or unsubstituted pyrrolyl. In some embodiments,  is substituted or unsubstituted imidazolyl. In some embodiments,  is substituted or unsubstituted pyrazolyl.

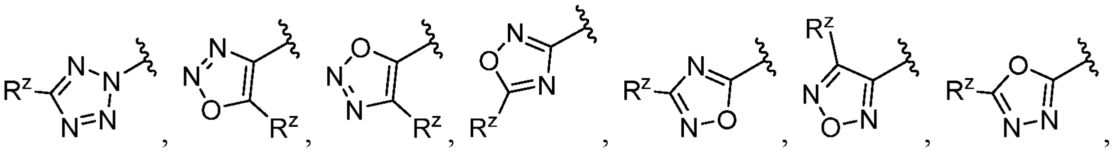
[00187] In some embodiments,  is 

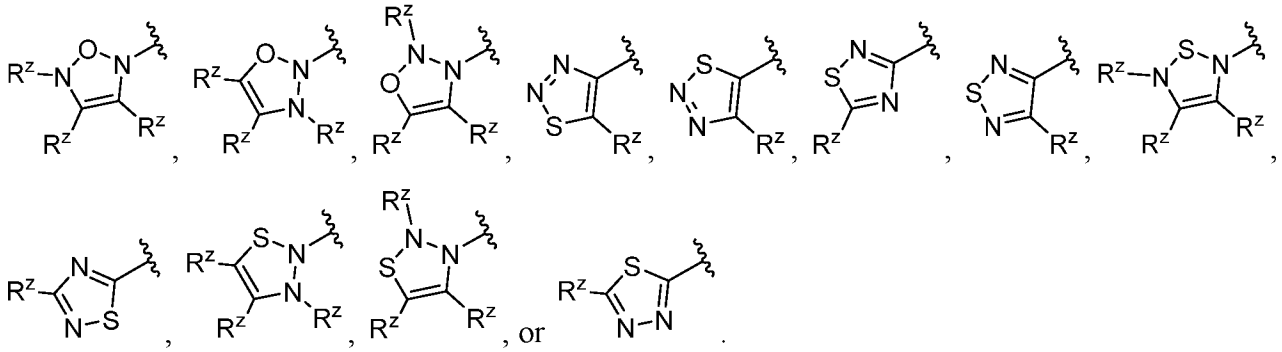


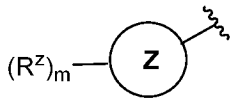


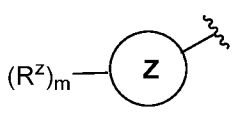


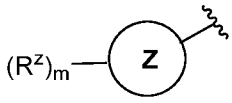
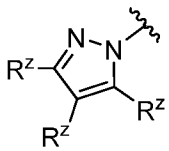
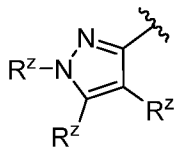
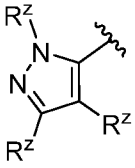
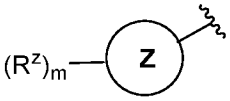
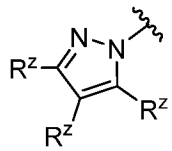
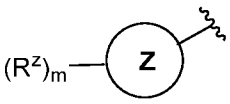
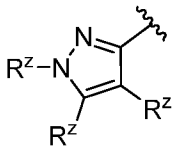
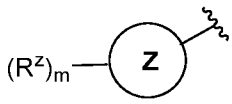
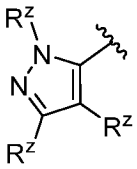


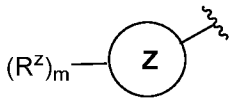
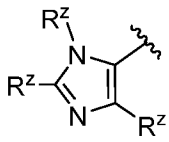
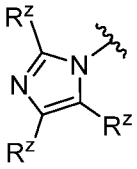
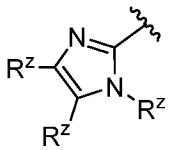
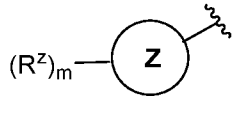
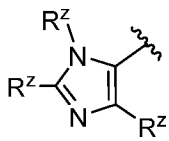
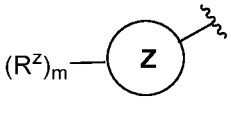
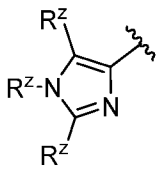
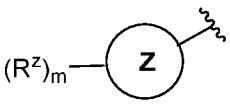
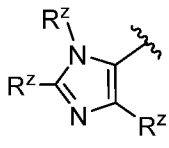
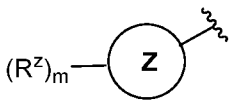
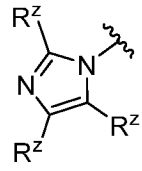
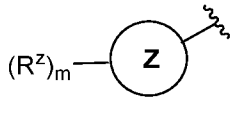
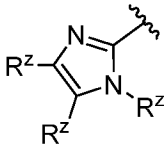


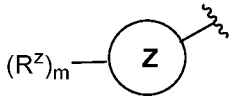
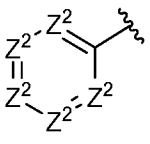


[00188] In some embodiments,  is

[00189] In some embodiments,  is

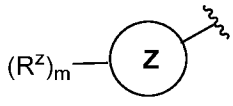
[00190] In some embodiments,  is  ,  , or  . In one embodiment,  is  . In another embodiment,  is  . In another embodiment,  is  .

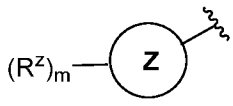
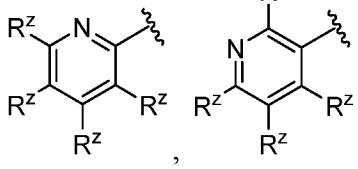
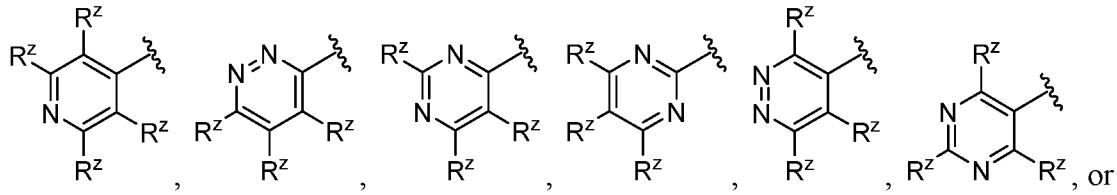
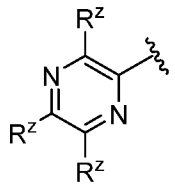
[00191] In some embodiments,  is  ,  ,  , or  . In one embodiment,  is  or  . In another embodiment,  is  . In yet another embodiment,  is  . In yet another embodiment,  is  . In yet another embodiment,  is  .

[00192] In some embodiments,  is  ;

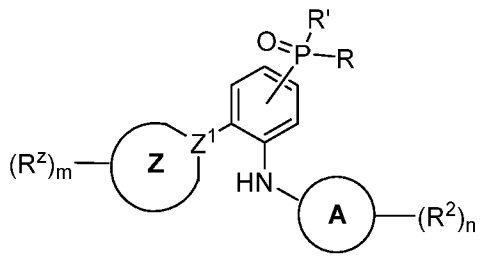
each Z^2 is independently CR^z or N; and

at least one Z^2 is N.

[00193] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

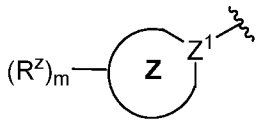
[00194] In some embodiments,  is  ,  , or  .

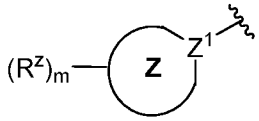
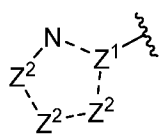
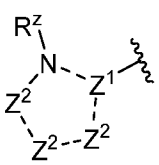
[00195] In some embodiments, the compound of Formula (I) has the structure of Formula (Ia):



Formula (Ia)

wherein Z^1 is –N-, –CH-, or -C-.

[00196] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom, and the at least one N atom is adjacent to Z^1.

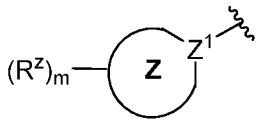
[00197] In some embodiments,  is  or  ;

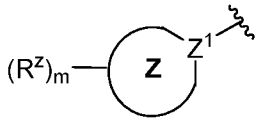
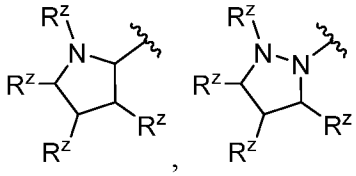
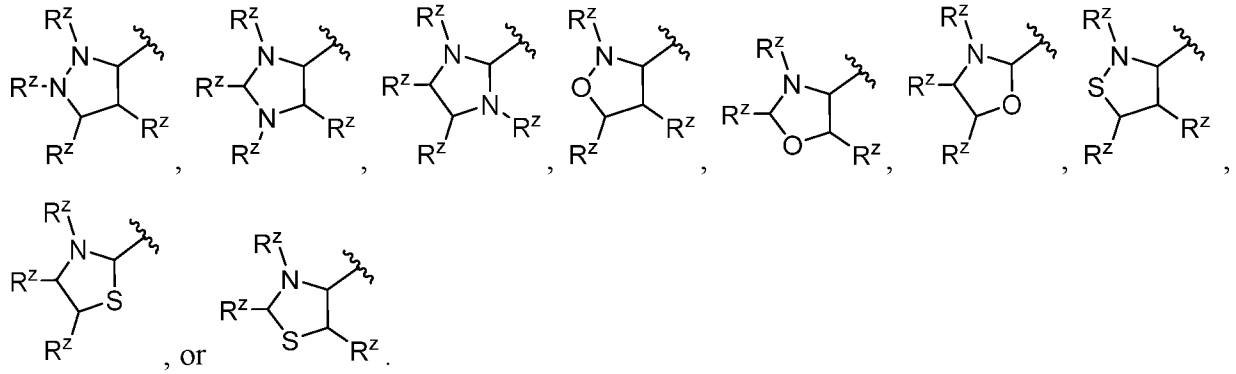
Z^1 is –N-, –CH-, or -C-;

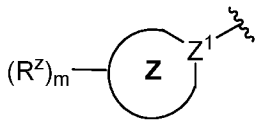
each Z^2 is independently CR^z, NR^z, N, O, or S;

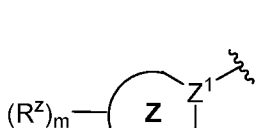
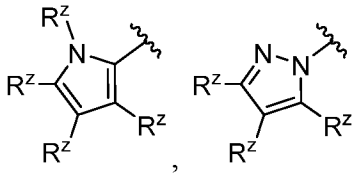
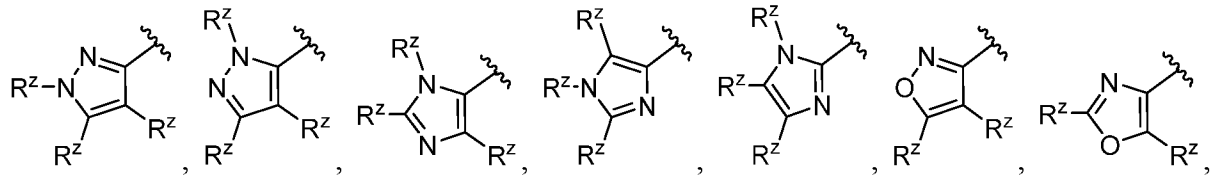
each - - is independently a single or double bond; and

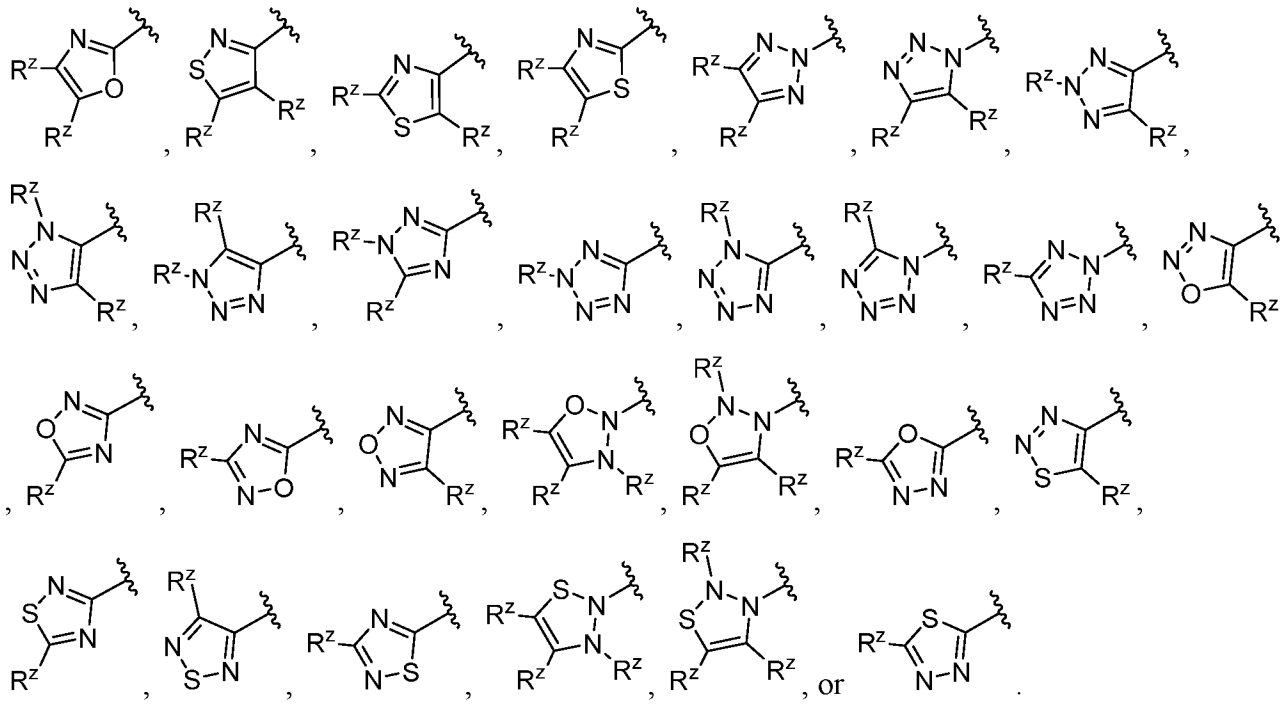
with the provision that the 5-membered heterocyclic ring contains at least one N atom.

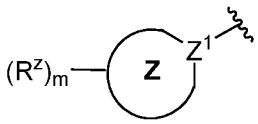
[00198] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

[00199] In some embodiments,  is  ,  , or .

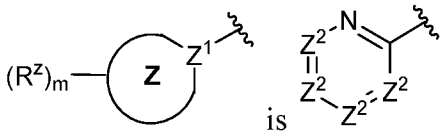
[00200] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazoyl, substituted or unsubstituted tetrazoyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

[00201] In some embodiments,  is  ,  .

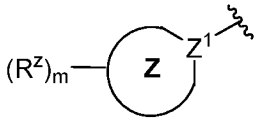




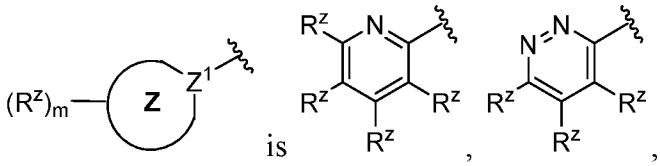
[00202] In some embodiments, is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom, and wherein the at least one N atom is adjacent to Z^1.



[00203] In some embodiments, is ; and each Z^2 is independently CR^z or N.

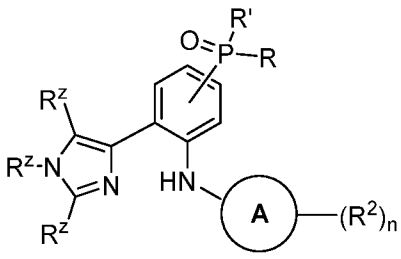


[00204] In some embodiments, is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.



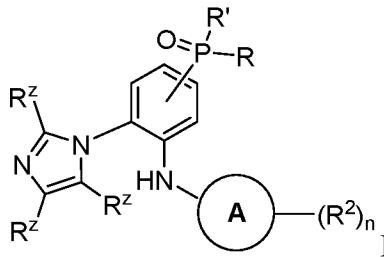
[00205] In some embodiments, is , , , , , or .

[00206] In some embodiments, the compound of Formula (I) has the structure of Formula (II-a):



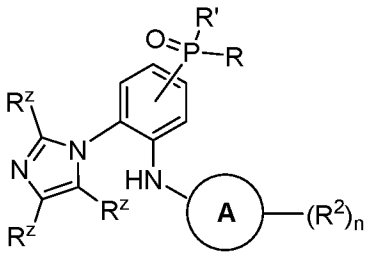
Formula (II-a).

[00207] In some embodiments, the compound of Formula (I) has a structure of Formula (II-b):



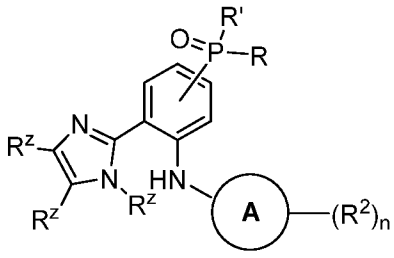
Formula (II-b).

[00208] In some embodiments, the compound of Formula (I) has a structure of Formula (II-c):



Formula (II-c).

[00209] In some embodiments, the compound of Formula (I) has a structure of Formula (II-d):



Formula (II-d).

[00210] In some embodiments, the compound of Formula (I) is a compound having a structure selected from Formulas (II-a), (II-b), (II-c), and (II-d).

[00211] In some embodiments, each R^z is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, each R^z 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 aryl, or substituted or unsubstituted heteroaryl. In some embodiments, each R^z is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted aryl. In some embodiments, each R^z is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl. In some embodiments, each R^z is independently hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl. In some embodiments, each R^z is independently hydrogen, -F, -Cl, - methyl, ethyl, n-propyl, iso-propyl, or cyclopropyl. In some embodiments, each R^z is methyl.

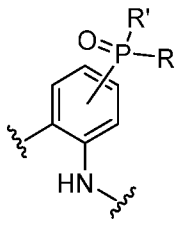
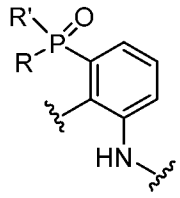
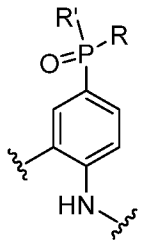
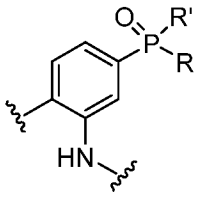
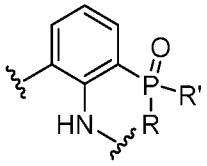
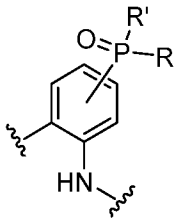
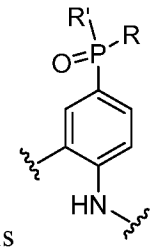
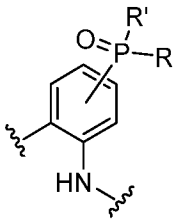
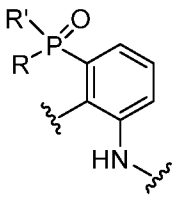
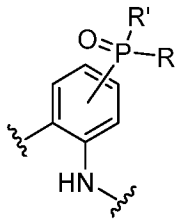
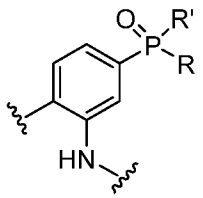
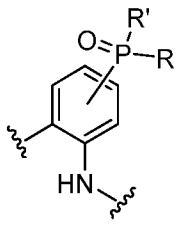
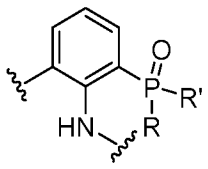
[00212] In some embodiments, each R^z is -L^1-Y^1. In some embodiments, L^1 is substituted or unsubstituted C_1-C_4alkylene; and Y^1 is substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00213] In some embodiments, each R^z is -L^2-L^3-Y^2. In some embodiments, L^2 is substituted or unsubstituted C_1-C_6alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -NR^3(SO_2)-, -(SO_2)NR^3-, -(SO_2)NR^3-(C=O)-, -(SO_2)NR^3-(C=O)O-, -NR^3(SO_2)NR^3-(C=O)-, or -NR^3(SO_2)NR^3-(C=O)O-; each R^3 is independently H or substituted or unsubstituted C_1-C_6alkyl; and Y^2 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

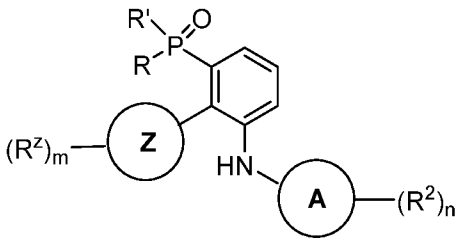
[00214] In some embodiments, L^2 is absent; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -NR^3(SO_2)-, -(SO_2)NR^3-, -(SO_2)NR^3-(C=O)-, -(SO_2)NR^3-(C=O)O-, -NR^3(SO_2)NR^3-(C=O)-, or -NR^3(SO_2)NR^3-(C=O)O-; each R^3 is independently H or substituted or unsubstituted C_1-C_6alkyl; and Y^2 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00215] 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.

[00216] In one specific embodiment, m is 1 and R^z is methyl.

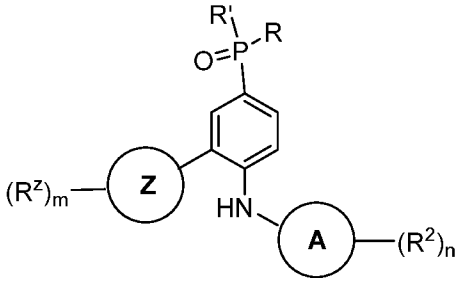
In some embodiments,  is  ,  ,  , or  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  .

[00217] In some embodiments, the compound of Formula (I) has a structure of Formula (III-a):



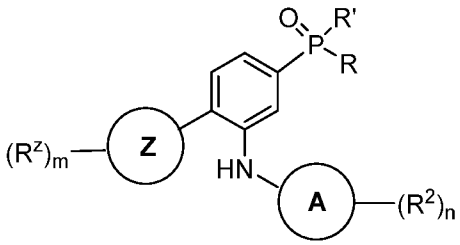
Formula (III-a).

[00218] In some embodiments, the compound of Formula (I) has a structure of Formula (III-b):



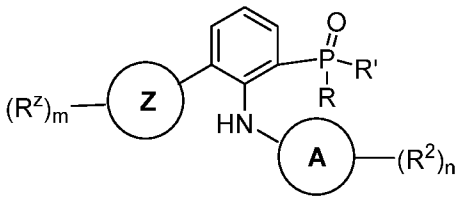
Formula (III-b).

[00219] In some embodiments, the compound of Formula (I) has a structure of Formula (III-c):



Formula (III-c).

[00220] In some embodiments, the compound of Formula (I) has a structure of Formula (III-d):



Formula (III-d).

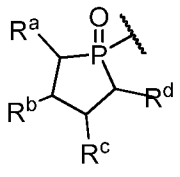
[00221] In some embodiments, the compound of Formula (I) is a compound having a structure selected from Formulas (III-a), (III-b), (III-c), and (III-d).

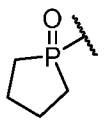
[00222] In some embodiments, R and R' are each independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

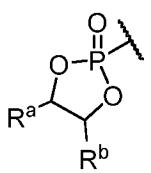
[00223] In some embodiments, R and R' are each independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R and R' are each independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted aryl. In some embodiments, R and R' are each independently substituted or unsubstituted C_1-C_6alkyl or substituted or unsubstituted C_1-C_6alkoxy. In some embodiments, R and R' are each independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, or phenyl. In

some embodiments, R and R' are each independently methyl, ethyl, n-propyl, methoxy, ethoxy, n-propoxy, or iso-propoxy. In one embodiment, R and R' are each methyl. In another embodiment, R and R' are each ethyl. In yet another embodiment, R and R' are each methoxy. In yet another embodiment, R and R' are each ethoxy.

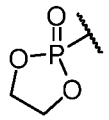
[00224] In some embodiments, R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S. In some embodiments, R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 5- or 6-membered heterocycloalkyl. In some embodiments, R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 5-membered heterocycloalkyl.

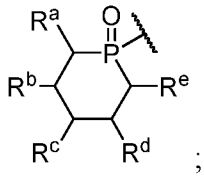
[00225] In some embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  ; wherein R^a, R^b, R^c, and R^d are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In certain embodiments, R^a, R^b, R^c, and R^d are each independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl. In certain embodiments, R^a, R^b, R^c, and R^d are each independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkoxy. In certain embodiments, R^a, R^b, R^c, and R^d are each independently hydrogen or halogen. In certain embodiments, R^a, R^b, R^c, and R^d are each hydrogen. In certain embodiments, R^a, R^b, R^c, and R^d are each independently hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, methoxy, or ethoxy.

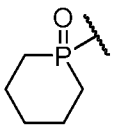
[00226] In one embodiment, R and R' taken together with the phosphorus atom to which they are attached to form  .

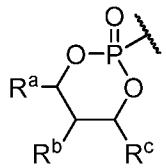
[00227] In some embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  ; wherein R^a and R^b are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In

certain embodiments, R^a and R^b are each independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl. In certain embodiments, R^a and R^b are each independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkoxy. In certain embodiments, R^a and R^b are each independently hydrogen or halogen. In certain embodiments, R^a and R^b are each hydrogen. In certain embodiments, R^a and R^b are each independently hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, methoxy, or ethoxy.

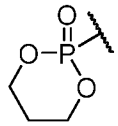
[00228] In one embodiment, R and R' taken together with the phosphorus atom to which they are attached to form  .

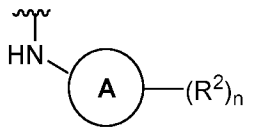
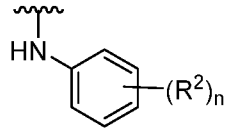
[00229] In some embodiments, R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 6-membered heterocycloalkyl. In some embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  ; wherein R^a, R^b, R^c, R^d and R^e are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In certain embodiments, R^a, R^b, R^c, R^d and R^e are each independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl. In certain embodiments, R^a, R^b, R^c, R^d and R^e are each independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkoxy. In certain embodiments, R^a, R^b, R^c, R^d and R^e are each independently hydrogen or halogen. In certain embodiments, R^a, R^b, R^c, R^d and R^e are each hydrogen. In certain embodiments, R^a, R^b, R^c, R^d and R^e are each independently hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, methoxy, or ethoxy.

[00230] In one embodiment, R and R' taken together with the phosphorus atom to which they are attached to form  .

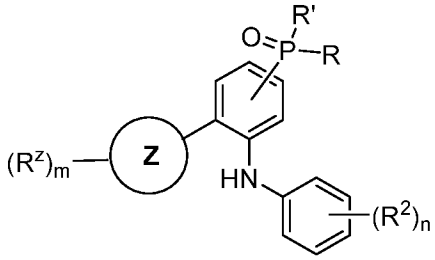
[00231] In some embodiments, R and R' taken together with the phosphorus atom to which they are attached to form  ; wherein R^a, R^b, and R^c are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In certain embodiments, R^a, R^b, and R^c are each independently hydrogen, halogen, or substituted or

unsubstituted C_1-C_6alkyl. In certain embodiments, R^a, R^b, and R^c are each independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkoxy. In certain embodiments, R^a, R^b, and R^c are each independently hydrogen or halogen. In certain embodiments, R^a, R^b, and R^c are each hydrogen. In certain embodiments, R^a, R^b, and R^c are each independently hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, methoxy, or ethoxy.

[00232] In one embodiment, R and R' taken together with the phosphorus atom to which they are attached to form  .

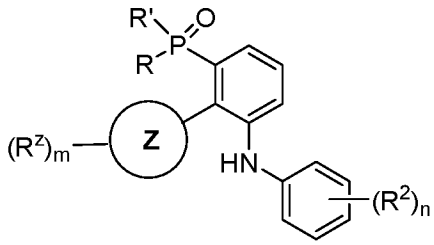
[00233] In some embodiments,  is  .

[00234] In some embodiments, the compound of Formula (I) has a structure of Formula (IV):



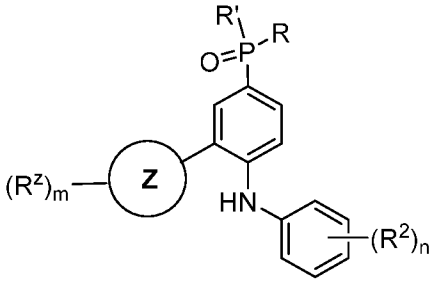
Formula (IV).

[00235] In some embodiments, the compound of Formula (I) has a structure of Formula (IV-a):



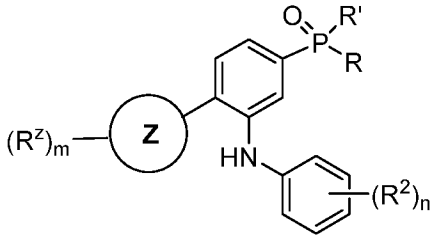
Formula (IV-a).

[00236] In some embodiments, the compound of Formula (I) has a structure of Formula (IV-b):



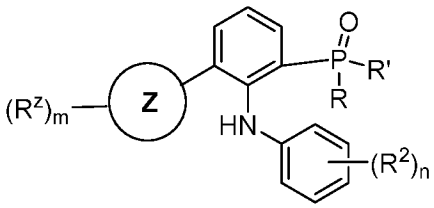
Formula (IV-b).

[00237] In some embodiments, the compound of Formula (I) has a structure of Formula (IV-c):



Formula (IV-c).

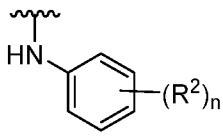
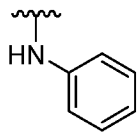
[00238] In some embodiments, the compound of Formula (I) has a structure of Formula (IV-d):

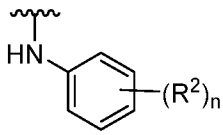
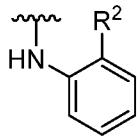
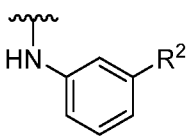
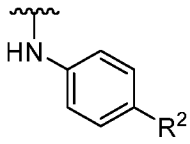


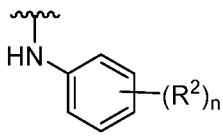
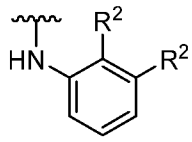
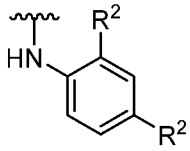
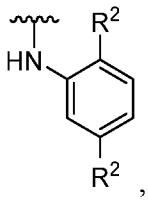
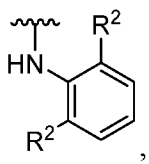
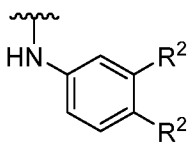
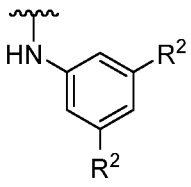
Formula (IV-d).

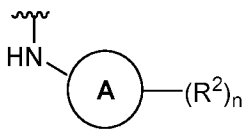
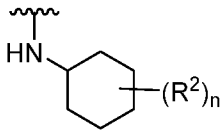
[00239] In some embodiments, the compound of Formula (I) is a compound having a structure selected from Formulas (IV), (IV-a), (IV-b), (IV-c), and (IV-d).

[00240] In some embodiments, the compound of Formula (I) is a compound having a structure selected from Formulas (IV-a), (IV-b), (IV-c), and (IV-d).

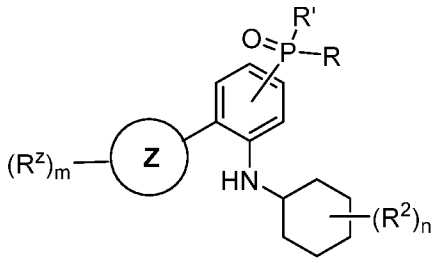
[00241] In some embodiments,  is  .

[00242] In some embodiments,  is  ,  , or  .

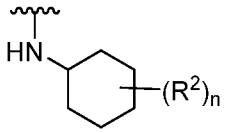
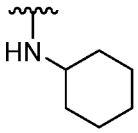
[00243] In some embodiments,  is  ,  ,  ,  ,  , or  .

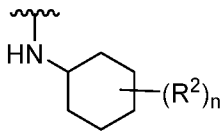
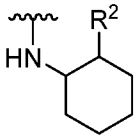
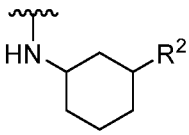
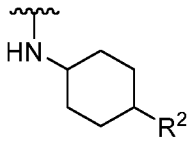
[00244] In some embodiments,  is  .

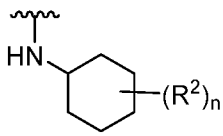
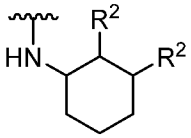
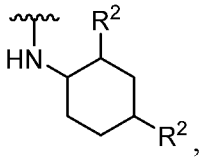
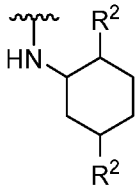
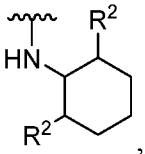
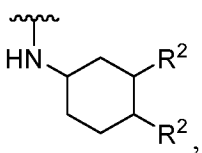
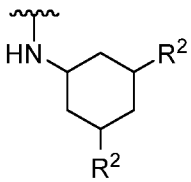
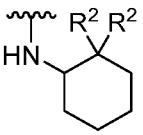
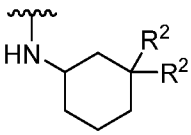
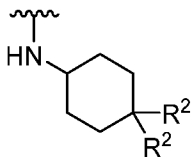
[00245] In some embodiments, the compound of Formula (I) has a structure of Formula (V):



Formula (V).

[00246] In some embodiments,  is  .

[00247] In some embodiments,  is  ,  , or  .

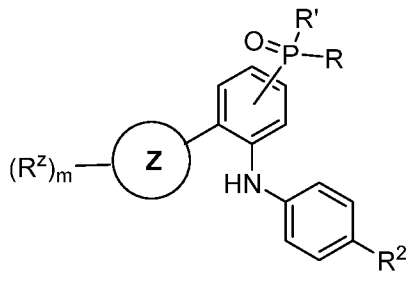
[00248] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  , or  .

[00249] In some embodiments, each R^2 is independently hydrogen, halogen, nitro, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-S(R^4)_5$, $-(S{=}O)R^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl;
each R^4 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl.

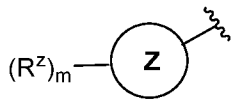
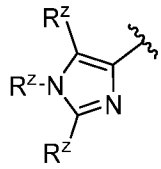
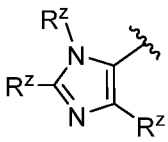
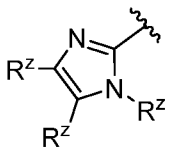
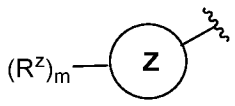
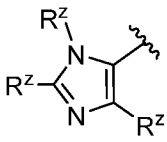
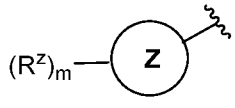
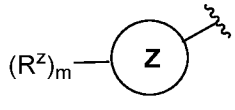
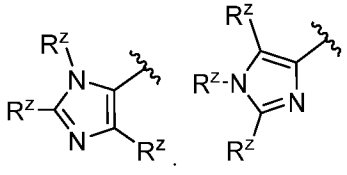
[00250] In some embodiments, each R^2 is independently F, Cl, Br, I, nitro, -CN, $-SF_5$, $-SCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-C(=O)OCH_3$ $-S(=O)_2CH_3$, $-N(CH_3)_2$, $-NH(CH_3)$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^2 is independently F, Cl, -CN, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$. In some embodiments, each R^2 is independently F, Cl, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$. In some embodiments, each R^2 is independently F, Cl, $-SF_5$, $-SCF_3$, or $-CF_3$. In some embodiments, each R^2 is independently F, Cl, $-SF_5$, $-OCF_3$, $-SCF_3$, or $-CF_3$. In one embodiment, each R^2 is $-CF_3$. In another embodiment, each R^2 is $-SF_5$. In yet another embodiment, each R^2 is $-SCF_3$. In yet another embodiment, each R^2 is $-OCF_3$.

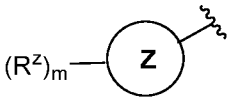
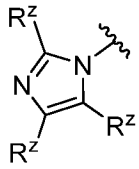
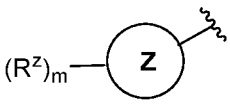
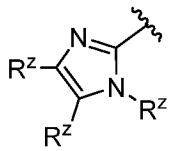
[00251] In some embodiments, n is 0, 1, 2, 3, or 4. In some embodiments, n is 0, 1, 2, or 3. In some embodiments, n is 0, 1, or 2. In some embodiments, n is 1 or 2. In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

[00252] In some embodiments, the compound of Formula (I) has a structure of Formula (VI):

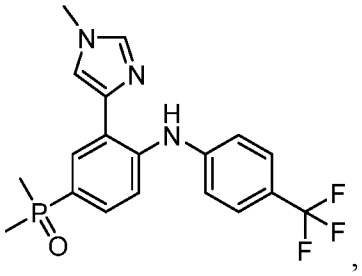
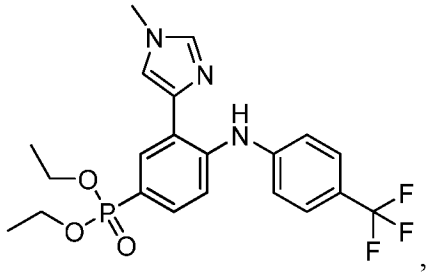
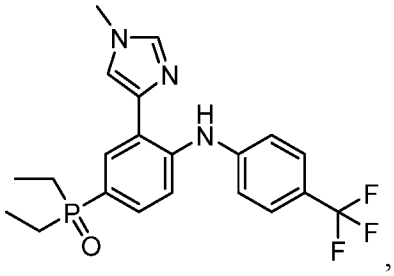


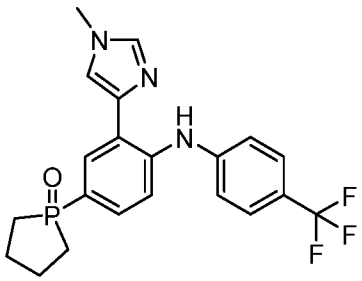
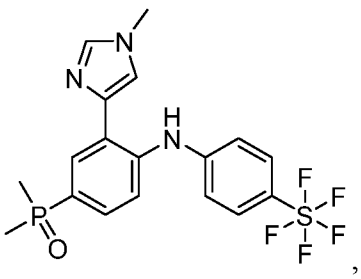
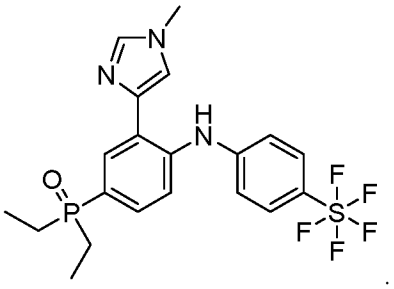
Formula (VI).

[00253] In certain embodiments of compounds of Formula (VI),  is  ,  ,  , or  . In certain embodiments of compounds of Formula (VI),  is  or  . In certain embodiments of compounds of Formula (VI),  is  . In certain embodiments of compounds of Formula (VI),  is  . In certain

embodiments of compounds of Formula (VI),  is  . In certain embodiments of compounds of Formula (VI),  is  .

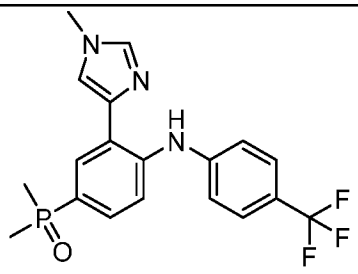
[00254] In some embodiments, the compound of Formula (I) is selected from the group consisting of:

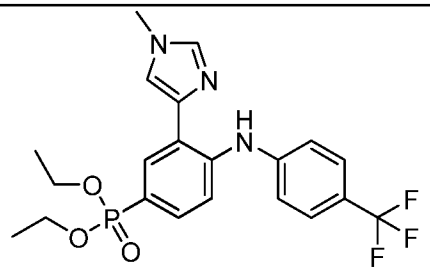
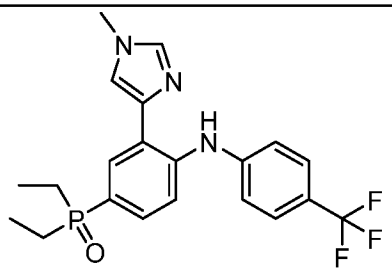
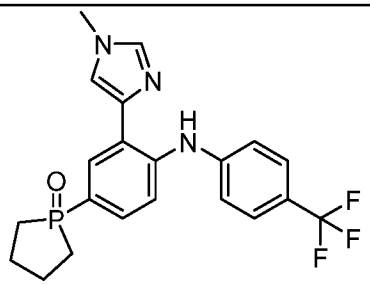
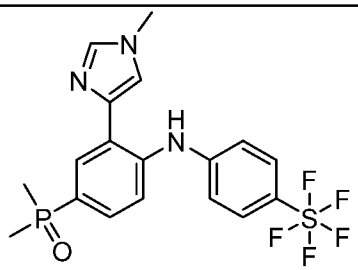
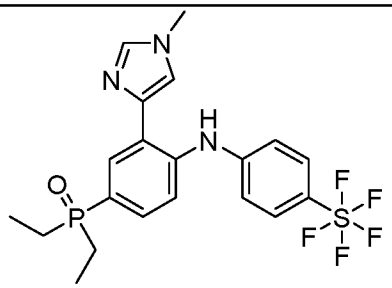
 ,  ,  ,

 ,  , and  .

[00255] In some embodiments, the compound disclosed herein has the structure provided in Table 1.

TABLE 1

Compound No.	Structure	Name
1		Dimethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphine oxide

Compound No.	Structure	Name
2		Diethyl (3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphonate
3		Diethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphine oxide
4		1-(3-(1-Methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phospholane 1-oxide
5		Dimethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)phenyl)phosphine oxide
6		Diethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(pentafluoro-λ6-sulfaneyl)phenyl)amino)phenyl)phosphine oxide

[00256] In some embodiments, provided herein is a pharmaceutically acceptable salt or solvate thereof of a compound described in Table 1.

Preparation of the Compounds

[00257] 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).

[00258] 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.

[00259] 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.

[00260] In some embodiments, the compounds disclosed herein are prepared as described in the Examples section.

Further Forms of Compounds

Isomers

[00261] 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

[00262] 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.

[00263] 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

[00264] 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.

[00265] 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

[00266] 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.

[00267] 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

[00268] 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.

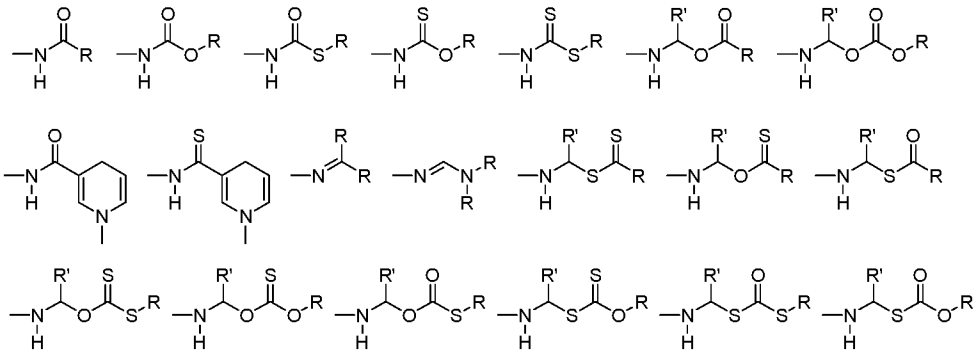
[00269] In some embodiments, prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e. g., two, three, or four) amino acid residues is covalently

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.

[00270] 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.

[00271] 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.

[00272] Amine derived prodrugs include, but are not limited to, the following groups and combinations of groups:



as well as sulfonamides and phosphonamides.

[00273] 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

[00274] 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.

[00275] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

Pharmaceutical Compositions

[00276] 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.

[00277] 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.

[00278] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I), (Ia), (II-a), (II-b), (II-c), (II-d), (III-a), (III-b), (III-c), (III-d), (IV), (IV-a), (IV-b), (IV-c), (IV-d), (V), or (VI), or a pharmaceutically acceptable salt thereof.

[00279] Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (I), (Ia), (II-a), (II-b), (II-c), (II-d), (III-a), (III-b), (III-c), (III-d), (IV), (IV-a), (IV-b), (IV-c), (IV-d), (V), or (VI), or a pharmaceutically acceptable salt thereof.

[00280] 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.

[00281] 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.

[00282] 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.

[00283] 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.

[00284] 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.

[00285] In some instances, a tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets are prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets are made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, are optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[00286] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms contain optionally inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[00287] 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.

[00288] In some embodiments, formulations for rectal or vaginal administration are presented as a suppository, which are prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene

glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[00289] Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component is optionally mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which are required in some embodiments.

[00290] In some embodiments, the ointments, pastes, creams and gels contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[00291] In some embodiments, powders and sprays contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00292] Compositions and compounds disclosed herein are alternatively administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (*e.g.*, fluorocarbon propellant) suspension could be used. Sonic nebulizers are used because they minimize exposing the agent to shear, which result in degradation of the compounds contained in the subject compositions in some embodiments. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[00293] Pharmaceutical compositions suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which are reconstituted into sterile injectable solutions or dispersions just prior to use, which optionally contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[00294] Examples of suitable aqueous and non-aqueous carriers employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. In some embodiments, proper fluidity is maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants

[00295] Also contemplated are enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal collophorium, and several commercially available enteric dispersion systems (*e.g.*, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure will recognize that it is not comprehensive and that there are other enteric materials that meet the objectives of the present disclosure.

[00296] In some embodiments, the dose of the composition comprising at least one compound as described herein differ, depending upon the patient's (*e.g.,* human) condition, that is,

stage of the disease, general health status, age, and other factors that a person skilled in the medical art will use to determine dose.

[00297] 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.

[00298] 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

[00299] 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.

[00300] 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.

[00301] 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.

[00302] 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.

[00303] 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.

[00304] 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.

[00305] 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 TEtOAcD (TEAD)

[00306] In some embodiments, un-phosphorylated and/or dephosphorylated YAP/TAZ accumulates in the nucleus. Within the nucleus, YAP/TAZ interacts with the TEtOAcD family of transcription factors (e.g., TEtOAcD1, TEtOAcD2, TEtOAcD3, or TEtOAcD4) to activate genes involved in anti-apoptosis and proliferation, such as for example *CTFG*, *Cyr61*, and *FGF1*.

[00307] In some embodiments, the compounds disclosed herein modulate the interaction between YAP/TAZ and TEtOAcD. In some embodiments, the compounds disclosed herein bind to TEtOAcD, YAP, or TAZ and prevent the interaction between YAP/TAZ and TEtOAcD.

YAP/TAZ regulation mediated by G-proteins/GPCRs

[00308] 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).

[00309] 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.

[00310] 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

[00311] $G_q\alpha$ (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.

[00312] 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.

[00313] 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*.

[00314] 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*.

[00315] 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

[00316] $G_{12/13}\alpha$ 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.

[00317] 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.

[00318] 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

[00319] $G_{i/o}\alpha$ (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.

[00320] 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.

[00321] 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

[00322] $G_s\alpha$ (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.

[00323] 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

[00324] 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.

[00325] 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.

[00326] 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.

[00327] 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.

[00328] 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).

[00329] 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. 1 and/or 2. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein and/or its coupled GPCR. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of the $G_q\alpha$ family proteins such as G_q, $G_{q/11}$, $G_{q/14}$, and $G_{q/15}$; the $G_{12/13}\alpha$ family of proteins such as G_{12} and G_{13}; or the $G_i\alpha$ family of proteins such as $G_i\alpha1$, $G_i\alpha2$, $G_i\alpha3$, $G_i\alpha4$, $G_o\alpha$, G_t, G_{gust}, and G_z. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_q. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/11}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/14}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/15}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{12}. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{13}. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha1$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha2$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha3$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha4$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_o\alpha$. In some

embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_t. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{gust}. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_z.

[00330] 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.

[00331] 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).

[00332] 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.

[00333] 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.

[00334] 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.

[00335] Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

[00336] 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.

[00337] 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.

[00338] 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.

[00339] 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.

[00340] 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.

[00341] 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.

[00342] In yet another aspect, provided herein are uses of a compound of Formula (I), (Ia), (II-a), (II-b), (II-c), (II-d), (III-a), (III-b), (III-c), (III-d), (IV), (IV-a), (IV-b), (IV-c), (IV-d), (V), or (VI) 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.

[00343] 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), (Ia), (II-a), (II-b), (II-c), (II-d), (III-a), (III-b), (III-c), (III-d), (IV), (IV-a), (IV-b), (IV-c), (IV-d), (V), or (VI) as disclosed herein, or a pharmaceutical composition comprising the compound disclosed herein, and a pharmaceutically acceptable excipient, as disclosed herein.

[00344] In another aspect, provided herein are pharmaceutical compositions comprising a compound Formula (I), (Ia), (II-a), (II-b), (II-c), (II-d), (III-a), (III-b), (III-c), (III-d), (IV), (IV-a), (IV-b), (IV-c), (IV-d), (V), or (VI) 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

[00345] 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.

[00346] 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.

[00347] 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.

[00348] 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.

[00349] 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.

[00350] 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.

[00351] 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.

[00352] 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.

[00353] 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.

[00354] 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.

[00355] 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.

[00356] 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.

[00357] 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

[00358] 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.

[00359] 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

[00360] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

List of abbreviations

[00361] 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
Bn	benzyl
BOC or Boc	*tert*-butyl carbamate
t-Bu	*tert*-butyl
Cy	cyclohexyl
°C	degrees Celsius
DBA or dba	dibenzylideneacetone
DCE	dichloroethane ($ClCH_2CH_2Cl$)
DCM	dichloromethane (CH_2Cl_2)
DIAD	diisopropyl azodicarboxylate
DIPEA or DIEA	diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	dimethylformamide

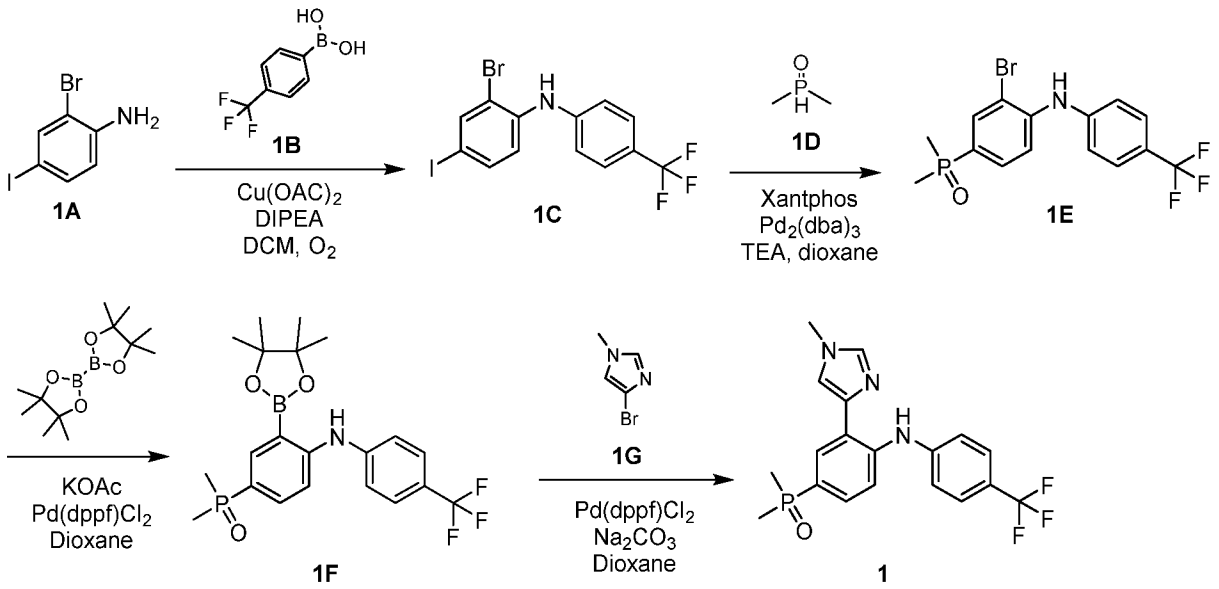
DMA	*N,N*-dimethylacetamide
DMSO	dimethylsulfoxide
Dppf or dppf	1,1'-bis(diphenylphosphino)ferrocene
EA or EtOAc	ethyl acetate
eq	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz
LAH	lithium aluminum anhydride
LCMS	liquid chromatography mass spectrometry
m/z	mass-to-charge ratio
M	molar
Me	methyl
MeI	methyl iodide
MeOH	methanol
mg	milligram(s)
MHz	megahertz
umol	micromole(s)
uL	microliter(s)
mL	milliliter(s)
mmol	millimole(s)
MS	mass spectroscopy
MsCl	methanesulfonyl chloride
MW	microwave radiation
NCS	*N*-chlorosuccinimide
NMM	*N*-methyl-morpholine
NMP	*N*-methyl-pyrrolidin-2-one
NMR	nuclear magnetic resonance
PE	petroleum ether
Ph	phenyl

prep-HPLC	preparative high pressure liquid chromatography
prep-TLC	preparative thin layer chromatography
Py	pyridine
RP-HPLC	reverse phase-high pressure liquid chromatography
RT	retention time
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
XPhos Pd G II	chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)

I. Chemical Synthesis

[00362] 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: Dimethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphine oxide (Compound 1)



2-Bromo-4-iodo-*N*-[4-(trifluoromethyl)phenyl]aniline (1C)

[00363] To a solution of 2-bromo-4-iodo-aniline (**1A**, 200 mg, 0.67 mmol, 1 *eq*), [4-(trifluoromethyl)phenyl]boronic acid (**1B**, 153.0 mg, 0.80 mmol, 1.2 *eq*) and $Cu(OAc)_2$ (146.3 mg, 0.80 mmol, 1.2 *eq*) in DCM (4 mL) was added DIPEA (173.5 mg, 1.34 mmol, 2 *eq*). The reaction mixture was stirred at 25 °C for 16 hours under O_2. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (20 mL) and the resultant mixture was extracted with EA (30 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 column chromatography on silica gel (petroleum ether: ethyl acetate = 1:0 to 10:1) to give intermediate **1C** (60 mg, 98% purity) as red oil. ^1H NMR (400MHz, $CDCl_3$) δ 7.88 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.51 (dd, J = 1.9, 8.6 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.6 Hz, 1H), 6.19 (s, 1H).

2-Bromo-4-dimethylphosphoryl-*N*-[4-(trifluoromethyl)phenyl]aniline (1E)

[00364] A solution of $Pd_2(dba)_3$ (10.3 mg, 11.3 umol, 0.05 *eq*) and Xantphos (13.0 mg, 22.6 umol, 0.1 *eq*) in dioxane (0.5 mL) was stirred at 25 °C for 20 min. A solution of intermediate **1C** (100 mg, 0.22 mmol, 1 *eq*), methylphosphonoylmethane (**1D**, 17.6 mg, 0.22 mmol, 1 *eq*) and TEA (34.3 mg, 0.33 mmol, 1.5 *eq*) in dioxane (0.5 mL) dropwise. The reaction mixture was stirred at 25 °C for 16 hours. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EA (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 column chromatography on silica gel (ethyl acetate : methol = 1:0 to 5:1) to give intermediate **1E** (45 mg, 46.6% yield, 92% purity) as a light yellow

solid. LCMS (ESI): RT = 0.863 min, mass calcd for $C_{15}H_{14}BrF_3NOP$ 390.99 m/z, found 392.1 $[M+H]^+$,

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

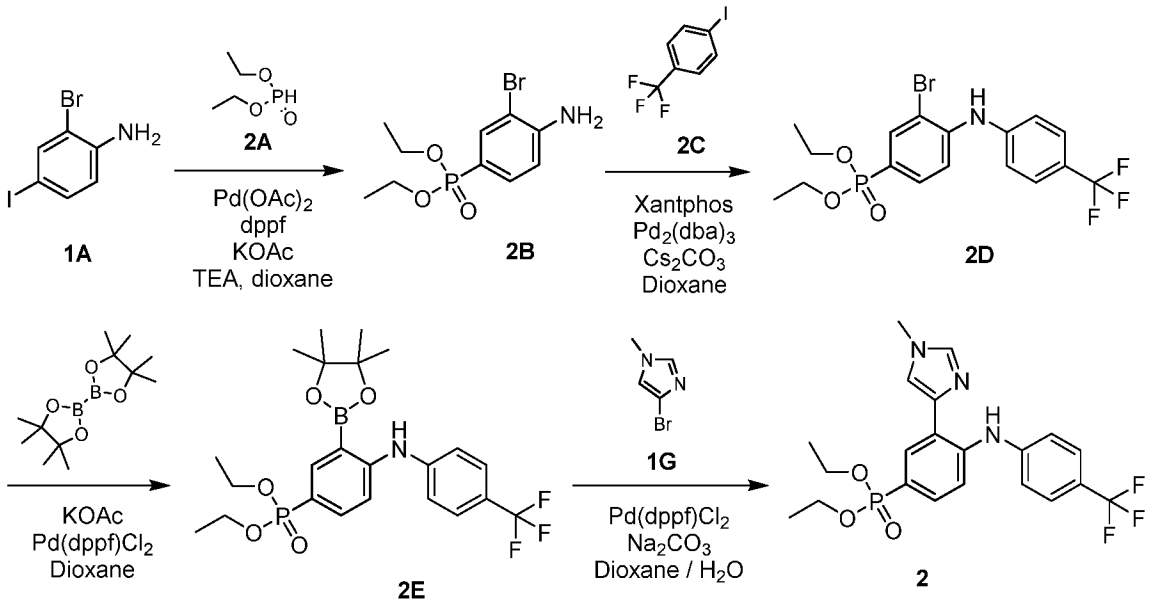
[00365] To a solution of intermediate **1E** (45 mg, 0.11 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (43.7 mg, 0.17 mmol, 1.5 *eq*) and KOAc (22.5 mg, 0.22 mmol, 2 *eq*) in dioxane (2 mL) was added Pd(dppf)Cl_2 (4.2 mg, 5.7 umol, 0.05 *eq*), and then the reaction mixture was stirred at 90 °C for 1 hour under N_2. The crude product intermediate **1F** (50 mg, 113.84 umol) was used in the next step without further purification.

4-Dimethylphosphoryl-2-(1-methylimidazol-4-yl)-*N*-[4-(trifluoromethyl)phenyl]aniline (Compound 1)

[00366] To a solution of intermediate **1F** (50 mg, 0.11 mmol, 1 *eq*), 4-bromo-1-methyl-imidazole (**1G**, 21.9 mg, 0.13 mmol, 1.2 *eq*) and Na_2CO_3 (24.1 mg, 0.22 mmol, 2 *eq*) in dioxane (2 mL) and H_2O (0.4 mL) was added Pd(dppf)Cl_2 (4.1 mg, 5.6 umol, 0.05 *eq*) under N_2. The suspension was degassed under vacuum and purged with N_2 several times. The reaction mixture was stirred at 90°C for 2 hours under N_2. The reaction mixture was concentrated under reduced pressure, and was diluted with water (10 mL) and 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*-TLC (Petroleum ether: Ethyl acetate=10:1) to give a crude product, which was purified by *prep*-HPLC (column: Waters Xbridge 150*25mm* 5um; mobile phase: [water(0.05%NH_3H_2O)-ACN]; B%: 34%-64%, 9.5min) to afford **Compound 1** (2.08 mg, 4.4% yield, 96% purity) as a light yellow solid. LCMS (ESI): RT = 0.756 min, mass calcd for $C_{19}H_{19}F_3N_3OP$ 393.12 m/z, found 394.2 $[M+H]^+$,

^{1}H NMR (400MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.97 (dd, *J* = 1.8, 12.3 Hz, 1H), 7.58 - 7.48 (m, 4H), 7.36 (d, *J* = 1.0 Hz, 1H), 7.34 - 7.28 (m, 3H), 3.78 (s, 3H), 1.76 (s, 3H), 1.72 (s, 3H).

Example 2: Diethyl (3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphonate (Compound 2)



Diethyl (4-amino-3-bromophenyl)phosphonate (2B)

[00367] To a solution of $Pd(OAc)_2$ (75.3 mg, 0.33 mmol, 0.05 *eq*), dppf (372.1 mg, 0.67 mmol, 0.1 *eq*) and KOAc (131.7 mg, 1.34 mmol, 0.2 *eq*) in dioxane (20 mL) was added TEA (1.36 g, 13.43 mmol, 1.87 mL, 2 *eq*) under N_2, and then the reaction mixture was stirred at 65 °C for 15 min. After 2-bromo-4-iodo-aniline (**1A**, 2 g, 6.71 mmol, 543.48 uL, 1 *eq*) and 1-ethoxyphosphonoyloxyethane (**2A**, 1.11 g, 8.06 mmol, 1.04 mL, 1.2 *eq*) in dioxane (5 mL) were added dropwise, the reaction mixture was stirred at 110 °C for 16 hours. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (20 mL) and the resultant mixture was extracted with EtOAc (40 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 column chromatography on silica gel (petroleum ether: ethyl acetate = 1:0 to 1:2) to give intermediate **2B** (520 mg, 17% yield, 69 % purity) as brown oil.

Diethyl (3-bromo-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphonate (2D)

[00368] To a solution of intermediate **2B** (400 mg, 1.30 mmol, 1 *eq*), 1-iodo-4-(trifluoromethyl)benzene (**2C**, 423.7 mg, 1.56 mmol, 1.2 *eq*), Xantphos (75.1 mg, 0.12 mmol, 0.1 *eq*) and Cs_2CO_3 (634.4 mg, 1.95 mmol, 1.5 *eq*) in Dioxane (5 mL) was added $Pd_2(dba)_3$ (59.4 mg, 64.9 umol, 0.05 *eq*) under N_2. The suspension was degassed under vacuum and purged with N_2 several times. The mixture was stirred under N_2 at 100°C for 2 hours. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (15 mL) and the resultant mixture was extracted with EtOAc (30 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

column chromatography on silica gel (petroleum ether: ethyl acetate = 1:0to 1:1) to give intermediate **2D** (450 mg, 74% yield, 97% purity) as a light yellow solid. LCMS (ESI): RT = 0.977 min, mass calcd for $C_{17}H_{18}BrF_3NO_3P$ 451.02 m/z, found 454.1 $[M+H]^+$.

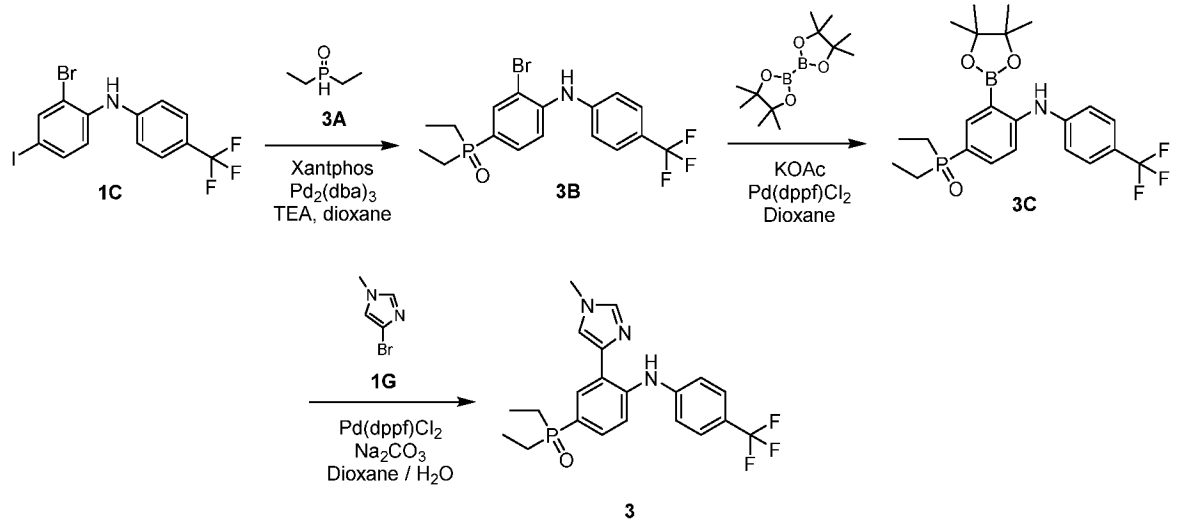
Diethyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl) amino)phenyl)phosphonate (2E)

[00369] To a solution of intermediate **2D** (250 mg, 0.55 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (210.5 mg, 0.82 mmol, 1.5 *eq*) and KOAc (108.5 mg, 1.11 mmol, 2 *eq*) in dioxane (5 mL) was added $Pd(dppf)Cl_2$ (20.2 mg, 27.6 umol, 0.05 *eq*), and then the reaction mixture was stirred at 90 °C for 2 hours under N_2. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (15 mL) and the resultant mixture was extracted with EtOAc (30 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 column chromatography on silica gel (petroleum ether: ethyl acetate = 1:0 to 2:1) to give intermediate **2E** as a brown solid. LCMS (ESI): RT = 1.080 min, mass calcd for $C_{23}H_{30}BF_3NO_5P$ 499.19 m/z, found 500.3 $[M+H]^+$.

Diethyl (3-(1-methyl-1*H*-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl) Phosphonate (Compound 2)

[00370] To a solution of intermediate **2E** (100 mg, 0.20 mmol, 1 *eq*), 4-bromo-1-methyl-imidazole (**1G**, 32.2 mg, 0.20 mmol, 1 *eq*) and Na_2CO_3 (42.4 mg, 0.40 mmol, 2 *eq*) in Dioxane (2 mL) and H_2O (0.4 mL) was added $Pd(dppf)Cl_2$ (7.3 mg, 10.0 umol, 0.05 *eq*) under N_2. The suspension was degassed under vacuum and purged with N_2 several times. The mixture was stirred at 90°C for 2 hours under N_2. The reaction mixture was concentrated under reduced pressure. The 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 column chromatography on silica gel (DCM: MeOH = 1:0 to 10:1) to give a crude product, which was purified by *prep*-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 56%-86%, 7.8min) to afford **Compound 2** (7.90 mg, 8.6% yield, 99% purity) as a white solid. LCMS (ESI): RT = 0.823 min, mass calcd for $C_{21}H_{23}F_3N_3O_3P$ 453.14 m/z, found 454.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 10.80 (br s, 1H), 8.01 - 7.91 (m, 1H), 7.57 - 7.47 (m, 5H), 7.37 - 7.30 (m, 3H), 4.23 - 4.00 (m, 4H), 3.82 - 3.75 (m, 3H), 1.34 (t, *J*=7.0 Hz, 6H).

Example 3: Diethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphine oxide (Compound 3)



2-Bromo-4-diethylphosphoryl-*N*-[4-(trifluoromethyl)phenyl]aniline (3B)

[00371] A solution of $Pd_2(dba)_3$ (31.0 mg, 33.9 umol, 0.05 *eq*) and Xantphos (39.2 mg, 67.8 umol, 0.1 *eq*) in dioxane (2.5 mL) was stirred at 25 °C for 20 min. A solution of intermediate **1C** (300 mg, 0.67 mmol, 1 *eq*), 1-ethylphosphonoylethane (**3A**, 72.0 mg, 0.67 mumol, 1 *eq*) and TEA (103.0 mg, 1.02 mmol, 1.5 *eq*) in dioxane (2.5 mL) was added dropwise. The reaction mixture was stirred at 25 °C for 16 hours. The reaction mixture was concentrated under reduced pressure. The 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 column chromatography on silica gel (ethyl acetate: methol = 1:0 to 10:1) to give intermediate **3B** (150 mg, 46.8% yield, 89% purity) as a brown solid. LCMS (ESI): RT = 0.897 min, mass calcd for $C_{17}H_{18}BrF_3NOP$ 419.03 m/z, found 420.2 $[M+H]^+$.

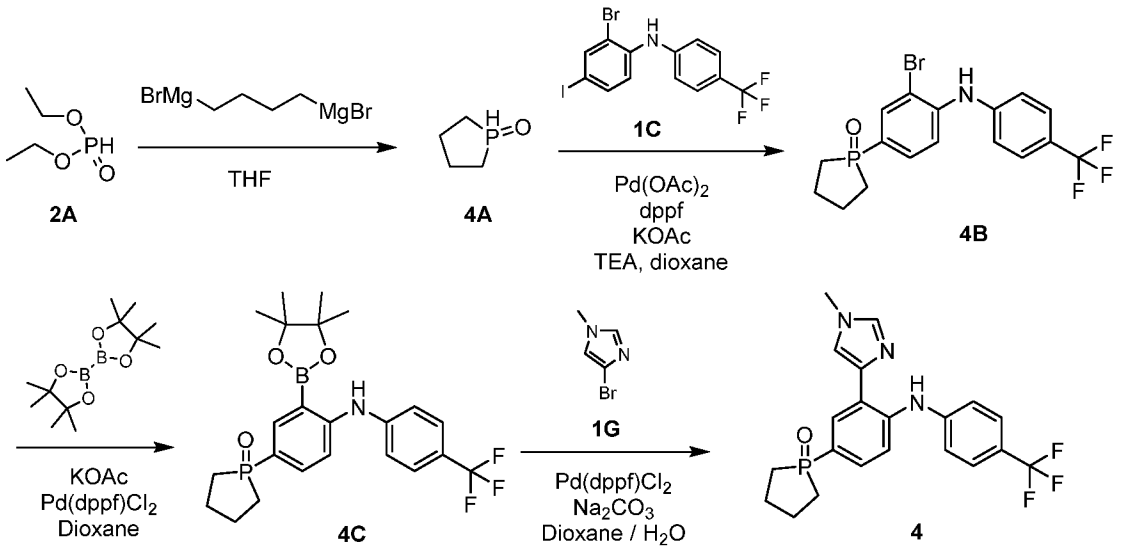
4-Diethylphosphoryl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-[4-(trifluoromethyl)phenyl]aniline (3C)

[00372] To a solution of intermediate **3B** (140 mg, 0.33 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (126.9 mg, 0.50 mmol, 1.5 *eq*) and KOAc (65.4 mg, 0.66 mmol, 2 *eq*) in dioxane (2 mL) was added $Pd(dppf)Cl_2$ (12.1 mg, 16.6 umol, 0.05 *eq*), and then the reaction mixture was stirred at 90 °C for 4 hours under N_2. Intermediate **3C** (150 mg, crude) was obtained as black solution, which was used in the next step without further purification.

4-Diethylphosphoryl-2-(1-methylimidazol-4-yl)-*N*-[4-(trifluoromethyl)phenyl]aniline (Compound 3)

[00373] To a solution of intermediate **3C** (150 mg, 0.32 mmol, 1 *eq*), 4-bromo-1-methyl-imidazole (**1G**, 77.5 mg, 0.48 mmol, 1.5 *eq*) and Na_2CO_3 (68.0 mg, 0.64 mmol, 2 *eq*) in dioxane (2.5 mL) and H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (11.7 mg, 16.0 umol, 0.05 *eq*) under N_2. The suspension was degassed under vacuum and purged with N_2 several times. The mixture was stirred at 90°C for 4 hours under N_2. The reaction mixture was concentrated under reduced pressure. The 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*-TLC (DCM: MeOH = 10:1) to give a residue as a crude product, which was purified by p*rep*-HPLC (column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water (0.05% HCl)-ACN]; B%: 15%-45%, 6.5min) to afford **Compound 3** (3.62 mg, 2.4% yield, 99% purity, HCl) as a whtie solid. LCMS (ESI): RT = 0.710 min, mass calcd for $C_{21}H_{23}F_3N_3OP$ 421.15 m/z, found 422.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.99 (s, 1H), 7.88 - 7.80 (m, 2H), 7.78 - 7.71 (m, 1H), 7.61 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 3.98 (s, 3H), 2.22 - 1.98 (m, 4H), 1.14 (td, *J* = 7.7, 17.2 Hz, 6H).

Example 4: 1-(3-(1-Methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phospholane 1-oxide (Compound 4)



1phospholane 1-oxide (4A)

[00374] A solution of 1-ethoxyphosphonoyloxyethane (**2A**, 1 g, 7.24 mmol, 0 .93 mL, 1 *eq*) in THF (10 mL) was added to a solution of bromo-[4-(bromomagnesio)butyl]magnesium (0.57 M,

18.92 mL, 1.5 *eq*) at 0 °C, and then the reaction mixture was allowed to warm up to 65 °C for 2 hours. The reaction mixture was quenched with MeOH (300 mL) at 0 °C, and then the suspension was filtered. The filtrate was concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (DCM: MeOH = 1:0 to 10:1) to give intermediate **4A** (132 mg, 1.27 mmol, 17.5% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 6.90 (br s, 1H), 2.09 - 1.97 (m, 4H), 1.86 - 1.74 (m, 4H).

2-Bromo-4-(1-oxo-1phospholan-1-yl)-*N*-[4-(trifluoromethyl)phenyl]aniline (4B)

[00375] A solution of $Pd_2(dba)_3$ (31.0 mg, 33.9 umol, 0.05 *eq*) and Xantphos (39.2 mg, 67.8 umol, 0.1 *eq*) in dioxane (2 mL) was stirred at 25 °C for 20 min. A solution of intermediate **1C** (300 mg, 0.67 mmol, 1 *eq*), intermediate **4A** (70.6 mg, 0.67 mmol, 1 *eq*) and TEA (103.0 mg, 1.02 mmol, 0.14 mL, 1.5 *eq*) in dioxane (3 mL) was added dropwise, and then the reaction mixture was stirred at 25 °C for 16 hours. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (15 mL) and the resultant mixture was extracted with EtOAc (30 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 column chromatography on silica gel (ethyl acetate: methol = 1:0 to 10:1) to give intermediate **4B** (205 mg, 475.50 umol, 70.06% yield, 97% purity) as a brown solid.

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

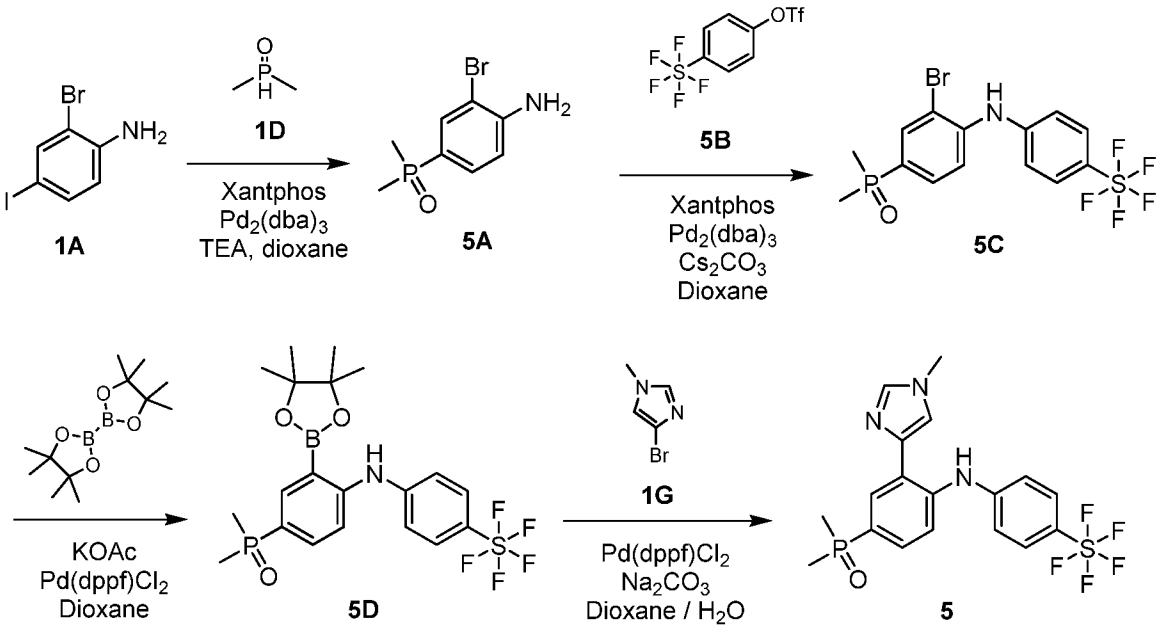
[00376] To a solution of intermediate **4B** (80 mg, 0.19 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (242.8 mg, 0.95 mmol, 5 *eq*) and KOAc (37.5 mg, 0.38 mmol, 2 *eq*) in dioxane (1.5 mL) was added $Pd(dppf)Cl_2$ (14.0 mg, 19.1 umol, 0.1 *eq*), and then the reaction mixture was stirred at 90 °C for 6 hours under N_2. The crude product of intermediate **4C** (89 mg, crude) was obtained as a black solution, which was used in the next step without further purification.

2-(1-Methylimidazol-4-yl)-4-(1-oxo-1phospholan-1-yl)-*N*-[4-(trifluoromethyl)phenyl]aniline (Compound 4)

[00377] To a solution of intermediate **4C** (89 mg, 0.19 mmol, 1 *eq*), 4-bromo-1-methyl-imidazole (**1G**, 46.2 mg, 0.28 mmol, 1.5 *eq*) and Na_2CO_3 (40.5 mg, 0.38 mmol, 2 *eq*) in dioxane (2.5 mL) and H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (7.0 mg, 9.5 umol, 0.05 *eq*) under N_2. The

suspension was degassed under vacuum and purged with N_2 several times. The mixture was stirred at 90°C for 16 hours under N_2. The reaction mixture was concentrated under reduced pressure. The 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 column chromatography on silica gel (DCM: MeOH = 1:0 to 20:1) to give a crude product, which was purified by *prep*-HPLC (column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water (0.05%HCl)-ACN]; B%: 15%-45%, 6.5min) to afford **Compound 4** (4.90 mg, 10.5 umol, 5.51% yield, 98% purity, HCl) as a white solid. LCMS (ESI): RT = 0.780 min, mass calcd for $C_{21}H_{21}F_3N_3OP$ 419.14 m/z, found 420.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3CD) δ 9.00 (s, 1H), 7.93 - 7.83 (m, 2H), 7.78 (br t, *J* = 9.3 Hz, 1H), 7.62 (br d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.22 (br d, *J* = 8.0 Hz, 2H), 3.99 (s, 3H), 2.20 (br d, *J* = 8.3 Hz, 4H), 2.05 (br s, 4H).

Example 5: Dimethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(pentafluoro-λ⁶-sulfaneyl)phenyl)amino)phenyl)phosphine oxide (Compound 5)



2-bromo-4-dimethylphosphoryl-aniline

[00378] A solution of $Pd_2(dba)_3$ (122.9 mg, 0.13 mmol, 0.05 *eq*) and Xantphos (155.3 mg, 0.26 mmol, 0.1 *eq*) in dioxane (1 mL) was stirred at 25 °C for 20 min. A solution of 2-bromo-4-iodo-aniline (**1A**, 800 mg, 2.69 mmol, 1 *eq*), methylphosphonoylmethane (**1D**, 419.1 mg, 5.37 mmol, 2 *eq*) and TEA (407.5 mg, 4.03 mmol, 0.56 mL, 1.5 *eq*) in Dioxane (1 mL) was added dropwise, and then the reaction mixture was stirred at 25 °C for 16 hours. The reaction mixture was concentrated under reduced pressure. The 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 column chromatography on silica gel (EA: MeOH = 1:0 to 10:1) to give intermediate **5A** (553 mg, 2.23 mmol, 83.0% yield) as yellow oil.

2-bromo-4-dimethylphosphoryl-*N*-[4-(pentafluoro-sulfanyl)phenyl]aniline

[00379] To a solution of intermediate **5A** (230 mg, 0.92 mmol, 1 *eq*), [4-(pentafluoro-sulfanyl)phenyl] trifluoromethanesulfonate (**5B**, 326.5 mg, 0.92 mmol, 1 *eq*), Xantphos (53.6 mg, 92.7 umol, 0.1 *eq*) and Cs_2CO_3 (453.1 mg, 1.39 mmol, 1.5 *eq*) in dioxane (2 mL) was added $Pd_2(dba)_3$ (42.4 mg, 46.3 umol, 0.05 *eq*) under N_2. The suspension was degassed under vacuum and purged with N_2 several times. The mixture was stirred under N_2 at 100°C for 1 hour. The reaction mixture was concentrated under reduced pressure. The 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*-TLC (DCM: MeOH = 10:1) to give intermediate **5C** (260 mg, 0.46 mmol, 49.8% yield, 80% purity) as a light yellow solid.

4-dimethylphosphoryl-*N*-[4-(pentafluoro-λ⁶-sulfanyl)phenyl]-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

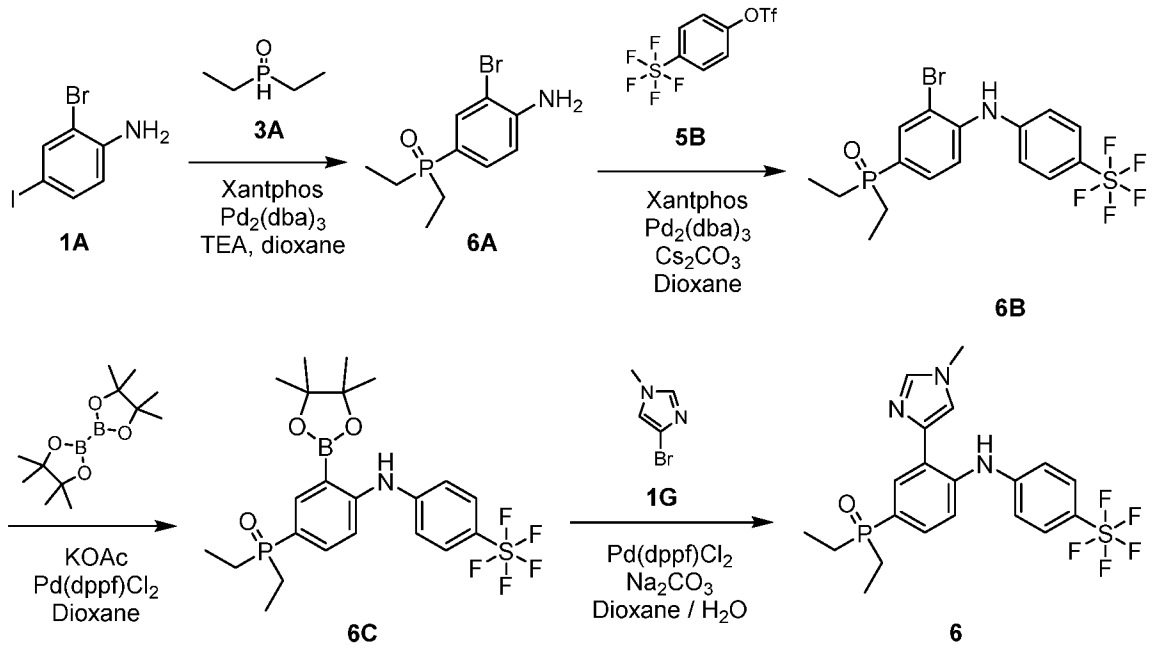
[00380] To a solution of intermediate **5C** (150 mg, 0.33 mmol, 1 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (126.9 mg, 0.49 mmol, 1.5 eq) in dioxane (1 mL) was added $Pd(dppf)Cl_2$ (24.3 mg, 33.3 umol, 0.1 eq) and KOAc (65.40 mg, 0.66 mmol, 2.0 eq). The reaction mixture was stirred at 90 °C for 2 hr under N_2. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (DCM: MeOH = 100/1 to 101) to give intermediate **5D** (120 mg, 0.24 mmol, 72% yield) as a black solid, which was used in the next step without further purification.

4-dimethylphosphoryl-2-(1-methylimidazol-4-yl)-*N*-[4-(pentafluoro-λ⁶-sulfanyl)phenyl]aniline (Compound 5)

[00381] To a solution of intermediate **5D** (60 mg, 0.12 mmol, 1 eq) and **1G** (48.5 mg, 030 mmol, 2.5 eq) in H_2O (0.1 mL) and dioxane (1 mL) was added Na_2CO_3 (25.5 mg, 0.24 mmol, 2.0 eq) and $Pd(dppf)Cl_2$ (8.8 mg, 12.0 umol, 0.1 eq). The mixture was stirred at 90 °C for 16 hr under N_2. The reaction mixture was filtered and concentrated under reduced pressure to give a residue.

The residue was purified by *prep*-HPLC (column: 3_Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 15%-45%, 6.5 min) to afford **Compound 5** (6.96 mg, 14.1 umol, 11.7% yield, 99% purity, HCl) as a white solid. LCMS (ESI): RT = 0.768 min, mass calcd for: $C_{18}H_{19}F_5N_3OPS$ 451.09 m/z found 452.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.88 (s, 1H), 8.16 - 7.96 (m, 2H), 7.79 (t, J = 9.0 Hz, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.64 - 7.51 (m, 1H), 7.11 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 1.71 (d, J = 13.6 Hz, 6H).

Example 6: Diethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(pentafluoro-λ^6-sulfaneyl)phenyl)amino)phenyl)phosphine oxide (Compound 6)



(4-Amino-3-bromophenyl)diethylphosphine oxide (6A)

[00382] Intermediate **6A** was prepared using the procedure for intermediate **5A** using **3A** in lieu of **1D**.

2-Bromo-4-diethylphosphoryl-*N*-[4-(pentafluoro-sulfanyl)phenyl]aniline (6B)

[00383] To a solution of intermediate **6A** (50 mg, 0.18 mmol, 1 *eq*), [4-(pentafluoro-sulfanyl)phenyl] trifluoromethanesulfonate (**5B**, 63.7 mg, 0.18 mmol, 1 *eq*), Xantphos (10.4 mg, 18.1 umol, 0.1 *eq*) and Cs_2CO_3 (88.5 mg, 0.27 mmol, 1.5 *eq*) in dioxane (1 mL) was added $Pd_2(dba)_3$ (8.2 mg, 9.0 umol, 0.05 *eq*) under N_2. The suspension was degassed under vacuum and purged with N_2 several times. The mixture was stirred under N_2 at 100°C for 1 hour. The reaction mixture was concentrated under reduced pressure. The 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 column chromatography over silica gel (DCM: MeOH = 1:0 to 10:1) to give intermediate **6B** (45 mg, 80.9 umol, 44.6% yield, 86% purity) as a light yellow oil. LCMS (ESI): RT = 0.911 min, mass calcd for: $C_{16}H_{18}BrF_5NOPS$ 477.00 m/z found 478.0 $[M+H]^+$;

4-Diethylphosphoryl-*N*-[4-(pentafluoro-sulfanyl)phenyl]-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[00384] To a solution of intermediate **6B** (45 mg, 94.0 umol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (35.8 mg, 0.14 mmol, 1.5 *eq*) and KOAc (18.4 mg, 0.18 mmol, 2 *eq*) in dioxane (2 mL) was added $Pd(dppf)Cl_2$ (3.4 mg, 4.7 umol, 0.05 *eq*), and then the reaction mixture was stirred at 90 °C for 2 hours under N_2. Intermediate **6C** (49 mg, 93.2 umol, 99.1% yield) was obtained as black solution, which was used in the next step without further purification.

2-[4-methoxy-3-(2-methyltetrazol-5-yl)phenyl]-3-[4-(trifluoromethyl)phenyl]sulfanyl-pyrazine

[00385] To a solution of intermediate **6C** (49 mg, 93.2 umol, 1 *eq*), 4-bromo-1-methyl-imidazole (**1G**, 22.5 mg, 0.14 mmol, 1.5 *eq*) and Na_2CO_3 (19.7 mg, 0.18 mmol, 2 *eq*) in dioxane (2 mL) and H_2O (0.4 mL) was added $Pd(dppf)Cl_2$ (3.4 mg, 4.6 umol, 0.05 *eq*) under N_2. The suspension was degassed under vacuum and purged with N_2 several times. The mixture was stirred at 90 °C for 16 hours under N_2. The reaction mixture was concentrated under reduced pressure. The 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: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.05%HCl)-ACN]; B%: 20%-50%, 6.5 min) to afford **Compound 6** (2.42 mg, 4.55 umol, 4.88% yield, 97% purity, HCl) as a white solid. LCMS (ESI): RT = 0.799 min, mass calcd for: $C_{20}H_{23}F_5N_3OPS$ 479.12 m/z found 480.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.00 (s, 1H), 7.91 - 7.62 (m, 6H), 7.15 (br d, J = 8.3 Hz, 2H), 3.98 (s, 3H), 2.09 (br s, 4H), 1.14 (br s, 6H).

II. Biological Evaluation

Example A1: YAP Reporter Assay

[00386] 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.

[00387] 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.

[00388] 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).

[00389] 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.

[00390] 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.

[00391] 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.

[00392] 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.

[00393] 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.

[00394] 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 No.	Compound Name	Firefly Luciferase IC_{50} (µM)
1	Dimethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphine oxide	A
2	Diethyl (3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphonate	A
3	Diethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phosphine oxide	A
4	1-(3-(1-Methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)phospholane 1-oxide	A
5	Dimethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(pentafluoro-λ^6-sulfaneyl)phenyl)amino)phenyl)phosphine oxide	A
6	Diethyl(3-(1-methyl-1H-imidazol-4-yl)-4-((4-(pentafluoro-λ^6-sulfaneyl)phenyl)amino)phenyl)phosphine oxide	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

[00395] 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

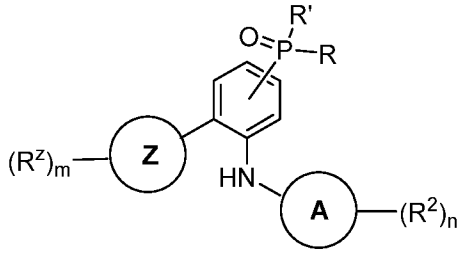
[00396] Cancer cell lines are plated in 384-well plates 24 hrs before drug treatment. Post incubation for various time periods with the test compounds, starting from 3 μM (final concentration in assay plate), 1:3 dilution, and 10 points in duplicates, the number of viable cells and proliferative cells 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.

[00397] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

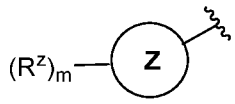
WHAT IS CLAIMED IS:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein,



is a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl ring containing at least one N atom, or a substituted or unsubstituted monocyclic heteroaryl ring containing at least one N atom;

each R^z 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, -L^1-Y^1, or -L^2-L^3-Y^2;

m is 0, 1, 2, 3, 4, or 5;

L^1 is substituted or unsubstituted C_1-C_6alkylene, substituted or unsubstituted C_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2- C_{10}heterocycloalkylene;

Y^1 is 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;

L^2 is absent, substituted or unsubstituted C_1-C_6alkylene, substituted or unsubstituted C_3-C_{10}cyclolalkylene, or substituted or unsubstituted 3- to 10-membered heterocycloalkylene;

L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -O-NR^3(C=O)-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -NR^3(SO_2)-,-(SO_2)NR^3-, -(SO_2)NR^3-(C=O)-, -(C=O)-NR^3(SO_2)-, -(SO_2)NR^3-(C=O)O-, -O(C=O)-NR^3(SO_2)-, -NR^3(SO_2)NR^3-(C=O)-, -(C=O)-NR^3(SO_2)NR^3-, -O(C=O)-NR^3(SO_2)-NR^3-, or -NR^3(SO_2)NR^3-(C=O)O-;

each R^3 is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl;

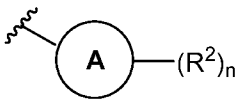
Y^2 is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-

membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

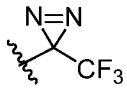
or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

R and R' are each independently 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_1-C_6alkoxy, 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 and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.



is substituted or unsubstituted phenyl or substituted or unsubstituted cyclohexyl;

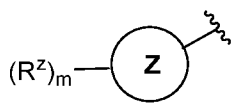
each R^2 is independently hydrogen, halogen, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-S(R^4)_5$, $-(S{=}O)R^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6haloalkyl, substituted 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, substituted or unsubstituted heteroaryl, or 

;

n is 0, 1, 2, 3, 4, or 5; and

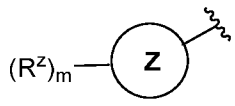
each R^4 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

2. The compound or pharmaceutically acceptable salt of claim 1, wherein:

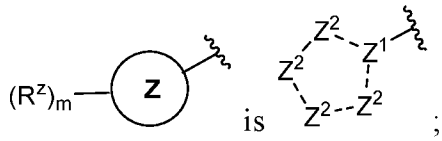


is a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl ring containing at least one N atom.

3. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein:

 is a substituted or unsubstituted monocyclic 5-membered heterocycloalkyl ring containing 1-4 N atoms, 0-2 O atoms, and 0-2 S atoms.

4. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein:

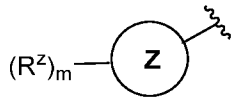
 ;

Z^1 is –N-, –CH-, or -C-;

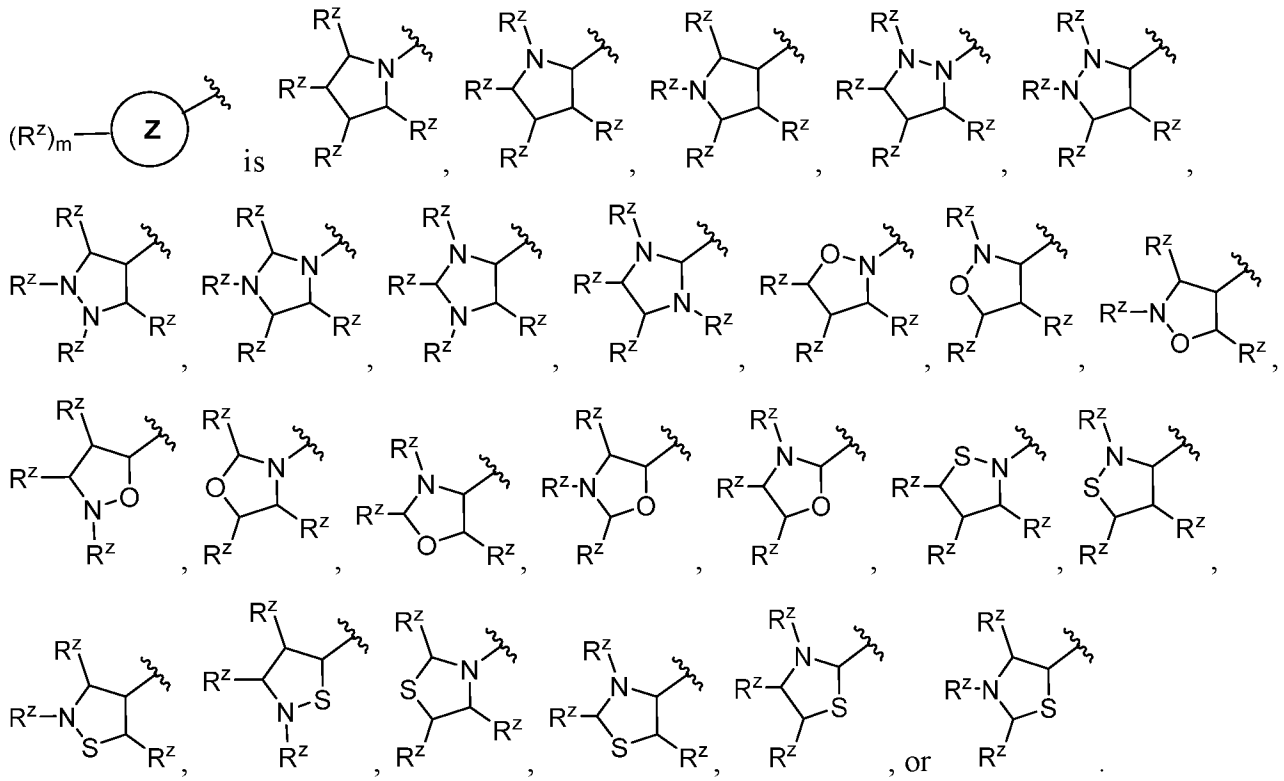
each Z^2 is independently -CR^z, -CHR^z-, -$C(R^z)_2$-, -NR^z-, -N-, -O-, or –S-;

each - - is independently a single or double bond.

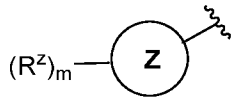
5. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein:

 is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

6. The compound or pharmaceutically acceptable salt of claim 5, wherein:

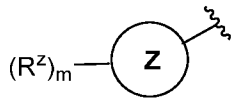


7. The compound or pharmaceutically acceptable salt of claim 1, wherein:



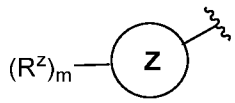
is a substituted or unsubstituted monocyclic heteroaryl ring containing at least one N atom.

8. The compound or pharmaceutically acceptable salt of claim 7, wherein:



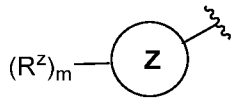
is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing at least one N atom.

9. The compound or pharmaceutically acceptable salt of claim 8, wherein:



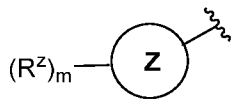
is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 1 N atom.

10. The compound or pharmaceutically acceptable salt of claim 8, wherein:



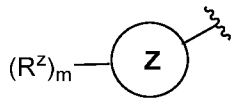
is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 2 N atoms.

11. The compound or pharmaceutically acceptable salt of claim 8, wherein:



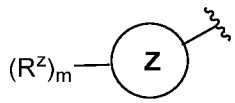
is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 3 N atoms.

12. The compound or pharmaceutically acceptable salt of claim 8, wherein:



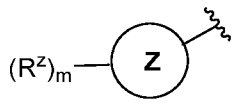
is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring containing 4 N atoms.

13. The compound or pharmaceutically acceptable salt of claim 7, wherein:

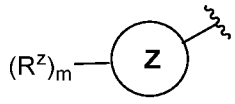


is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazoyl, substituted or unsubstituted tetrazoyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

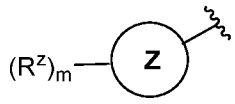
14. The compound or pharmaceutically acceptable salt of claim 13, wherein:


is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, or substituted or unsubstituted isoxazolyl.

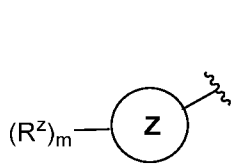
15. The compound or pharmaceutically acceptable salt of claim 13 or 14, wherein:

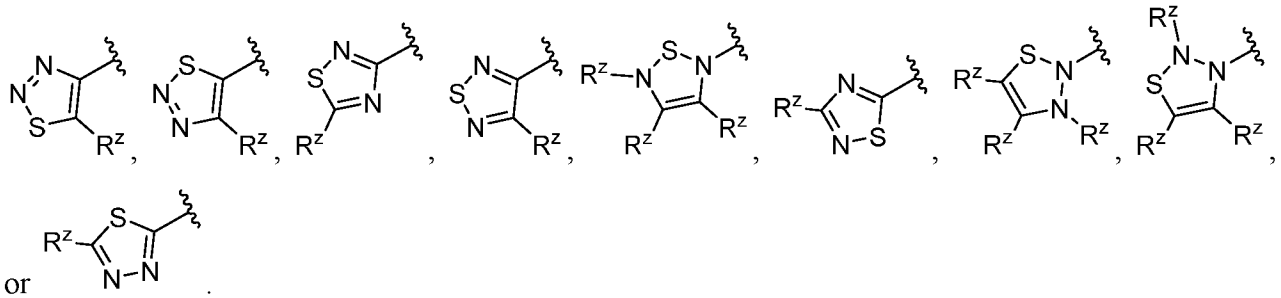

is substituted or unsubstituted imidazolyl or substituted or unsubstituted pyrazolyl.

16. The compound or pharmaceutically acceptable salt of any one of claims 13-15, wherein:


is substituted or unsubstituted imidazolyl.

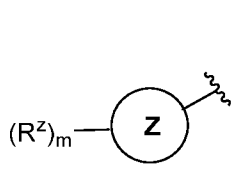
17. The compound or pharmaceutically acceptable salt of claim 13, wherein:

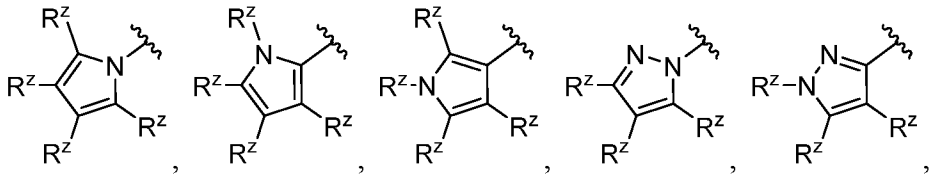

is

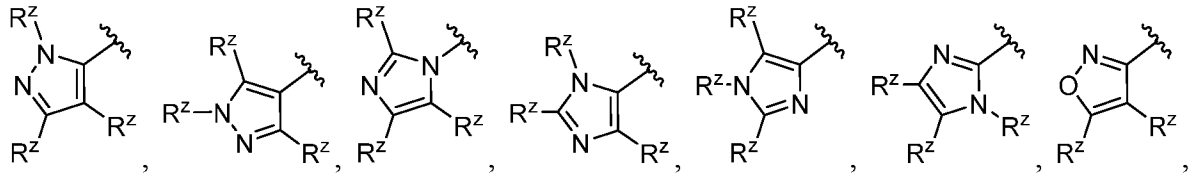


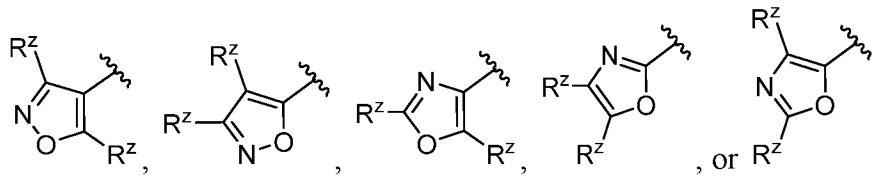
or .

18. The compound or pharmaceutically acceptable salt of claim 17, wherein:



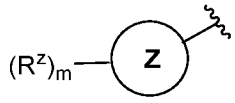
is 



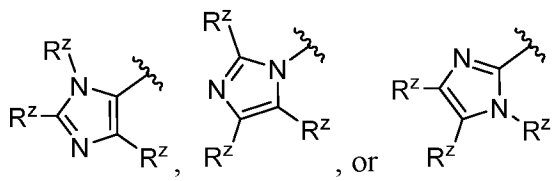


, or .

19. The compound or pharmaceutically acceptable salt of claim 17 or 18, wherein:

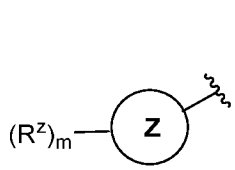


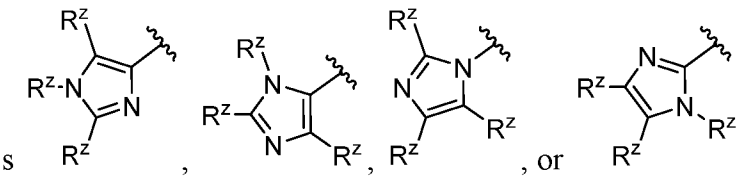
is 



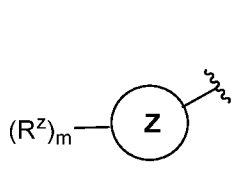
, or .

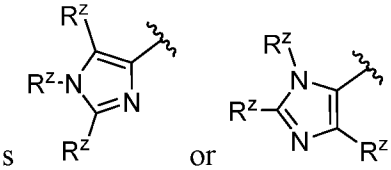
20. The compound or pharmaceutically acceptable salt of any one of claims 17-19, wherein:



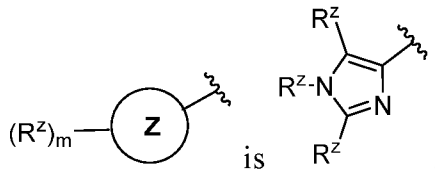
is  .

21. The compound or pharmaceutically acceptable salt of any one of claims 17-20, wherein:

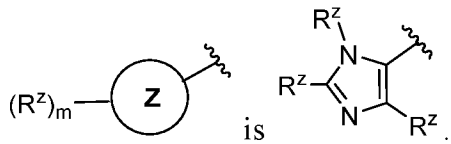


is  .

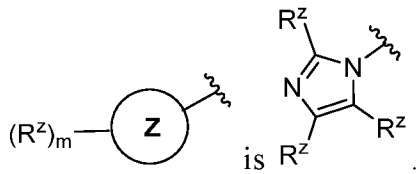
22. The compound or pharmaceutically acceptable salt of claim 21, wherein:



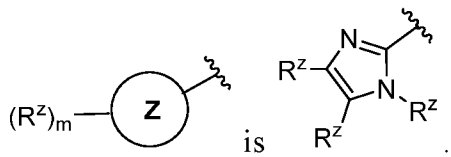
23. The compound or pharmaceutically acceptable salt of claim 21, wherein:



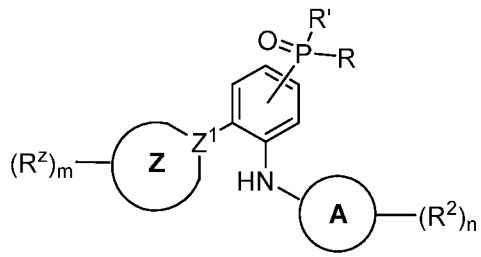
24. The compound or pharmaceutically acceptable salt of any one of claims 17-20, wherein:



25. The compound or pharmaceutically acceptable salt of any one of claims 17-20, wherein:



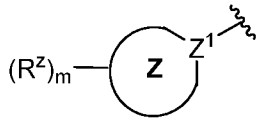
26. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has the structure of Formula (Ia)



Formula (Ia)

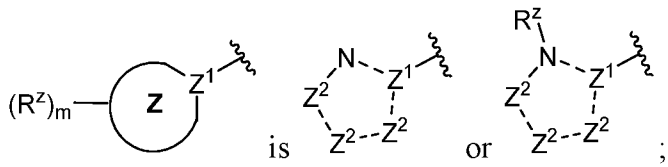
wherein: Z^1 is –N-, –CH-, or -C-.

27. The compound or pharmaceutically acceptable salt of claim 26, wherein:



is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom, and the at least one N atom is adjacent to Z^1.

28. The compound or pharmaceutically acceptable salt of claim 26 or 27, wherein:



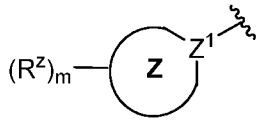
Z^1 is –N-, –CH-, or -C-;

each Z^2 is independently CR^z, NR^z, N, O, or S;

each -- is independently a single or double bond; and

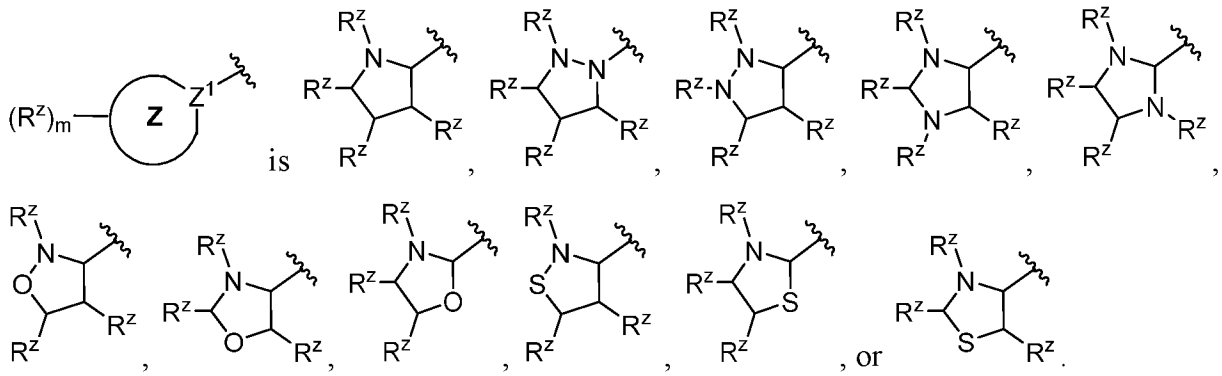
with the provision that the 5-membered heterocyclic ring contains at least one N atom.

29. The compound or pharmaceutically acceptable salt of claim 26 or 27, wherein:

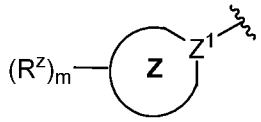


is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

30. The compound or pharmaceutically acceptable salt of claim 29, wherein:

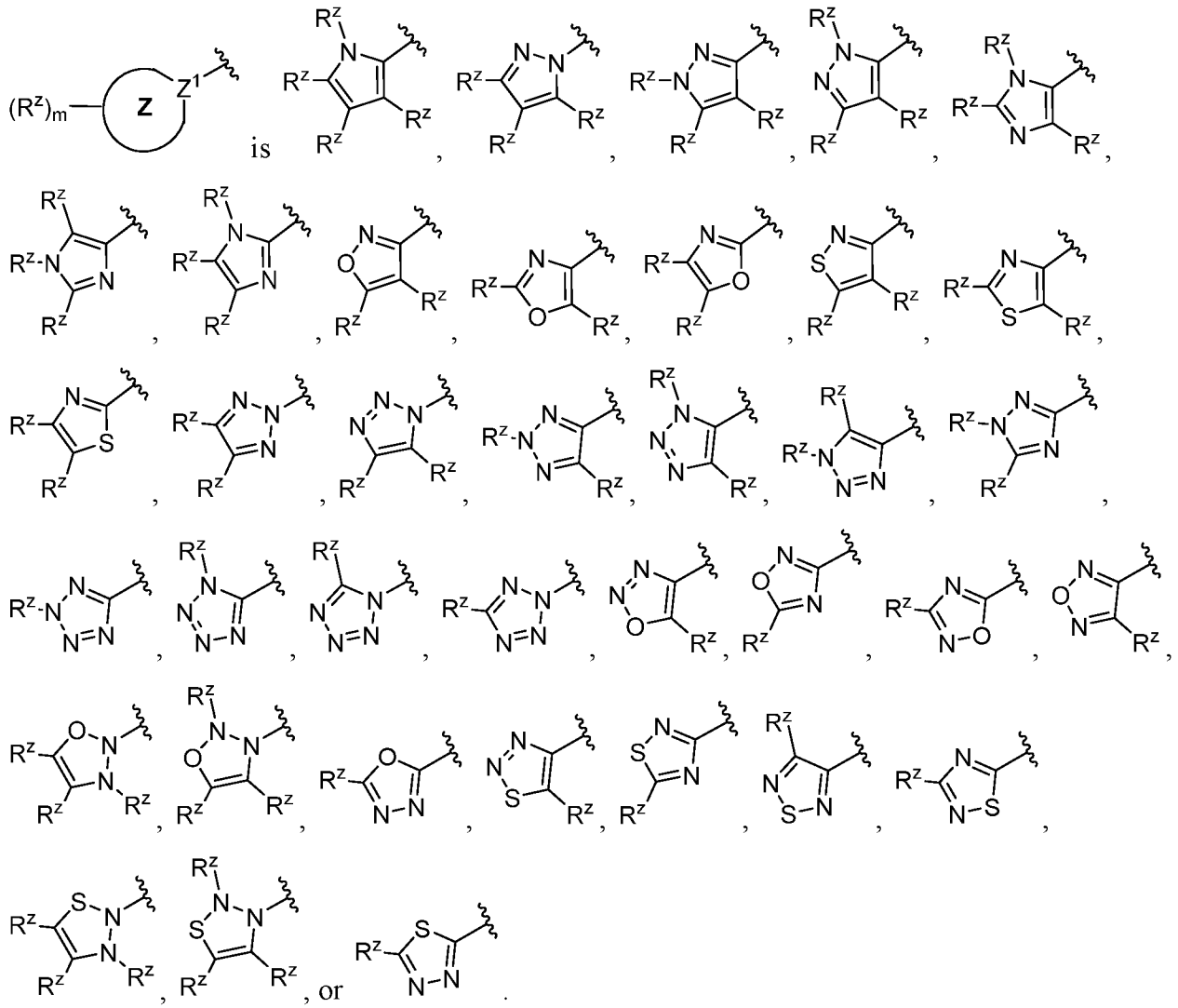


31. The compound or pharmaceutically acceptable salt of claim 26, wherein:

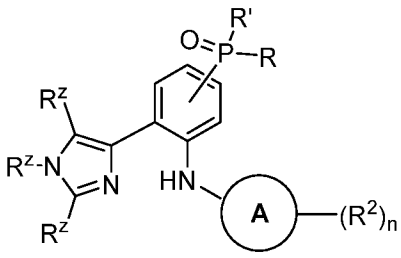


is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazoyl, substituted or unsubstituted tetrazoyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

32. The compound or pharmaceutically acceptable salt of claim 26, wherein:

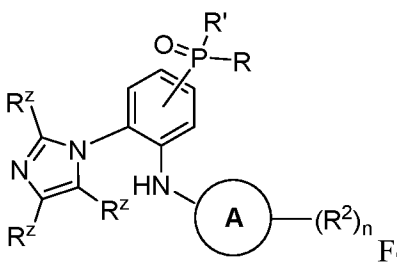


33. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has a structure of Formula (II-a):



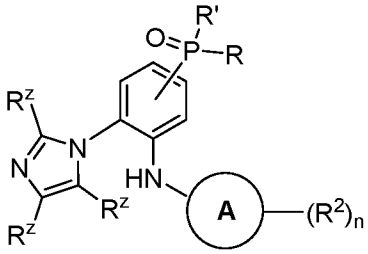
Formula (II-a).

34. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has a structure of Formula (II-b):



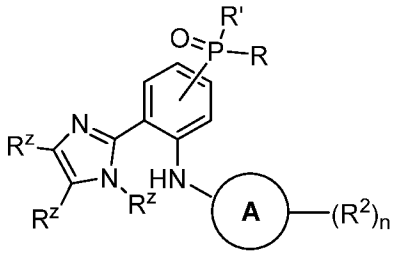
Formula (II-b).

35. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has a structure of Formula (II-c):



Formula (II-c).

36. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has a structure of Formula (II-d):



Formula (II-d).

37. The compound or pharmaceutically acceptable salt of any one of claims 1-36, wherein:

each R^z 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 aryl, or substituted or unsubstituted heteroaryl.

38. The compound or pharmaceutically acceptable salt of claim 37, wherein:

each R^z is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted aryl.

39. The compound or pharmaceutically acceptable salt of claim 37 or 38, wherein:

each R^z is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl.

40. The compound or pharmaceutically acceptable salt of claim 37 or 38, wherein:

each R^z is independently hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

41. The compound or pharmaceutically acceptable salt of claim 40, wherein:

each R^z is independently hydrogen, -F, -Cl, - methyl, ethyl, n-propyl, iso-propyl, or cyclopropyl.

42. The compound or pharmaceutically acceptable salt of claim 40, wherein:

each R^z is methyl.

43. The compound or pharmaceutically acceptable salt of any one of claims 1-36, wherein R^z is $-L^1-Y^1$.

44. The compound or pharmaceutically acceptable salt of claim 43, wherein:
L^1 is substituted or unsubstituted C_1-C_4alkylene; and
Y^1 is substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

45. The compound or pharmaceutically acceptable salt of any one of claims 1-36, wherein R^z is $-L^2-L^3-Y^2$.

46. The compound or pharmaceutically acceptable salt of claim 45, wherein:
L^2 is substituted or unsubstituted C_1-C_6alkylene;
L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -NR^3(SO_2)-, -(SO_2)NR^3-, -(SO_2)NR^3-(C=O)-, -(SO_2)NR^3-(C=O)O-, -NR^3(SO_2)NR^3-(C=O)-, or -NR^3(SO_2)NR^3-(C=O)O-;
each R^3 is independently H or substituted or unsubstituted C_1-C_6alkyl; and
Y^2 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

47. The compound or pharmaceutically acceptable salt of claim 45, wherein:
L^2 is absent;
L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-,
-NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -NR^3(SO_2)-,
-(SO_2)NR^3-, -(SO_2)NR^3-(C=O)-, -(SO_2)NR^3-(C=O)O-, -NR^3(SO_2)NR^3-(C=O)-,
or -NR^3(SO_2)NR^3-(C=O)O-;
each R^3 is independently H or substituted or unsubstituted C_1-C_6alkyl; and
Y^2 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

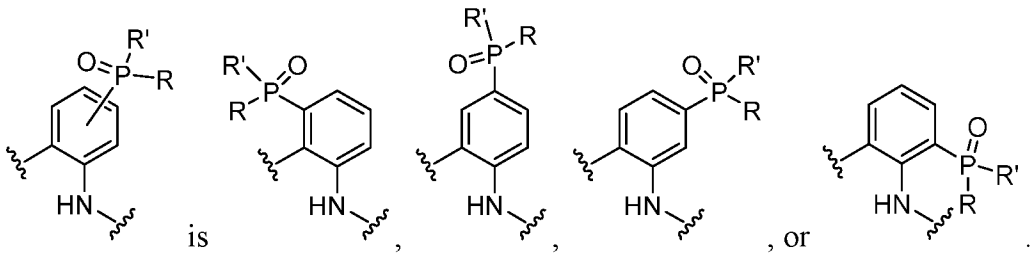
48. The compound or pharmaceutically acceptable salt of any one of claims 1-47, wherein m is 1, 2, or 3.

49. The compound or pharmaceutically acceptable salt of claim 48, wherein m is 1 or 2.

50. The compound or pharmaceutically acceptable salt of claim 48, wherein m is 1.

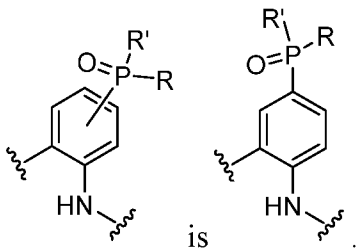
51. The compound or pharmaceutically acceptable salt of any one of claims 1-42, wherein m is 1 and R^z is methyl.

52. The compound or pharmaceutically acceptable salt of any one of claims 1-51, wherein:



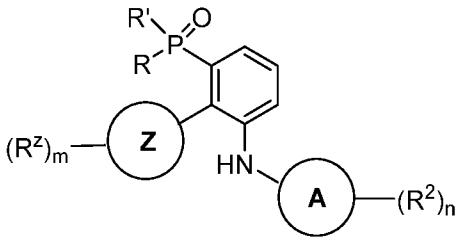
is , , , or .

53. The compound or pharmaceutically acceptable salt of claim 52, wherein:



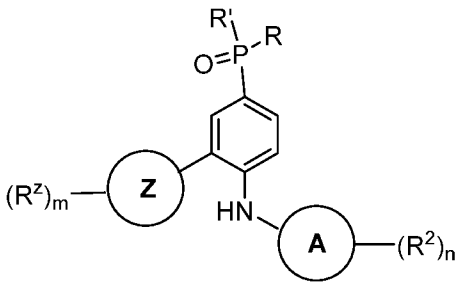
is .

54. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has a structure of Formula (III-a):



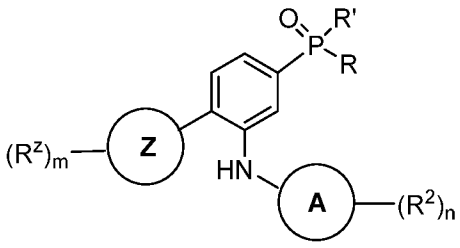
Formula (III-a).

55. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has a structure of Formula (III-b):



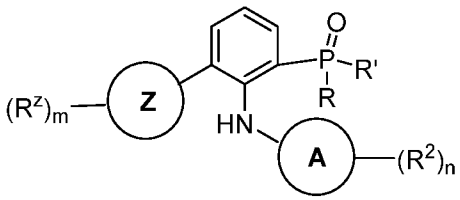
Formula (III-b).

56. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has a structure of Formula (III-c):



Formula (III-c).

57. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has a structure of Formula (III-d):



Formula (III-d).

58. The compound or pharmaceutically acceptable salt of any one of claims 1-57, wherein:
R and R' are each independently 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_1-C_6alkoxy, 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.

59. The compound or pharmaceutically acceptable salt of claim 58, wherein:
R and R' are each independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

60. The compound or pharmaceutically acceptable salt of claim 58, wherein:
R and R' are each independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted aryl.

61. The compound or pharmaceutically acceptable salt of claim 58, wherein:
R and R' are each independently substituted or unsubstituted C_1-C_6alkyl or substituted or unsubstituted C_1-C_6alkoxy.

62. The compound or pharmaceutically acceptable salt of claim 58, wherein:
R and R' are each independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, or phenyl.

63. The compound or pharmaceutically acceptable salt of claim 58, wherein:

R and R' are each independently methyl, ethyl, n-propyl, methoxy, ethoxy, n-propoxy, or iso-propoxy.

64. The compound or pharmaceutically acceptable salt of claim 63, wherein:
R and R' are each methyl.

65. The compound or pharmaceutically acceptable salt of claim 63, wherein:
R and R' are each ethyl.

66. The compound or pharmaceutically acceptable salt of claim 58, wherein:
R and R' are each methoxy.

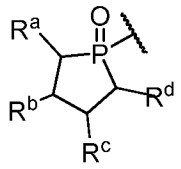
67. The compound or pharmaceutically acceptable salt of claim 58, wherein:
R and R' are each ethoxy.

68. The compound or pharmaceutically acceptable salt of any one of claims 1-57, wherein:
R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

69. The compound or pharmaceutically acceptable salt of claim 68, wherein:
R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 5- or 6-membered heterocycloalkyl.

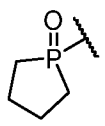
70. The compound or pharmaceutically acceptable salt of claim 68 or 69, wherein:
R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 5-membered heterocycloalkyl.

71. The compound or pharmaceutically acceptable salt of claim 70, wherein:
R and R' taken together with the phosphorus atom to which they are attached to form



; wherein R^a, R^b, R^c, and R^d are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

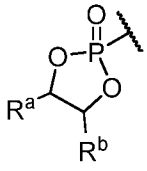
72. The compound or pharmaceutically acceptable salt of claim 71, wherein:
R and R' taken together with the phosphorus atom to which they are attached to form



.

73. The compound or pharmaceutically acceptable salt of claim 70, wherein:

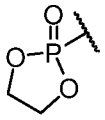
R and R' taken together with the phosphorus atom to which they are attached to form



; wherein R^a and R^b are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

74. The compound or pharmaceutically acceptable salt of claim 73, wherein:

R and R' taken together with the phosphorus atom to which they are attached to form



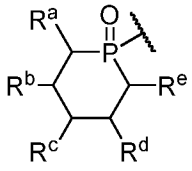
.

75. The compound or pharmaceutically acceptable salt of claim 68 or 69, wherein:

R and R' taken together with the phosphorus atom to which they are attached to form a substituted or unsubstituted P-containing 6-membered heterocycloalkyl.

76. The compound or pharmaceutically acceptable salt of claim 70, wherein:

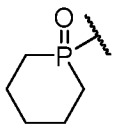
R and R' taken together with the phosphorus atom to which they are attached to form



; wherein R^a, R^b, R^c, R^d and R^e are each independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

77. The compound or pharmaceutically acceptable salt of claim 76, wherein:

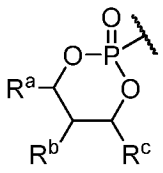
R and R' taken together with the phosphorus atom to which they are attached to form



.

78. The compound or pharmaceutically acceptable salt of claim 70, wherein:

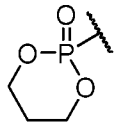
R and R' taken together with the phosphorus atom to which they are attached to form



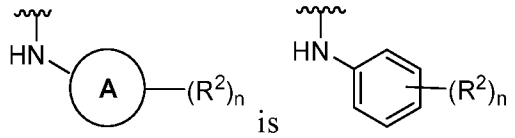
; wherein R^a, R^b, and R^c are each independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl.

79. The compound or pharmaceutically acceptable salt of claim 78, wherein:

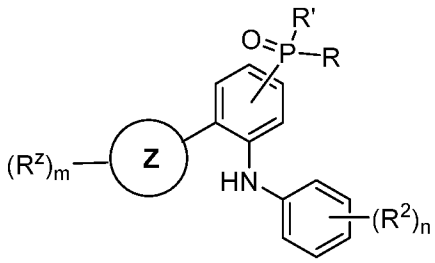
R and R' taken together with the phosphorus atom to which they are attached to form



80. The compound or pharmaceutically acceptable salt of any one of claims 1-79, wherein:

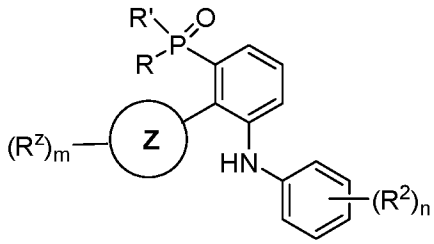


81. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has the structure of Formula (IV):



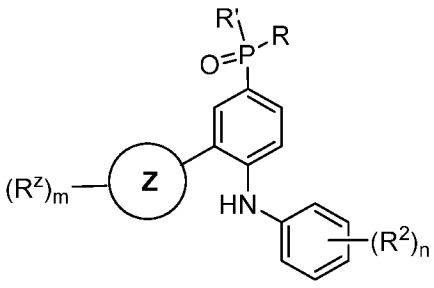
Formula (IV).

82. The compound or pharmaceutically acceptable salt of claim 81, wherein the compound has the structure of Formula (IV-a):



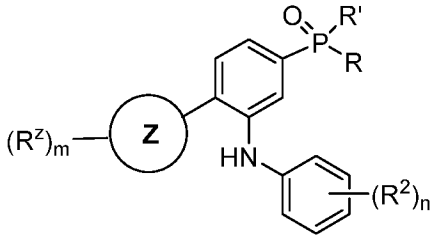
Formula (IV-a).

83. The compound or pharmaceutically acceptable salt of claim 81, wherein the compound has the structure of Formula (IV-b):



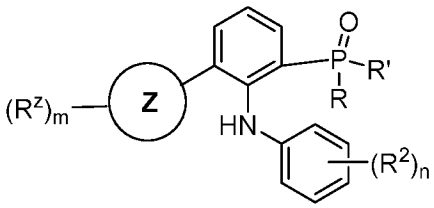
Formula (IV-b).

84. The compound or pharmaceutically acceptable salt of claim 81, wherein the compound has the structure of Formula (IV-c), or a pharmaceutically acceptable salt thereof:



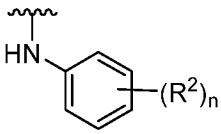
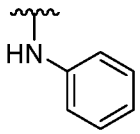
Formula (IV-c).

85. The compound or pharmaceutically acceptable salt of claim 81, wherein the compound has the structure of Formula (IV-d), or a pharmaceutically acceptable salt thereof:

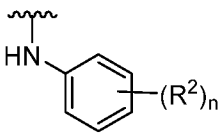
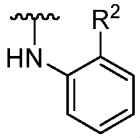
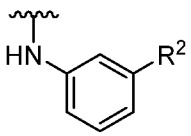
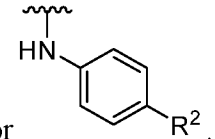


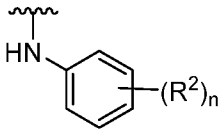
Formula (IV-d).

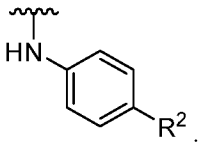
86. The compound or pharmaceutically acceptable salt of any one of claims 80-85, wherein:

 is  .

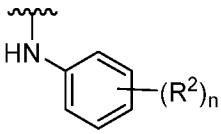
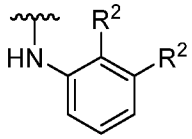
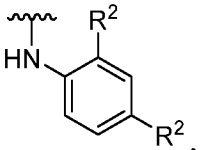
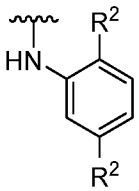
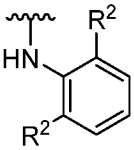
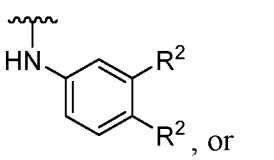
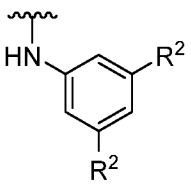
87. The compound or pharmaceutically acceptable salt of any one of claims 80-85, wherein:

 is  ,  , or  .

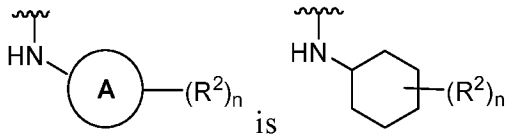
88. The compound or pharmaceutically acceptable salt of claim 87, wherein: 

is  .

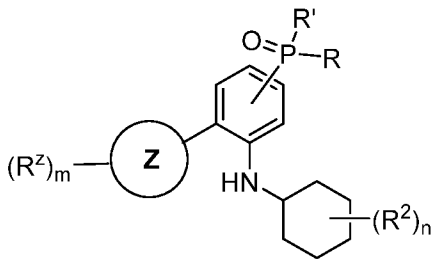
89. The compound or pharmaceutically acceptable salt of any one of claims 80-85, wherein:

 is  ,  ,  ,  ,  , or  .

90. The compound or pharmaceutically acceptable salt of any one of claims 1-79, wherein:

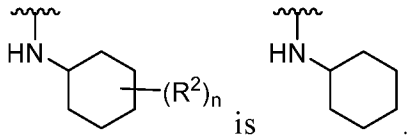


91. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has the structure of Formula (V):

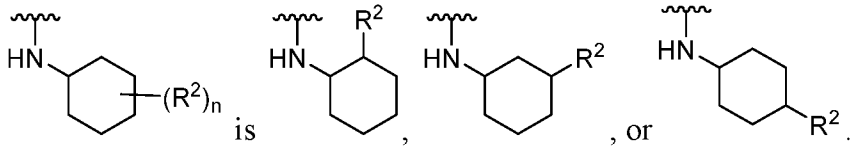


Formula (V).

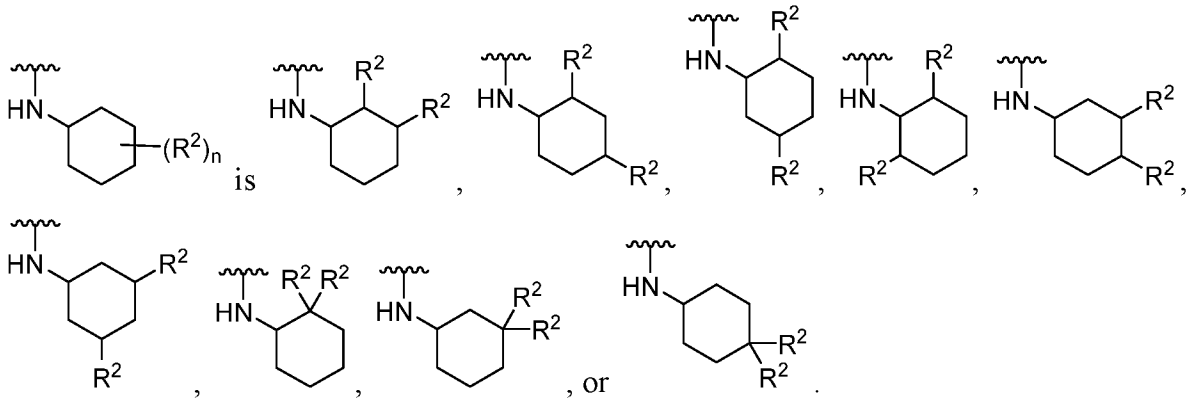
92. The compound or pharmaceutically acceptable salt of claim 90 or 91, wherein:



93. The compound or pharmaceutically acceptable salt of claim 90 or 91, wherein:



94. The compound or pharmaceutically acceptable salt of claim 90 or 91, wherein:



95. The compound or pharmaceutically acceptable salt of any one of claims 1-94, wherein:

each R^2 is independently hydrogen, halogen, nitro, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-S(R^4)_5$, $-(S=O)R^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl;

each R^4 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or

unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl.

96. The compound or pharmaceutically acceptable salt of claim 95, wherein each R^2 is independently F, Cl, Br, I, nitro, -CN, -SF_5, -SCF_3, -OCH_2F, -$OCHF_2$, -OCF_3, -$C(=O)OCH_3$ - $S(=O)_2CH_3$, - $N(CH_3)_2$, -$NH(CH_3)$, -CH_2F, -CHF_2, or -CF_3.

97. The compound or pharmaceutically acceptable salt of claim 95, wherein each R^2 is independently F, Cl, -CN, -OCF_3, -CHF_2, -SCF_3, or -CF_3.

98. The compound or pharmaceutically acceptable salt of claim 95, wherein each R^2 is independently F, Cl, -OCF_3, -CHF_2, -SCF_3, or -CF_3.

99. The compound or pharmaceutically acceptable salt of claim 95, wherein each R^2 is independently F, Cl, -SF_5, -SCF_3, or -CF_3.

100. The compound or pharmaceutically acceptable salt of claim 95, wherein each R^2 is independently F, Cl, -SF_5, -OCF_3, -SCF_3, or -CF_3.

101. The compound or pharmaceutically acceptable salt of claim 95, wherein each R^2 is -CF_3.

102. The compound or pharmaceutically acceptable salt of claim 95, wherein each R^2 is -SF_5.

103. The compound or pharmaceutically acceptable salt of claim 95, wherein each R^2 is -SCF_3.

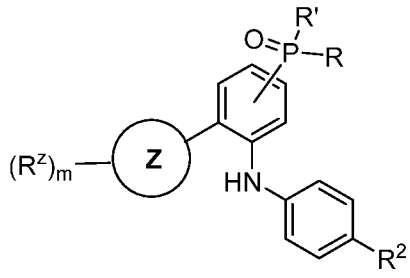
104. The compound or pharmaceutically acceptable salt of claim 95, wherein each R^2 is -OCF_3.

105. The compound or pharmaceutically acceptable salt of any one of claims 1-104, wherein n is 0, 1, or 2.

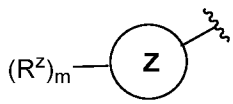
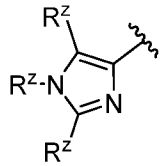
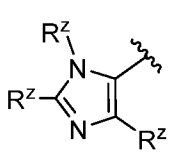
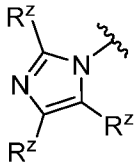
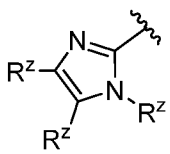
106. The compound or pharmaceutically acceptable salt of claim 105, wherein n is 1 or 2.

107. The compound or pharmaceutically acceptable salt of claim 105, wherein n is 1.

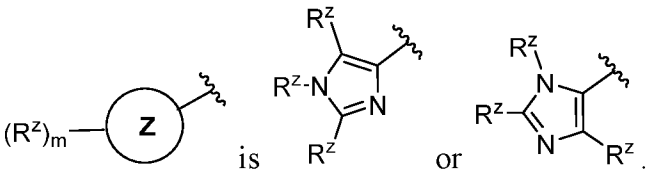
108. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound has the structure of Formula (VI):



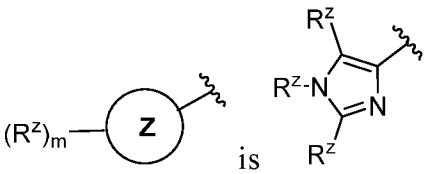
Formula (VI).

109. The compound or pharmaceutically acceptable salt of claim 108, wherein  is  ,  ,  , or  .

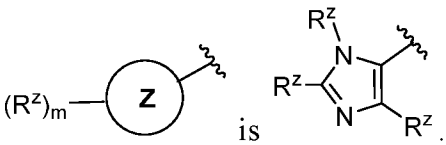
110. The compound or pharmaceutically acceptable salt of claim 109, wherein:



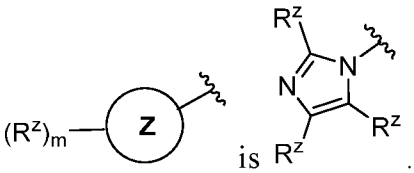
111. The compound or pharmaceutically acceptable salt of claim 110, wherein:



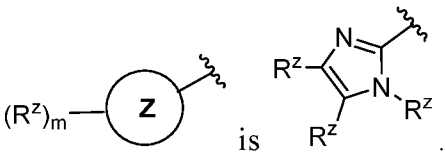
112. The compound or pharmaceutically acceptable salt of claim 110, wherein:



113. The compound or pharmaceutically acceptable salt of claim 109, wherein:



114. The compound or pharmaceutically acceptable salt of claim 109, wherein:



115. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1.

116. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one of claims 1-115, and a pharmaceutically acceptable excipient.

117. 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 the compound or pharmaceutically acceptable salt of any one of claims 1-115, or a pharmaceutical composition of claim 116.

118. 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 the compound or pharmaceutically acceptable salt of any one of claims 1-115, or a pharmaceutical composition of claim 116.

119. The method of claim 117 or claim 118, wherein the subject has cancer, polycystic kidney disease or liver fibrosis.
120. The method of claim 119, 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.
121. 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 of any one of claims 1-115, or a pharmaceutical composition of claim 116.
122. The method of claim 121, 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.
123. 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 of any one of claims 1-115, or a pharmaceutical composition of claim 116.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/026028

A. CLASSIFICATION OF SUBJECT MATTER

C07F 9/6506(2006.01)i; **C07F 9/6584**(2006.01)i; **A61K 31/66**(2006.01)i; **A61P 35/00**(2006.01)i; **A61P 31/12**(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)

C07F 9/6506(2006.01); A61K 31/131(2006.01); A61K 31/135(2006.01); A61K 31/136(2006.01); A61K 31/18(2006.01); A61P 35/00(2006.01); C07D 233/61(2006.01); C07D 275/06(2006.01); C07D 417/12(2006.01); C07F 9/6533(2006.01); C07F 9/6584(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: YAP(yes-associated protein), TAZ(transcriptional co-activator with PDZ-binding motif) YAP/TAz inhibitor, TEAD(transcriptional enhancer associate domain), phenyl phosphine oxide-based compound, Hippo pathway network, cancer, pharmaceutical composition

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2019-040380 A1 (VIVACE THERAPEUTICS, INC.) 28 February 2019 (2019-02-28) abstract; claims 1, 56; page 41	1-15,17-19,26-36,54-57,81-85,91,108-115
A	US 2020-0048288 A1 (ARIAD PHARMACEUTICALS, INC.) 13 February 2020 (2020-02-13) claims 1, 21, 22; paragraph [0053]	1-15,17-19,26-36,54-57,81-85,91,108-115
A	WO 2020-243415 A2 (IKENA ONCOLOGY, INC.) 03 December 2020 (2020-12-03) the entire document	1-15,17-19,26-36,54-57,81-85,91,108-115

☑ 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
18 January 2023	**18 January 2023**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office **189 Cheongsa-ro, Seo-gu, Daejeon** **35208, Republic of Korea**	**JUN, Sun Ae**
Facsimile No. **+82-42-481-8578**	Telephone No. **+82-42-481-8150**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018-204532 A1 (VIVACE THERAPEUTICS, INC.) 08 November 2018 (2018-11-08) the entire document	1-15,17-19,26-36,54-57,81-85,91,108-115
A	CN 110709396 A (INVENTIVA) 17 January 2020 (2020-01-17) the entire document	1-15,17-19,26-36,54-57,81-85,91,108-115

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/026028

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.: **117-123**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 117-123 pertain to methods for treatment of the human body by surgery or therapy (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. ☑ Claims Nos.: **22,23,38, 41, 42, 44, 46, 47, 49, 50, 53, 59-67, 69, 71-74, 76-79, 88, 96-104, 106, 107, 120, 122**
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 22,23,38, 41, 42, 44, 46, 47, 49, 50, 53, 59-67, 69, 71-74, 76-79, 88, 96-104, 106, 107, 120, 122 are regarded to be unclear because they refer to claims which do not comply with PCT Rule 6.4(a).

3. ☑ Claims Nos.: **16, 20,21,24,25, 37, 39, 40, 43, 45, 48, 51, 52, 58, 68, 70, 75, 80, 86, 87, 89, 90, 92-95, 105, 116-119, 121, 123**
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/US2022/026028

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/026028

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/026028

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