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(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

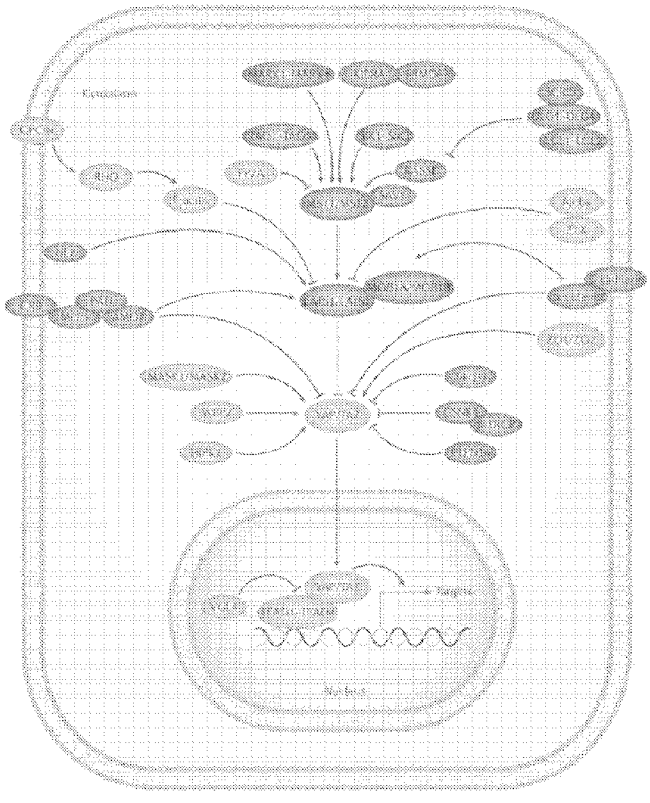
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(71) Demandeur/Applicant:

(54) Titre : COMPOSES BENZOCARBONYLE
(54) Title: BENZOCARBONYL COMPOUNDS

FIG.1



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

(21) 3 084 648

(13) A1

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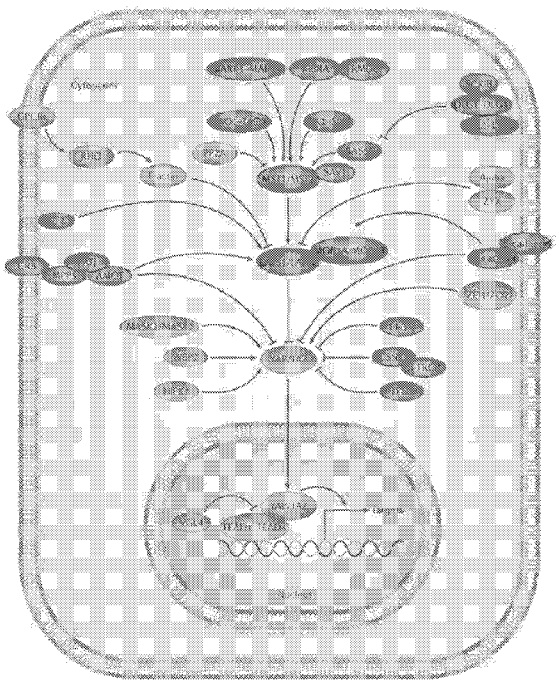
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(54) Title: BENZOCARBONYL COMPOUNDS

FIG.1



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

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BENZOCARBONYL COMPOUNDS

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 62/595,197 filed on December 06, 2017, which incorporated herein by reference in its entirety.

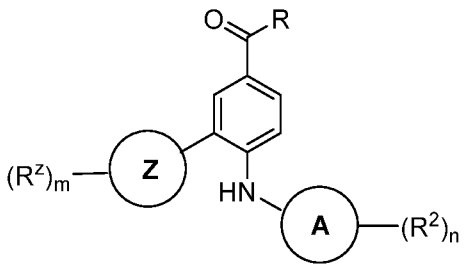
BACKGROUND OF THE DISCLOSURE

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

SUMMARY OF THE DISCLOSURE

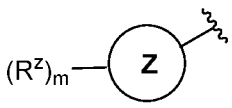
[0003] Provided herein are benzocarbonyl compounds and pharmaceutical compositions comprising said compounds. In some embodiments, the subject compounds are useful for the treatment of cancer.

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



Formula (I)

wherein,



is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom or a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom;

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, 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 C_2-C_{10} 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_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2-C_{10}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 H or substituted or unsubstituted C_1-C_6alkyl;

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;

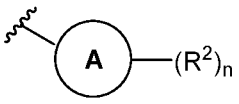
or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to

form a substituted or unsubstituted N-containing heterocycle;

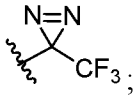
R is -OR^1 or -$N(R^1)_2$;

each R^1 is independently H, -$(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^1 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;



is substituted or unsubstituted phenyl or substituted or unsubstituted cyclohexyl;

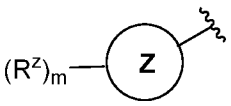
each R^2 is independently H, -F, -I, -Cl, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or 

;

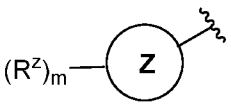
n is 0, 1, 2, 3, 4, or 5; and

each R^4 is independently 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

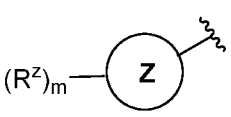
or two R^4 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

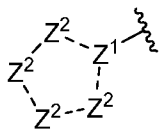
[0005] In some embodiments, 

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

[0006] In some embodiments, 

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

[0007] In some embodiments, 

is 

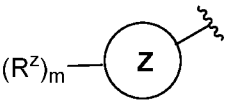
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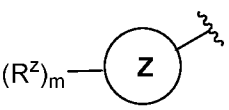
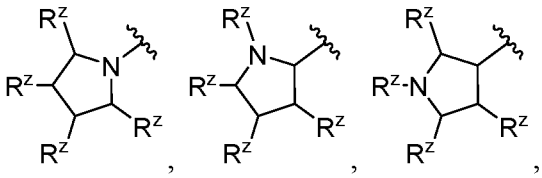
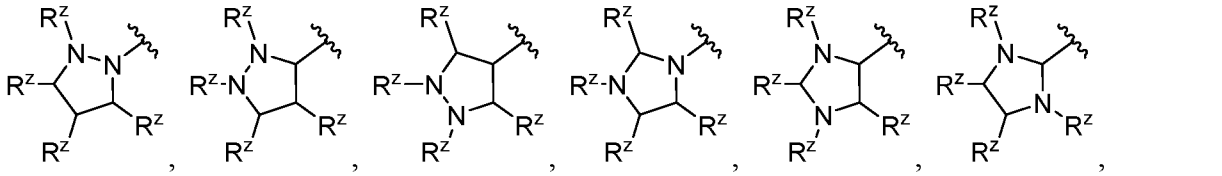
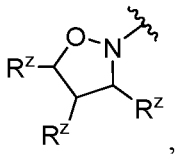
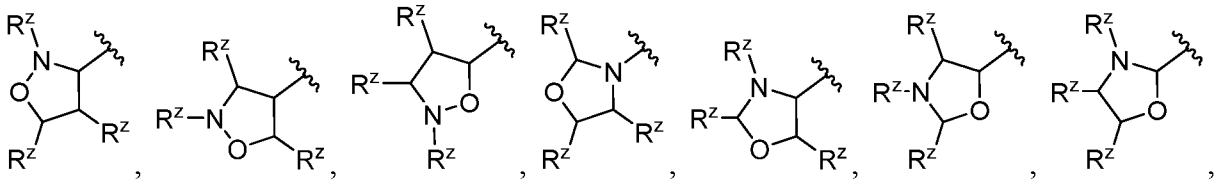
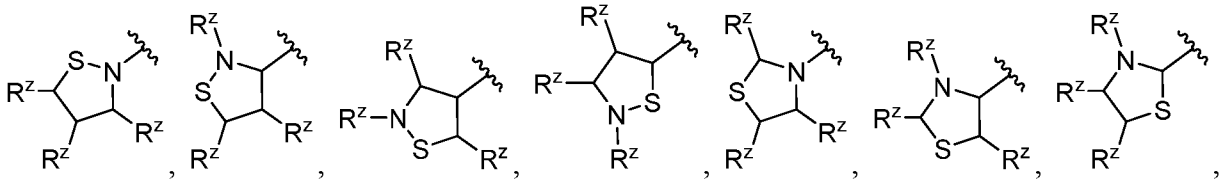
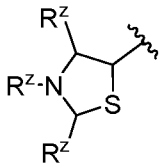
Z^1 is -N-, -CH-, or -C-;

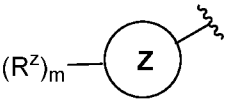
each Z^2 is independently $-CR^z$-, $-CHR^z$-, $-C(R^z)_2$-, $-NR^z$-, -N-, -O-, or -S-;

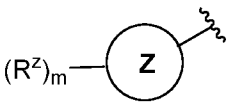
each - - is independently a single or double bond; and

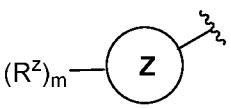
with the provision that the 5-membered heterocyclic ring contains at least one N atom.

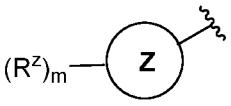
[0008] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

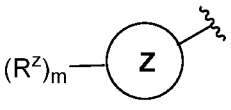
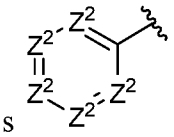
[0009] In some embodiments,  is  ,  ,  ,  ,  , or  .

[0010] 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 triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

[0011] In some embodiments,  is , or .

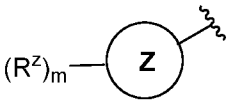
[0012] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom.

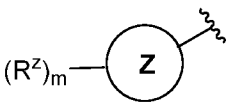
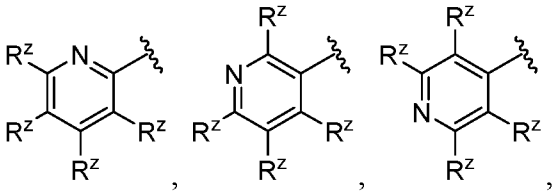
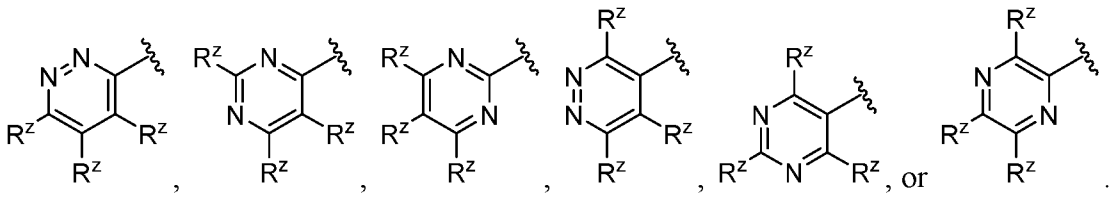
[0013] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing 1 or 2 N atoms.

[0014] In some embodiments,  is  ;

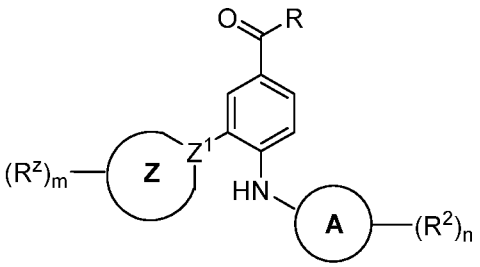
each Z^2 is independently CR^z or N; and

at least one Z^2 is N.

[0015] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[0016] In some embodiments,  is  ,  , or .

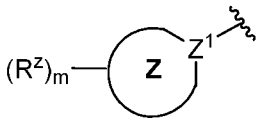
[0017] In some embodiments, the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:

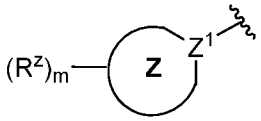
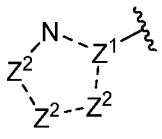
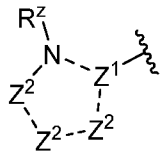


Formula (Ia)

wherein:

Z^1 is -N-, -CH-, or -C-.

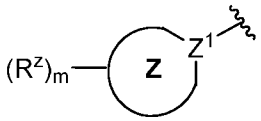
[0018] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom, and the at least one N atom is adjacent to Z^1.

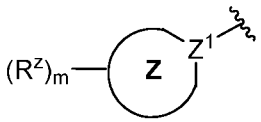
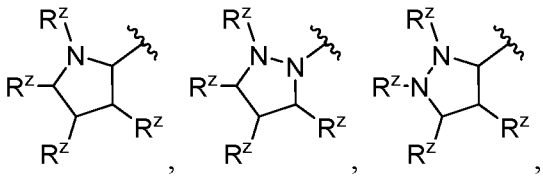
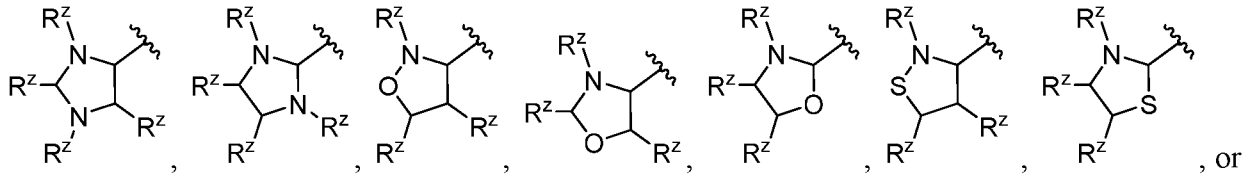
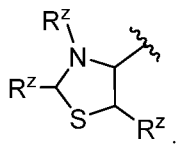
[0019] In some embodiments,  is  or  ;

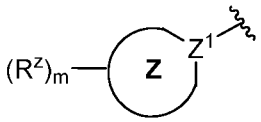
Z^1 is -N-, -CH-, or -C-;

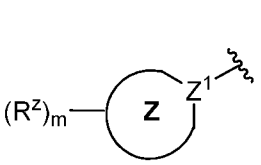
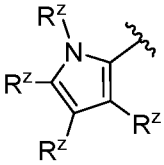
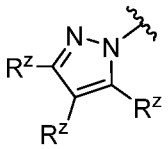
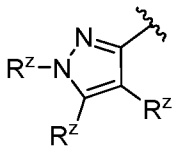
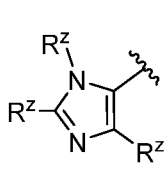
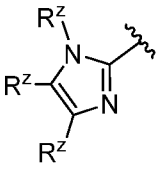
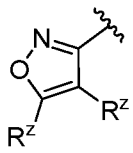
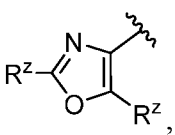
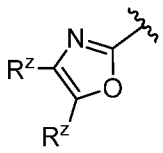
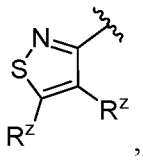
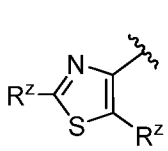
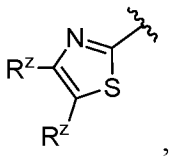
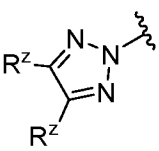
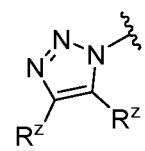
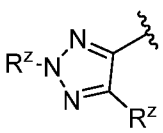
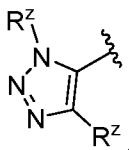
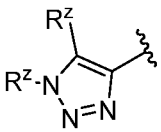
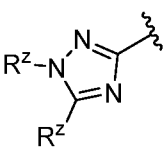
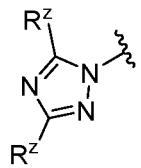
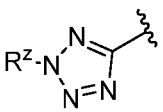
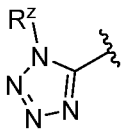
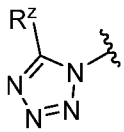
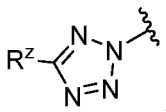
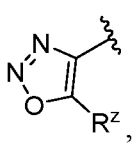
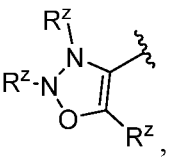
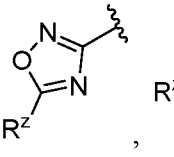
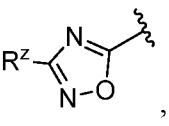
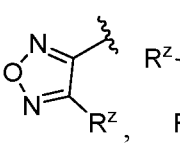
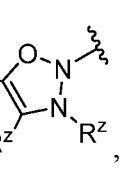
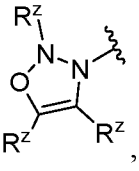
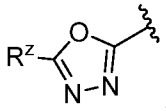
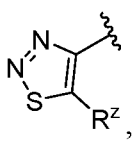
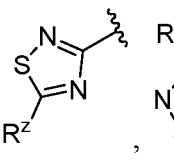
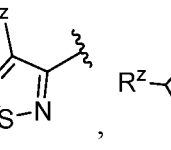
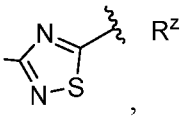
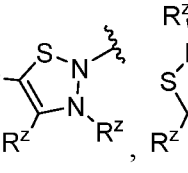
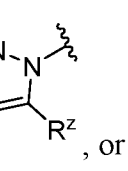
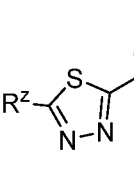
each Z^2 is independently $-CR^z-$, $-CHR^z-$, $-C(R^z)_2-$, $-NR^z-$, -N-, -O-, or -S-; and

each - - is independently a single or double bond.

[0020] 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.

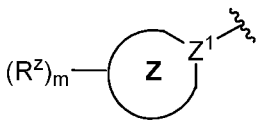
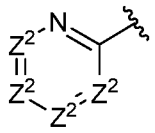
[0021] In some embodiments,  is  ,  , or  .

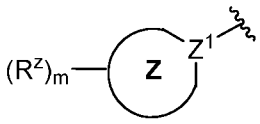
[0022] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

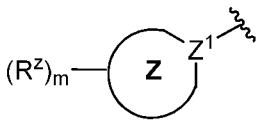
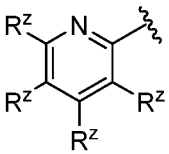
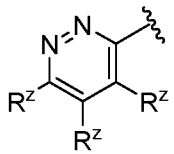
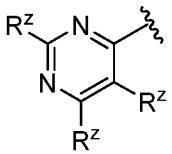
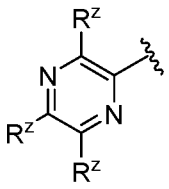
[0023] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , , , , , or .

[0024] 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.

[0025] In some embodiments,  is  ; and each Z^2 is independently CR^z or N.

[0026] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[0027] In some embodiments,  is  ,  ,  ,  , or  .

[0028] In some embodiments, each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0029] In some embodiments, each R^z is independently H, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

[0030] In some embodiments, each R^z is independently H, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[0031] 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.

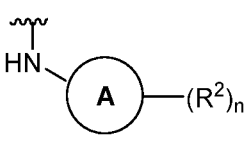
[0032] In some embodiments, each R^z is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1-C_6alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -

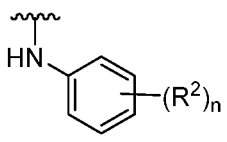
$NR^3(C=O)O$-, -$NR^3(SO_2)NR^3$-, -$NR^3(SO_2)$-, -$(SO_2)NR^3$-, -$(SO_2)NR^3$-(C=O)-, -$(SO_2)NR^3$-(C=O)O-, -$NR^3(SO_2)NR^3$-(C=O)-, or -$NR^3(SO_2)NR^3$-(C=O)O-; each R^3 is independently H or substituted or unsubstituted C_1-C_6alkyl; and Y^2 is H, substituted or unsubstituted C_1-C_6alkyl, substituted 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.

[0033] 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.

[0034] In some embodiments, R is -OR^1; and R^1 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

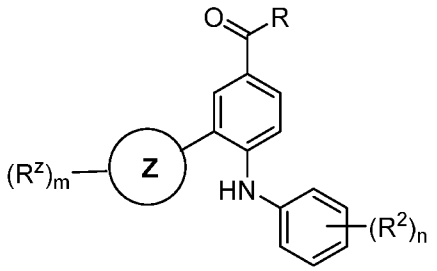
[0035] In some embodiments, R is -$N(R^1)_2$; and each R^1 is independently H, -$(SO_2)R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two R^1 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. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[0036] In some embodiments, 

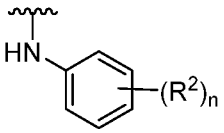
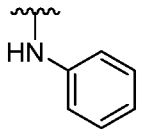
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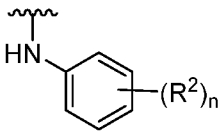
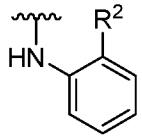
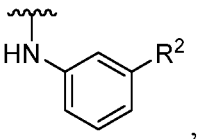
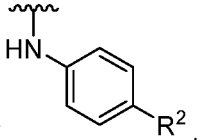
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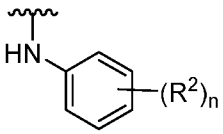
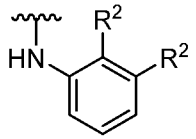
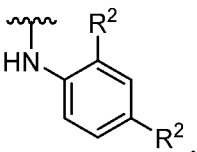
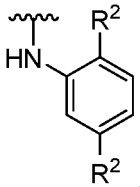
[0037] In some embodiments, the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:

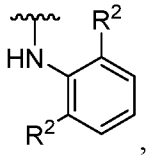
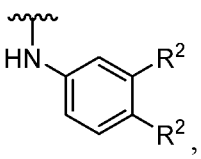
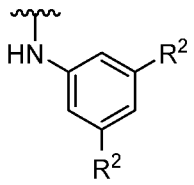


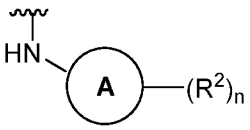
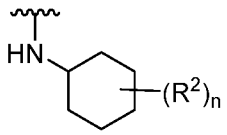
Formula (Ib).

[0038] In some embodiments,  is  .

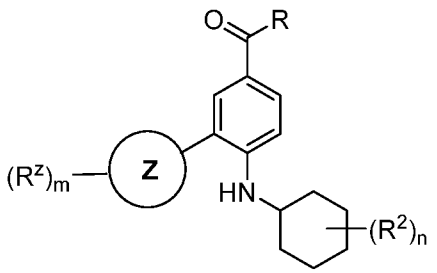
[0039] In some embodiments,  is  ,  , or  .

[0040] In some embodiments,  is  ,  ,  ,

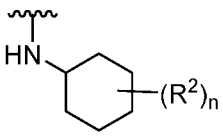
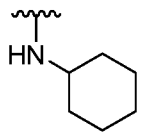
 ,  , or  .

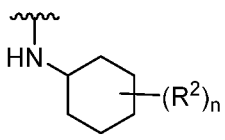
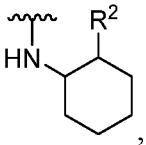
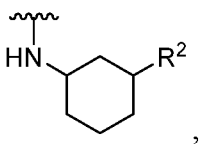
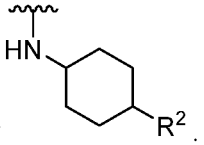
[0041] In some embodiments,  is  .

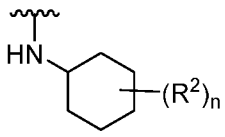
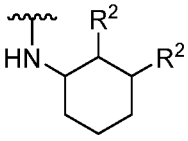
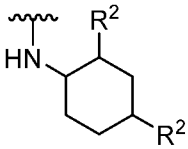
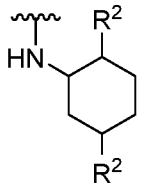
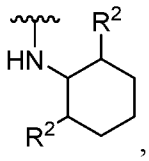
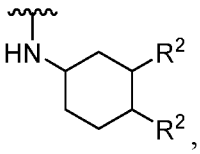
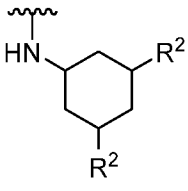
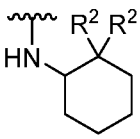
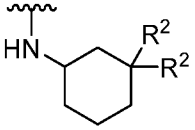
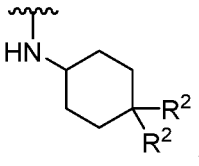
[0042] In some embodiments, the compound has the structure of Formula (Ic), or a pharmaceutically acceptable salt thereof:



Formula (Ic).

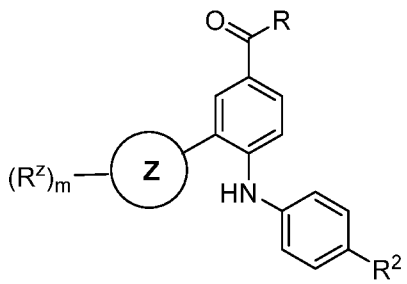
[0043] In some embodiments,  is  .

[0044] In some embodiments,  is  ,  , or  .

[0045] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  , or  .

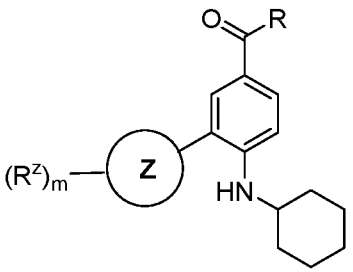
[0046] In some embodiments, each R^2 is independently H, -F, -I, -Cl, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted aryl.

[0047] In some embodiments, the compound has the structure of Formula (Id), or a pharmaceutically acceptable salt thereof:



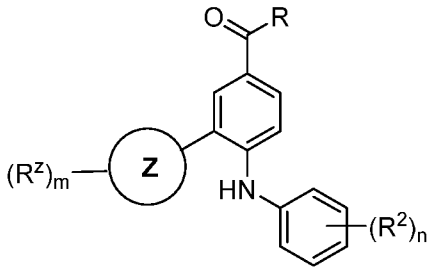
Formula (Id).

[0048] In some embodiments, the compound has the structure of Formula (Ie), or a pharmaceutically acceptable salt thereof:



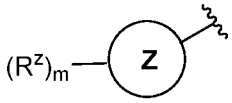
Formula (Ie).

[0049] Provided in another aspect is a compound of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II)

wherein,

 is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom or a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom;

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, 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 C_2-C_{10} 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_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2-C_{10}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 H or substituted or unsubstituted C_1-C_6alkyl;

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;

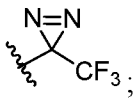
or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to

form a substituted or unsubstituted N-containing heterocycle;

R is $-OR^1$ or $-N(R^1)_2$;

each R^1 is independently H, $-(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^1 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

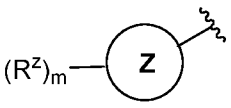
each R^2 is independently H, -F, -I, -Cl, N_3, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or 

;

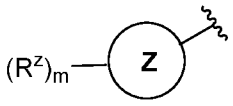
n is 0, 1, 2, 3, 4, or 5; and

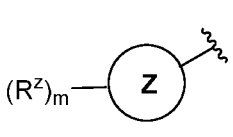
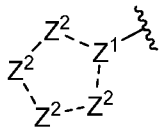
each R^4 is independently H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

[0050] In some embodiments, 

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

[0051] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing 1-4 N atoms, 0-2 O atoms, and 0-2 S atoms.

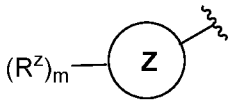
[0052] In some embodiments,  is  ;

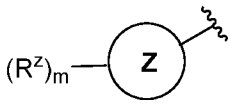
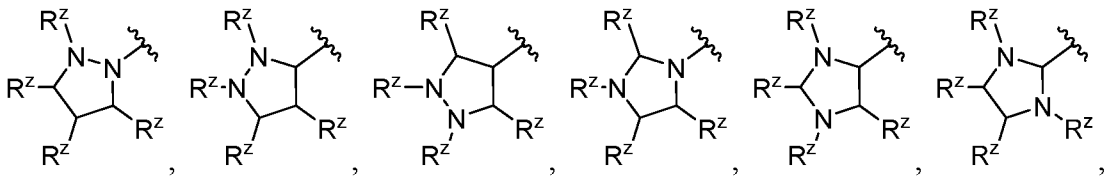
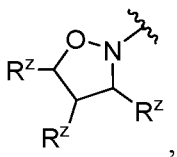
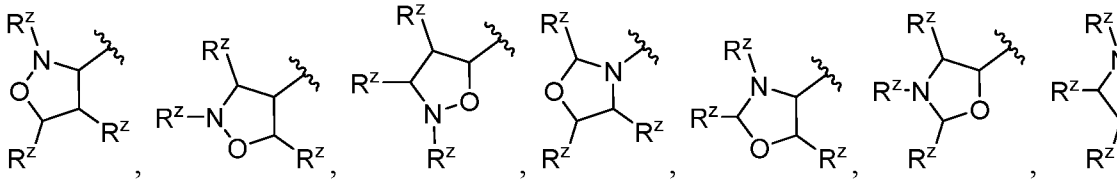
Z^1 is -N-, -CH-, or -C-;

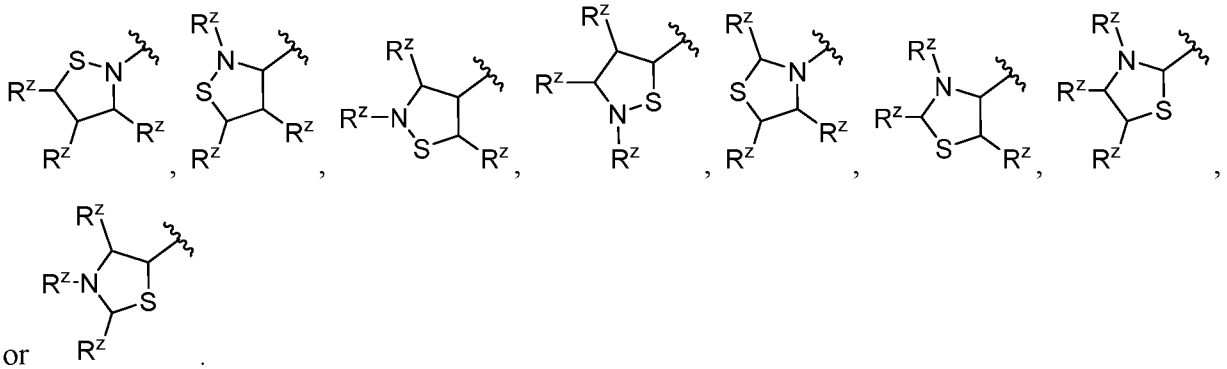
each Z^2 is independently $-CR^z-$, $-CHR^z-$, $-C(R^z)_2-$, $-NR^z-$, -N-, -O-, or -S-;

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

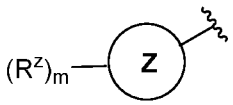
with the provision that the 5-membered heterocyclic ring contains at least one N atom.

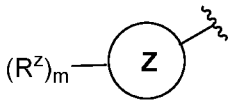
[0053] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

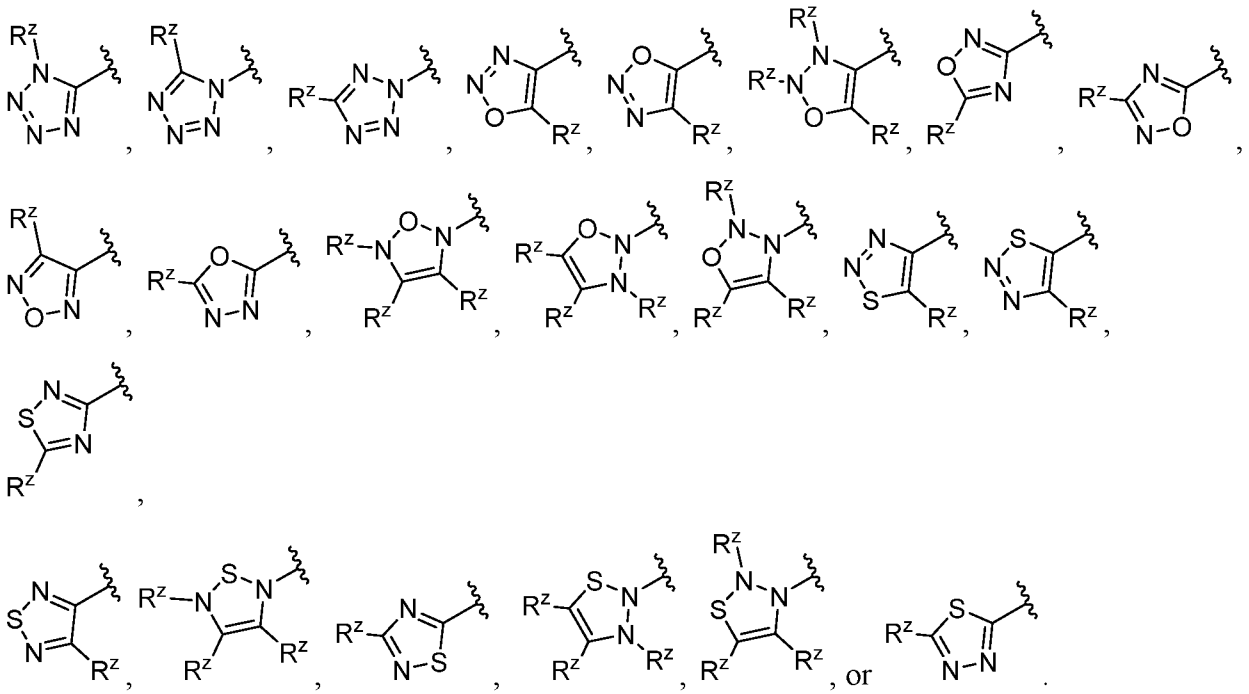
[0054] In some embodiments,  is  ,  ,  ,  .

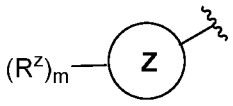


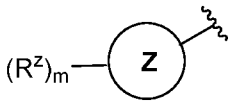
or .

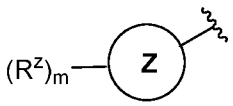
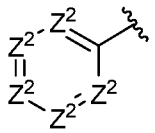
[0055] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

[0056] In some embodiments,  is



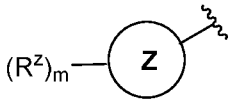
[0057] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom.

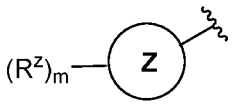
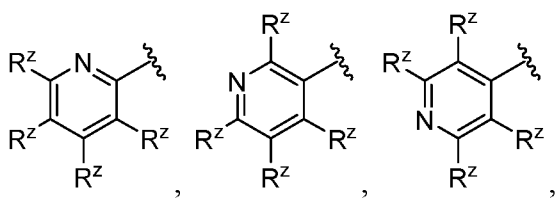
[0058] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing 1 or 2 N atoms.

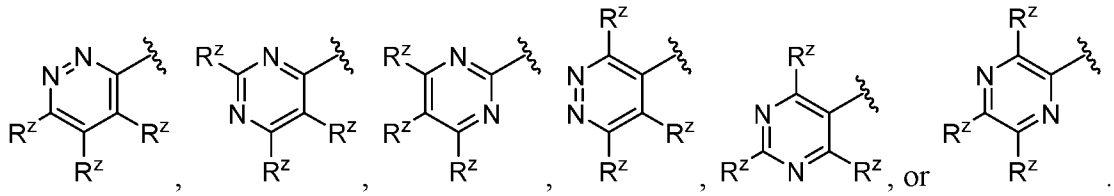
[0059] In some embodiments,  is  ;

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

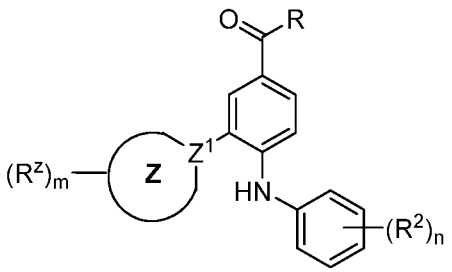
at least one Z^2 is N.

[0060] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[0061] In some embodiments,  is  ,



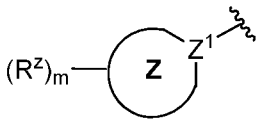
[0062] In some embodiments, the compound has the structure of Formula (IIa), or a pharmaceutically acceptable salt thereof:

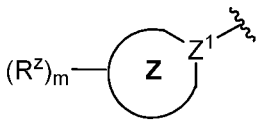
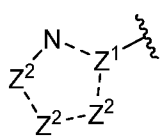
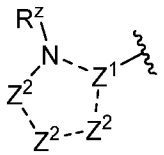


Formula (IIa)

wherein:

Z^1 is -N-, -CH-, or -C-.

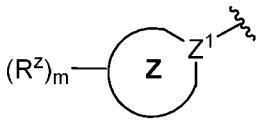
[0063] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom, and the at least one N atom is adjacent to Z^1.

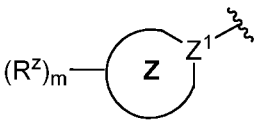
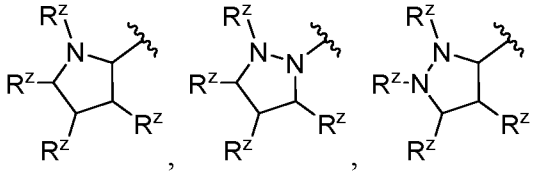
[0064] In some embodiments,  is  or  ;

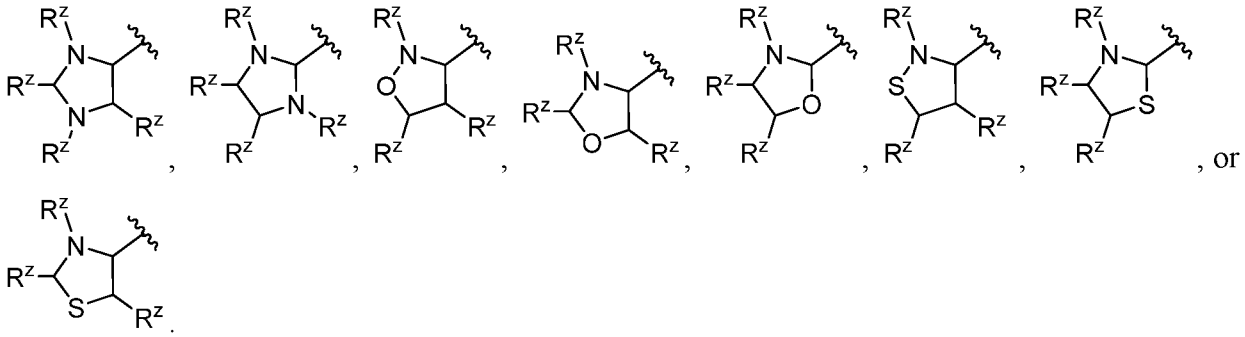
Z^1 is -N-, -CH-, or -C-;

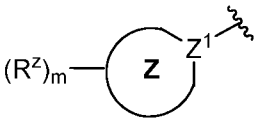
each Z^2 is independently $-CR^z-$, $-CHR^z-$, $-C(R^z)_2-$, $-NR^z-$, -N-, -O-, or -S-; and

each - - is independently a single or double bond.

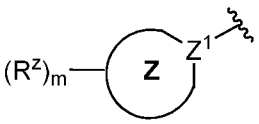
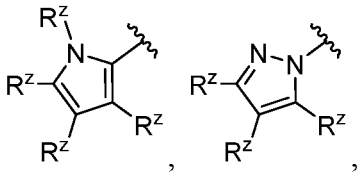
[0065] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

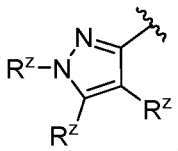
[0066] In some embodiments,  is  ,

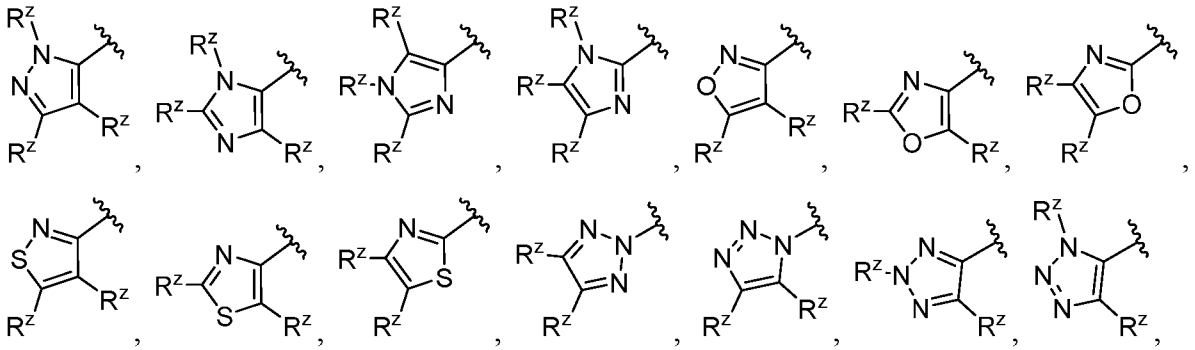


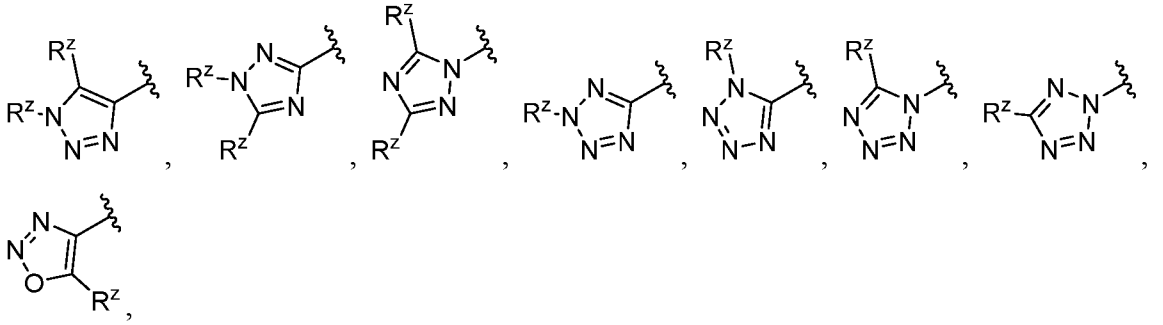


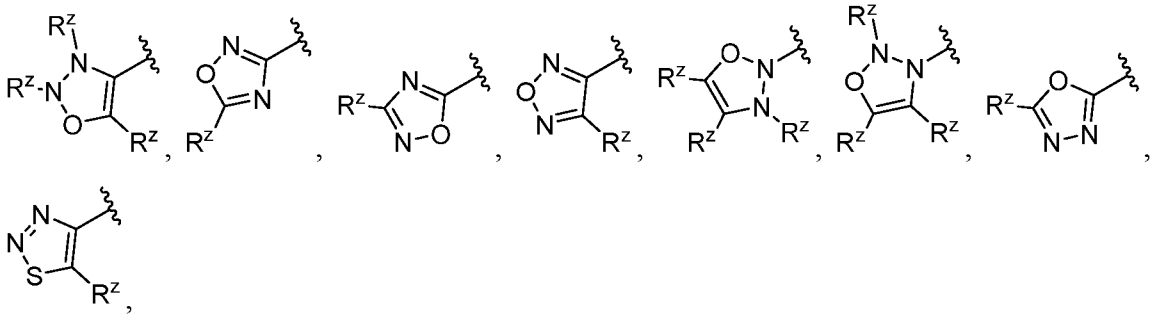
[0067] In some embodiments, is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

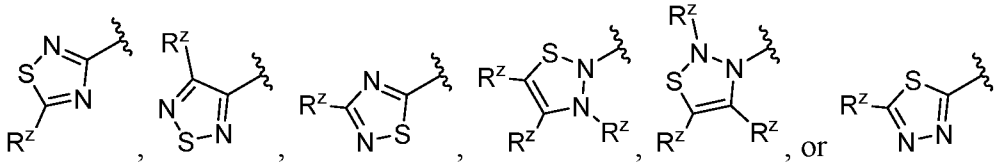
[0068] In some embodiments,  is 

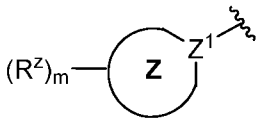


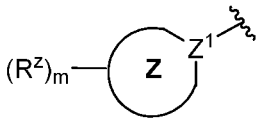
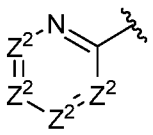


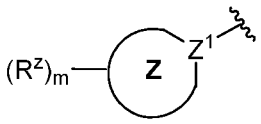


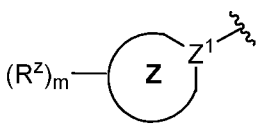
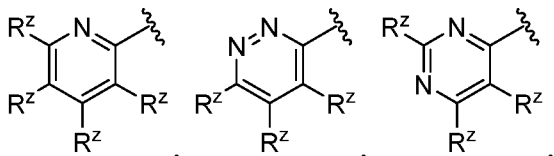


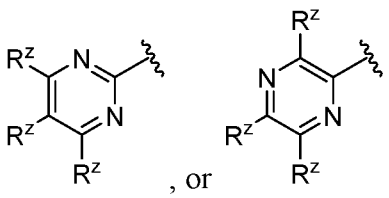


[0069] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom, and wherein the at least one N atom is adjacent to Z^1.

[0070] In some embodiments,  is  ; and each Z^2 is independently CR^z or N.

[0071] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[0072] In some embodiments,  is 



[0073] In some embodiments, each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0074] In some embodiments, each R^z is independently H, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

[0075] In some embodiments, each R^z is independently H, -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 $-L^1-Y^1$. 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.

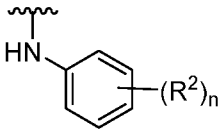
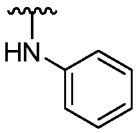
[0076] In some embodiments, each R^z is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1-C_6alkylene; L^3 is -O-, -S-, -(S=O)-, $-(SO_2)-$, $-NR^3-$, -(C=O)-, -(C=O)O-, -O(C=O)-, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(SO_2)NR^3-(C=O)O-$, $-NR^3(SO_2)NR^3-(C=O)-$, 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.

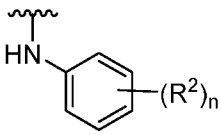
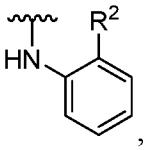
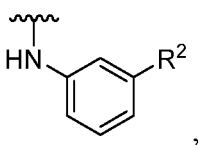
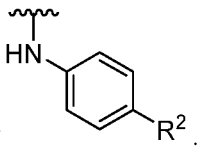
[0077] In some embodiments, L^2 is absent; L^3 is -O-, -S-, -(S=O)-, $-(SO_2)-$, $-NR^3-$, -(C=O)-, -(C=O)O-, -O(C=O)-, $-(C=O)NR^3-$, $-(C=O)NR^3-O-$, $-NR^3(C=O)-$, $-NR^3(C=O)NR^3-$, $-O(C=O)NR^3-$, $-NR^3(C=O)O-$, $-NR^3(SO_2)NR^3-$, $-NR^3(SO_2)-$, $-(SO_2)NR^3-$, $-(SO_2)NR^3-(C=O)-$, $-(SO_2)NR^3-(C=O)O-$, $-NR^3(SO_2)NR^3-(C=O)-$, 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.

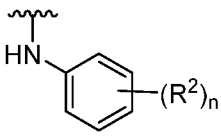
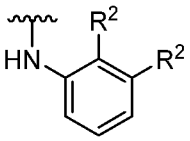
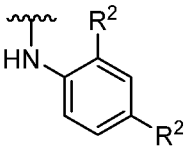
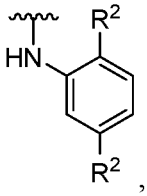
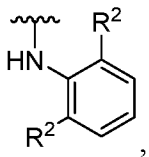
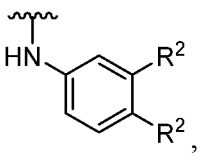
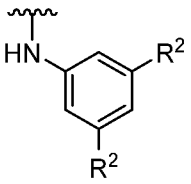
[0078] In some embodiments, R is $-OR^1$; and R^1 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or

substituted or unsubstituted heteroaryl. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[0079] In some embodiments, R is $-N(R^1)_2$; and each R^1 is independently H, $-(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two R^1 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. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

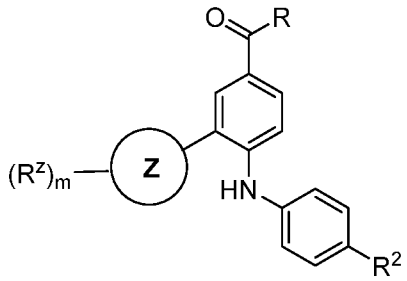
[0080] In some embodiments,  is  .

[0081] In some embodiments,  is  ,  , or  .

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

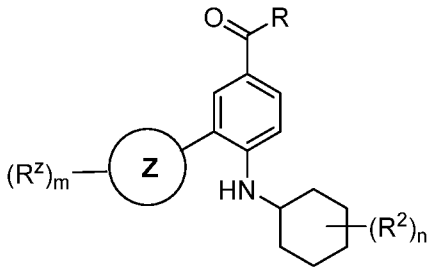
[0083] In some embodiments, each R^2 is independently H, -F, -I, -Cl, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted aryl.

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



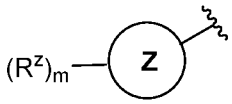
Formula (IIb).

[0085] Provided in another aspect is a compound of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein,

 is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom or a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom;

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, 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 C_2-C_{10} 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_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2-C_{10}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 H or substituted or unsubstituted C_1-C_6alkyl;

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;

or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to

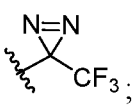
form a substituted or unsubstituted N-containing heterocycle;

R is -OR^1 or -$N(R^1)_2$;

each R^1 is independently H, -$(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^1 on the same N atom are taken together with the N atom to which they are attached to form

a substituted or unsubstituted N-containing heterocycle;

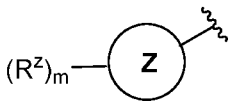
each R^2 is independently H, halogen, -N_3, -CN, -OR^4, -SR^4, -$(SO_2)R^4$, -$N(R^4)_2$, -CO_2R^4, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or  ;

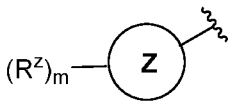
n is 0, 1, 2, 3, 4, or 5; and

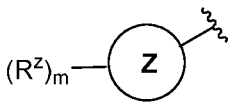
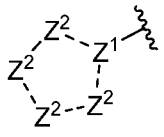
each R^4 is independently H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted

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

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

[0086] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom.

[0087] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing 1-4 N atoms, 0-2 O atoms, and 0-2 S atoms.

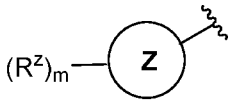
[0088] In some embodiments,  is  ;

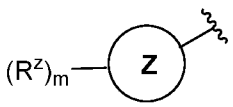
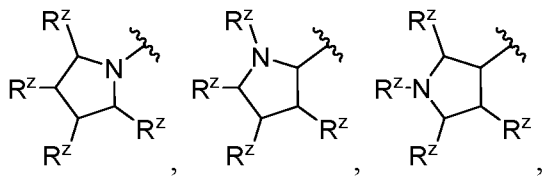
Z^1 is -N-, -CH-, or -C-;

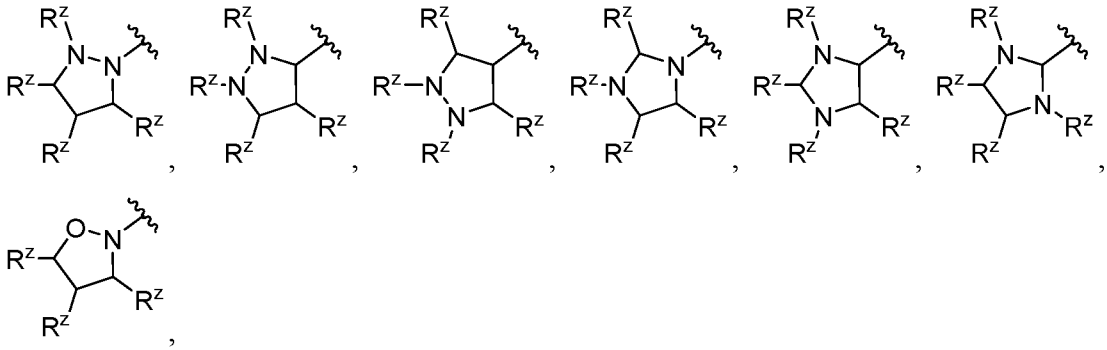
each Z^2 is independently -CR^z-, -CHR^z-, -$C(R^z)_2$-, -NR^z-, -N-, -O-, or -S-;

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

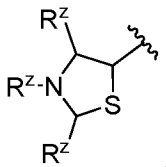
with the provision that the 5-membered heterocyclic ring contains at least one N.

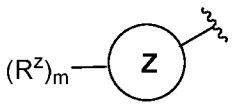
[0089] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

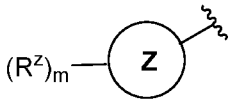
[0090] In some embodiments,  is  ,

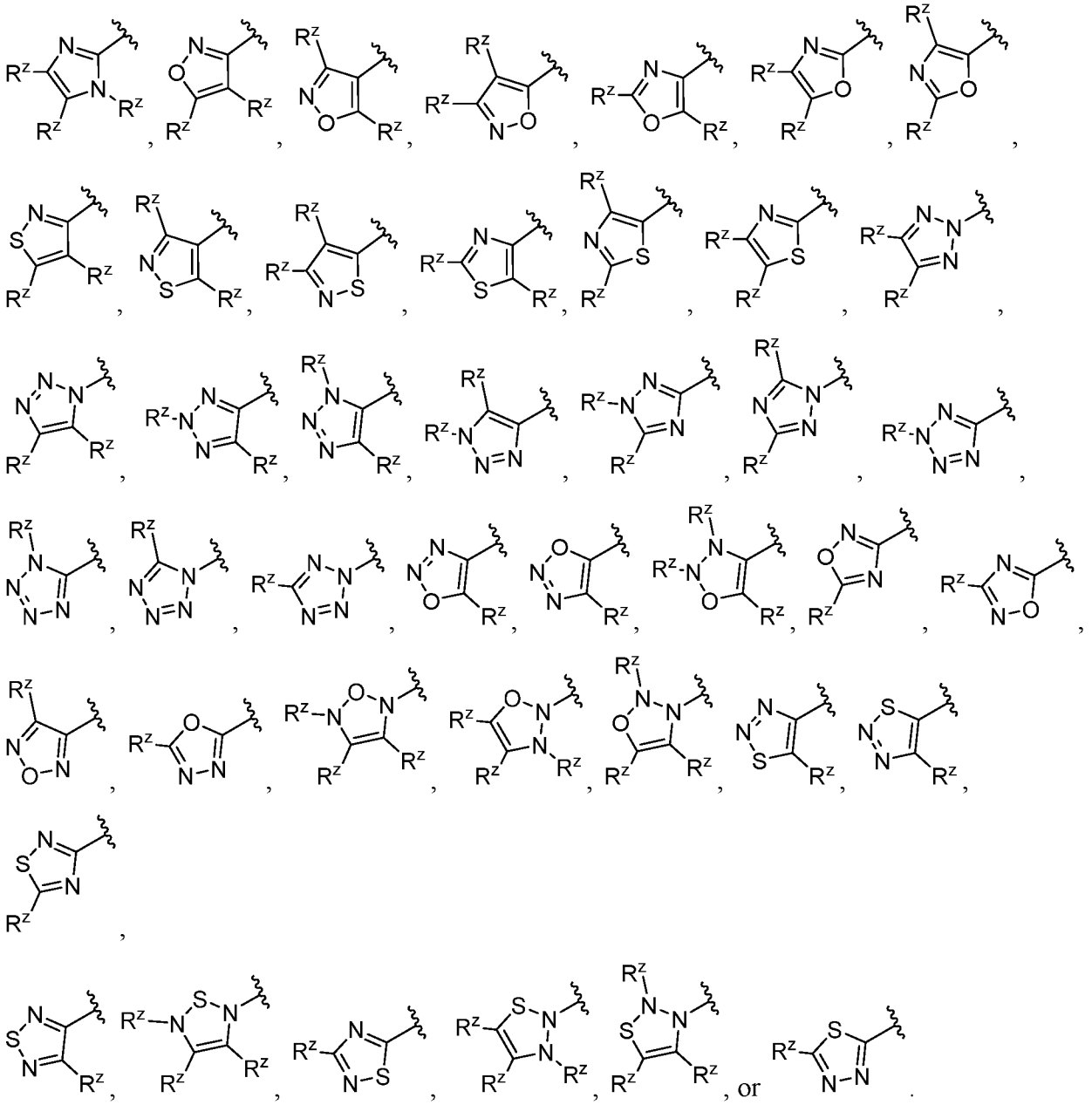


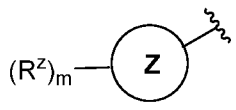
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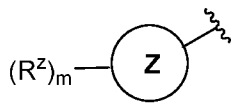


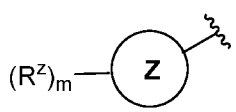
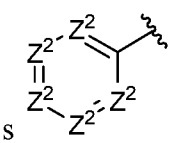
[0091] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

[0092] In some embodiments,  is



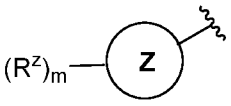
[0093] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom.

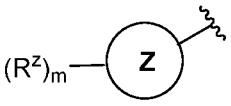
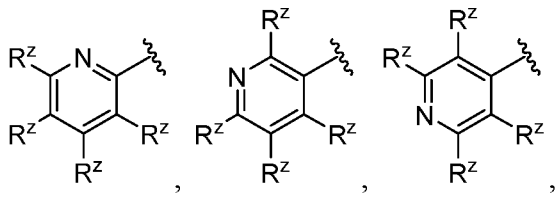
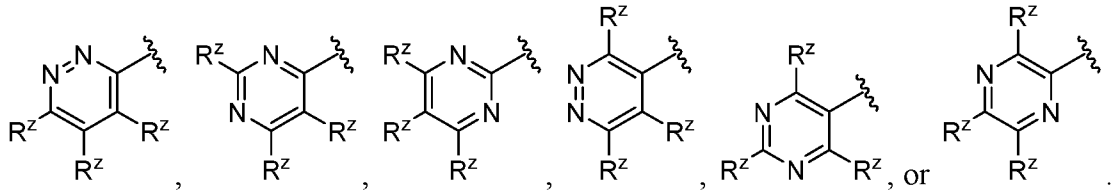
[0094] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing 1 or 2 N atoms.

[0095] In some embodiments,  is  ;

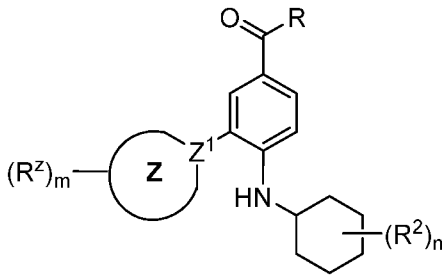
each Z^2 is independently CR^z or N; and

at least one Z^2 is N.

[0096] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

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

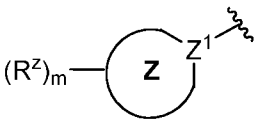
[0098] In some embodiments, the compound has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:

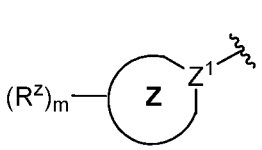
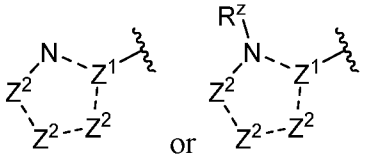


Formula (IIIa)

wherein:

Z^1 is -N-, -CH-, or -C-.

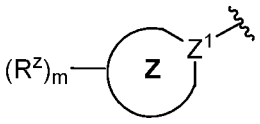
[0099] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom, and the at least one N atom is adjacent to Z^1.

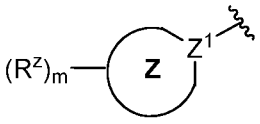
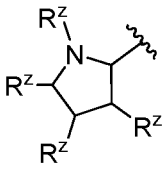
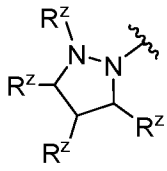
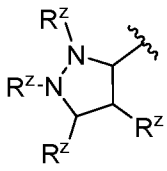
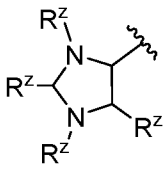
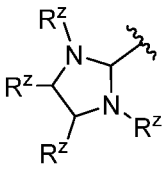
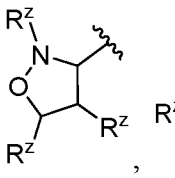
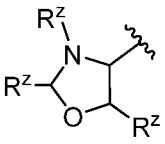
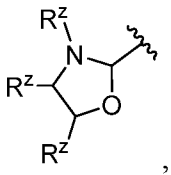
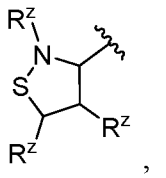
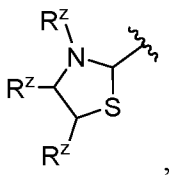
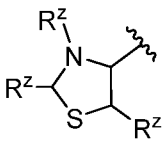
[00100] In some embodiments,  is  ;

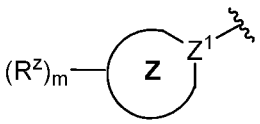
Z^1 is -N-, -CH-, or -C-;

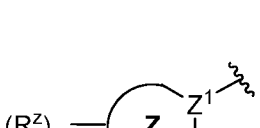
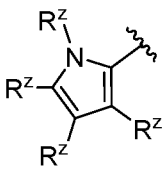
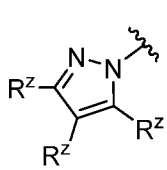
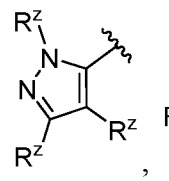
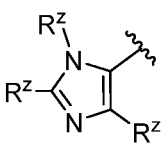
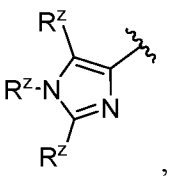
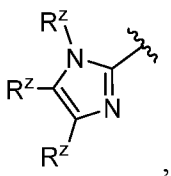
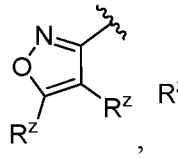
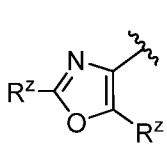
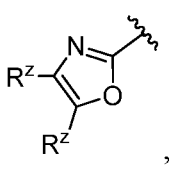
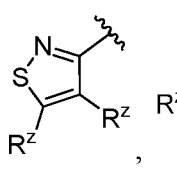
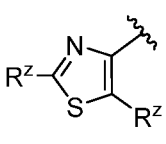
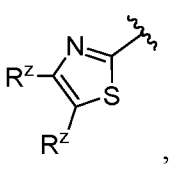
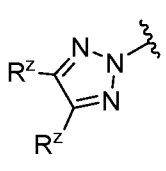
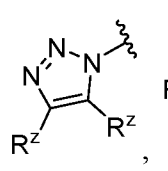
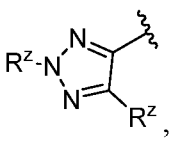
each Z^2 is independently $-CR^z-$, $-CHR^z-$, $-C(R^z)_2-$, $-NR^z-$, -N-, -O-, or -S-; and

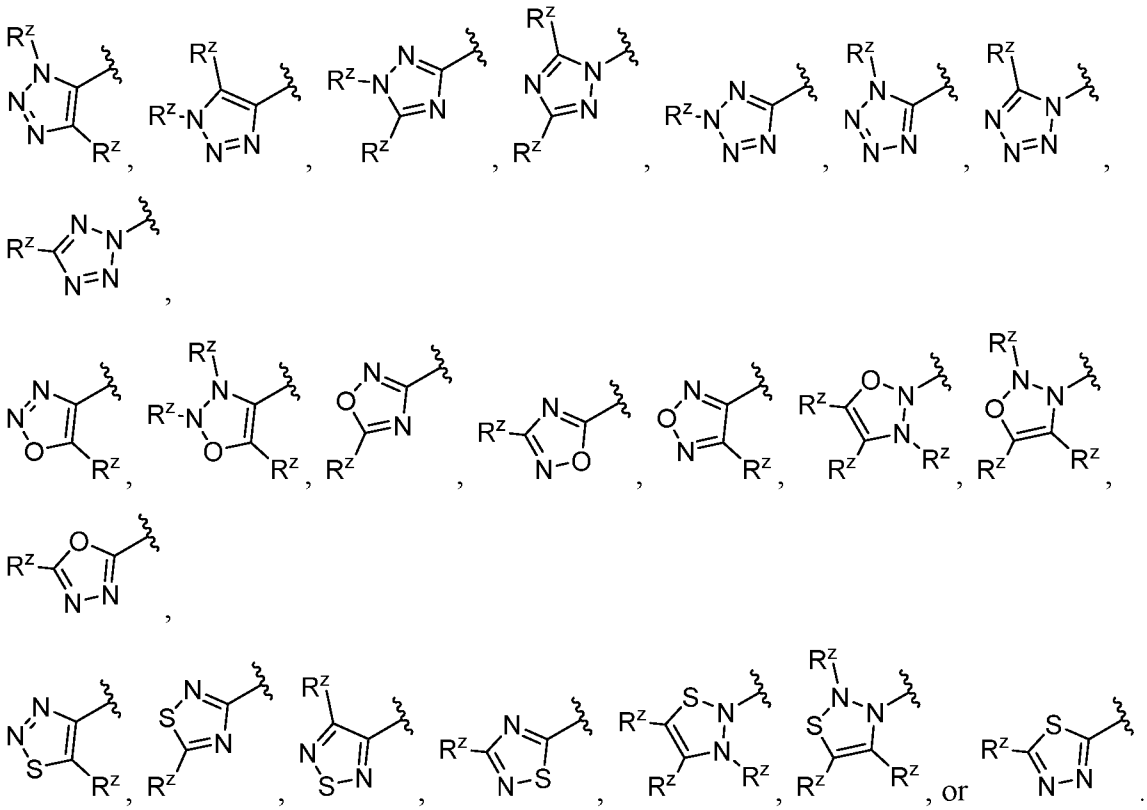
each - - is independently a single or double bond.

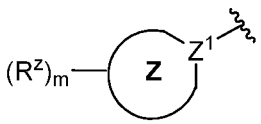
[00101] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

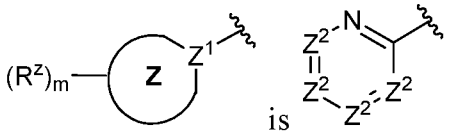
[00102] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

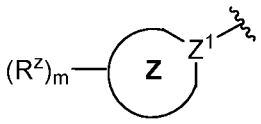
[00103] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

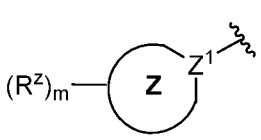
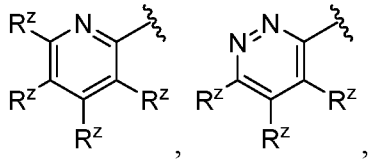
[00104] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

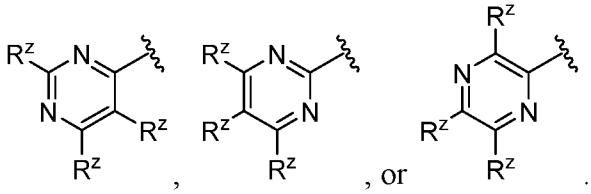


[00105] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom, and wherein the at least one N atom is adjacent to Z^1.

[00106] In some embodiments,  is ; and each Z^2 is independently CR^z or N.

[00107] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[00108] In some embodiments,  is  ,



[00109] In some embodiments, each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00110] In some embodiments, each R^z is independently H, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

[00111] In some embodiments, each R^z is independently H, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[00112] 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.

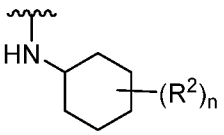
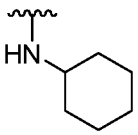
[00113] In some embodiments, each R^z is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1-C_6alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -$NR^3$$(SO_2)$$NR^3$-, -$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.

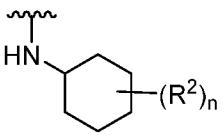
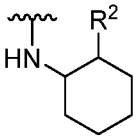
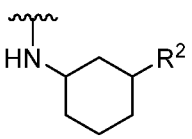
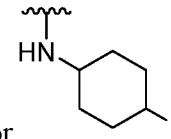
[00114] In some embodiments, L^2 is absent; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -$NR^3$$(SO_2)$$NR^3$-, -$NR^3$$(SO_2)$-, -$(SO_2)$$NR^3$-, -$(SO_2)$$NR^3$-(C=O)-, -$(SO_2)$$NR^3$-(C=O)O-, -$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

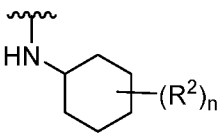
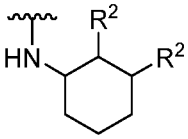
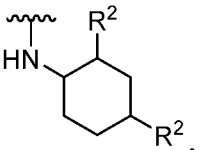
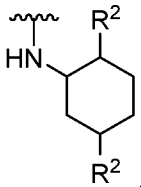
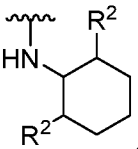
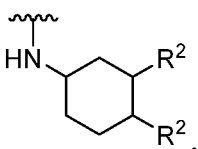
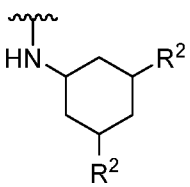
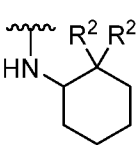
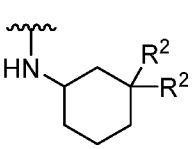
unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

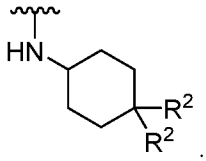
[00115] In some embodiments, R is $-OR^1$; and R^1 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[00116] In some embodiments, R is $-N(R^1)_2$; and each R^1 is independently H, $-(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two R^1 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. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[00117] In some embodiments,  is  .

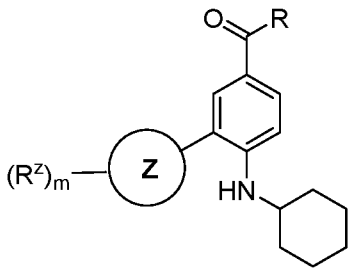
[00118] In some embodiments,  is  ,  ,  or .

[00119] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  , or



[00120] In some embodiments, each R^2 is independently H, halogen, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

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



Formula (IIIb).

[00122] In some embodiments, the compound exhibits an IC_{50} of no more than about 3.000 μM.

[00123] Provided in another aspect is a compound, or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1, or a pharmaceutically acceptable salt thereof.

[00124] Provided in another aspect is a pharmaceutical composition comprising a pharmaceutically acceptable excipient and any one of the compounds disclosed herein or a pharmaceutically acceptable salt thereof.

[00125] Provided herein is a method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound of any one of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof.

INCORPORATION BY REFERENCE

[00126] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[00127] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[00128] **FIG. 1** illustrates a schematic representation of the Hippo signaling network. Hippo pathway components shaded in dark gray indicate components that inhibit YAP/TAZ activity. Hippo pathway components shaded in light gray indicate components that promote YAP/TAZ activity. Pointed and blunt arrowheads indicate activating and inhibitory interactions, respectively. Abbreviations: α-CAT (α-Catenin), AJUB (Ajuba), AMOT (Angiomotin), β-TRCP (β-transducing repeat containing protein), CK1 (Casein Kinase 1), CRB (Crumbs), E-CAD (E-cadherin), EX (Expanded), GPCR (G-protein coupled receptor), HIPK (Homeodomain interacting protein kinase), KIBRA (Kidney brain), LATS (Large tumor suppressor), LGL (Lethal giant larvae), MASK (Multiple ankyrin single KH), MER (Merlin), MOB (Mps one binder), MST (Mammalian sterile 20 like), PALS (Protein Associated with Lin-7), PATJ (Pals1-associated tight junction protein), PP2A (Protein phosphatase 2A), PTPN14 (Protein tyrosine phosphatase non-receptor type 14), RASSF (Ras associated factor), SAV (Salvador), SCRIB (Scribble), SIK (Salt inducible kinase), TAO (Thousand and one amino acid protein), TAZ (transcriptional coactivator with PDZ-binding motif), TEAD (TEA domain protein), VGL4 (Vestigial-like 4), WBP2 (WW domain binding protein 2), YAP (Yes associated protein), ZO (Zonula occludens), ZYX (Zyxin).

[00129] **FIG. 2** illustrates a schematic representation of the Hippo signaling pathway regulated by G alpha proteins.

DETAILED DESCRIPTION OF THE DISCLOSURE

Certain Terminology

[00130] 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.

[00131] 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.

[00132] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00133] 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).

[00134] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[00135] "Amino" refers to the $-NH_2$ radical.

[00136] "Cyano" refers to the -CN radical.

[00137] "Nitro" refers to the $-NO_2$ radical.

[00138] "Oxa" refers to the -O- radical.

[00139] "Oxo" refers to the =O radical.

[00140] "Thioxo" refers to the =S radical.

[00141] "Imino" refers to the =N-H radical.

[00142] "Oximo" refers to the =N-OH radical.

[00143] "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), and 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2), and $-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

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

[00145] "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, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[00146] "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, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[00147] "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, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or

heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[00148] "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from five to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin, and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-CN$, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[00149] "Aryloxy" refers to a radical bonded through an oxygen atom of the formula –O-aryl, where aryl is as defined above.

[00150] "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.

[00151] "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.

[00152] "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.

[00153] "Carbocyclyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, and in some embodiments, include fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. In some embodiments, the carbocyclyl is saturated, (*i.e.*, containing single C-C bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) A fully saturated carbocyclyl radical is also referred to as "cycloalkyl." Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In certain embodiments, a cycloalkyl comprises three to eight carbon atoms (*e.g.*, 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 "carbocyclyl" is meant to include carbocyclyl radicals that are optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-$N(R^a)_2$, -R^b-$N(R^a)_2$, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)$N(R^a)_2$, -R^b-O-R^c-C(O)$N(R^a)_2$, -R^b-$N(R^a)$C(O)OR^a, -R^b-$N(R^a)$C(O)R^a, -R^b-$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tOR^a$ (where t is 1 or 2),

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

[00154] "Carbocyclylalkyl" refers to a radical of the formula $-R^c$-carbocyclyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical are optionally substituted as defined above.

[00155] "Halo" or "halogen" refers to bromo, chloro, fluoro, or iodo substituents.

[00156] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, 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.

[00157] "Heterocyclyl" or "heterocycle" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which include fused or bridged ring systems in some embodiments. The heteroatoms in the heterocyclyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. In some embodiments, the heterocyclyl is attached to the rest of the molecule through any atom of the ring(s). In some embodiments, the heterocyclyl is saturated, (*i.e.*, containing single bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) A fully saturated heterocyclyl radical is also referred to as "heterocycloalkyl." Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, 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. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally

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

[00158] "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.

[00159] "Heterocyclylalkyl" refers to a radical of the formula $–R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocyclyl group.

[00160] "Heterocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula $–O-R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkoxy radical is optionally substituted as defined above for a heterocyclyl group.

[00161] "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]pridinyl, 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 carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted

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

[00162] "*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.

[00163] "*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.

[00164] "Heteroaryloxy" refers to radical bonded through an oxygen atom of the formula –O-heteroaryl, where heteroaryl is as defined above.

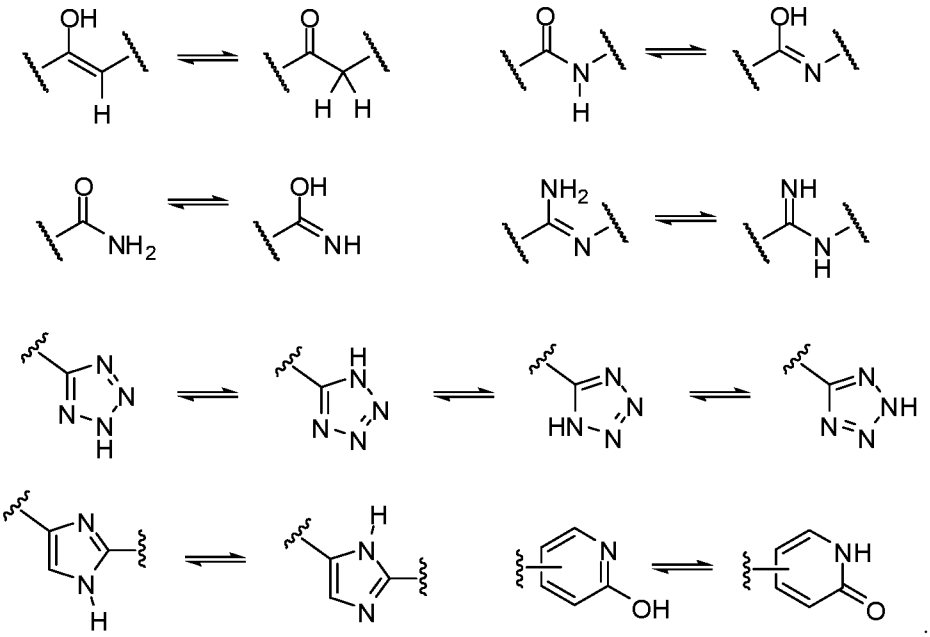
[00165] "Heteroarylalkyl" refers to a radical of the formula –R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl 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.

[00166] "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.

[00167] 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.

[00168] 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:



[00169] "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.

[00170] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Pharmaceutically acceptable salts

of the compounds described herein are optionally pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[00171] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19 (1997), which is hereby incorporated by reference in its entirety). In some embodiments, acid addition salts of basic compounds are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[00172] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. In some embodiments, pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts, and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, for example, isopropylamine, trimethylamine,

diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins, and the like. See Berge et al., *supra*.

[00173] 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.

[00174] "Prodrug" is meant to indicate a compound that is converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some embodiments, a prodrug is inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.,* Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam).

[00175] A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

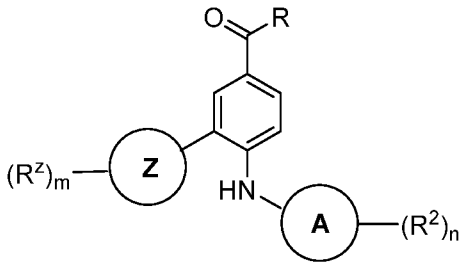
[00176] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. In some embodiments, prodrugs of an active compound, as described herein, are prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active

compound. Prodrugs include compounds wherein a hydroxy, amino, or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino, or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol or amine functional groups in the active compounds and the like.

Compounds

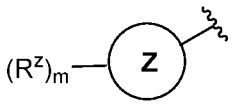
[00177] In some embodiments, the compounds disclosed herein are benzocarbonyl compounds.

[00178] Provided in one aspect is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein,



is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom or a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom;

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, 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 C_2-C_{10} 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_2-

C_{10}cyclolkylene, or substituted or unsubstituted C_2-C_{10}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 H or substituted or unsubstituted C_1-C_6alkyl;

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;

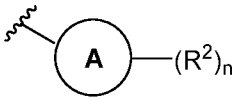
or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to

form a substituted or unsubstituted N-containing heterocycle;

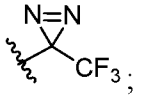
R is -OR^1 or -$N(R^1)_2$;

each R^1 is independently H, -(SO_2)R^4, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^1 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;



is substituted or unsubstituted phenyl or substituted or unsubstituted cyclohexyl;

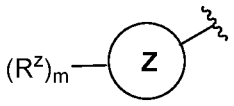
each R^2 is independently H, -F, -I, -Cl, -N_3, -CN, -OR^4, -SR^4, -(SO_2)R^4, -$N(R^4)_2$, -CO_2R^4, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or 

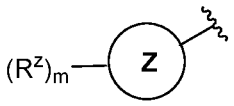
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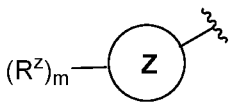
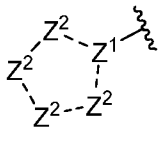
n is 0, 1, 2, 3, 4, or 5; and

each R^4 is independently 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

[00179] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom.

[00180] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing 1-4 N atoms, 0-2 O atoms, and 0-2 S atoms.

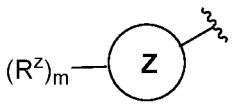
[00181] In some embodiments,  is  ;

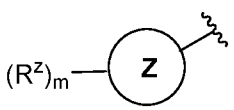
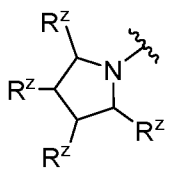
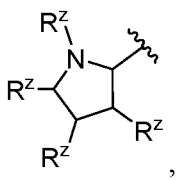
Z^1 is -N-, -CH-, or -C-;

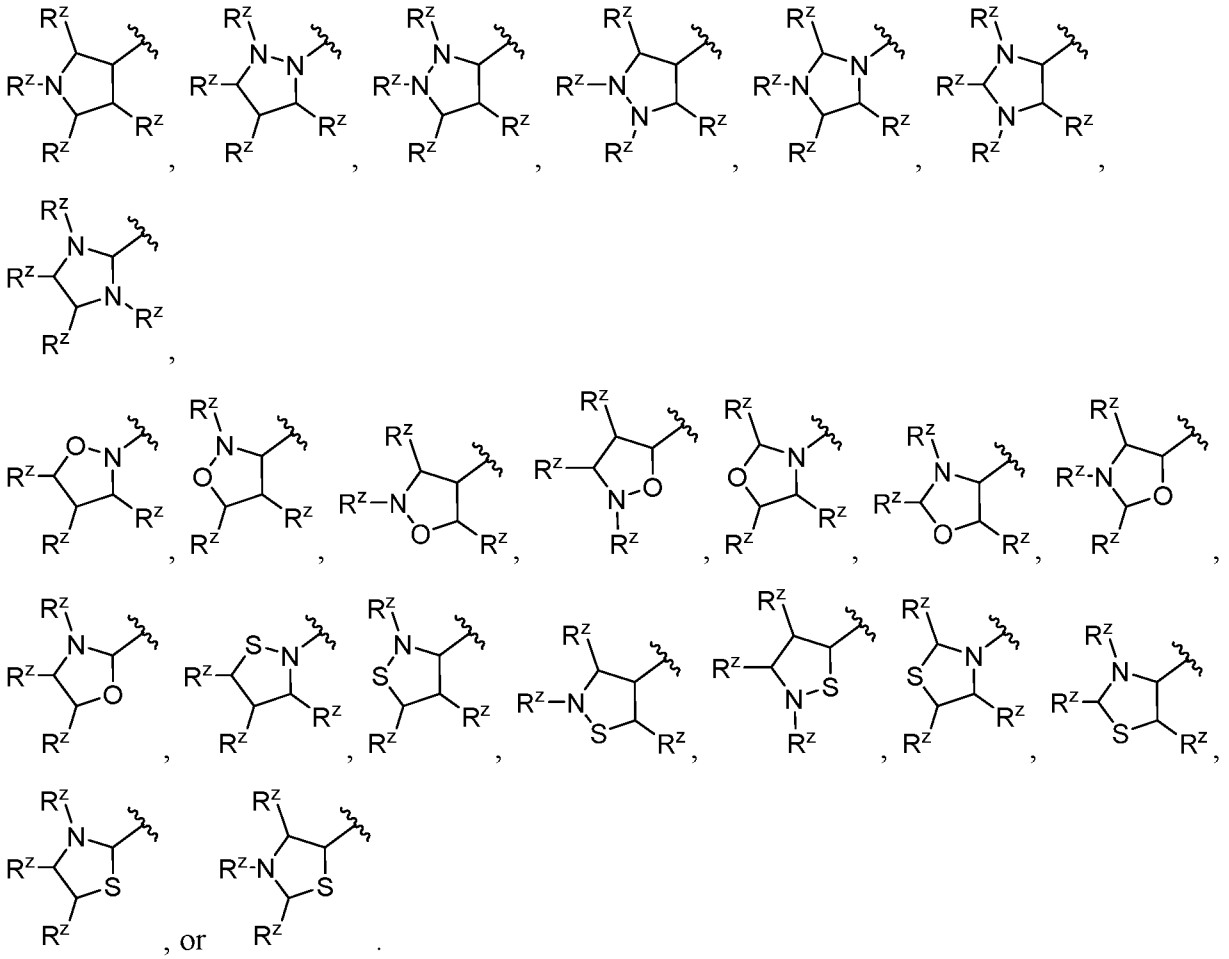
each Z^2 is independently $-CR^z$-, $-CHR^z$-, $-C(R^z)_2$-, $-NR^z$-, -N-, -O-, or -S-;

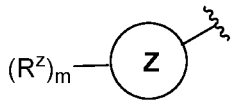
each - - is independently a single or double bond; and

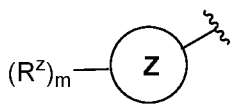
with the provision that the 5-membered heterocyclic ring contains at least one N atom.

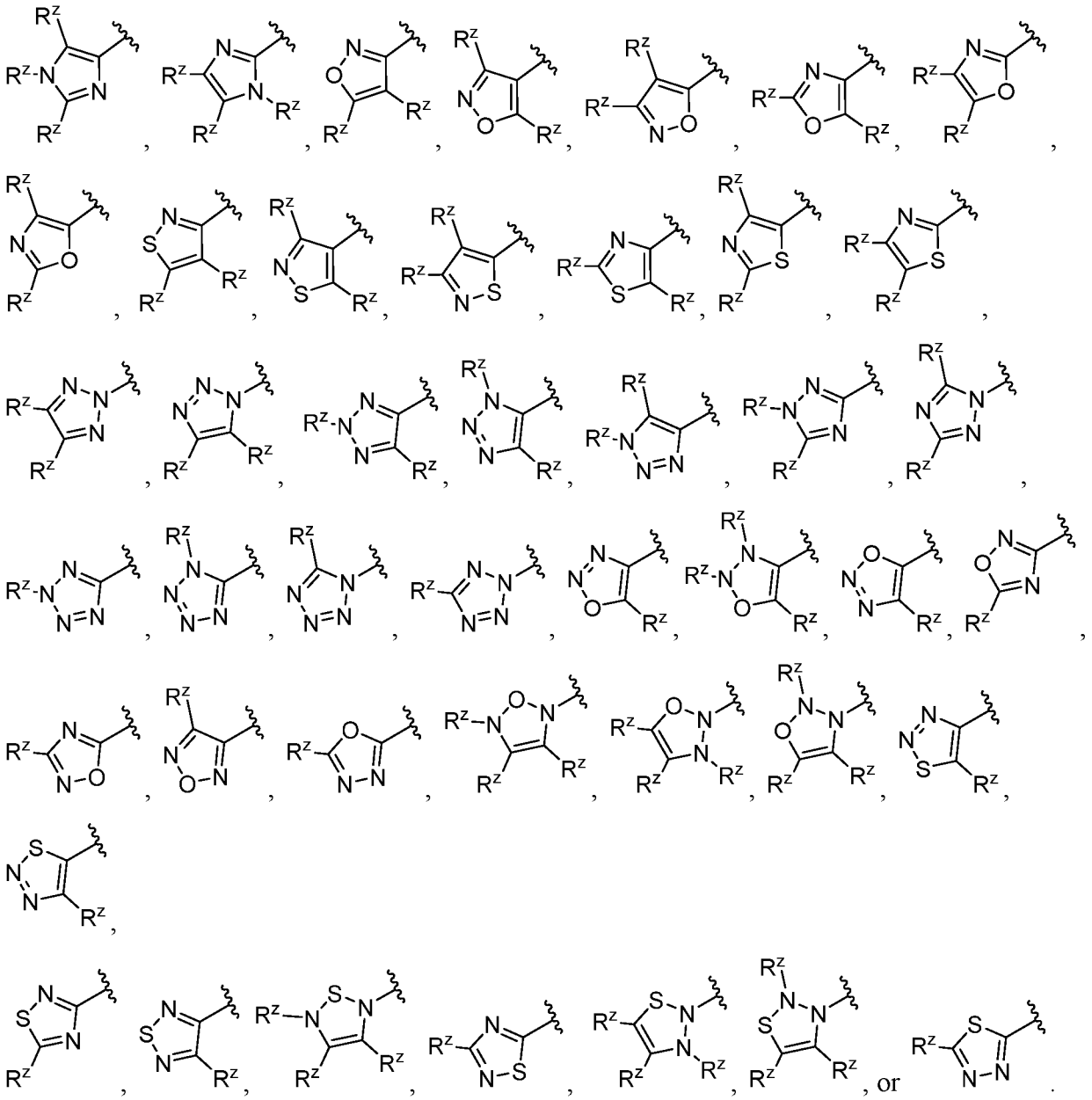
[00182] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

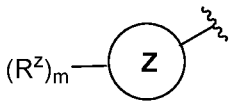
[00183] In some embodiments,  is  ,  ,

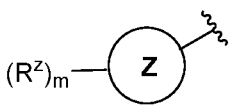


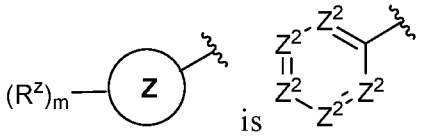
[00184] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

[00185] In some embodiments,  is



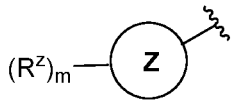
[00186] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom.

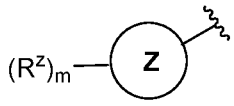
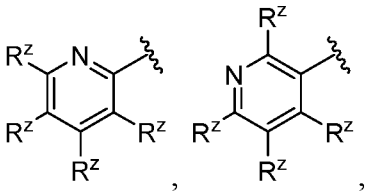
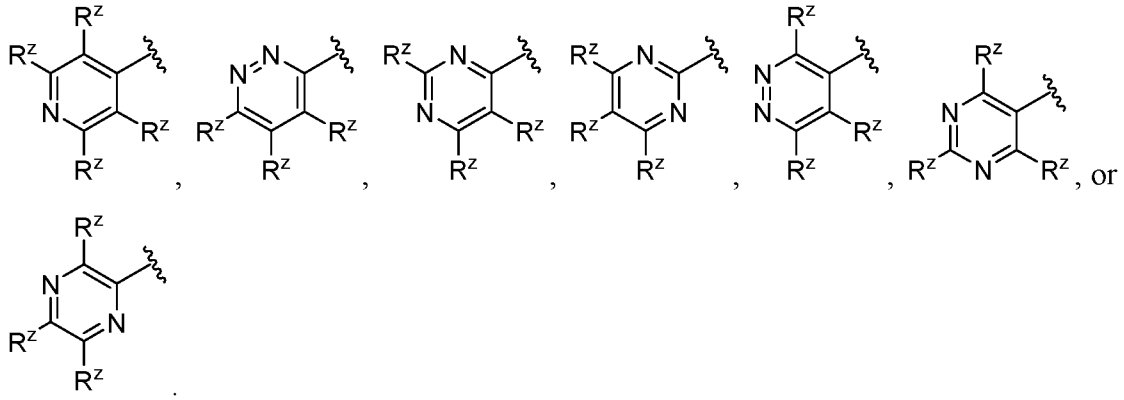
[00187] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing 1 or 2 N atoms.

[00188] In some embodiments,  is ;

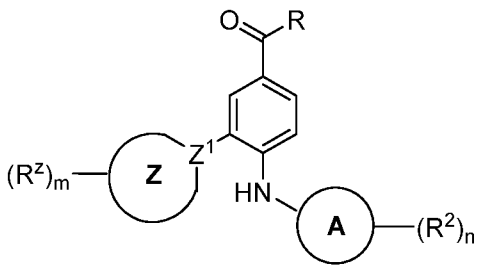
each Z^2 is independently CR^z or N; and

at least one Z^2 is N.

[00189] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[00190] In some embodiments,  is  ,  , or .

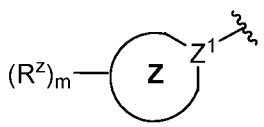
[00191] In some embodiments, the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:

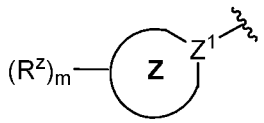
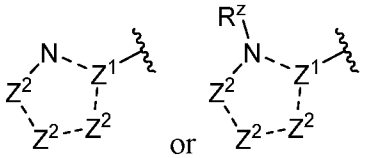


Formula (Ia)

wherein:

Z^1 is -N-, -CH-, or -C-.

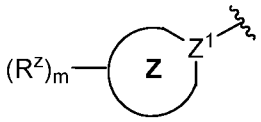
[00192] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom, and the at least one N atom is adjacent to Z^1.

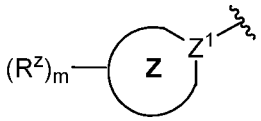
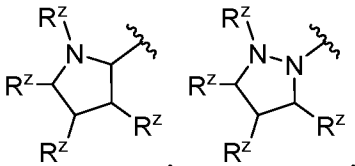
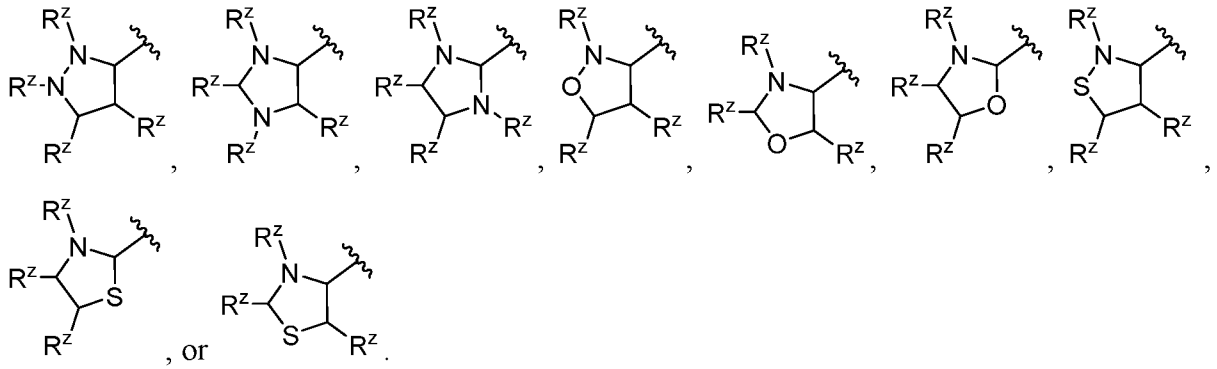
[00193] In some embodiments,  is  ;

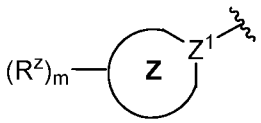
Z^1 is -N-, -CH-, or -C-;

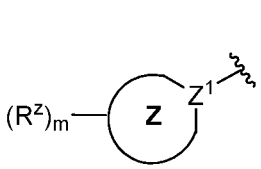
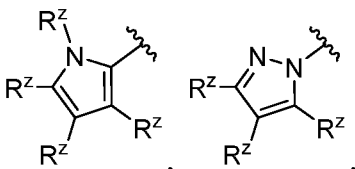
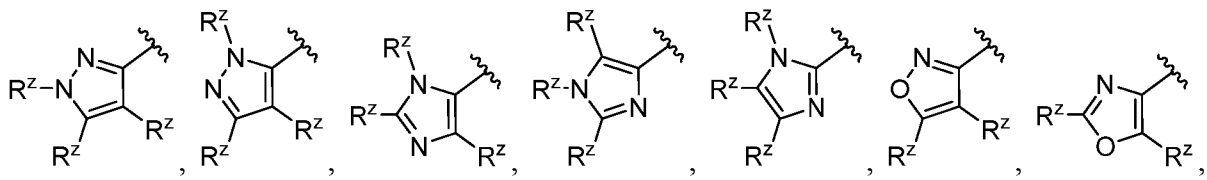
each Z^2 is independently -CR^z-, -CHR^z-, -$C(R^z)_2$-, -NR^z-, -N-, -O-, or -S-; and

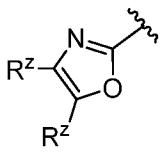
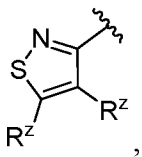
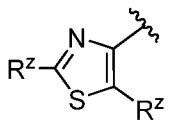
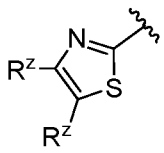
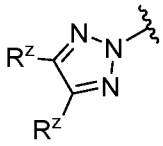
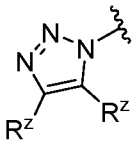
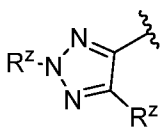
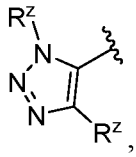
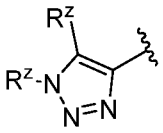
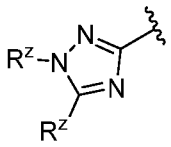
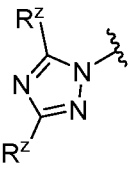
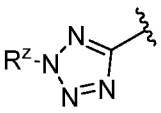
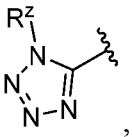
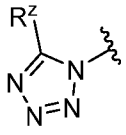
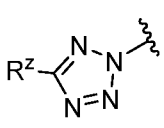
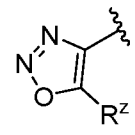
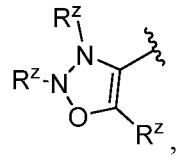
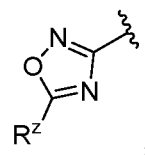
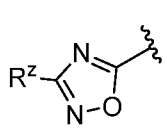
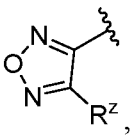
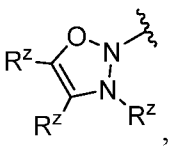
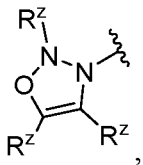
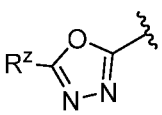
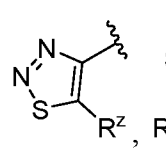
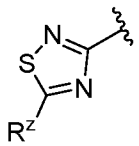
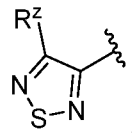
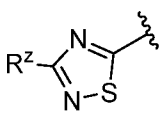
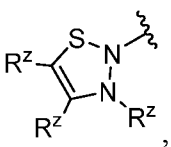
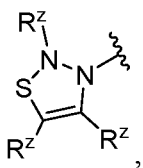
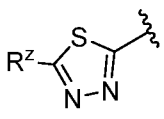
each - - is independently a single or double bond.

[00194] 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.

[00195] In some embodiments,  is  ,  , or .

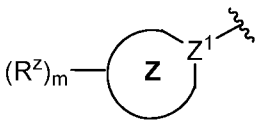
[00196] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

[00197] In some embodiments,  is  ,  .

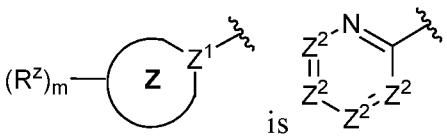































, or

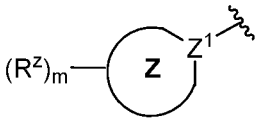
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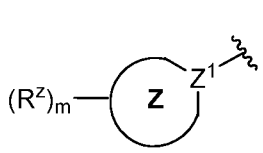
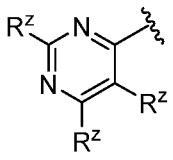
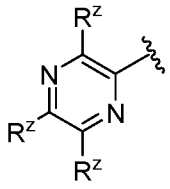
[00198] In some embodiments, is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom, and wherein the at least one N atom is adjacent to Z^1.



[00199] In some embodiments, is ; and each Z^2 is independently CR^z or N.



[00200] In some embodiments, is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[00201] In some embodiments,  is  ,  ,  ,  , or  .

[00202] In some embodiments, each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00203] In some embodiments, each R^z is independently H, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

[00204] In some embodiments, each R^z is independently H, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

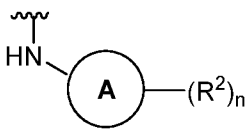
[00205] In some embodiments, each R^z is $-L^1-Y^1$. In some embodiments, L^1 is substituted or unsubstituted C_1-C_4alkylene; and Y^1 is substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

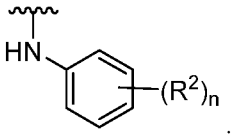
[00206] In some embodiments, each R^z is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1-C_6alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -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.

[00207] 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.

[00208] In some embodiments, R is -OR^1; and R^1 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

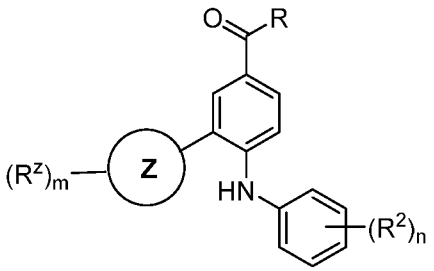
[00209] In some embodiments, R is -$N(R^1)_2$; and each R^1 is independently H, -(SO_2)R^4, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two R^1 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. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[00210] In some embodiments, 

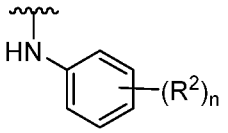
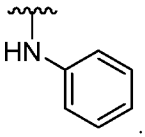
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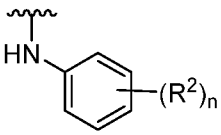
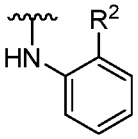
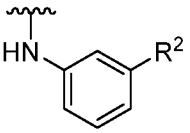
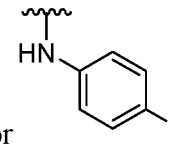
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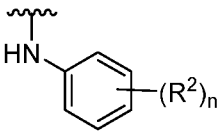
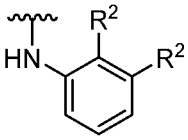
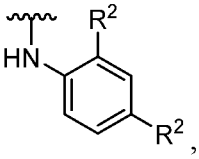
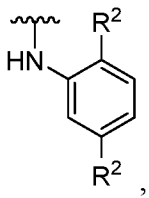
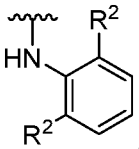
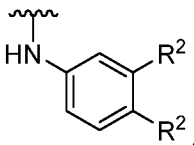
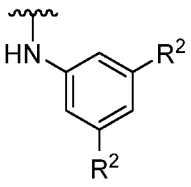
[00211] In some embodiments, the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:

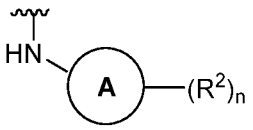
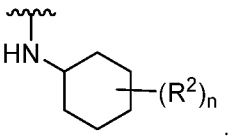


Formula (Ib).

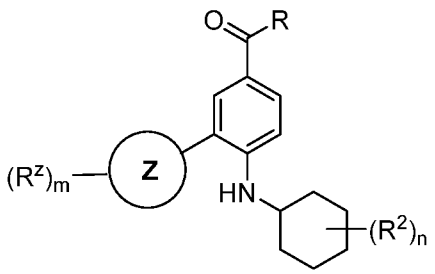
[00212] In some embodiments,  is  .

[00213] In some embodiments,  is  ,  , or  .

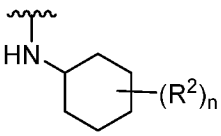
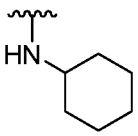
[00214] In some embodiments,  is  ,  ,  ,  ,  , or  .

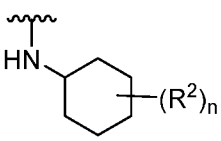
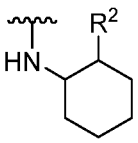
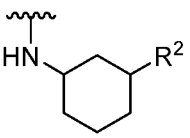
[00215] In some embodiments,  is  .

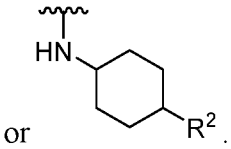
[00216] In some embodiments, the compound has the structure of Formula (Ic), or a pharmaceutically acceptable salt thereof:

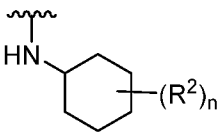
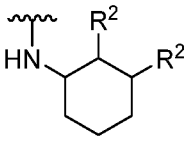
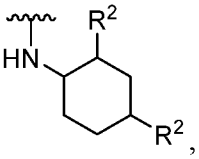
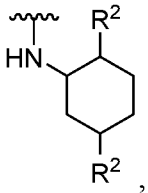
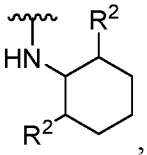
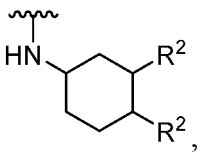
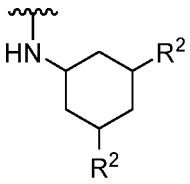
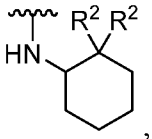
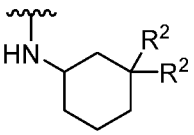
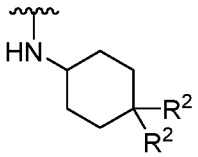


Formula (Ic).

[00217] In some embodiments,  is  .

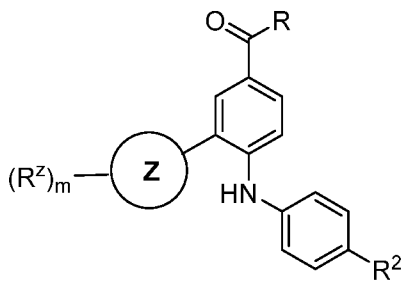
[00218] In some embodiments,  is  ,  ,


or .

[00219] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  , or  .

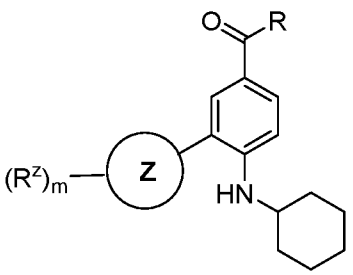
[00220] In some embodiments, each R^2 is independently H, -F, -I, -Cl, -N_3, -CN, -OR^4, -SR^4, -$(SO_2)R^4$, -$N(R^4)_2$, -CO_2R^4, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted aryl.

[00221] In some embodiments, the compound has the structure of Formula (Id), or a pharmaceutically acceptable salt thereof:



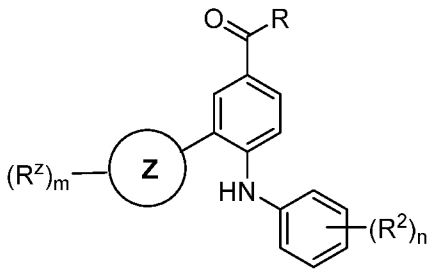
Formula (Id).

[00222] In some embodiments, the compound has the structure of Formula (Ie), or a pharmaceutically acceptable salt thereof:



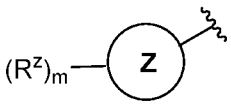
Formula (Ie).

[00223] Provided in another aspect is a compound of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II)

wherein,

 is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom or a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom;

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, 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 C_2-C_{10} 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_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2-C_{10}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 H or substituted or unsubstituted C$_1$-C$_6$alkyl;

Y^2 is H, substituted or unsubstituted C$_1$-C$_6$alkyl, substituted or unsubstituted C$_1$-C$_6$haloalkyl, substituted or unsubstituted C$_1$-C$_6$heteroalkyl, substituted or unsubstituted C$_3$-C$_{10}$cycloalkyl, substituted or unsubstituted C$_2$-C$_{10}$heterocycloalkyl, substituted or unsubstituted 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

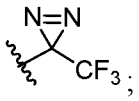
form a substituted or unsubstituted N-containing heterocycle;

R is -OR^1 or -N(R^1)$_2$;

each R^1 is independently H, -(SO$_2$)R^4, substituted or unsubstituted C$_1$-C$_6$alkyl, substituted or unsubstituted C$_1$-C$_6$haloalkyl, substituted or unsubstituted C$_1$-C$_6$heteroalkyl, substituted or unsubstituted C$_3$-C$_{10}$cycloalkyl, substituted or unsubstituted C$_2$-C$_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^1 on the same N atom are taken together with the N atom to which they are attached to form

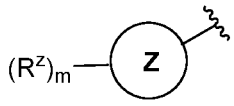
a substituted or unsubstituted N-containing heterocycle;

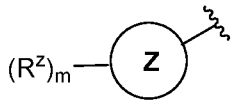
each R^2 is independently H, -F, -I, -Cl, N$_3$, -CN, -OR^4, -SR^4, -(SO$_2$)R^4, -N(R^4)$_2$, -CO$_2$R^4, substituted or unsubstituted C$_1$-C$_6$alkyl, substituted or unsubstituted C$_1$-C$_6$haloalkyl, substituted or unsubstituted C$_1$-C$_6$heteroalkyl, substituted or unsubstituted C$_3$-C$_{10}$cycloalkyl, substituted or unsubstituted C$_2$-C$_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or  ;

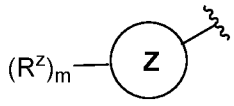
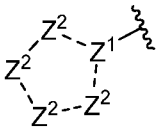
n is 0, 1, 2, 3, 4, or 5; and

each R^4 is independently H, substituted or unsubstituted C$_1$-C$_6$alkyl, substituted or unsubstituted C$_1$-C$_6$haloalkyl, substituted or unsubstituted C$_1$-C$_6$heteroalkyl, substituted or unsubstituted C$_3$-C$_{10}$cycloalkyl, substituted or unsubstituted C$_2$-C$_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

[00224] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom.

[00225] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing 1-4 N atoms, 0-2 O atoms, and 0-2 S atoms.

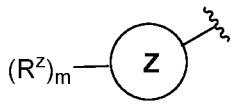
[00226] In some embodiments,  is  ;

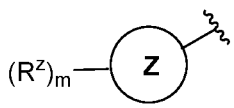
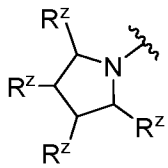
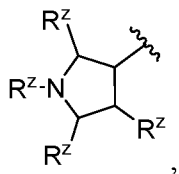
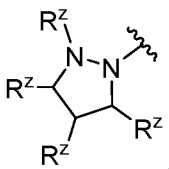
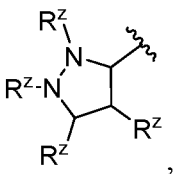
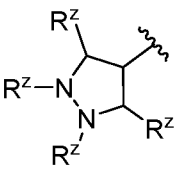
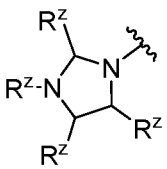
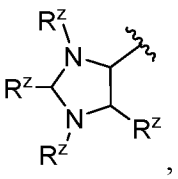
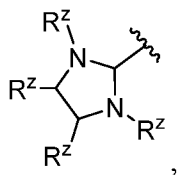
Z^1 is -N-, -CH-, or -C-;

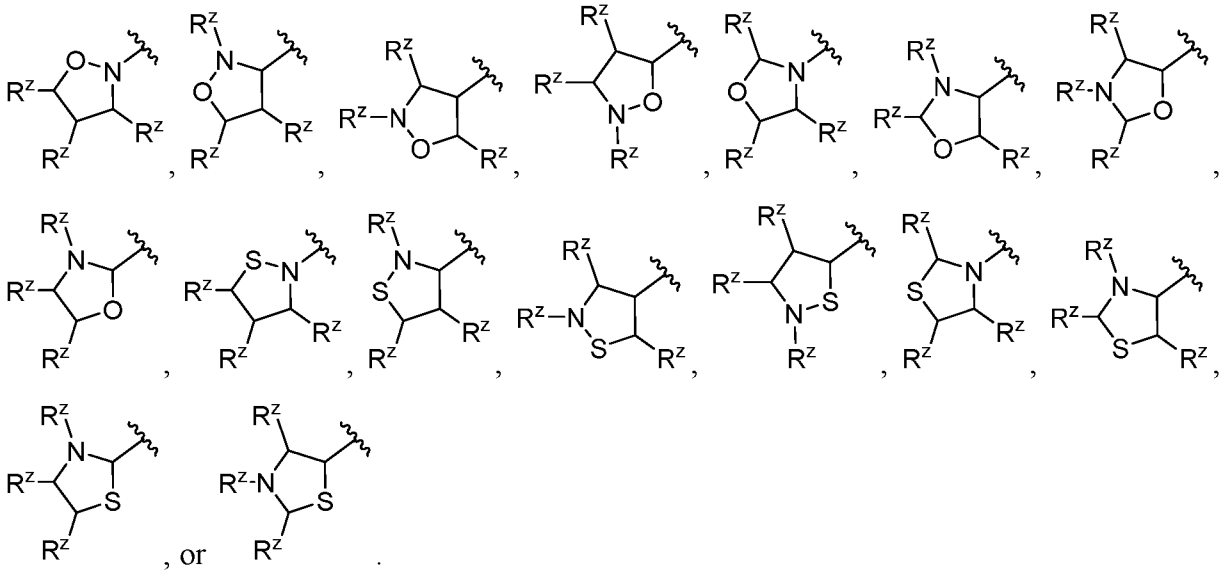
each Z^2 is independently $-CR^z-$, $-CHR^z-$, $-C(R^z)_2-$, $-NR^z-$, -N-, -O-, or -S-;

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

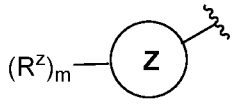
with the provision that the 5-membered heterocyclic ring contains at least one N atom.

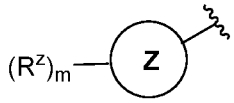
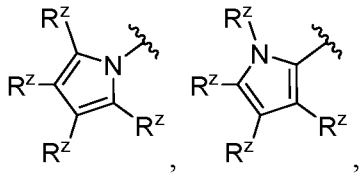
[00227] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

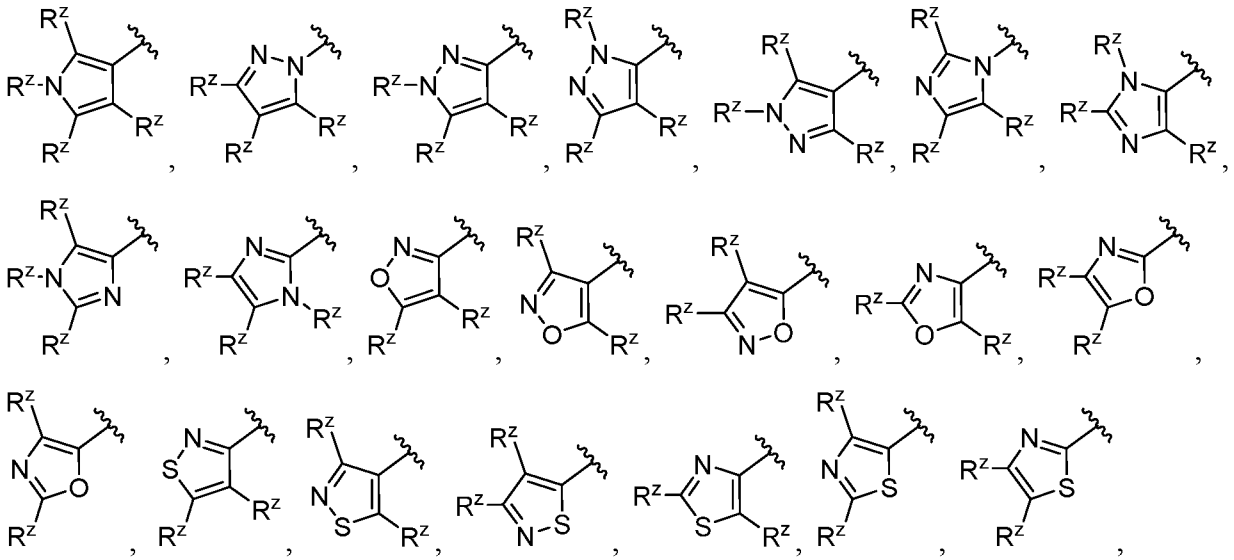
[00228] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  ,

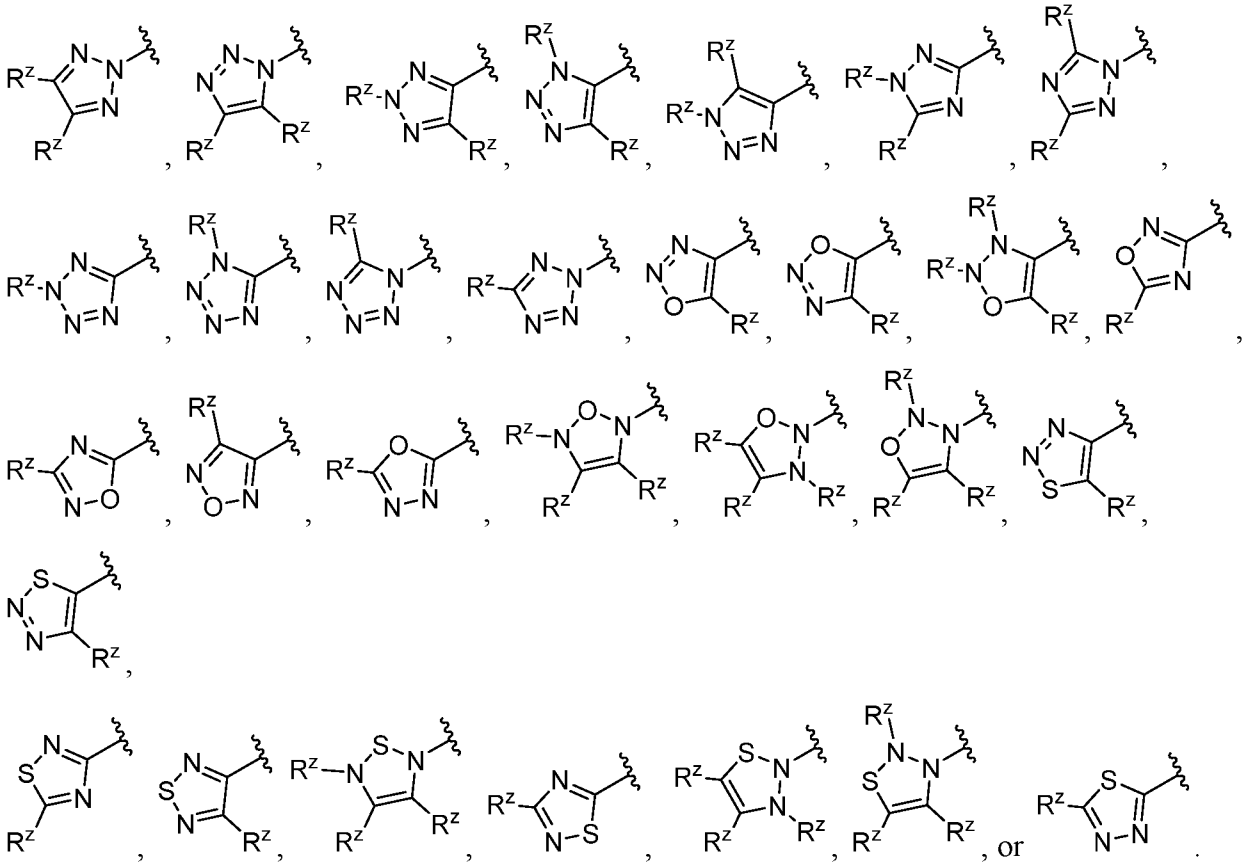


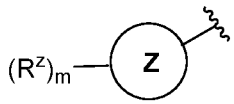
, or .

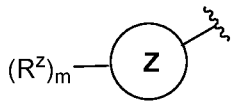
[00229] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

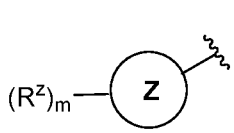
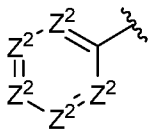
[00230] In some embodiments,  is 





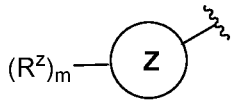
[00231] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom.

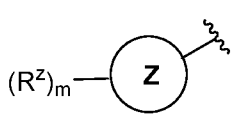
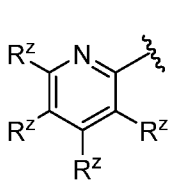
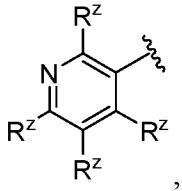
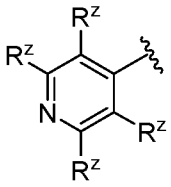
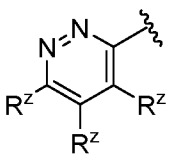
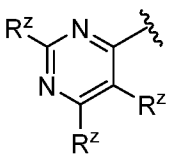
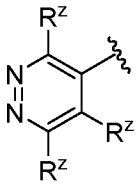
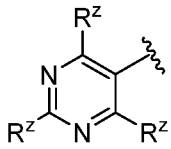
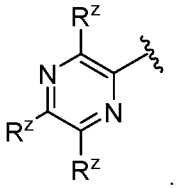
[00232] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing 1 or 2 N atoms.

[00233] In some embodiments,  is  ;

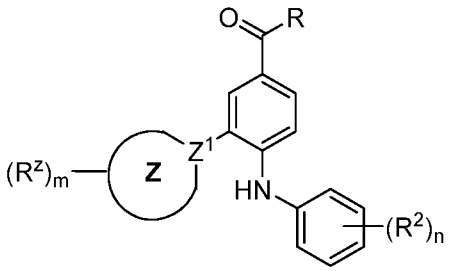
each Z^2 is independently CR^z or N; and

at least one Z^2 is N.

[00234] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[00235] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  , or  .

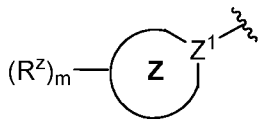
[00236] In some embodiments, the compound has the structure of Formula (IIa), or a pharmaceutically acceptable salt thereof:

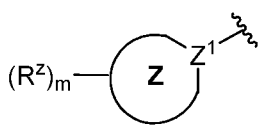
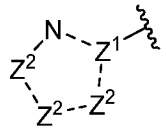
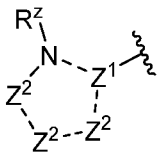


Formula (IIa)

wherein:

Z^1 is -N-, -CH-, or -C-.

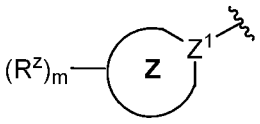
[00237] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom, and the at least one N atom is adjacent to Z^1.

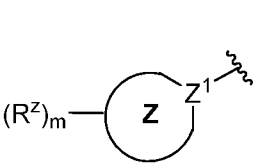
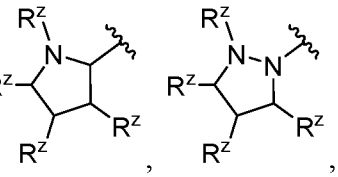
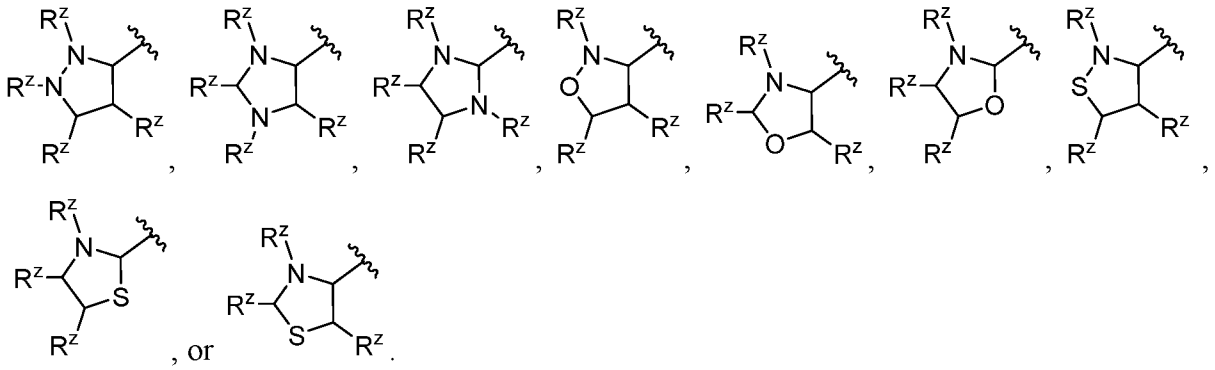
[00238] In some embodiments,  is  or  ;

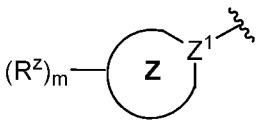
Z^1 is -N-, -CH-, or -C-;

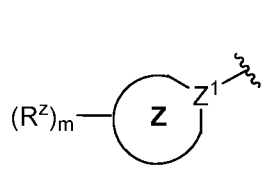
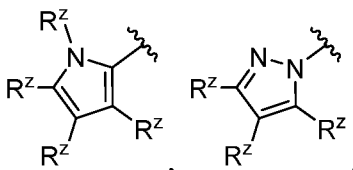
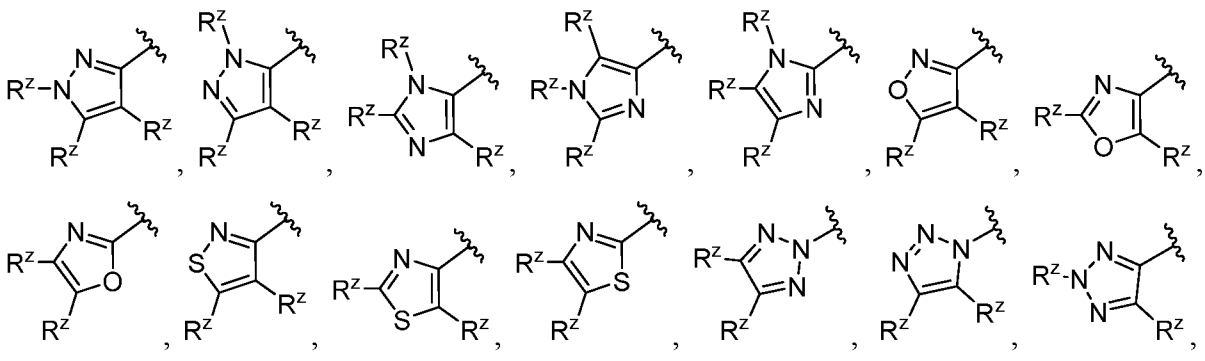
each Z^2 is independently $-CR^z-$, $-CHR^z-$, $-C(R^z)_2-$, $-NR^z-$, -N-, -O-, or -S-; and

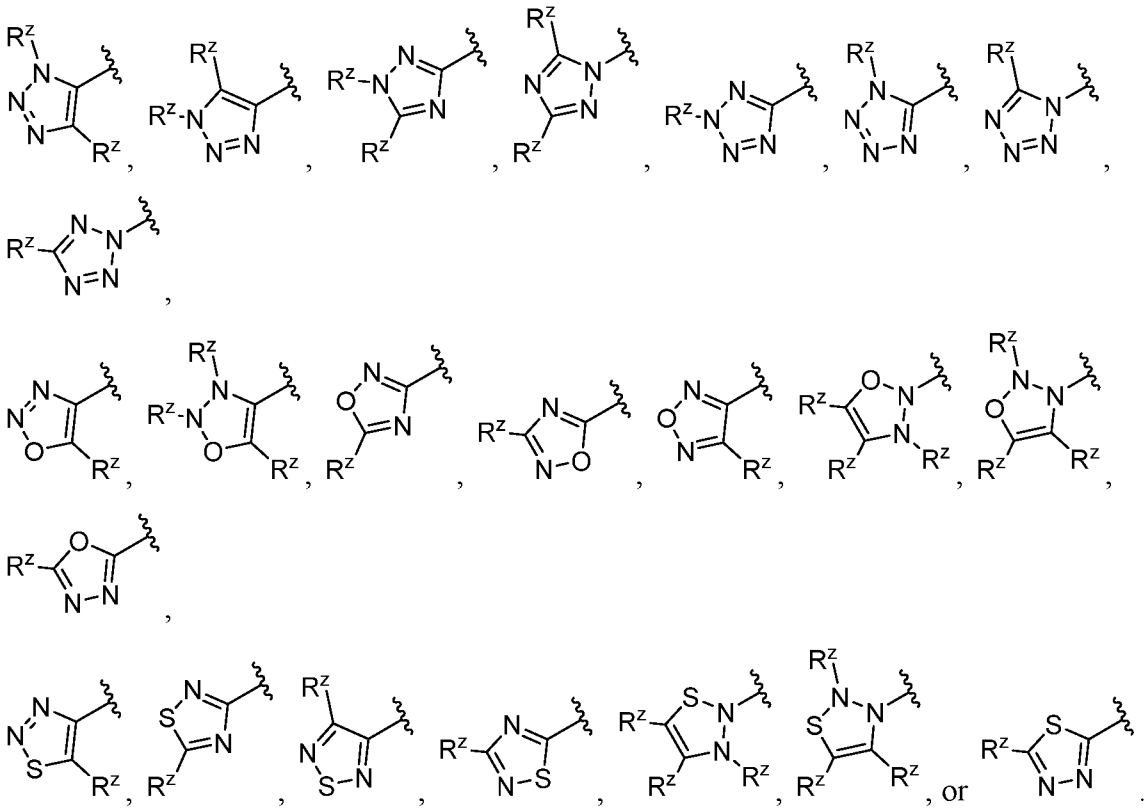
each - - is independently a single or double bond.

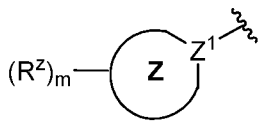
[00239] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

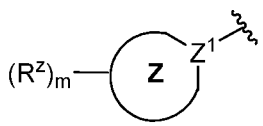
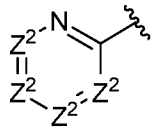
[00240] In some embodiments,  is  ,  , or .

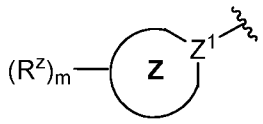
[00241] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

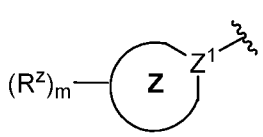
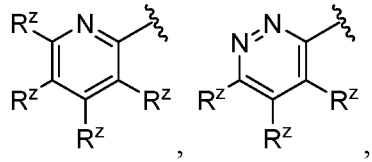
[00242] In some embodiments,  is  , 

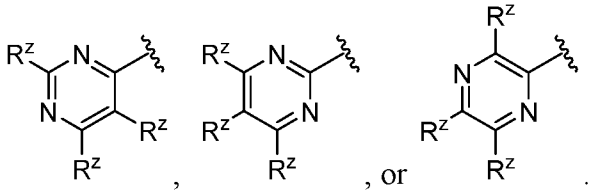


[00243] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom, and wherein the at least one N atom is adjacent to Z^1.

[00244] In some embodiments,  is  ; and each Z^2 is independently CR^z or N.

[00245] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[00246] In some embodiments,  is  ,



[00247] In some embodiments, each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00248] In some embodiments, each R^z is independently H, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

[00249] In some embodiments, each R^z is independently H, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[00250] 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.

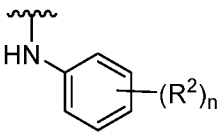
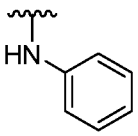
[00251] In some embodiments, each R^z is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1-C_6alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -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.

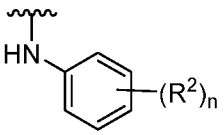
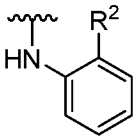
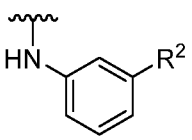
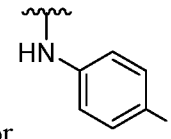
[00252] In some embodiments, L^2 is absent; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -NR^3(SO_2)-, -(SO_2)NR^3-, -(SO_2)NR^3-(C=O)-, -(SO_2)NR^3-(C=O)O-, -NR^3(SO_2)NR^3-(C=O)-, 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

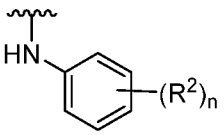
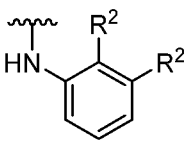
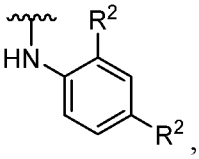
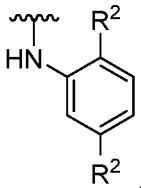
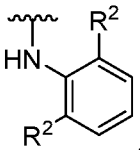
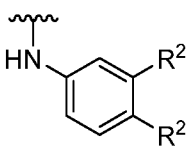
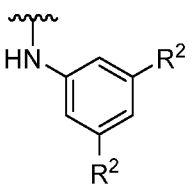
unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00253] In some embodiments, R is $-OR^1$; and R^1 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[00254] In some embodiments, R is $-N(R^1)_2$; and each R^1 is independently H, $-(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two R^1 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. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

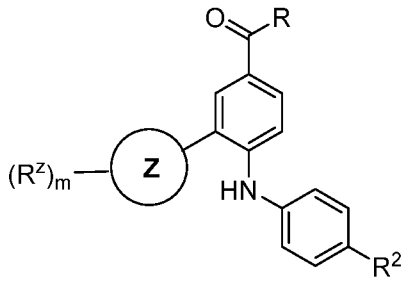
[00255] In some embodiments,  is  .

[00256] In some embodiments,  is  ,  ,  or .

[00257] In some embodiments,  is  ,  ,  ,  ,  , or  .

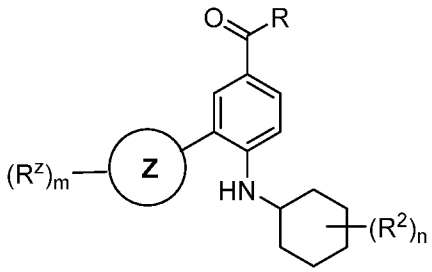
[00258] In some embodiments, each R^2 is independently H, -F, -I, -Cl, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted aryl.

[00259] In some embodiments, the compound has the structure of Formula (IIb), or a pharmaceutically acceptable salt thereof:



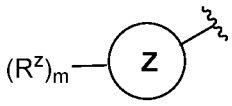
Formula (IIb).

[00260] Provided in another aspect is a compound of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein,



is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom or a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom;

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, 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 C_2-C_{10} 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_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2-C_{10}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 H or substituted or unsubstituted C_1-C_6alkyl;

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;

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;

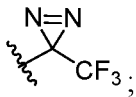
R is -OR^1 or -$N(R^1)_2$;

each R^1 is independently H, -(SO_2)R^4, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^1 on the same N atom are taken together with the N atom to which they are attached to form

a substituted or unsubstituted N-containing heterocycle;

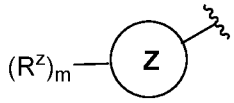
each R^2 is independently H, halogen, -N_3, -CN, -OR^4, -SR^4, -(SO_2)R^4, -$N(R^4)_2$, -CO_2R^4,

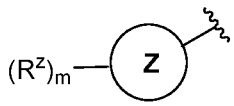
substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or  ;

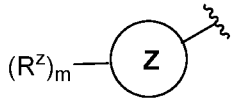
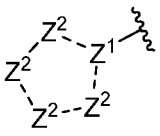
n is 0, 1, 2, 3, 4, or 5; and

each R^4 is independently 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

[00261] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom.

[00262] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing 1-4 N atoms, 0-2 O atoms, and 0-2 S atoms.

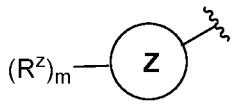
[00263] In some embodiments,  is  ;

Z^1 is -N-, -CH-, or -C-;

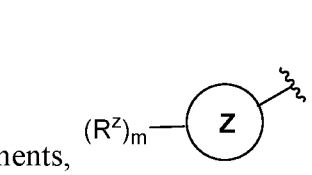
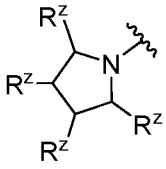
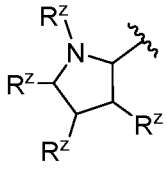
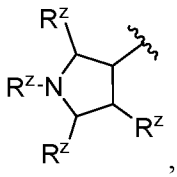
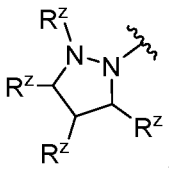
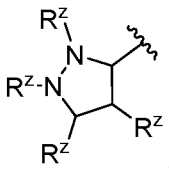
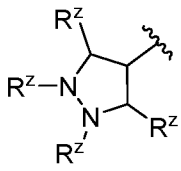
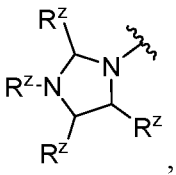
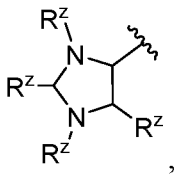
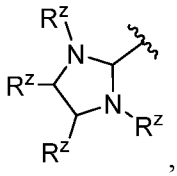
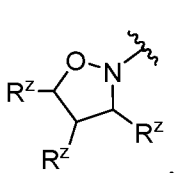
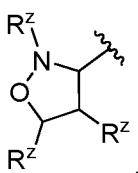
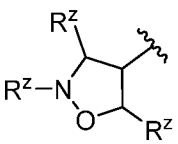
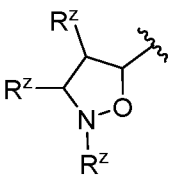
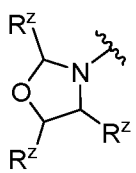
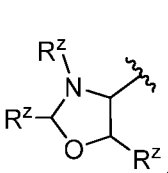
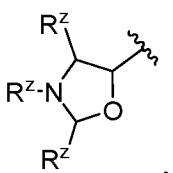
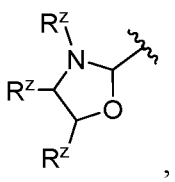
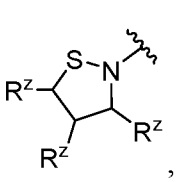
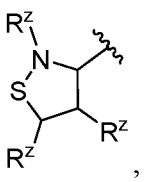
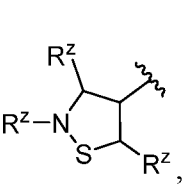
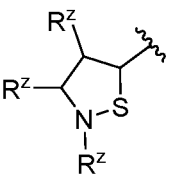
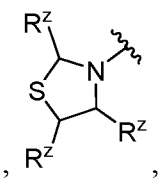
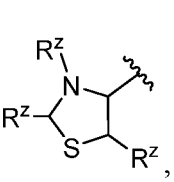
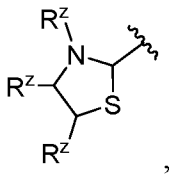
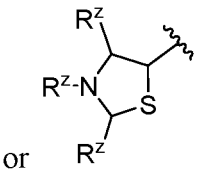
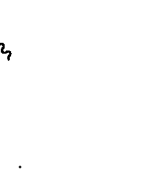
each Z^2 is independently $-CR^z$-, $-CHR^z$-, $-C(R^z)_2$-, $-NR^z$-, -N-, -O-, or -S-;

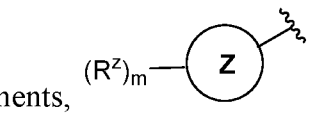
each - - is independently a single or double bond; and

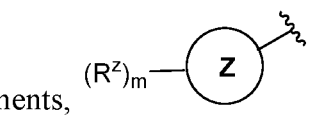
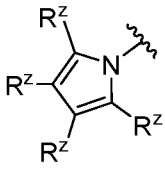
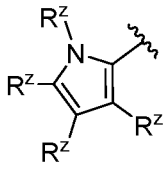
with the provision that the 5-membered heterocyclic ring contains at least one N.

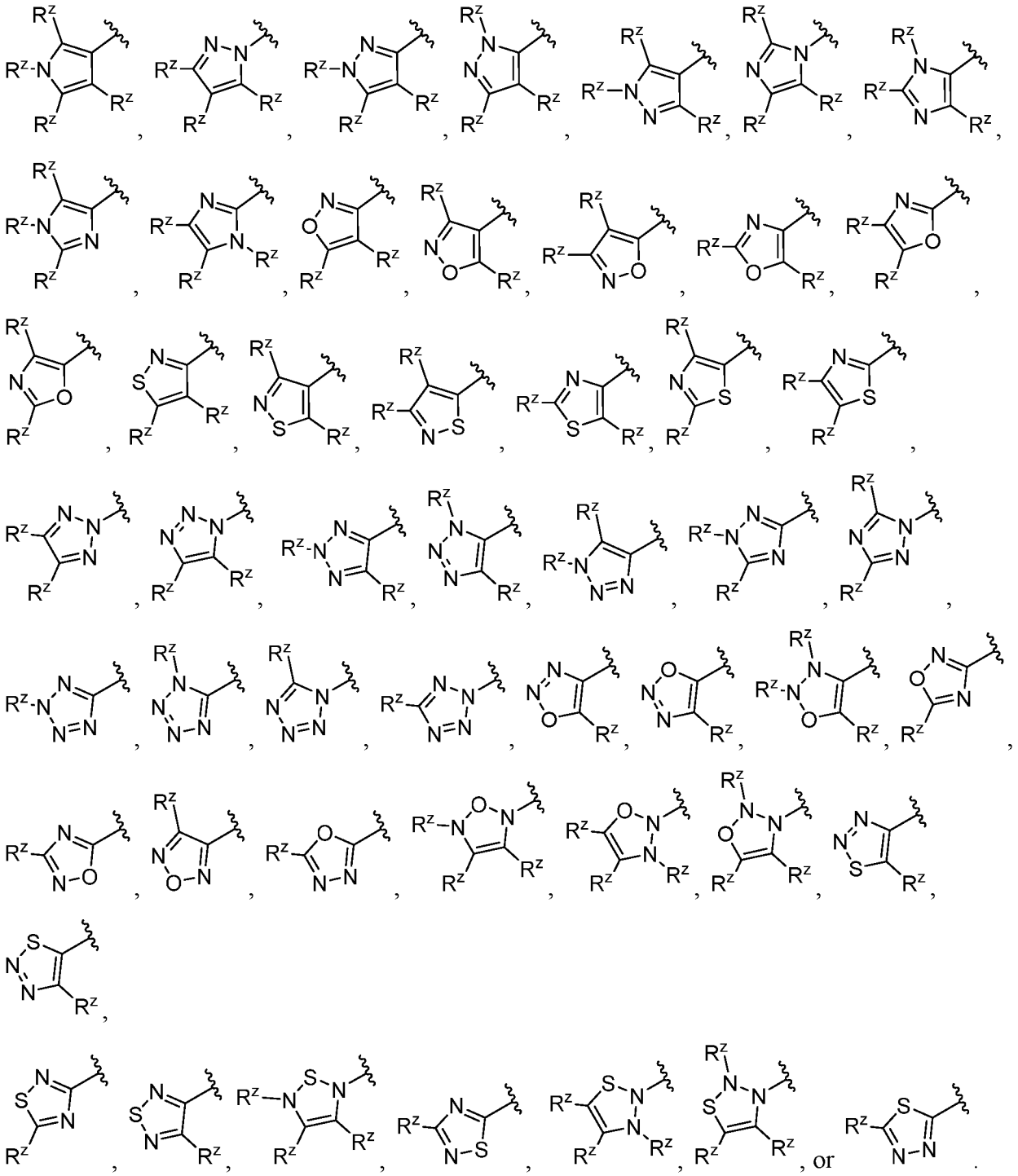
[00264] In some embodiments,  is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted

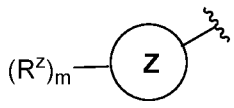
isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

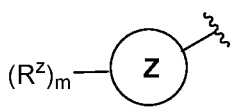
[00265] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , , , or .

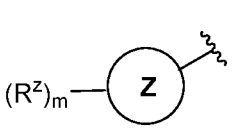
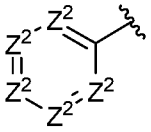
[00266] In some embodiments,  is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

[00267] In some embodiments,  is  ,  ,



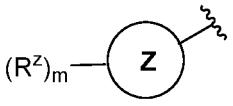
[00268] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom.

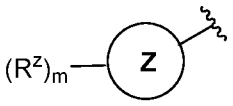
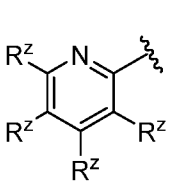
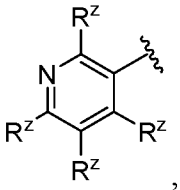
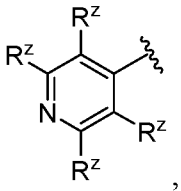
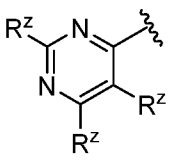
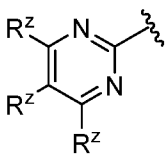
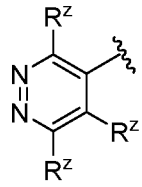
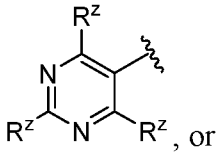
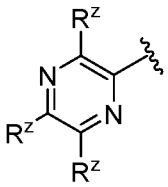
[00269] In some embodiments,  is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing 1 or 2 N atoms.

[00270] In some embodiments,  is  ;

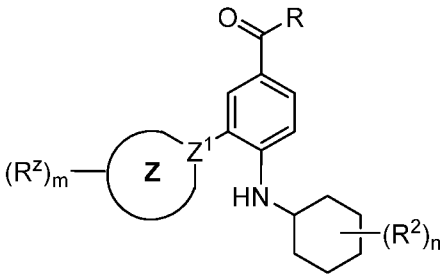
each Z^2 is independently CR^z or N; and

at least one Z^2 is N.

[00271] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[00272] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  , or  .

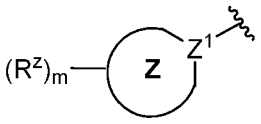
[00273] In some embodiments, the compound has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:

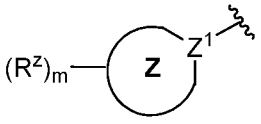
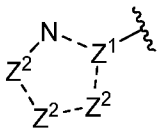
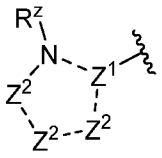


Formula (IIIa)

wherein:

Z^1 is -N-, -CH-, or -C-.

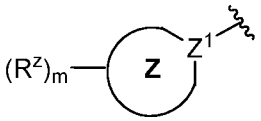
[00274] In some embodiments,  is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom, and the at least one N atom is adjacent to Z^1.

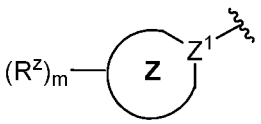
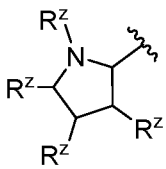
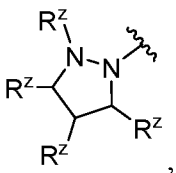
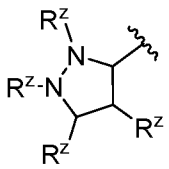
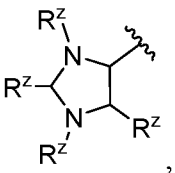
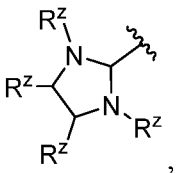
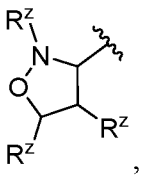
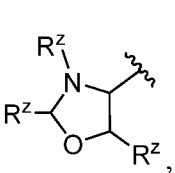
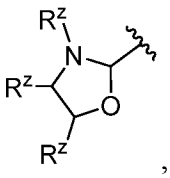
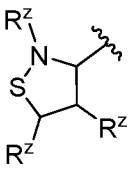
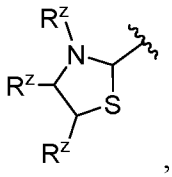
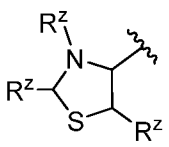
[00275] In some embodiments,  is  or  ;

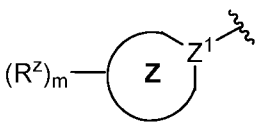
Z^1 is -N-, -CH-, or -C-;

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

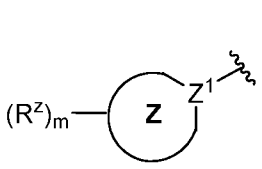
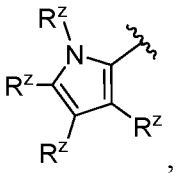
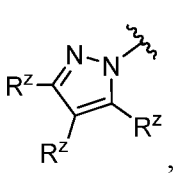
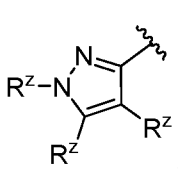
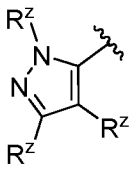
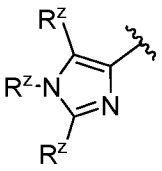
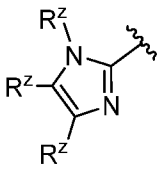
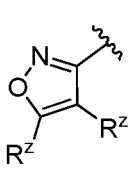
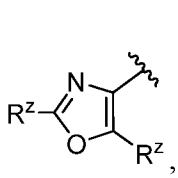
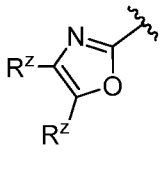
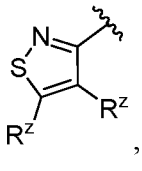
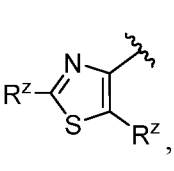
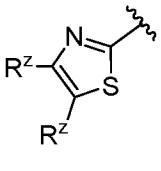
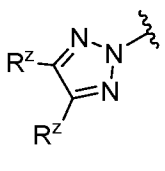
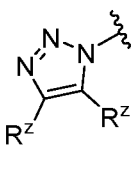
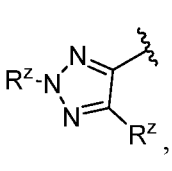
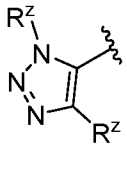
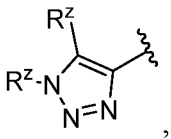
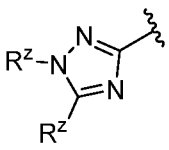
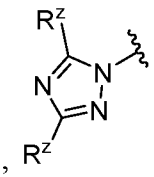
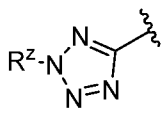
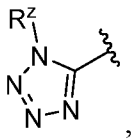
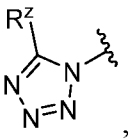
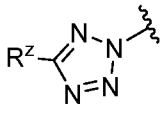
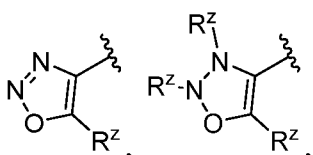
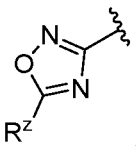
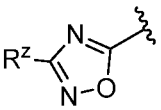
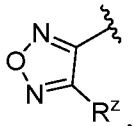
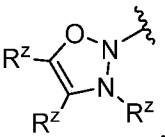
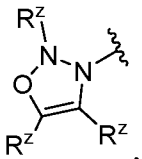
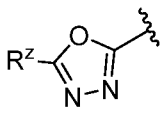
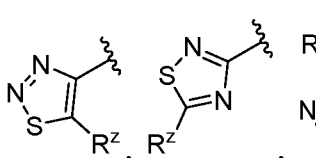
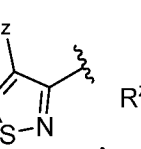
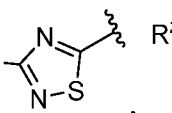
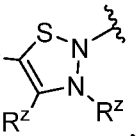
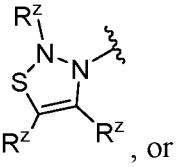
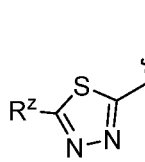
each - - is independently a single or double bond.

[00276] 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.

[00277] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[00278] 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

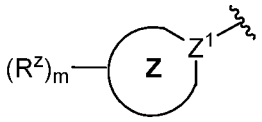
triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted dithiazolyl.

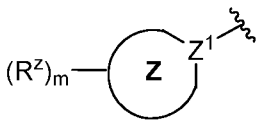
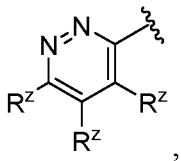
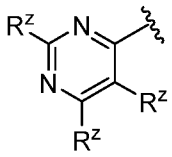
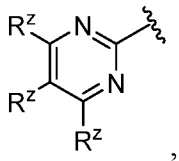
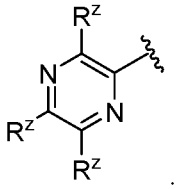
[00279] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  , , , , , , , , , or .

[00280] 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.

[00281] In some embodiments, is ; and

each Z^2 is independently CR^z or N.

[00282] In some embodiments,  is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

[00283] In some embodiments,  is  ,  ,  ,  , or  .

[00284] In some embodiments, each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00285] In some embodiments, each R^z is independently H, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

[00286] In some embodiments, each R^z is independently H, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[00287] 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.

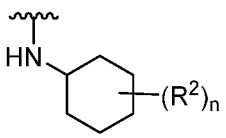
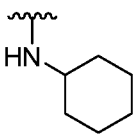
[00288] In some embodiments, each R^z is $-L^2-L^3-Y^2$. In some embodiments, L^2 is substituted or unsubstituted C_1-C_6alkylene; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -$NR^3$$(SO_2)$$NR^3$-, -$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

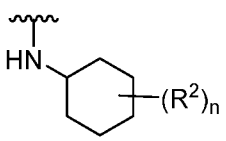
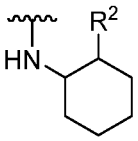
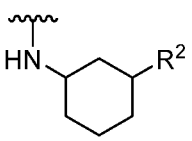
unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

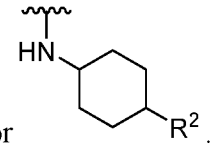
[00289] In some embodiments, L^2 is absent; L^3 is -O-, -S-, -(S=O)-, -(SO_2)-, -NR^3-, -(C=O)-, -(C=O)O-, -O(C=O)-, -(C=O)NR^3-, -(C=O)NR^3-O-, -NR^3(C=O)-, -NR^3(C=O)NR^3-, -O(C=O)NR^3-, -NR^3(C=O)O-, -NR^3(SO_2)NR^3-, -NR^3(SO_2)-, -(SO_2)NR^3-, -(SO_2)NR^3-(C=O)-, -(SO_2)NR^3-(C=O)O-, -NR^3(SO_2)NR^3-(C=O)-, 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.

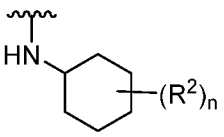
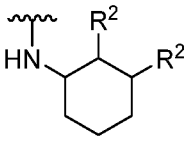
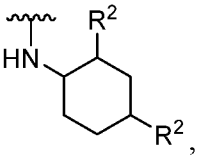
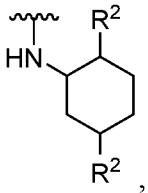
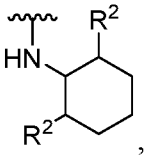
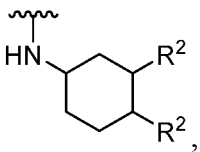
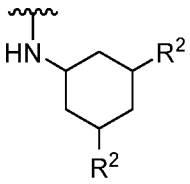
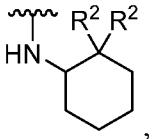
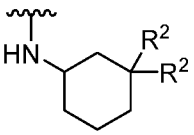
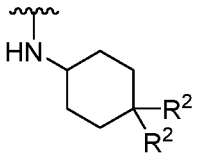
[00290] In some embodiments, R is -OR^1; and R^1 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[00291] In some embodiments, R is -$N(R^1)_2$; and each R^1 is independently H, -(SO_2)R^4, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two R^1 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. In some embodiments, R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

[00292] In some embodiments,  is  .

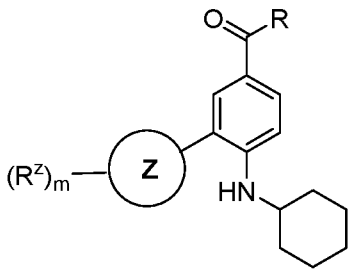
[00293] In some embodiments,  is  ,  ,


or .

[00294] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  , or  .

[00295] In some embodiments, each R^2 is independently H, halogen, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

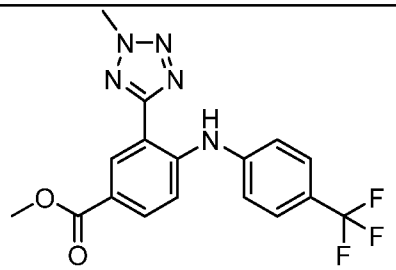
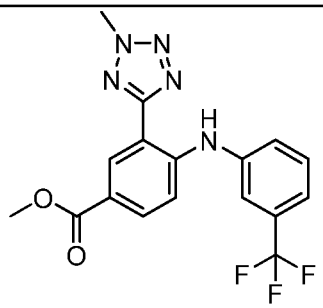
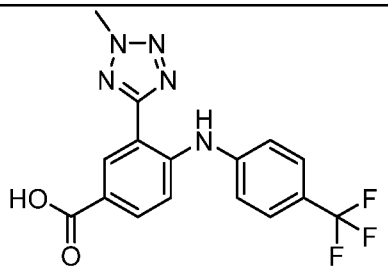
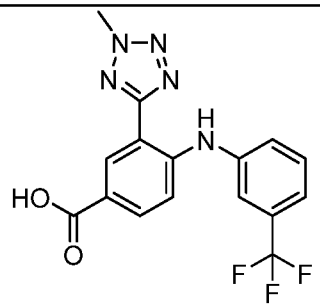
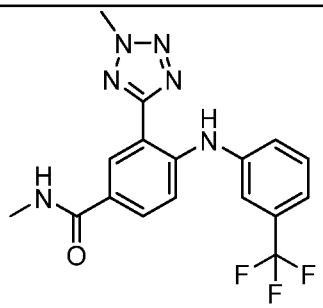
[00296] In some embodiments, the compound has the structure of Formula (IIIb), or a pharmaceutically acceptable salt thereof:

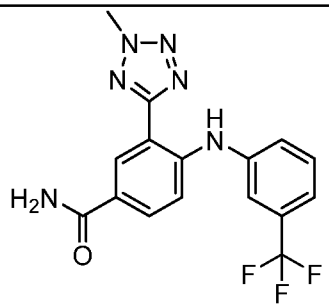
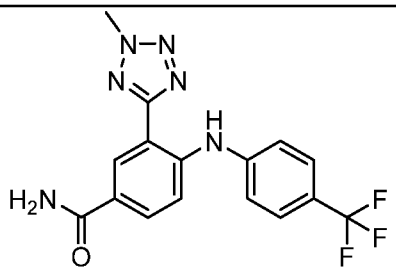
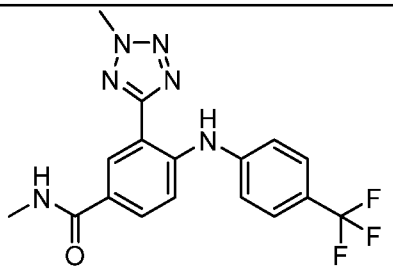
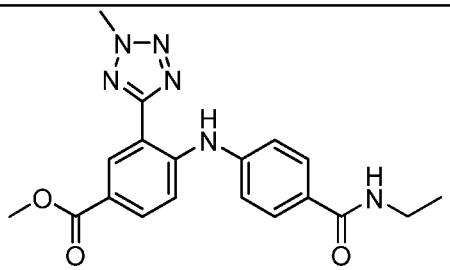
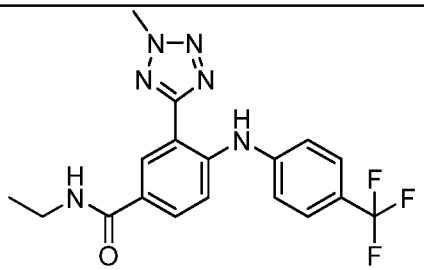
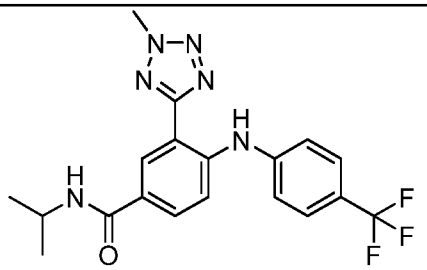


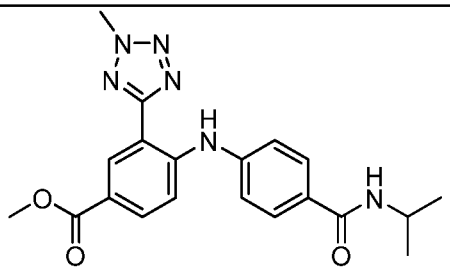
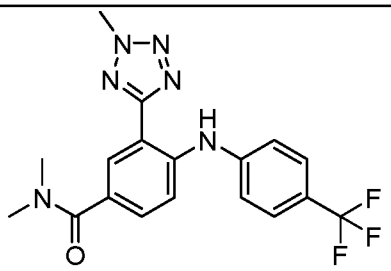
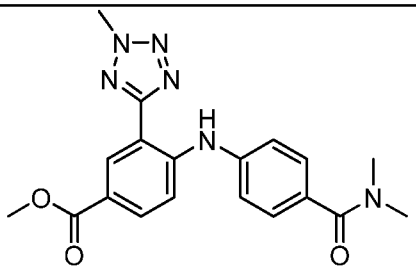
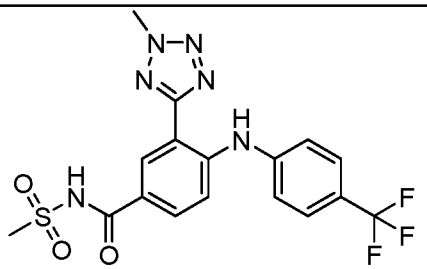
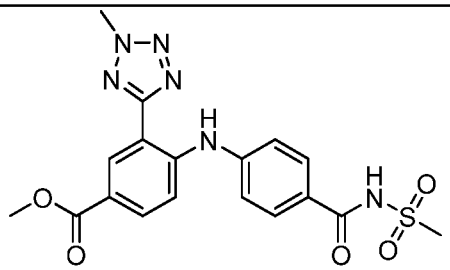
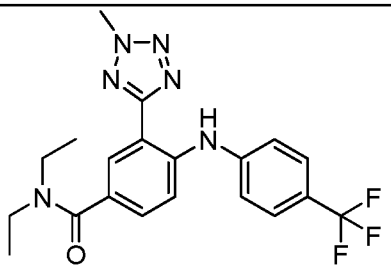
Formula (IIIb).

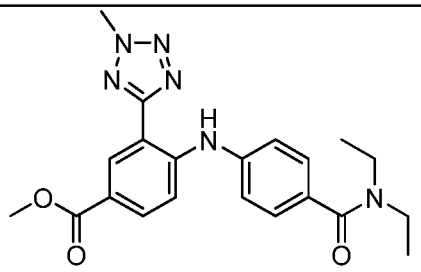
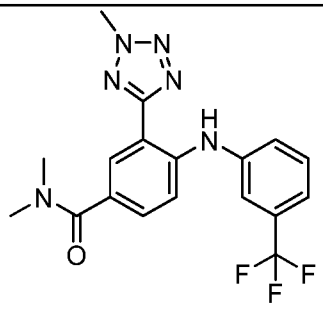
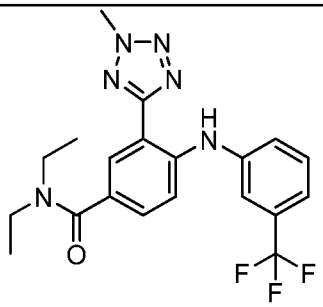
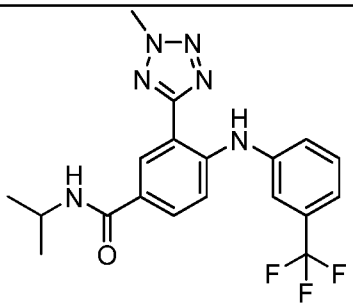
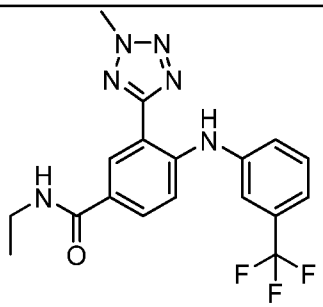
[00297] In some embodiments, the compound disclosed herein has the structure provided in Table 1.

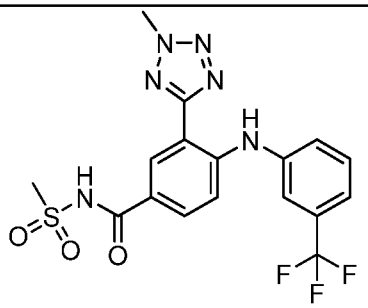
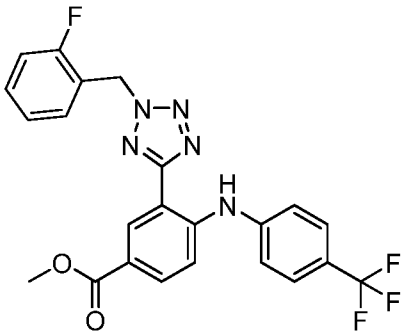
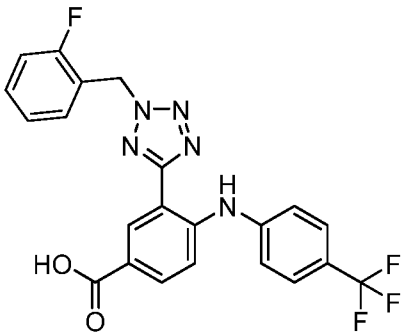
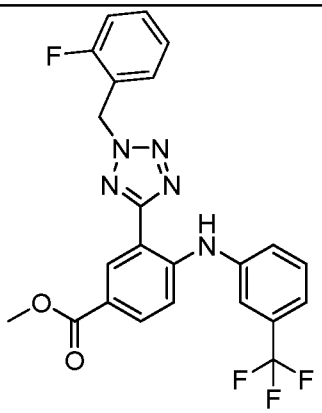
TABLE 1

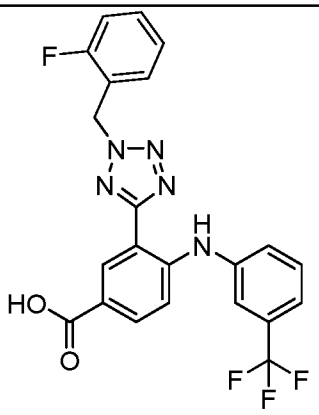
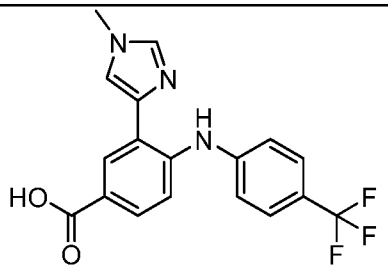
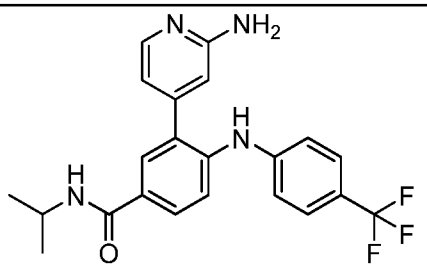
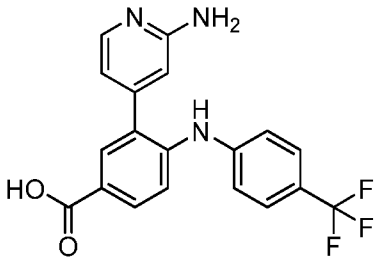
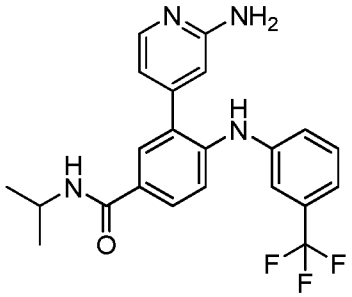
Compound No.	Structure	Name
1		methyl 3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate
2		methyl 3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoate
3		3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
4		3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoic acid
5		N-methyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide

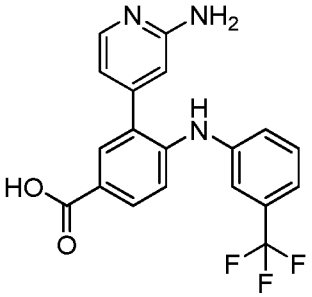
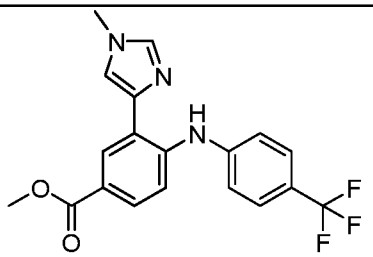
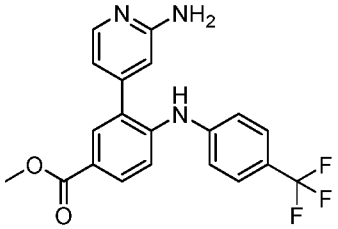
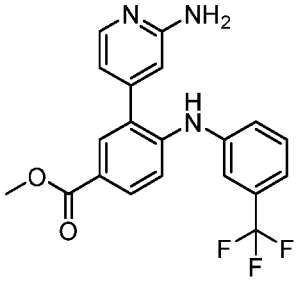
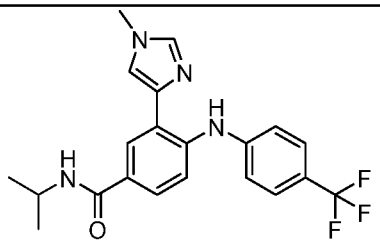
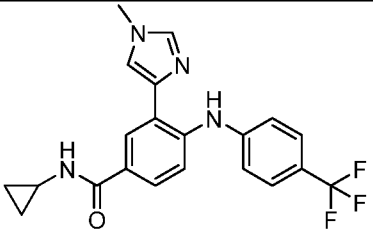
Compound No.	Structure	Name
6		3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide
7		3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide
8		N-methyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide
9		methyl 4-((4-(ethylcarbamoyl)phenyl)amino)-3-(2-methyl-2H-tetrazol-5-yl)benzoate
10		N-ethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide
11		N-isopropyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide

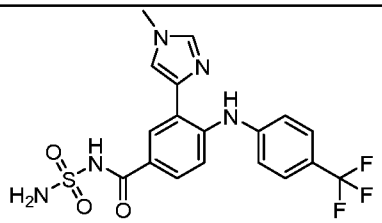
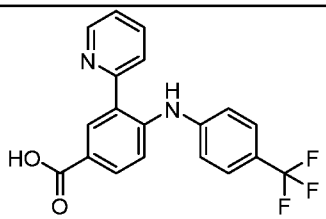
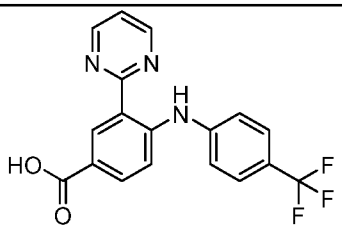
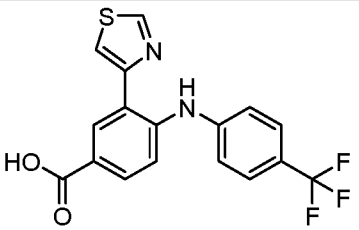
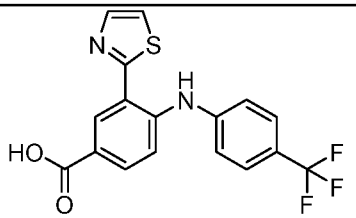
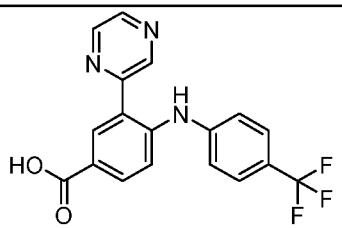
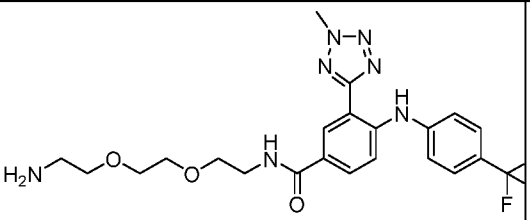
Compound No.	Structure	Name
12		methyl 4-((4-(isopropylcarbamoyl)phenyl)amino)-3-(2-methyl-2H-tetrazol-5-yl)benzoate
13		N,N-dimethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide
14		methyl 4-((4-(dimethylcarbamoyl)phenyl)amino)-3-(2-methyl-2H-tetrazol-5-yl)benzoate
15		3-(2-methyl-2H-tetrazol-5-yl)-N-(methylsulfonyl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide
16		methyl 3-(2-methyl-2H-tetrazol-5-yl)-4-((4-((methylsulfonyl)carbamoyl)phenyl)amino)benzoate
17		N,N-diethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide

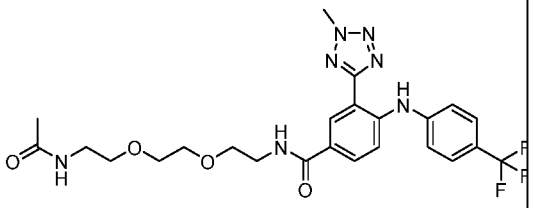
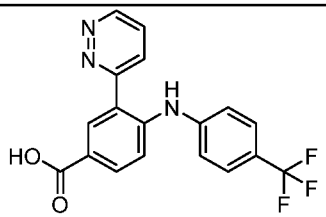
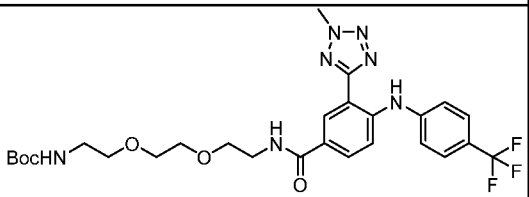
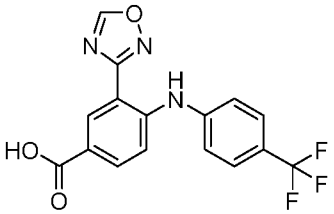
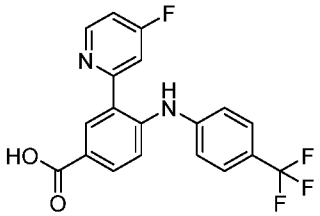
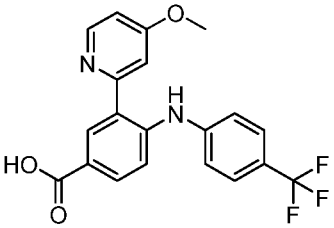
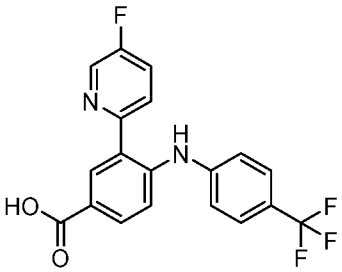
Compound No.	Structure	Name
18		methyl 4-((4-(diethylcarbamoyl)phenyl)amino)-3-(2-methyl-2H-tetrazol-5-yl)benzoate
19		N,N-dimethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide
20		N,N-diethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide
21		N-isopropyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide
22		N-ethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide

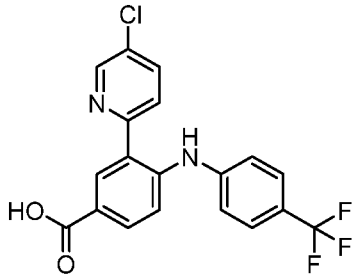
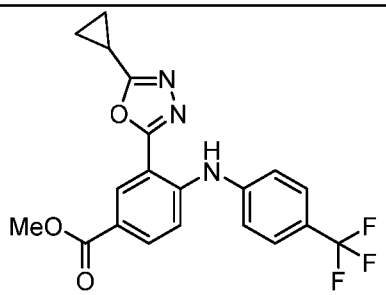
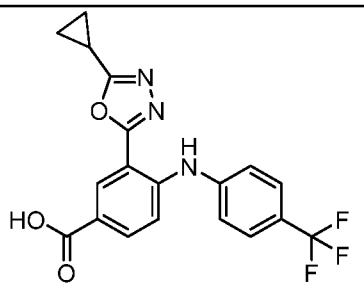
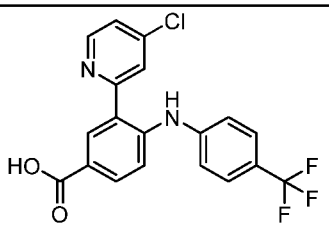
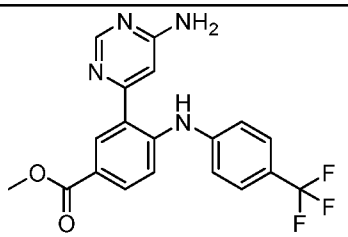
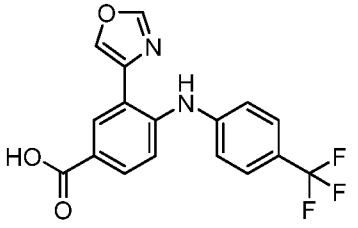
Compound No.	Structure	Name
23		3-(2-methyl-2H-tetrazol-5-yl)-N-(methylsulfonyl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide
24		methyl 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate
25		3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
26		methyl 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoate

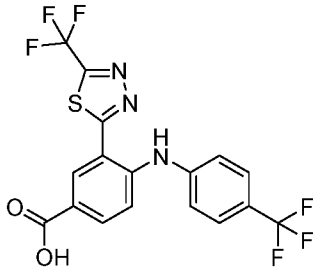
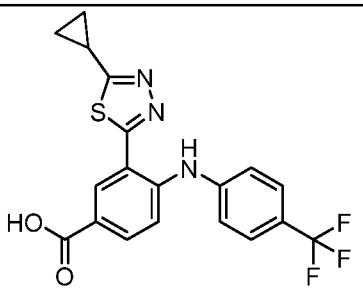
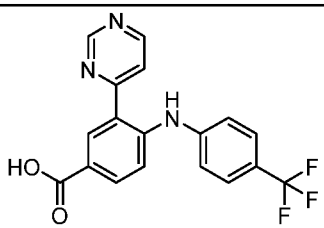
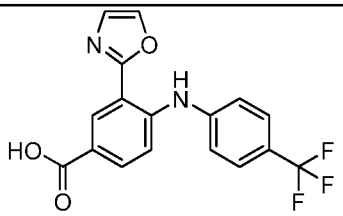
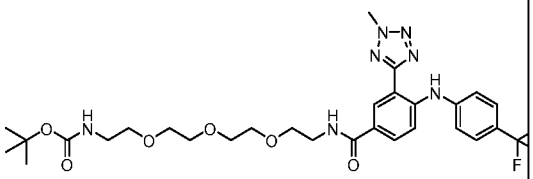
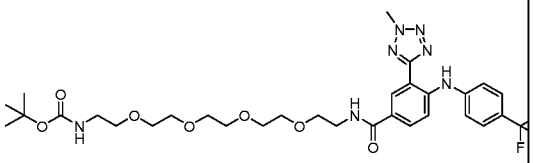
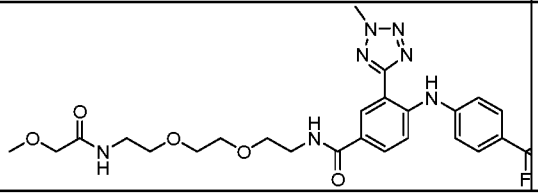
Compound No.	Structure	Name
27		3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoic acid
28		3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
29		3-(2-aminopyridin-4-yl)-N-isopropyl-4-((4-(trifluoromethyl)phenyl)amino)benzamide
30		3-(2-aminopyridin-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
31		3-(2-aminopyridin-4-yl)-N-isopropyl-4-((3-(trifluoromethyl)phenyl)amino)benzamide

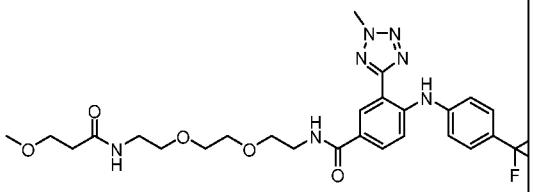
Compound No.	Structure	Name
32		3-(2-aminopyridin-4-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoic acid
33		methyl 3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate
34		methyl 3-(2-amino-4-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate
35		methyl 3-(2-amino-4-pyridyl)-4-[3-(trifluoromethyl)anilino]benzoate
36		*N*-Isopropyl-3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzamide
37		*N*-cyclopropyl-3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzamide

Compound No.	Structure	Name
38		3-(1-methylimidazol-4-yl)-*N*-sulfamoyl-4-[4-(trifluoromethyl)anilino]benzamide
39		3-(pyridin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
40		3-(pyrimidin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
41		3-(thiazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
42		3-(thiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
43		3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
44		N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide

Compound No.	Structure	Name
45		N-(2-(2-(2-acetamidoethoxy)ethoxy)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide
46		3-pyridazin-3-yl-4-[4-(trifluoromethyl)anilino]benzoic acid
47		tert-butyl (2-(2-(2-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamido)ethoxy)ethoxy)ethyl)carbamate
48		3-(1,2,4-oxadiazol-3-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid
49		3-(4-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid
50		3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
51		3-(5-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid

Compound No.	Structure	Name
52		3-(5-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid
53		methyl 3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate
54		3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
55		3-(4-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid
56		methyl 3-(6-aminopyrimidin-4-yl)-4-[4-(trifluoromethyl)anilino]benzoate
57		3-(oxazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

Compound No.	Structure	Name
58		4-[4-(trifluoromethyl)anilino]-3-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]benzoic acid
59		3-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
60		3-pyrimidin-4-yl-4-[4-(trifluoromethyl)anilino]benzoic acid
61		3-(oxazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid
62		tert-butyl (1-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)-1-oxo-5,8,11-trioxa-2-azatridecan-13-yl)carbamate
63		tert-butyl (1-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)-1-oxo-5,8,11,14-tetraoxa-2-azahexadecan-16-yl)carbamate
64		3-(2-methyl-2H-tetrazol-5-yl)-N-(4-oxo-2,8,11-trioxa-5-azatridecan-13-yl)-4-((4-

Compound No.	Structure	Name
		(trifluoromethyl)phenyl)amino)benzamide
65		3-(2-methyl-2H-tetrazol-5-yl)-N-(5-oxo-2,9,12-trioxa-6-azatetradecan-14-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide

Preparation of the Compounds

[00298] 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).

[00299] 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.

[00300] 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.

[00301] In some embodiments, the compounds disclosed herein are prepared as described in the Examples section.

Further Forms of Compounds Disclosed Herein

Isomers

[00302] Furthermore, in some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (*E*),

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

Labeled compounds

[00303] 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.

[00304] 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

[00305] 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.

[00306] 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

[00307] 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.

[00308] 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

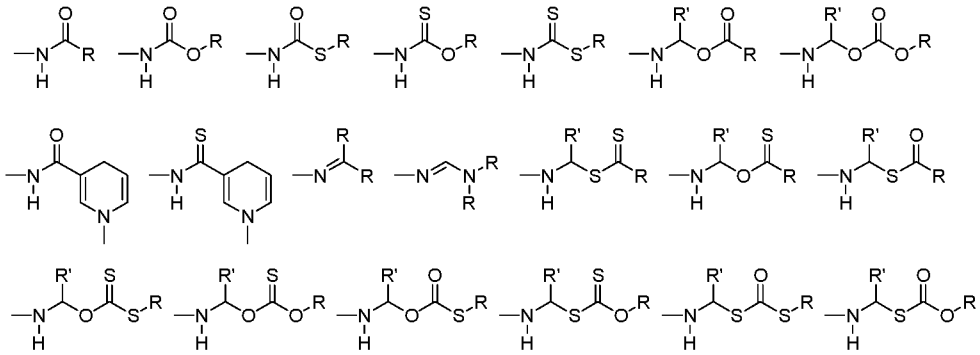
[00309] In some embodiments, the compounds described herein exist in prodrug form. The disclosure provides for methods of treating diseases by administering such prodrugs. The disclosure further provides for methods of treating diseases by administering such prodrugs as pharmaceutical compositions.

[00310] 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 include 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.

[00311] 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.

[00312] 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.

[00313] Amine-derived prodrugs include, but are not limited to, the following groups and combinations of groups:



as well as sulfonamides and phosphonamides.

[00314] 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

[00315] 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.

[00316] 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

[00317] 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.

[00318] 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.

[00319] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any one of the compounds disclosed herein or a pharmaceutically acceptable salt thereof.

[00320] Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and any one of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof.

[00321] 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.

[00322] 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.

[00323] 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.

[00324] 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.

[00325] 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.

[00326] 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.

[00327] 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.

[00328] 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.

[00329] 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.

[00330] 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.

[00331] 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.

[00332] 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.

[00333] 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.

[00334] 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.

[00335] 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

[00336] 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.

[00337] 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.

[00338] 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.

[00339] 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

[00340] The Hippo signaling network (also known as the Salvador/Warts/Hippo (SWH) pathway) is a master regulator of cell proliferation, death, and differentiation. In some embodiments, the main function of the Hippo signaling pathway is to regulate negatively the transcriptional co-activators Yes-associated protein (YAP) and its paralogue, the transcriptional

co-activator with PDZ-binding motif (TAZ; also known as WWTR1) (**FIG. 1**). The Hippo kinase cascade phosphorylates and inhibits YAP/TAZ by promoting its cytoplasmic retention and degradation, thereby inhibiting the growth promoting function regulated under the YAP/TAZ control. In an un-phosphorylated/de-phosphorylated state, YAP, also known as YAP1 or YAP65, together with TAZ, are transported into the nucleus where they interact with TEAD family of transcription factors to upregulate genes that promote proliferation and migration, and inhibit apoptosis. In some instances, unregulated upregulation of these genes involved in proliferation, migration, and anti-apoptosis leads to development of cancer. In some instances, overexpression of YAP/TAZ is associated with cancer.

[00341] Additional core members of the Hippo signaling pathway comprise the serine/threonine kinases MST1/2 (homologues of *Hippo/Hpo* in Drosophila), Lats1/2 (homologues of *Warts/Wts*), and their adaptor proteins Sav1 (homologue of *Salvador/Sav*) and Mob (MOBKL1A and MOBKL1B; homologues of *Mats*), respectively (**FIG. 1**). In general, MST1/2 kinase complexes with the scaffold protein Sav1, which in turn phosphorylates and activates Lats1/2 kinase. Lats1/2 is also activated by the scaffold protein Mob. The activated Lats1/2 then phosphorylates and inactivates YAP or its paralog TAZ. The phosphorylation of YAP/TAZ leads to their nuclear export, retention within the cytoplasm, and degradation by the ubiquitin proteasome system.

[00342] 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.

[00343] 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.

[00344] 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.

[00345] 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.

[00346] In some embodiments, the Hippo pathway is regulated upstream by several different families of regulators (**FIG. 1**). In some instances, the Hippo pathway is regulated by the G-protein and its coupled receptors, the Crumbs complex, regulators upstream of the MST kinases, and the adherens junction.

YAP/TAZ Interaction with TEAD

[00347] In some embodiments, un-phosphorylated and/or dephosphorylated YAP/TAZ accumulates in the nucleus. Within the nucleus, YAP/TAZ interacts with the TEAD family of transcription factors (e.g. TEAD1, TEAD2, TEAD3, or TEAD4) to activate genes involved in anti-apoptosis and proliferation, such as for example *CTFG*, *Cyr61*, and *FGF1*.

[00348] In some embodiments, the compounds disclosed herein modulate the interaction between YAP/TAZ and TEAD. In some embodiments, the compounds disclosed herein bind to TEAD, YAP, or TAZ and prevent the interaction between YAP/TAZ and TEAD.

YAP/TAZ regulation mediated by G-proteins/GPCRs

[00349] In some embodiments, the Hippo pathway is regulated by the G protein-coupled receptor (GPCR) and G protein (also known as guanine nucleotide-binding proteins) family of proteins (**FIG. 2**). G proteins are molecular switches that transmit extracellular stimuli into the cell through GPCRs. In some instances, there are two classes of G proteins: monomeric small GTPases and heterotrimeric G protein complexes. In some instances, the latter class of complexes comprise of alpha (G_α), beta (G_β), and gamma (G_γ) subunits. In some cases, there are several classes of G_α subunits: $G_{q/11}\alpha$, $G_{12/13}\alpha$, $G_{i/o}\alpha$ (G inhibitory, G other), and $G_s\alpha$ (G stimulatory).

[00350] 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.

[00351] 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

[00352] $G_q\alpha$ (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.

[00353] 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.

[00354] 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*.

[00355] 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*.

[00356] 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

[00357] $G_{12/13}\alpha$ 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.

[00358] 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.

[00359] 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

[00360] $G_{i/o}\alpha$ (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.

[00361] 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-HT_1 and 5-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.

[00362] 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

[00363] $G_s\alpha$ (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.

[00364] 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

[00365] 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.

[00366] 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.

[00367] 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.

[00368] 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.

[00369] 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).

[00370] In some embodiments, the compounds disclosed herein are inhibitors of one or more of the proteins encompassed by, or related to, the Hippo pathway. In some instances, the one or more proteins comprise a protein shown in FIGs. 1 and/or 2. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein and/or its coupled GPCR. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of the $G_q\alpha$ family proteins such as G_q, $G_{q/11}$, $G_{q/14}$, and $G_{q/15}$; the $G_{12/13}\alpha$ family of proteins such as G_{12} and G_{13}; or the $G_i\alpha$ family of proteins such as $G_i\alpha1$, $G_i\alpha2$, $G_i\alpha3$, $G_i\alpha4$, $G_o\alpha$, G_t, G_{gust}, and G_z. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_q. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/11}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/14}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/15}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{12}. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{13}. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha1$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha2$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha3$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha4$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_o\alpha$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_t. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{gust}. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_z.

[00371] 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.

[00372] 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).

[00373] 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.

[00374] 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.

[00375] 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.

[00376] Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

Diseases

Cancer

[00377] In some embodiments, the compounds disclosed herein are useful for treating cancer. In some embodiments, the cancer is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes- associated protein transcription coactivator (TAZ/YAP). In some embodiments, the cancer is mediated by modulation of the interaction of YAP/TAZ with TEAD. In some embodiments, the cancer is characterized by a mutant 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.

[00378] 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.

[00379] 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.

[00380] 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.

[00381] 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.

[00382] In some instances, the cancer is a hematologic malignancy. In some embodiments, the 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, the 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.

[00383] In some instances, the 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.

[00384] 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.

[00385] 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.

[00386] In some instances, the relapsed or refractory cancer is a relapsed or refractory hematologic malignancy. In some embodiments, the 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, the relapsed or refractory hematologic malignancy is a relapsed or refractory T-cell malignancy. In some instances, the 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.

[00387] 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.

[00388] 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.

[00389] 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

[00390] 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.

[00391] 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

[00392] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

List of abbreviations

[00393] As used above, and throughout the disclosure, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

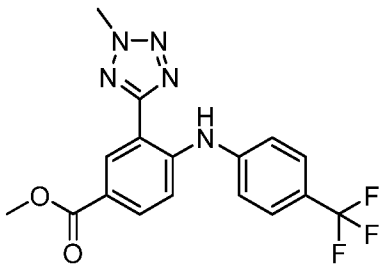
ACN or MeCN	acetonitrile
Bn	benzyl
BOC or Boc	*tert*-butyl carbamate
t-Bu	tert-butyl
Cy	cyclohexyl
DBA	dibenzylideneacetone
DCE	dichloroethane ($ClCH_2CH_2Cl$)
DCM	dichloromethane (CH_2Cl_2)
DIPEA or DIEA	diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	dimethylformamide
DMA	*N,N*-dimethylacetamide
DMSO	dimethylsulfoxide
Dppf or dppf	1,1'-bis(diphenylphosphino)ferrocene
eq	equivalent(s)
Et	ethyl
Et_2O	diethyl ether

EtOH	ethanol
EtOAc	ethyl acetate
HPLC	high performance liquid chromatography
LAH	lithium aluminum anhydride
LCMS	liquid chromatography mass spectrometry
Me	methyl
MeOH	methanol
MS	mass spectroscopy
NMM	*N*-methyl-morpholine
NMP	*N*-methyl-pyrrolidin-2-one
NMR	nuclear magnetic resonance
RP-HPLC	reverse phase-high pressure liquid chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

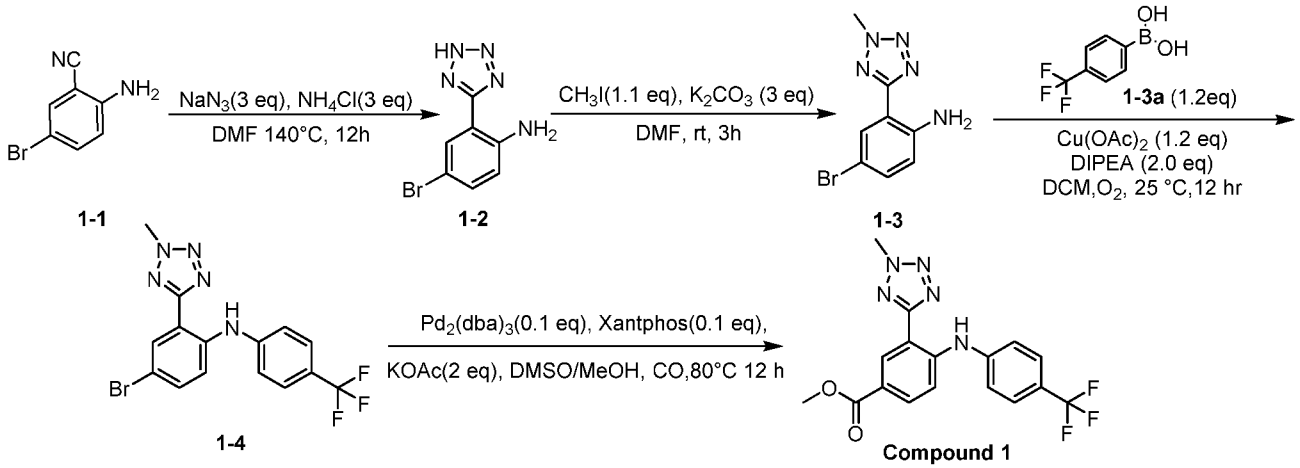
I. Chemical Synthesis

[00394] 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: Methyl 3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoate (Compound 1)



Preparation of Compound 1:



Step 1: 4-bromo-2-(2H-tetrazol-5-yl)aniline

[00395] To a solution of compound **1-1** (5 g, 25.38 mmol, 1 eq) in DMF (20 mL) were added NaN_3 (4.89 g, 75.22 mmol, 2.96 eq) and NH_4Cl (4.07 g, 76.13 mmol, 2.66 mL, 3 eq). The mixture was stirred at 140 °C for 16 hr. The reaction was monitored by LCMS. LCMS showed that the main peak was the desired MS. The reaction solution was added to H_2O (100 mL). The aqueous phase was adjusted to pH=5 and extracted with ethyl acetate (50 mL*3). The combined organic phase was washed with brine (50 mL*5), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was used the next step without purification. Compound **1-2** (3.3 g, crude).

Step 2: 4-bromo-2-(2-methyltetrazol-5-yl)aniline

[00396] To a solution of compound **1-2** (6.6 g, 27.49 mmol, 1 eq) in DMF (30 mL) were added CH_3I (8.63 g, 60.80 mmol, 3.79 mL, 2.21 eq) and K_2CO_3 (11.40 g, 82.48 mmol, 3 eq). The mixture was stirred at 25 °C for 3 hr. TLC showed the reaction was finished. The reaction solution was added to H_2O (200 mL). The aqueous phase was extracted with ethyl acetate (50 mL*3). The combined organic phase was washed with brine (50 mL*5), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO_2) to provide compound **1-3**.

Step 3: 4-bromo-2-(2-methyltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline

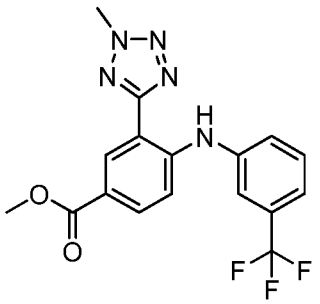
[00397] To the solution of **1-3** (1.2 g, 4.74 mmol, 1 eq) in DCM (10 mL) were added compound **1-3a** (1.08 g, 5.69 mmol, 1.2 eq) , $Cu(OAc)_2$ (1.03 g, 5.69 mmol, 1.2 eq) and DIPEA (1.84 g, 14.22 mmol, 2.48 mL, 3 eq). The mixture was stirred at 25 °C for 16 hr under O_2 at 15 psi. The reaction was monitored by LCMS. LCMS showed that the starting material remained and the main peak was the desired MS. The reaction solution was added to H_2O (100 mL). The aqueous phase was extracted with ethyl acetate (50 mL*3). The combined organic phase was washed with brine (50 mL*5), dried with anhydrous Na_2SO_4, filtered, and concentrated in

vacuum. The residue was purified by column chromatography (SiO_2) to provide compound **1-4** (1.3 g, 3.04 mmol, 64.04% yield).

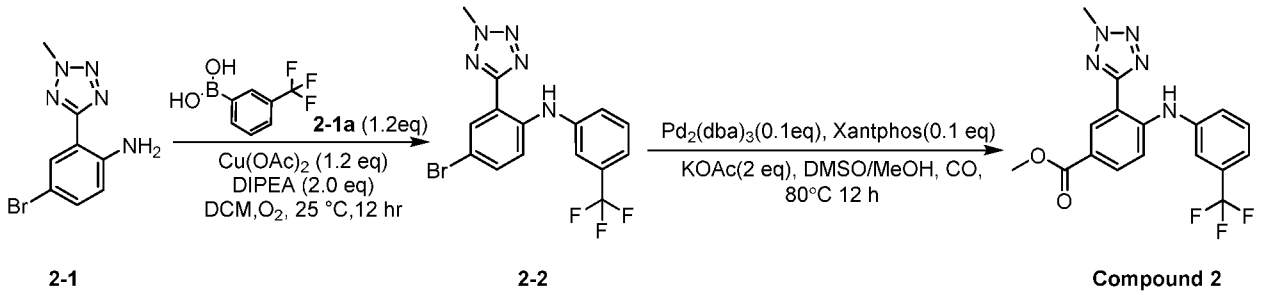
Step 4: 4-bromo-2-(2-methyltetrazol-5-yl)-N-[4-(trifluoromethyl)phenyl]aniline

[00398] To a mixture of compound **1-4** (0.56 g, 1.41 mmol, 1 eq) in DMSO (10 mL) and MeOH (2 mL) were added Xantphos (81.3 mg, 0.14 mmol, 0.1 eq), $Pd_2(dba)_3$ (128.7 mg, 0.14 mmol, 0.1 eq) and KOAc (414.0 mg, 4.22 mmol, 3 eq). The suspension was degassed under vacuum and purged with CO several times. The mixture was stirred for 12 hrs at 45 psi at 80 °C. TLC showed the reaction was finished. The mixture was quenched by EA (30 mL), and the mixture was filtered and the filtered cake was washed with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO_2) to give the title compound (0.45 g, 1.07 mmol, 76.32% yield). 30 mg of the title compound was re-purified by prep-HPLC to give **Compound 1** (15.28 mg, 0.040 mmol, 2.88% yield). LCMS (ESI): RT =0.847 min, mass calc. for: $C_{17}H_{14}F_3N_5O_2$ 377.11, m/z found 377.9 [M+H]+; ^{1}H NMR (400MHz, CD_3OD) δ 8.83 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 2.0, 8.8 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.55 - 7.41 (m, 3H), 4.48 (s, 3H), 3.91 (s, 3H).

Example 2: Preparation of 4-bromo-2-(2-methyltetrazol-5-yl)-N-[3-(trifluoromethyl)phenyl]
aniline (Compound 2)



Preparation of Compound 2:



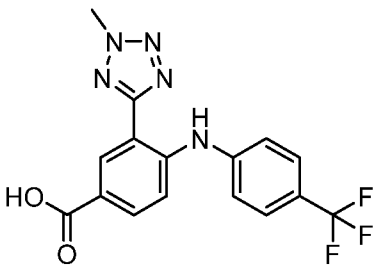
Step 1: **4-bromo-2-(2-methyl-2H-tetrazol-5-yl)-N-(3-(trifluoromethyl)phenyl)aniline**

[00399] To a mixture of compound **2-1** (2 g, 7.87 mmol, 1 eq) and compound **2-1a** (1.49 g, 7.87 mmol, 1 eq) in DCM (20 mL) were added $Cu(OAc)_2$ (1.43 g, 7.87 mmol, 1 eq) and DIPEA (1.02 g, 7.87 mmol, 1.37 mL, 1 eq) in one portion at 25°C under O_2. The mixture was stirred for 48 hrs under 15 Psi. TLC (PE/EA=3/1) showed the reaction was finished. The mixture was quenched by EA (30 mL), and the mixture was filtered and the filtered cake was washed with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was triturated by PE (20 mL), and the mixture was filtered and the filtered cake was washed with PE (10 mL*3). The filtered cake was concentrated in vacuum. The crude product was used for next step directly. Compound **2** (2.6 g, crude) was obtained. LCMS (ESI): RT = 0.926 min, mass calc. for: $C_{15}H_{11}BrF_3N_5$ 397.01, m/z found 399.7 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.32 (d, J = 2.3 Hz, 1H), 7.50 - 7.36 (m, 4H), 7.28 (s, 1H), 4.45 (s, 3H).

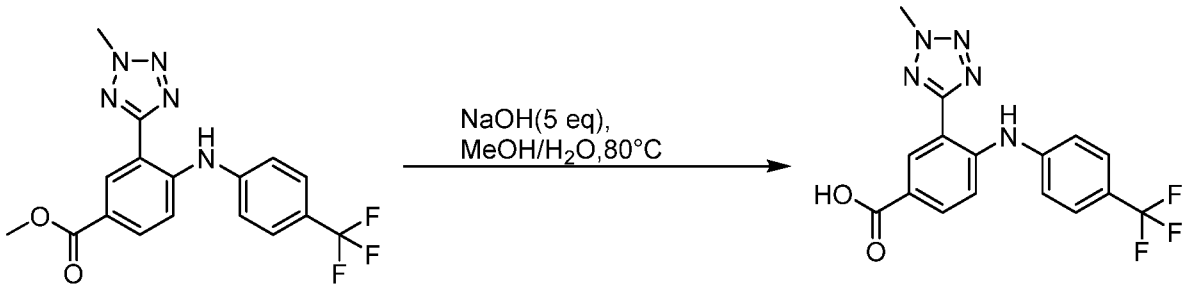
Step 2: methyl 3-(2-methyltetrazol-5-yl)-4-[3-(trifluoromethyl)anilino]benzoate

[00400] To a mixture of **2-2** (1 g, 2.51 mmol, 1 eq) in DMSO (10 mL) and MeOH (2 mL) were added Xantphos (145.3 mg, 0.25 mmol, 0.1 eq), $Pd_2(dba)_3$ (229.9 mg, 0.25 mmol, 0.1 eq) and KOAc (739.4 mg, 7.53 mmol, 3 eq). The suspension was degassed under vacuum and purged with CO several times. The mixture was stirred for 12 hrs at 45 psi at 80 °C. TLC (PE/EA=5/1) showed the reaction was finished. The mixture was quenched by EA (30 mL), and the mixture was filtered and the filtered cake was washed with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (Si_2O) to give **Compound 2** (0.8 g, 1.91 mmol, 76.05% yield). 30 mg of the product was re-purified by prep-HPLC to give **Compound 2** (10.7 mg, 0.028 mmol, 1.13% yield). LCMS (ESI): RT =0.853 min, mass calc. for: $C_{17}H_{14}F_3N_5O_2$ 377.11, m/z found 377.9 $[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.85 (d, J = 2.3 Hz, 1H), 7.99 - 7.93 (m, 1H), 7.62 - 7.55 (m, 3H), 7.46 - 7.40 (m, 1H), 7.39 - 7.33 (m, 1H), 4.52 - 4.47 (m, 3H), 3.91 (s, 3H).

Example 3: 3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 3)



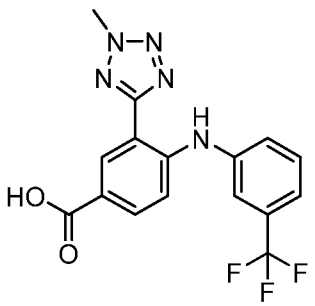
Preparation of Compound 3:



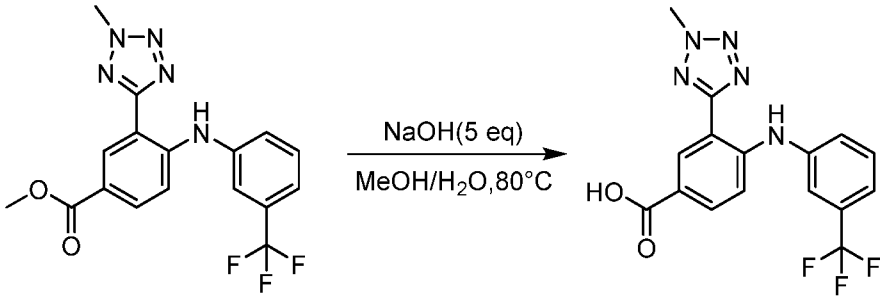
Compound 1 **Compound 3**

[00401] To a mixture of **Compound 1** (0.2 g, 0.53 mmol, 1 eq) in MeOH (5 mL) and H_2O (1 mL) was added NaOH (106.0 mg, 2.65 mmol, 5 eq). The mixture was stirred for 3 hrs at 80 °C. TLC (PE/EA=5/1) showed the reaction was finished. The mixture was quenched by H_2O (30 mL) and adjusted pH to 4 with HCl (4 M). The mixture was extracted with EA (30mL *3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude product was used for next step directly. After repurification by prep-HPLC, 30 mg of **Compound 3** (0.120 g, 0.28 mmol, 54.22% yield) was obtained. Further purification resulted in **Compound 3** (9.09 mg, 0.024 mmol, 4.67% yield). LCMS (ESI): RT = 0.779 min, mass calc. for: $C_{16}H_{12}F_3N_5O_2$ 363.09, m/z found 363.9 [M+H]+; ^{1}H NMR (400MHz, CD_3OD) δ 8.83 (d, *J* = 2.0 Hz, 1H), 7.98 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.58 - 7.42 (m, 3H), 4.48 (s, 3H).

Example 4: 3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 4)



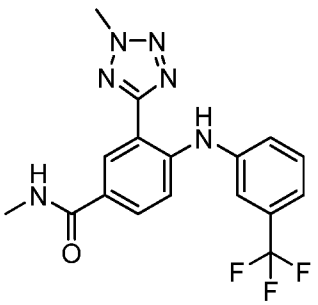
Preparation of Compound 4:



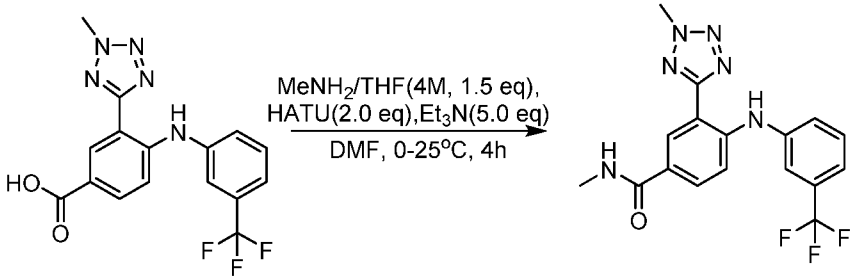
Compound 2 Compound 4

[00402] To a mixture of **Compound 2** (0.35 g, 0.92 mmol, 1 eq) in MeOH (10 mL) and H_2O (2 mL) was added NaOH (37.1 mg, 0.92 mmol, 1 eq). The mixture was stirred for 3 hrs at 80 °C. TLC (PE/EA=5/1) showed the reaction was finished. The mixture was quenched by H_2O (30 mL) and adjusted pH to 4 with HCl (4 M).The mixture was extracted with EA (30 mL *3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give **Compound 4**. (0.2 g, 0.53 mmol, 58.16% yield). The crude product was used for next step directly. 30 mg of the product was re-purified by prep-HPLC to give **Compound 4** (19.87 mg, 0.054 mmol, 5.90% yield). LCMS (ESI): RT =0.771 min, mass calc. for: $C_{16}H_{12}F_3N_5O_2$ 363.09, m/z found 363.9 [M+H]+; ^{1}H NMR (400MHz, CD_3OD) δ 8.85 (d, J = 2.3 Hz, 1H), 7.99 - 7.93 (m, 1H), 7.62 - 7.55 (m, 3H), 7.46 - 7.40 (m, 1H), 7.39 - 7.33 (m, 1H), 4.52 - 4.47 (m, 3H), 3.91 (s, 3H).

Example 5: N-methyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino) benzamide (Compound 5)



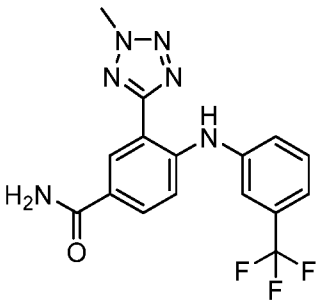
Preparation of Compound 5:



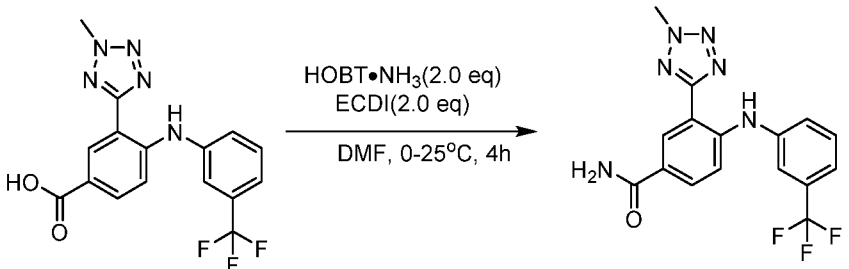
Compound 4 Compound 5

[00403] To a mixture of **Compound 4** (80 mg, 0.22 mmol, 1 eq) in DMF (10 mL) were added HATU (167.4 mg, 0.44 mmol, 2 eq) and Et_3N (22.2 mg, 0.22 mmol, 30.65 uL, 1 eq). The mixture was stirred for 0.5 hrs at 25°C. Then $MeNH_2$ (2 M, 0.55 mL, 5 eq) was added to the mixture. The mixture was stirred for 1.5 hrs at 25°C. LCMS showed the reaction was finished. The mixture was quenched by H_2O (30 mL), and the mixture was extracted with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC, and **Compound 5** (34.4 mg, 0.091 mmol, 41.61% yield) was obtained. LCMS (ESI): RT =0.742 min, mass calc. for: $C_{17}H_{15}F_3N_6O$ 376.13, m/z found 376.9 [M+H]+; ^1H NMR (400MHz, CD_3OD) δ 8.69 (d, J = 2.3 Hz, 1H), 7.79 (dd, J = 2.0, 8.8 Hz, 1H), 7.57 - 7.51 (m, 3H), 7.41 - 7.34 (m, 2H), 4.47 (s, 3H), 2.93 (s, 3H).

Example 6: 3-(2-methyl-2H-tetrazol-5-yl)-4-((3Z(trifluoromethyl)phenyl)amino)benzamide (Compound 6)



Preparation of Compound 6:

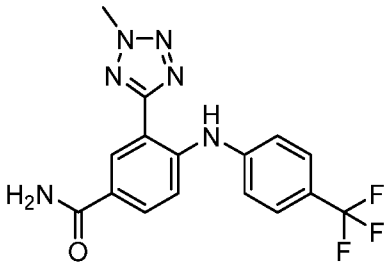


Compound 4 Compound 6

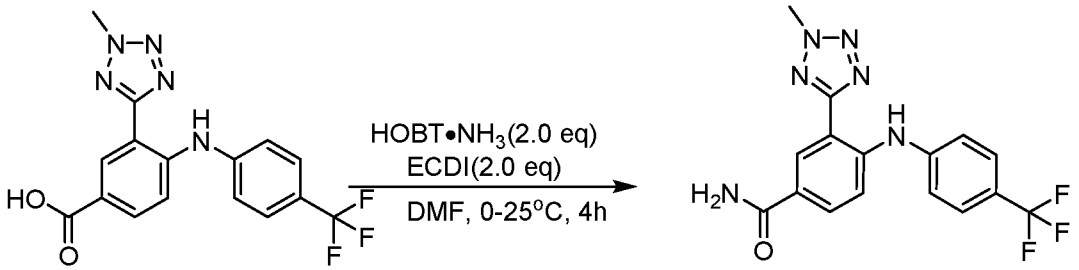
[00404] To a mixture of **Compound 4** (0.1 g, 0.27 mmol, 1 eq) in DMF (10 mL) was added ammonium;1-oxidobenzotriazole (83.7 mg, 0.55 mmol, 2 eq). The mixture was stirred for 0.5 hrs at 25°C. Then EDCI (105.5 mg, 0.55 mmol, 2 eq) was added to the mixture. The mixture was stirred for 1.5 hrs at 25°C. LCMS showed the reaction was finished. The mixture was quenched by H_2O (30 mL), and the mixture was extracted with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC to give **Compound 6** (22.42

mg, 61.26 umol, 22.26% yield). LCMS (ESI): RT =0.722 min, mass calc. for: $C_{16}H_{13}F_3N_6O$ 362.11, m/z found 362.9 $[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.74 (d, J = 2.3 Hz, 1H), 7.85 (dd, J = 2.0, 8.8 Hz, 1H), 7.57 - 7.51 (m, 3H), 7.40 - 7.33 (m, 2H), 4.47 (s, 3H)

Example 7: 3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide (Compound 7)



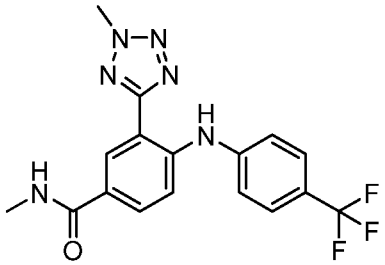
Preparation of Compound 7:



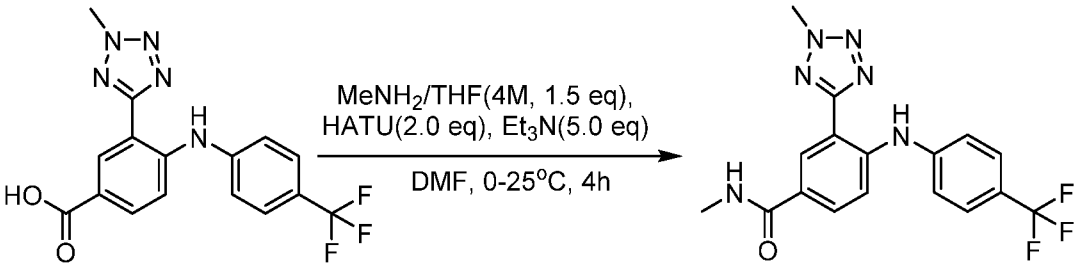
Compound 3 **Compound 7**

[00405] To a mixture of **Compound 3** (0.03 g, 0.082 mmol, 1 eq) in DMF (10 mL) was added ammonium;1-oxidobenzotriazole (25.1 mg, 0.16 mmol, 2 eq). The mixture was stirred for 0.5 hrs at 0°C. Then EDCI (31.6 mg, 0.16 mmol, 2 eq) was added to the mixture. The mixture was stirred for 1.5 hrs at 25°C. LCMS showed the reaction was complete. The mixture was quenched by H_2O (30 mL), and the mixture was extracted with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC to obtain **Compound 7** (21.70 mg, 0.059 mmol, 71.80% yield). LCMS (ESI): RT =0.732 min, mass calc. for: $C_{16}H_{13}F_3N_6O$ 362.11, m/z found 362.9 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ 9.08 (s, 1H), 8.59 (d, J = 2.3 Hz, 1H), 8.02 (br s, 1H), 7.96 (dd, J = 2.1, 8.7 Hz, 1H), 7.67 - 7.62 (m, J = 8.5 Hz, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.42 - 7.36 (m, J = 8.5 Hz, 2H), 7.30 (br s, 1H), 4.47 (s, 3H).

Example 8: N-methyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino) benzamide (Compound 8)



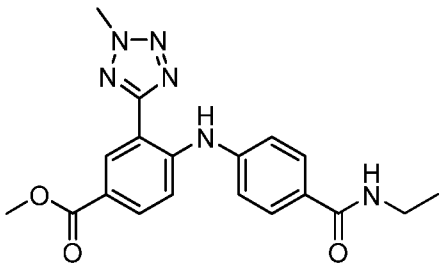
Preparation of Compound 8:



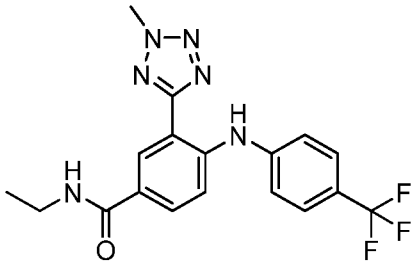
Compound 3 **Compound 8**

[00406] To a mixture of **Compound 3** (30 mg, 0.082 mmol, 1 eq) in DMF (10 mL) were added HATU (62.8 mg, 0.16 mmol, 2 eq) and Et_3N (8.3 mg, 0.082 mmol, 11.49 uL, 1 eq). The mixture was stirred for 0.5 hr at 25°C. Then $MeNH_2$ (2 M, 0.20 mL, 5 eq) was added to the mixture. The mixture was stirred for 1.5 hr at 25°C. LCMS showed the reaction was finished. The mixture was quenched by H_2O (30 mL), and the mixture was extracted with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC to obtain **Compound 8** (5.16 mg, 0.013 mmol, 16.60% yield). LCMS (ESI): RT = 0.739 min, mass calc. for: $C_{17}H_{15}F_3N_6O$ 376.13, m/z found 376.9 $[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.69 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 2.1, 8.7 Hz, 1H), 7.66 - 7.60 (m, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.47 - 7.39 (m, J = 8.5 Hz, 2H), 4.48 (s, 3H), 2.94 (s, 3H).

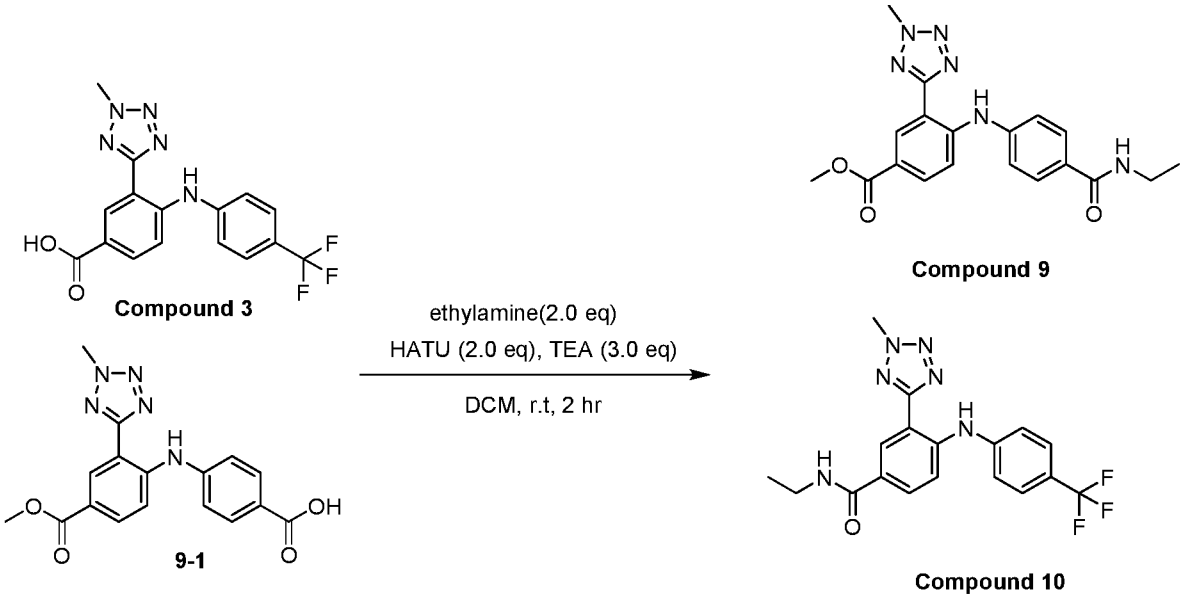
Example 9: methyl 4-((4-(ethylcarbamoyl)phenyl)amino)-3-(2-methyl-2H-tetrazol-5-yl)benzoate (Compound 9)



and N-ethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide (Compound 10)

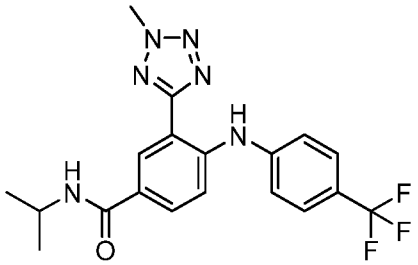


Preparation of Compound 9 and Compound 10:

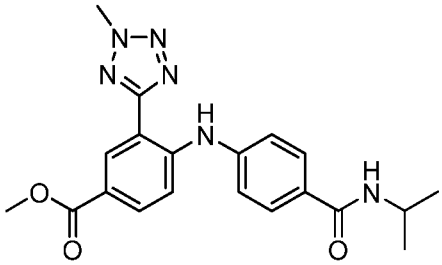


[00407] To a solution of **Compound 3** (80 mg, 0.22 mmol, 1 *eq*) and **9-1** (77.8 mg, 0.22 mmol, 1 *eq*) in DCM (5 mL) were added TEA (66.8 mg, 0.66 mmol, 91.95 uL, 3 *eq*), HATU (167.4 mg, 0.44 mmol, 2 *eq*) in one portion. The mixture was stirred at 25 °C for 1 hr. Then the ethylamine (19.8 mg, 0.44 mmol, 28.82 uL, 2 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 15 hr. LCMS showed the reactant was consumed completely, 50% **Compound 10** and 35% **Compound 9** was detected. The mixture was washed by NaCl (2 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC, and **Compound 10** (3.72 mg, 0.0092 mmol, 4.20% yield) was obtained. It was checked by LCMS and 1HNMR. LCMS (ESI): RT = 0.772 min, mass calc. for $C_{18}H_{17}F_3N_6O$ 390.14, m/z found 391.9$[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ 9.07 (s, 1H), 8.59 - 8.52 (m, 2H), 7.93 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 4.50 - 4.46 (m, 3H), 3.33 - 3.28 (m, 2H), 1.18 - 1.10 (m, 3H). **Compound 9** (8.85 mg, 0.022 mmol, 10.35% yield) was also obtained. LCMS (ESI): RT = 0.704 min, mass calc. for $C_{19}H_{20}N_6O_3$ 380.40, m/z found 381.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ 9.12 (s, 1H), 8.58 - 8.52 (m, 2H), 7.97 - 7.93 (m, 1H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 4.50 - 4.45 (m, 3H), 3.85 - 3.79 (m, 3H), 3.33 - 3.28 (m, 3H), 1.14 (t, *J* = 7.2 Hz, 3H).

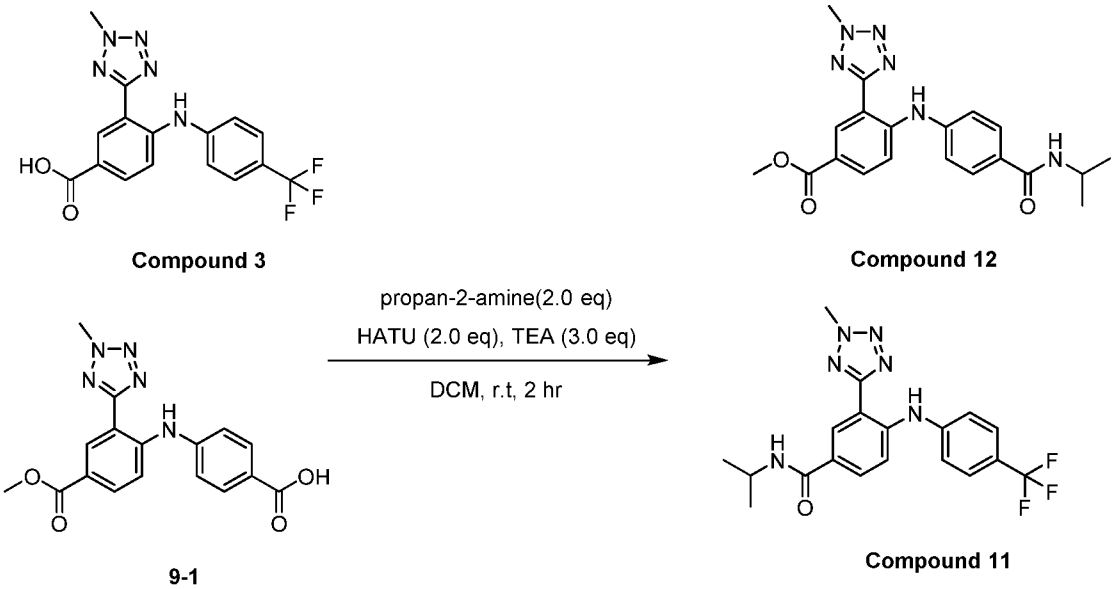
Example 10: N-isopropyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4 (trifluoromethyl)phenyl)amino) benzamide (Compound 11)



and methyl 4-((4-(isopropylcarbamoyl)phenyl)amino)-3-(2-methyl-2H-tetrazol-5-yl)benzoate (Compound 12)



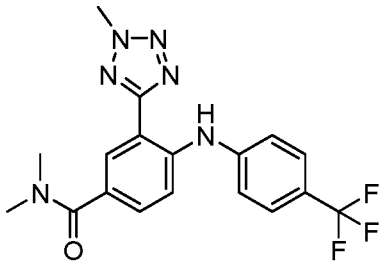
Preparation of Compound 11 and Compound 12:



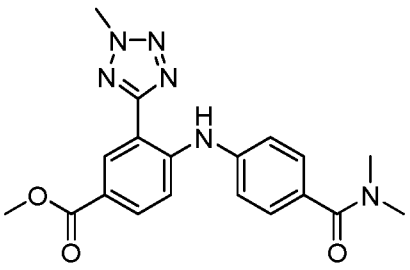
[00408] To a solution of **Compound 3** (70 mg, 0.19 mmol, 1 *eq*) and **9-1** (68.0 mg, 0.19 mmol, 1 *eq*) in DCM (5 mL) were added HATU (146.5 mg, 0.38 mmol, 2 *eq*), propan-2-amine (22.7 mg, 0.38 mmol, 33.11 uL, 2 *eq*), TEA (58.4 mg, 0.57 mmol, 80.46 uL, 3 *eq*) in one portion. The mixture was stirred at 25 °C for 1 hr. Then the propan-2-amine (22.7 mg, 0.38 mmol, 33.11 uL, 2 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 15 hr. LCMS showed the reactant was consumed completely, and 39% **Compound 11** and 51% **Compound**

12 was detected. The mixture was washed by NaCl (3ml*3) then dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC to obtain **Compound 11** (12.77 mg, 0.030 mmol, 15.73% yield). LCMS (ESI): RT = 0.790 min, mass calc. for $C_{19}H_{19}F_3N_6O$ 404.39, m/z found 405.0 $[M+H]^+$; 1H NMR (400MHz, DMSO-d6) δ 9.05 (s, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.94 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.67 - 7.62 (m, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.39 - 7.34 (m, *J* = 8.5 Hz, 2H), 4.47 (s, 3H), 4.17 - 4.08 (m, 1H), 1.19 (s, 3H), 1.17 (s, 3H). **Compound 12** (25.3 mg, 0.063 mmol, 32.98% yield) was also obtained. LCMS (ESI): RT = 0.727 min, mass calc. for $C_{20}H_{22}N_6O_3$ 394.43, m/z found 395.0$[M+H]^+$; 1H NMR (400MHz, DMSO-d6) δ 9.10 (s, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 8.32 (d, *J* = 7.5 Hz, 1H), 7.95 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 4.47 (s, 3H), 4.18 - 4.08 (m, 1H), 3.82 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H)

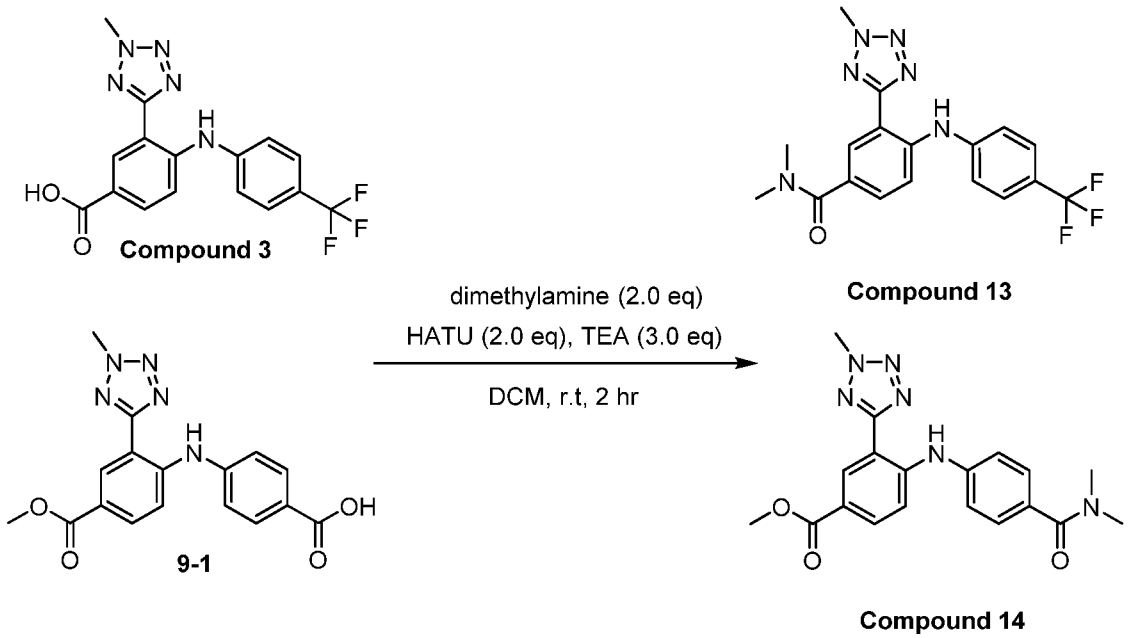
Example 11: N,N-dimethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino) benzamide (Compound 13)



and methyl 4-((4-(dimethylcarbamoyl)phenyl)amino)-3-(2-methyl-2H-tetrazol-5-yl)benzoate (Compound 14)

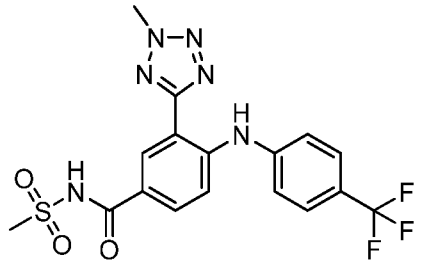


Preparation of Compound 13 and Compound 14:

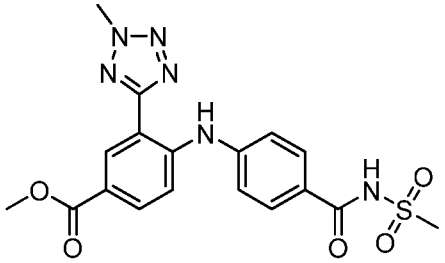


[00409] To a solution of **Compound 3** (70 mg, 0.19 mmol, 1 *eq*), **9-1** (68.0 mg, 0.19 mmol, 1 *eq*) in DCM (3 mL) were added HATU (146.5 mg, 0.38 mmol, 2 *eq*) and TEA (58.4 mg, 0.57 mmol, 80.46 uL, 3 *eq*). The mixture was stirred at 25 °C for 1 hr. Then the N-methylmethanamine (2 M, 192.68 uL, 2 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 15 hr. LCMS showed the reactant was consumed completely, and 17% **Compound 13** and 35% **Compound 14** was detected. The mixture was washed by NaCl (3mL*3) then dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC to obtain **Compound 13** (7.92 mg, 20.29 umol, 10.53% yield) was obtained. LCMS (ESI): RT = 0.771 min, mass calc. for $C_{18}H_{17}F_3N_6O$ 390.14, m/z found 391.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.07 (s, 1H), 7.63-7.61 (d, J = 8.4 Hz, 2H), 7.55-7.50 (m, 2H), 7.36-7.34 (d, J = 8.4 Hz, 2H), 4.45 (s, 3H), 3.01 (s, 6H). **Compound 14** (32.71 mg, 0.085 mmol, 44.63% yield) was also obtained. LCMS (ESI): RT = 0.708 min, mass calc. for $C_{19}H_{20}N_6O_3$ 380.16, m/z found 381.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.07-8.06 (d, J = 1.6 Hz, 1H), 7.89-7.87 (d, J = 8.8 Hz, 2H), 7.59-7.52 (m, 2H), 7.27-7.25 (d, J = 8.8 Hz, 2H), 4.45 (s, 3H), 3.81 (s, 3H), 3.01 (s, 3H).

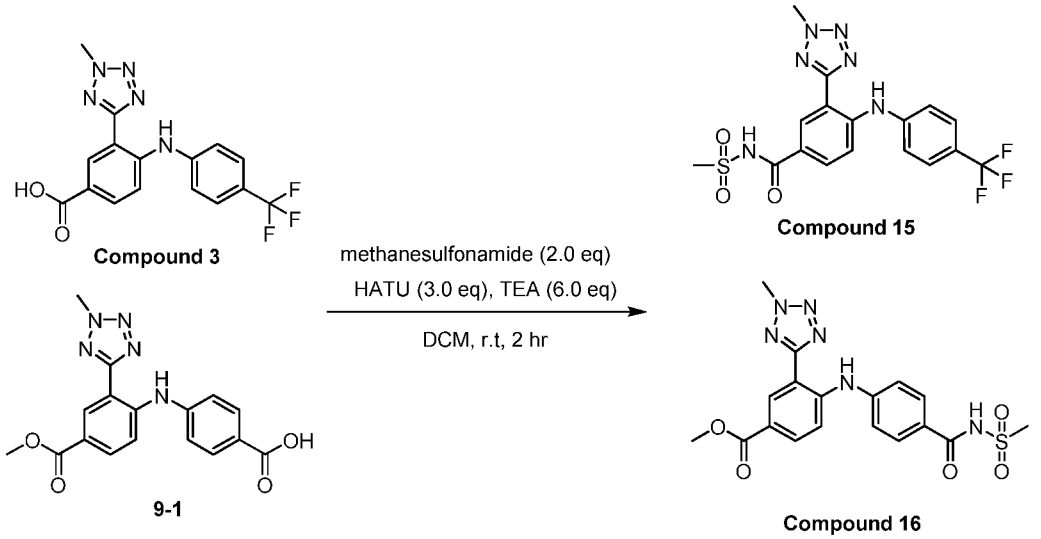
Example 12: 3-(2-methyl-2H-tetrazol-5-yl)-N-(methylsulfonyl)-4-((4-(trifluoromethyl)phenyl) amino)benzamide (Compound 15)



and methyl 3-(2-methyl-2H-tetrazol-5-yl)-4-((4-((methylsulfonyl)carbamoyl)phenyl)amino) benzoate (Compound 16)



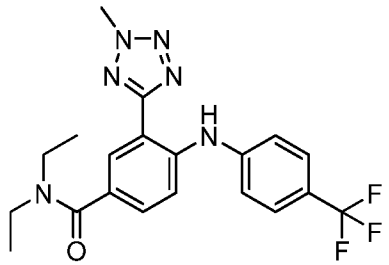
Preparation of Compound 15 and Compound 16:



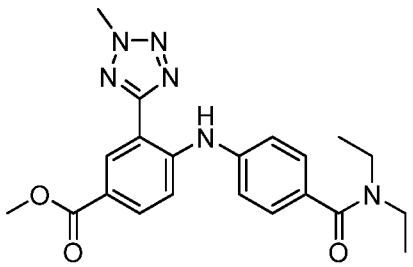
[00410] To a solution **Compound 3** (70 mg, 0.19 mmol, 1 *eq*) and **9-1** (68.0 mg, 0.19 mmol, 1 *eq*) in DCM (3 mL) were added TEA (116.9 mg, 1.16 mmol, 160.91 uL, 6 *eq*) HATU (219.7 mg, 0.57 mmol, 3 *eq*) in one portion. The mixture was stirred at 25 °C for 1 hr. Then the methanesulfonamide (36.6 mg, 0.38 mmol, 2 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 15 hr. LCMS showed the reactant was consumed completely. The mixture was washed by NaCl (3mL*3) then dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC to give **Compound 15** (4.73 mg, 0.010 mmol, 5.57% yield). LCMS (ESI): RT = 0.761 min, mass calc. for $C_{17}H_{15}F_3N_6O_3S$ 440.40, m/z found 463.0 $[M+Na]^+$; 1H NMR (400MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.68 (d, *J* = 2.3 Hz, 2H), 7.86 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 4.49 (s, 3H), 3.47 (s, 3H) **Compound 16** (6.22 mg, 0.014 mmol, 7.50% yield) was also

obtained. LCMS (ESI): RT = 0.696 min, mass calc. for C18H18N6O5S 430.44, m/z found 453.0[M+Na]$^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.85 (s, 1H), 8.69 (d, *J* = 2.3 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.88 (dd, *J* = 2.3, 9.0 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 4.49 (s, 3H), 3.93 (s, 3H), 3.47 (s, 3H).

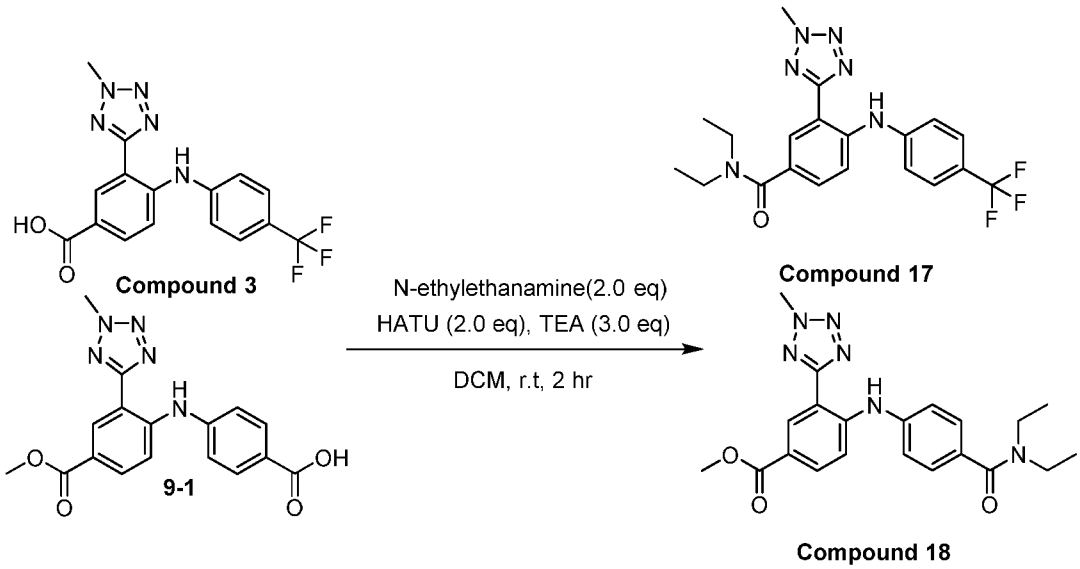
Example 13: N,N-diethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino) benzamide (Compound 17)



and methyl 4-((4-(diethylcarbamoyl)phenyl)amino)-3-(2-methyl-2H-tetrazol-5-yl)benzoate (Compound 18)



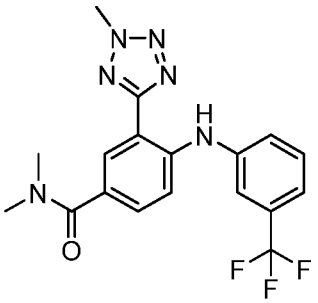
Preparation of Compound 17 and Compound 18:



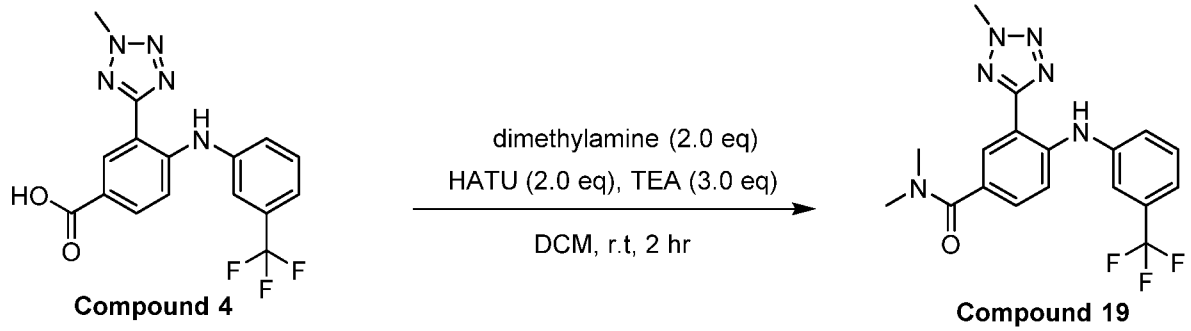
[00411] To a solution of **Compound 3** (70 mg, 0.19 mmol, 1 *eq*) and **9-1** (68.0 mg, 0.19 mmol, 1 *eq*) in DCM (3 mL) were added TEA (58.4 mg, 0.57 mmol, 80.46 uL, 3 *eq*) and HATU (146.5 mg, 0.38 mmol, 2 *eq*). The mixture was stirred at 25 °C for 1hr. Then the N-

ethylethanamine (28.1 mg, 0.38 mmol, 39.70 uL, 2 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 15 hr. LCMS showed the reactant was consumed completely, and 46% **Compound 17** and 40% **Compound 18** was detected. The mixture was washed by NaCl (3 mL*3) then dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC to obtain **Compound 17** (9.61 mg, 0.022 mmol, 11.92% yield). LCMS (ESI): RT = 0.809 min, mass calc. for $C_{20}H_{21}F_3N_6O$ 418.41, m/z found 419.1$[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.26 (d, *J* = 2.0 Hz, 1H), 7.63 (t, *J* = 8.8 Hz, 3H), 7.52 - 7.45 (m, 1H), 7.45 - 7.40 (m, 2H), 4.49 (s, 3H), 3.50 (br s, 4H), 1.38 - 1.18 (m, 9H). **Compound 18** was also obtained (7.22 mg, 0.017 mmol, 9.17% yield). LCMS (ESI): RT = 0.748 min, mass calc. for $C_{21}H_{24}N_6O_3$ 408.45, m/z found 409.0$[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.25 (d, *J* = 1.8 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 4.49 (s, 3H), 3.90 (s, 3H), 3.50 (br s, 4H), 1.27 (br s, 6H).

Example 14: N,N-dimethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino) benzamide (Compound 19)



Preparation of Compound 19:

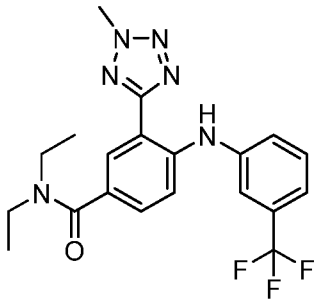


Compound 4 **Compound 19**

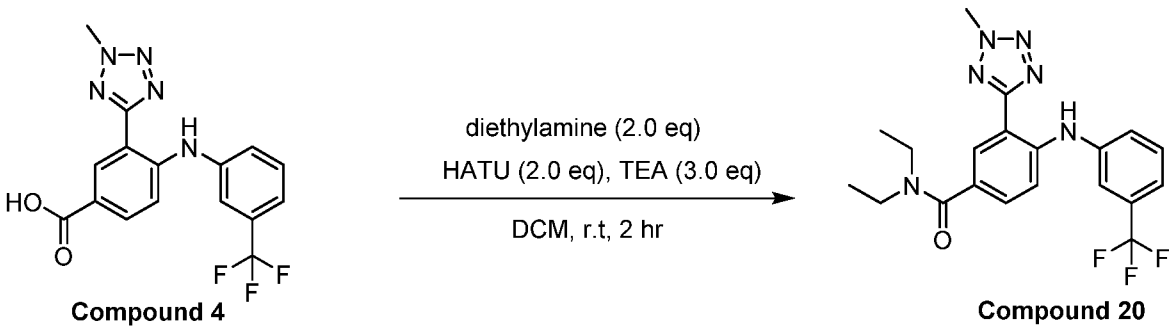
[00412] To a mixture of **Compound 4** (50 mg, 0.14 mmol, 1 *eq*) and TEA (41.8 mg, 0.41 mmol, 57.5 uL, 3 *eq*) in DCM (2 mL) was added HATU (104.7 mg, 0.28 mmol, 2 *eq*) in one portion at 25°C under N_2. The mixture was stirred at 25 °C for 1 hr. dimethylamine (12.4 mg, 0.28 mmol, 13.9 uL, 2 *eq*) was added in the mixture under N_2, the reaction was stirred at 25 °C for 1 hr. LCMS showed the starting material was consumed completely and the desired mass was

detected. The reaction mixture was quenched by addition brine (5 mL) and extracted with DCM (10mL * 2). The combined organic layers was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 19** (28.4 mg, 0.065 mmol, 46.90% yield). LCMS (ESI): RT = 0.763 min, mass calcd for $C_{18}H_{17}F_3N_6O$ 390.36, m/z found 391 $[M+H]^+$. ^1H NMR (400MHz, $CDCl_3$) δ 9.20 (br s, 1H), 8.33 (s, 1H), 7.53 (s, 1H), 7.47 (br d, J = 5.0 Hz, 3H), 7.39 - 7.30 (m, 2H), 4.46 (s, 3H), 3.13 (s, 6H).

Example 14: N,N-diethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino) benzamide (Compound 20)



Preparation of Compound 20:

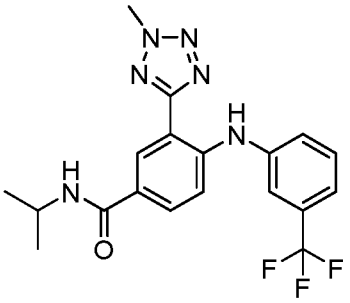


Compound 4 **Compound 20**

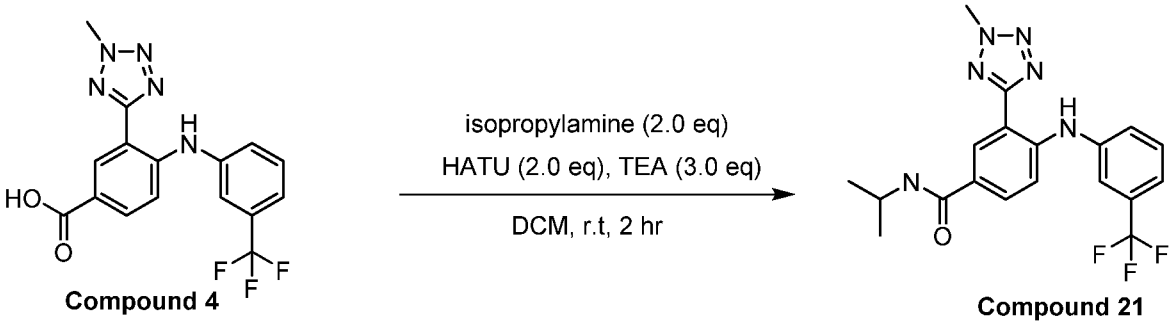
[00413] To a mixture of **Compound 4** (50 mg, 0.13 mmol, 1 *eq*) and TEA (41.7 mg, 0.41 mmol, 57.47 uL, 3 *eq*) in DCM (2 mL) was added HATU (104.6 mg, 0.27 mmol, 2 *eq*) in one portion at 25°C and stirred for 1 hr. Diethylamine (20.1 mg, 0.27 mmol, 28.3 uL, 2 *eq*) was added in the mixture, the mixture was stirred at 25 °C and stirred for 1 hr. LCMS showed the starting material was consumed completely and 96% of desired mass was detected. The reaction mixture was quenched by addition brine (5 mL) and extracted with DCM (10 mL * 2). The combined organic layers was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 20** (29.2 mg, 0.06 mmol, 46.64% yield). LCMS and ^{1}HNMR indicated it was desired compound. LCMS (ESI): RT = 0.812 min, mass calcd for $C_{20}H_{21}F_3N_6O$ 418.42, m/z found 441 $[M+Na]^+$. ^1H NMR

(400MHz, $CDCl_3$) δ 9.16 (br s, 1H), 8.29 (d, *J* = 1.5 Hz, 1H), 7.52 (s, 1H), 7.47 (d, *J* = 5.0 Hz, 2H), 7.43 - 7.36 (m, 2H), 7.33 (br d, *J* = 4.0 Hz, 1H), 4.46 (s, 3H), 3.49 (br s, 4H), 1.24 (br t, *J* = 6.5 Hz, 6H).

Example 15: N-isopropyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino) benzamide (Compound 21)



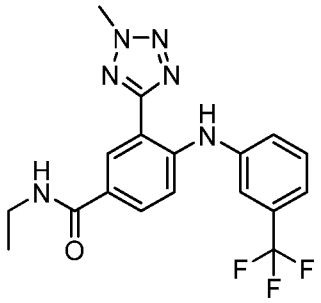
Preparation of Compound 21:



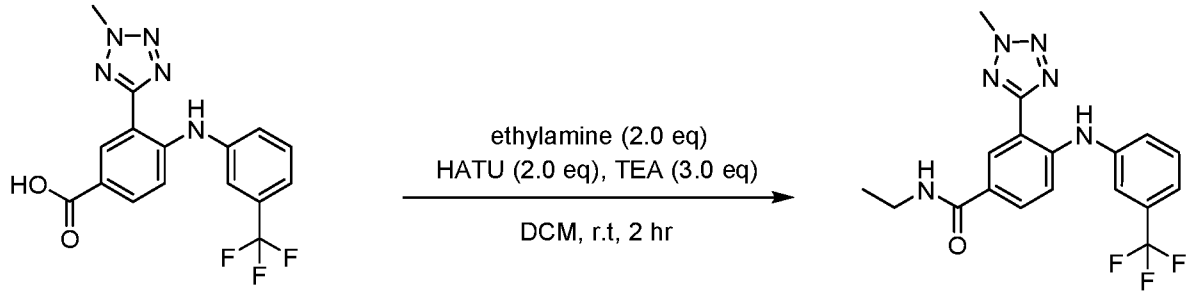
Compound 4 **Compound 21**

[00414] To a mixture of **Compound 4** (50 mg, 0.13 mmol, 1 *eq*) and TEA (41.7 mg, 0.41 mmol, 57.4 uL, 3 *eq*) in DCM (2 mL) was added HATU (104.6 mg, 0.27 mmol, 2 *eq*) in one portion, the mixture was stirred at 25°C for 1 hr. Isopropylamine (16.2 mg, 0.27 mmol, 23.65 uL, 2 *eq*) was added in the mixture and stirred for 1 hr at the temperature. LCMS showed the starting material was consumed completely and 91.4% of desired mass was detected. The reaction mixture was quenched by addition of brine (5 mL) and extracted with DCM (10 mL * 2). The combined organic layers was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 21** (42.3 mg, 0.095 mmol, 69.72% yield). LCMS and ^{1}HNMR indicated it was desired compound. LCMS (ESI): RT = 0.788 min, mass calcd for $C_{19}H_{19}F_3N_6O$ 404.39, m/z found 405 $[M+H]^+$. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.57 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.52 (s, 1H), 7.51 - 7.46 (m, 2H), 7.39 - 7.34 (m, 2H), 5.96 (br d, *J* = 8.5 Hz, 1H), 4.48 (s, 3H), 4.37 - 4.28 (m, 1H), 1.29 (d, *J* = 6.5 Hz, 6H).

Example 16: N-ethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl) amino)benzamide (Compound 22)



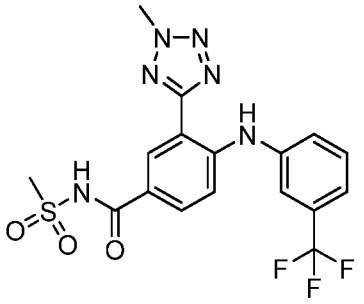
Preparation of Compound 22:



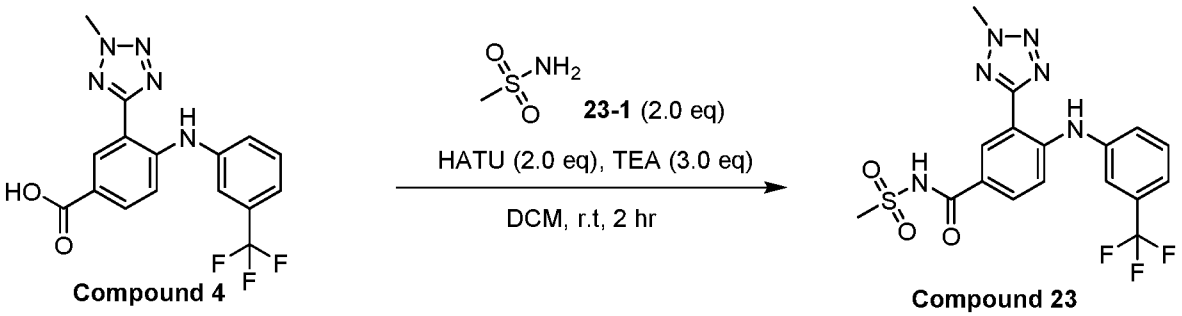
Compound 4 **Compound 22**

[00415] To a mixture of **Compound 4** (50 mg, 0.13 mmol, 1 *eq*) and TEA (41.7 mg, 0.41 mmol, 57.47 uL, 3 *eq*) in DCM (2 mL) was added HATU (104.6 mg, 0.27 mmol, 2 *eq*) in one portion at 25°C under N_2.The mixture was stirred at 25 °C for 1 hr, ethylamine (12.4 mg, 0.27 mmol, 18.01 uL, 2 *eq*) was added in the reaction. The mixture was stirred at 25 °C for 1 hr. LCMS showed the starting material was consumed completely and the desired mass was detected. The reaction mixture was quenched by addition brine (5 mL) and extracted with DCM (10mL * 2). The combined organic layers was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 22** (38 mg, 0.086 mmol, 62.75% yield). LCMS (ESI): RT = 0.772 min, mass calcd for $C_{18}H_{17}F_3N_6O$ 390.36, m/z found 391 $[M+H]^+$. ^1H NMR (400MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.59 (d, *J* = 2.5 Hz, 1H), 7.82 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.53 (s, 1H), 7.50 - 7.46 (m, 2H), 7.39 - 7.34 (m, 2H), 6.15 (br s, 1H), 4.47 (s, 3H), 3.61 - 3.46 (m, 2H), 1.28 (t, *J* = 7.3 Hz, 3H).

Example 17: 3-(2-methyl-2H-tetrazol-5-yl)-N-(methylsulfonyl)-4-((3-(trifluoromethyl)phenyl)
amino)benzamide (Compound 23)



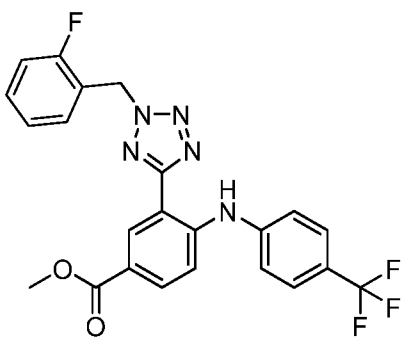
Preparation of Compound 23:



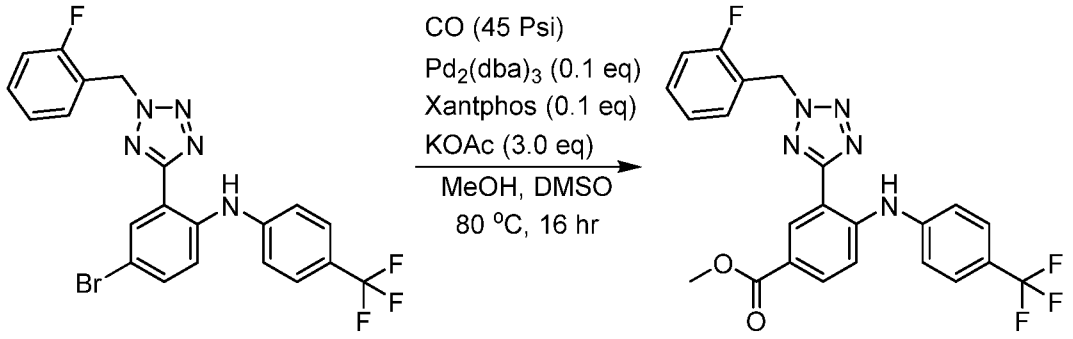
Compound 4 Compound 23

[00416] To a mixture of **Compound 4** (50 mg, 0.13 mmol, 1 *eq*) and TEA (41.7 mg, 0.41 mmol, 57.47 uL, 3 *eq*) in DCM (2 mL) was added HATU (104.6 mg, 0.27 mmol, 2 *eq*) in one portion, the mixture was stirred at 25 °C for 1 hr, methanesulfonamide **23-1** (26.1 mg, 0.27 mmol, 2 *eq*) was added in the mixture and stirred for 1 hr at 25°C. LCMS showed the starting material was consumed completely and 84.3% of desired mass was detected. The reaction mixture was quenched by addition brine (5 mL) and extracted with DCM (10 mL * 2). The combined organic layers was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound 23** (10 mg, 0.02 mmol, 15.24% yield). LCMS and ^{1}HNMR indicated it was desired compound. LCMS (ESI): RT = 0.754 min, mass calcd for $C_{17}H_{15}F_3N_6O_3S$ 440.40, m/z found 441 $[M+H]^+$. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.72 - 8.67 (m, 2H), 7.85 (dd, J = 2.3, 8.8 Hz, 1H), 7.57 - 7.49 (m, 3H), 7.47 - 7.43 (m, 1H), 7.33 (d, J = 9.0 Hz, 1H), 4.50 (s, 3H), 3.47 (s, 3H).

Example 18: methyl 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl) amino)benzoate (Compound 24)



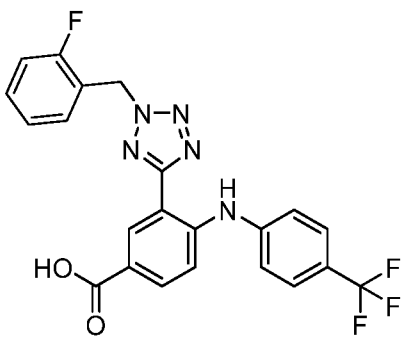
Preparation of Compound 24:



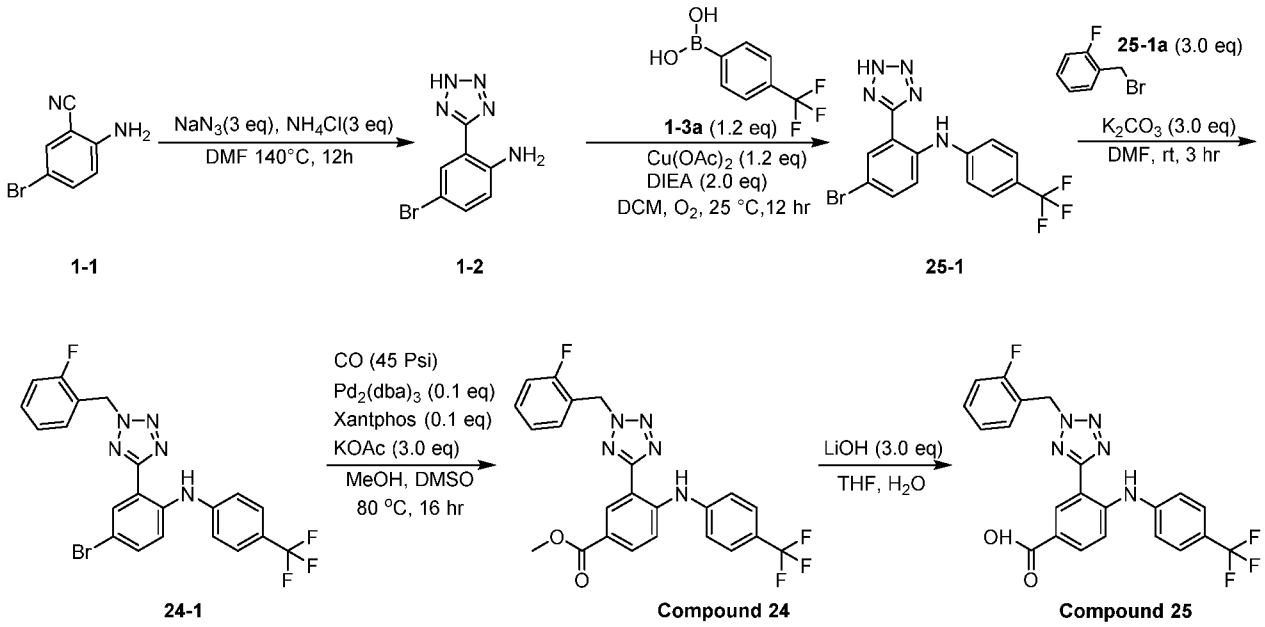
24-1 **Compound 24**

[00417] To a mixture of **24-1** (1.2 g, 2.44 mmol, 1 *eq*) in DMSO (10 mL) and MeOH (2 mL) were added Xantphos (141.0 mg, 0.24 mmol, 0.1 *eq*), $Pd_2(dba)_3$ (223.2 mg, 0.24 mmol, 0.1 *eq*) and KOAc (717.7 mg, 7.31 mmol, 3 *eq*). The suspension was degassed under vacuum and purged with CO several times. The mixture was stirred for 12 hrs under CO 45 psi at 80 °C. LCMS showed the reaction was complete. The mixture was quenched by EA (30 mL), and the mixture was filtered and the filtered cake was washed with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (Si_2O) to obtain crude **Compound 24** (0.15 g, 0.31 mmol, 13.05% yield) was obtained, and (0.03 g, 0.063 mmol, 1 *eq*) was separated by prep-HPLC. It was monitored by LCMS. It was re-purified by prep-HPLC to obtain **Compound 24** (9.51 mg, 0.020 mmol). LCMS (ESI): RT = 0.930 min, mass calc. for: $C_{23}H_{17}F_4N_5O_2$ 471.13, m/z found 472.0 $[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.82 (d, *J* = 2.0 Hz, 1H), 7.98 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.68 - 7.64 (m, *J* = 8.5 Hz, 2H), 7.58 - 7.39 (m, 5H), 7.29 - 7.20 (m, 2H), 6.06 (s, 2H), 3.91 (s, 3H).

Example19: 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino) benzoic acid (Compound 25)



Preparation of Compound 25:



Step 1: 4-bromo-2-(2H-tetrazol-5-yl)aniline

[00418] To a solution of **1-1** (10 g, 50.75 mmol, 1 eq) in DMF (50 mL) were added NaN_3 (24.42 g, 375.6 mmol, 7.40 eq) and NH_4Cl (8.14 g, 152.2 mmol, 5.32 mL, 3 eq). The mixture was stirred at 140 °C for 12 hr. TLC showed that the reaction was complete. The reaction solution was added to H_2O (200 mL). The aqueous phase was adjust to pH=5 with $NaHCO_3$ and extracted with ethyl acetate (150 mL*3). The combined organic phase was washed with brine (50 mL*5), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was used the next step without purification. Compound **1-2** (30 g, crude) was obtained.

Step 2: 4-bromo-2-(2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00419] To a mixture of **1-2** (3 g, 12.50 mmol, 1 *eq*) and [4-(trifluoromethyl)phenyl]boronic acid **1-3a** (2.37 g, 12.5 mmol, 1 *eq*) in DCM (20 mL) were added $Cu(OAc)_2$ (4.54 g, 25.0 mmol, 2 *eq*) and DIPEA (8.08 g, 62.50 mmol, 10.88 mL, 5 *eq*) in one portion at 25°C under O_2. The mixture was stirred for 18 hrs under O_2 (15psi). LCMS showed the reaction was finished. The mixture was quenched by EA (30 mL), and the mixture was filtered and the filtered cake was washed with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was triturated by PE (20 mL), and the mixture was filtered and the filtered cake was washed with PE (10 mL*3). The filtered cake was concentrated in vacuum. The crude product **Compound 25-1** (4 g, crude) was used for next step directly.

Step 3: 4-bromo-2-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00420] To the solution of **25-1** (4 g, 10.41 mmol, 1 *eq*) in DMF (20 mL) were added **25-1a** (3.94 g, 20.8 mmol, 2.51 mL, 2 *eq*) and Cs_2CO_3 (6.79 g, 20.8 mmol, 2 *eq*). The mixture was stirred at 25 °C for 3 hr. TLC showed the reaction was complete. The reaction solution was added to H_2O (30 mL). The mixture was extracted with ethyl acetate (20 mL*3). The combined organic phase was washed with brine (10 mL*5), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (Si_2O). **24-1**(1.5 g, 2.36 mmol, 22.71% yield) was obtained.

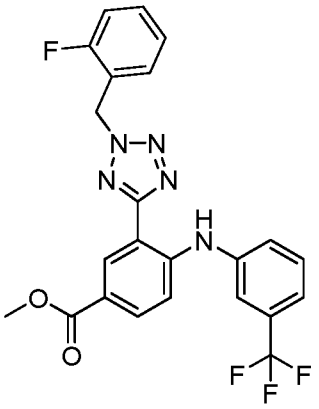
Step 4: methyl 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino) benzoate

[00421] To a mixture of **24-1** (1.2 g, 2.44 mmol, 1 *eq*) in DMSO (10 mL) and MeOH (2 mL) were added Xantphos (141.0 mg, 0.24 mmol, 0.1 *eq*), $Pd_2(dba)_3$ (223.2 mg, 0.24 mmol, 0.1 *eq*) and KOAc (717.7 mg, 7.31 mmol, 3 *eq*). The suspension was degassed under vacuum and purged with CO several times. The mixture was stirred for 12 hrs under CO 45 psi at 80 °C. LCMS showed the reaction was complete. The mixture was quenched by EA (30 mL), and the mixture was filtered and the filtered cake was washed with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na2SO4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (Si_2O). **Compound 24** (0.15 g, 0.31 mmol, 13.05% yield) was obtained.

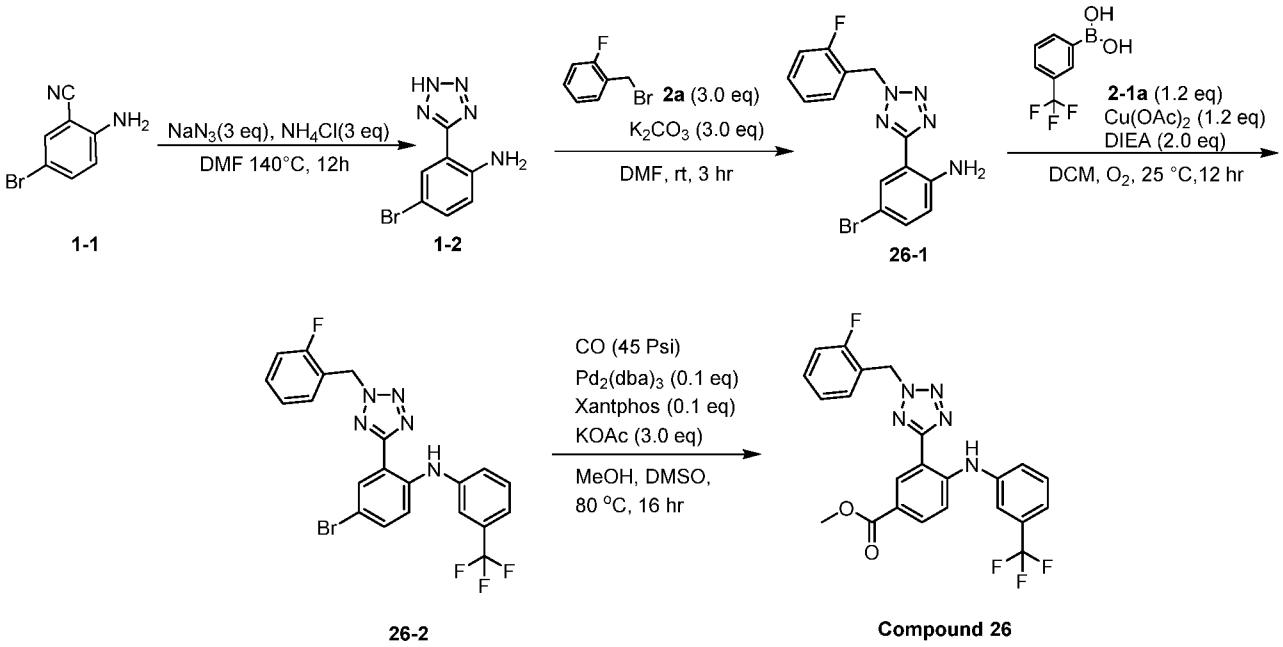
Step 5: 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00422] To a solution of **Compound 24** (0.03 g, 0.063 mmol, 1 *eq*) in MeOH (1 mL) and H_2O (0.1 mL) was added LiOH (7.6 mg, 0.031 mmol, 5 *eq*). The mixture was stirred at 60 °C for 3 hr. LCMS showed the reaction was complete. The mixture was quenched by H_2O (30 mL) and adjusted pH to 4 with HCl (4M). The mixture was extracted with EA (30mL *3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC to give **Compound 25** (5.08 mg, 0.011 mmol, 17.45% yield) was obtained. LCMS (ESI): RT = 0.848 min, mass calc. for: $C_{22}H_{15}F_4N_5O_2$ 457.12, m/z found 458.0 $[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.86 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 1.8, 8.8 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.59 - 7.53 (m, 2H), 7.50 - 7.40 (m, 3H), 7.29 - 7.20 (m, 2H), 6.06 (s, 2H).

Example 20: methyl 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl) amino)benzoate (Compound 26)



Preparation of Compound 26:



Step 1: 4-bromo-2-(2H-tetrazol-5-yl)aniline

[00423] To a solution of **1-1** (10 g, 50.75 mmol, 1 eq) in DMF (50 mL) were added NaN_3 (24.42 g, 375.64 mmol, 7.40 eq) and NH_4Cl (8.14 g, 152.26 mmol, 5.32 mL, 3 eq). The mixture was stirred at 140 °C for 12 hr. TLC showed that the reaction was complete. The reaction solution was added to H_2O (200 mL). The aqueous phase was adjusted to pH=5 and extracted with ethyl acetate (150 mL*3). The combined organic phase was washed with brine (50 mL*5), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was used the next step without purification. **1- 2** (30 g, crude) was obtained.

Step 2: 4-bromo-2-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)aniline

[00424] To a solution of **1-2** (3 g, 12.50 mmol, 1 eq) in DMF (20 mL) were added 1-(bromomethyl)-2-fluoro-benzene (4.72 g, 24.99 mmol, 3.01 mL, 2 eq) and Cs_2CO_3 (8.14 g, 24.99 mmol, 2 eq). The mixture was stirred at 25 °C for 3 hr. TLC (PE/EA=5/1) showed the reaction was complete. The reaction solution was added to H_2O (50 mL). The mixture was

extracted with ethyl acetate (20 mL*3). The combined organic phase was washed with brine (10 mL*5), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO_2), and **26-1** (1.5 g, 4.08 mmol, 32.68% yield) was obtained.

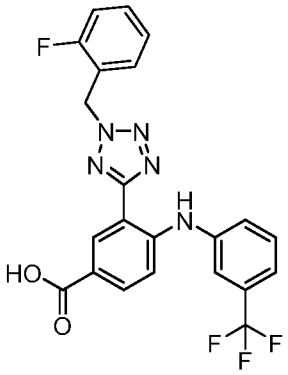
Step 3: 4-bromo-2-[2-[(2-fluorophenyl)methyl]tetrazol-5-yl]-N-[3-(trifluoromethyl)phenyl] aniline

[00425] To a mixture of **26-1** (1.5 g, 4.31 mmol, 1 eq) and **2-1a** (981.9 mg, 5.17 mmol, 1.2 eq) in DCM (20 mL) were added $Cu(OAc)_2$ (1.56 g, 8.62 mmol, 2 eq) and DIPEA (2.78 g, 21.54 mmol, 3.75 mL, 5 eq) in one portion at 25°C under O2. The mixture was stirred for 18 hrs under 15psi. TLC showed the reaction was finished. The mixture was quenched by EA (30 mL), and the mixture was extracted with EA(20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO_2). **26-2** (1.2 g, 2.14 mmol, 49.68% yield) was obtained.

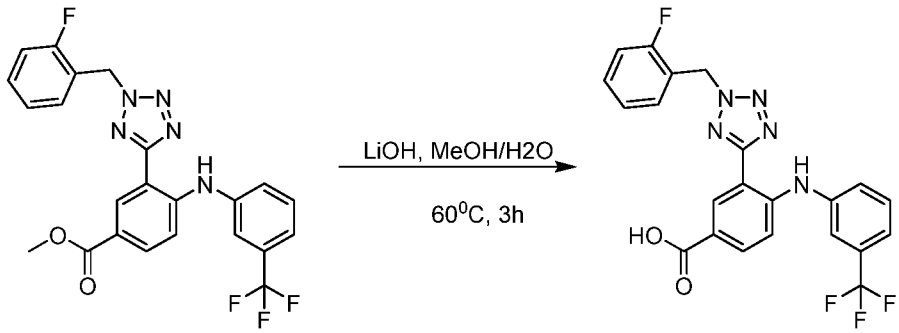
Step 4: methyl 3-[2-[(2-fluorophenyl)methyl]tetrazol-5-yl]-4-[3-(trifluoromethyl)anilino] benzoate

[00426] To a mixture of **26-2** (1.2 g, 2.44 mmol, 1 eq) in DMSO (10 mL) and MeOH (2 mL) were added Xantphos (141.0 mg, 0.24 mmol, 0.1 eq), $Pd_2(dba)_3$ (223.2 mg, 0.24 mmol, 0.1 eq) and KOAc (717.7 mg, 7.31 mmol, 3 eq). The suspension was degassed under vacuum and purged with CO several times. The mixture was stirred for 12 hrs at 45 psi at 80 °C. TLC showed the reaction was complete. The mixture was quenched by EA (30 mL), and the mixture was filtered and the filtered cake was washed with EA (20 mL*3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO_2). **Compound 26** (0.2 g, 0.28 mmol, 11.83% yield) was obtained. **Compound 26** (0.03 g, 0.063 mmol, 1 eq) was further separated by prep-HPLC. It was monitored by LCMS and HPLC. **Compound 26** (8.67 mg, 0.018 mmol, 28.90% yield) was obtained. LCMS (ESI): RT = 0.921 min, mass calc. for: $C_{23}H_{17}F_4N_5O_2$ 471.13, m/z found 472.0 [M+H]+; ^{1}H NMR (400MHz, CD_3OD) δ 8.84 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 2.0, 8.8 Hz, 1H), 7.61 - 7.36 (m, 7H), 7.29 - 7.19 (m, 2H), 6.06 (s, 2H), 3.91 (s, 3H).

Example 21: 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino) benzoic acid (Compound 27)



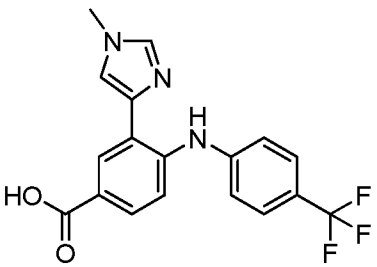
Preparation of Compound 27:



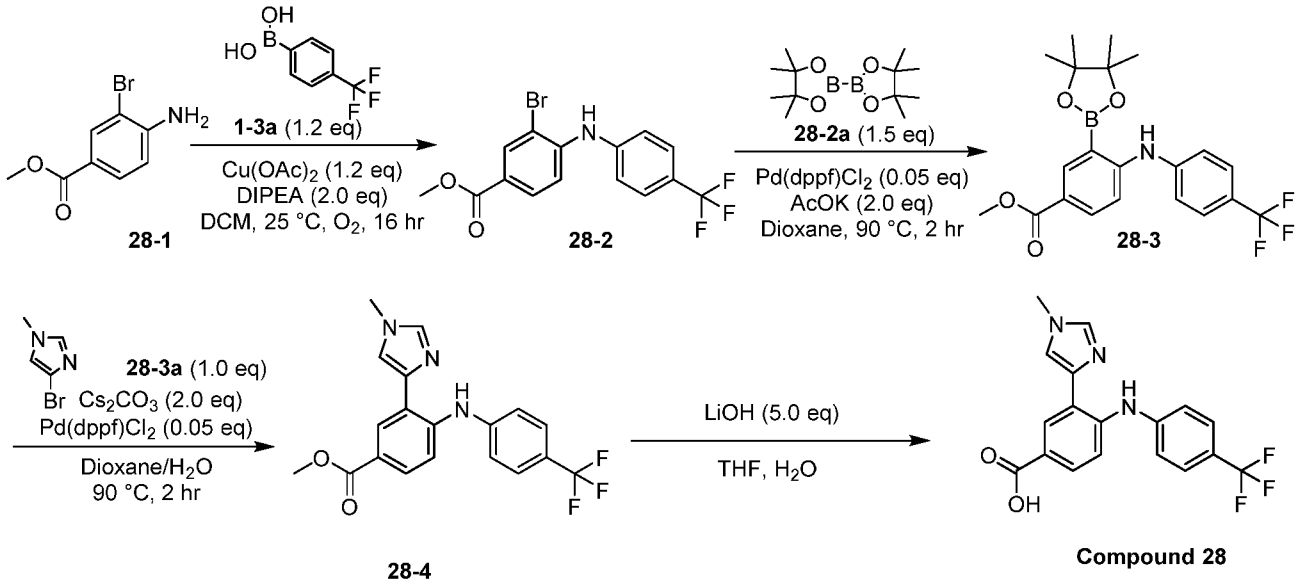
Compound 26 Compound 27

[00427] To a solution of **Compound 26** (30 mg, 0.063 mmol, 1 eq) in MeOH (1 mL) and H_2O (0.1 mL) was added LiOH (15.24 mg, 0.63 mmol, 10 eq). The mixture was stirred at 60 °C for 3 hr. LCMS showed the reaction was complete. The mixture was quenched by H_2O (30 mL) and adjusted pH to 4 with HCl (4M). The mixture was extracted with EA (30 mL *3). The combined organic phase was washed with brine (20 mL*3), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by pre-HPLC. **Compound 27** (6.62 mg, 0.014 mmol, 22.74% yield) was obtained. LCMS (ESI): RT = 0.844 min, mass calc. for: $C_{22}H_{15}F_4N_5O_2$ 458.12, m/z found 458.0 $[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.87 (d, J = 2.0 Hz, 1H), 7.99 (dd, J = 1.9, 8.9 Hz, 1H), 7.61 - 7.38 (m, 7H), 7.29 - 7.19 (m, 2H), 6.07 (s, 2H).

Example 22: 3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 28)



Preparation of Compound 28:



Step 1: methyl 3-bromo-4-((4-(trifluoromethyl)phenyl)amino)benzoate

[00428] To a solution of methyl 4-amino-3-bromo-benzoate (**28-1**, 400 mg, 1.74 mmol, 1 *eq*) and [4-(trifluoromethyl)phenyl]boronic acid (**1-3a**, 396.3 mg, 2.09 mmol, 1.2 *eq*) in DCM (3 mL) were added $Cu(OAc)_2$ (379.0 mg, 2.09 mmol, 1.2 *eq*) and DIPEA (449.4 mg, 3.48 mmol, 0.6 mL, 2 *eq*) under O_2 (15 psi). The mixture was stirred at 25 °C for 16 hr. TLC indicated that the starting material was consumed and that several new spots were formed. The reaction mixture was combined with another batch to work up. The reaction mixture was filtered. The filtered cake was washed with ethyl acetate (10 ml*3) and the combined organic layers was washed by NaCl (15 mL*3) then concentrated in vacuum to give crude product. The residue was purified by column chromatography (SiO_2). Methyl 3-bromo-4-[4-(trifluoromethyl)anilino]benzoate (**28-2**, 200 mg, 0.22 mmol, 6.6% yield) was obtained.

Step 2: methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl) amino)benzoate

[00429] The mixture of methyl 3-bromo-4-[4-(trifluoromethyl)anilino]benzoate (**28-2**, 200 mg, 0.53 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 (**28-2a**, 203.6 mg, 0.80 mmol, 1.5 *eq*) in dioxane (2 mL) were added $Pd(dppf)Cl_2$ (19.5 mg, 27 umol, 0.05 *eq*) and AcOK (104.9 mg, 1.07 mmol, 2 *eq*). The mixture was stirred at 90 °C for 2 hr. LCMS showed the starting material was consumed completely and the desired mass was detected. H_2O (8 mL) was added to the solution. The mixture was extracted with ethyl acetate (12 mL*3). The combined organic layers were washed with brine (20 mL*2), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO_2). Methyl 3-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)-4-[4-(trifluoromethyl)anilino]benzoate (**28-3**, 150 mg, 0.35 mmol, 66.62% yield) was obtained.

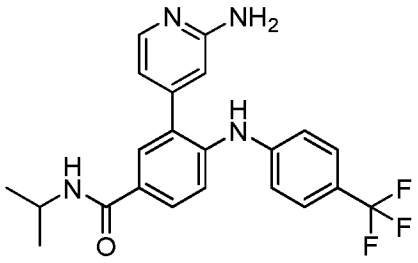
Step 3: methyl 3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate

[00430] To a solution of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)anilino]benzoate (**28-3**, 150 mg, 0.35 mmol, 1 *eq*) and 4-bromo-1-methyl-imidazole (**28-3a**, 57.3 mg, 0.35 mmol, 1 *eq*) in dioxane (2 mL) was added Cs_2CO_3 (232 mg, 0.71 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (13 mg, 17.8 umol, 0.05 *eq*), H_2O (6.42 mg, 0.35 mmol, 6.4 uL, 1 *eq*). The mixture was stirred at 90 °C for 2 hr. LCMS showed the starting material was consumed completely and the desired mass was detected. TLC indicated that the starting material was consumed completely and that two new spots were formed. H_2O (8 mL) was added to the solution. The mixture was extracted with ethyl acetate (12 mL*3). The combined organic layers were washed with brine (15 mL*2), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO_2). Methyl 3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzoate (**28-4**, 50 mg, 0.13 mmol, 37.4% yield) was obtained.

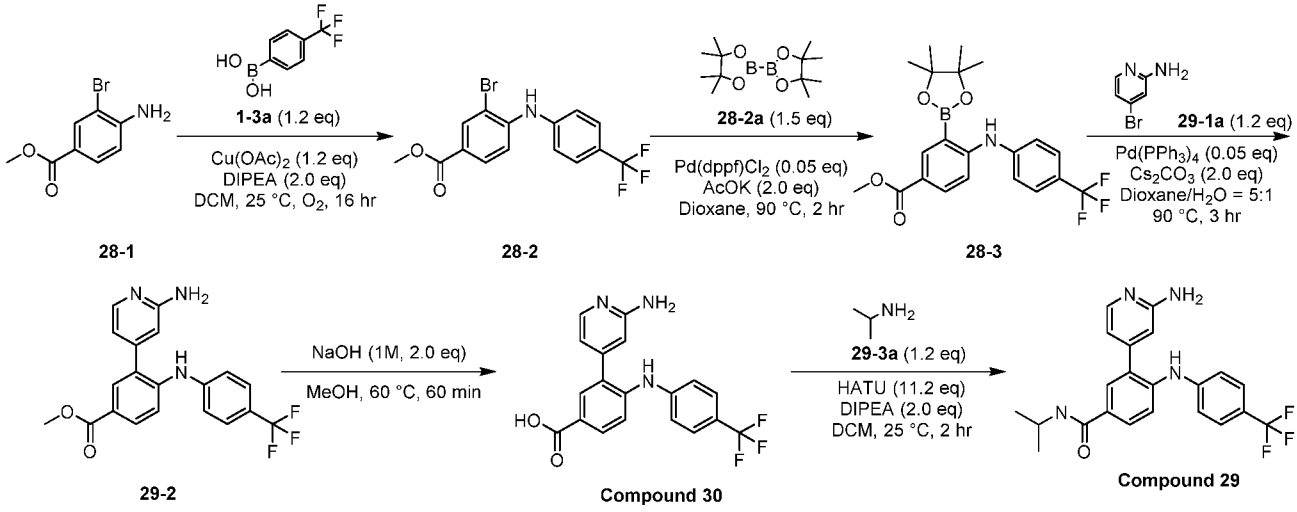
Step 4: 3-(1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00431] The mixture of methyl 3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (**28-4**, 25 mg, 66.6 umol, 1 *eq*) in THF (1 mL) was added into a solution of LiOH (7.9 mg, 0.33 mmol, 5 *eq*) and H_2O (1.20 mg, 66.6 umol, 1.20 uL, 1 *eq*). The mixture was stirred at 60 °C for 16 hr. LCMS showed the starting material was consumed and the desired mass was detected. The reaction mixture was combined with another batch to work up. H_2O (6 mL) was added to the solution. The mixture was extracted with ethyl acetate (10 mL*3). The combined organic layers were washed with brine (15 mL*2), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC. **Compound 28** (4.01 mg, 9.8 umol, 7.42% yield, HCl) was obtained. LCMS (ESI): RT = 0.673 min, mass calc. for $C_{18}H_{14}F_3N_3O_2$ 361.10, m/z found 361.9 $[M+H]^+$; δ^1H NMR (400MHz, CD_3OD) δ = 8.95 (s, 1H), 8.16 (s, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.81 (s, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 3.98 (s, 3H).

Example 23: 3-(2-aminopyridin-4-yl)-N-isopropyl-4-((4-(trifluoromethyl)phenyl)amino) benzamide (Compound 29)



Preparation of Compound 29:



Step 1: methyl 3-bromo-4-[4-(trifluoromethyl)anilino]benzoate

[00432] To a solution of **28-1** (1.00 g, 4.35 mmol, 1.0 *eq*), **1-3a** (991.0 mg, 5.22 mmol, 1.2 *eq*) and $Cu(OAc)_2$ (947.0 mg, 5.22 mmol, 1.2 *eq*) in DCM (10 mL) was added DIPEA (1.12 g, 8.69 mmol, 2.0 *eq*) under O_2. The mixture was stirred at 25 °C for 16 hr under O_2. TLC indicated that **28-1** remained, and that several new spots were formed. LCMS showed that **28-1** remained with several new peaks and 27% of desired compound was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to obtain **28-2** (300.0 mg, 17.7% yield).

Step 2: methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)anilino]

benzoate

[00433] To a solution of **28-2** (100 mg, 0.27 mmol, 1.0 *eq*), **28-2a** (102 mg, 0.40 mmol, 1.5 *eq*) and AcOK (52.5 mg, 0.53 mmol, 2.0 *eq*) in dioxane (1 mL) was added $Pd(dppf)Cl_2$ (9.8 mg, 13 umol, 0.05 *eq*). The mixture was stirred at 90°C for 2 hr. LCMS showed that **28-2** was completely consumed and detected several new peaks and 68% of the desired compound. TLC indicated **28-2** was consumed completely and several new spots were formed. The mixture was diluted with water (15 mL) and the resultant mixture was extracted with EA (40 mL * 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 (SiO_2) to obtain **28-3**(100 mg, 0.24 mmol, 88.8% yield).

Step 3: methyl 3-(2-amino-4-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate

[00434] To a solution of **28-3** (100 mg, 0.24 mmol, 1.0 *eq*), **29-1a** (49 mg, 0.28 mmol, 1.2 *eq*) and Cs_2CO_3 (155 mg, 0.47 mmol, 2.0 *eq*) in dioxane (1.5 mL) and H_2O (0.3 mL) was added $Pd(dppf)Cl_2$ (8.7 mg, 12 mmol, 0.05 *eq*) under N_2.The mixture was stirred at 90 °C for 3 hr LCMS showed that **28-3** was consumed completely and one main peak with desired MS was detected. TLC indicated **28-3** was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EA (30mL * 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 (SiO_2) to obtain **29-2** (70 mg, 0.18 mmol, 76.1% yield).

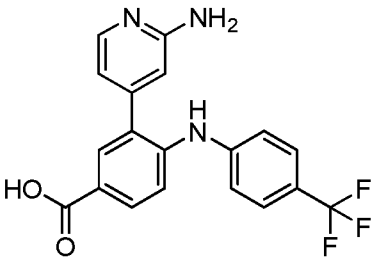
Step 4: 3-(2-amino-4-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid

[00435] To a solution of **29-2** (40 mg, 0.10 mmol, 1.0 *eq*) in MeOH(0.5 mL) was added NaOH (1 M, 0.2 mL, 2.0 *eq*). The mixture was stirred at 60°C for 1 hr. LCMS showed **29-2** was consumed completely and one main peak with desired MS was detected. The reaction mixture was adjusted with HCl (1M) to pH~6. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EA (40 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to obtain **Compound 30** (25 mg, crude).

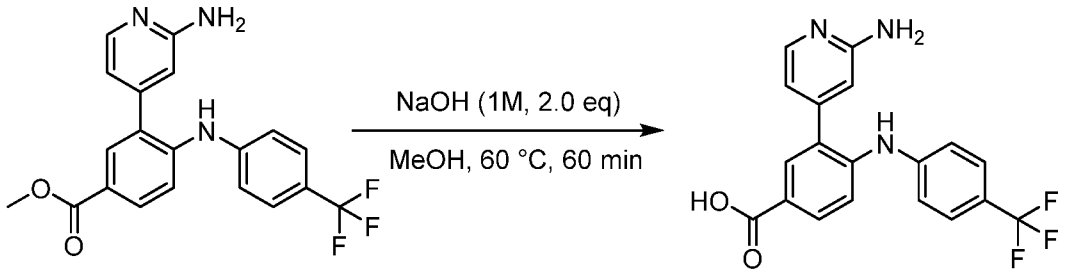
Step 5: 33-(2-amino-4-pyridyl)-*N*-isopropyl-4-[4-(trifluoromethyl)anilino]benzamide

[00436] To a solution of **Compound 30** (25 mg, 67 umol, 1.0 *eq*), **29-3a** (4.8 mg, 80 umol, 1.2 *eq*) and DIPEA (17 mg, 0.13 mmol, 2.0 *eq*) in DCM (1 mL) was added HATU (285 mg, 0.75 mmol, 11.2 *eq*) at 0°C for 5 min. And then the mixture was stirred at 25°C for 2 hr. LCMS showed **Compound 30** was consumed completely, and one main peak with desired MS was detected. The mixture was diluted with water (15 mL) and the resultant mixture was extracted with EA (40 mL * 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 to obtain **Compound 29** (8.17 mg, 29.4% yield). LCMS (ESI): RT=0.832 min, mass calcd. for $C_{22}H_{21}F_3N_4O$ 414.17, m/z found 415.4 $[M+H]^+$, ^1H NMR (400 MHz,$CDCl_3$) δ 8.15 (d, J = 5.02 Hz, 1 H), 7.69 (m, 2 H), 7.53 (d, J = 8.53 Hz, 2 H) ,7.43 (d, J = 8.28 Hz, 1 H), 7.12 (d, J = 8.53 Hz, 2 H), 6.72 (d, J = 5.27 Hz, 1 H), 6.57 (s, 1 H), 5.96 (s, 1 H), 5.85 (br d, J = 6.27 Hz, 1 H), 4.61 (br s, 2 H), 4.30 (m, 1 H), 1.27 (d, J = 6.53 Hz, 6 H).

Example 24: 3-(2-aminopyridin-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 30)



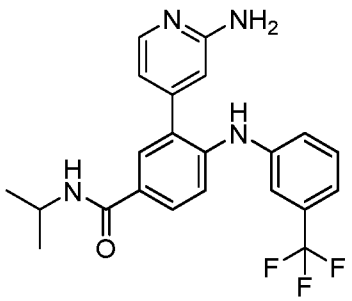
Preparation of Compound 30:



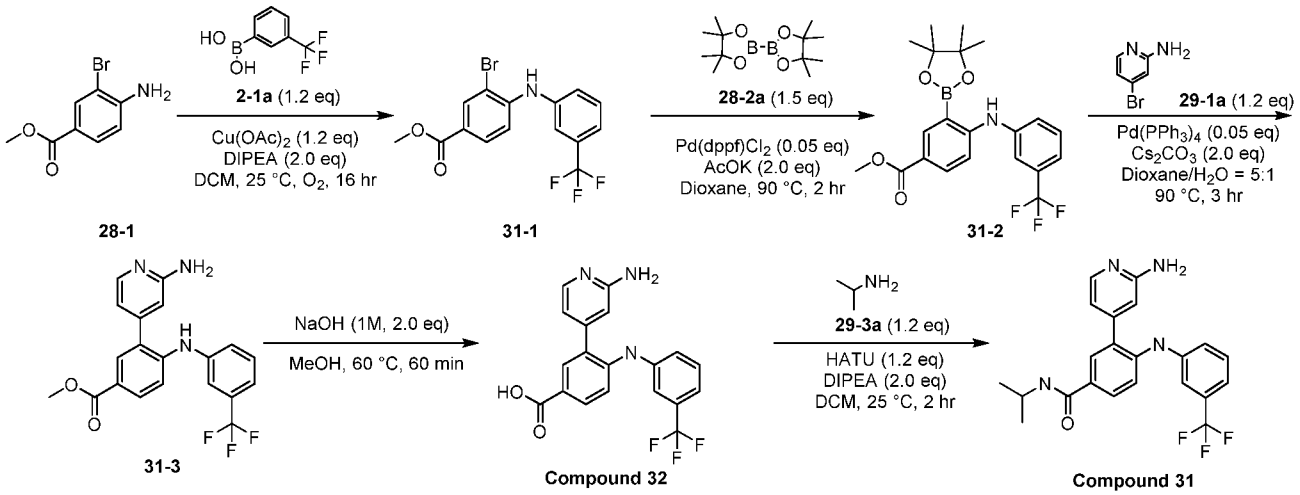
29-2 **Compound 30**

[00437] To a solution of **29-2** (30.0 mg, 77 umol, 1.0 *eq*) in MeOH (0.5 mL) was added NaOH (1 M, 0.2 mL, 2.0 *eq*). The mixture was stirred at 60°C for 1 hr. LCMS showed that **29-2** was consumed completely and one main peak with desired MS was detected. The reaction mixture was adjusted with HCl (1M) to pH~6. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EA (40 mL * 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 to obtain **Compound 30** (2.93 mg, 10.1% yield). LCMS (ESI): RT= 0.811 min, mass calcd. for $C_{19}H_{14}F_3N_3O_2$ 373.10, m/z found 374.4 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.33 (s, 1 H), 7.90 (m, 2 H), 7.82 (s, 1 H), 7.52 (d, J = 8.38 Hz, 2 H), 7.46 (d, J = 8.50 Hz, 1 H), 7.16 (d, J = 8.25 Hz, 2 H), 6.54 (s, 2 H), 5.98 (s, 2 H).

Example 25: 3-(2-aminopyridin-4-yl)-N-isopropyl-4-((3-(trifluoromethyl)phenyl)amino) benzamide (Compound 31)



Preparation of Compound 31:



Step 1: methyl 3-bromo-4-[3-(trifluoromethyl)anilino]benzoate

[00438] To a solution of **28-1** (3.50 g, 15.2 mmol, 1.0 *eq*), **2-1a** (3.47 g, 18.3 mmol, 1.2 *eq*) and $Cu(OAc)_2$ (3.32 g, 18.3 mmol, 1.2 *eq*) in DCM (10 mL) was added DIPEA (3.93 g, 30.4 mmol, 2.0 *eq*) under O_2. The mixture was stirred at 25 °C for 16 hr under O_2. TLC indicated that **28-1** remained with several new spots detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to obtain **31-1** (1.8 g, 29.7% yield).

Step 2: methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[3-(trifluoromethyl)anilino]

benzoate

[00439] To a solution of **31-1** (1.8 g, 4.80 mmol, 1.0 *eq*), **28-2a** (1.80 g, 7.2 mmol, 1.5 *eq*) and AcOK (944 mg, 9.6 mmol, 2.0 *eq*) in dioxane (10 mL) was added $Pd(dppf)Cl_2$ (176 mg, 0.24 mmol, 0.05 *eq*). The mixture was stirred at 90°C for 2 hr under N_2. LCMS showed that **31-1** was completely, and one main peak with desired MS was detected. TLC indicated that **31-1** was consumed completely and one new spot was formed. The reaction mixture was concentrated under reduced pressure .The mixture was diluted with water (20 mL), and the resultant mixture was extracted with EA (60 mL * 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 (SiO_2) to obtain **31-2** (1.9 g, 93.8% yield).

Step 3: methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[3-(trifluoromethyl)anilino]

benzoate

[00440] To a solution of **31-2** (800.0 mg, 1.90 mmol, 1.0 *eq*), **29-1a** (394.0 mg, 2.28 mmol, 1.2 *eq*) and Cs_2CO_3 (1.24 g, 3.80 mmol, 2.0 *eq*) in dioxane (1.5 mL) and H_2O (0.3

mL) was added Pd(dppf)Cl_2 (69.0 mg, 95 umol, 0.05 *eq*) under N_2.The mixture was stirred at 90 °C for 3 hr. . TLC indicated that **31-2** was consumed completely, and one new spot was formed. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (15 mL) and the resultant mixture was extracted with EA (40 mL * 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 (SiO_2) to obtain compound **31-3** (250 mg, 34.0% yield).

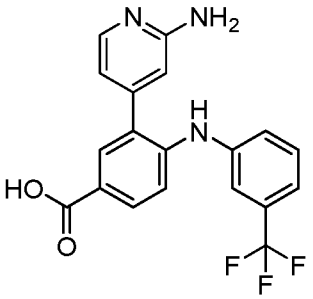
Step 4: 3-(2-Amino-4-pyridyl)-4-[3-(trifluoromethyl)anilino]benzoic acid

[00441] To a solution of **31-3** (200 mg, 0.52 mmol, 1.0 *eq*) in MeOH (0.5 mL) was added NaOH (1 M, 1.0 mL, 2.0 *eq*). The mixture was stirred at 60°C for 1 hr. LCMS showed **31-3** was consumed completely and one main peak with desired MS was detected. The reaction mixture was adjusted with HCl (1M) to pH~6. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EA (40 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure to obtain **Compound 32** (150 mg, crude).

Step 5: 3-(2-amino-4-pyridyl)-*N*-isopropyl-4-[3-(trifluoromethyl)anilino]benzamide

[00442] To a solution of **Compound 32** (50 mg, 0.13 mmol, 1.0 *eq*), **29-3a** (10 mg, 0.16 mmol, 1.2 *eq)* and DIPEA (35 mg, 0.27 mmol, 2.0 *eq*) in DCM (1 mL) was added HATU (61 mg, 0.16 mmol, 1.2 *eq*) at 0°C for 5 min. And then the mixture was stirred at 25°C for 2 hr. LCMS showed **Compound 32** was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure. Then the mixture was diluted with water (15 mL) and the resultant mixture was extracted with EA (40 mL * 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 to obtain **Compound 31** (14.74 mg, 26.3% yield). LCMS (ESI): RT=0.813 min, mass calcd. for $C_{22}H_{21}F_3N_4O$ 414.17, m/z found 415.4 $[M+H]^+$, ^1H NMR (400 MHz,$CDCl_3$) δ ppm 8.16 (br s, 1 H), 7.68 (m, 2 H), 7.41 (m, 1 H), 7.33 (m, 2 H) ,7.25 (m, 2 H), 6.75 (d, J = 4.63 Hz, 1 H), 6.59 (s, 1 H), 5.92 (m, 2 H), 4.59 (br s, 2 H) ,4.38 - 4.22 (m, 1 H), 1.27 (d, J = 6.50 Hz, 6 H).

Example 26: 3-(2-aminopyridin-4-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 32)



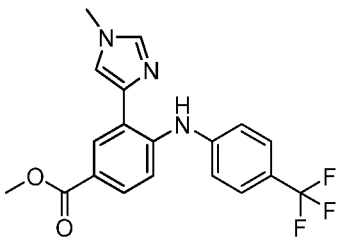
Preparation of Compound 32:



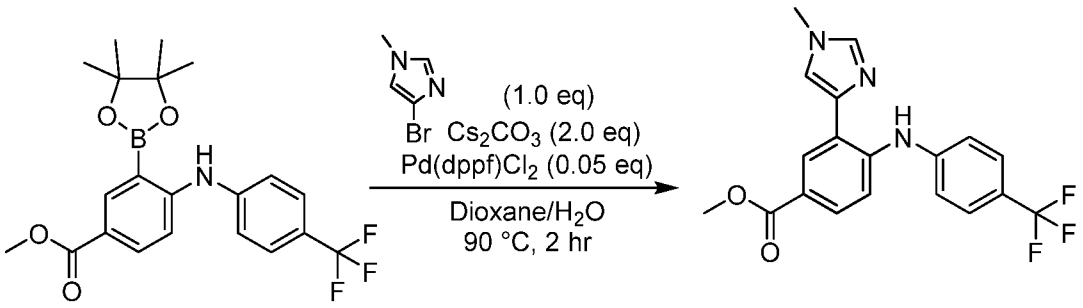
31-3 **Compound 32**

[00443] To a solution of **31-3** (50.0 mg, 0.13 mmol, 1.0 *eq*) in MeOH (0.5 mL) was added NaOH (1M, 0.3 mL, 2.0 *eq*). The mixture was stirred at 60°C for 30 min. LCMS showed that **31-3** was consumed completely and one main peak with desired MS was detected. The reaction mixture was adjusted with HCl (1M) to pH~6. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EA (40 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. MeOH (10 mL) was added, and then the suspension was filtered and washed with MeOH (10 mL * 3) to obtain **Compound 32** (4.78 mg, 9.7% yield). LCMS (ESI): RT= 0.808 min, mass calcd. for $C_{19}H_{14}F_3N_3O_2$ 373.10, m/z found 374.4 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.20 (s, 1 H), 7.91 (d, J = 5.25 Hz, 1 H), 7.86 (dd, J = 8.50, 2.00 Hz, 1 H), 7.79 (d, J = 2.13 Hz, 1 H), 7.43 (m, 1 H), 7.37 (m, 2 H), 7.31 (s, 1 H), 7.17 (d, J = 7.63 Hz, 1 H), 6.55 (m, 2 H), 5.97 (s, 2 H).

Example 27: methyl 3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (Compound 33)



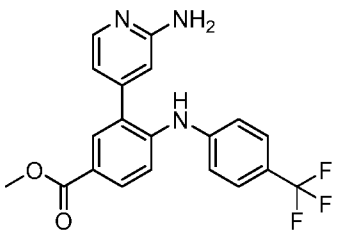
Preparation of Compound 33:



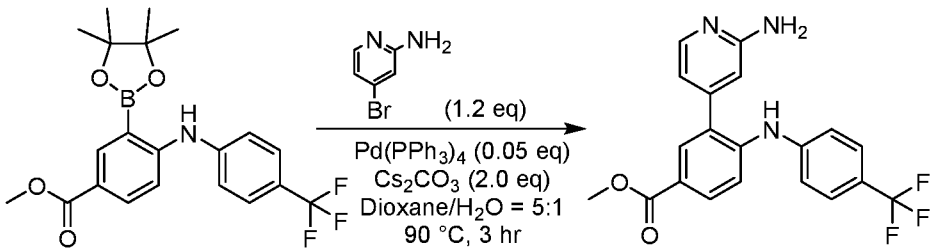
Compound 33

[00444] To a solution of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)anilino]benzoate (100 mg, 0.23 mmol, 1 *eq*) and 4-bromo-1-methyl-imidazole (38.2 mg, 0.23 mmol, 1 *eq*) in dioxane (3 mL) was added Cs_2CO_3 (154.7 mg, 0.47 mmol, 2 *eq*) and H_2O (4.2 mg, 0.23 mmol, 4.28 uL, 1 *eq*), $Pd(dppf)Cl_2$ (8.6 mg, 11.8 umol, 0.05 *eq*). The mixture was stirred at 90 °C for 2 hr. H_2O (6 mL) was added to the solution. The mixture was extracted with ethyl acetate (10 mL*3). The combined organic layers were washed with brine (15 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC to obtain the title compound (1.49 mg, 3.6 umol, 1.52% yield, HCl). Mass calc. for $C_{19}H_{16}F_3N_3O_2$ 375.12, m/z found 375.9 $[M+H]^+$; ^1H NMR (400MHz, CD_3OD) ^1H NMR (400MHz, METHANOL-d_4) δ = 8.93 (br s, 1H), 8.16 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 1.8, 8.5 Hz, 1H), 7.82 (br s, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 8.3 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H).

Example 28: methyl 3-(2-amino-4-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate (Compound 34)



Preparation of Compound 34:

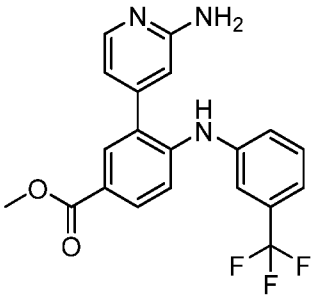


Compound 34

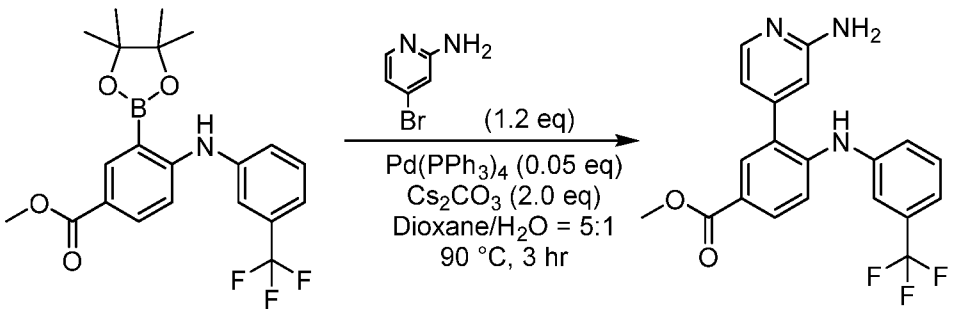
[00445] To a solution of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)anilino]benzoate (30 mg, 71 umol, 1.0 *eq*), 4-bromopyridin-2-amine (15 mg, 86

umol, 1.2 *eq*) and Cs_2CO_3 (46 mg, 0.14 mmol, 2.0 *eq*) in dioxane (1.0 mL) and H_2O (0.2 mL) was added Pd(dppf)Cl_2 (2.6 mg, 3.6 umol, 0.05 *eq*) under N_2. The mixture was stirred at 90 °C for 3 hr. The reaction mixture was concentrated under reduced pressure. Then the mixture was diluted with water (15 mL) and the resultant mixture was extracted with EA (40 mL * 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 to obtain the title compound (6.96 mg, 24.7% yield). Mass calcd. for $C_{20}H_{16}F_3N_3O_2$ 387.12, m/z found 388.4 $[M+H]^+$, ^{1}HNMR (400 MHz,$CDCl_3$) δ 8.09 (d, J = 5.13 Hz, 1 H), 7.88 (m, 2 H), 7.49 (d, J = 8.38 Hz, 2 H), 7.34 (d, J = 8.63 Hz, 1 H), 7.10 (d, J = 8.25 Hz, 2 H), 6.67 (d, J = 5.13 Hz, 1 H), 6.51 (s, 1 H), 6.01 (s, 1 H), 4.57 (br s, 2 H), 3.83 (m, 3 H).

Example 29: methyl 3-(2-amino-4-pyridyl)-4-[3-(trifluoromethyl)anilino]benzoate (Compound 35)



Preparation of Compound 35:

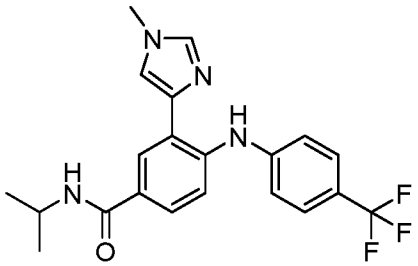


Compound 35

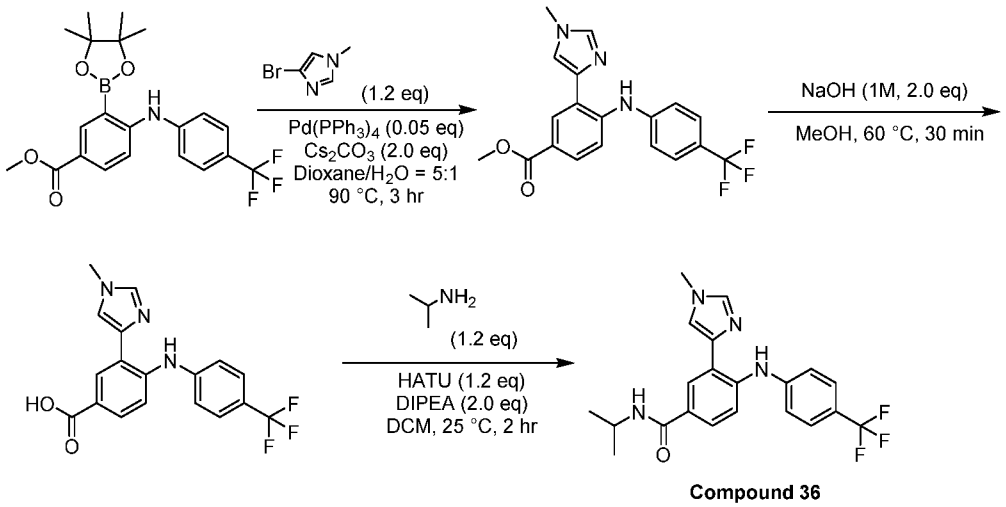
[00446] To a solution of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoate (50 mg, 0.12 mmol, 1.0 *eq*), 4-bromopyridin-2-amine (25 mg, 0.14 mmol, 1.2 *eq*) and Cs_2CO_3 (77 mg, 0.24 mmol, 2.0 *eq*) in dioxane (1.5 mL) and H_2O (0.3 mL) was added Pd(dppf)Cl_2 (4.3 mg, 6 umol, 0.05 *eq*) under N_2. The mixture was stirred at 90 °C for 3 hr. The reaction mixture was concentrated under reduced pressure. Then the mixture was diluted with water (10 mL) and the resultant mixture was extracted with EA (30 mL * 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 to obtain the title compound

(2.59 mg, 5.52% yield). Mass calcd. for $C_{20}H_{16}F_3N_3O_2$ 387.12, m/z found 388.4 $[M+H]^+$, ^1H NMR (400 MHz,$CDCl_3$) δ 8.10 (d, J = 5.25 Hz, 1 H), 7.86 (m, 2 H), 7.37 (m, 1 H), 7.29 (s, 1 H), 7.23 (dd, J = 8.07, 5.82 Hz, 3 H), 6.68 (d, J = 5.25 Hz, 1 H), 6.52 (s, 1 H), 6.00 (s, 1 H), 4.52 (br s, 2 H), 3.83 (s, 3 H).

Example 30: *N*-Isopropyl-3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzamide (Compound 36)



Preparation of Compound 36:



Compound 36

Step 1: methyl 3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzoate

[00447] To a solution of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)anilino]benzoate (1.35 g, 3.20 mmol, 1.0 *eq*), 4-bromo-1-methyl-imidazole (619 mg, 3.85 mmol, 1.2 *eq*) and Cs_2CO_3 (2.09 g, 6.41 mmol, 2.0 *eq*) in dioxane (15 mL) and H_2O (3 mL) was added $Pd(dppf)Cl_2$ (117 mg, 0.16 mmol, 0.05 *eq*). The mixture was stirred at 90 °C for 3 hr under N_2. The reaction mixture was concentrated under reduced pressure .Then the mixture was diluted with water (15 mL) and the resultant mixture was extracted with EA (40 mL * 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 (SiO_2) to obtain methyl 3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzoate (600 mg, 49.9% yield).

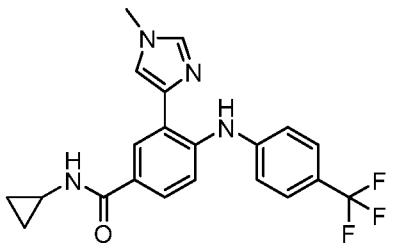
Step 2: 3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid

[00448] To a solution of methyl 3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzoate (300 mg, 0.80 mmol, 1.0 *eq*) in MeOH (5 mL) was added NaOH (1 M, 1.6 mL, 2.0 *eq*). The mixture was stirred at 60 °C for 30 min. The reaction mixture was added HCl (1M) to PH ~6. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EA (40 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure to obtain 3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid (220 mg, crude).

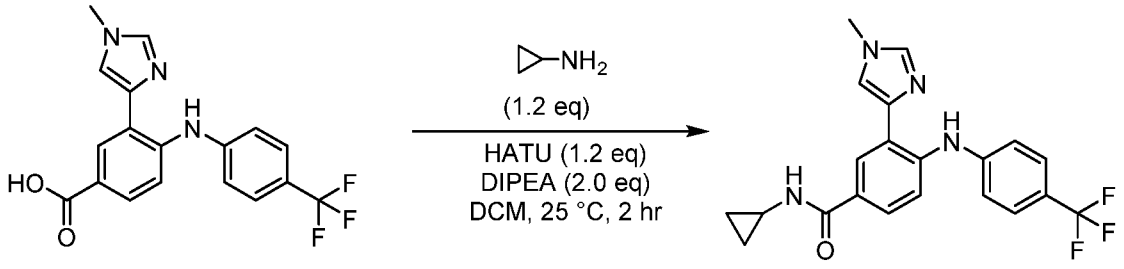
Step 3: *N*-isopropyl-3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzamide

[00449] To a solution of 3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid (30 mg, 83 umol, 1.0 *eq*), isopropylamine (5.9 mg, 0.10 mmol, 1.2 *eq)* and DIPEA (22 mg, 0.17 mmol, 2.0 *eq*) in DCM (1 mL) was added HATU (38 mg, 0.10 mmol, 1.2 *eq*) at 0°C. And then the mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure .Then the mixture was diluted with water (15 mL) and the resultant mixture was extracted with EA (40 mL * 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 to obtain the title compound (12.49 mg, 37.0% yield). Mass calcd. for $C_{22}H_{21}F_3N_4O$ 402.17, m/z found 403.5 $[M+H]^+$, ^1H NMR (400 MHz,$CDCl_3$) δ ppm 10.61 (s, 1 H), 8.02 (s, 1 H), 7.51 (m, 3 H), 7.44 (s, 2 H), 7.29 (m, 3 H), 5.86 (br d, J = 7.75 Hz, 1 H), 4.30 (m, 1 H) ,3.77 (s, 3 H), 1.27 (d, J = 6.63 Hz, 6 H).

Example 31: *N*-cyclopropyl-3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzamide (Compound 37)



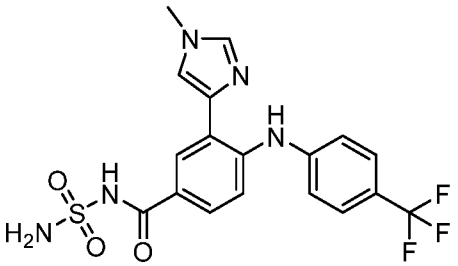
Preparation of Compound 37:



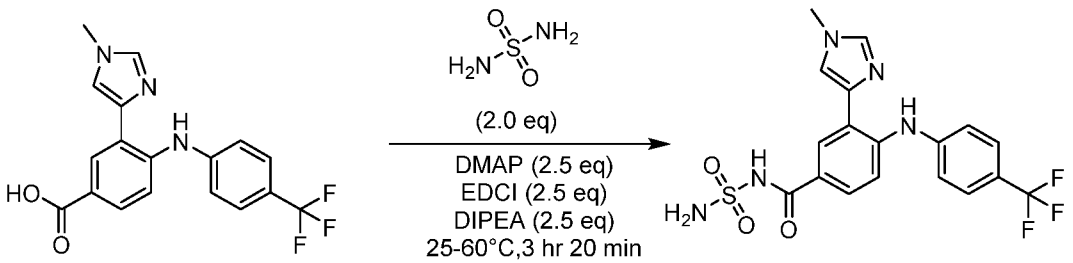
Compound 37

[00450] To a solution of 3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid (30 mg, 83 umol, 1.0 *eq*) cyclopropylamine (5.7 mg, 0.1 mmol, 1.2 *eq*) and DIPEA (21.5 mg, 0.17 mmol, 2.0 *eq*) in DCM (1 mL) was added HATU (38 mg, 0.10 mmol, 1.2 *eq*) at 0°C. And then the mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure .Then the mixture was diluted with water (5 mL) and the resultant mixture was extracted with EA (20 mL * 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 to obtain the title compound (15.03 mg, 44.8% yield). Mass calcd. for $C_{21}H_{19}F_3N_4O$ 400.15, m/z found 401.5 $[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.55 (br s, 1 H), 7.95 (s, 1 H), 7.44 (m, 3 H), 7.35 (d, J = 1.00 Hz, 2 H), 7.22 (m, 3 H), 6.13 (br s, 1 H), 3.70 (s, 3 H), 2.84 (tq, J = 7.05, 3.55 Hz, 1 H), 0.80 (m, 2 H), 0.55 (m, 2 H).

Example 32: 3-(1-methylimidazol-4-yl)-*N*-sulfamoyl-4-[4-(trifluoromethyl)anilino]benzamide (Compound 38)



Preparation of Compound 38:

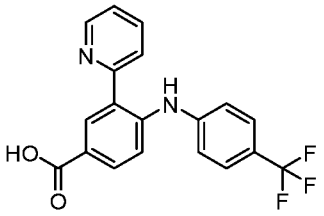


Compound 38

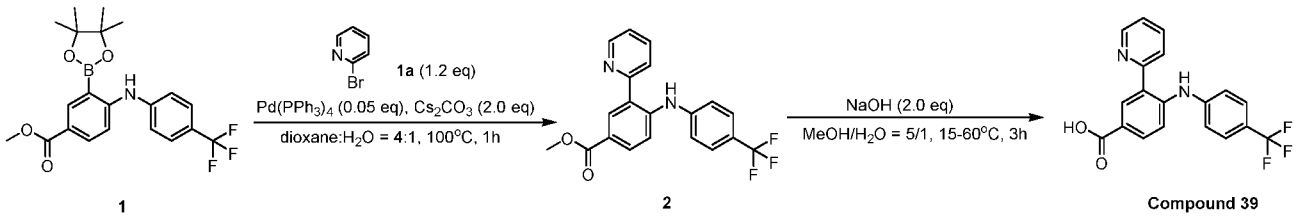
[00451] To a solution of 3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid (48 mg, 0.13 mmol, 1.0 *eq*) in DCM (2 mL) were added DMAP (41 mg, 0.33 mmol, 2.5 *eq*), EDCI (64 mg, 0.33 mmol, 2.5 *eq*) and DIPEA (43 mg, 0.33 mmol, 2.5 *eq*). And the mixture stirred at 25°C for 20 minutes. Then sulfuric diamide (26 mg, 0.27 mmol, 2.0 *eq*) was added to the solution. The mixture heated at 60°C for 3 hr under N_2. The mixture was diluted with water (5 mL) and the resultant mixture was extracted with EA (20 mL * 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 to obtain the title compound (2.71 mg, 4.6% yield). Mass

calcd. for $C_{18}H_{16}F_3N_5O_3S$ 439.09, m/z found 440.4 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 11.67 (br s, 1 H), 11.10 (br s, 1 H), 8.31 (s, 1 H), 7.88 (s, 1 H), 7.77 (m, 2 H), 7.64 (br d, J = 8.25 Hz, 2 H), 7.47 (br d, J = 8.63 Hz, 1 H), 7.35 (br d, J = 8.25 Hz, 2 H), 7.24 (br s, 2 H), 3.77 (s, 3 H).

Example 33: 3-(pyridin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 39)



Preparation of Compound 39:



Step 1: methyl 3-(pyridin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate

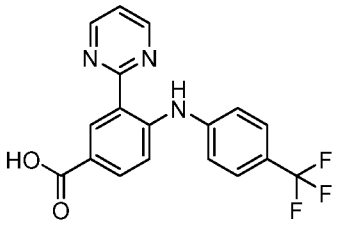
[00452] To a solution of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (50 mg, 0.12 mmol, 1 *eq*) in dioxane (0.8 mL) and H_2O (0.2 mL) were added Cs_2CO_3 (77.3 mg, 0.24 mmol, 2 *eq*), $Pd(PPh_3)_4$ (7 mg, 5.9 umol, 0.05 *eq*) and 2-btomopyridine (22.5 mg, 0.14 mmol, 13 uL, 1.2 *eq*). The mixture was stirred at 100°C for 1 hr. The reaction mixture was filtered and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2) to obtain methyl 3-(pyridin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (20 mg, 49 umol, 41.6% yield).

Step 2: 3-(pyridin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

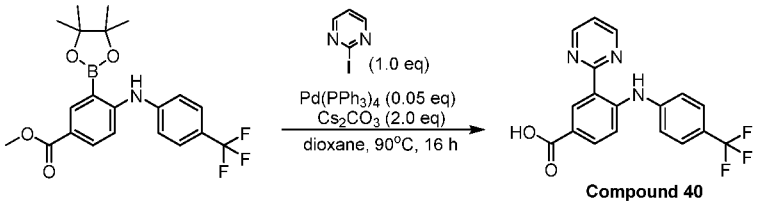
[00453] To a solution of methyl 3-(pyridin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (15 mg, 40 umol, 1 *eq*) in MeOH (0.5 mL) was added NaOH (8 mg, 0.2 mmol, 5 *eq*) in H_2O (0.1 mL). The mixture was stirred at 60°C for 0.5 hr. The reaction mixture was concentrated in vacuum. The residue was dissolve in H_2O (5 mL) and adjust PH = 4 with 1M aq. HCl. The crude product was purified by prep-HPLC to obtain the title compound (6 mg, 16.7 umol, 41% yield). Mass calcd. For $C_{19}H_{13}F_3N_2O_2$, 358.09 m/z found 358.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.55 (br s, 1H), 8.75 (br d, J = 4.3 Hz, 1H),

8.27 (d, J = 1.8 Hz, 1H), 8.08 - 7.99 (m, 1H), 7.97 - 7.90 (m, 2H), 7.62 - 7.48 (m, 4H), 7.31 (d, J = 8.5 Hz, 2H).

Example 34: 3-(pyrimidin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 40)



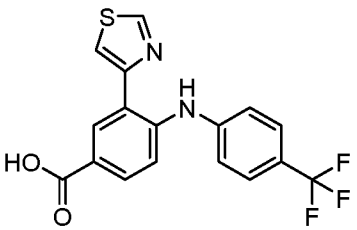
Preparation of Compound 40:



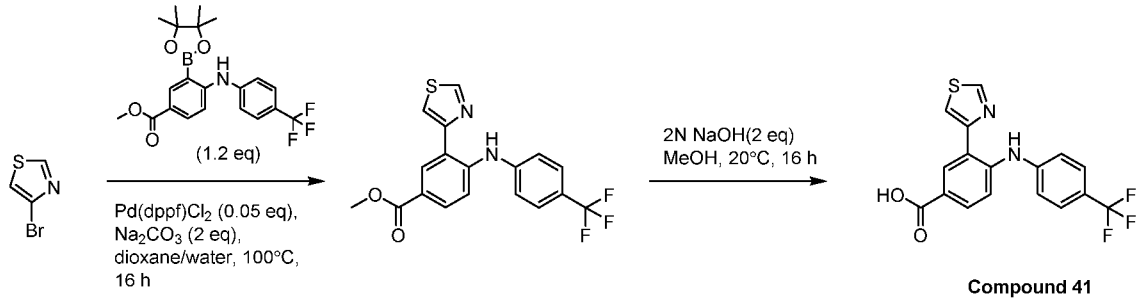
Step 3: 3-(pyrimidin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00454] To a solution of 2-iodopyrimidine (100 mg, 0.48 mmol, 1 *eq*) in dioxane (2 mL) and H_2O (0.4 mL) were added Cs_2CO_3 (316 mg, 0.97 mmol, 2 *eq*), $Pd(PPh_3)_4$ (28 mg, 24.2 umol, 0.05 *eq*) and methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (245.4 mg, 0.58 mmol, 1.2 *eq*). The mixture was stirred at 90°C for 16 hr. The reaction mixture was concentrated in vacuum and the residue was diluted with EA (20 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC to give the title compound (33 mg, 90.9 umol, 18.7% yield). Mass calcd. For $C_{18}H_{12}F_3N_3O_2$, 359.09 m/z found 359.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.68 (br s, 1H), 11.64 (s, 1H), 9.15 (d, J = 2.0 Hz, 1H), 9.01 (d, J = 5.0 Hz, 2H), 7.93 (dd, J = 2.0, 8.8 Hz, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.55 - 7.49 (m, 4H).

Example 35: 3-(thiazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 41)



Preparation of Compound 41:



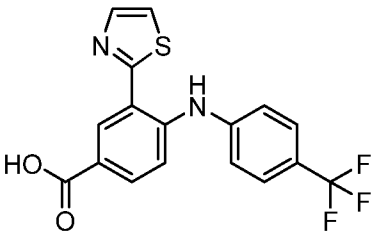
Step 1: methyl 3-(thiazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate

[00455] The mixture of 4-bromothiazole (100 mg, 0.61 mmol, 1 *eq*), methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (308.2 mg, 0.73 mmol, 1.2 *eq*) , Na_2CO_3 (129.2 mg, 1.22 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (22.3 mg, 30.5 umol, 0.05 *eq*) in Water (0.3 mL) and dioxane (3 mL) at 20°C was purged and degassed with N_2 for 3 times, and then stirred at 100°C under N_2 for 16 h. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give methyl 3-(thiazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (140 mg, 0.35 mmol, 57.1% yield). Mass calc. for $C_{18}H_{13}F_3N_2O_2S$ 378.06, m/z found 378.9$[M+1]^+$.

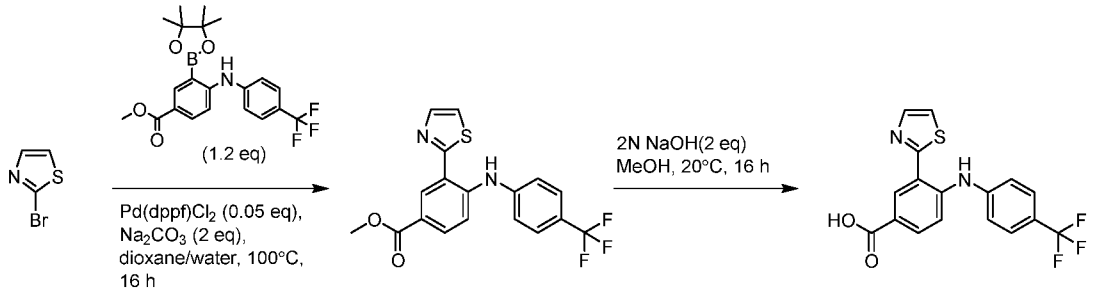
Step 2: 3-(thiazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00456] To a solution of methyl 3-(thiazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (140 mg, 0.37 mmol, 1 *eq*) in MeOH (5 mL) at 20°C was added NaOH (2 M, 1.9 mL, 10 *eq*) drop-wise, and the mixture was stirred at 20°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give the title compound (36.36 mg, 91.5 umol, 24.7% yield). Mass calc. for $C_{17}H_{11}F_3N_2O_2S$ 364.05, m/z found 365.0$[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.79 (brs, 1H), 9.76 (s, 1H), 9.33 (d, J = 1.8 Hz, 1H), 8.38 (s, 1H), 8.20 (d, J = 1.8 Hz, 1H), 7.88 (dd, J = 2.0, 8.5 Hz, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H).

Example 36: 3-(thiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 42)



Preparation of Compound 42:



Compound 42

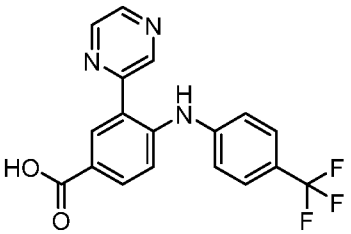
Step 1: methyl 3-(thiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate

[00457] The mixture of 2-bromothiazole (100 mg, 0.61 mmol, 55.0 uL, 1 *eq*), methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (308.16 mg, 0.73 mmol, 1.2 *eq*), Na_2CO_3 (129.2 mg, 1.22 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (22.3 mg, 30.5 umol, 0.05 *eq*) in Water (0.3 mL) and dioxane (3 mL) at 20°C was purged and degassed with N_2 for 3 times, and then stirred at 100°C under N_2 for 16 h. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give methyl 3-(thiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (100 mg, 0.26 mmol, 43.4% yield). Mass calc. for $C_{18}H_{13}F_3N_2O_2S$ 378.06, m/z found 378.9$[M+1]^+$.

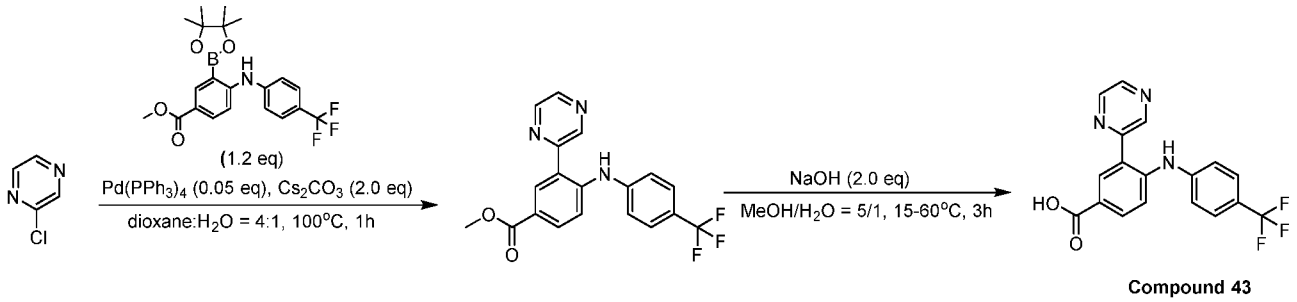
Step 2: 3-(thiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00458] To a solution of methyl 3-(thiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (100 mg, 0.26 mmol, 1 *eq*) in MeOH (5 mL) at 20°C was added NaOH (2 M, 1.3 mL, 10 *eq*), and then the mixture was stirred at 20°C under N_2 for 16 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give the title compound (18.53 mg, 47.7 umol, 18.1% yield). Mass calc. for $C_{17}H_{11}F_3N_2O_2S$ 364.05, m/z found 364.7$[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.74 (brs, 1H), 8.46 (s, 1H), 8.04 (d, J = 3.0 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 3.3 Hz, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.59 - 7.51 (m, 1H), 7.41 (d, J = 8.0 Hz, 2H).

Example 37: 3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 43)



Preparation of Compound 43:



Compound 43

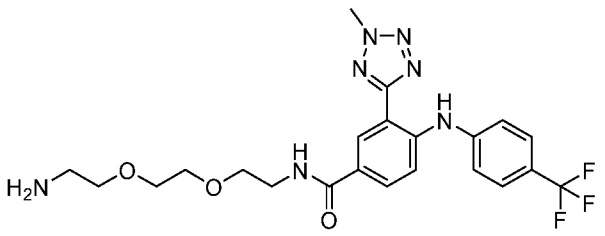
Step 1: methyl 3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate

[00459] To a solution of 2-chloropyrazine (50 mg, 0.44 mmol, 39 uL, 1 *eq*) in dioxane (1 mL) and H_2O (0.2 mL) were added Cs_2CO_3 (284 mg, 0.87 mmol, 2 *eq*), $Pd(PPh_3)_4$ (25 mg, 21.8 umol, 0.05 *eq*) and methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (340 mg, 0.53 mmol, 1.2 *eq*). The reaction mixture was degassed for 3 times and stirred at 90°C for 16 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with brine (5 mL). Then the organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2) to give methyl 3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (200 mg, 0.35 mmol, 80% yield).

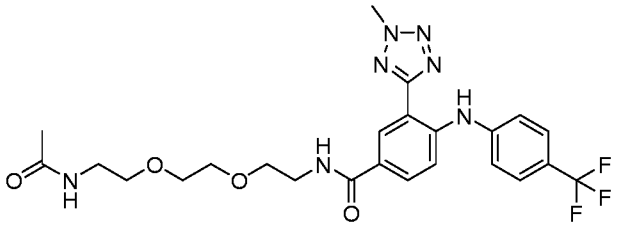
Step 2: 3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00460] To a solution of methyl 3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (154 mg, 0.27 mmol, 1 *eq*) in MeOH (1 mL) were added NaOH (2 M, 0.4 mL, 3 *eq*). The mixture was stirred at 60 °C for 3 hr. The reaction mixture was concentrated in vacuum. The crude product was purified by prep-HPLC to obtain the title compound (18 mg, 47 umol, 17.5% yield). Mass calcd. For $C_{18}H_{12}F_3N_3O_2$, 359.09 m/z found 359.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.83 (br s, 1H), 9.59 (s, 1H), 9.02 (d, J = 1.5 Hz, 1H), 8.75 (dd, J = 1.5, 2.5 Hz, 1H), 8.62 (d, J = 2.5 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 2.1, 8.6 Hz, 1H), 7.56 (dd, J = 8.6, 11.5 Hz, 3H), 7.23 (d, J = 8.5 Hz, 2H).

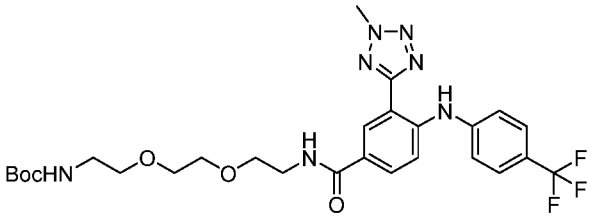
Example 38: N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide (Compound 44)



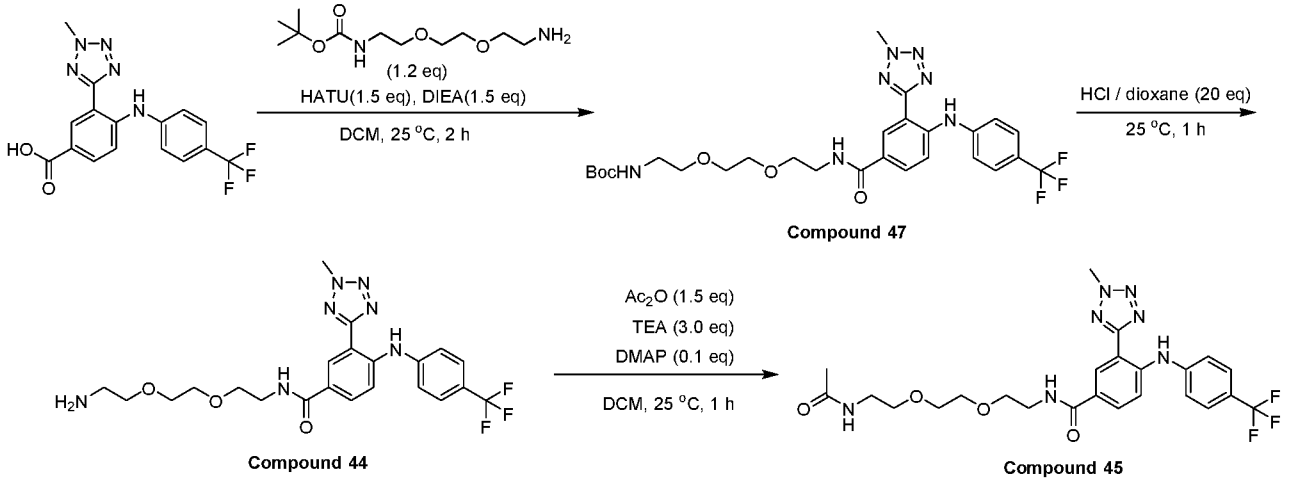
N-(2-(2-(2-acetamidoethoxy)ethoxy)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide (Compound 45)



and tert-butyl (2-(2-(2-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamido)ethoxy)ethoxy)ethyl)carbamate (Compound 47)



Preparation of Compound 44, Compound 45, and Compound 47:



Step 1: tert-butyl (2-(2-(2-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamido)ethoxy)ethoxy)ethyl)carbamate

[00461] To a solution of 3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid (300 mg, 0.83 mmol, 1 *eq*) and tert-butyl N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]carbamate (246.1 mg, 0.99 mmol, 1.2 *eq*) in DCM (2 mL) was added HATU (470.9 mg, 1.24 mmol, 1.5 *eq*) and DIEA (160.1 mg, 1.24 mmol, 0.22 mL, 1.5 *eq*). The mixture was stirred at 25 °C for 2 hr. H_2O (30 mL) was added to the solution. The mixture was extracted with ethyl acetate (35 mL*3). The combined organic layers were washed with brine (40 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The tert-butyl N-[2-[2-[2-[[3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoyl]amino]ethoxy]ethoxy]ethyl]carbamate (300 mg, 0.50 mmol, 60.5% yield) was used to the next step without purification. Part of the residue (100 mg)

was purified by prep-HPLC to afford the pure product (21.0 mg). Mass calc. for $C_{27}H_{34}F_3N_7O_5$ 593.60, m/z found 616.1 $[M+Na]^+$; ^1H NMR (400MHz, DMSO-d_6) δ = 9.08 (s, 1H), 8.64 - 8.53 (m, 2H), 7.94 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 6.77 (br t, *J* = 5.5 Hz, 1H), 4.48 (s, 3H), 3.57 - 3.49 (m, 6H), 3.47 - 3.36 (m, 4H), 3.05 (br d, *J* = 6.0 Hz, 2H), 1.36 (s, 9H).

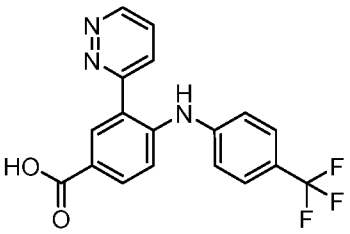
Step 2: N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide

[00462] To a solution of tert-butyl N-[2-[2-[2-[[3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoyl]amino]ethoxy]ethoxy]ethyl]carbamate (200 mg, 0.34 mmol, 1 *eq*) in HCl/dioxane (2 mL). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated in vacuum to give crude product. The N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzamide (150 mg, 0.29 mmol, 87.5% yield) was used to the next step without purification. Part of product (70 mg) was purified by prep-HPLC to afford the pure product (27.34 mg). Mass calc. for $C_{22}H_{26}F_3N_7O_3$ 493.48, m/z found 494.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.65 - 8.61 (m, 1H), 8.57 (d, *J* = 2.0 Hz, 1H), 7.95 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.88 (br s, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 4.48 (s, 3H), 3.63 - 3.53 (m, 8H), 3.48 - 3.45 (m, 2H), 3.01 - 2.92 (m, 2H).

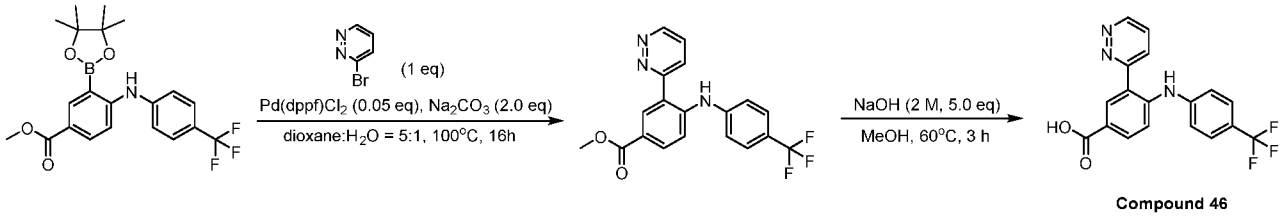
Step 3: N-(2-(2-(2-acetamidoethoxy)ethoxy)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide

[00463] To a solution of N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzamide (50 mg, 0.10 mmol, 1 *eq*) in DCM (2 mL) was added Ac2O (15.5 mg, 0.15 mmol, 14.2 uL, 1.5 *eq*), DMAP (1.2 mg, 10.1 umol, 0.1 *eq*) and TEA (30.8 mg, 0.30 mmol, 42.3 uL, 3 *eq*) .The mixture was stirred at 25 °C for 1 hr. H_2O (10 mL) was added to the solution. The mixture was extracted with ethyl acetate (20 mL*3). The combined organic layers were washed with brine (30 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC to give compound N-[2-[2-(2-acetamidoethoxy)ethoxy]ethyl]-3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzamide (39.4 mg, 72.9 umol, 71.9% yield). Mass calc. for $C_{24}H_{28}F_3N_7O_4$ 535.52, m/z found 536.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.65 - 8.55 (m, 2H), 7.99 - 7.85 (m, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 4.48 (s, 3H), 3.58 - 3.51 (m, 7H), 3.46 - 3.38 (m, 4H), 3.20 - 3.14 (m, 2H), 1.79 (s, 3H)

Example 39: 3-pyridazin-3-yl-4-[4-(trifluoromethyl)anilino]benzoic acid (Compound 46)



Preparation of Compound 46:



Compound 46

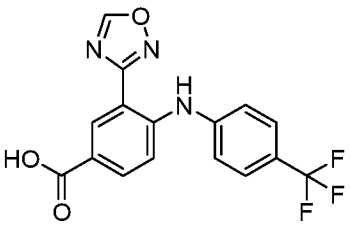
Step 1: methyl 3-pyridazin-3-yl-4-[4-(trifluoromethyl)anilino]benzoate

[00464] To a solution of 3-bromopyridazine (50 mg, 0.31 mmol, 1 *eq*) and methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (159 mg, 0.38 mmol, 1.2 *eq*) in dioxane (1 mL) and H_2O (0.2 mL) were added Pd(dppf)Cl_2 (11.5 mg, 15.72 umol, 0.05 *eq*) and Na_2CO_3 (66 mg, 0.63 mmol, 2 *eq*). The mixture was degassed and purged with N_2 for 3 times and stirred at 100°C for 16 hr. The reaction mixture was filtered and concentrated in vacuum. The residue was diluted with EA (20 mL) and washed with brine (5 mL*2). The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2) to give methyl 3-pyridazin-3-yl-4-[4-(trifluoromethyl)anilino]benzoate (30 mg, 73 umol, 23.2% yield).

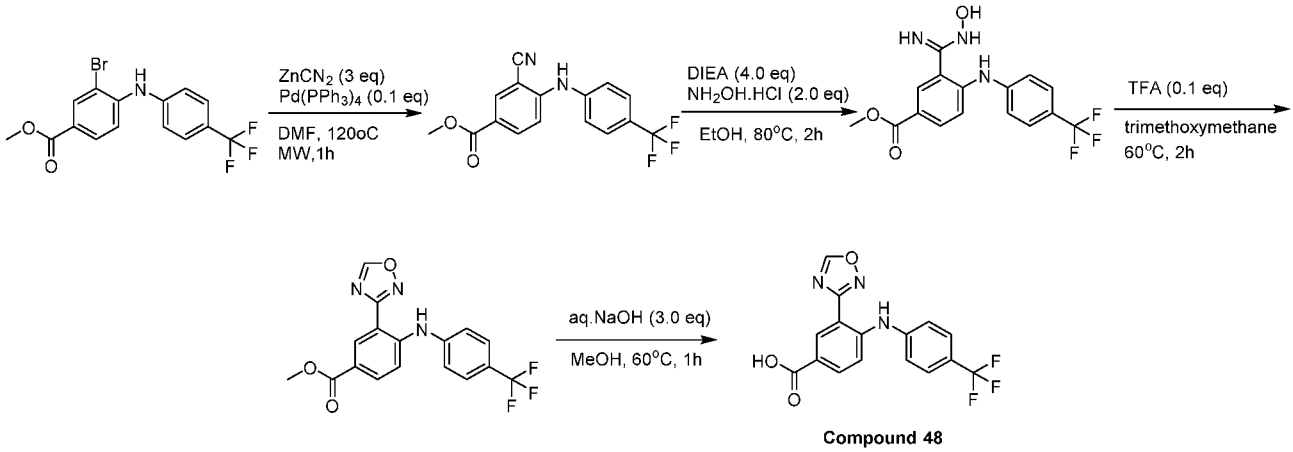
Step 2: 3-pyridazin-3-yl-4-[4-(trifluoromethyl)anilino]benzoic acid

[00465] To a solution of methyl 3-pyridazin-3-yl-4-[4-(trifluoromethyl)anilino]benzoate (30 mg, 80.4 umol, 1 *eq*) in MeOH (1 mL) was added NaOH (2 M, 0.2 mL, 5 *eq*). The mixture was stirred at 60°C for 3 hr. The reaction mixture was concentrated in vacuum. The crude product was purified by prep-HPLC to give the title compound (11 mg, 30.6 umol, 38.1% yield). Mass calcd. For $C_{18}H_{12}F_3N_3O_2$, 359.09 m/z found 359.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.87 (br s, 1H), 9.93 (s, 1H), 9.22 (dd, J = 1.3, 4.8 Hz, 1H), 8.27 (d, J = 1.8 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.99 (dd, J = 1.9, 8.7 Hz, 1H), 7.78 (dd, J = 4.9, 8.7 Hz, 1H), 7.58 (dd, J = 4.3, 8.5 Hz, 3H), 7.25 (d, J = 8.5 Hz, 2H).

Example 40: 3-(1,2,4-oxadiazol-3-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid (Compound 48)



Preparation of Compound 48:



Step 1: methyl 3-cyano-4-((4-(trifluoromethyl)phenyl)amino)benzoate

[00466] To a solution of methyl 3-bromo-4-((4-(trifluoromethyl)phenyl)amino)benzoate (300 mg, 0.8 mmol, 1 *eq*) and $Zn(CN)_2$ (282.4 mg, 2.41 mmol, 3 *eq*) in N,N-dimethylacetamide (10 mL) was added $Pd(PPh_3)_4$ (92.65 mg, 80.2 umol, 0.1 *eq*). The reaction was bubbled with N_2 atmosphere and heated at 120°C under microwave for 1 hr. The reaction was diluted with EA (30 mL) and washed with brine (2*15 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to give methyl 3-cyano-4-((4-(trifluoromethyl)phenyl)amino)benzoate (200 mg, 0.6 mmol, 77.8% yield).

Step 2: methyl 3-(N-hydroxycarbamimidoyl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate

[00467] To a solution of methyl 3-cyano-4-((4-(trifluoromethyl)phenyl)amino)benzoate (200 mg, 0.62 mmol, 1 *eq*) and $NH_2OH.HCl$ (86.7 mg, 1.25 mmol, 2 *eq*) in EtOH (10 mL) was added DIEA (322.8 mg, 2.50 mmol, 0.4 mL, 4 *eq*). The reaction was heated at 80°C for 2 hr. The reaction was concentrated. The crude product was diluted with EA (20 mL) and washed with water (2*10 mL). The organic layer was dried over Na_2SO_4 and concentrated to give methyl 3-(N-hydroxycarbamimidoyl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (140 mg, 0.32 mmol, 52.6% yield).

Step 3: methyl 3-(1,2,4-oxadiazol-3-yl)-4-[4-(trifluoromethyl)anilino]benzoate

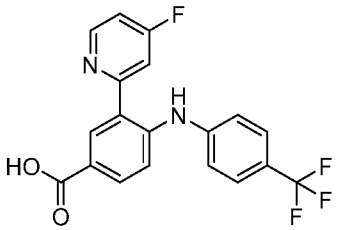
[00468] A solution of methyl 3-(N-hydroxycarbamimidoyl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (70 mg, 0.19 mmol, 1 *eq*) and TFA (2.26 mg, 19.8 umol, 1 uL, 0.1 *eq*) in trimethoxymethane (2 mL) was heated at 60°C for 2 hr. The reaction was

concentrated. The residue was purified by prep-TLC to give methyl 3-(1,2,4-oxadiazol-3-yl)-4-[4-(trifluoromethyl)anilino]benzoate (17 mg, 35.9 umol, 18.1% yield).

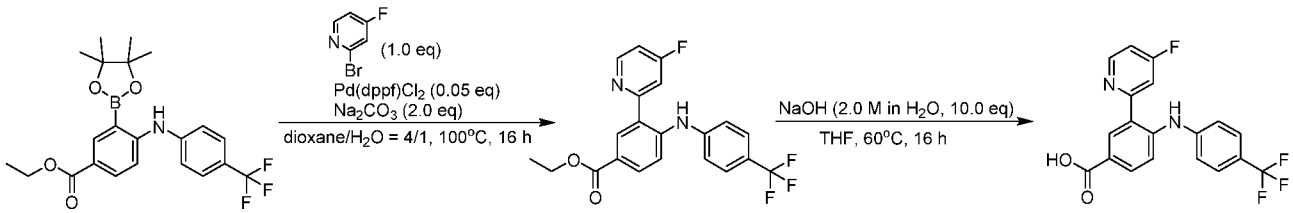
Step 4: 3-(1,2,4-oxadiazol-3-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid

[00469] To a solution of methyl 3-(1,2,4-oxadiazol-3-yl)-4-[4-(trifluoromethyl)anilino]benzoate (17 mg, 35.8 umol, 1 *eq*) in MeOH (1 mL) was added NaOH (2 M, 53 uL, 3 *eq*). The reaction was heated at 60°C for 1 hr. The reaction was concentrated. The residue was adjusted pH to 5 with 1N aq. HCl and extracted with EA (3*5 mL). The organic layers was dried over Na_2SO_4 and concentrated. The crude product was purified by prep-HPLC to give the title compound (3.49 mg, 10 umol, 27.8% yield). Mass calcd. For $C_{16}H_{16}F_3N_3O_3$, 349.07 m/z found 350.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 1.51 Hz, 1H), 8.01 (dd, J = 8.41, 1.88 Hz, 1H), 7.58 (d, J = 8.78 Hz, 2H), 7.32 (d, J = 8.28 Hz, 1H), 7.18 (d, J = 8.53 Hz, 2H), 6.12 (br s, 1H).

Example 41: 3-(4-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid (Compound 49)



Preparation of Compound 49:



Compound 49

Step 1: ethyl 3-(4-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate

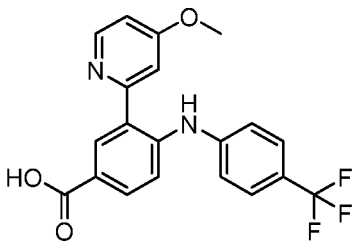
[00470] To a solution of 2-bromo-4-fluoropyridine (80 mg, 0.45 mmol, 1 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added Na_2CO_3 (96 mg, 0.90 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (16 mg, 22 umol, 0.05 *eq*) and ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (198 mg, 0.45 mmol, 1 *eq*). The mixture was stirred at 100°C for 16 hr. The reaction mixture was filtered and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2) to give ethyl 3-(4-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate (120 mg, 0.30 mmol, 65% yield). ^1H NMR (400 MHz,

$CDCl_3$) δ 11.21 (br s, 1H), 8.63 (dd, *J* = 5.6, 8.7 Hz, 1H), 8.37 (d, *J* = 2.0 Hz, 1H), 7.97 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.64 - 7.54 (m, 3H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.05 (ddd, *J* = 2.3, 5.7, 8.1 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

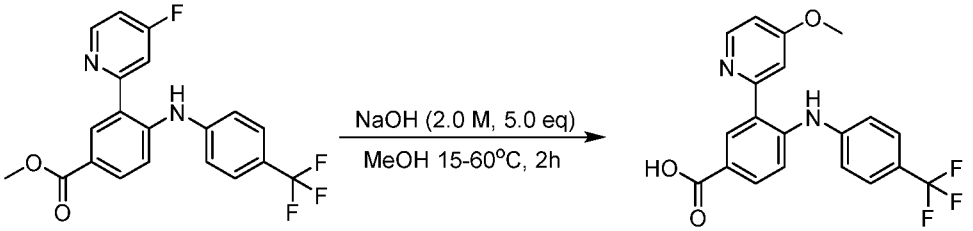
Step 2: 3-(4-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid

[00471] To a solution of ethyl 3-(4-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate (120 mg, 0.30 mmol, 1 *eq*) in THF (2 mL) was added NaOH (2 M, 1.5 mL, 10 *eq*). The mixture was stirred at 60°C for 16 hr. The reaction mixture was concentrated in vacuum. The residue was quenched with H_2O (5 mL), adjusted pH = 2~3 with 1M.aq.HCl and extracted with EA (15 mL*3). The combined organic phase was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC to give the title compound (61 mg, 0.15 mmol, 51% yield). Mass calcd. For $C_{19}H_{12}F_4N_2O_2$, 376.08 m/z found 376.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.78 (br s, 1H), 10.51 (s, 1H), 8.75 (dd, *J* = 5.8, 9.0 Hz, 1H), 8.28 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.81 (dd, *J* = 2.3, 11.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.37 (ddd, *J* = 2.4, 5.9, 8.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H).

Example 42: 3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 50)



Preparation of Compound 50:

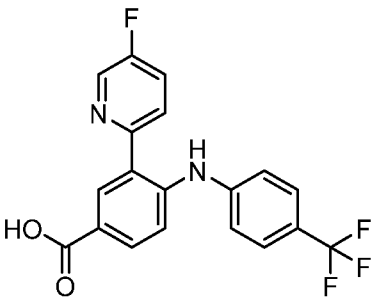


Compound 50

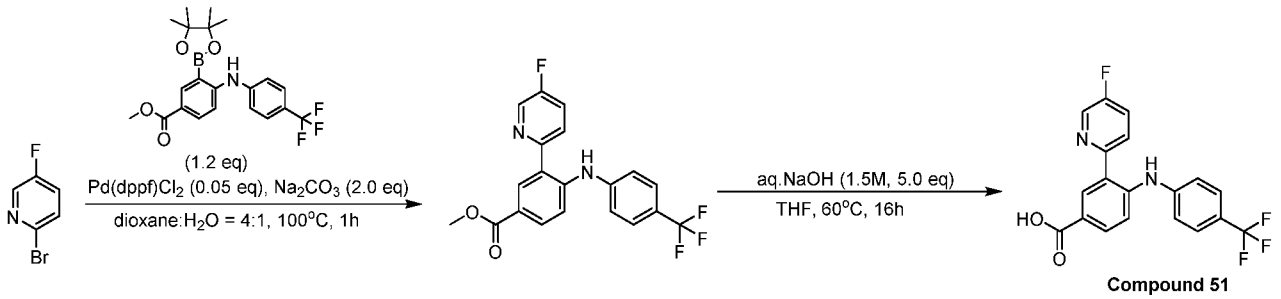
[00472] To a solution of methyl 3-(4-fluoropyridin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (30 mg, 77 umol, 1 *eq*) in MeOH (1 mL) and THF (1 mL) was added NaOH (2 M, 0.2 mL, 5 *eq*). The mixture was stirred at 60°C for 2 hr. The reaction mixture was concentrated in vacuum. The aqueous phase was adjust to pH = 4 with 1 M. aq. HCl and extracted with EA (10 mL*3). The combined organic phase was washed with brine

(5 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC to give the title compound (4.52 mg, 11.6 umol, 15.1% yield). Mass calcd. For $C_{20}H_{15}F_3N_2O_3$, 388.10 m/z found 388.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.70 (br d, J = 6.5 Hz, 1H), 8.14 (s, 1H), 8.01 (br d, J = 8.5 Hz, 1H), 7.65 - 7.51 (m, 4H), 7.40 (br s, 1H), 7.24 (br d, J = 8.5 Hz, 2H), 4.04 (s, 3H).

Example 43: 3-(5-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid (Compound 51)



Preparation of Compound 51:



Step 1: methyl 3-(5-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate

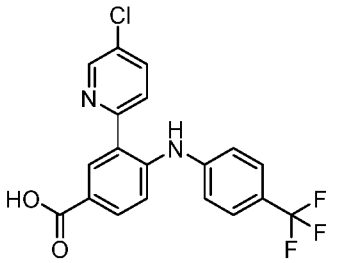
[00473] To a solution of 2-bromo-5-fluoropyridine (50 mg, 0.28 mmol, 1 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added Na_2CO_3 (60 mg, 0.56 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (10 mg, 14 umol, 0.05 *eq*) and methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (143 mg, 0.34 mmol, 1.2 *eq*). The mixture was stirred at 100°C for 3 hr. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2) to give compound **2** (60 mg, 0.15 mmol, 53% yield).

Step 2: 3-(5-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid

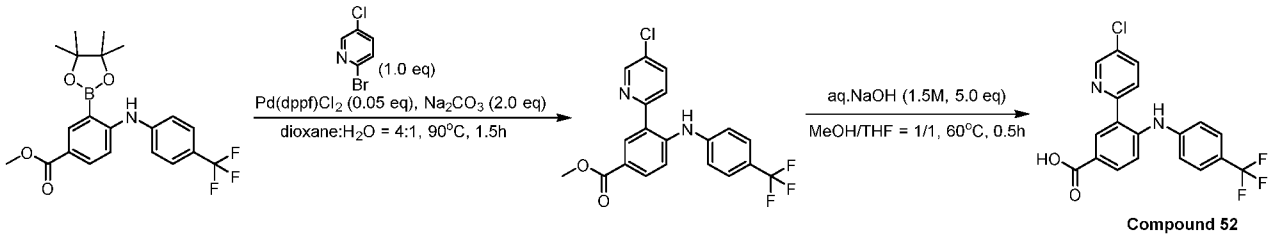
[00474] To a solution of compound **2** (60 mg, 0.15 mmol, 1 *eq*) in THF (1 mL) was added NaOH (2 M, 0.4 mL, 5 *eq*) . The mixture was stirred at 60°C for 16 hr. The reaction mixture was concentrated in vacuum. The aqueous phase was adjusted pH = 4 with 1 M aq. HCl and extracted with EA (10 mL*3). The organic phase was washed with brine (5 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC to give the

title compound (25.8 mg, 68 umol, 45% yield). Mass calcd. for $C_{19}H_{12}F_4N_2O_2$, 376.08 m/z found 376.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 9.97 (d, J=2.1 Hz, 1H), 8.71 (d, J = 2.8 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.91 (dd, J = 2.4, 8.4 Hz, 2H), 7.88 - 7.80 (m, 1H), 7.57 (d, J=8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H).

Example 44: 3-(5-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid (Compound 52)



Preparation of Compound 52:



Step 1: methyl 3-(5-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate

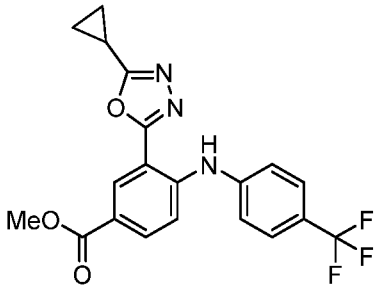
[00475] To a solution of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (109 mg, 0.26 mmol, 1 *eq*) and 2-bromo-5-chloropyridine (55 mg, 0.29 mmol, 1.1 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added $Pd(dppf)Cl_2$ (9.5 mg, 13 umol, 0.05 *eq*) and Na_2CO_3 (55 mg, 0.52 mmol, 2 *eq*). The mixture was stirred at 90°C for 1.5 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with brine (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2) to give methyl 3-(5-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate (62 mg, 0.15 mmol, 57% yield).

Step 2: 3-(5-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid

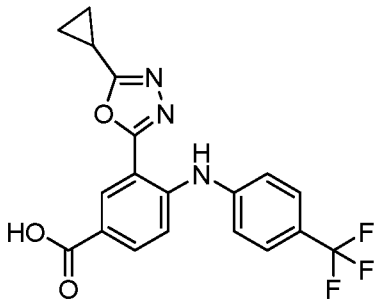
[00476] To a solution of methyl 3-(5-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate (62 mg, 0.15 mmol, 1 *eq*) in THF (1 mL) and MeOH (1 mL) was added NaOH (1.5 M, 0.5 mL, 5 *eq*). The mixture was stirred at 60°C for 0.5 hr. The reaction mixture was concentrated in vacuum and adjust pH = 4 with 1M aq. HCl. Then the mixture was extracted with EA (10 mL*2). The organic phase was washed with brine (5 mL) and dried over

Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC to give the title compound (5.35 mg, 13 umol, 8.9% yield). Mass calcd. For $C_{19}H_{12}ClF_3N_2O_2$, 392.05 m/z found 392.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.96 (br s, 1H), 8.76 (d, J = 2.4 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 2.6, 8.6 Hz, 1H), 7.91 (dd, J = 2.0, 8.6 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H).

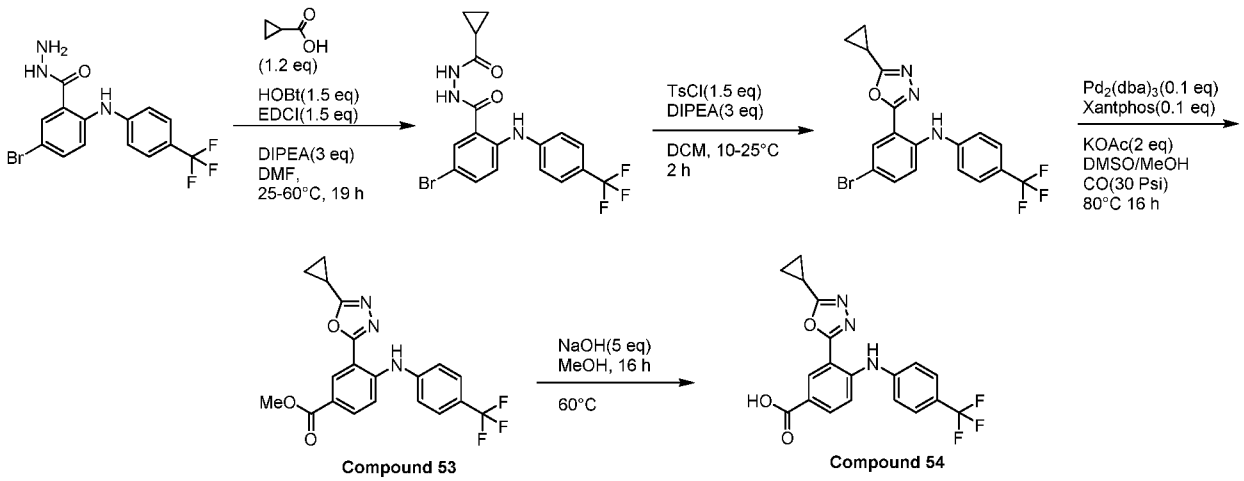
Example 45: methyl 3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (Compound 53)



and 3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 54)



Preparation of Compound 53 and Compound 54:



Step 1: 5-bromo-N'-(cyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide

[00477] A mixture of 5-bromo-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide (1.5 g, 4.01 mmol, 1 *eq*), cyclopropanecarboxylic acid (517.7 mg, 6.01 mmol, 0.5 mL, 1.5 *eq*), HOBt (812.6 mg, 6.01 mmol, 1.5 *eq*), EDCI (1.15 g, 6.01 mmol, 1.5 *eq*) and DIPEA (1.55 g, 12.03 mmol, 2.1 mL, 3 *eq*) in DMF (10 mL) was stirred at 25°C for 16 h. Then the mixture was stirred at 60°C for 3 h. The mixture was diluted with EA(200 mL), washed with brine(15 mL*4), dried with Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2) to give 5-bromo-N'-(cyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide (0.9 g, 2.04 mmol, 50.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 10.33 - 10.19 (m, 1H), 9.34 (br s, 1H), 7.81 (d, *J*=2.3 Hz, 1H), 7.64 - 7.54 (m, 3H), 7.41 (d, *J*=8.8 Hz, 1H), 7.28 (d, *J*=8.4 Hz, 2H), 1.73 - 1.64 (m, 1H), 0.84 - 0.73 (m, 4H).

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

[00478] To a mixture of 5-bromo-N'-(cyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide (860 mg, 1.94 mmol, 1 *eq*) and DIPEA (754.0 mg, 5.83 mmol, 1.0 mL, 3 *eq*) in DCM (15 mL) was added TosCl (556.1 mg, 2.92 mmol, 1.5 *eq*) at 10°C. Then the mixture was stirred at 25°C for 2 h. The mixture was diluted with DCM (200 mL), washed with 1 M HCl(20 mL) and brine(15 mL*2) in turns, dried with Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2) to give 4-bromo-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (800 mg, 1.89 mmol, 97.2% yield). 50 mg of the product was additionally purified by TLC (10.64 mg, 24.9 umol, 1.3% yield). MS: mass calc. for $C_{18}H_{13}BrF_3N_3O$ 423.02, m/z found 426.04 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.01 (d, *J* = 2.3 Hz, 1H), 7.69 - 7.59 (m, 3H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 2.38 - 2.27 (m, 1H), 1.21 - 1.09 (m, 4H).

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

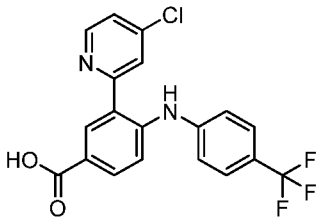
[00479] A mixture of 4-bromo-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (400 mg, 0.94 mmol, 1 *eq*), Xantphos (54.6 mg, 94 umol, 0.1 *eq*), KOAc (185.1 mg, 1.89 mmol, 2 *eq*) and $Pd_2(dba)_3$ (86.4 mg, 94 umol, 0.1 *eq*) in DMSO (3 mL) and MeOH (5 mL) was degassed and refilled with CO for three times at 10°C. Then the mixture was stirred at 80°C for 16 h under 30 Psi of CO. The reaction mixture was diluted with DCM (100 mL), washed with 1 M HCl (15 mL*2) and brine (15 mL), dried by anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to give methyl 3-(5-cyclopropyl-1,3,4-oxadiazol-2-

yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (270 mg, 0.67 mmol, 71% yield). 50 mg of the product was additionally purified by prep-HPLC (7.92 mg, 19.6 umol, 2.1% yield). Mass calc. for $C_{20}H_{16}F_3N_3O_3$ 403.11, m/z found 403.8 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 2.0, 8.8 Hz, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.52 (dd, J = 8.7, 11.7 Hz, 3H), 3.86 (s, 3H), 2.42 - 2.31 (m, 1H), 1.25 - 1.09 (m, 4H).

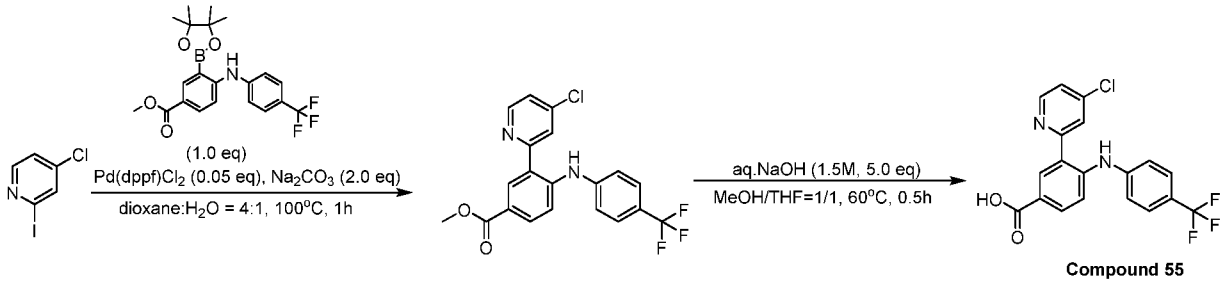
Step 4: 3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00480] To a mixture of methyl 3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (220 mg, 0.55 mmol, 1 *eq*) in MeOH (10 mL) was added NaOH (2 M, 1.4 mL, 5 *eq*). Then the mixture was stirred at 60°C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL*2). The separated aqueous layer was acidified to pH~2 with 1 M HCl and extracted with EA (15 mL*5). The combined organic layers were dried by anhydrous Na_2SO_4 to give a residue. The residue was purified by prep-HPLC to give 3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (48.93 mg, 0.13 mmol, 23.1% yield). Mass calc. for: $C_{19}H_{14}F_3N_3O_3$ 389.10, m/z found 390.0 $[M+1]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.38 (d, J = 1.9 Hz, 1H), 7.97 (dd, J = 1.8, 8.8 Hz, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.50 (dd, J = 8.6, 17.1 Hz, 3H), 2.40 - 2.29 (m, 1H), 1.24 - 1.09 (m, 4H).

Example 46: 3-(4-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid (Compound 55)



Preparation of Compound 55:



Compound 55

Step 1: methyl 3-(4-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate

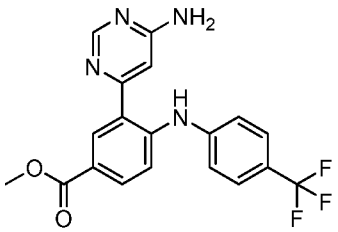
[00481] To a solution of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (110 mg, 0.26 mmol, 1 *eq*) and 4-chloro-2-iodopyridine

(68 mg, 0.29 mmol, 1.1 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added $Pd(dppf)Cl_2$ (9 mg, 13 umol, 0.05 *eq*) and Na_2CO_3 (55 mg, 0.52 mmol, 2 *eq*). The mixture was stirred at 90°C for 1 hr. The reaction mixture was concentrated in vacuum. The residue was diluted with EA (20 mL), washed with brine (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2) to give methyl 3-(4-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate (63 mg, 0.15 mmol, 59.6% yield).

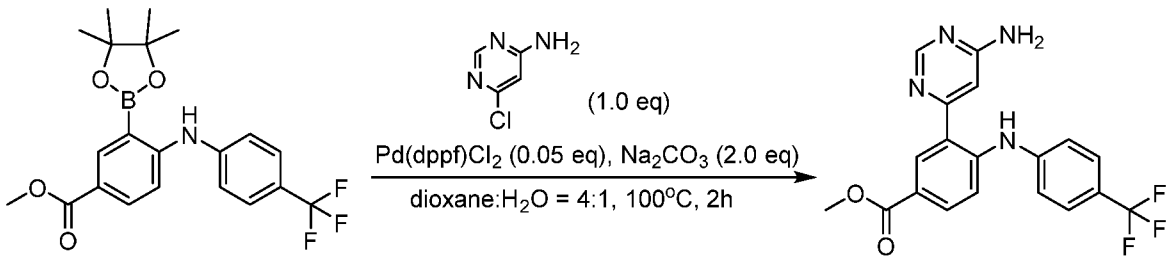
Step 2: 3-(4-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid

[00482] To a solution of methyl 3-(4-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate (62 mg, 0.15 mmol, 1 *eq*) in THF (1 mL) and MeOH (1 mL) was added NaOH (1.5 M, 0.5 mL, 5 *eq*). The mixture was stirred at 60°C for 0.5 hr. The reaction mixture was concentrated in vacuum and adjust pH = 4 with 1M aq. HCl. Then the mixture was extracted with EA (10 mL*2). The organic phase was washed with brine (5 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC to give the title compound (13 mg, 31 umol, 20.4% yield). Mass calcd. For $C_{19}H_{12}ClF_3N_2O_2$, 392.05 m/z found 392.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.69 (d, J = 5.3 Hz, 1H), 8.26 (d, J = 1.8 Hz, 1H), 7.97 (s, 1H), 7.93 (dd, J = 2.0, 8.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.56 (dd, J = 2.0, 5.5 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H).

Example 47: methyl 3-(6-aminopyrimidin-4-yl)-4-[4-(trifluoromethyl)anilino]benzoate (Compound 56)



Preparation of Compound 56:

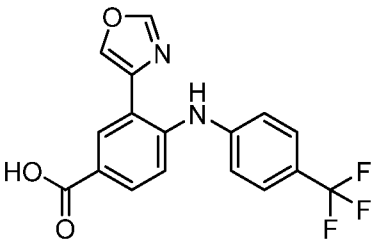


Compound 56

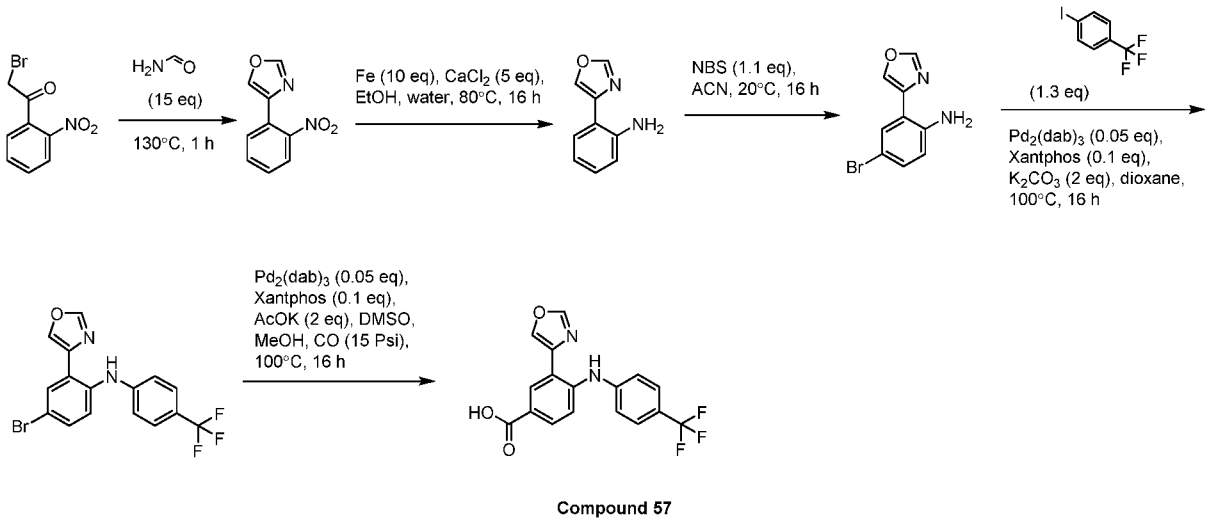
[00483] To a solution of 6-chloropyrimidin-4-amine (70 mg, 0.54 mmol, 1 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added Na_2CO_3 (114 mg, 1 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (20 mg, 27 umol, 0.05 *eq*) and methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((4-

(trifluoromethyl)phenyl)amino)benzoate (273 mg, 0.65 mmol, 1.2 *eq*). The mixture was stirred at 100°C for 2 hr. The reaction mixture was concentrated in vacuum to give the residue. Then the residue was diluted with EA (20 mL) and filtered and the filtrate was washed with water (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2) to give the title compound (155 mg, 0.39 mmol, 71.6% yield). Mass calcd. For $C_{19}H_{15}F_3N_4O_2$, 388.11 m/z found 388.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H), 8.65 (s, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 7.94 (dd, *J* = 1.9, 8.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 1.0 Hz, 1H), 5.06 (br s, 2H), 4.01 - 3.90 (m, 3H).

Example 48: 3-(oxazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 57)



Preparation of Compound 57:



Compound 57

Step 1: 4-(2-nitrophenyl)oxazole

[00484] The solution of 2-bromo-1-(2-nitrophenyl)ethan-1-one (8.0 g, 32.78 mmol, 1 *eq*) and formamide (22.15 g, 491.72 mmol, 19.6 mL, 15 *eq*) (neat reaction) was stirred at 130°C for 1 h. The mixture was cooled to 20°C, and then diluted with water (100 mL). The filtrate was extracted with EA (100 mL *3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 4-(2-

nitrophenyl)oxazole (1.0 g, 5.10 mmol, 15.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 4.6 Hz, 1H), 7.87 (dd, *J*= 1.3, 7.8 Hz, 1H), 7.79 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.65 (dt, *J* = 1.3, 7.6 Hz, 1H), 7.50 (dt, *J* = 1.4, 7.8 Hz, 1H).

Step 2: 2-(oxazol-4-yl)aniline

[00485] The mixture of 4-(2-nitrophenyl)oxazole (900 mg, 4.73 mmol, 1 *eq*), $CaCl_2$ (2.63 g, 23.66 mmol, 5 *eq*) and Fe (2.64 g, 47.33 mmol, 10 *eq*) in EtOH (10 mL) and water (2 mL) was stirred at 80°C for 16 h. The mixture was cooled to 20°C, and then filtered to remove the solid. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 2-(oxazol-4-yl)aniline (600 mg, 3.60 mmol, 76.0% yield). Mass calc. for $C_9H_8N_2O$ 160.06, m/z found 160.8 $[M+1]^+$.

Step 3: 4-bromo-2-(oxazol-4-yl)aniline

[00486] To a solution of 2-(oxazol-4-yl)aniline (100 mg, 0.62 mmol, 1 *eq*) in ACN (2 mL) at 20°C was added NBS (122.2 mg, 0.69 mmol, 1.1 *eq*), and the mixture was stirred at 20°C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 4-bromo-2-(oxazol-4-yl)aniline (40 mg, 0.14 mmol, 21.7% yield). Mass calc. for $C_9H_7BrN_2O$ 237.97, m/z found 240.7 $[M+3]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.93 (d, *J* = 0.8 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 5.10 (brs, 2H).

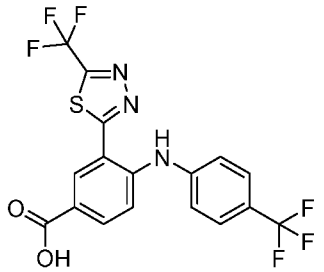
Step 4: 4-bromo-2-(oxazol-4-yl)-*N*-(4-(trifluoromethyl)phenyl)aniline

[00487] The mixture of 4-bromo-2-(oxazol-4-yl)aniline (40 mg, 0.17 mmol, 1 *eq*), 1-iodo-4-(trifluoromethyl)benzene (59.2 mg, 0.22 mmol, 32 uL, 1.3 *eq*), $Pd_2(dba)_3$ (7.7 mg, 8.4 umol, 0.05 *eq*), Xantphos (9.7 mg, 16.7 umol, 0.10 *eq*) and K_2CO_3 (46.3 mg, 0.33 mmol, 2 *eq*) in dioxane (2 mL) at 20°C was purged and degassed with N_2 for 3 times, and the mixture was stirred at 100°C under N_2 for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 4-bromo-2-(oxazol-4-yl)-*N*-(4-(trifluoromethyl)phenyl)aniline (30 mg, 61.9 umol, 37.0% yield). Mass calc. for $C_{16}H_{10}BrF_3N_2O$ 381.99, m/z found 382.8 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.02 (s, 1H), 7.97 (s, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.66 - 7.61 (m, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 4.1 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 2H).

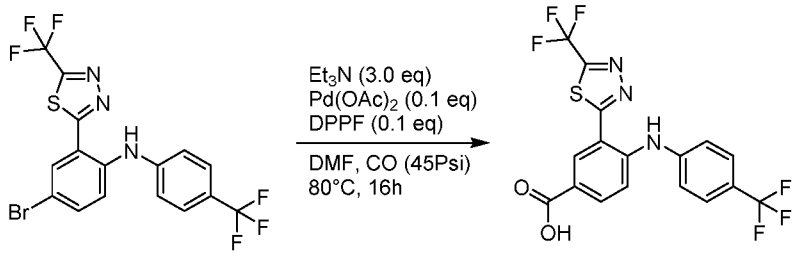
Step 5: 3-(oxazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00488] The mixture of 4-bromo-2-(oxazol-4-yl)-*N*-(4-(trifluoromethyl)phenyl)aniline (100 mg, 0.26 mmol, 1 *eq*), $Pd_2(dba)_3$ (12.0 mg, 13.1 umol, 0.05 *eq*), Xantphos (15.1 mg, 26.1 umol, 0.10 *eq*) and AcOK (51.2 mg, 0.52 mmol, 2 *eq*) in DMSO (3 mL) and MeOH (1 mL) at 20°C was purged and degassed with CO for 3 times and then stirred at 100°C under CO (15 Psi) for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give the title compound (24.53 mg, 70.4 umol, 27.0% yield). Mass calc. for $C_{17}H_{11}F_3N_2O_3$ 348.07, m/z found 348.9 $[M+1]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ 12.81 (brs, 1H), 9.00 (s, 1H), 8.61 (s, 1H), 8.54 (s, 1H), 8.44 (d, *J* = 1.5 Hz, 1H), 7.87 (dd, *J* = 1.8, 8.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H).

Example 49: 4-[4-(trifluoromethyl)anilino]-3-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]benzoic acid (Compound 58)



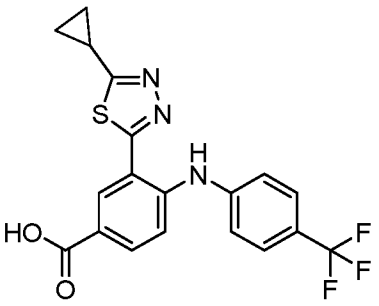
Preparation of Compound 58:



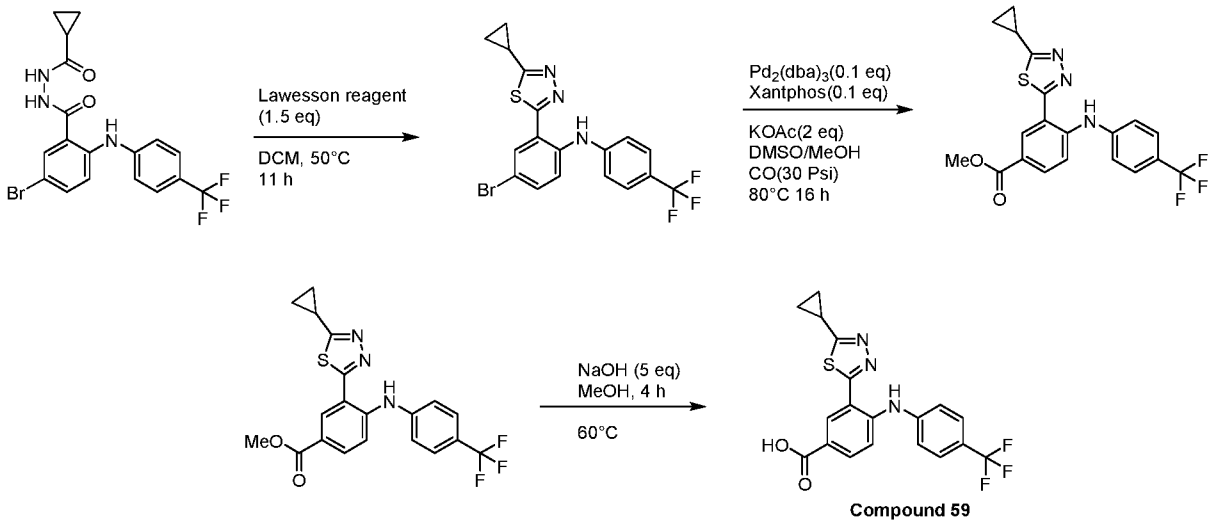
Compound 58

[00489] To a mixture of 4-bromo-2-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (50 mg, 0.1 mmol, 1 *eq*) , DPPF (5.9 mg, 10 umol, 0.1 *eq*) and $Pd(OAc)_2$ (2.4 mg, 10 umol, 0.1 *eq*) in DMF (40 mL) was added Et_3N (32.4 mg, 0.32 mmol, 44.59 uL, 3 *eq*) , de-gassed and purged with CO for three times. The reaction mixture was heated at 80°C for 16 hours under CO (45 Psi). The reaction was filtered and concentrated. The residue was purified by prep-HPLC to give the title compound (1.42 mg, 3.28 umol, 3% yield). Mass calc. for $C_{17}H_9F_6N_3O_2S$ 433.03, m/z found 434.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 10.6 (s, 1 H), 8.34 (d, *J* = 2.0 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.51 - 7.40 (m, 3H).

Example 50: 3-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 59)



Preparation of Compound 59:



Step 1: 4-bromo-2-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline

[00490] A mixture of compound 5-bromo-N'-(cyclopropanecarbonyl)-2-((4-(trifluoromethyl)phenyl)amino)benzohydrazide (240 mg, 0.54 mmol, 1 *eq*) and 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4dithiadiphosphetane (329.3 mg, 0.81 mmol, 1.5 *eq*) in DCM (10 mL) was stirred at 50°C for 5 hr under N_2. Then the mixture was stirred at 50°C for 6 hr. The mixture was directly purified by prep-TLC to give 4-bromo-2-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (110 mg, 0.23 mmol, 43.1% yield). Mass calc. for $C_{18}H_{13}BrF_3N_3S$ 439.00, m/z found 441.7 $[M+3]^+$.

Step 2: methyl 3-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate

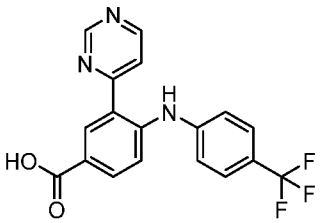
[00491] A mixture of 4-bromo-2-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (50 mg, 0.11 mmol, 1 *eq*), Xantphos (6.57 mg, 11.4 umol, 0.1 *eq*), KOAc (22.3 mg, 0.23 mmol, 2 *eq*) and $Pd_2(dba)_3$ (10.4 mg, 11.4 umol, 0.1 *eq*) in DMSO (3 mL) and MeOH (3 mL) was degassed and refilled with CO for three times at 10°C. Then the mixture was stirred at 80°C for 16 h under 30 Psi of CO. The reaction mixture was filtered via a

pad of Celite and the filtrate was concentrated to remove most of methanol. The resulting residue was diluted with EA(100 mL), washed with brine (15 mL*3), dried by anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-TLC to give methyl 3-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (70 mg, crude). Mass calc. for $C_{20}H_{16}F_3N_3O_2S$ 419.42, m/z found 420.0 $[M+1]^+$.

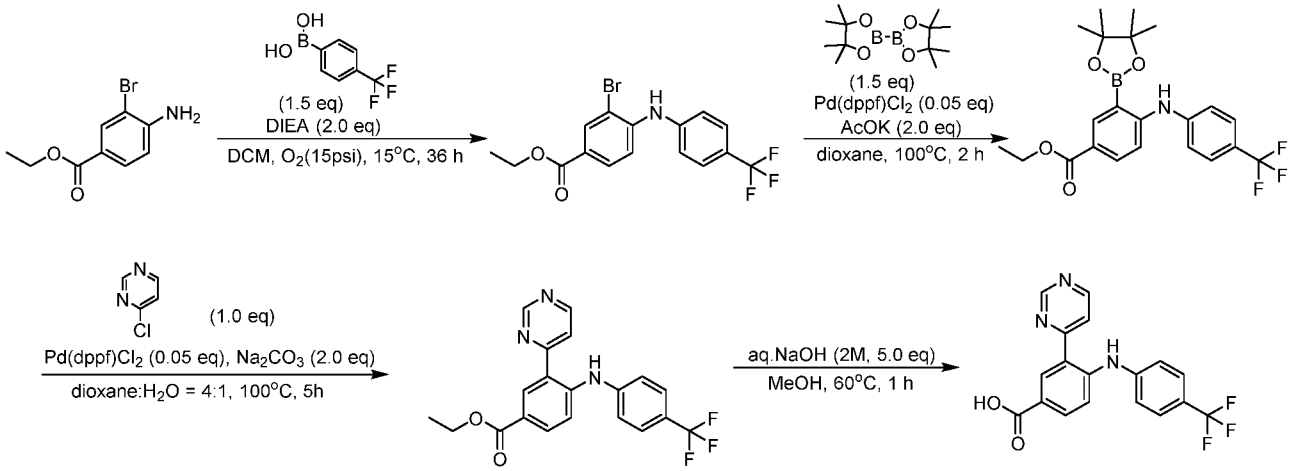
Step 3: 3-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00492] To a mixture of methyl 3-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (70 g, 166.9 mmol, 1 *eq*) in MeOH (2.5 mL) was added NaOH (2 M, 417.2 mL, 5 *eq*). Then the mixture was stirred at 60°C for 4 h. The reaction mixture was acidified to pH~2 with 1 M HCl and extracted with EA (15 mL*5). The combined organic layers were dried over anhydrous Na_2SO_4 to give a residue. Then the residue was purified by prep-HPLC to give the title compound (2.63 mg, 6.1 umol, 3.63e-3% yield). Mass calc. for: $C_{19}H_{14}F_3N_3O_2S$ 405.08, m/z found 406.0 $[M+1]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.33 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 2.0, 8.6 Hz, 1H), 7.67 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 2.63 - 2.55 (m, 1H), 1.29 - 1.24 (m, 2H), 1.15 - 1.04 (m, 2H).

Example 51: 3-pyrimidin-4-yl-4-[4-(trifluoromethyl)anilino]benzoic acid (Compound 60)



Preparation of Compound 60:



Compound 60

Step 1: ethyl 3-bromo-4-[4-(trifluoromethyl)anilino]benzoate

[00493] To a solution of ethyl 4-amino-3-bromobenzoate (4 g, 16.4 mmol, 1 *eq*) in DCM (70 mL) were added DIEA (4.24 g, 32.8 mmol, 5.7 mL, 2 *eq*), $Cu(OAc)_2$ (4.46 g, 24.58 mmol, 1.5 *eq*) and (4-(trifluoromethyl)phenyl)boronic acid (4.67 g, 24.58 mmol, 1.5 *eq*). The mixture was degassed and purged with O_2 for 3 times and stirred at 15°C for 36 hr under O_2 atmosphere (15psi). The reaction mixture was concentrated in vacuum to give the residue and the residue was diluted with EA (50 mL), washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatography (SiO_2) to give ethyl 3-bromo-4-[4-(trifluoromethyl)anilino]benzoate (600 mg, 1.39 mmol, 8.5% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 1.8, 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.32 - 7.29 (m, 2H), 6.57 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H).

Step 2: ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)anilino] benzoate

[00494] To a solution of ethyl 3-bromo-4-[4-(trifluoromethyl)anilino]benzoate (600 mg, 1.55 mmol, 1 *eq*) in dioxane (6 mL) were added AcOK (303 mg, 3.09 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (56 mg, 77 umol, 0.05 *eq*) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (589 mg, 2.32 mmol, 1.5 *eq*). The mixture was stirred at 100°C for 2 hr. The reaction mixture was filtered and concentrated in vacuum to give the residue. The crude product was purified by column chromatography (SiO_2) to give ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)anilino] benzoate (340 mg, 0.69 mmol, 45% yield).

Step 3: ethyl 3-pyrimidin-4-yl-4-[4-(trifluoromethyl)anilino]benzoate

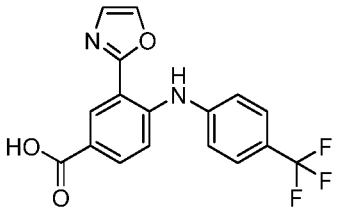
[00495] To a solution of 4-chloropyrimidine (40 mg, 0.35 mmol, 1 *eq*) and Na_2CO_3 (74 mg, 0.70 mmol, 2 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added $Pd(dppf)Cl_2$ (12 mg, 17 umol, 0.05 *eq*) and ethyl ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)anilino] benzoate (167 mg, 0.38 mmol, 1.1 *eq*). The mixture was stirred at 100°C for 5 hr. The reaction mixture was filtered and concentrated in vacuum. The crude product was used for the next step directly (105 mg, 0.20 mmol, 56% yield).

Step 4: 3-pyrimidin-4-yl-4-[4-(trifluoromethyl)anilino]benzoic acid

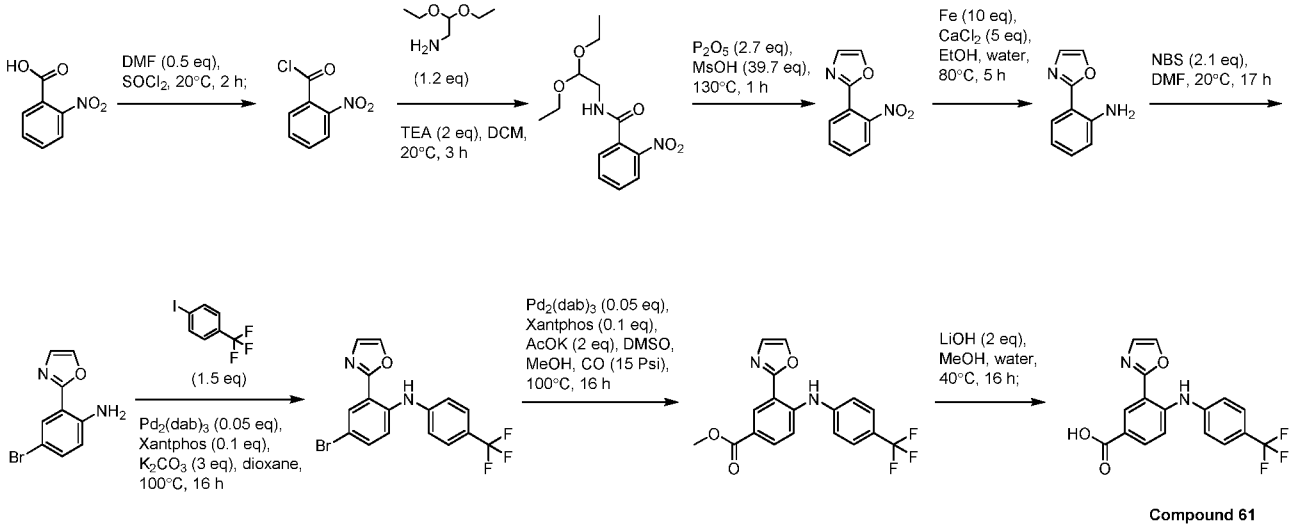
[00496] To a solution of ethyl 3-pyrimidin-4-yl-4-[4-(trifluoromethyl)anilino]benzoate (100 mg, 0.18 mmol, 1 *eq*) in MeOH (1 mL) was added NaOH (2 M, 0.5 mL, 5 *eq*). The mixture was stirred at 60°C for 1 hr. The reaction mixture was concentrated in vacuum. Then the aqueous phase was adjusted to pH = 4 with 1M.aq.HCl and extracted with EA (15 mL*3). The combined organic phase was washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and

concentrated in vacuum. The crude product was purified by prep-HPLC to give the title compound (39.6 mg, 0.11 mmol, 59.3% yield). Mass calcd. For $C_{18}H_{12}F_3N_3O_2$, 359.09 m/z found 359.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.39 (br s, 1H), 9.30 (s, 1H), 8.86 (br d, J = 5.0 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H), 8.01 - 7.93 (m, 2H), 7.62 (br d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.8 Hz, 1H), 7.33 (br d, J = 8.3 Hz, 2H).

Example 52: 3-(oxazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid (Compound 61)



Preparation of Compound 61:



Step 1: 2-nitrobenzoyl chloride

[00497] To a solution of 2-nitrobenzoic acid (1.0 g, 5.98 mmol, 1 *eq*) in $SOCl_2$ (5 mL) at 20°C was added DMF (218.7 mg, 2.99 mmol, 0.2 mL, 0.5 *eq*) drop-wise, and the mixture was stirred at 20°C for 2 h. The mixture was concentrated to remove $SOCl_2$ and give 2-nitrobenzoyl chloride (1.11 g, 5.98 mmol, 100.00% yield, which was used directly for next step.

Step 2: *N*-(2,2-diethoxyethyl)-2-nitrobenzamide

[00498] To a solution of 2,2-diethoxyethan-1-amine (956.0 mg, 7.18 mmol, 1.0 mL, 1.2 *eq*) and TEA (1.21 g, 11.96 mmol, 1.7 mL, 2 *eq*) in DCM (20 mL) at 20°C was added 2-nitrobenzoyl chloride (1.11 g, 5.98 mmol, 0.8 mL, 1 *eq*) in DCM (5 mL) drop-wise, and the mixture was stirred at 20°C for 3 h. The mixture was concentrated to give a residue. The residue was diluted with water (50 mL) and extracted with EA (50 mL *3). The combined organic layers

were washed with water (30 mL), saturated NH_4Cl solution (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give *N*-(2,2-diethoxyethyl)-2-nitrobenzamide (1.60 g, 5.67 mmol, 94.8% yield), which was used directly for next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.72 - 7.66 (m, 1H), 7.63 - 7.57 (m, 1H), 7.54 (dd, *J* = 1.3, 7.5 Hz, 1H), 6.04 (brs, 1H), 4.69 (t, *J* = 5.3 Hz, 1H), 3.77 (qd, *J*= 7.1, 9.4 Hz, 2H), 3.68 - 3.58 (m, 4H), 1.24 (t, *J* = 7.0 Hz, 6H).

Step 3: 2-(2-nitrophenyl)oxazole

[00499] The solution of *N*-(2,2-diethoxyethyl)-2-nitrobenzamide (1.0 g, 3.54 mmol, 1 *eq*), P_2O_5 (1.35 g, 9.51 mmol, 0.6 mL, 2.7 *eq*) and MsOH (13.50 g, 140.47 mmol, 10.0 mL, 39.7 *eq*) (neat reaction) was stirred at 130°C for 1 h. The reaction mixture was cooled to 20°C, then diluted with water (100 mL) and extracted with EA (100 mL *3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 2-(2-nitrophenyl)oxazole (640 mg, 1.63 mmol, 46.1% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 1.4, 7.7 Hz, 1H), 7.81 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.77 (d, *J* = 0.8 Hz, 1H), 7.69 (dt, *J* = 1.4, 7.6 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.31 (s, 1H).

Step 4: 2-(oxazol-2-yl)aniline

[00500] The mixture of 2-(2-nitrophenyl)oxazole (320 mg, 0.82 mmol, 1 *eq*), $CaCl_2$ (452.9 mg, 4.08 mmol, 5 *eq*) and Fe (455.8 mg, 8.16 mmol, 10 *eq*) in water (2 mL) and EtOH (10 mL) was stirred at 80°C for 5 h. The mixture was cooled to 20°C, and then filtered to remove the solid. The filtrate was concentrated under reduced pressure to give a residue. The residue was diluted with water (10 mL) and saturated Na_2CO_3 solution (10 mL), and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 2-(oxazol-2-yl)aniline (110 mg, 0.65 mmol, 79.9% yield), which was used directly for next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.30 (s, 1H), 7.27 - 7.21 (m, 1H), 6.84 - 6.75 (m, 2H), 5.95 (brs, 2H).

Step 5: 4-bromo-2-(oxazol-2-yl)aniline

[00501] To a solution of 2-(oxazol-2-yl)aniline (110 mg, 0.69 mmol, 1 *eq*) in DMF (2 mL) at 20°C was added NBS (134.5 mg, 0.76 mmol, 1.1 *eq*) in DMF (1 mL) drop-wise, and the mixture was stirred at 20°C for 16 h. After addition of 1 eq NBS and the reaction continued to work for another 1 h. The mixture was diluted with water (20 mL) and then extracted with EA (20 mL *3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The

residue was purified by flash silica gel chromatography to give 4-bromo-2-(oxazol-2-yl)aniline (100 mg, 0.40 mmol, 57.9% yield). Mass calc. for $C_9H_7BrN_2O$ 237.97, m/z found 240.7 $[M+3]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 2.3 Hz, 1H), 7.67 (s, 1H), 7.29 (d, J = 2.3 Hz, 1H), 7.24 (s, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.97 (brs, 2H).

Step 6: 4-bromo-2-(oxazol-2-yl)-*N*-(4-(trifluoromethyl)phenyl)aniline

[00502] The mixture of 4-bromo-2-(oxazol-2-yl)aniline (100 mg, 0.42 mmol, 1 *eq*), 1-iodo-4-(trifluoromethyl)benzene (170.7 mg, 0.63 mmol, 92 uL, 1.5 *eq*), $Pd_2(dba)_3$ (19.2 mg, 20.9 umol, 0.05 *eq*), Xantphos (24.2 mg, 41.8 umol, 0.10 *eq*) and K_2CO_3 (173.4 mg, 1.25 mmol, 3 *eq*) in dioxane (3 mL) at 20°C was purged and degassed with N_2 for 3 times, and the mixture was stirred at 100°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to give 4-bromo-2-(oxazol-2-yl)-*N*-(4-(trifluoromethyl)phenyl)aniline (120 mg, 0.28 mmol, 67.4% yield). Mass calc. for $C_{16}H_{10}BrF_3N_2O$ 381.99, m/z found 382.7 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.73 (s, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 2.1 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.29 (s, 1H).

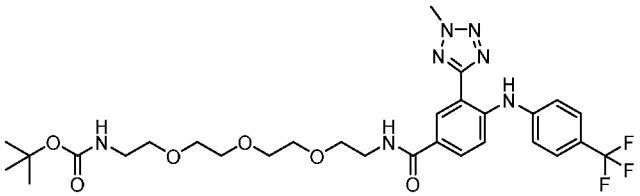
Step 7: methyl 3-(oxazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate

[00503] The mixture of 4-bromo-2-(oxazol-2-yl)-*N*-(4-(trifluoromethyl)phenyl)aniline (120 mg, 0.31 mmol, 1 eq), $Pd_2(dba)_3$ (14.3 mg, 15.7 umol, 0.05 eq), Xantphos (18.1 mg, 31.3 umol, 0.10 eq) and KOAc (61.5 mg, 0.63 mmol, 2 eq) in DMSO (3 mL) and MeOH (1 mL) at 20°C was purged and degassed with CO for 3 times, and the mixture was stirred at 100°C under CO (15 Psi) for 16 h. The residue was purified by prep-HPLC to give methyl 3-(oxazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (30.0 mg, 82.8 umol, 26.4% yield). Mass calc. for $C_{18}H_{13}F_3N_2O_3$ 362.09, m/z found 362.9 $[M+1]^+$.

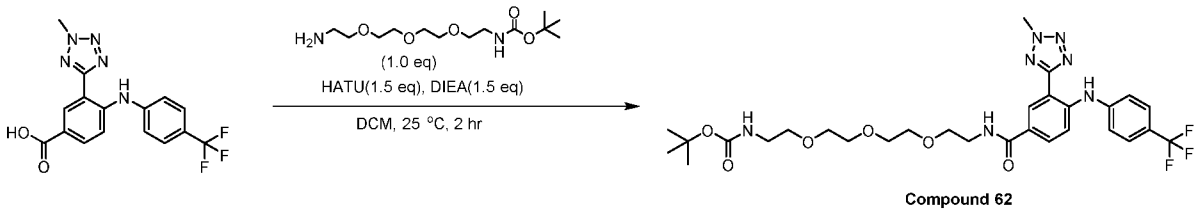
Step 8: 3-(oxazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid

[00504] To a solution of methyl 3-(oxazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate (30.0 mg, 82.8 umol, 1 eq) in MeOH (1 mL) and water (1 mL) at 20°C was added $LiOH.H_2O$ (7.0 mg, 0.17 mmol, 2 eq), and the mixture was stirred at 40°C for 16 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give the title compound (18.35 mg, 52.2 umol, 63.0% yield). Mass calc. for $C_{17}H_{11}F_3N_2O_3$ 348.07, m/z found 348.9 $[M+1]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 12.81 (brs, 1H), 10.52 (s, 1H), 8.55 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 0.8 Hz, 1H), 7.94 (dd, J = 2.0, 8.8 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 0.8 Hz, 1H), 7.54 (dd, J = 4.8, 8.5 Hz, 3H).

Example 53: tert-butyl (1-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)-1-oxo-5,8,11-trioxa-2-azatridecan-13-yl)carbamate (Compound 62)



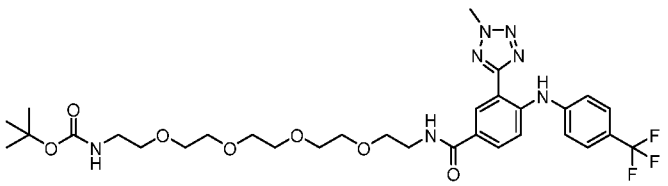
Preparation of Compound 62:



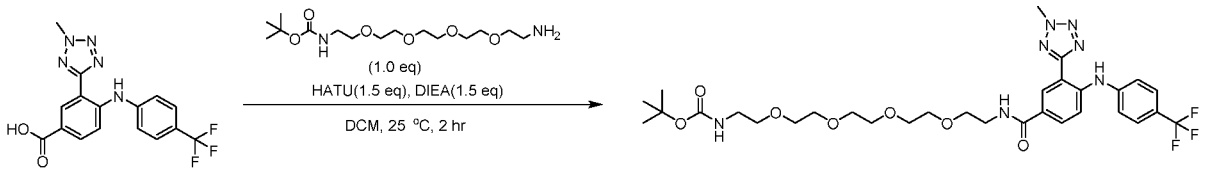
Compound 62

[00505] The mixture of 3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid (50 mg, 0.13 mmol, 1 *eq*), DIEA (26.6 mg, 0.20 mmol, 35.9 uL, 1.5 *eq*) and HATU (78.5 mg, 0.20 mmol, 1.5 *eq*) in DCM (2 mL) was stirred at 25 °C for 1 hr. Then tert-butyl N-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]ethyl]carbamate (40.2 mg, 0.13 mmol, 1 *eq*) was added at the mixture and the mixture was stirred at 25 °C for another 1 hr. The reaction mixture was diluted with H_2O (5 mL) and the mixture was extracted with EA (15 mL * 3). The combined organic phase was washed with brine (10 mL*3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC to give tert-butyl N-[2-[2-[2-[2-[[3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoyl]amino]ethoxy]ethoxy]ethoxy]ethyl]carbamate (30 mg, 47.0 umol, 34.1% yield). Mass calcd for $C_{29}H_{38}F_3N_7O_6$ 637.65, m/z found 660.2 $[M+Na]^+$; ^1H NMR (400MHz, METHANOL-d_4) δ = 8.74 (d, *J* = 2.3 Hz, 1H), 7.89 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 4.54 - 4.48 (m, 3H), 3.74 - 3.57 (m, 12H), 3.48 (t, *J* = 5.6 Hz, 2H), 3.19 (t, *J* = 5.5 Hz, 2H), 1.42 (s, 9H).

Example 54: tert-butyl (1-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)-1-oxo-5,8,11,14-tetraoxa-2-azahexadecan-16-yl)carbamate (Compound 63)



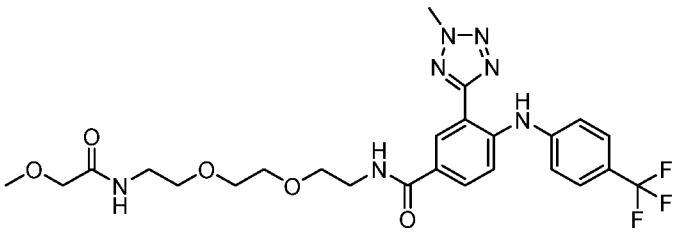
Preparation of Compound 63:



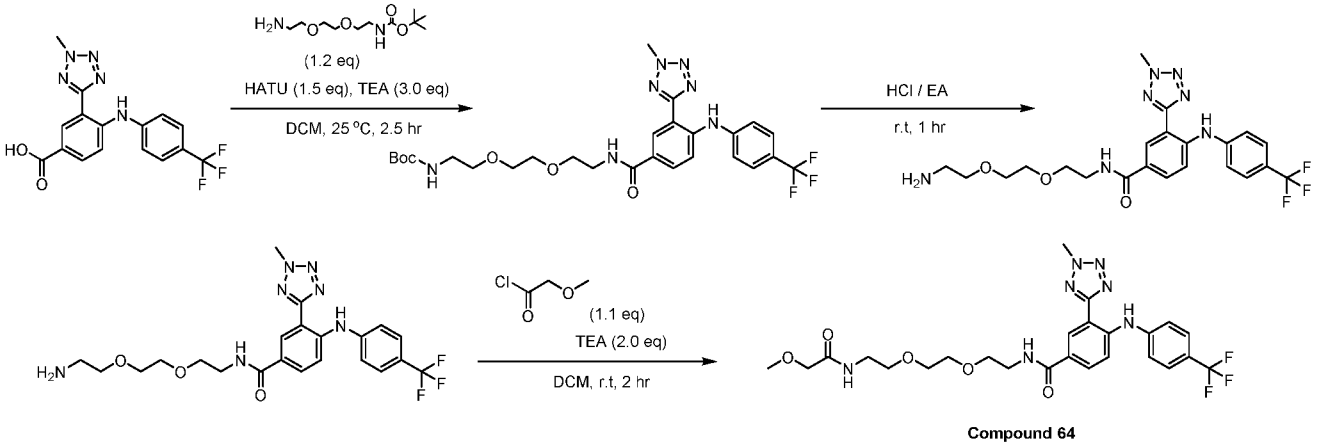
Compound 63

[00506] The mixture of 3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid (50 mg, 0.13 mmol, 1 *eq*), HATU (78.5 mg, 0.20 mmol, 1.5 *eq*) and DIEA (26.6 mg, 0.20 mmol, 35.9 uL, 1.5 *eq*) in DCM (1 mL) was stirred at 25 °C for 1 hr. Then tert-butyl N-[2-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]ethoxy]ethyl]carbamate (46.3 mg, 0.13 mmol, 1 *eq*) was added at the mixture and the mixture was stirred at 25 °C for another 1 hr. The reaction mixture was diluted with H_2O (5 mL) and the mixture was extracted with EA (10 mL * 3). The combined organic phase was washed with brine (10 mL*3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC to give compound tert-butyl N-[2-[2-[2-[2-[2-[[3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoyl]amino]ethoxy]ethoxy]ethoxy]ethoxy]ethyl]carbamate (30 mg, 44.0 umol, 31.9% yield). Mass calcd for $C_{31}H_{42}F_3N_7O_7$ 681.70, m/z found 704.2 $[M+Na]^+$. ^1H NMR (400MHz, METHANOL-d_4) δ = 8.74 (d, *J* = 2.0 Hz, 1H), 7.89 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 3.65 - 3.58 (m, 1H), 3.74 - 3.53 (m, 17H), 3.47 (t, *J* = 5.5 Hz, 2H), 3.19 (t, *J* = 5.6 Hz, 2H), 1.43 (s, 9H).

Example 55: 3-(2-methyl-2H-tetrazol-5-yl)-N-(4-oxo-2,8,11-trioxa-5-azatridecan-13-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide (Compound 64)



Preparation of Compound 64:



Compound 64

Step 1: tert-butyl (2-(2-(2-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamido)ethoxy)ethoxy)ethyl)carbamate

[00507] To a solution of 3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoic acid (200 mg, 0.55 mmol, 1 *eq*) in DCM (5 mL) was added HATU (0.31 g, 0.82 mmol, 1.5 *eq*) and TEA (0.16 g, 1.65 mmol, 0.22 mL, 3 *eq*). The mixture was stirred at 25 °C for 0.5 hr. Then tert-butyl N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]carbamate (0.16 g, 0.66 mmol, 1.2 *eq*) was added to the solution. The reaction was stirred at 25 °C for 2 hr. H_2O (6 mL) was added to the solution. The mixture was extracted with ethyl acetate (5 mL*3). The combined organic layers were washed with brine (10 mL*2), dried over anhydrous Na2SO4, filtered and concentrated in vacuum. Compound tert-butyl N-[2-[2-[2-[[3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoyl]amino]ethoxy]ethoxy]ethyl]carbamate (210 mg, crude).

Step 2: N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide

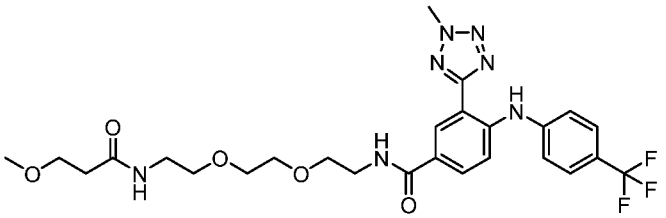
[00508] To a 0 °C solution of tert-butyl N-[2-[2-[2-[[3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzoyl]amino]ethoxy]ethoxy]ethyl]carbamate (160 mg, 0.26 mmol, 1 eq) in EtOAc (5 mL) was added HCl/EtOAc (4 M, 1.35 mL, 20 eq). The mixture was stirred at 15 °C for 1 hr, and then the reaction mixture was concentrated under reduced pressure to give crude N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzamide hydrochloride (150 mg) as a yellow oil.

Step 3: 3-(2-methyl-2H-tetrazol-5-yl)-N-(4-oxo-2,8,11-trioxa-5-azatridecan-13-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide

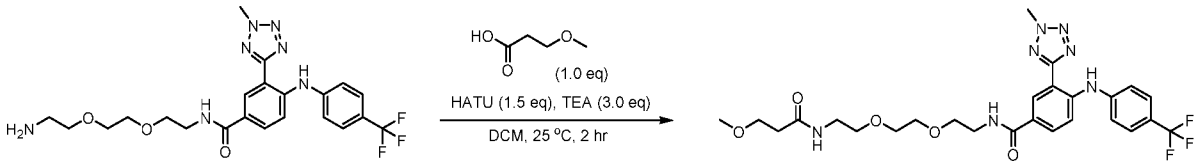
[00509] To a solution of N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzamide (35 mg, 70.9 umol, 1 *eq*) in DCM (1 mL) was added TEA (14.3 mg, 0.14 mmol, 19.7 uL, 2 *eq*) and 2-methoxyacetyl chloride (8.4 mg, 78.0 umol, 7.1

uL, 1.1 *eq*). The mixture was stirred at 19 °C for 2 hr. H_2O (6 mL) was added to the solution. The mixture was extracted with ethyl acetate (10 mL*3). The combined organic layers were washed with brine (15 mL*2), dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC to give compound N-[2-[2-[2-[(2-methoxyacetyl)amino]ethoxy]ethoxy]ethyl]-3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzamide (3.3 mg, 5.6 umol, 7.8% yield, HCl). Mass calc. for $C_{25}H_{30}F_3N_7O_5$ 565.54, m/z found 566.1 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d_4) δ = 8.73 (d, *J* = 2.3 Hz, 1H), 7.89 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 4.50 (s, 3H), 3.86 (s, 2H), 3.73 - 3.67 (m, 6H), 3.64 - 3.58 (m, 4H), 3.43 (s, 2H), 3.38 (s, 3H).

Example 56: 3-(2-methyl-2H-tetrazol-5-yl)-N-(5-oxo-2,9,12-trioxa-6-azatetradecan-14-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide (Compound 65)



Preparation of Compound 65:



Compound 65

[00510] To a solution of N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzamide (50 mg, 0.10 mmol, 1 *eq*) and 3-methoxypropanoic acid (10.5 mg, 0.10 mmol, 9.5 uL, 1 *eq*) in DCM (2 mL) was added HATU (57.7 mg, 0.15 mmol, 1.5 *eq*) and TEA (30.7 mg, 0.30 mmol, 42.3 uL, 3 *eq*). The mixture was stirred at 15 °C for 2 hr. H_2O (6 mL) was added to the solution. The mixture was extracted with ethyl acetate (10 mL*3). The combined organic layers were washed with brine (15 mL*2), dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC. Compound N-[2-[2-[2-(3-methoxypropanoylamino)ethoxy]ethoxy]ethyl]-3-(2-methyltetrazol-5-yl)-4-[4-(trifluoromethyl)anilino]benzamide (16.2 mg, 26.3 umol, 25.9% yield, HCl). Mass calc. for $C_{26}H_{32}F_3N_7O_5$ 579.57, m/z found 580.1 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d_4) δ = 8.71 (d, *J* = 2.3 Hz, 1H), 7.87 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.8 Hz,

1H), 7.44 (d, *J* = 8.5 Hz, 2H), 4.49 (s, 3H), 3.73 - 3.56 (m, 12H), 3.40 - 3.36 (m, 2H), 3.30 (s, 3H), 2.45 (t, *J*=6.1 Hz, 2H).

II. Biological Evaluation

Example A1: YAP Reporter Assay

[00511] HEK293T cells stably transfected with 8XTBD luciferase reporter and pRLTK in 384-well plates were treated with the test compounds, starting from 3μM (final concentration in assay plate), 1:3 dilution, and 10 points in quadruplicates. Post 24-hr incubation with compounds at 37°C and 5% CO2, cells were lysed and 8XTBD-driven firefly luciferase and control TK-driven renilla luciferase activities were measured using Promega Dual-Luciferase Reporter Assay System.

[00512] Reagents: The reagents used for this study are: DMEM: Invitrogen# 11960077, Dual-Glo Luciferase Assay System: Promega-E2980, Puromycin Dihydrochloride: Invitrogen-A1113803, 384-well plate: PerkinElmer-6007480, L-GLUTAMINE: Invitrogen-25030164, Hygromycin B: Invitrogen-10687010, and Penicillin-Streptomycin: Merk-TMS-AB2-C

[00513] 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).

[00514] Cell Plating: The appropriate media was warmed at 37°C by water bath: Culture Medium, Assay Medium, 1* D-PBS, 0.05% trypsin-EDTA. The cells were trypsinized after removing all media, then washed with 1* sterile D-PBS and then with 2 ml 0.05% trypsin-EDTA. The cells were then incubated at RT for one minute. Then 10 ml/75cm2 flask Assay Medium was added to each flask. Using a 10 ml pipette, the cells were then gently resuspended in the media, until the clumps completely disappeared. The cells were then transferred into 50 ml centrifuge tubes and were centrifuged at 800 rpm for 5 mins. The medium was removed and the cells were resuspended with Assay Medium. An aliquot of cells was used to count the cell density (cells/ml). The cell suspension was then diluted with Assay Medium to a concentration of 6x104 cells/ml. 50ul cells suspension was then plated to 384-well plate (PerkinElmer-6007480), 3x103 cells/well and the cells were incubated in an incubator at 37°C, 5% CO2.

[00515] Compound Treatment: In the afternoon (incubation of the plate with 3-4 hrs), the test compounds were added by Echo, starting from 3uM (final concentration in the assay plate), 1:3 dilution, 10 points, quadruplicates. The plate was placed at 37°C, 5% CO2 incubator for 24hrs.

[00516] Detection: The Dual-Glo Luciferase Reagent was prepared by transferring the contents of one bottle of Dual-Glo Luciferase Buffer to one bottle of Dual-Glo Luciferase Substrate to create the Dual-Glo Luciferase Reagent. Mixing was performed by inversion until the substrate was thoroughly dissolved. After mixing, the reagent was aliquoted into 15 ml tubes. In the afternoon (24hrs post compound treatment), the DMEM+ medium in the 384 well plates were aspirated by Microplate Washer.

[00517] Measuring firefly luciferase activity: 20ul Dual-Glo Luciferase Reagent was added to the 384-well plates. The plates were protected from light to prevent interference with the assay. The plates were shaken for 1min followed centrifuging plates at 1000rpm for 30 seconds. After waiting at least 10 minutes, the firefly luminescence was measured by Envision.

[00518] Measuring renilla luciferase activity: 20ul Stop-Glo Reagent was added to the 384-well plates. The plates were shaken for 1min and then centrifuged at 1000rpm for 30 seconds. After waiting at least 10 minutes, the renilla luminescence was measured by Envision.

[00519] Compound IC_{50} and maximum inhibition on the firefly luciferase and renilla luciferase activities were reported separately. IC_{50} for firefly luciferase activity are shown in the table below.

TABLE 2

Compound No.	Name	Firefly Luciferase IC_{50} (μM)
1	methyl 3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate	A
2	methyl 3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoate	A
3	3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
4	3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoic acid	A
5	N-methyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide	A
6	3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide	A
7	3-(2-methyl-2H-tetrazol-5-yl)-4-((4-	A

Compound No.	Name	Firefly Luciferase IC_{50} (μM)
	(trifluoromethyl)phenyl)amino)benzamide	
8	N-methyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	A
10	N-ethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	A
11	N-isopropyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	A
12	methyl 4-((4-(isopropylcarbamoyl)phenyl)amino)-3-(2-methyl-2H-tetrazol-5-yl)benzoate	C
13	N,N-dimethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	B
15	3-(2-methyl-2H-tetrazol-5-yl)-N-(methylsulfonyl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	A
17	N,N-diethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	B
19	N,N-dimethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide	B
20	N,N-diethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide	B
21	N-isopropyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide	A
22	N-ethyl-3-(2-methyl-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide	A
23	3-(2-methyl-2H-tetrazol-5-yl)-N-(methylsulfonyl)-4-((3-(trifluoromethyl)phenyl)amino)benzamide	A
24	methyl 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate	B

Compound No.	Name	Firefly Luciferase IC_{50} (μM)
25	3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
26	methyl 3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoate	B
27	3-(2-(2-fluorobenzyl)-2H-tetrazol-5-yl)-4-((3-(trifluoromethyl)phenyl)amino)benzoic acid	A
28	3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
29	3-(2-aminopyridin-4-yl)-N-isopropyl-4-((4-(trifluoromethyl)phenyl)amino)benzamide	B
30	3-(2-aminopyridin-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
33	methyl 3-(1-methyl-1H-imidazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate	A
34	methyl 3-(2-amino-4-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoate	A
36	*N*-isopropyl-3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzamide	A
37	*N*-cyclopropyl-3-(1-methylimidazol-4-yl)-4-[4-(trifluoromethyl)anilino]benzamide	A
38	3-(1-methylimidazol-4-yl)-*N*-sulfamoyl-4-[4-(trifluoromethyl)anilino]benzamide	A
39	3-(pyridin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
40	3-(pyrimidin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
41	3-(thiazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
42	3-(thiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A

Compound No.	Name	Firefly Luciferase IC_{50} (μM)
43	3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
44	N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	B
45	N-(2-(2-(2-acetamidoethoxy)ethoxy)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	A
46	3-pyridazin-3-yl-4-[4-(trifluoromethyl)anilino]benzoic acid	A
47	tert-butyl (2-(2-(2-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamido) ethoxy)ethoxy)ethyl)carbamate	B
49	3-(4-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid	A
50	3-(pyrazin-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
51	3-(5-fluoro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid	A
52	3-(5-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid	A
53	methyl 3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoate	A
54	3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
55	3-(4-chloro-2-pyridyl)-4-[4-(trifluoromethyl)anilino]benzoic acid	A
56	methyl 3-(6-aminopyrimidin-4-yl)-4-[4-(trifluoromethyl)anilino]benzoate	A

Compound No.	Name	Firefly Luciferase IC_{50} (μM)
57	3-(oxazol-4-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
58	4-[4-(trifluoromethyl)anilino]-3-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]benzoic acid	A
59	3-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
60	3-pyrimidin-4-yl-4-[4-(trifluoromethyl)anilino]benzoic acid	B
61	3-(oxazol-2-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzoic acid	A
63	tert-butyl (1-(3-(2-methyl-2H-tetrazol-5-yl)-4-((4-(trifluoromethyl)phenyl)amino)phenyl)-1-oxo-5,8,11,14-tetraoxa-2-azahexadecan-16-yl)carbamate	B
64	3-(2-methyl-2H-tetrazol-5-yl)-N-(4-oxo-2,8,11-trioxa-5-azatridecan-13-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	B
65	3-(2-methyl-2H-tetrazol-5-yl)-N-(5-oxo-2,9,12-trioxa-6-azatetradecan-14-yl)-4-((4-(trifluoromethyl)phenyl)amino)benzamide	B

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

A: ≤ 0.100 μM

B: > 0.100 μM to ≤ 1.000 μM

C: > 1.000 μM to ≤ 3.000 μM

D: > 3.000 μM

Example A2: Tumor Suppression Assay

[00520] 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

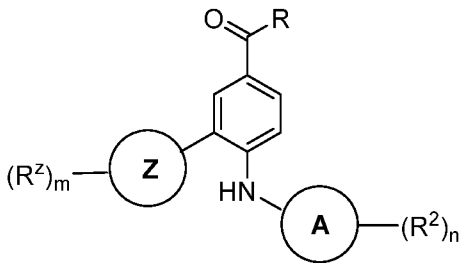
[00521] Cancer cell lines are plated in 384-well plates 24h before drug treatment. Post incubation for various time periods with the test compounds, starting from 3μM (final concentration in assay plate), 1:3 dilution, and 10 points in duplicates, the number of viable cells and proliferative cells are 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.

[00522] 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

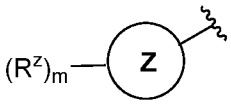
WHAT IS CLAIMED IS:

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



Formula (I)

wherein,



is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom or a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom;

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, 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 C_2-C_{10} 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_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2-C_{10}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 H or substituted or unsubstituted C_1-C_6alkyl;

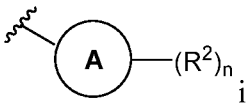
Y^2 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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;

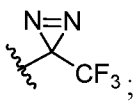
R is -OR^1 or -$N(R^1)_2$;

each R^1 is independently H, -$(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^1 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;



is substituted or unsubstituted phenyl or substituted or unsubstituted cyclohexyl;

each R^2 is independently H, -F, -I, -Cl, -N_3, -CN, -OR^4, -SR^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_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 aralkyl, substituted or unsubstituted aryl, or 

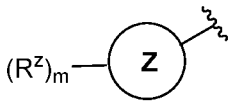
;

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

each R^4 is independently 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

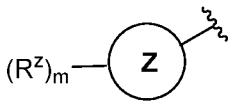
or two R^4 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

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



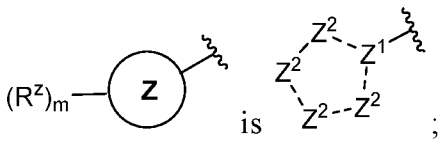
is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom.

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



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

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



;

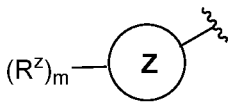
Z^1 is -N-, -CH-, or -C-;

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; and

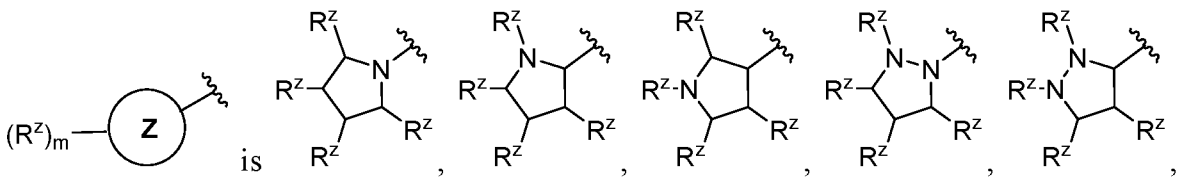
with the provision that the 5-membered heterocyclic ring contains at least one N atom.

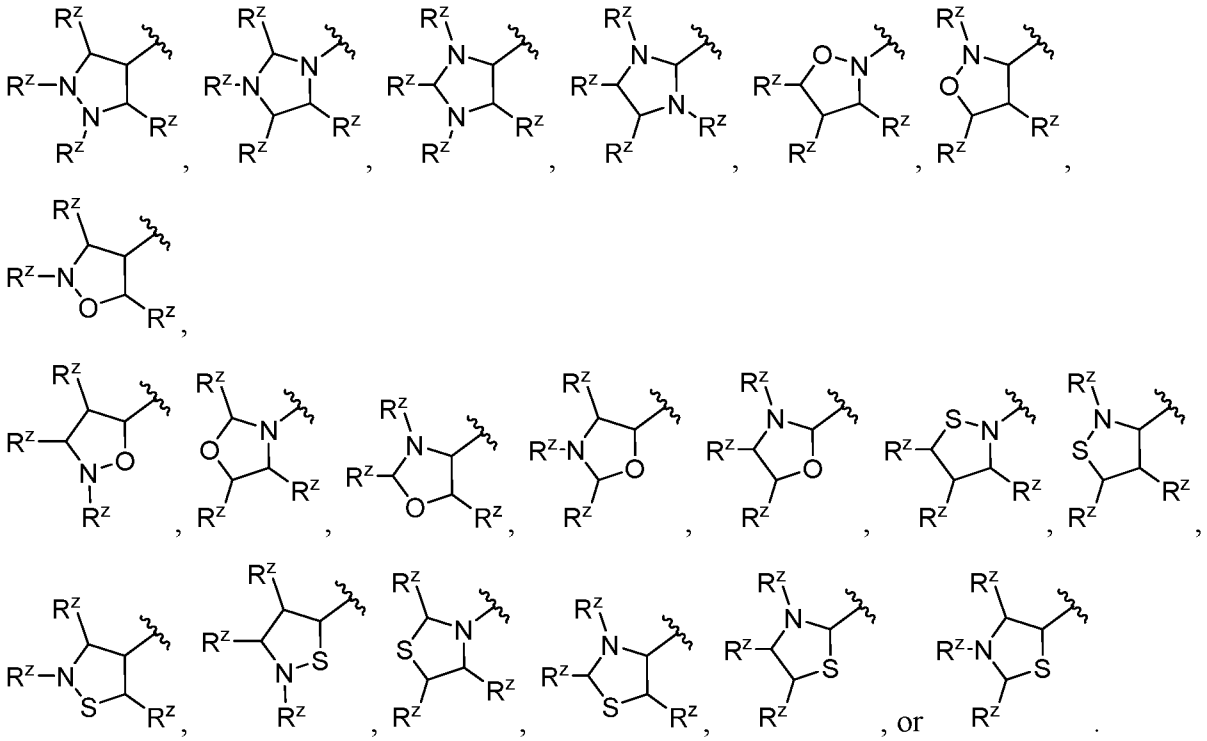
5. The compound, or pharmaceutically acceptable salt thereof, of claims 1 or 2, wherein:



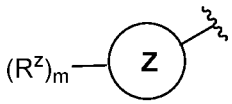
is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

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



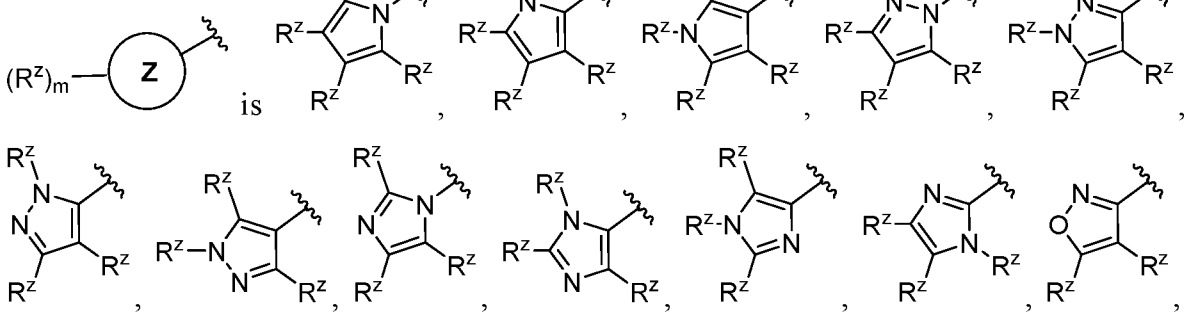


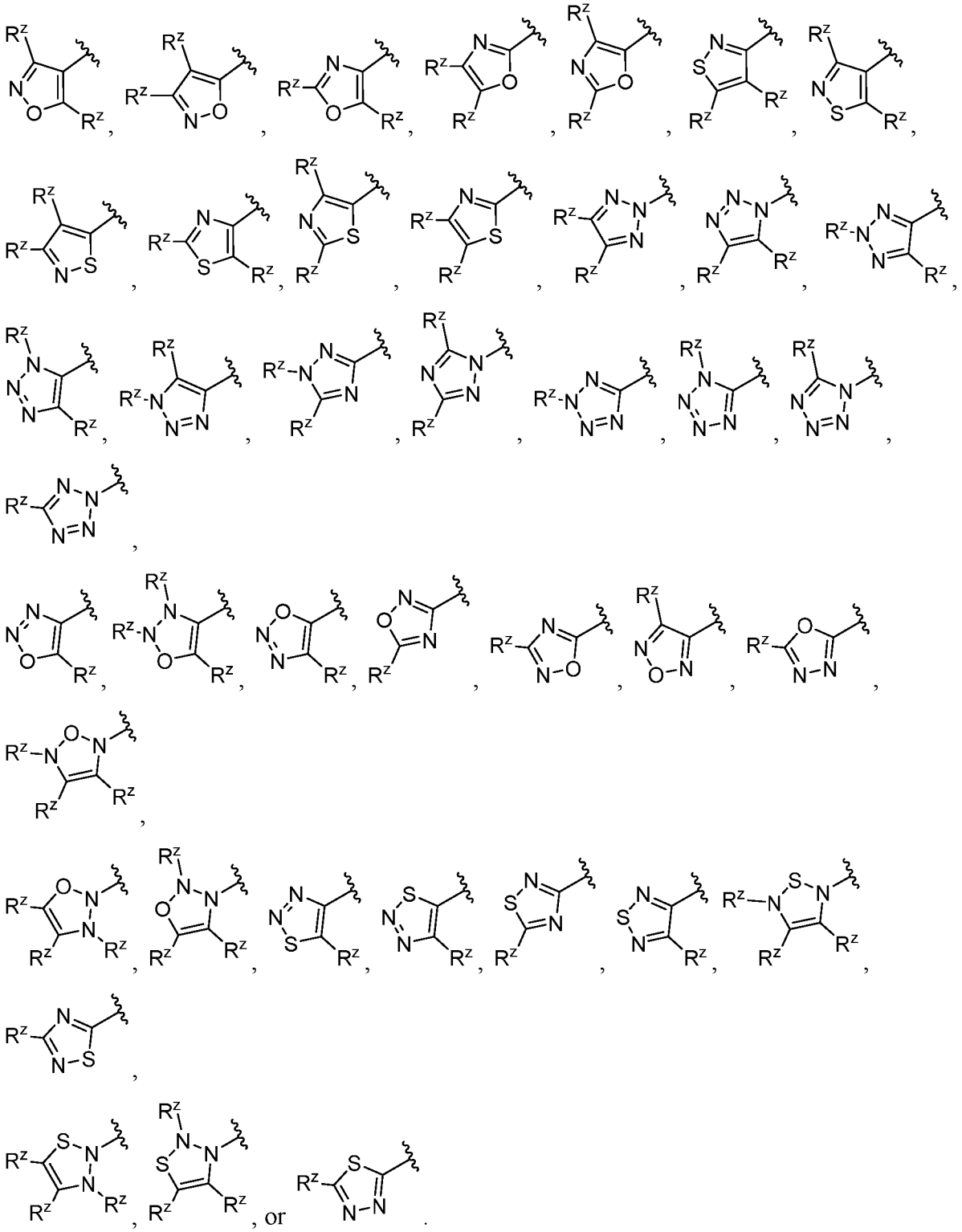
7. The compound, or pharmaceutically acceptable salt thereof, of claims 1 or 2, wherein:



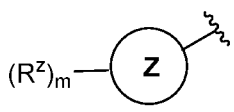
is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or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

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



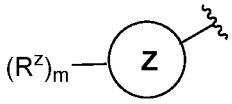


9. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein:

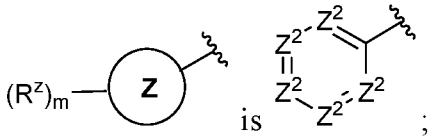


is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom.

10. The compound, or pharmaceutically acceptable salt thereof, of claims 1 or 9, wherein:


is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing 1 or 2 N atoms.

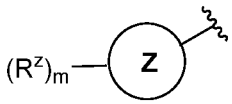
11. The compound, or pharmaceutically acceptable salt thereof, of claims 1 or 9, wherein:


is ;

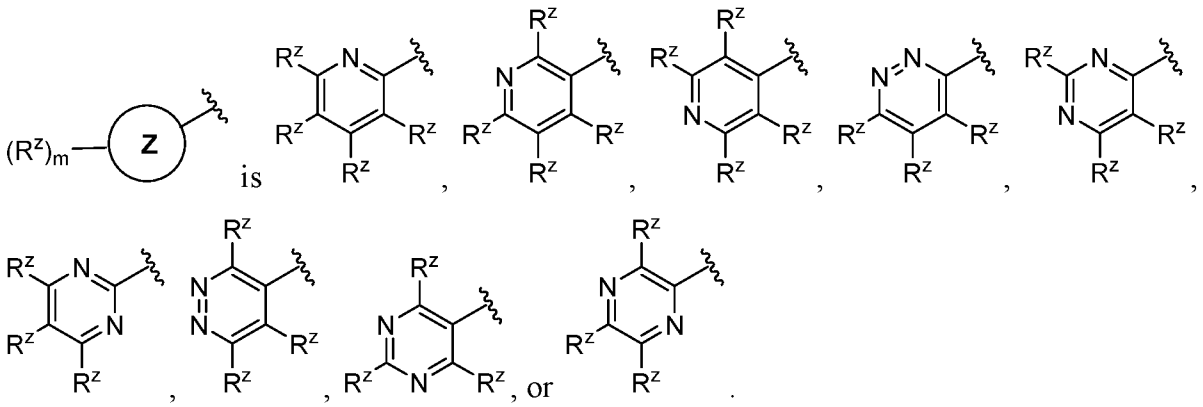
each Z^2 is independently CR^z or N; and

at least one Z^2 is N.

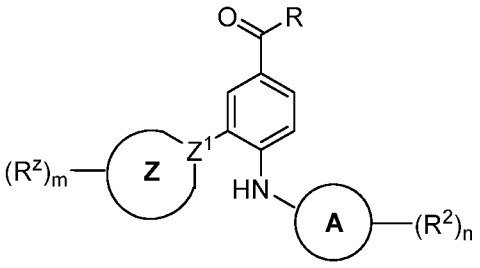
12. The compound, or pharmaceutically acceptable salt thereof, of claims 1 or 9, wherein:


is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

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


is , , , , , , , , , or .

14. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:

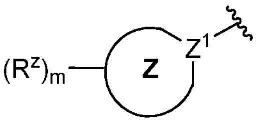


Formula (Ia)

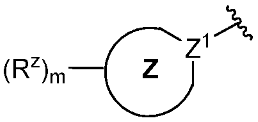
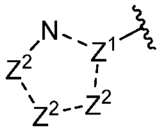
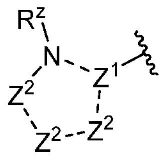
wherein:

Z^1 is -N-, -CH-, or -C-.

15. The compound, or pharmaceutically acceptable salt thereof, of claim 14, 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.

16. The compound, or pharmaceutically acceptable salt thereof, of claims 14 or 15, wherein:

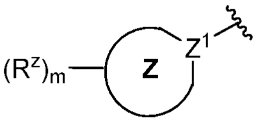

is  or  ;

Z^1 is -N-, -CH-, or -C-;

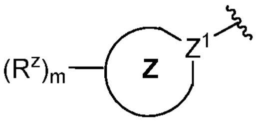
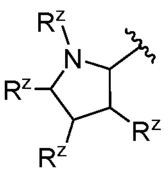
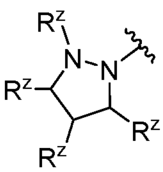
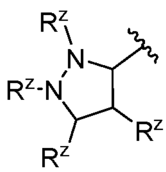
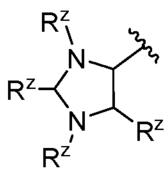
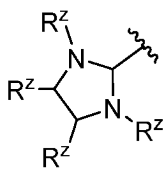
each Z^2 is independently $-CR^z-$, $-CHR^z-$, $-C(R^z)_2-$, $-NR^z-$, -N-, -O-, or -S-; and

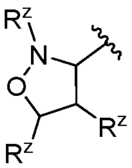
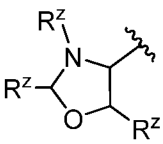
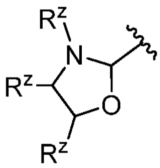
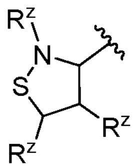
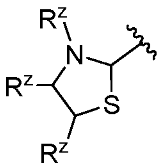
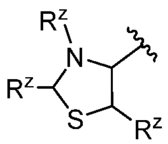
each - - is independently a single or double bond.

17. The compound, or pharmaceutically acceptable salt thereof, of claims 14 or 15, wherein:

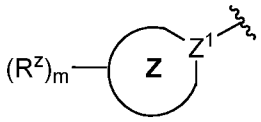

is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

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


is  ,  ,  ,  ,  ,

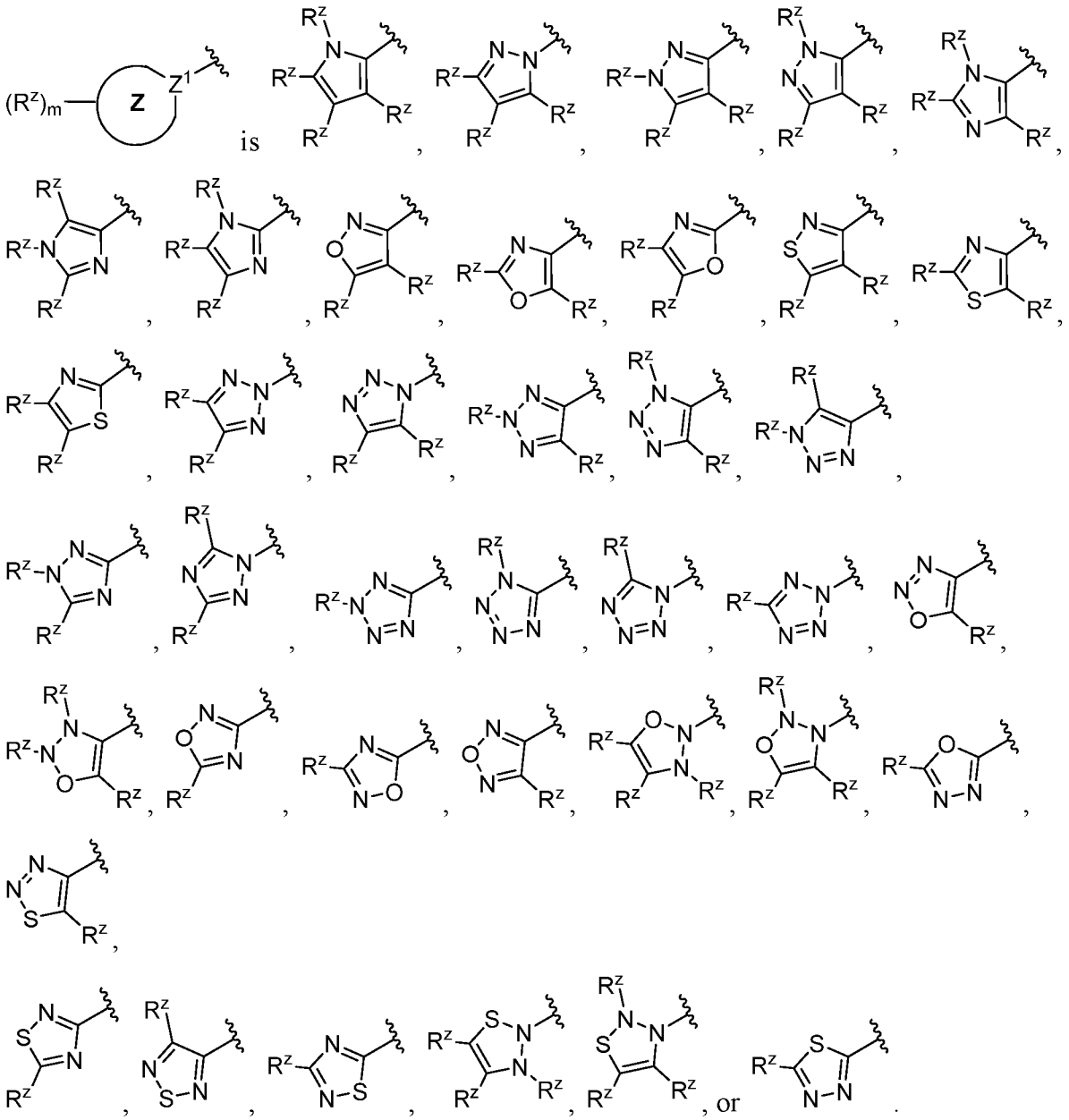
 ,  ,  ,  ,  , or  .

19. The compound, or pharmaceutically acceptable salt thereof, of claims 14 or 15, wherein:

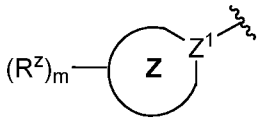


is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or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

20. The compound, or pharmaceutically acceptable salt thereof, of claim 19, wherein:



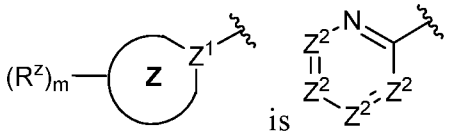
21. The compound, or pharmaceutically acceptable salt thereof, of claim 14, wherein:



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.

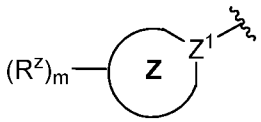
22. The compound, or pharmaceutically acceptable salt thereof, of claims 14 or 21, wherein:



; and

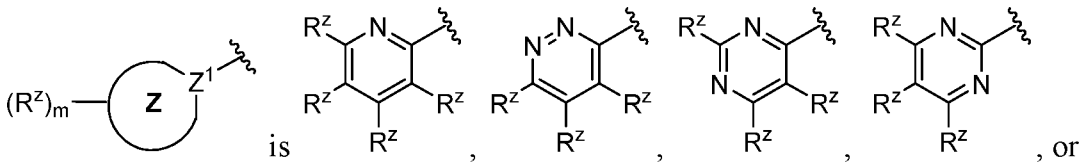
each Z^2 is independently CR^z or N.

23. The compound, or pharmaceutically acceptable salt thereof, of claims 14 or 21, wherein:

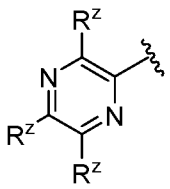


is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

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



, or



.

25. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-24, wherein:

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

26. The compound, or pharmaceutically acceptable salt thereof, of claim 25, wherein:
each R^z is independently H, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

27. The compound, or pharmaceutically acceptable salt thereof, of claims 25 or 26, wherein:
each R^z is independently H, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl,
tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

28. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-24, wherein:
each R^z is $-L^1-Y^1$.

29. The compound, or pharmaceutically acceptable salt thereof, of claim 28, 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.

30. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-24, wherein:
each R^z is $-L^2-L^3-Y^2$.

31. The compound, or pharmaceutically acceptable salt thereof, of claim 30, 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.

32. The compound, or pharmaceutically acceptable salt thereof, of claim 30, 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.

33. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-32, wherein:

R is -OR^1; and

R^1 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

34. The compound, or pharmaceutically acceptable salt thereof, of claim 33, wherein:

R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

35. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-32, wherein:

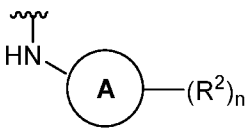
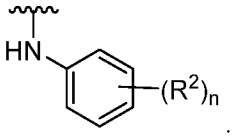
R is $-N(R^1)_2$; and

each R^1 is independently H, $-(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

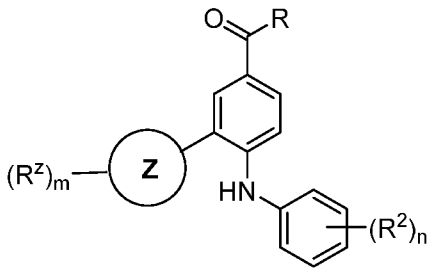
or two R^1 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

36. The compound, or pharmaceutically acceptable salt thereof, of claim 35, wherein:

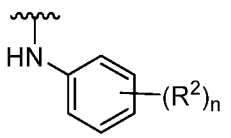
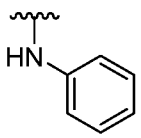
R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

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

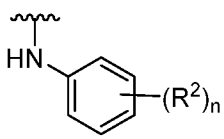
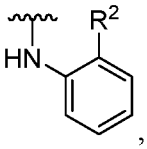
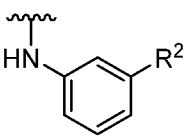
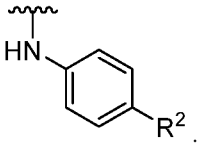
38. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:



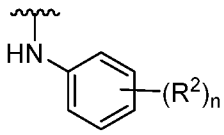
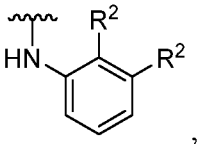
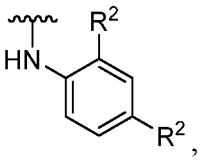
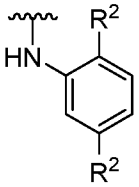
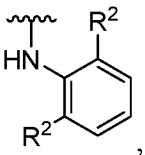
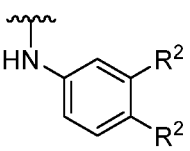
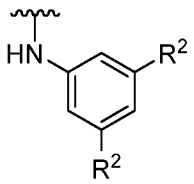
Formula (Ib).

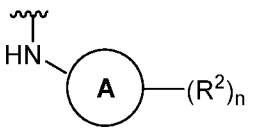
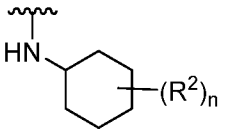
39. The compound, or pharmaceutically acceptable salt thereof, of claims 37 or 38, wherein:  is  .

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

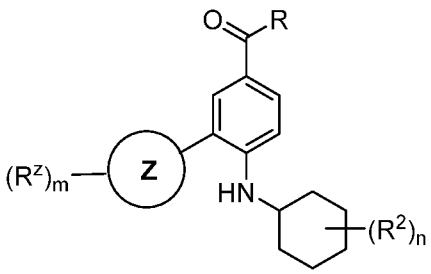

is

,

, or

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41. The compound, or pharmaceutically acceptable salt thereof, of claims 37 or 38, wherein:


is

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, or

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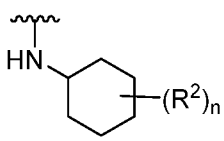
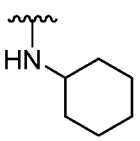
42. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-36, wherein:

is

.

43. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ic), or a pharmaceutically acceptable salt thereof:

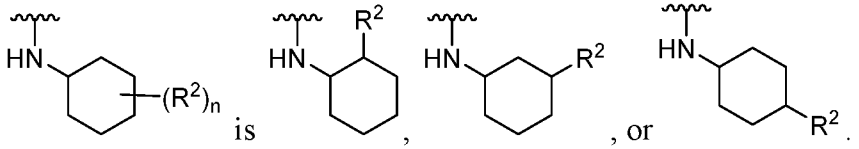


Formula (Ic).

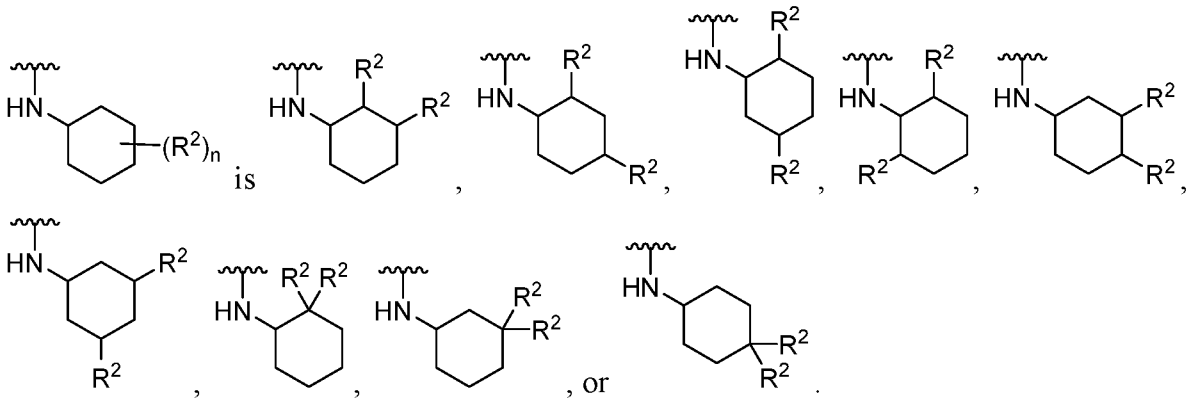
44. The compound, or pharmaceutically acceptable salt thereof, of claims 42 or 43, wherein:


is

.

45. The compound, or pharmaceutically acceptable salt thereof, of claims 42 or 43, wherein:



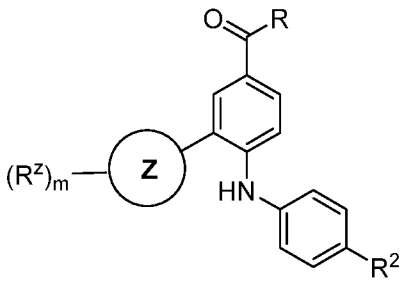
46. The compound, or pharmaceutically acceptable salt thereof, of claims 42 or 43, wherein:



47. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-46, wherein:

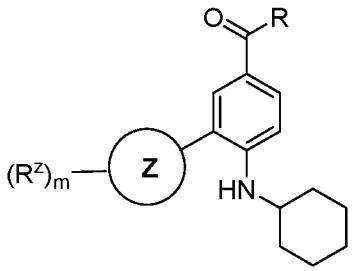
each R^2 is independently H, -F, -I, -Cl, -N_3, -CN, -OR^4, -SR^4, -$(SO_2)R^4$, -$N(R^4)_2$, -CO_2R^4, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted aryl.

48. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Id), or a pharmaceutically acceptable salt thereof:



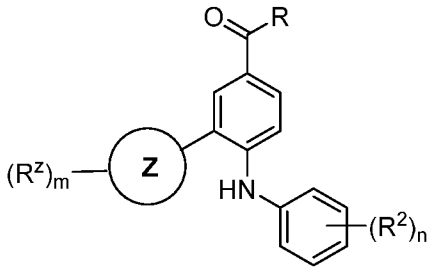
Formula (Id).

49. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound has the structure of Formula (Ie), or a pharmaceutically acceptable salt thereof:



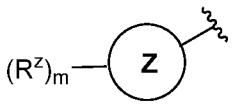
Formula (Ie).

50. A compound of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II)

wherein,

 is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom or a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom;

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, 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 C_2-C_{10} 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_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2-C_{10}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 H or substituted or unsubstituted C_1-C_6alkyl;

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;

or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to

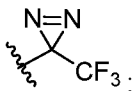
form a substituted or unsubstituted N-containing heterocycle;

R is -OR^1 or -$N(R^1)_2$;

each R^1 is independently H, -$(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^1 on the same N atom are taken together with the N atom to which they are attached to form

a substituted or unsubstituted N-containing heterocycle;

each R^2 is independently H, -F, -I, -Cl, N_3, -CN, -OR^4, -SR^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_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 aralkyl, substituted or unsubstituted aryl, or  ;

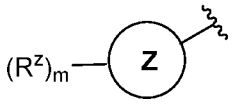
n is 0, 1, 2, 3, 4, or 5; and

each R^4 is independently 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

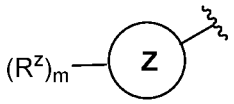
or two R^4 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

51. The compound, or pharmaceutically acceptable salt thereof, of claim 50, wherein:



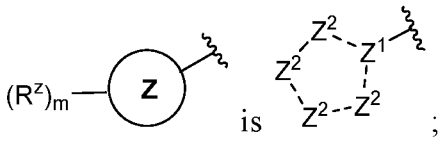
is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom.

52. The compound, or pharmaceutically acceptable salt thereof, of claims 50 or 51, wherein:



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

53. The compound, or pharmaceutically acceptable salt thereof, of claims 50 or 51, wherein:



;

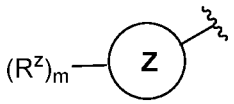
Z^1 is -N-, -CH-, or -C-;

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; and

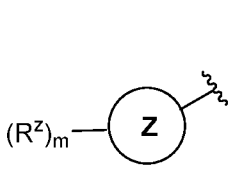
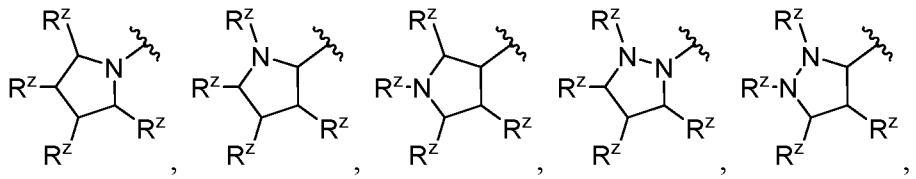
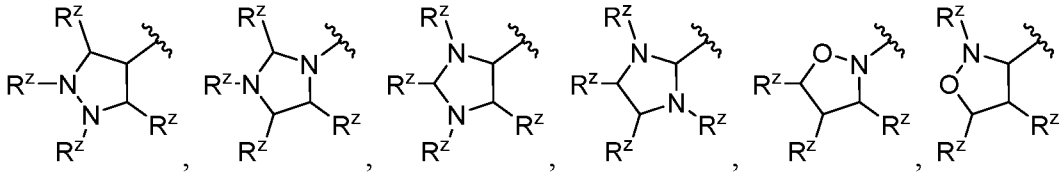
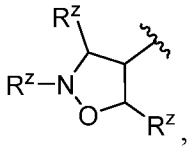
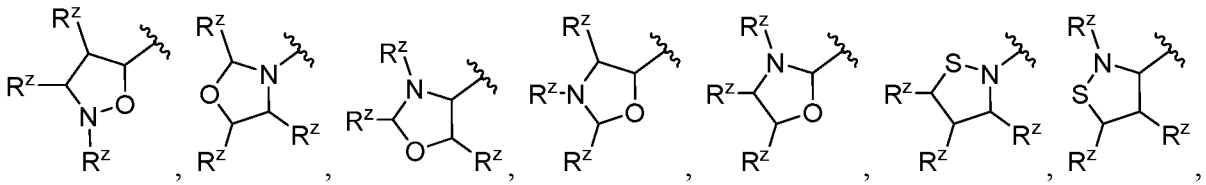
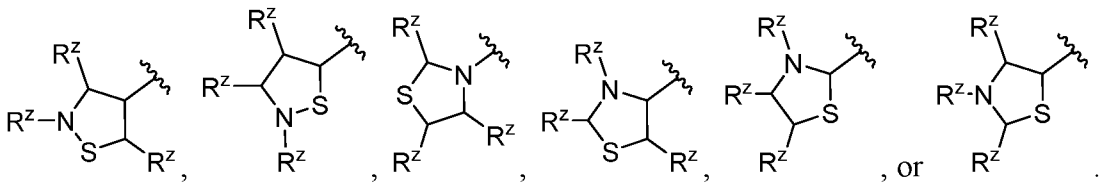
with the provision that the 5-membered heterocyclic ring contains at least one N atom.

54. The compound, or pharmaceutically acceptable salt thereof, of claims 50 or 51, wherein:

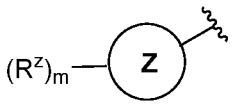


is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

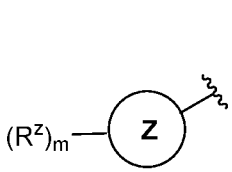
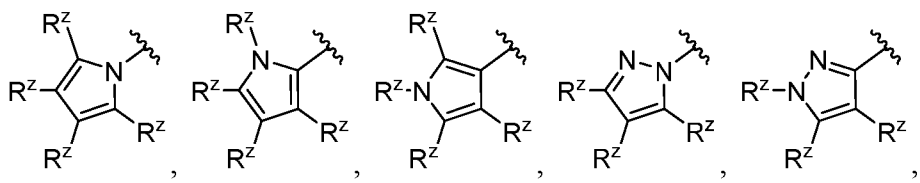
55. The compound, or pharmaceutically acceptable salt thereof, of claim 54, wherein:

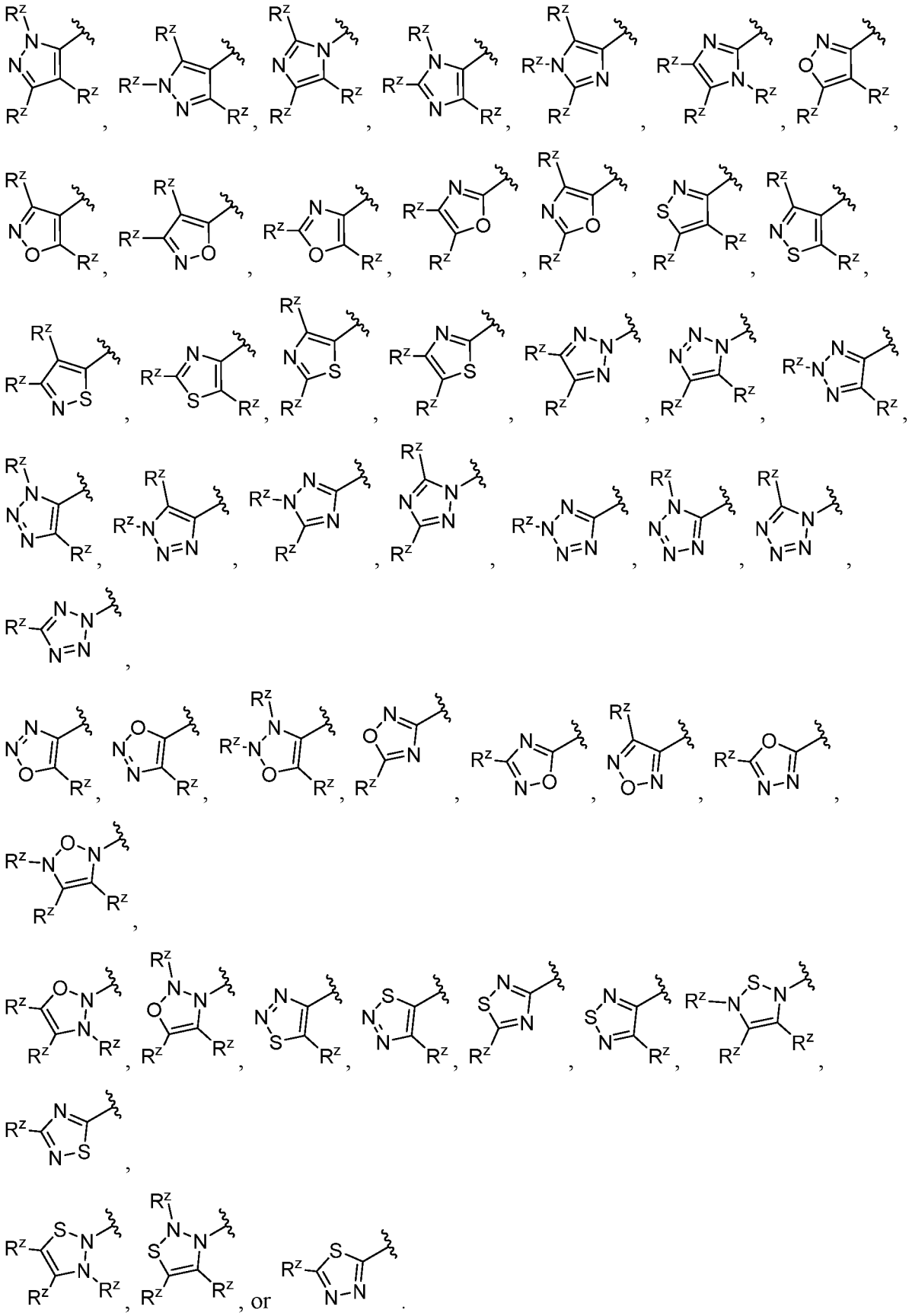

is 




, or .

56. The compound, or pharmaceutically acceptable salt thereof, of claims 50 or 51, wherein:

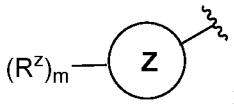

is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or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

57. The compound, or pharmaceutically acceptable salt thereof, of claim 56, wherein:

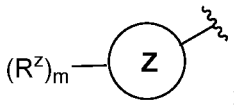

is 



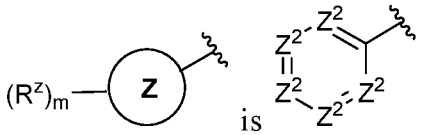
58. The compound, or pharmaceutically acceptable salt thereof, of claim 50, wherein:

 is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom.

59. The compound, or pharmaceutically acceptable salt thereof, of claims 50 or 58, wherein:

 is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing 1 or 2 N atoms.

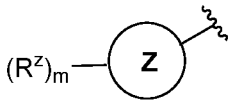
60. The compound, or pharmaceutically acceptable salt thereof, of claims 50 or 58, wherein:

 is ;

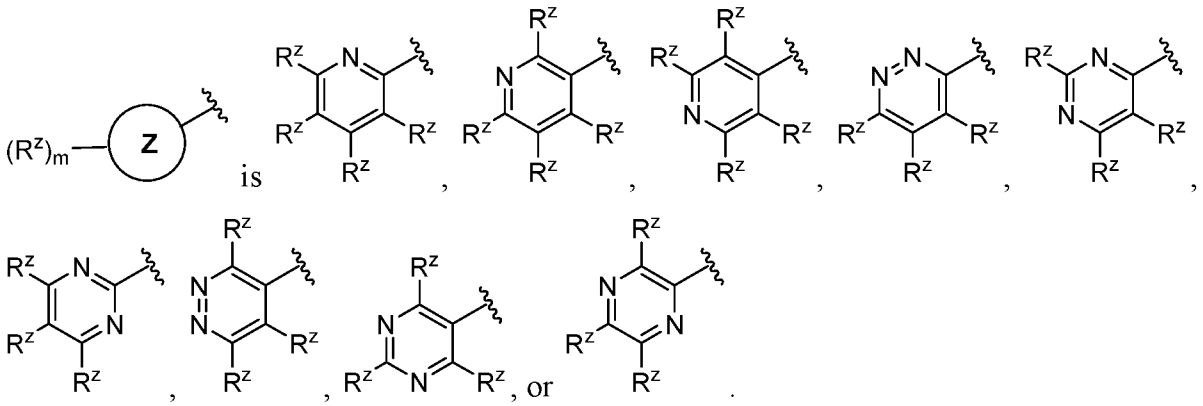
each Z^2 is independently CR^z or N; and

at least one Z^2 is N.

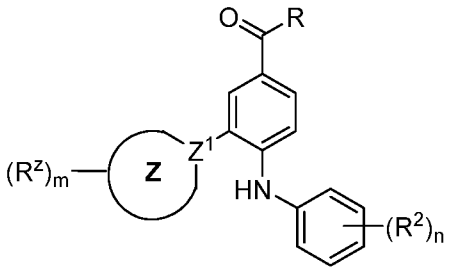
61. The compound, or pharmaceutically acceptable salt thereof, of claims 50 or 58, wherein:

 is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

62. The compound, or pharmaceutically acceptable salt thereof, of claim 61, wherein:



63. The compound, or pharmaceutically acceptable salt thereof, of claim 50, wherein the compound has the structure of Formula (IIa), or a pharmaceutically acceptable salt thereof:

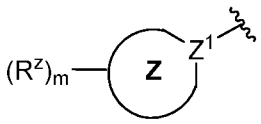


Formula (IIa)

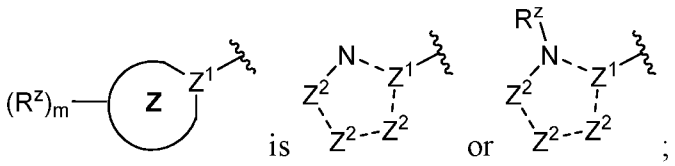
wherein:

Z^1 is -N-, -CH-, or -C-.

64. The compound, or pharmaceutically acceptable salt thereof, of claim 63, 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.

65. The compound, or pharmaceutically acceptable salt thereof, of claims 63 or 64, wherein:

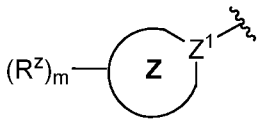
 ;

Z^1 is -N-, -CH-, or -C-;

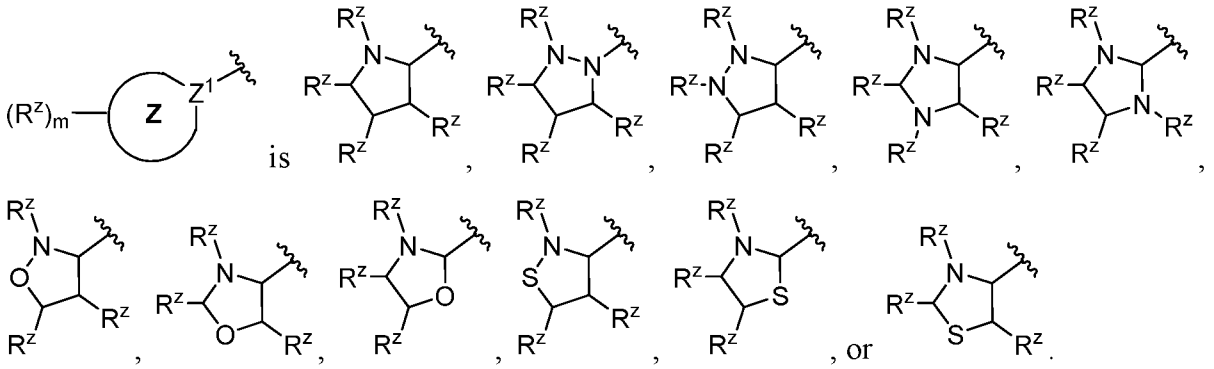
each Z^2 is independently $-CR^z-$, $-CHR^z-$, $-C(R^z)_2-$, $-NR^z-$, -N-, -O-, or -S-; and

each - - is independently a single or double bond.

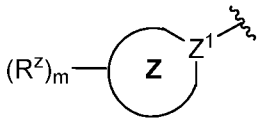
66. The compound, or pharmaceutically acceptable salt thereof, of claims 63 or 64, wherein:

 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.

67. The compound, or pharmaceutically acceptable salt thereof, of claim 66, wherein:

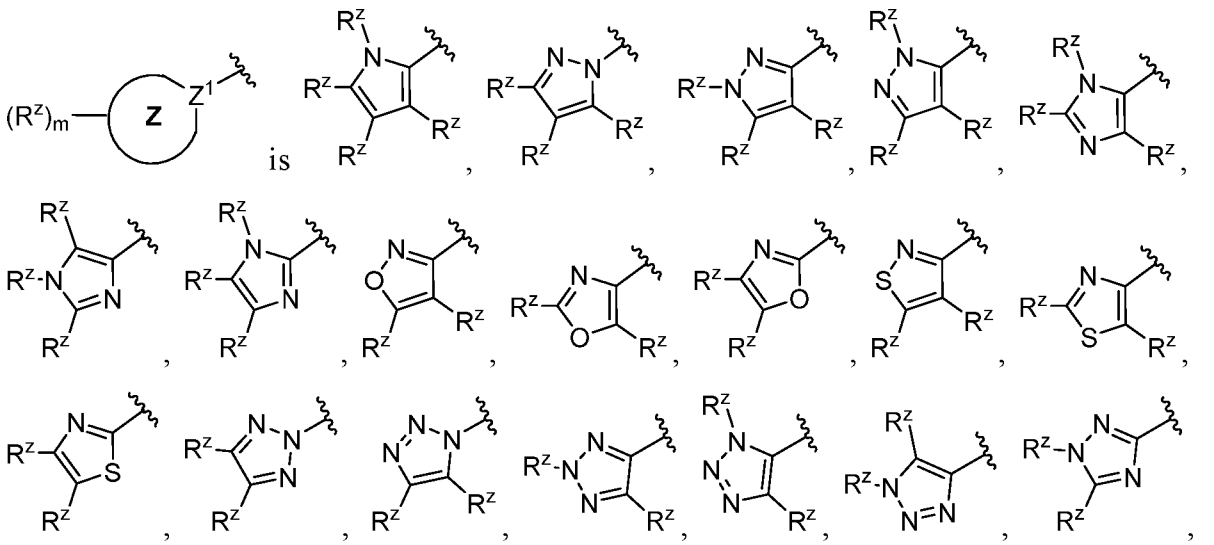


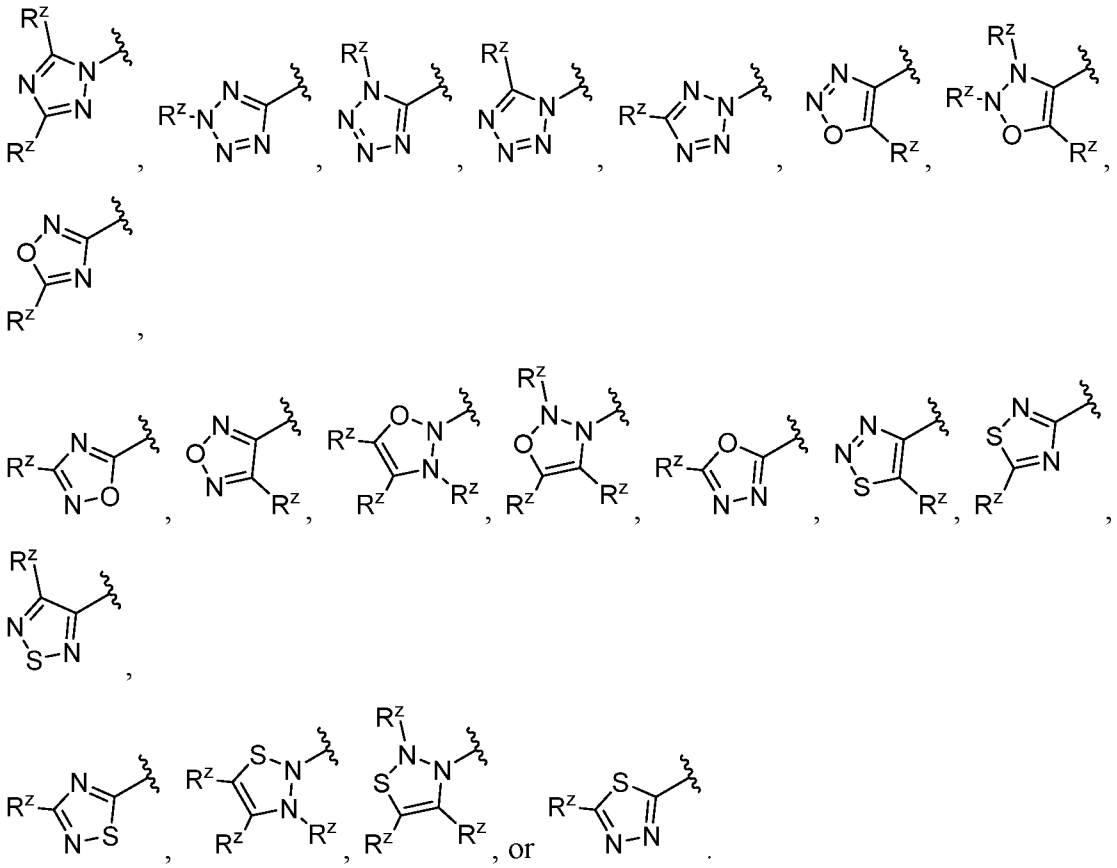
68. The compound, or pharmaceutically acceptable salt thereof, of claims 63 or 64, wherein:



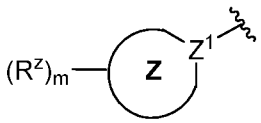
is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or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

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





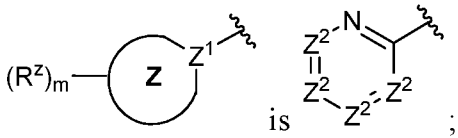
70. The compound, or pharmaceutically acceptable salt thereof, of claim 63, wherein:



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.

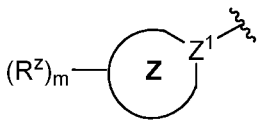
71. The compound, or pharmaceutically acceptable salt thereof, of claims 63 or 70, wherein:



; and

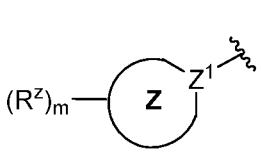
each Z^2 is independently CR^z or N.

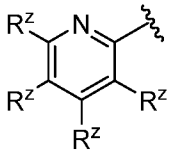
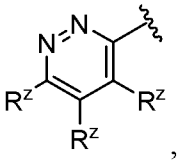
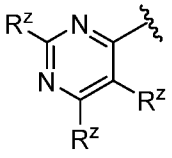
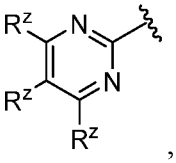
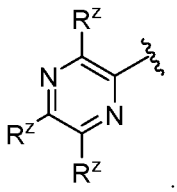
72. The compound, or pharmaceutically acceptable salt thereof, of claims 63 or 70, wherein:



is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

73. The compound, or pharmaceutically acceptable salt thereof, of claim 72, wherein:



is  ,  ,  ,  , or  .

74. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 50-73, wherein:

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

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

each R^z is independently H, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

76. The compound, or pharmaceutically acceptable salt thereof, of claims 74 or 75, wherein:

each R^z is independently H, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl,

tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

77. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 50-73, wherein:

each R^z is $-L^1-Y^1$.

78. The compound, or pharmaceutically acceptable salt thereof, of claim 77, 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.

79. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 50-73, wherein:
each R^z is $-L^2-L^3-Y^2$.

80. The compound, or pharmaceutically acceptable salt thereof, of claim 79, 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.

81. The compound, or pharmaceutically acceptable salt thereof, of claim 79, 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.

82. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 50-81, wherein:

R is $-OR^1$; and

R^1 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

83. The compound, or pharmaceutically acceptable salt thereof, of claim 82, wherein:

R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

84. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 50-81, wherein:

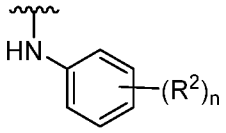
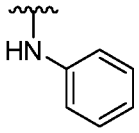
R is $-N(R^1)_2$; and

each R^1 is independently H, $-(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

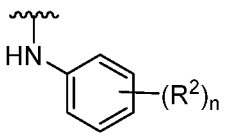
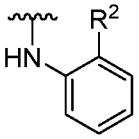
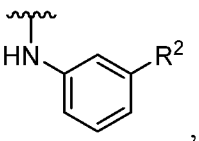
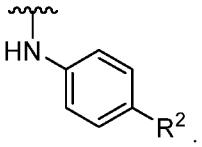
or two R^1 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

85. The compound, or pharmaceutically acceptable salt thereof, of claim 84, wherein:

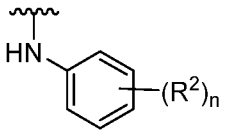
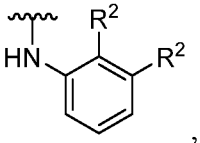
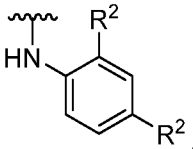
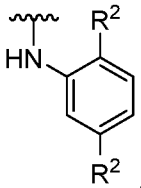
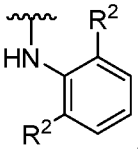
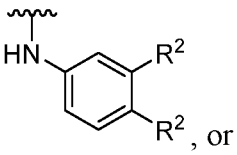
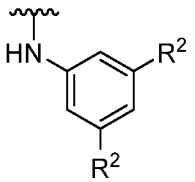
R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

86. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 50-85, wherein:  is  .

87. The compound, or pharmaceutically acceptable salt thereof, of claim 86, wherein:

 is  ,  , or  .

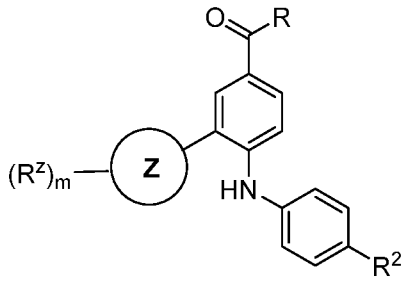
88. The compound, or pharmaceutically acceptable salt thereof, of claim 86, wherein:

 is  ,  ,  ,  ,  , or  .

89. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 50-88, wherein:

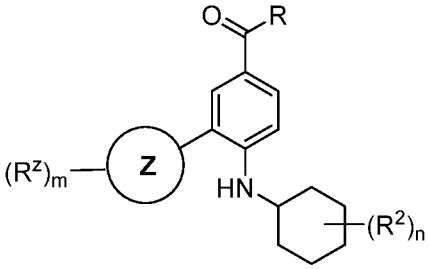
each R^2 is independently H, -F, -I, -Cl, -N_3, -CN, -OR^4, -SR^4, -$(SO_2)R^4$, -$N(R^4)_2$, -CO_2R^4, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted aryl.

90. The compound, or pharmaceutically acceptable salt thereof, of claim 50, wherein the compound has the structure of Formula (IIb), or a pharmaceutically acceptable salt thereof:



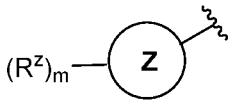
Formula (IIb).

91. A compound of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein,

 is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom or a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom;

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, 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 C_2-C_{10} 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_2-C_{10}cyclolkylene, or substituted or unsubstituted C_2-C_{10}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 H or substituted or unsubstituted C_1-C_6alkyl;

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;

or R^3 and Y^2 on the same N atom are taken together with the N atom to which they are attached to

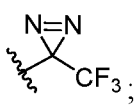
form a substituted or unsubstituted N-containing heterocycle;

R is -OR^1 or -$N(R^1)_2$;

each R^1 is independently H, -$(SO_2)R^4$, 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or two R^1 on the same N atom are taken together with the N atom to which they are attached to form

a substituted or unsubstituted N-containing heterocycle;

each R^2 is independently H, halogen, -N_3, -CN, -OR^4, -SR^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_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 aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or  ;

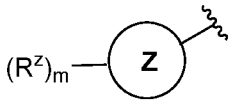
n is 0, 1, 2, 3, 4, or 5; and

each R^4 is independently 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

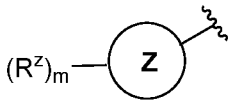
or two R^4 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

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



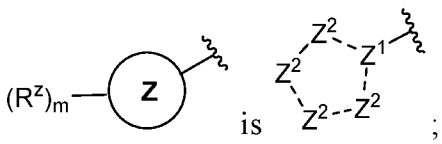
is a substituted or unsubstituted monocyclic 5-membered heterocyclic ring containing at least one N atom.

93. The compound, or pharmaceutically acceptable salt thereof, of claims 91 or 92, wherein:



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

94. The compound, or pharmaceutically acceptable salt thereof, of claims 91 or 92, wherein:



;

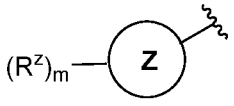
Z^1 is -N-, -CH-, or -C-;

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; and

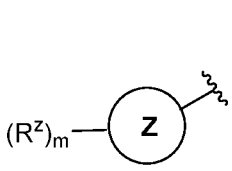
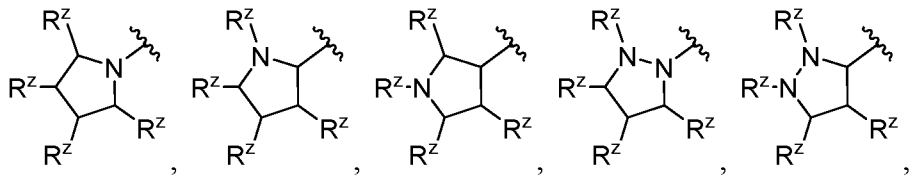
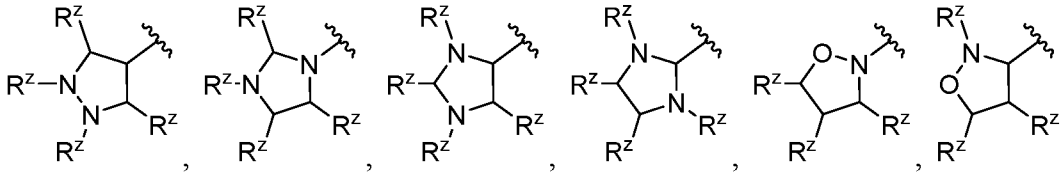
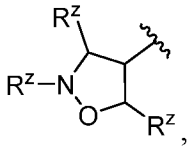
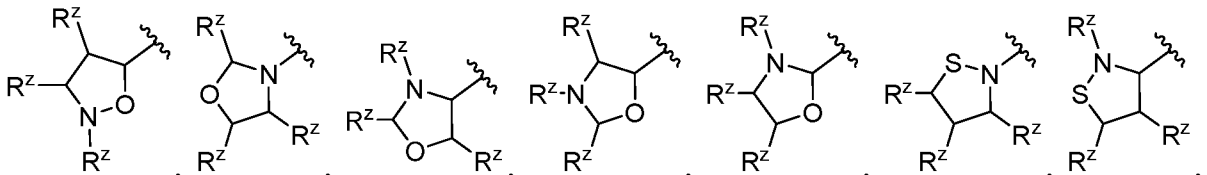
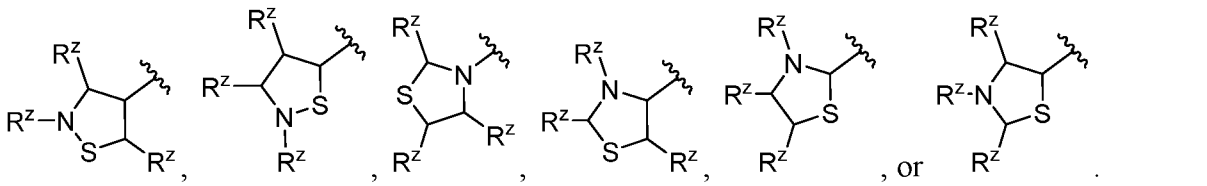
with the provision that the 5-membered heterocyclic ring contains at least one N.

95. The compound, or pharmaceutically acceptable salt thereof, of claims 91 or 92, wherein:

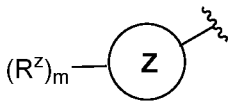


is substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted imidazolidinyl, substituted or unsubstituted pyrazolidinyl, substituted or unsubstituted oxazolidinyl, substituted or unsubstituted isoxazolidinyl, substituted or unsubstituted thiazolidinyl, or substituted or unsubstituted isothiazolidinyl.

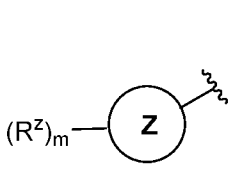
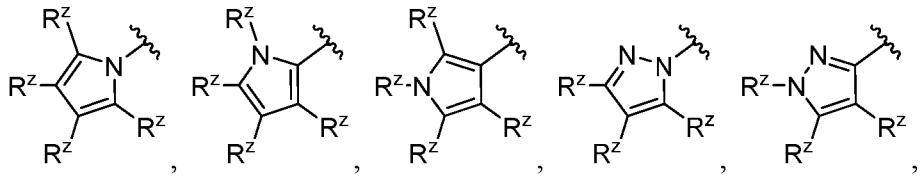
96. The compound, or pharmaceutically acceptable salt thereof, of claim 95, wherein:

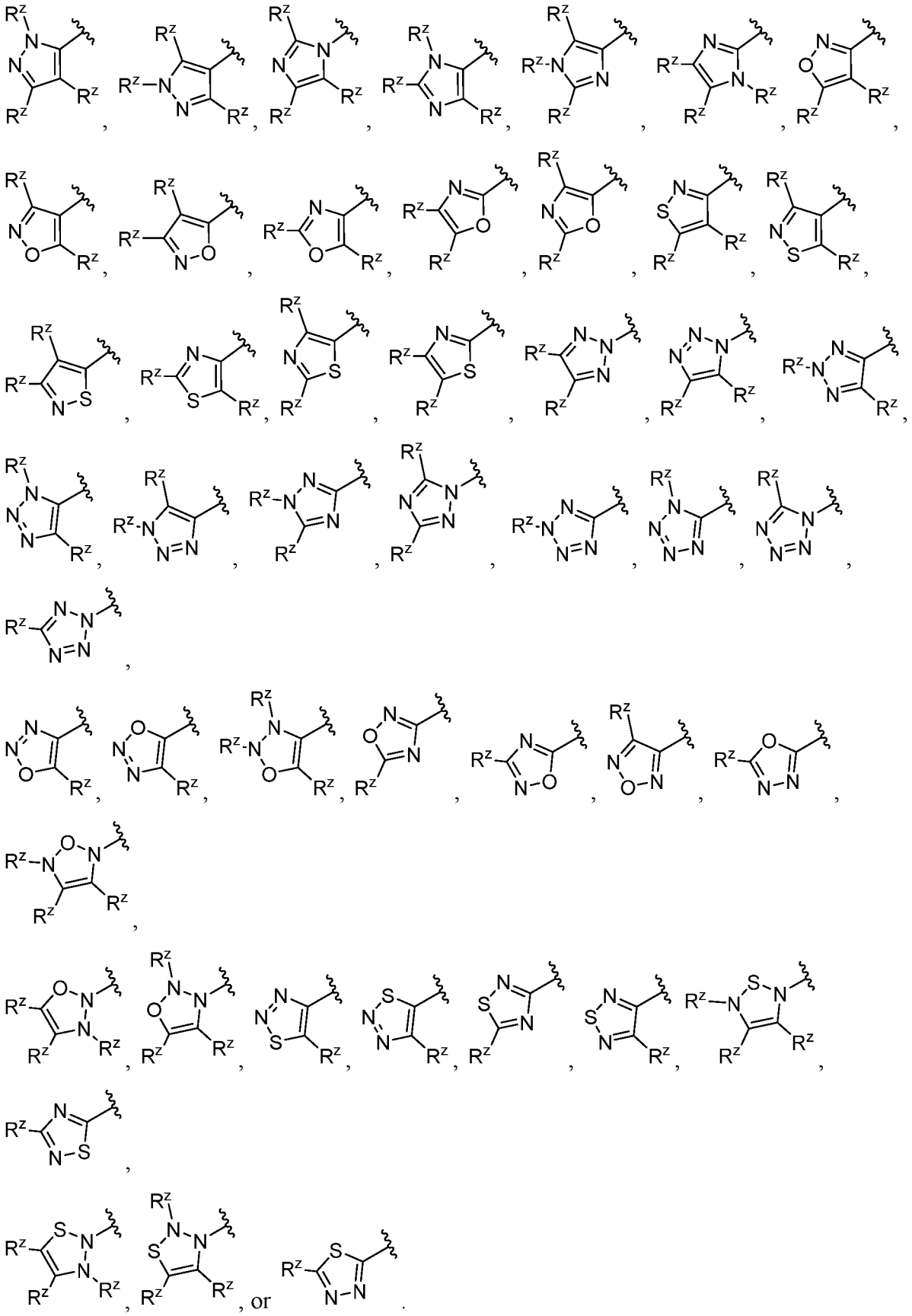

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, or .

97. The compound, or pharmaceutically acceptable salt thereof, of claims 91 or 92, wherein:

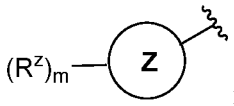

is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or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

98. The compound, or pharmaceutically acceptable salt thereof, of claim 97, wherein:

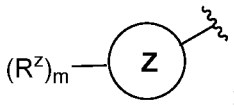

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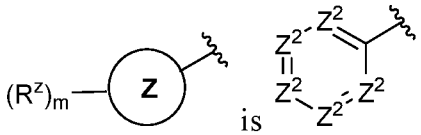
99. The compound, or pharmaceutically acceptable salt thereof, of claim 91, wherein:

 is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom.

100. The compound, or pharmaceutically acceptable salt thereof, of claims 91 or 99, wherein:

 is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing 1 or 2 N atoms.

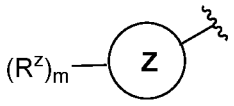
101. The compound, or pharmaceutically acceptable salt thereof, of claims 91 or 99, wherein:

 is ;

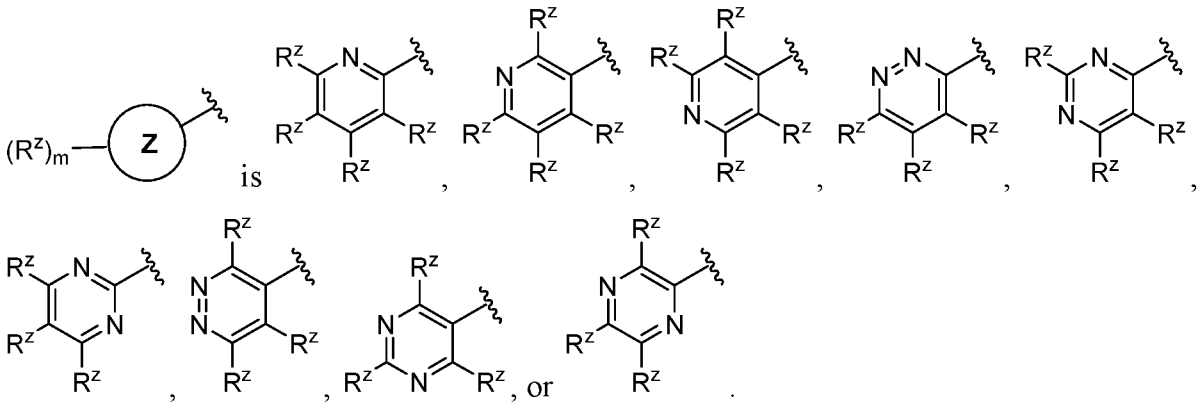
each Z^2 is independently CR^z or N; and

at least one Z^2 is N.

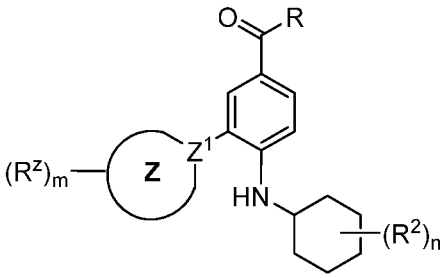
102. The compound, or pharmaceutically acceptable salt thereof, of claims 91 or 99, wherein:

 is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

103. The compound, or pharmaceutically acceptable salt thereof, of claim 102, wherein:



104. The compound, or pharmaceutically acceptable salt thereof, of claim 91, wherein the compound has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof:

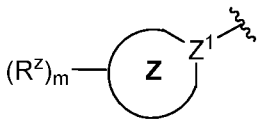


Formula (IIIa)

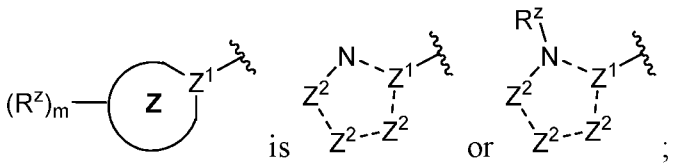
wherein:

Z^1 is -N-, -CH-, or -C-.

105. The compound, or pharmaceutically acceptable salt thereof, of claim 104, 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.

106. The compound, or pharmaceutically acceptable salt thereof, of claims 104 or 105, wherein:

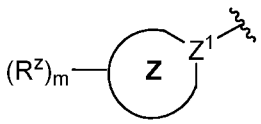
 ;

Z^1 is -N-, -CH-, or -C-;

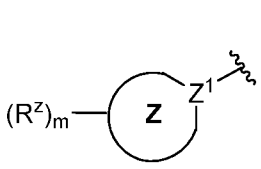
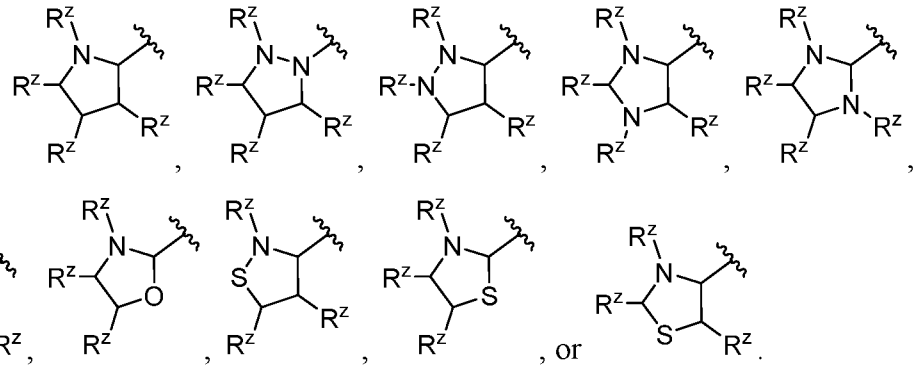
each Z^2 is independently $-CR^z-$, $-CHR^z-$, $-C(R^z)_2-$, $-NR^z-$, -N-, -O-, or -S-; and

each - - is independently a single or double bond.

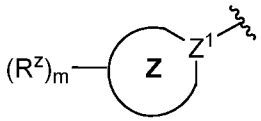
107. The compound, or pharmaceutically acceptable salt thereof, of claims 104 or 105, wherein:

 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.

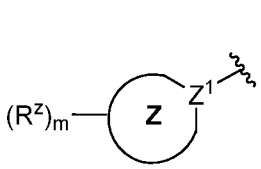
108. The compound, or pharmaceutically acceptable salt thereof, of claim 107, wherein:

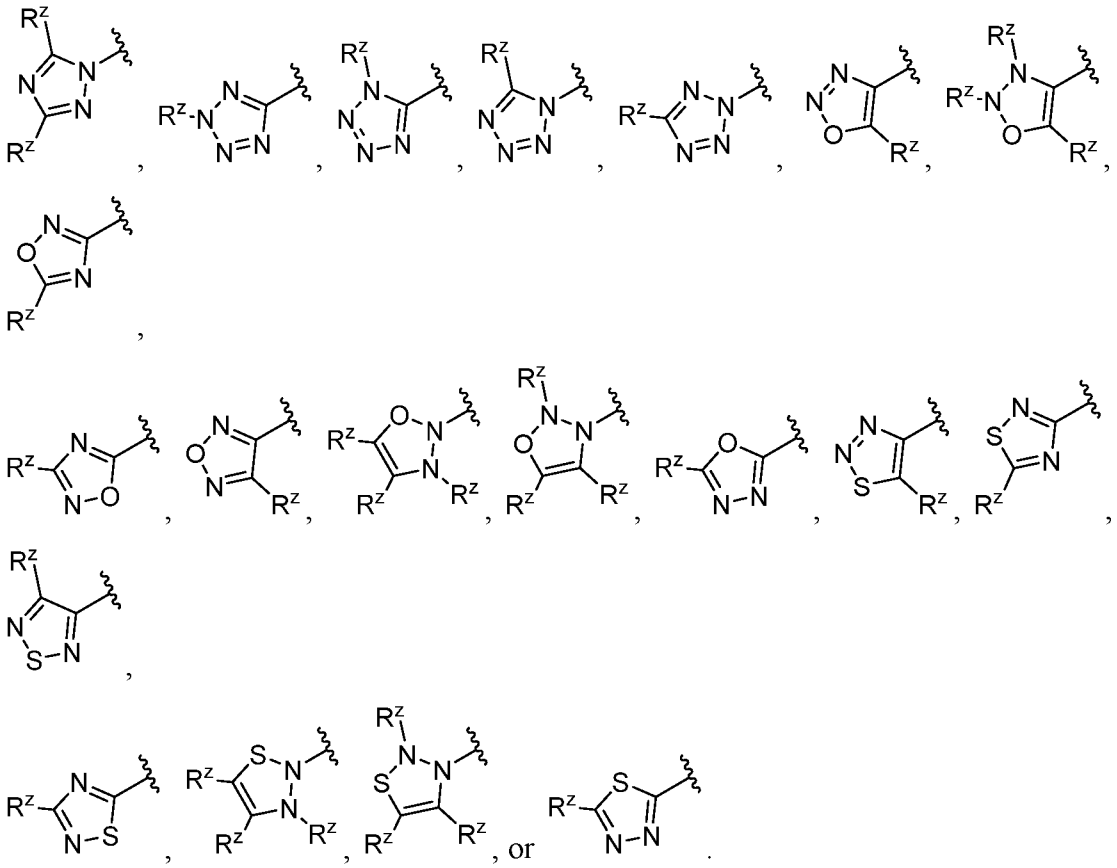

is 

109. The compound, or pharmaceutically acceptable salt thereof, of claims 104 or 105, wherein:

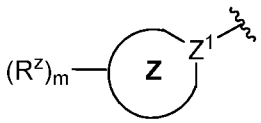

is substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or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

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


is

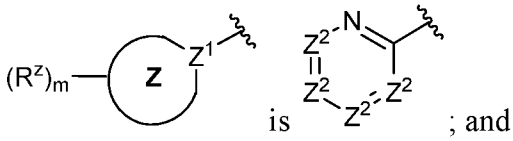


111. The compound, or pharmaceutically acceptable salt thereof, of claim 104, wherein:

 is a substituted or unsubstituted monocyclic 6-membered heteroaryl ring containing at least one N atom, and

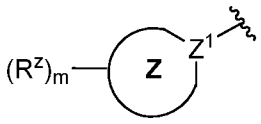
wherein the at least one N atom is adjacent to Z^1.

112. The compound, or pharmaceutically acceptable salt thereof, of claims 104 or 111, wherein:

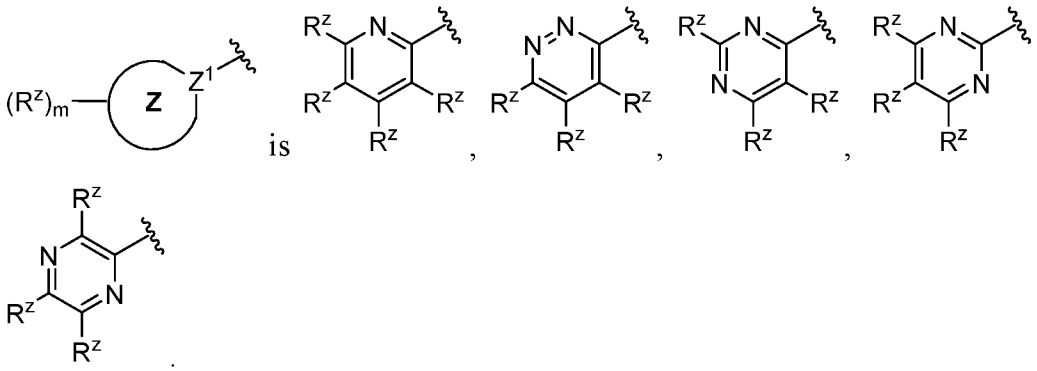
 is ; and

each Z^2 is independently CR^z or N.

113. The compound, or pharmaceutically acceptable salt thereof, of claims 140 or 111, wherein:

 is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted pyridazinyl.

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

 is , , , , or .

115. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 91-114, wherein:

each R^z is independently H, 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 C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

116. The compound, or pharmaceutically acceptable salt thereof, of claim 115, wherein:

each R^z is independently H, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, 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.

117. The compound, or pharmaceutically acceptable salt thereof, of claims 115 or 116, wherein:

each R^z is independently H, -F, -Cl, -Br, -I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl,

tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

118. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 91-114, wherein:
each R^z is $-L^1-Y^1$.

119. The compound, or pharmaceutically acceptable salt thereof, of claim 118, 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.

120. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 91-114, wherein:
each R^z is $-L^2-L^3-Y^2$.

121. The compound, or pharmaceutically acceptable salt thereof, of claim 120, 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.

122. The compound, or pharmaceutically acceptable salt thereof, of claim 120, 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.

123. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 91-122, wherein:

R is $-OR^1$; and

R^1 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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

124. The compound, or pharmaceutically acceptable salt thereof, of claim 123, wherein:

R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or phenyl.

125. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 91-122, wherein:

R is $-N(R^1)_2$; and

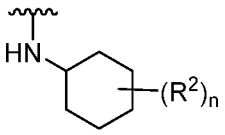
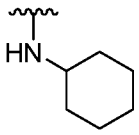
each R^1 is independently H, $-(SO_2)R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6haloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

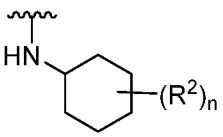
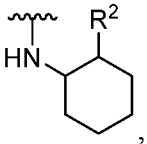
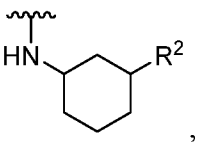
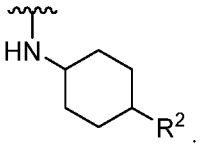
or two R^1 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

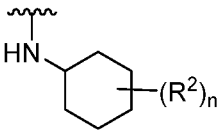
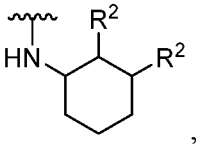
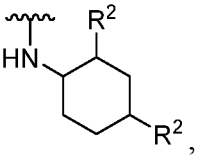
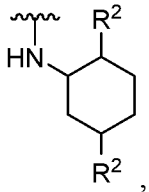
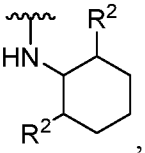
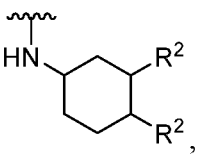
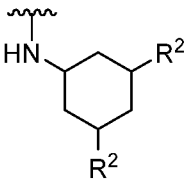
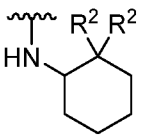
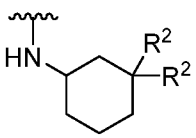
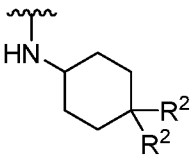
126. The compound, or pharmaceutically acceptable salt thereof, of claim 125, wherein:

R^1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl,

cyclopentyl, cyclohexyl, or phenyl.

127. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 91-126, wherein:  is  .

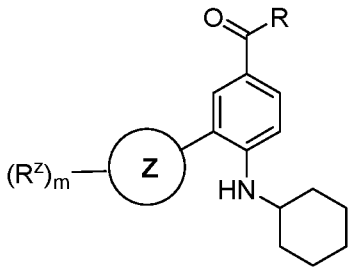
128. The compound, or pharmaceutically acceptable salt thereof, of claim 127, wherein:  is  ,  , or  .

129. The compound, or pharmaceutically acceptable salt thereof, of claim 127, wherein:  is  ,  ,  ,  ,  ,  ,  ,  , or  .

130. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 91-129, wherein:

each R^2 is independently H, halogen, $-N_3$, -CN, $-OR^4$, $-SR^4$, $-(SO_2)R^4$, $-N(R^4)_2$, $-CO_2R^4$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_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 aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

131. The compound, or pharmaceutically acceptable salt thereof, of claim 91, wherein the compound has the structure of Formula (IIIb), or a pharmaceutically acceptable salt thereof:



Formula (IIIb).

132. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-131, wherein the compound exhibits an IC_{50} of no more than about 3.000 μM.

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

134. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of any one of claims 1-131, or a pharmaceutically acceptable salt thereof.

135. A method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound of any one of claims 1-131, or a pharmaceutically acceptable salt thereof.

FIG.1

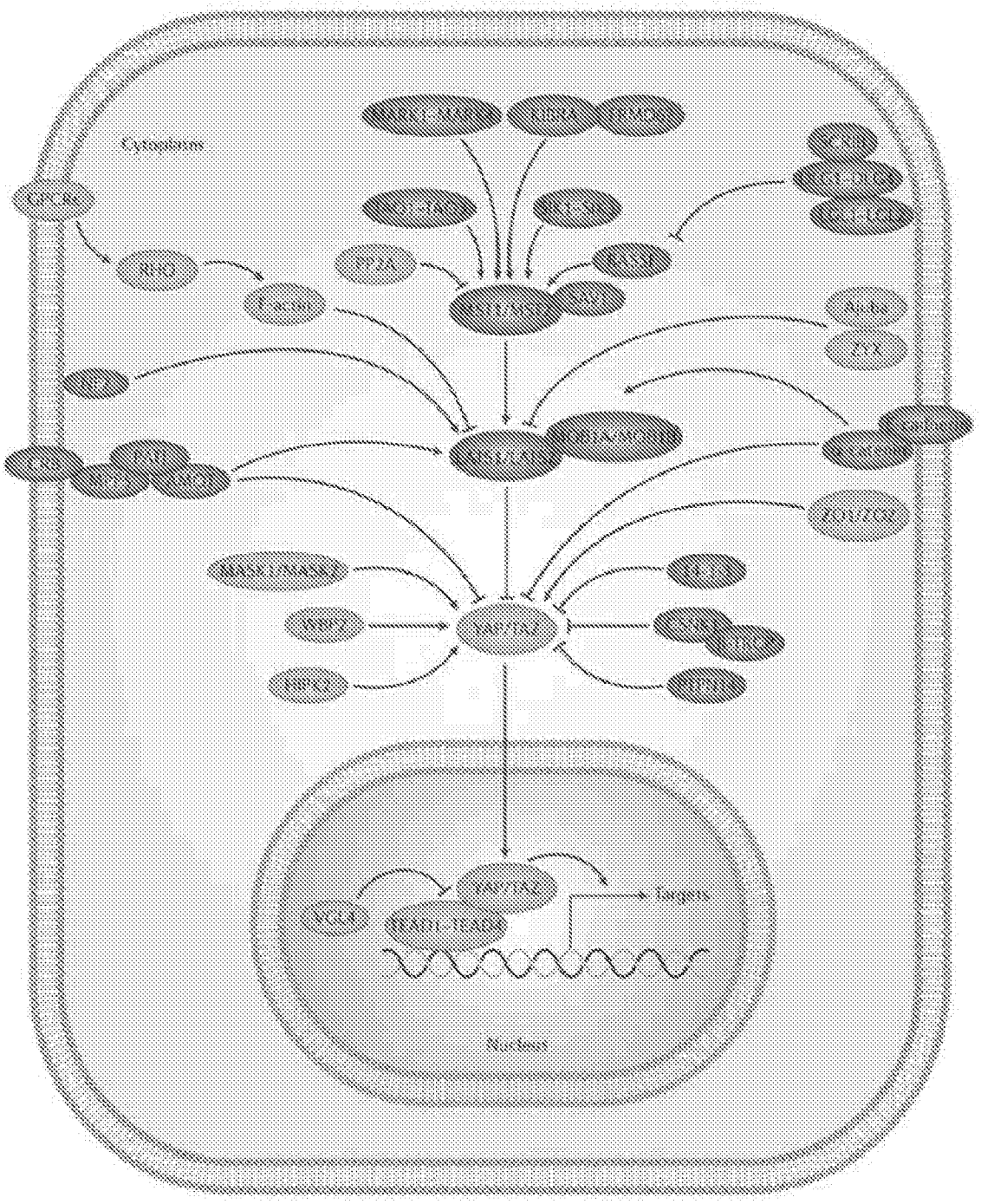
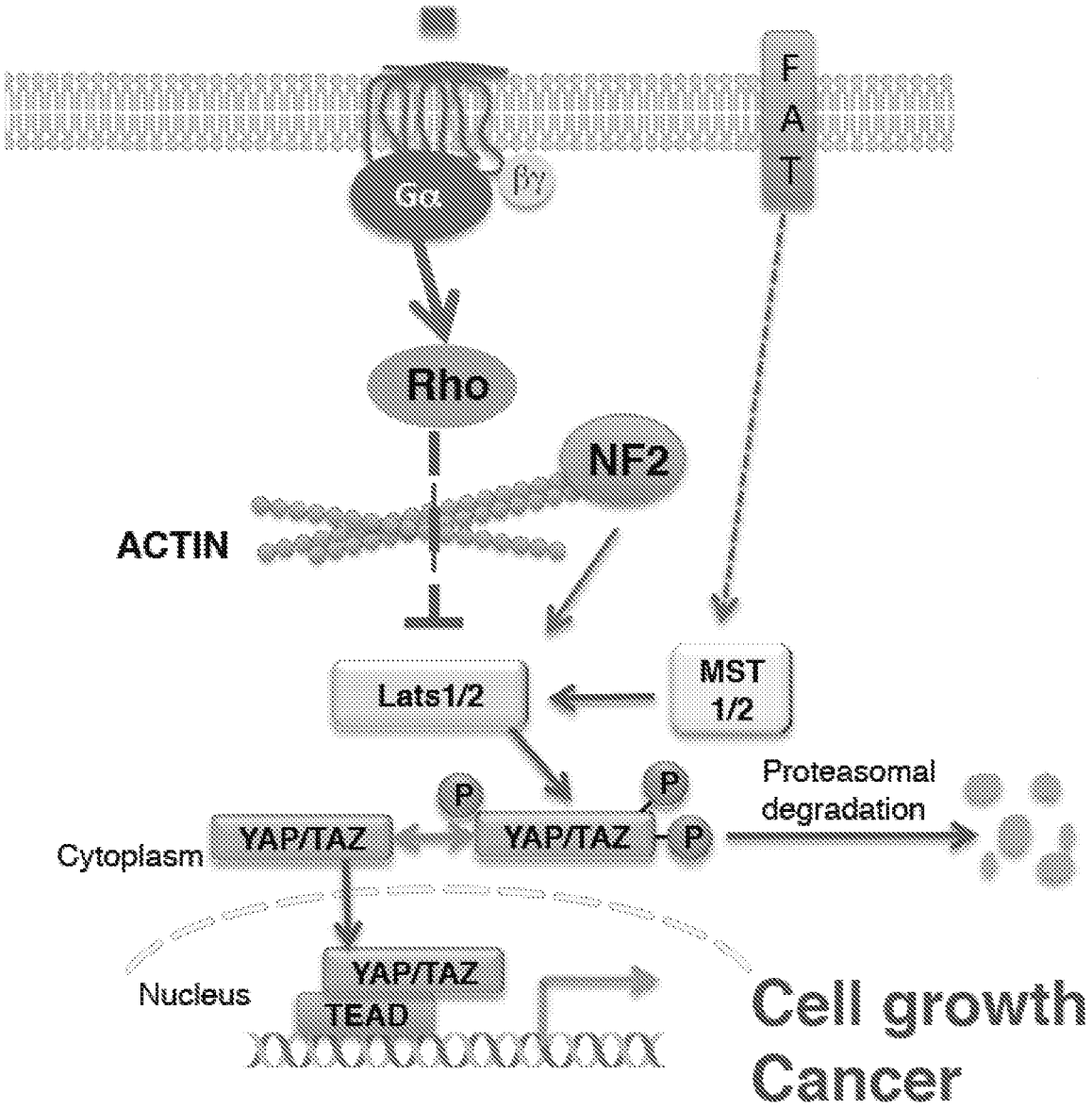


FIG. 2


GPCR
Gα
βγ
F
A
T
Rho
NF2
ACTIN
Lats1/2
MST
1/2
P
P
YAP/TAZ
YAP/TAZ
P
Proteasomal
degradation
Cytoplasm
YAP/TAZ
TEAD
Nucleus
Cell growth
Cancer