AKT3 MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit and priority of U.S. Provisional Application No. 63/021,987, filed on May 8, 2020, and U.S. Provisional Application No. 63/121,001, filed on December 3, 2020, the contents of each of which are incorporated herein by reference in their entireties.

INCORPORATION BY REFERENCE

[0002] Any patent, patent publication, journal publication, or other document cited herein is expressly incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] This invention is generally related to Akt3 modulators and methods for treating and preventing diseases by modulating Akt3 signaling.

BACKGROUND OF THE INVENTION

[0004] Chronic illnesses and diseases are long-lasting conditions that require ongoing medical attention and typically negatively affect the patient's quality of life. Chronic diseases are a leading cause of disability and death in the U.S. Common chronic diseases include, but are not limited to, heart disease, cancer, neurodegenerative diseases, diabetes, obesity, eating disorders, and arthritis. It is estimated that roughly 6 in 10 adults in the U.S. have a chronic disease, with 4 in 10 having two or more chronic diseases. Chronic diseases are also a leading driver of the U.S.'s $3.3 trillion annual health care costs (*see* "About Chronic Diseases", National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention; updated October 23, 2019). These statistics emphasize the need for new and improved treatments and prophylactic interventions for diseases such as, for example, cancer, inflammatory disease, neurodegenerative disease, pathogenic infection, immunodeficiency disorder, weight gain disorder, weight loss disorder, hormone imbalance, tuberous sclerosis, retinitis pigmentosa, and congestive heart failure.

[0005] Neurodegenerative diseases are debilitating conditions that are characterized by the progressive degeneration and death of nerve cells, also called neurons. Neurons are the building blocks of the nervous system and do not usually self-replenish following damage or

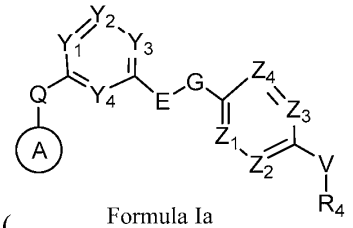
death. The loss or dysfunction of neurons in patients with neurodegenerative disease can affect body movement and brain function. Neurodegenerative diseases include, but are not limited, to Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, multiple sclerosis, prion disease, motor neuron disease, spinocerebellar ataxia, and spinal muscular atrophy. The symptoms of advanced neurodegenerative diseases can be devastating, with patients losing memory, control over movements, and personality. Existing treatments for neurodegenerative diseases can manage symptoms but generally cannot prevent or cure the disease. Such existing treatments typically have negative side effects which lead to further deterioration of patient quality of life.

[0006] A serious complication of chronic diseases such as neurodegenerative diseases and cancer is cachexia, or wasting syndrome. Cachexia is defined as weight loss greater than 5% of body weight in 12 months or less in the presence of chronic illness. Other symptoms of cachexia include muscle atrophy, fatigue, weakness, and, often, loss of appetite. The weight loss associated with cachexia is due to the loss of not only fat but also muscle mass. Patients with cachexia often lose weight even if they are still eating a normal diet. Like neurodegenerative diseases, there are currently no effective treatments for cachexia, which contributes to a large number of chronic disease-related deaths.

[0007] Thus, there is an unmet need for more effective and tolerable treatments and prophylactic interventions for these and other diseases and complications associated with the diseases.

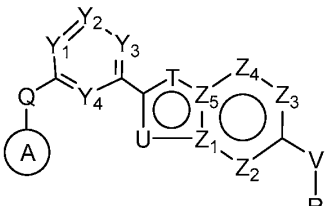
SUMMARY OF THE INVENTION

[0008] As used herein, Akt3 is RAC-gamma serine/threonine-protein kinase, which is an enzyme that, in humans, is encoded by the *Akt3* gene. In one aspect, a compound having a structure of Formula Ia, Ib, or Ic (

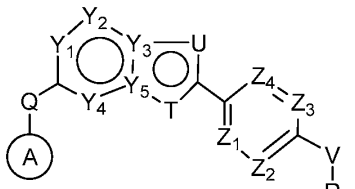


Formula Ia

,

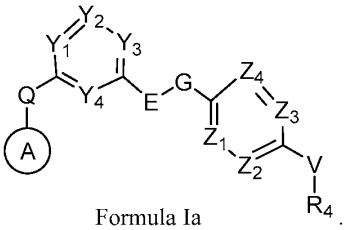

Formula Ib

, or


Formula Ic

), or a salt thereof, is described, where the various substituents are defined herein. In certain embodiments, the compound can modulate a property or effect of Akt3 *in vitro* or *in vivo*, and/or can also be used, individually or in combination with other agents, in the prevention or treatment of a variety of conditions. In other embodiments, methods for synthesizing the compounds are provided. In another aspect, pharmaceutical compositions including the compound and methods of using these compositions, individually or in combination with other agents or compositions, in the prevention or treatment of a variety of conditions are also described herein.

[0009] In one aspect, a compound of Formula Ia, Ib, or Ic,


Formula Ia

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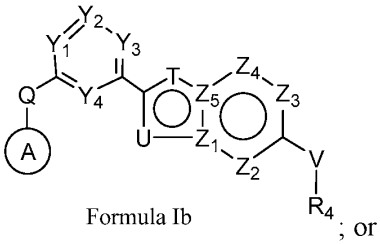
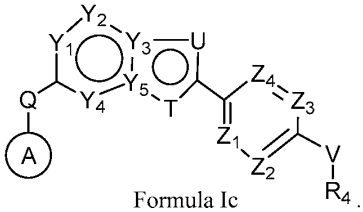

Formula Ib

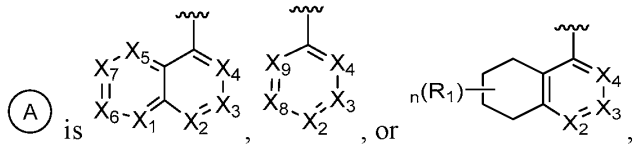
; or


Formula Ic

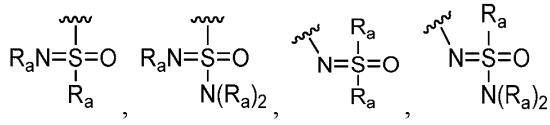
;

or a pharmaceutically acceptable salt thereof is described,

where:


is , , or ,

each occurrence of X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, and X_9 are independently CR_1 or N;

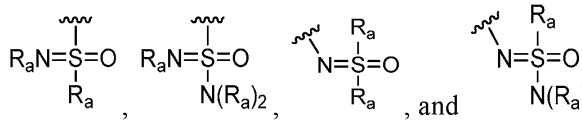
R_1 is selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, halogenated (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_4-C_{10})heterospiroalkyl, aryl, heteroaryl, –OR_a, –SR_a, –$N(R_a)_2$, –COR_a, –CO_2R_a, $CON(R_a)_2$, –CN, –NC, NO_2, N_3, –SO_2R_a, –$SO_2N(R_a)_2$, –$N(R_a)SO_2R_a$,  , and a partially saturated bicyclic heteroaryl optionally substituted by one or more (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, –SO_2R_a, or –$SO_2N(R_a)_2$;

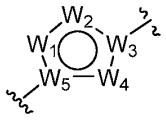
wherein the (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_4-C_{10})heterospiroalkyl, aryl, and heteroaryl of R_1 are each optionally substituted by one or more (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, –OR_a, –CN, or –$N(R_a)_2$;

n is an integer from 0-4 where valence permits;

Q is $C(R_a)_2$, O, NR_a, $N(C=O)R_a$, or NSO_2R_a;

Y_1, Y_2, Y_3, Y_4 and Y_5 are each independently N or CR_2 where valance permits;

R_2 is selected from the group consisting of H, halogen, D, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, halogenated (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_4-C_{10})heterospiroalkyl, aryl, heteroaryl, –OR_a, –SR_a, –$N(R_a)_2$, –COR_a, –CO_2R_a, $CON(R_a)_2$, –CN, –NC, NO_2, N_3, –SO_2R_a, –$SO_2N(R_a)_2$, –$N(R_a)SO_2R_a$,  , and ;

–E-G– is –(C=O)NR_x–, –NR_x(C=O)–, –$N(R_x)$(C=O)$N(R_x)$–, –O(C=O)$N(R_x)$–, –$N(R_x)$(C=O)O–, –SO_2NR_x–, –NR_xSO_2–, or  ; where;

each occurrence of R_x is independently H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, or heteroaryl; or wherein R_x and Y_3, R_x and Y_4, R_x and Z_1, or R_x and Z_4 taken together form an optionally substituted 5-6-membered heterocycle;

W_1, W_2, W_3, W_4, and W_5 are each independently CR_6, N, or NR_6 where valence permits;

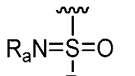
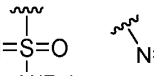
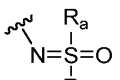
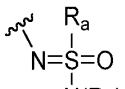
each occurrence of R_6 is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$haloalkyl;

each occurrence of T is independently O, N, NR_a, $N(C{=}O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits;

each occurrence of U is independently O, N, NR_a, $N(C{=}O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits;

each occurrence of R_b is independently H or $(C_1\text{-}C_6)$alkyl;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently N or CR_3 where valance permits;

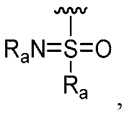
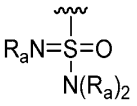
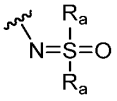
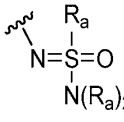
R_3 is selected from the group consisting of H, D, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$haloalkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$haloalkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$,  ,  ,  , and  ;

V is absent, $C(R_a)_2$, NR_a, $N(C{=}O)R_a$, NSO_2R_a or O;

R_4 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, aryl, and heteroaryl, each optionally substituted with one or more R_5;

or alternatively V and R_4 taken together form a $(C_3\text{-}C_7)$heterocycloalkyl or $(C_4\text{-}C_{10})$heterospiroalkyl;

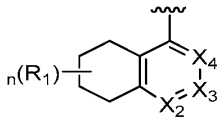
each occurrence of R_5 is independently selected from the group consisting of H, D, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$haloalkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$haloalkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, –

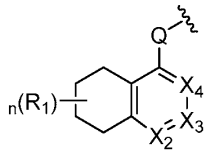
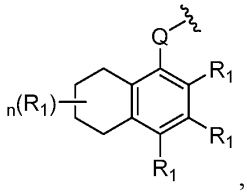
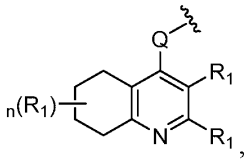
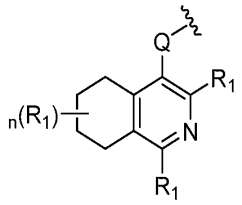
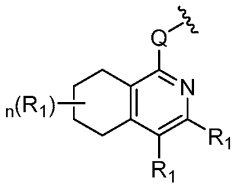
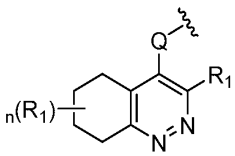
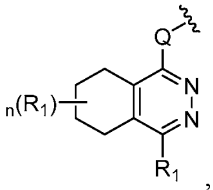
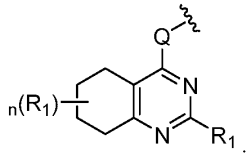
SO_2R_a, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$, $N(R_a)COR_a$,  ,  ,  , and  ; and

each occurrence of R_a is independently H, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, or heteroaryl, or two R_a taken together form a 4-6-membered ring optionally substituted with halogen or $(C_1\text{-}C_6)$alkyl.

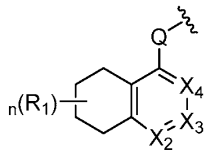
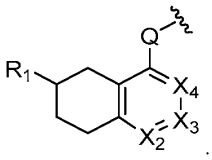
[0010] In any one of the embodiments disclosed herein, Q, T, and U are each independently O, NH, NCH_3, N(C=O)H, $N(C=O)CH_3$, $N(C=O)CH_2CH_3$, NSO_2CH_3, or $NSO_2CH_2CH_3$.

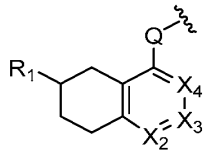
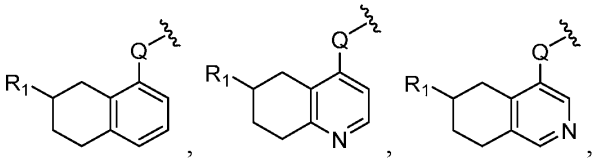
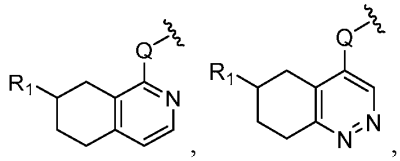
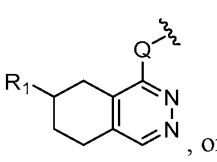
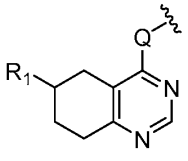
[0011] In any one of the embodiments disclosed herein, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, Y_1, Y_2, Y_3, Y_4, Y_5, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CH or N.

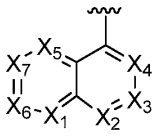
[0012] In any one of the embodiments disclosed herein, is  .

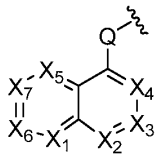
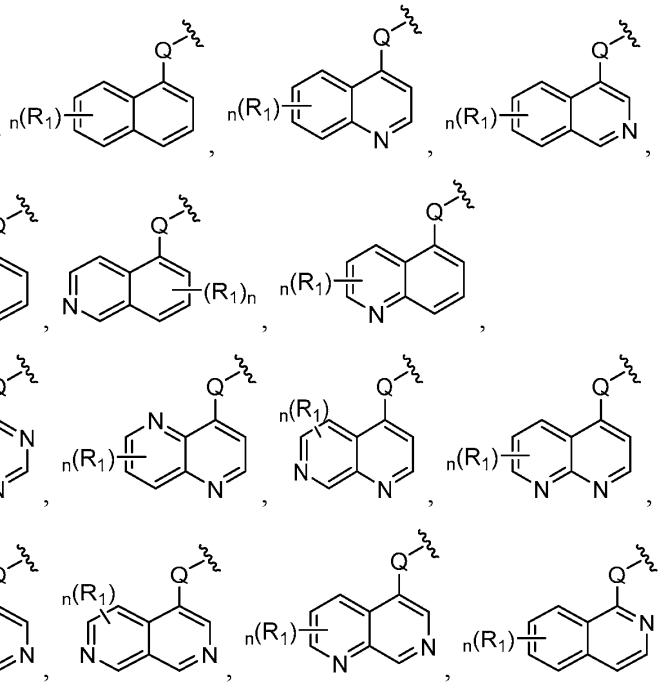
[0013] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or  .

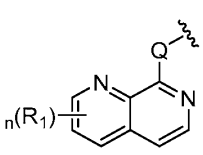
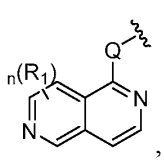
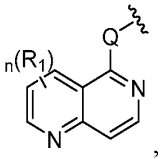
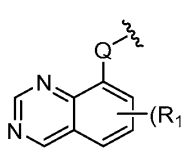
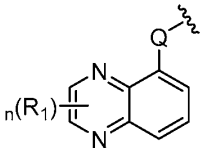
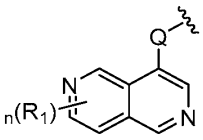
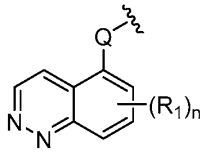
[0014] In any one of the embodiments disclosed herein, n is 0, 1, or 2.

[0015] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

[0016] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  , or  .

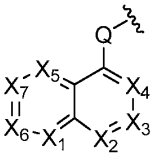
[0017] In any one of the embodiments disclosed herein, Ⓐ is  .

[0018] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

[0019] In any one of the embodiments disclosed herein, n is 0, 1, or 2.

[0020] In any one of the embodiments disclosed herein, the structural moiety



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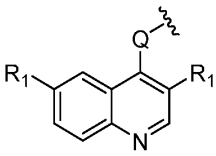
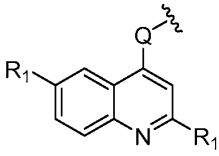
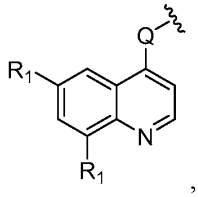
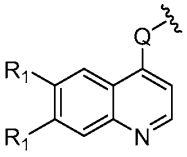
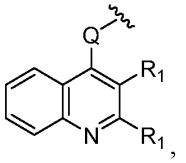
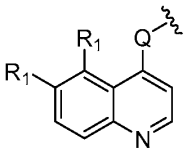
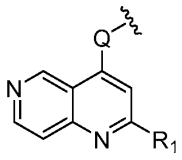
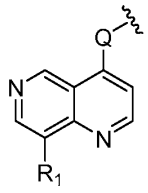
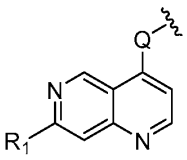
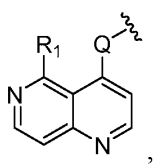
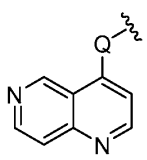
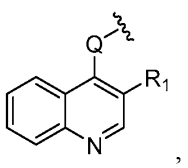
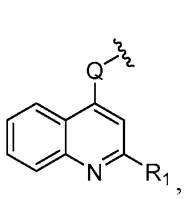
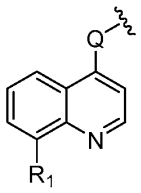
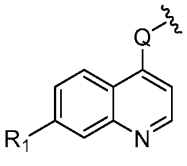
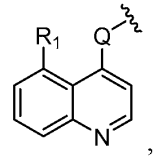
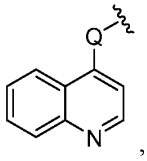
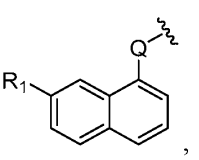
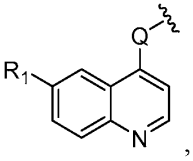

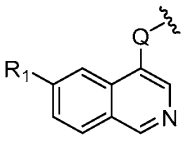
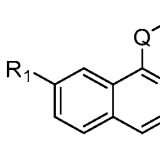
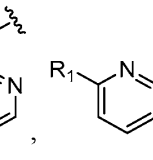
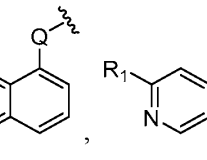
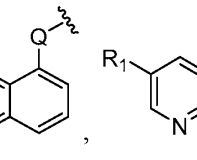
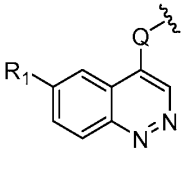
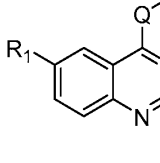
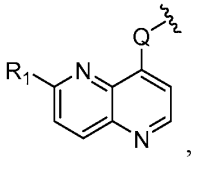
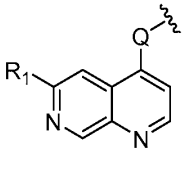
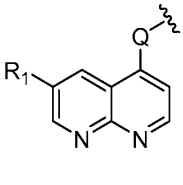

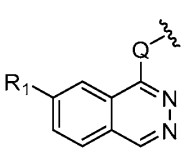
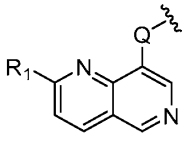
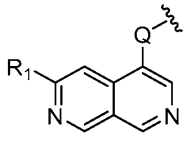
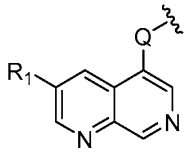
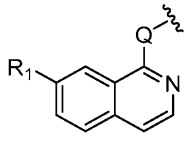
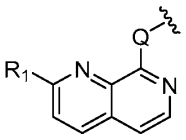
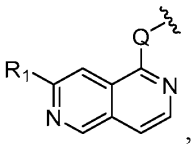
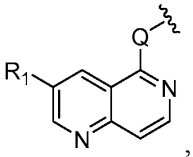
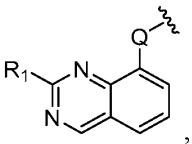
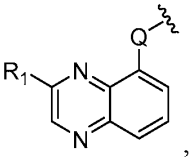
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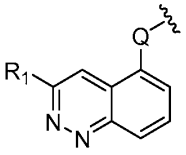
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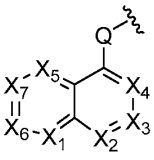
[0021] In any one of the embodiments disclosed herein, the structural moiety

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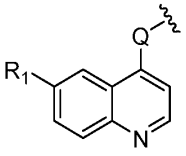
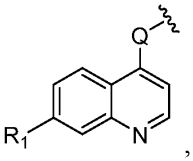
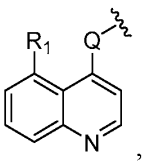
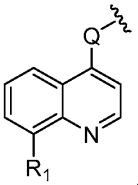
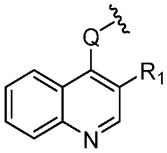
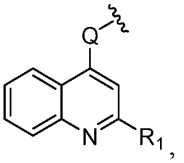
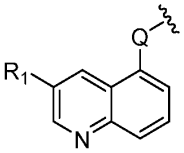
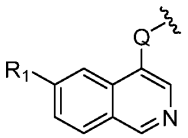
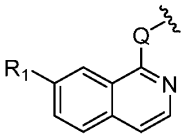
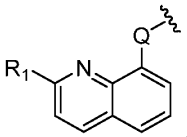
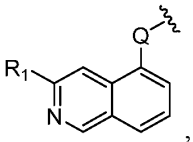
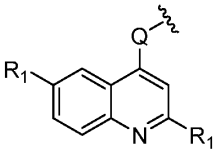
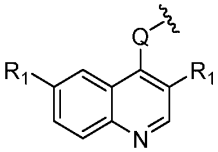
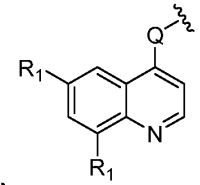
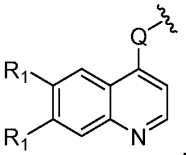
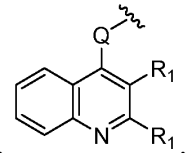
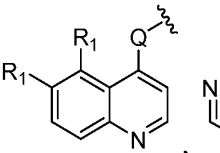
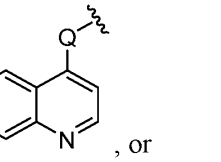
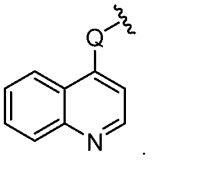

, or

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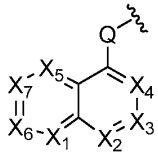
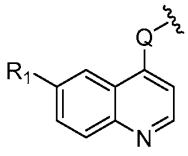
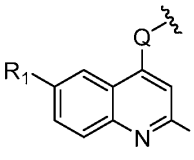
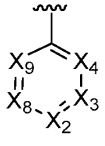
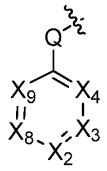
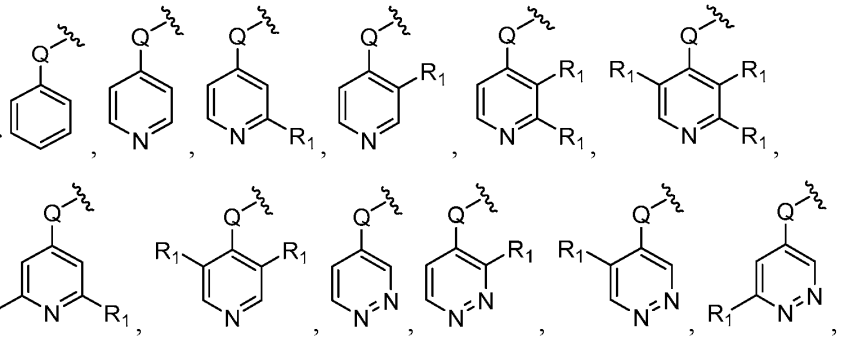
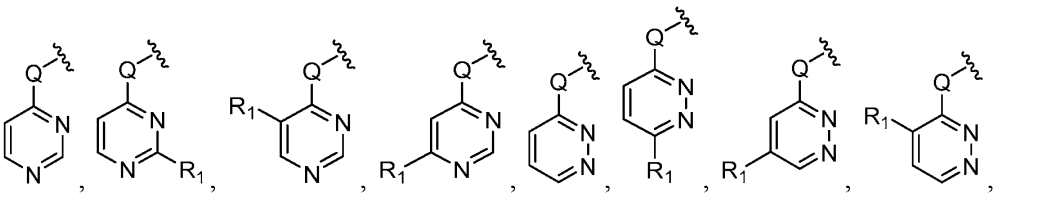
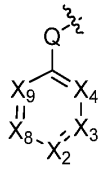
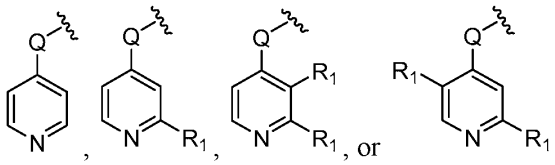
[0022] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  or  .

[0023] In any one of the embodiments disclosed herein, is  .

[0024] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  , ,  ,  , , or .

[0025] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

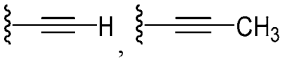
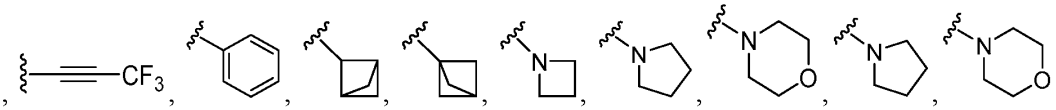
[0026] In any one of the embodiments disclosed herein, Q is O.

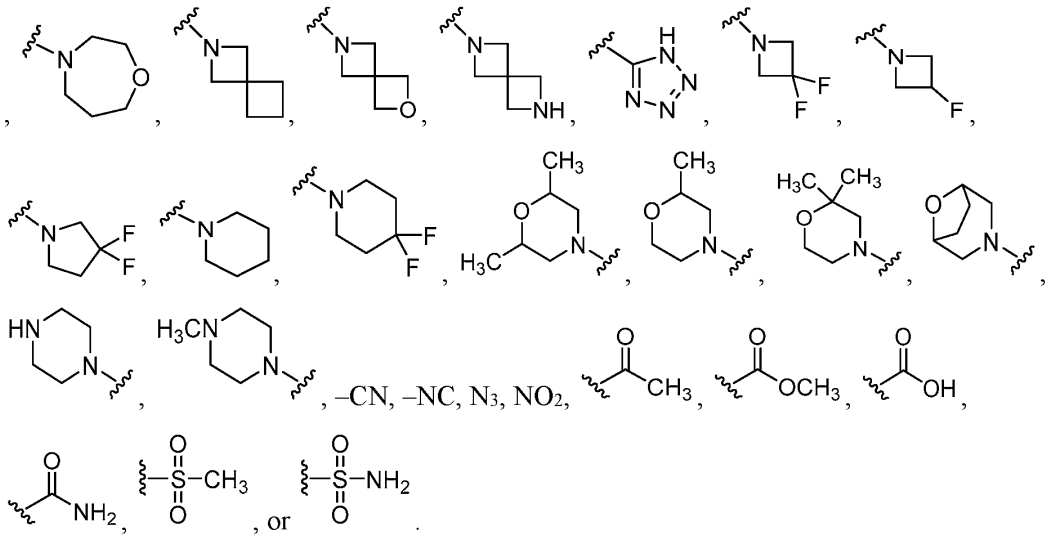
[0027] In any one of the embodiments disclosed herein, Q is NR_a, $N(C{=}O)R_a$, or NSO_2R_a.

[0028] In any one of the embodiments disclosed herein, each occurrence of R_1 is independently H, D, halogen, OR_a, $N(R_a)_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, aryl, $(C_4\text{-}C_{10})$bicycloalkyl, –CN, –NC, N_3, NO_2, COR_a, CO_2R_a, $CON(R_a)_2$, $–SO_2R_a$, or $–SO_2N(R_a)_2$; wherein the $(C_3\text{-}C_7)$heterocycloalkyl is optionally substituted with one or more $(C_1\text{-}C_6)$alkyl.

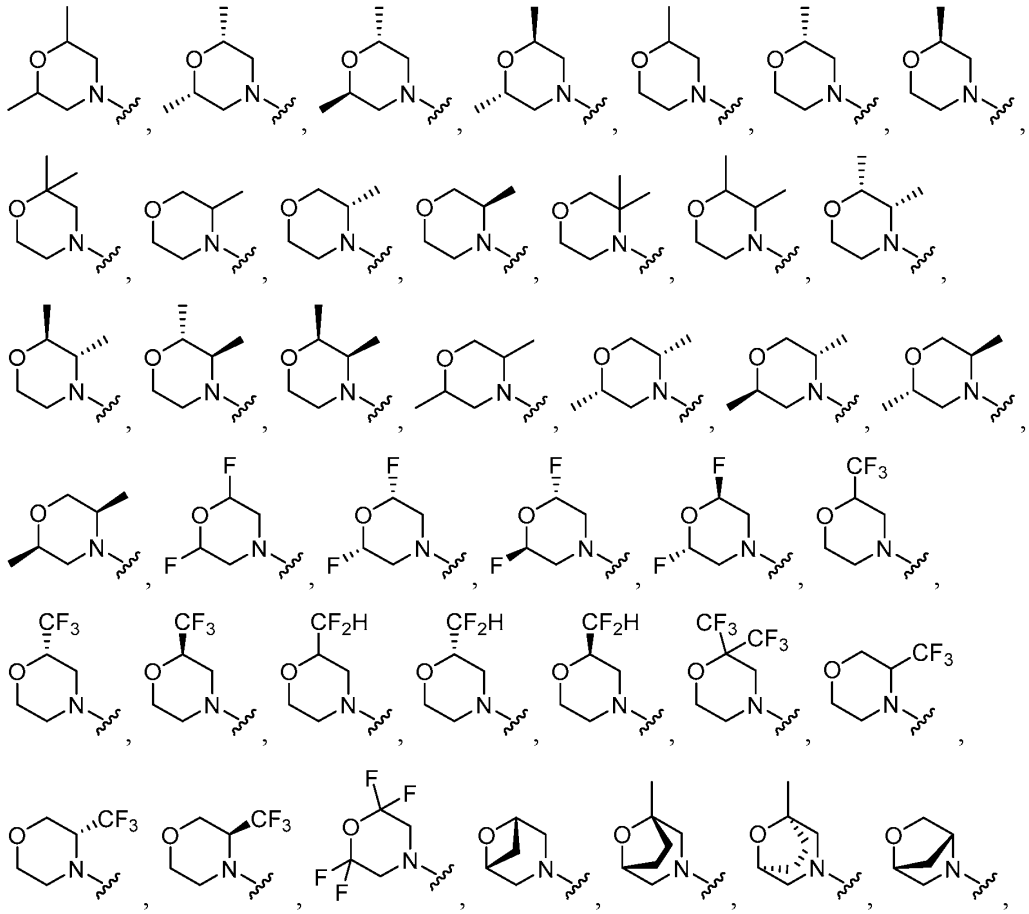
[0029] In any one of the embodiments disclosed herein, each occurrence of R_1 is independently H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $N(R_a)_2$, or –CN; wherein the $(C_3\text{-}C_7)$heterocycloalkyl is optionally substituted with one or more $(C_1\text{-}C_6)$alkyl.

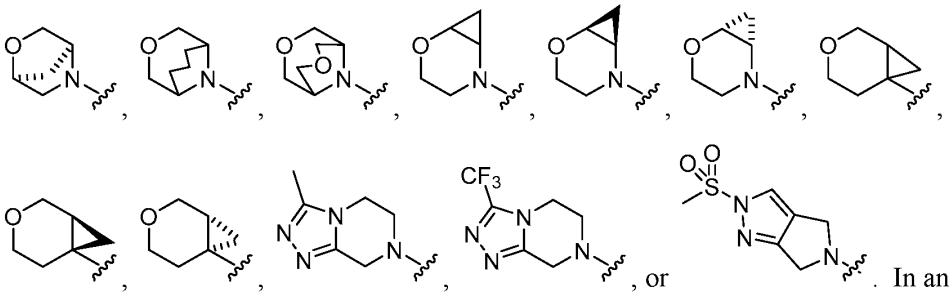
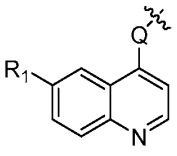
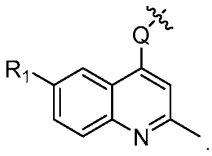
[0030] In any one of the embodiments disclosed herein, each occurrence of R_1 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, or $(C_3\text{-}C_7)$heterocycloalkyl; wherein the $(C_3\text{-}C_7)$heterocycloalkyl is optionally substituted with one or more $(C_1\text{-}C_6)$alkyl.

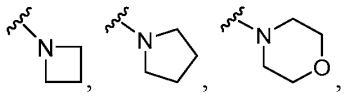
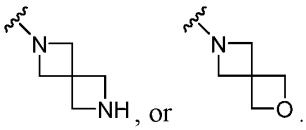
[0031] In any one of the embodiments disclosed herein, each occurrence of R_1 is independently H, D, F, Cl, Br, CH_3, OCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$,  ,  .

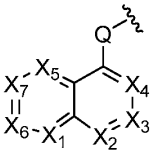
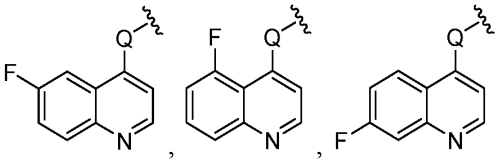
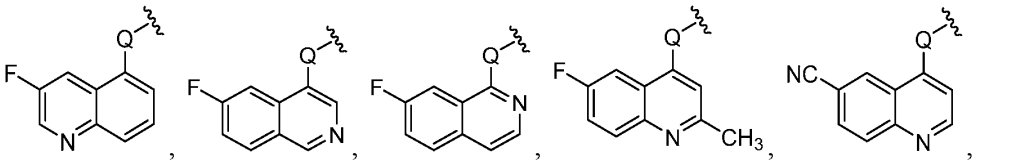
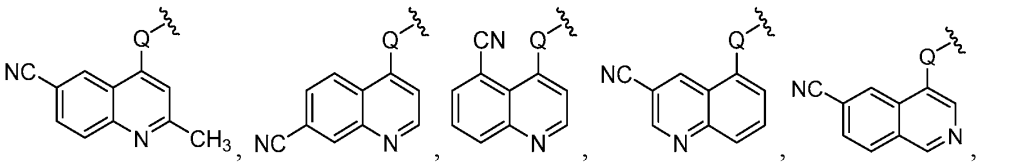
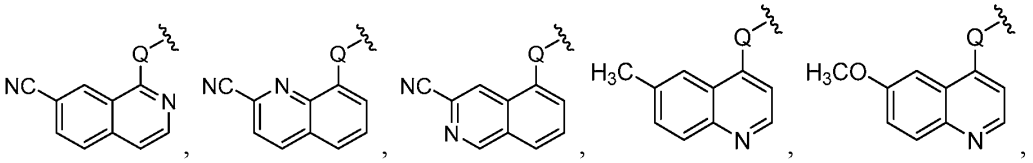


[0032] In any one of the embodiments disclosed herein, at least one occurrence of R_1 is




, or . In any one of the embodiments disclosed herein, Ⓐ is  or  .

[0033] In any one of the embodiments disclosed herein, each occurrence of R_1 is independently H, D, F, CH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, 
, or  .

[0034] In any one of the embodiments disclosed herein, the structural moiety  has the structure of 
, 
, 
, 
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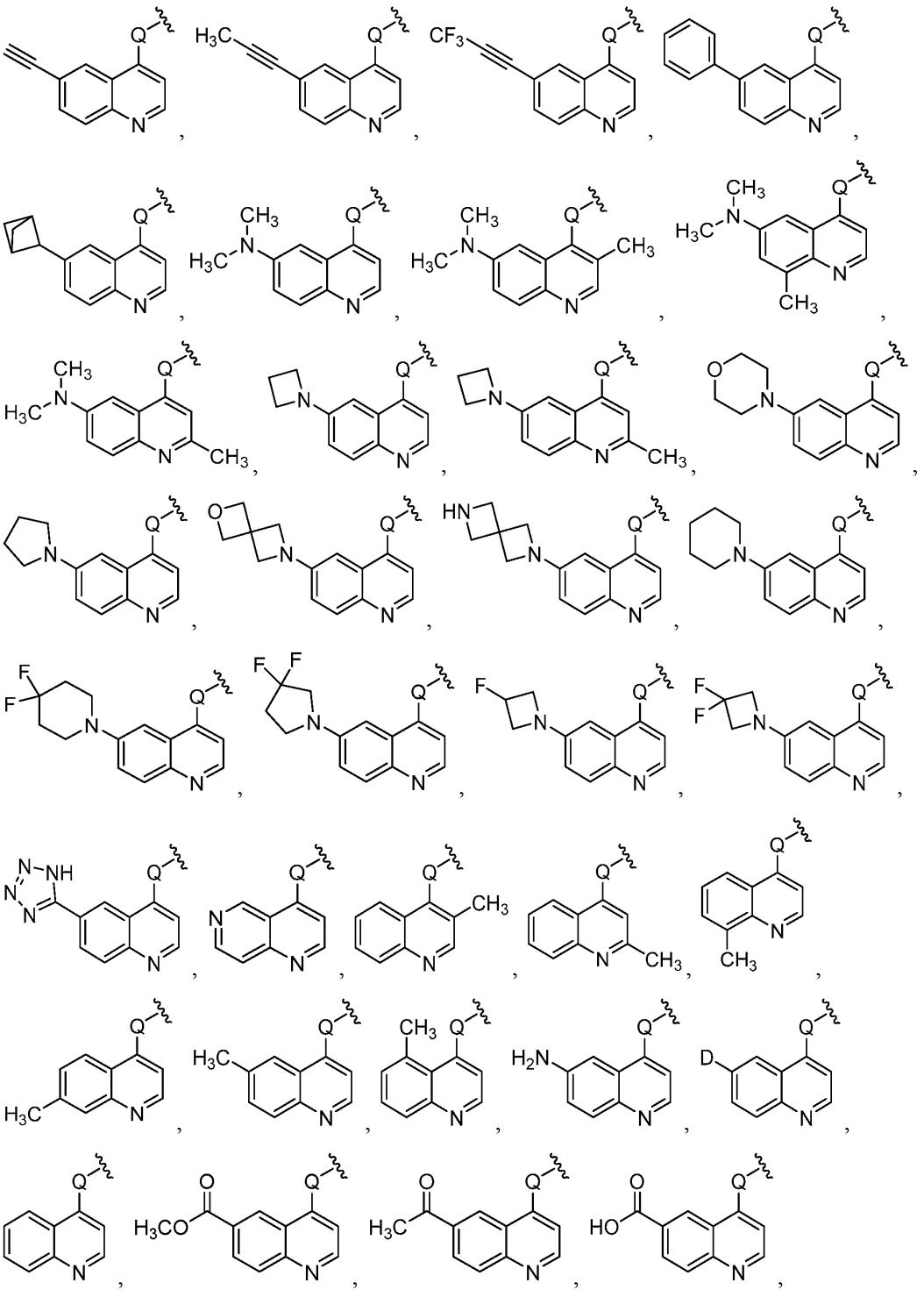
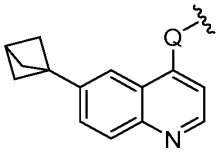
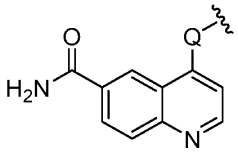
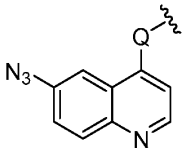
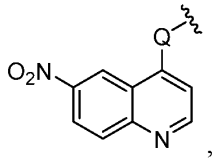
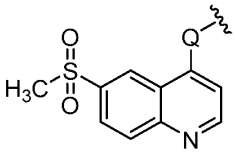
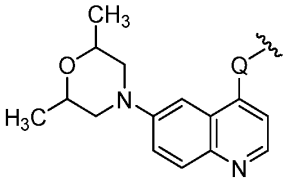
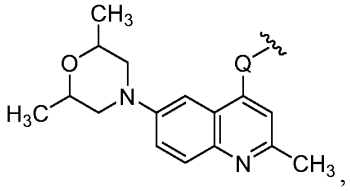
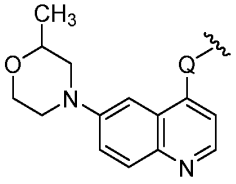
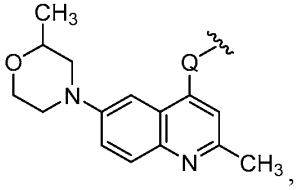
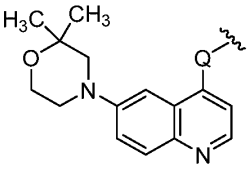
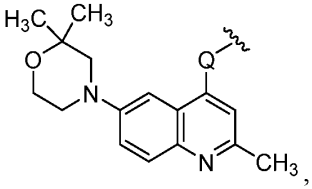
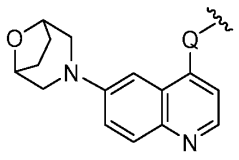
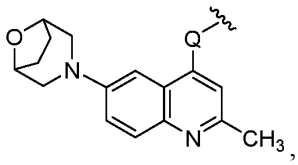
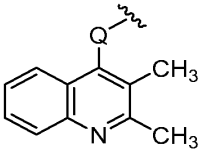
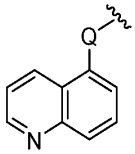
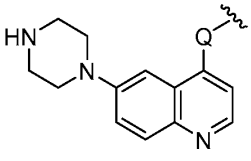
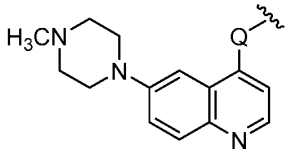


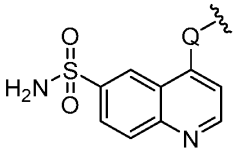
 ,  ,  ,  ,

 ,  ,  ,

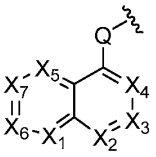
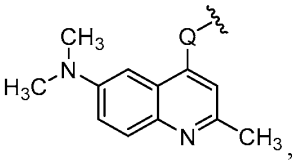
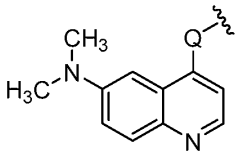
 ,  ,  ,

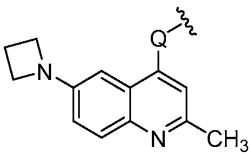
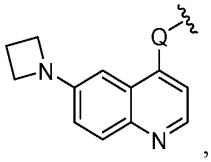
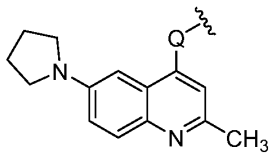
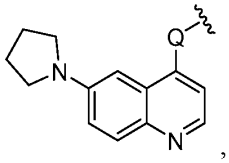
 ,  ,  ,

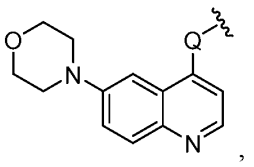
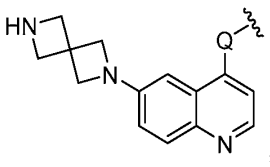
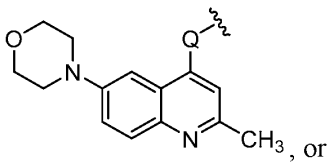
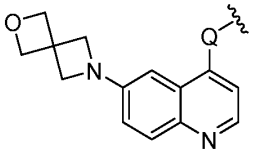
 ,  ,  ,  , or

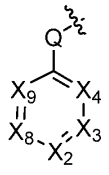
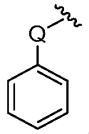
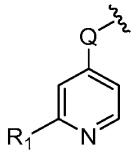
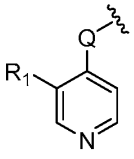
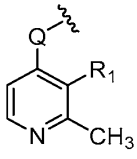
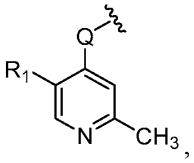
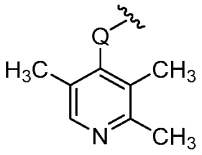
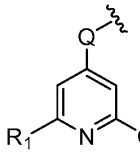
 , where Q is O or NH.

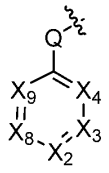
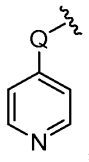
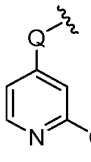
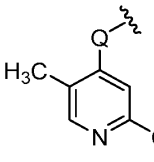
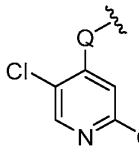
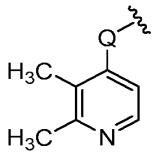
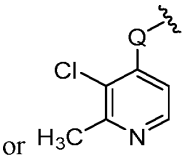
[0035] In any one of the embodiments disclosed herein, the structural moiety

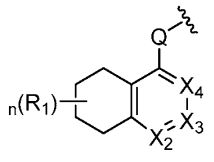
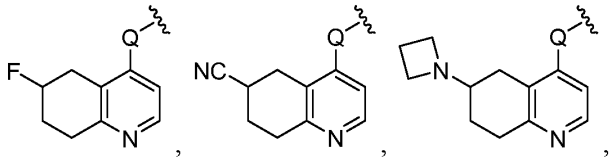
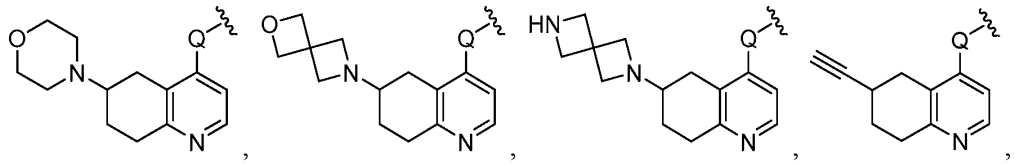
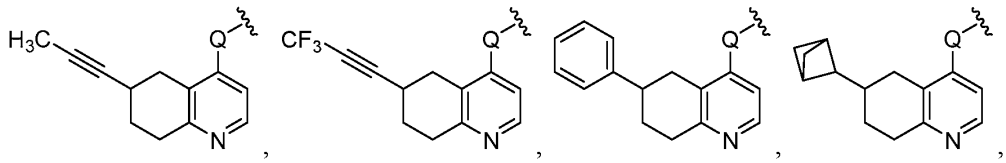
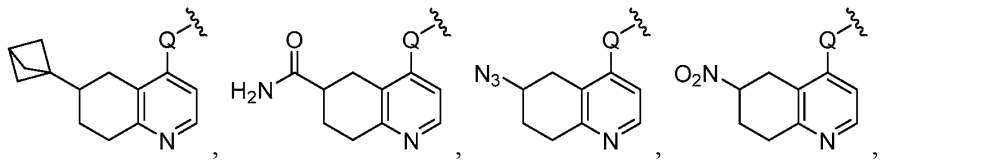
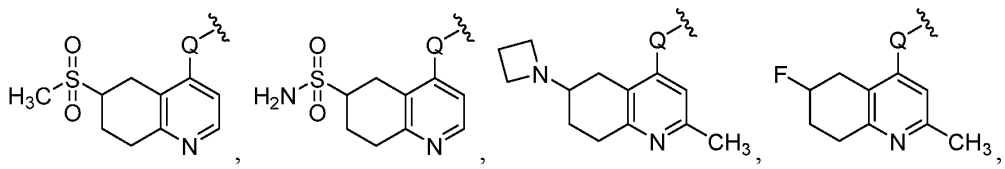
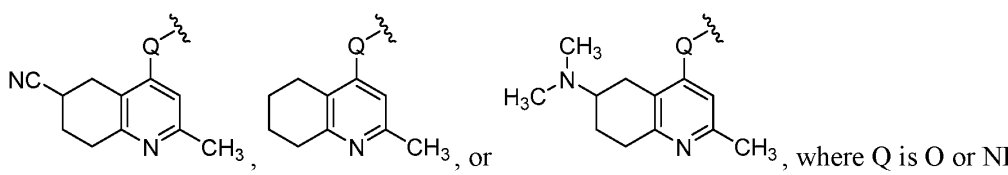
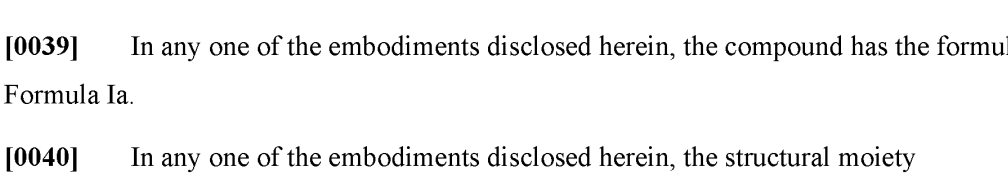
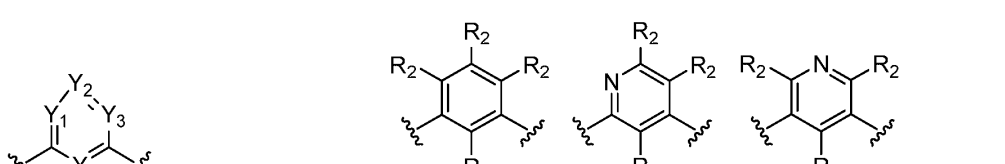
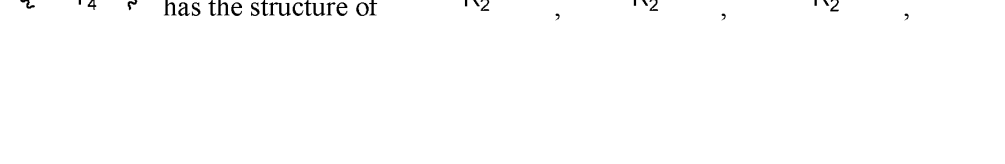
 has the structure of  ,  ,

 ,  ,  ,  ,




, or

, where Q is O or NH.

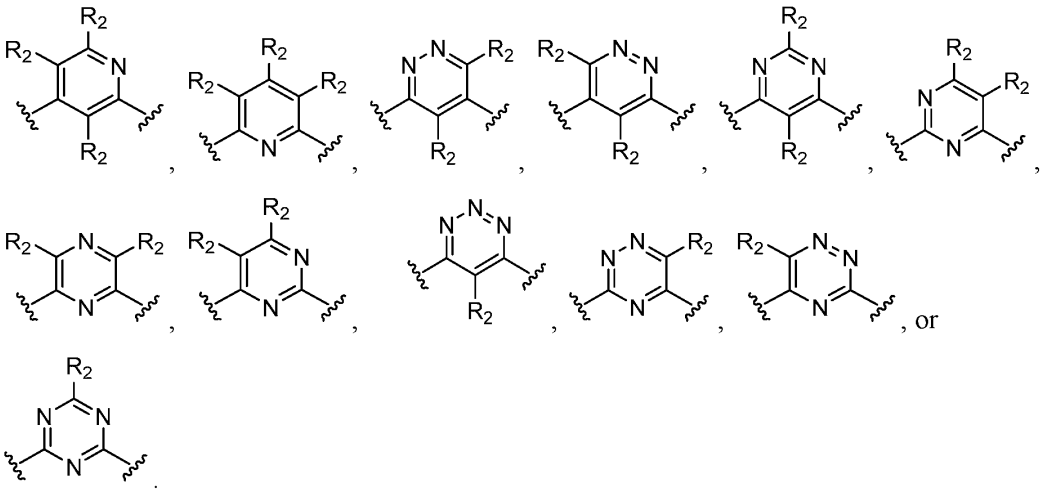
[0036] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or  , where Q is O or NH and R_1 is H, (C_1-C_6)alkyl, (C_3-C_7)heterocycloalkyl, halogenated (C_3-C_7)heterocycloalkyl, or halogen.

[0037] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or , where Q is O or NH.

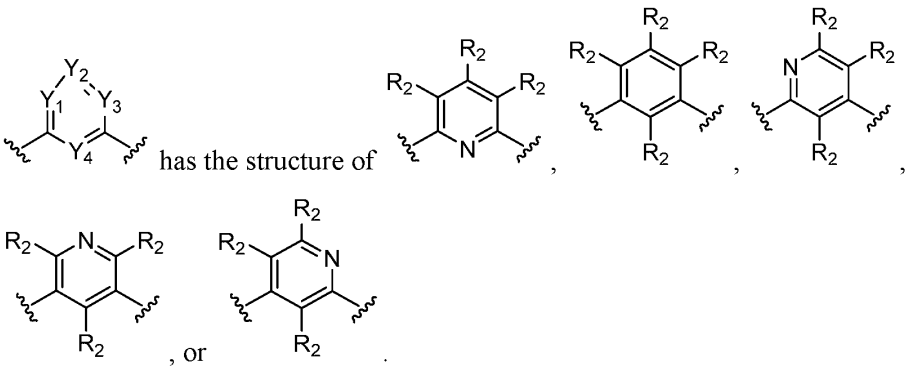
[0038] In any one of the embodiments disclosed herein, the structural moiety  has the structure of           , where Q is O or NH.

[0039] In any one of the embodiments disclosed herein, the compound has the formula of Formula Ia.

[0040] In any one of the embodiments disclosed herein, the structural moiety has the structure of

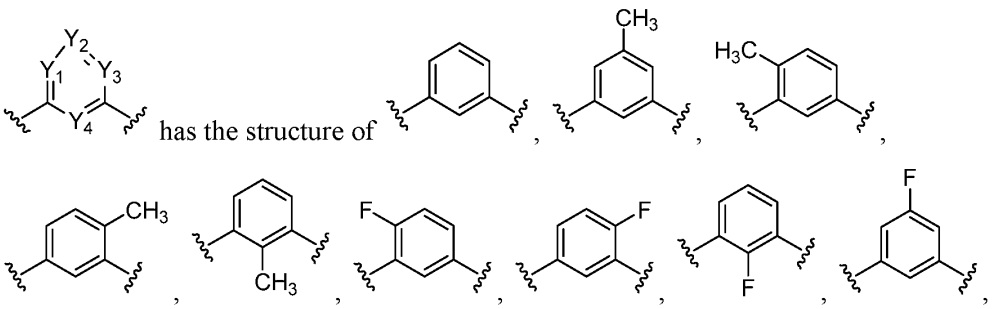


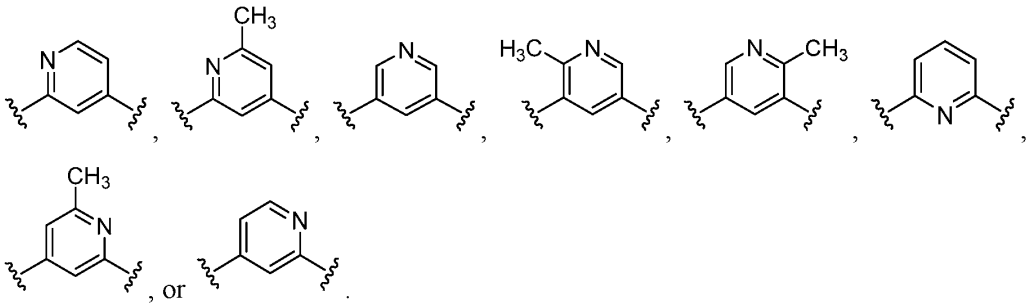
[0041] In any one of the embodiments disclosed herein, the structural moiety

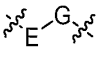
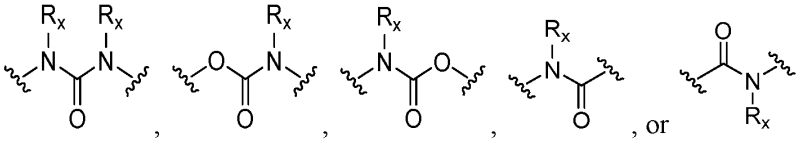


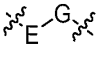
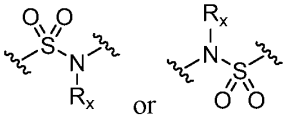
[0042] In any one of the embodiments disclosed herein, each occurrence of R_2 is independently H, halogen, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$.

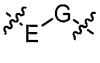
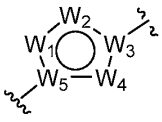
[0043] In any one of the embodiments disclosed herein, the structural moiety

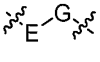
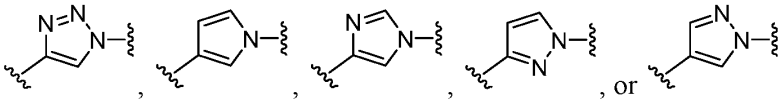


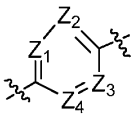
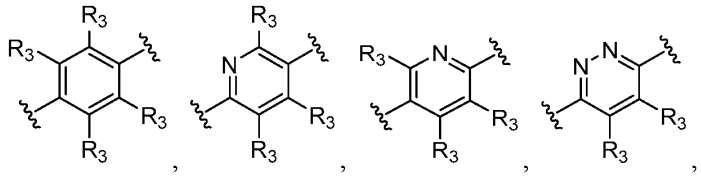
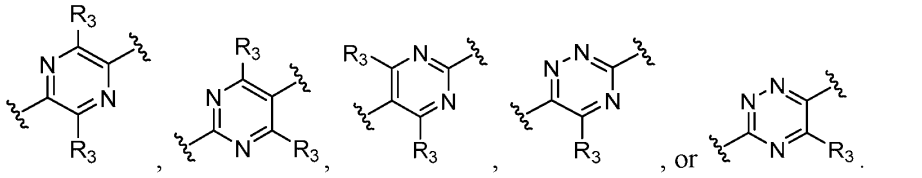


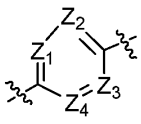
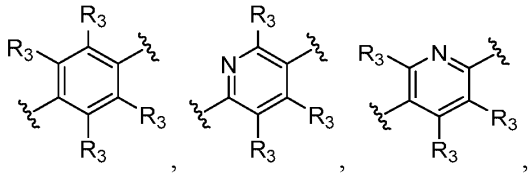
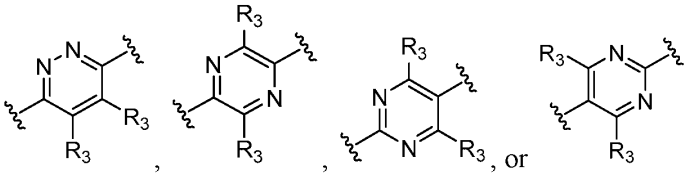
[0044] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

[0045] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

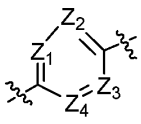
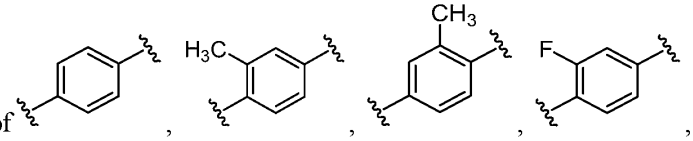
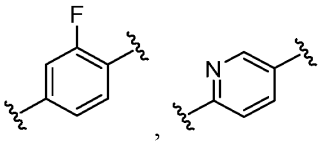
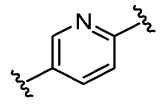
[0046] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

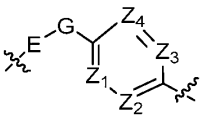
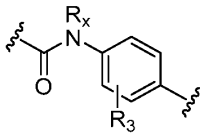
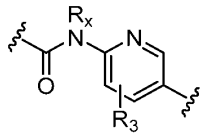
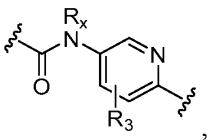
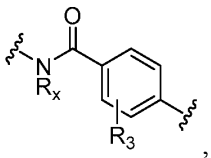
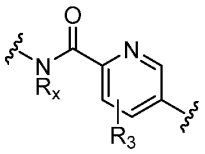
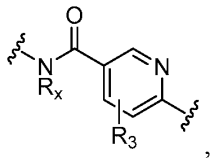
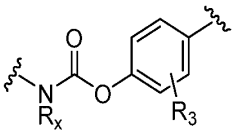
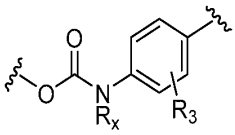
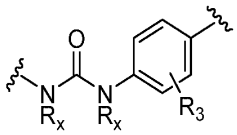
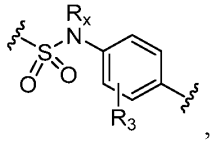
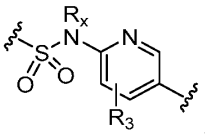
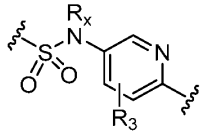
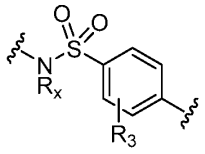
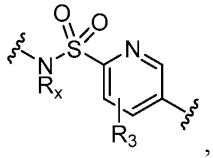
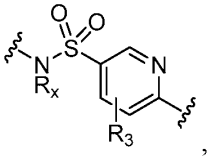
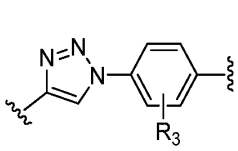
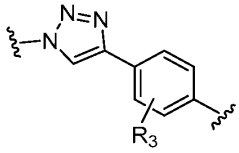
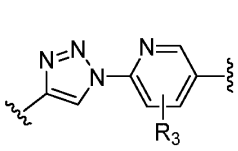
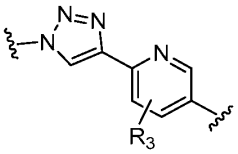
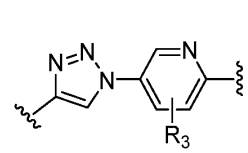
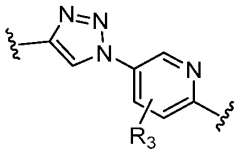
[0047] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

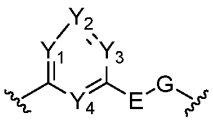
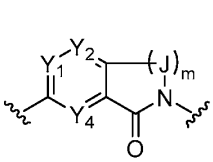
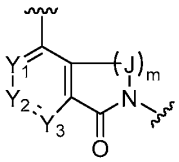
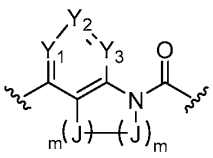
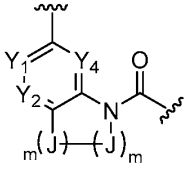
[0048] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  , or .

[0049] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  , or .

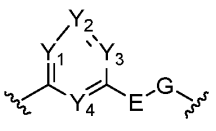
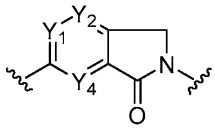
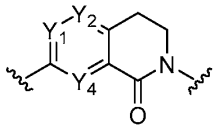
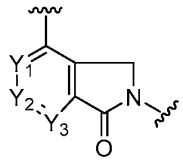
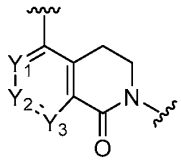
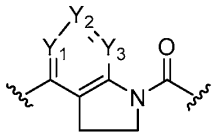
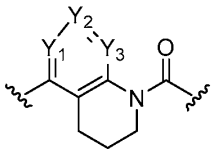
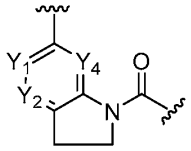
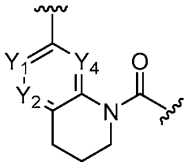
[0050] In any one of the embodiments disclosed herein, each occurrence of R_3 is H, halogen, CH_3, CF_3, OH, NH_2, $–NHCH_3$, or $–N(CH_3)_2$.

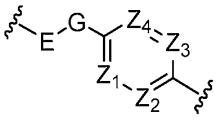
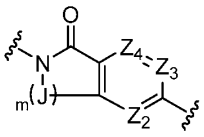
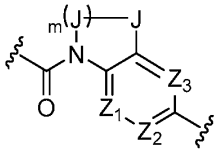
[0051] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  , or  .

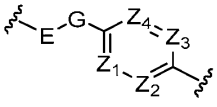
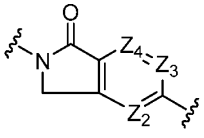
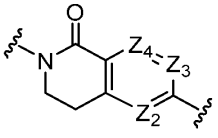
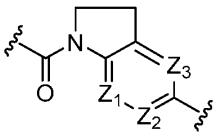
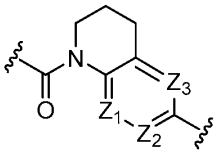
[0052] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or , where R_3 is H, CH_3, OH, halogen, or NH_2; and where R_x is H, CH_3, or CH_2CH_3.

[0053] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  , or  , where each occurrence of m is independently 1 or 2,

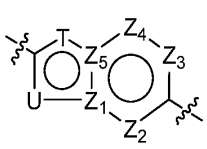
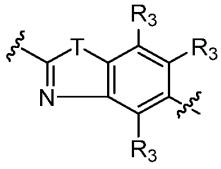
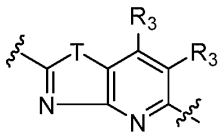
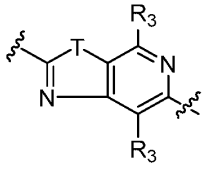
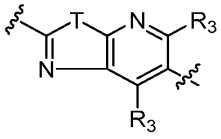
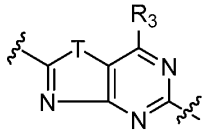
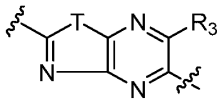
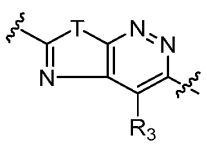
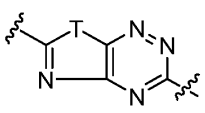
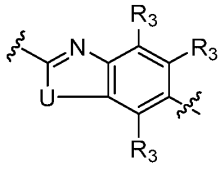
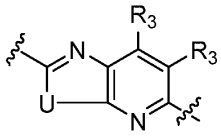
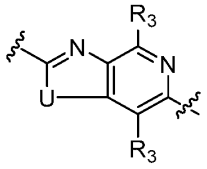
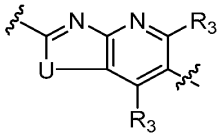
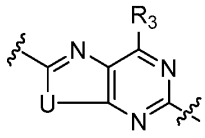
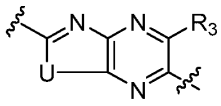
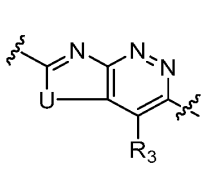
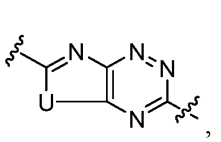
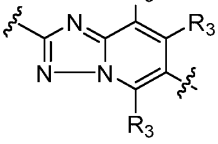
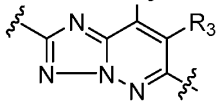
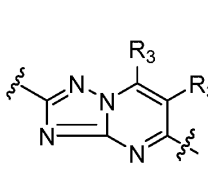
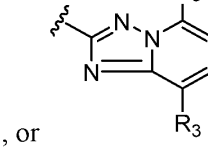
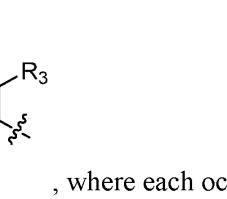
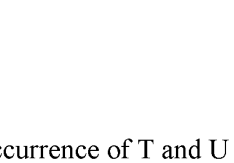
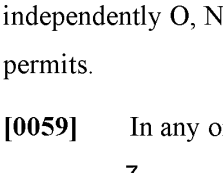
J is $C(R_y)_2$, and each occurrence of R_y is independently H, $(C_1\text{-}C_6)$alkyl, OH, $O(C_1\text{-}C_6)$alkyl, or halogen.

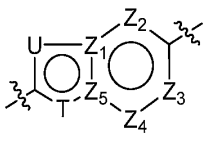
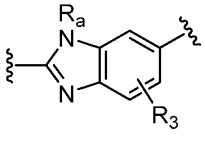
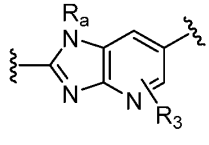
[0054] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  , or  , where Y_1, Y_2, Y_3, and Y_4 are each independently N, CH, CCH_3, or CF.

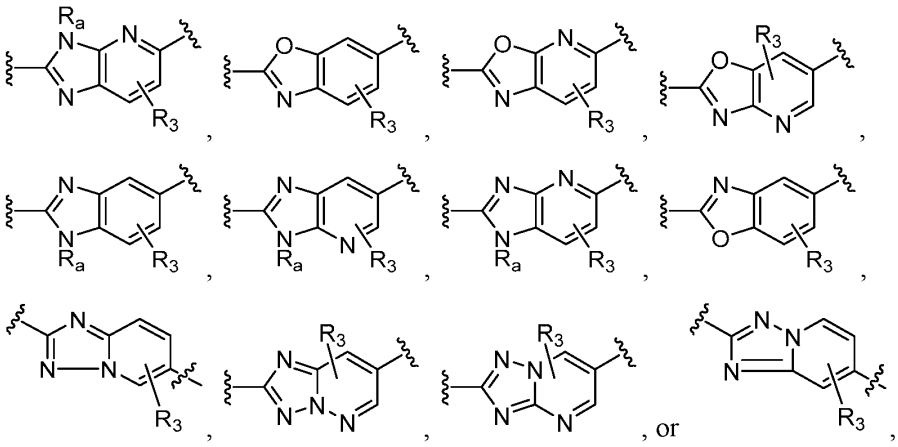
[0055] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  or  , where each occurrence of m is independently 1 or 2, J is $C(R_z)_2$, and each occurrence of R_z is independently H, $(C_1\text{-}C_6)$alkyl, OH, $O(C_1\text{-}C_6)$alkyl, or halogen.

[0056] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  , or  , where Z_1, Z_2, Z_3, and Z_4 are each independently N, CH, CCH_3, or CF.

[0057] In any one of the embodiments disclosed herein, the compound has the formula of Formula Ib.

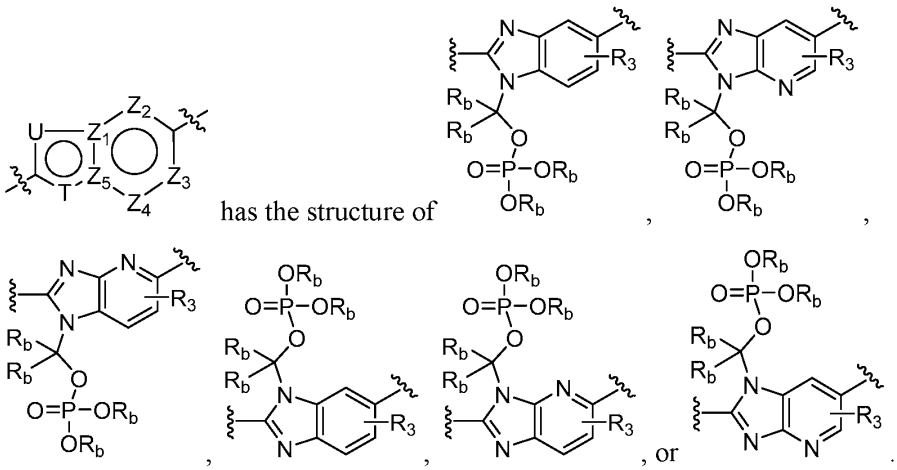
[0058] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or , where each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

[0059] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,



, where R_3 is H, CH_3, OH, halogen, or NH_2; and where R_a is H, CH_3, or CH_2CH_3.

[0060] In any one of the embodiments disclosed herein, the structural moiety



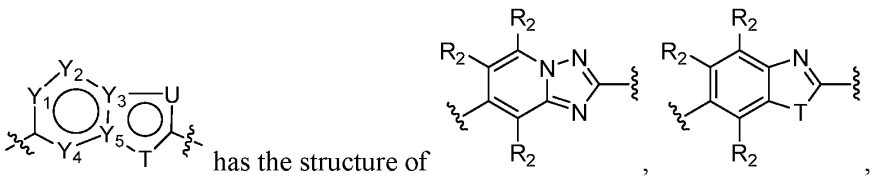
has the structure of , , , , or .

[0061] In any one of the embodiments disclosed herein, each occurrence of R_b is independently H or (C_1-C_6)alkyl.

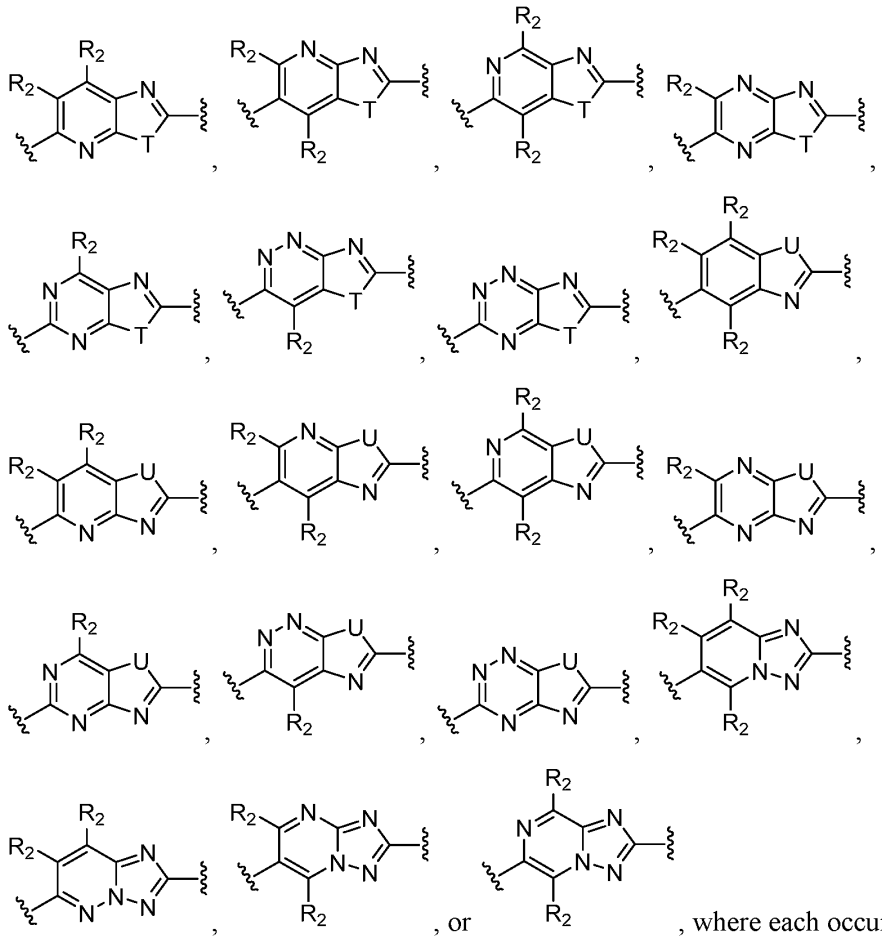
[0062] In any one of the embodiments disclosed herein, each occurrence of R_b is independently H, CH_3, CH_2CH_3, or $CH(CH_3)_2$.

[0063] In any one of the embodiments disclosed herein, the compound has the formula of Formula Ic.

[0064] In any one of the embodiments disclosed herein, the structural moiety

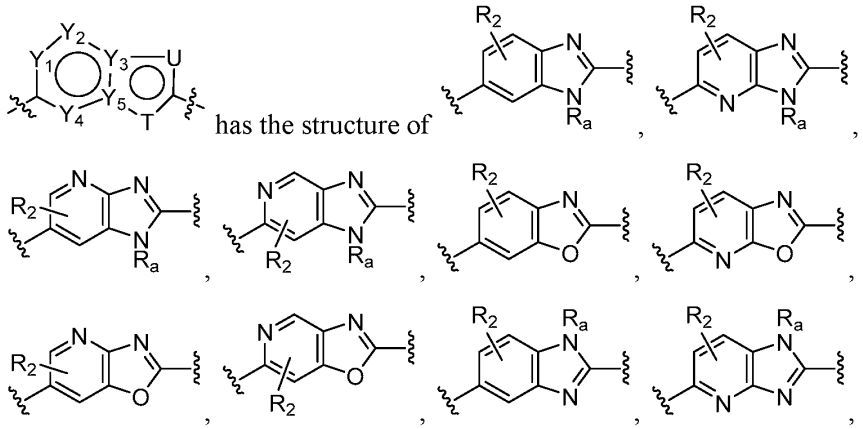


has the structure of , , .



where each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

[0065] In any one of the embodiments disclosed herein, the structural moiety



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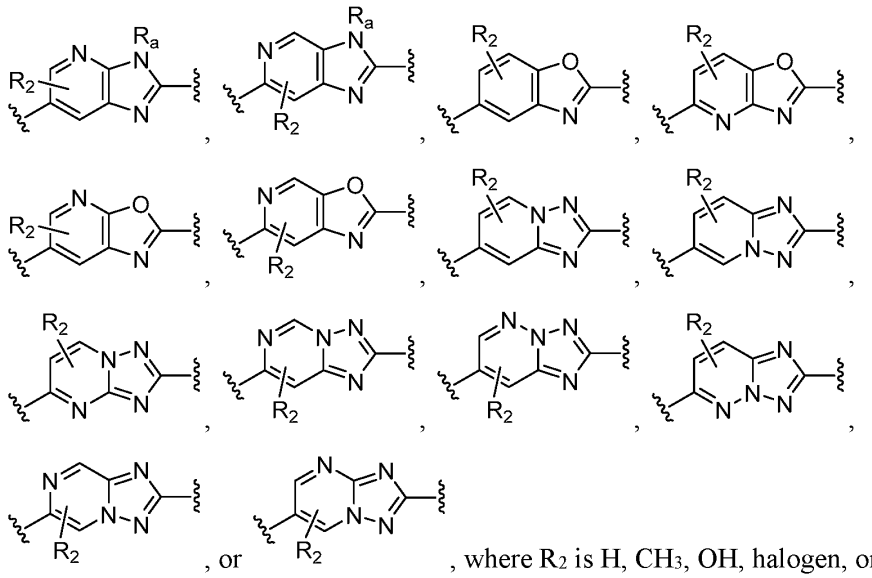
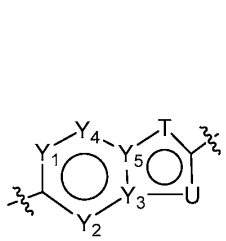


, where R_2 is H, CH_3, OH, halogen, or NH_2; and where R_a is H, CH_3, or CH_2CH_3.

[0066] In any one of the embodiments disclosed herein, the structural moiety



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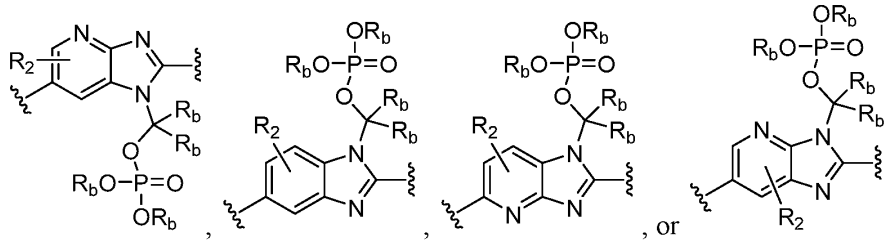
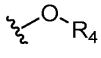
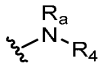


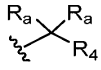
[0067] In any one of the embodiments disclosed herein, each occurrence of R_b is independently H or (C_1-C_6)alkyl.

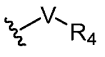
[0068] In any one of the embodiments disclosed herein, each occurrence of R_b is independently H, CH_3, CH_2CH_3, or $CH(CH_3)_2$.

[0069] In any one of the embodiments disclosed herein, each occurrence of R_2 is independently H, CH_3, OH, NH_2, or halogen.

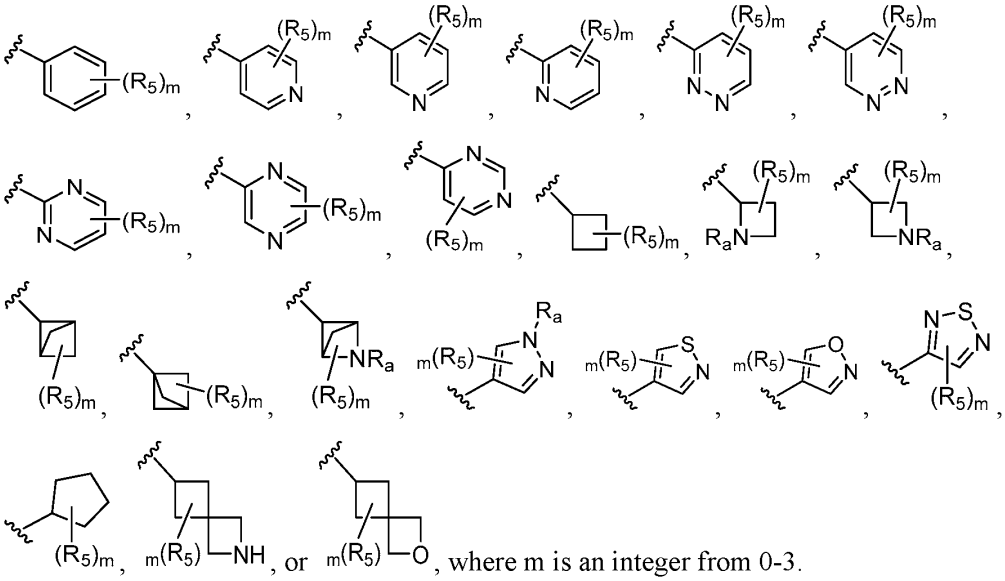
[0070] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

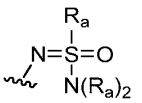
[0071] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

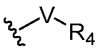
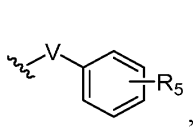
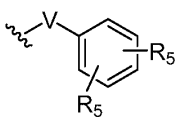
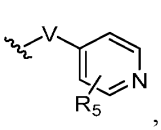
[0072] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  .

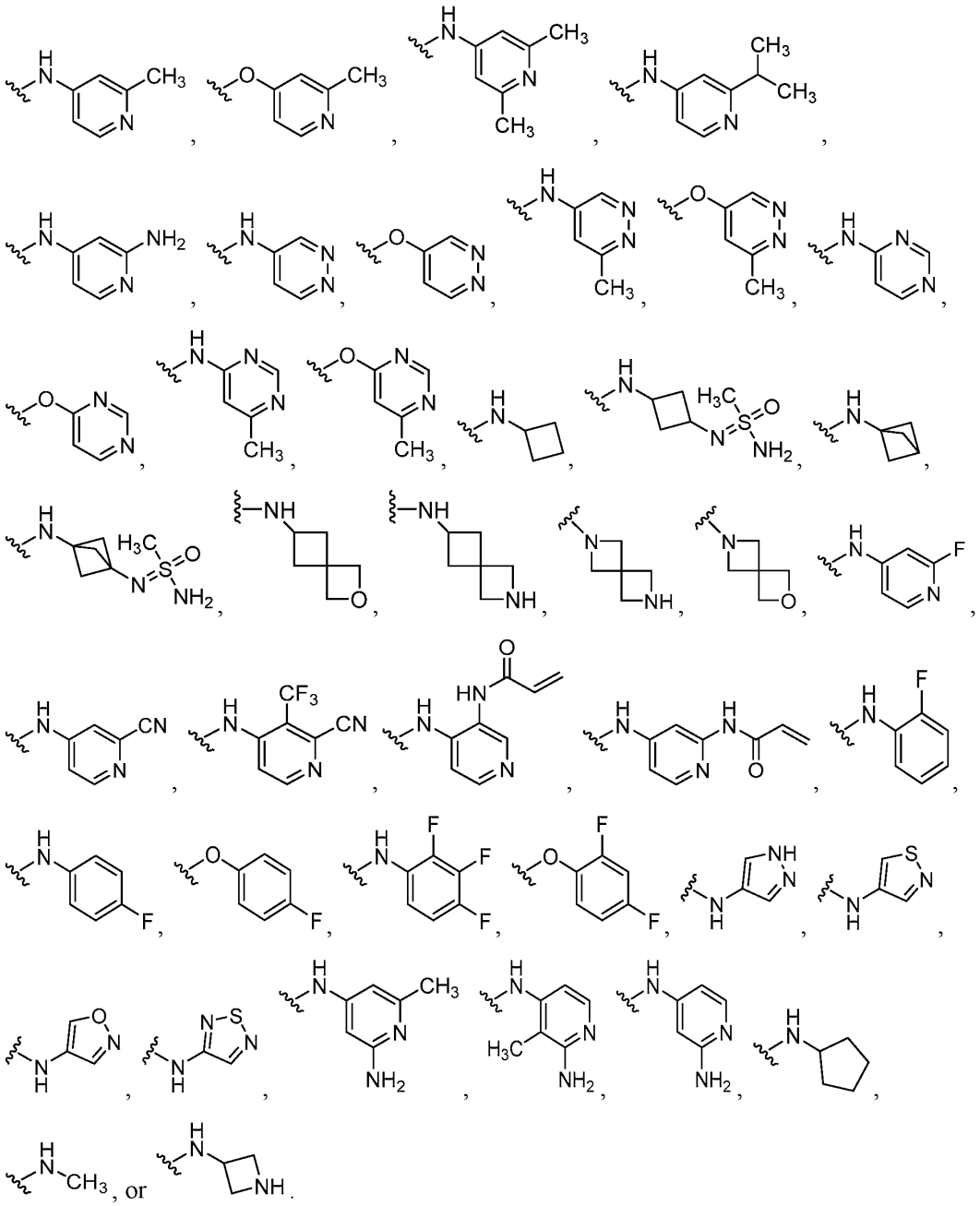
[0073] In any one of the embodiments disclosed herein, V and R_4 of the structural moiety  taken together form a (C_4-C_{10})heterospiroalkyl.

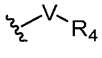
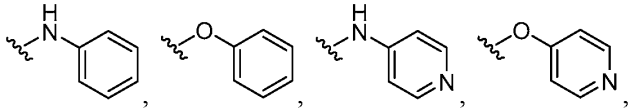
[0074] In any one of the embodiments disclosed herein, V is absent.

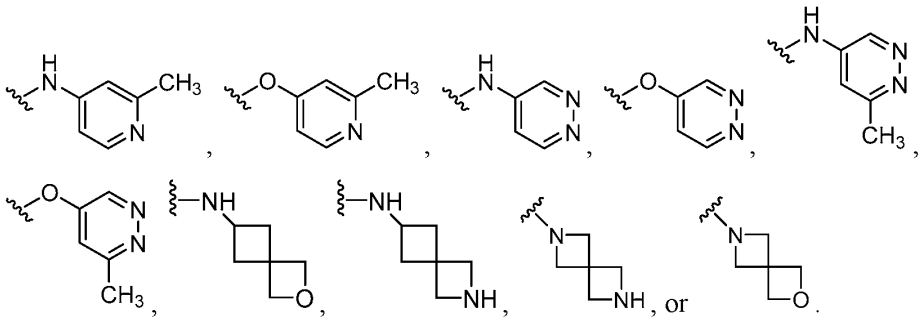
[0075] In any one of the embodiments disclosed herein, R_4 is (C_1-C_6)alkyl,  , where m is an integer from 0-3.

[0076] In any one of the embodiments disclosed herein, each occurrence of R_5 is independently H, (C_1-C_6)alkyl, halogen, OR_a, OH, NH_2, $N(R_a)COR_a$, CN, CF_3, (C_1-C_6)haloalkyl, or  and each occurrence of R_a is independently H, (C_2-C_6)alkenyl, or (C_1-C_6)alkyl.

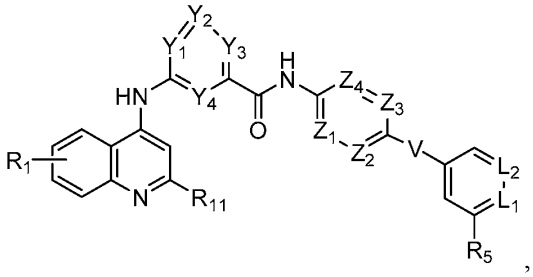
[0077] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  ,



[0082] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,



[0083] In any one of the embodiments disclosed herein, the compound of Formula Ia has



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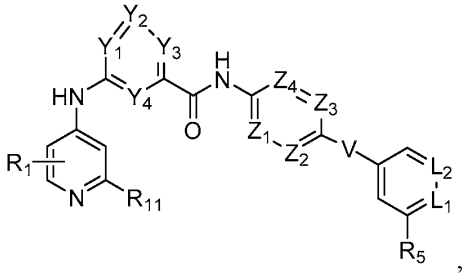

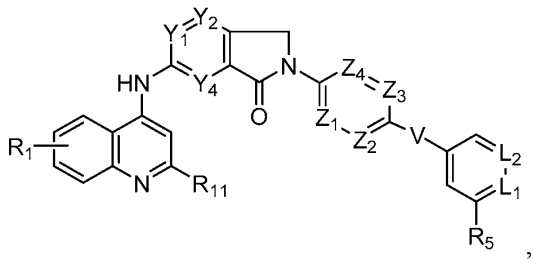

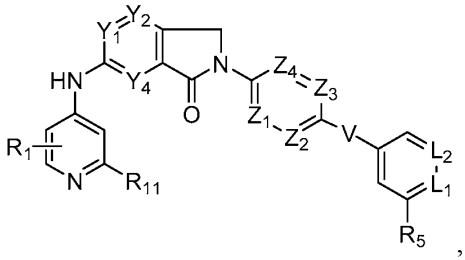

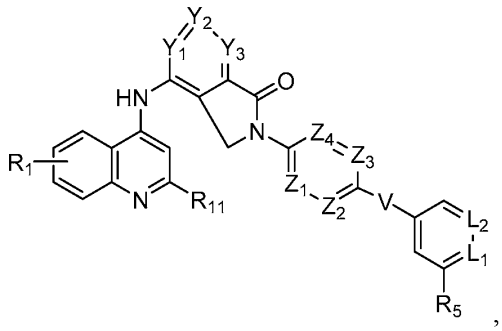

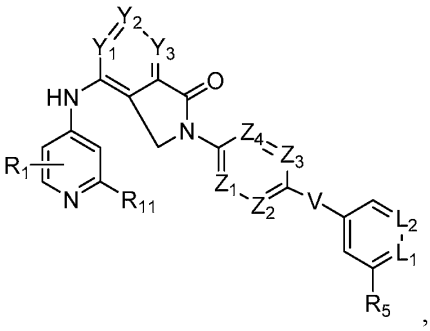
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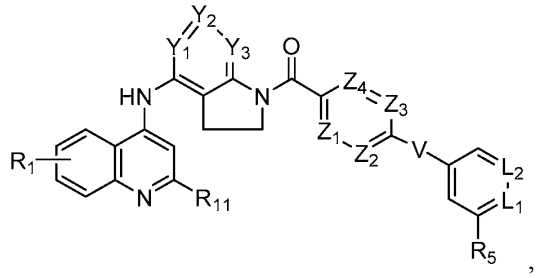
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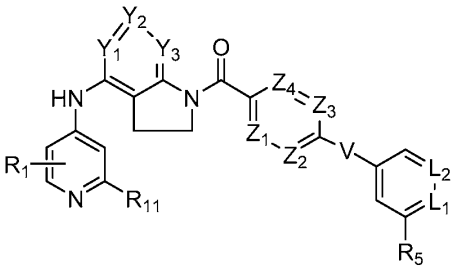
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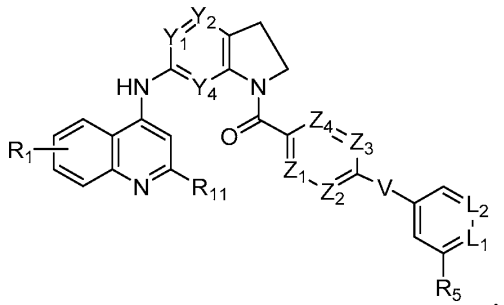
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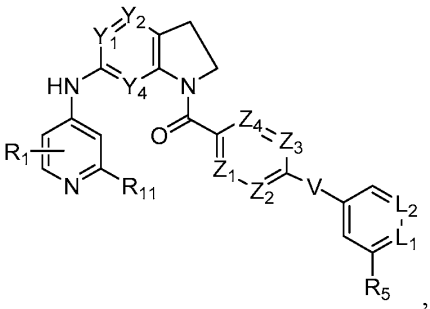
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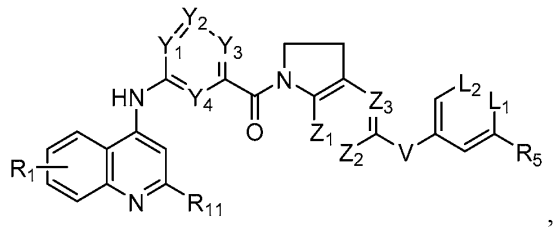
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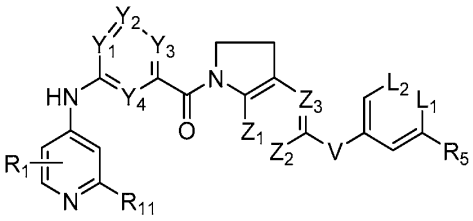
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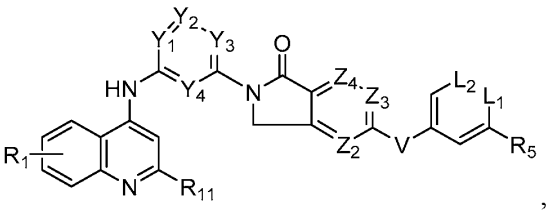
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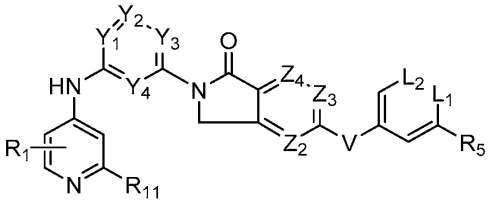
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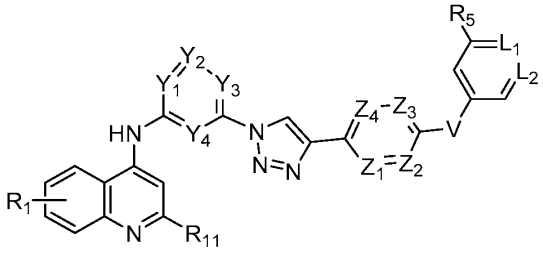
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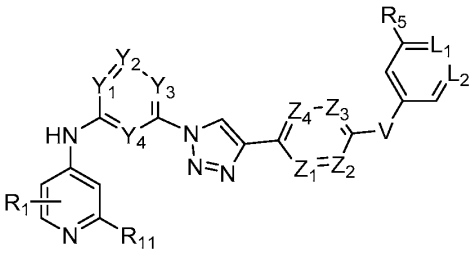
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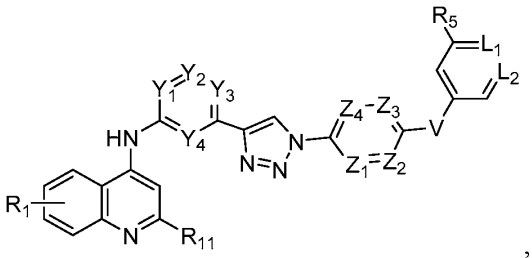
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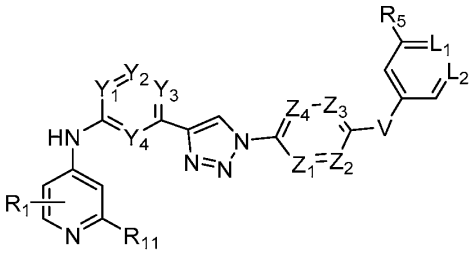
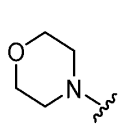
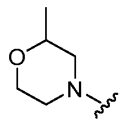
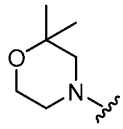
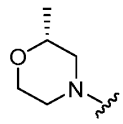
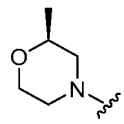
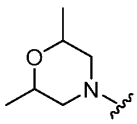
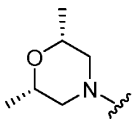
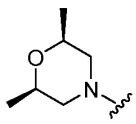
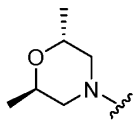
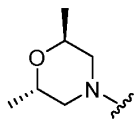
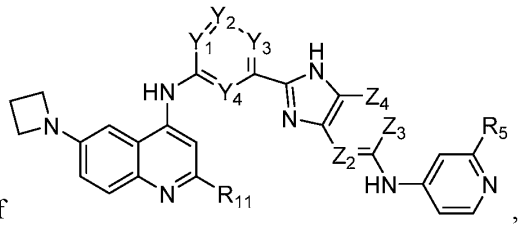
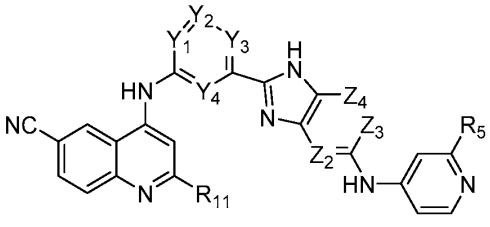

, where R_1 is H, $(C_1\text{-}C_6)$alkyl, $N(R_a)_2$, $(C_3\text{-}C_7)$heterocycloalkyl, or halogen; R_5 and R_{11} are each independently H or CH_3; Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, Z_3, Z_4, L_1, and L_2 are each independently CH or N; and V is NH or O.

[0084] In any one of the embodiments disclosed herein, R_1 is H, F, Cl, Br, CH_3, CH_2CH_3, $CH(CH_3)_2$, NH_2, NMe_2,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  .

[0085] In any one of the embodiments disclosed herein, the compound of Formula Ib has the structure of  ,

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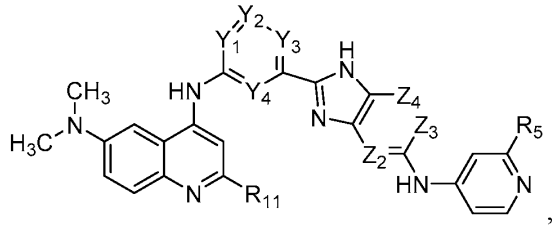
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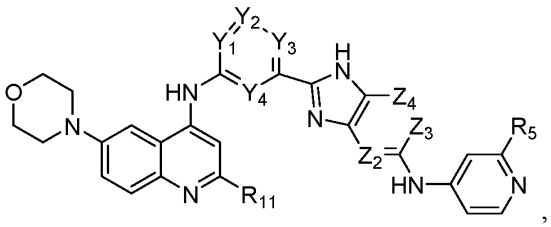

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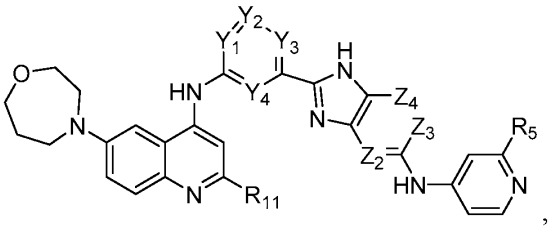

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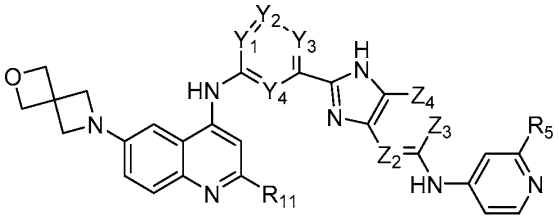

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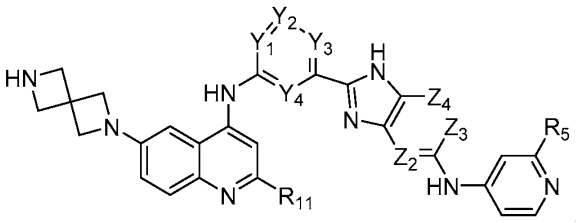
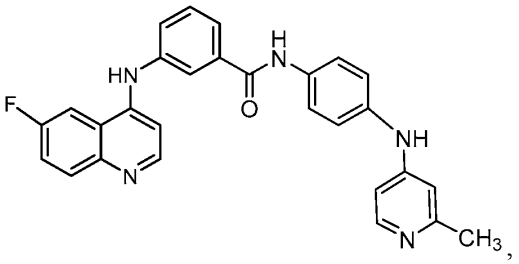


, where R_{11} and R_5 are each independently H or CH_3; and Y_1, Y_2, Y_3, Y_4, Z_2, Z_3, and Z_4 are each independently CH or N.

[0086] In any one of the embodiments disclosed herein, the compound of Formula Ia is



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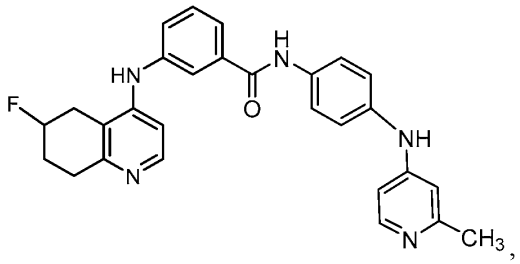

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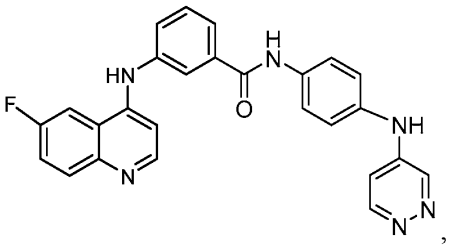

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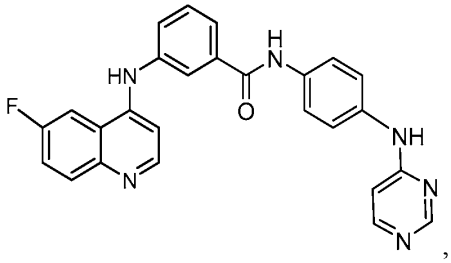

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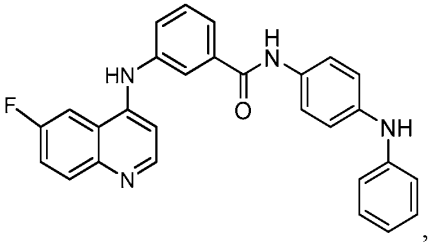
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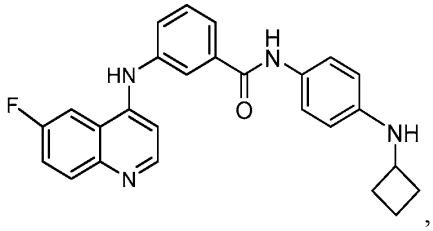
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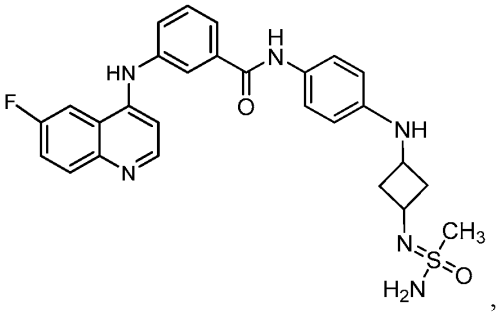
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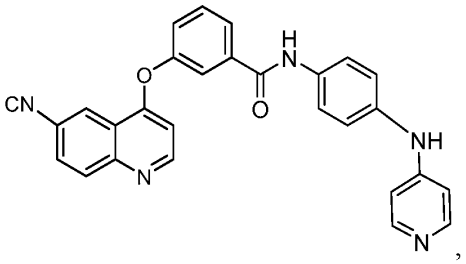
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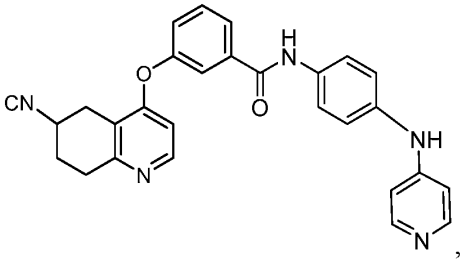
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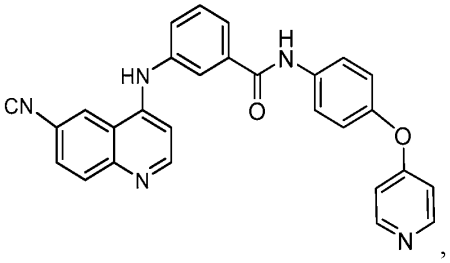
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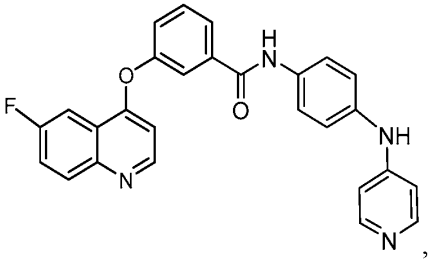
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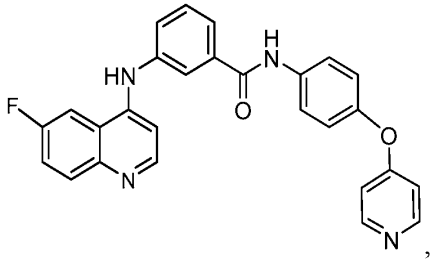
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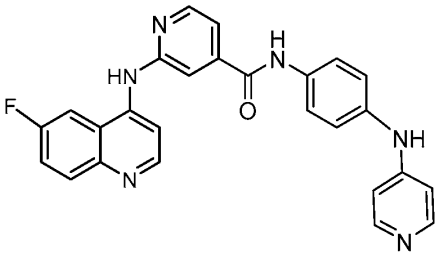
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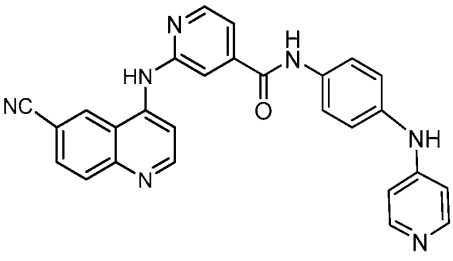
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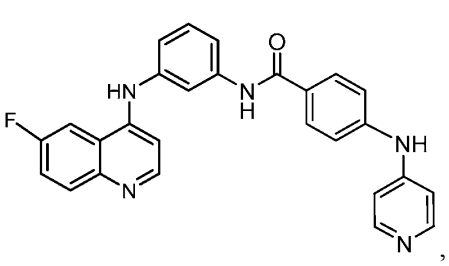
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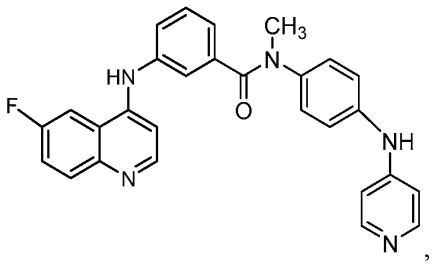
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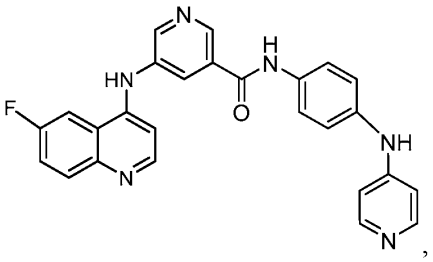
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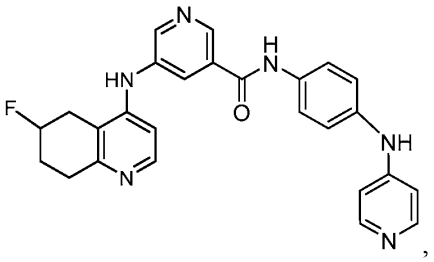
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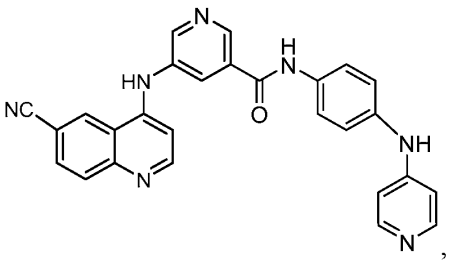
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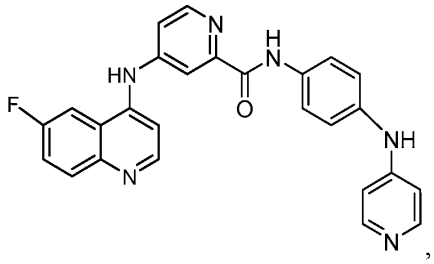
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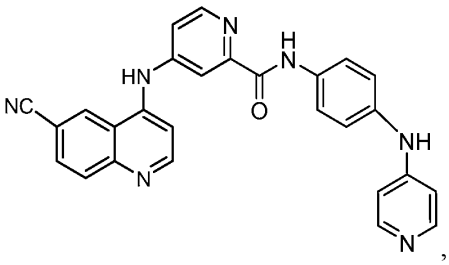
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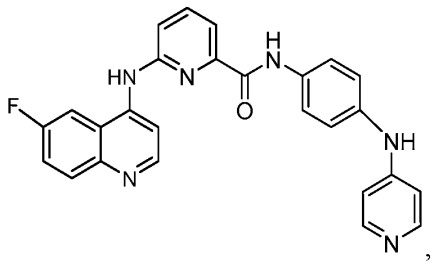
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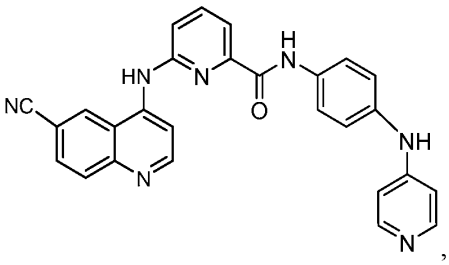
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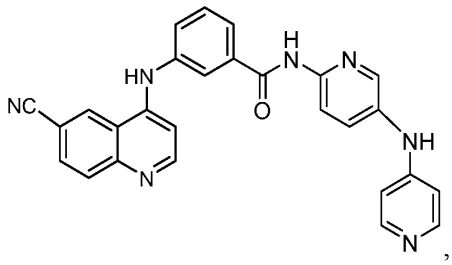
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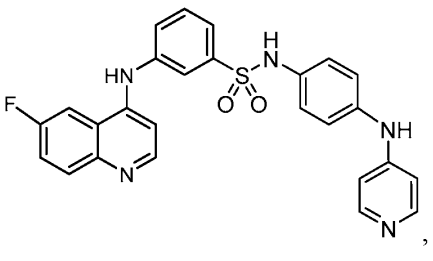
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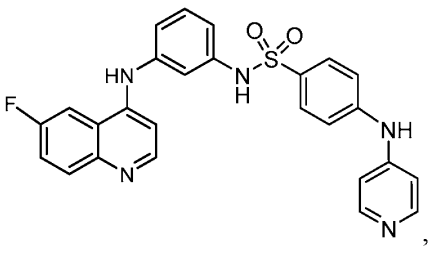
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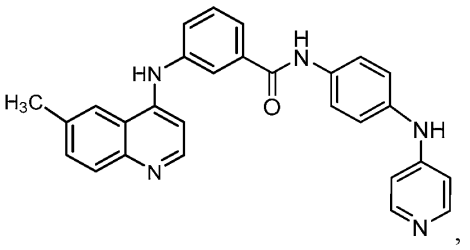
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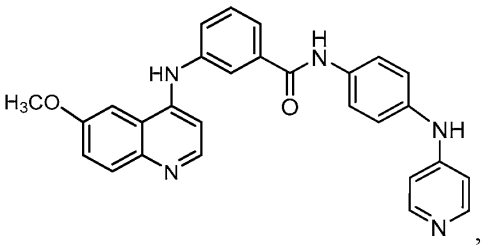
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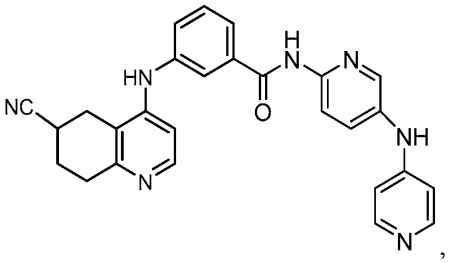
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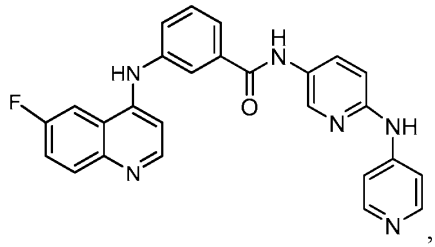
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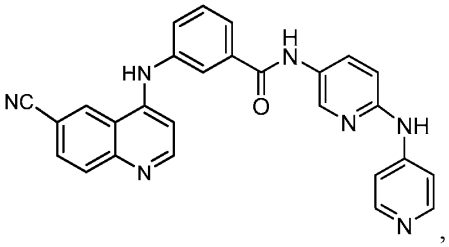
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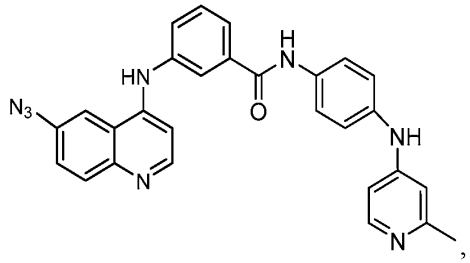
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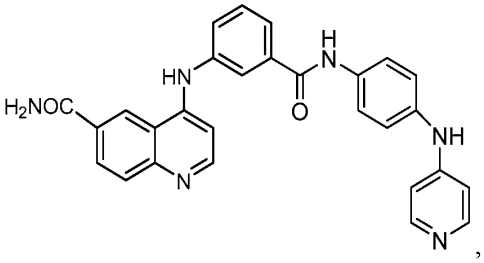
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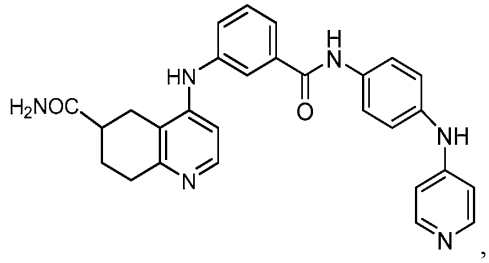
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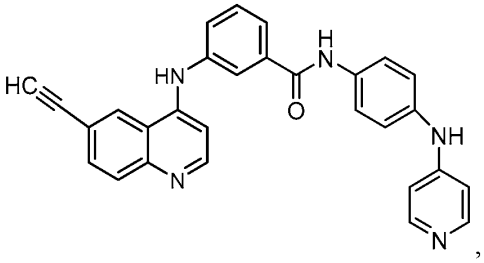
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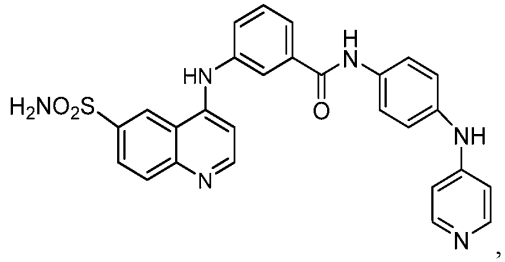
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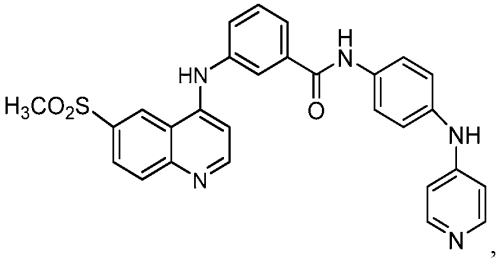
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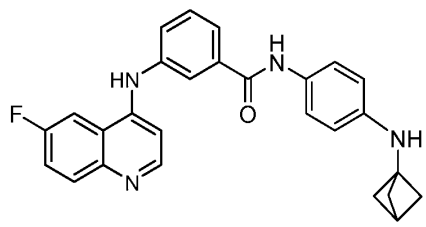
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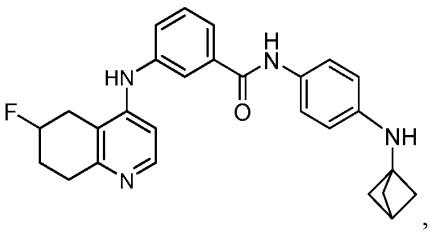

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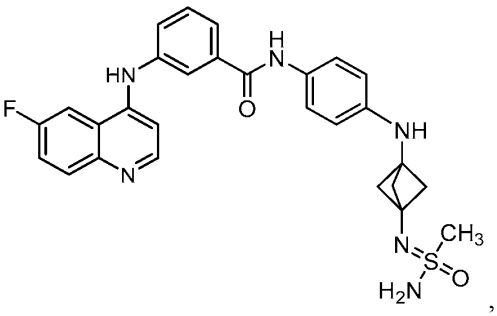

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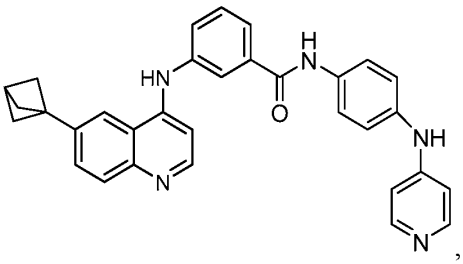

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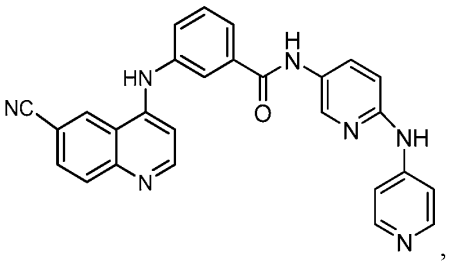

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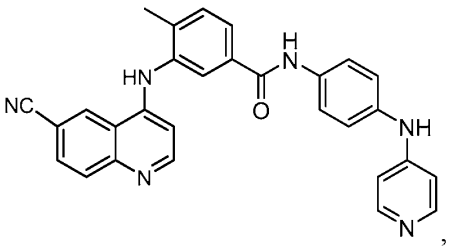

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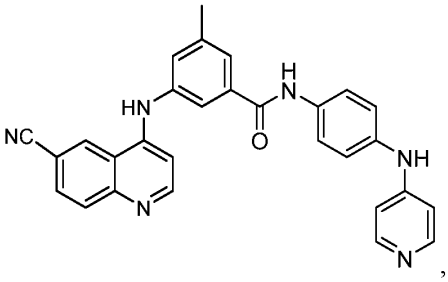

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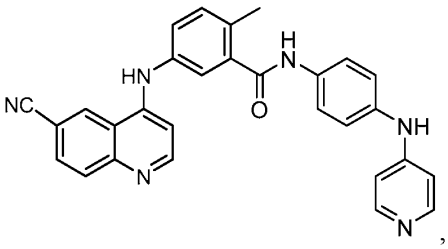

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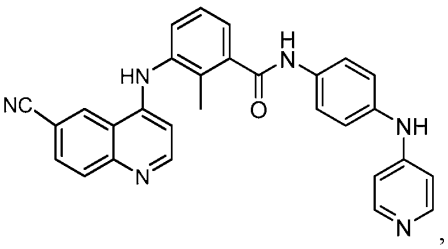

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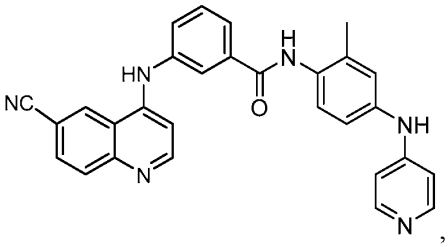

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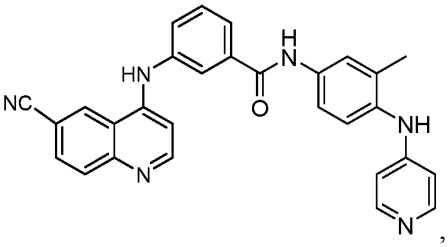

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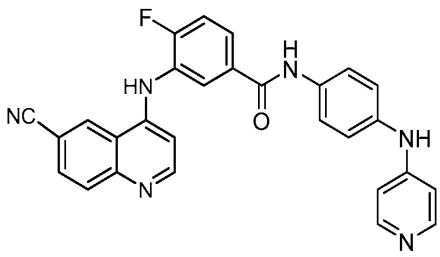
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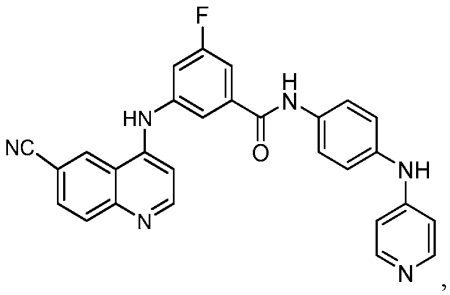
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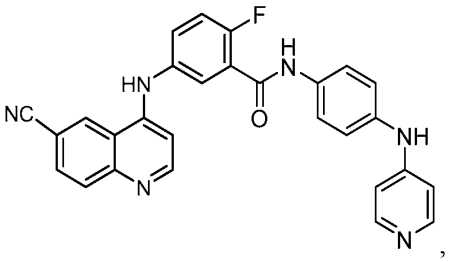
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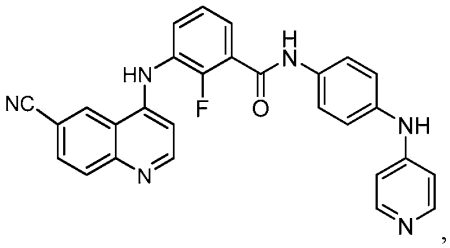
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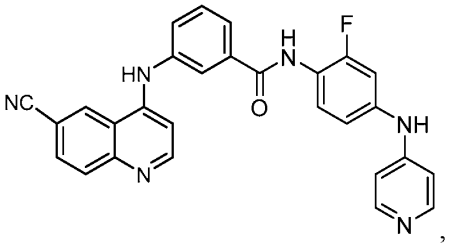
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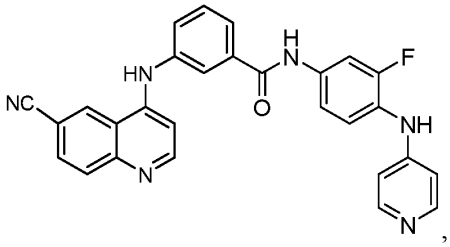
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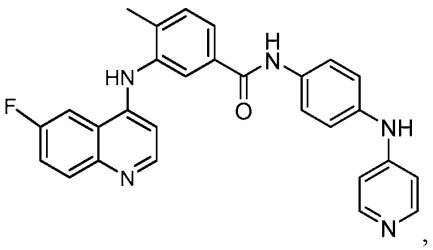
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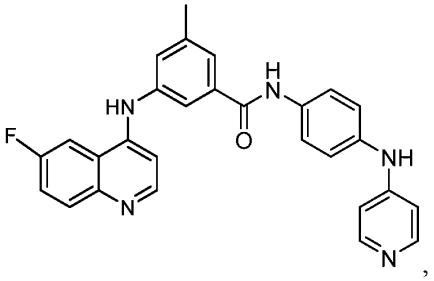
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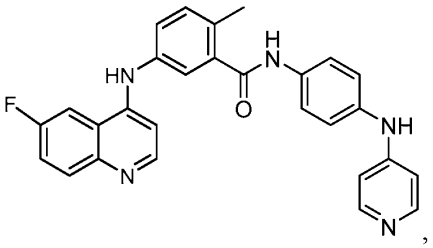
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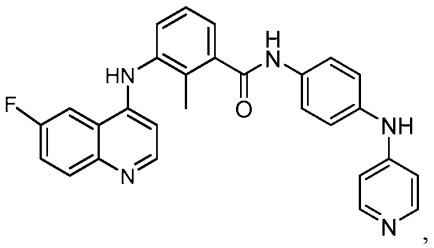
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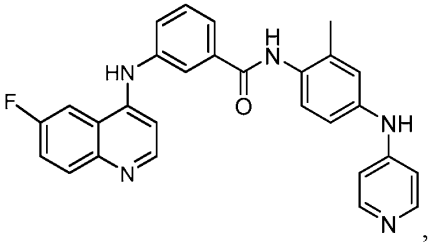
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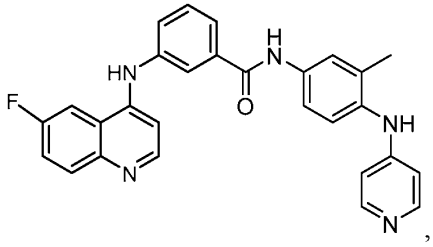
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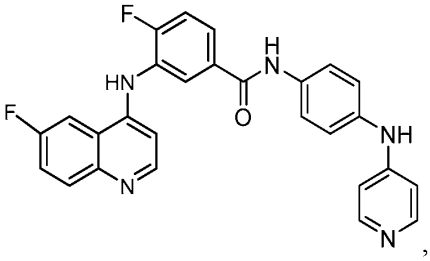
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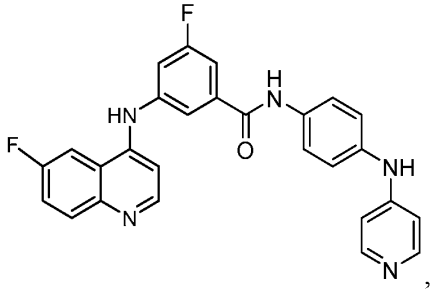
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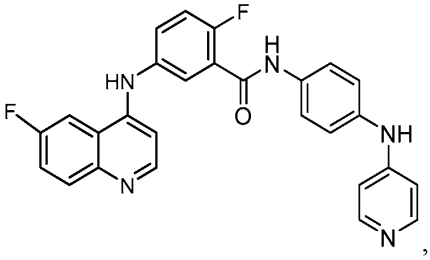
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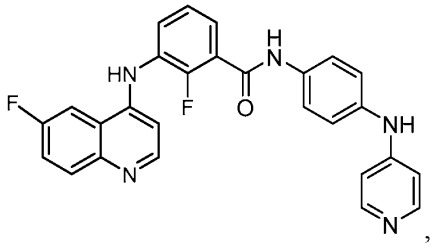
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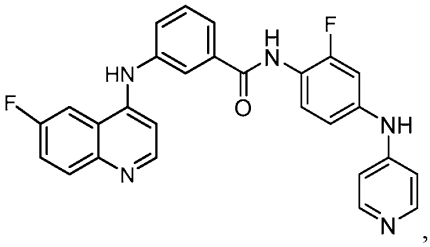
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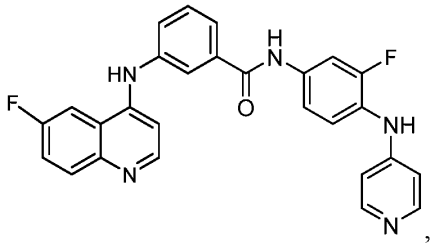
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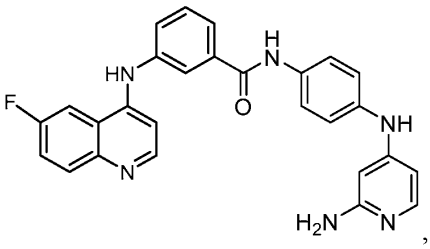
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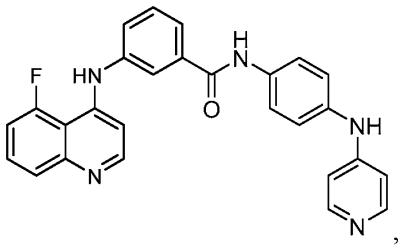
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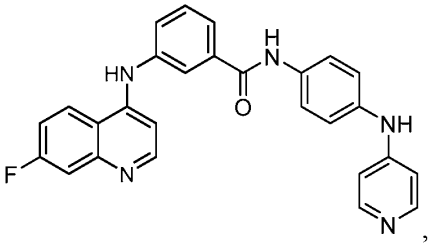
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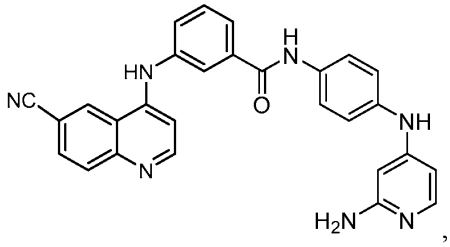
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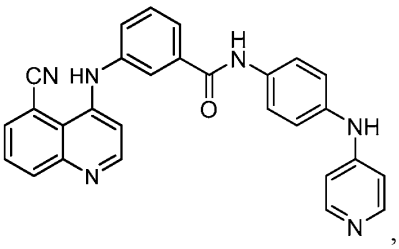
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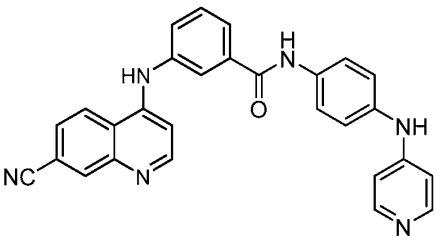
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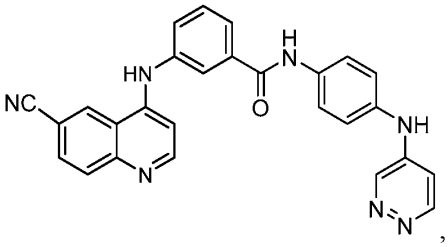
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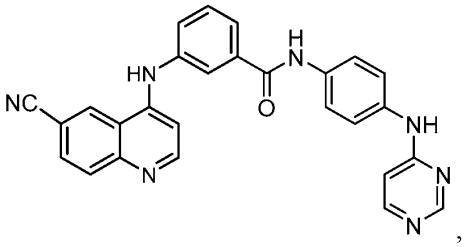
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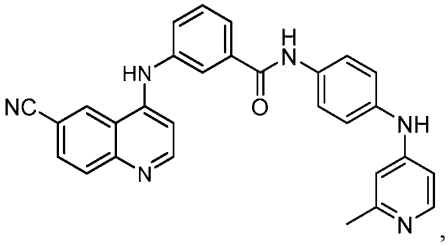
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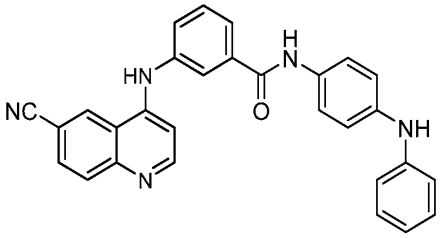
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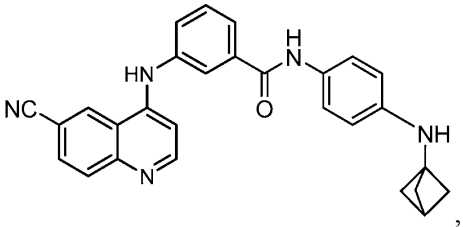
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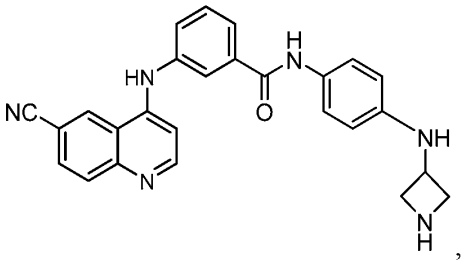
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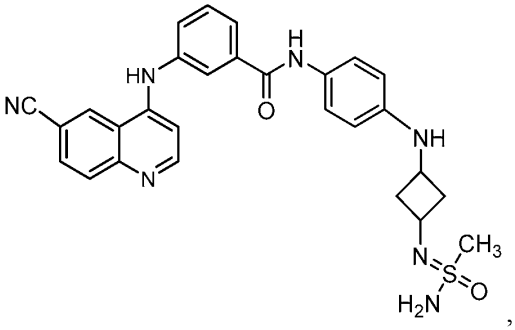
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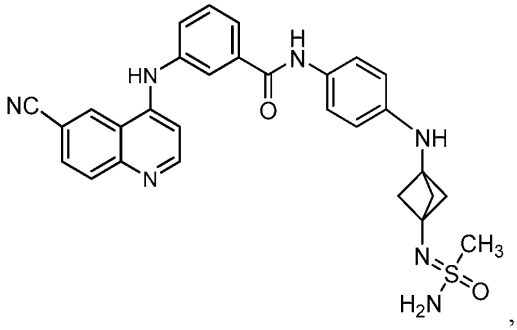
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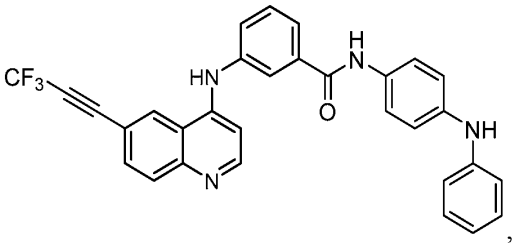
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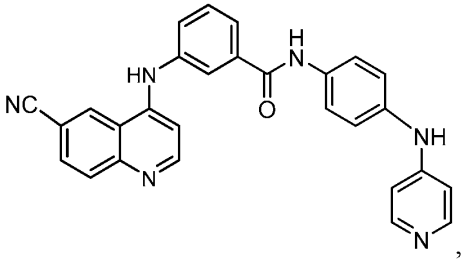
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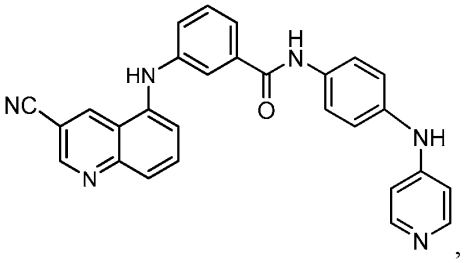
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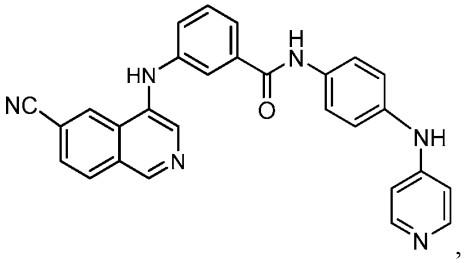
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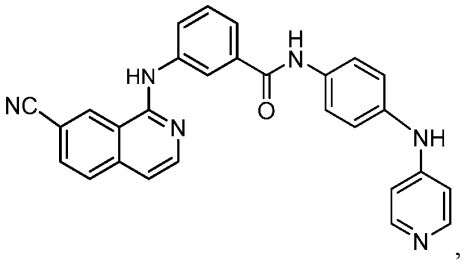
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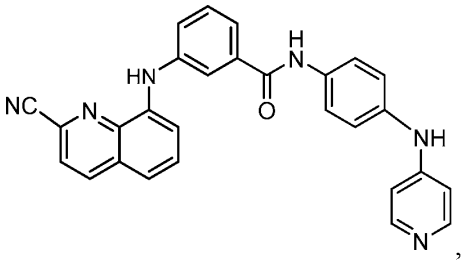
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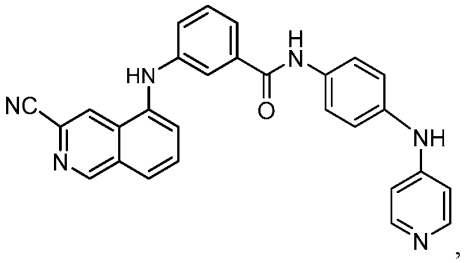
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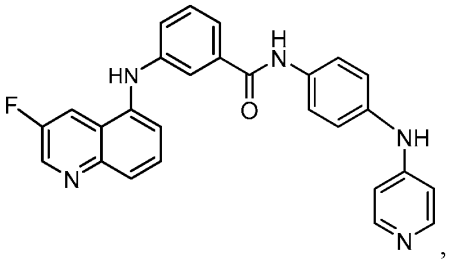
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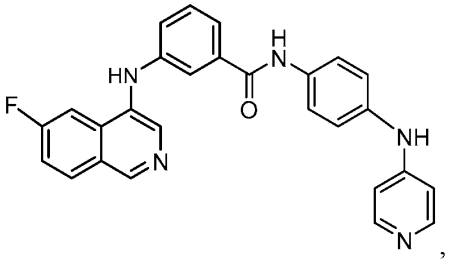
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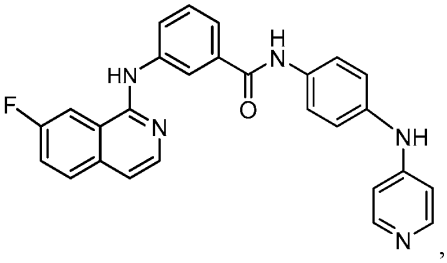
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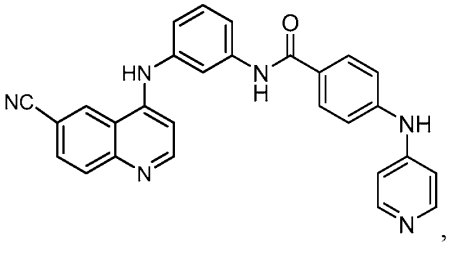
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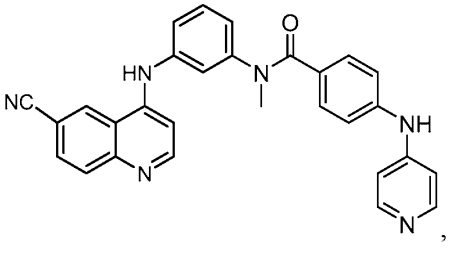
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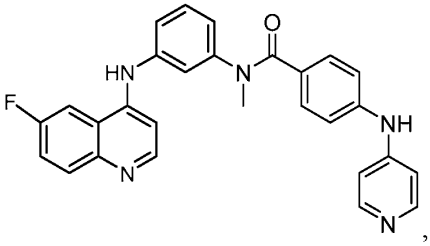
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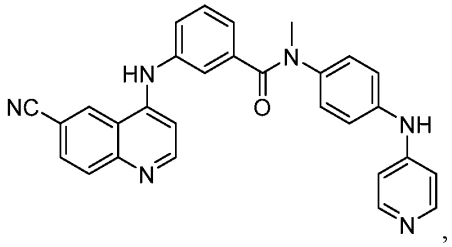
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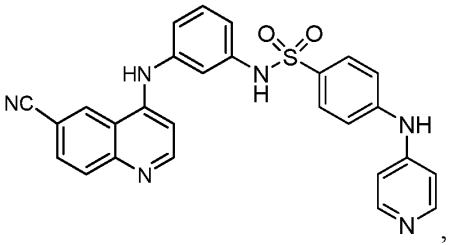
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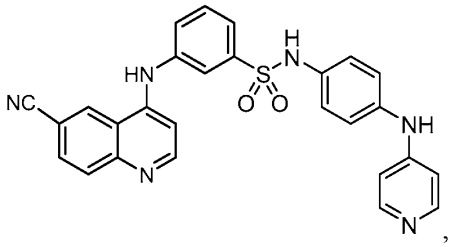
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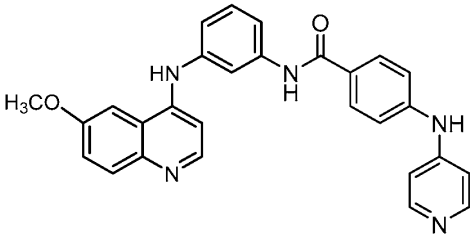
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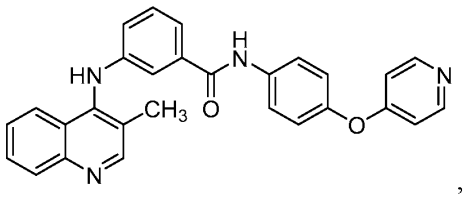
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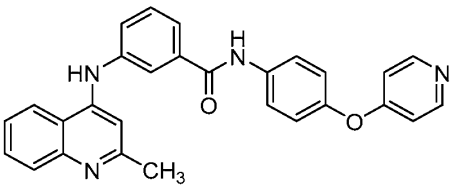
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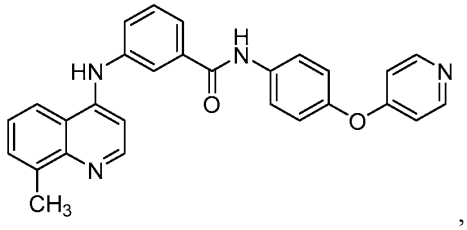
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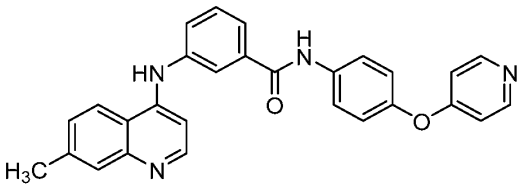
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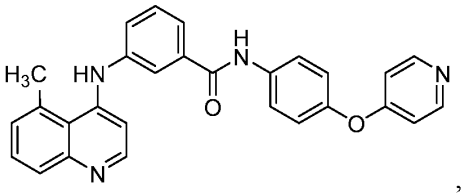
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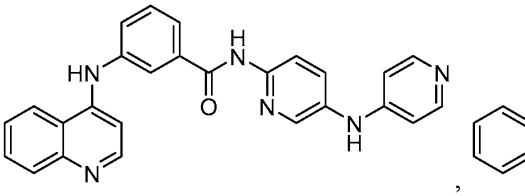
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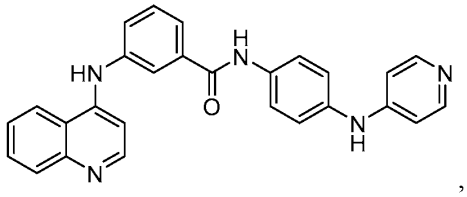
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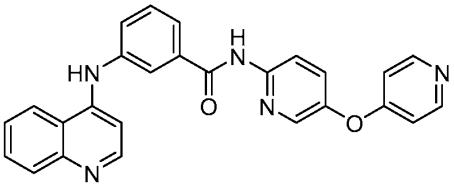
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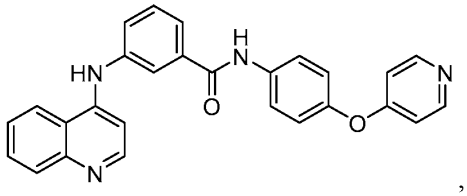
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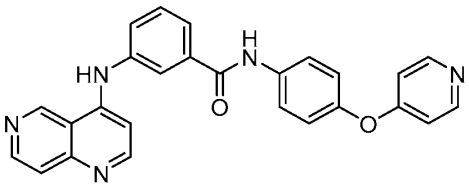
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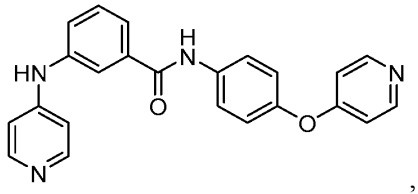
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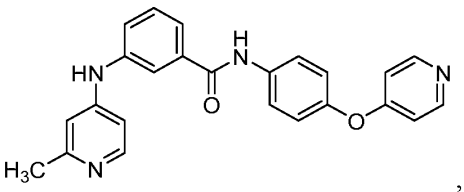
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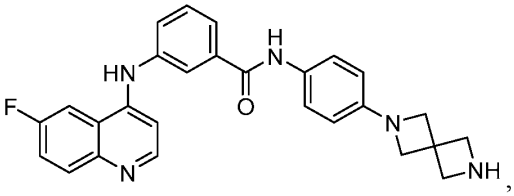
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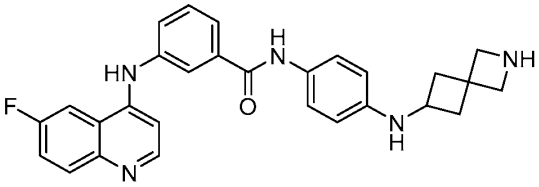
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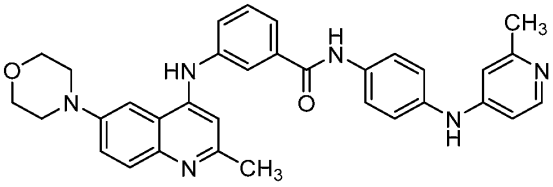
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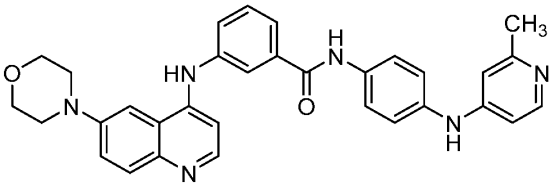
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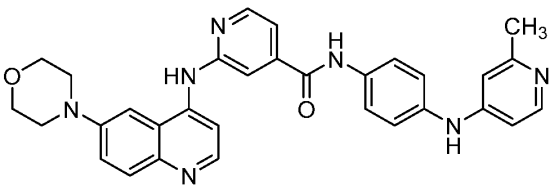
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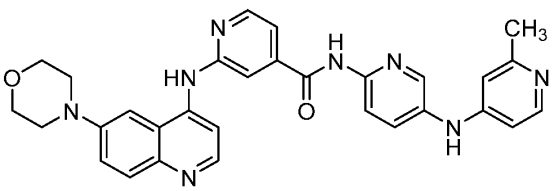
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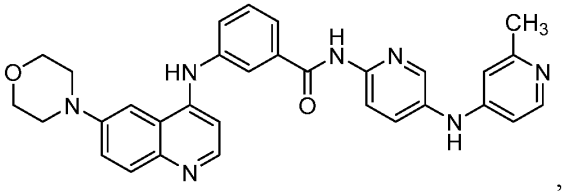
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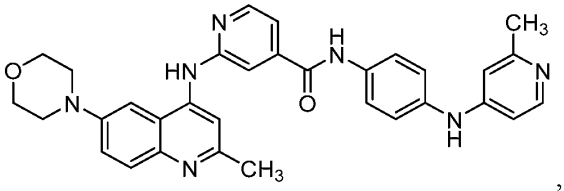
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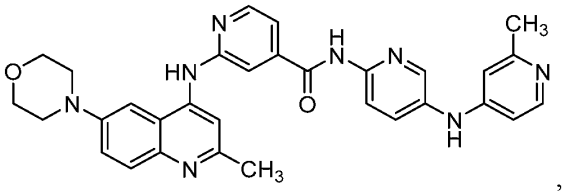
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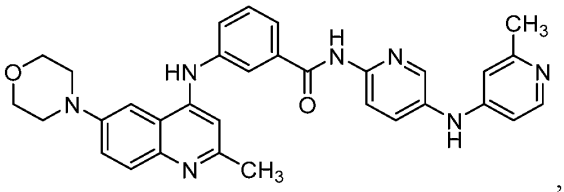
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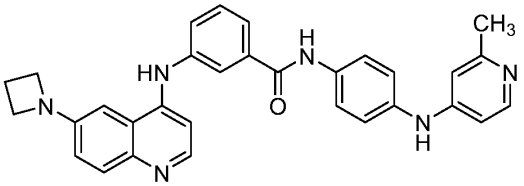
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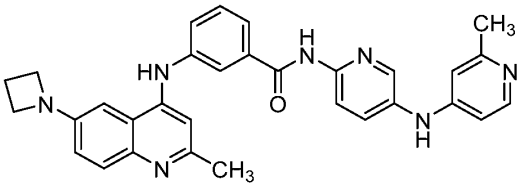
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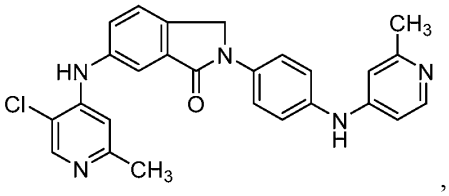
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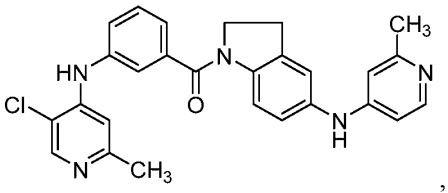
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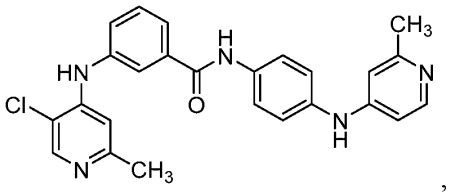
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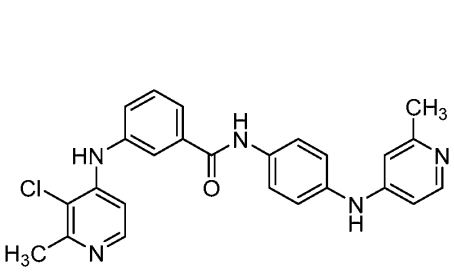
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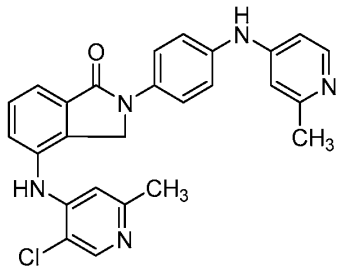
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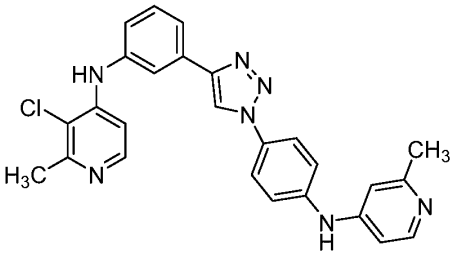
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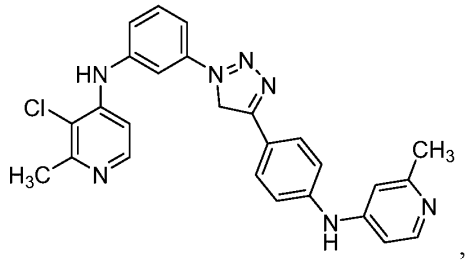
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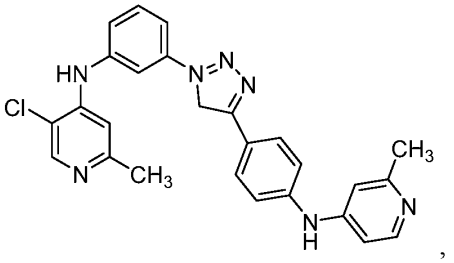
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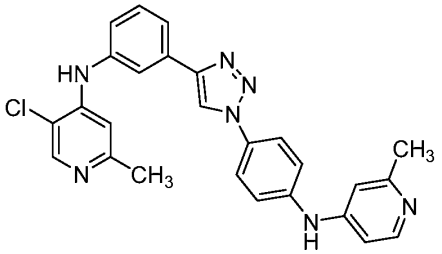
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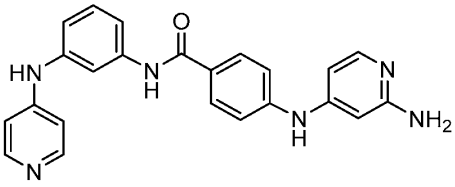
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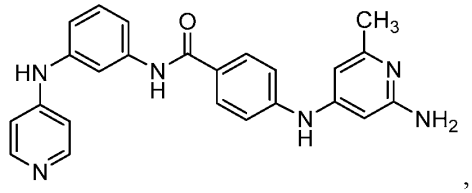
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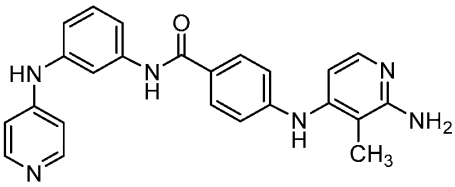
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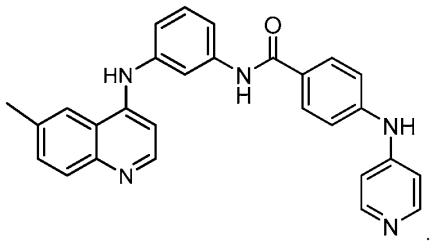
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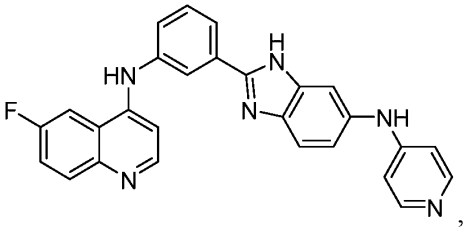
[0087] In any one of the embodiments disclosed herein, the compound of Formula Ib is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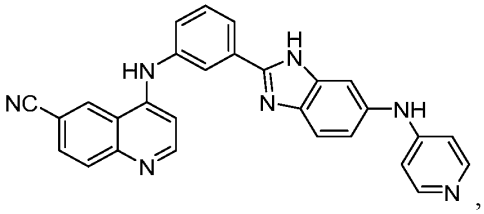
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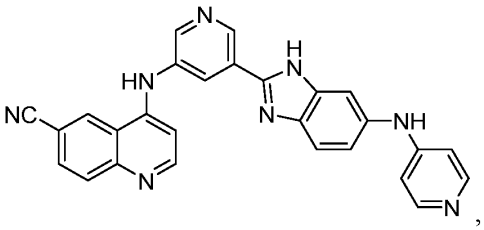
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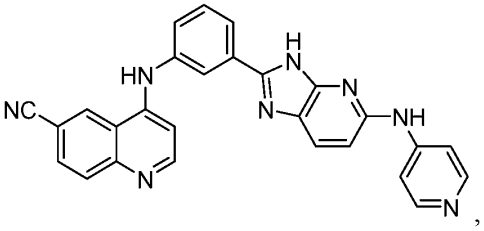
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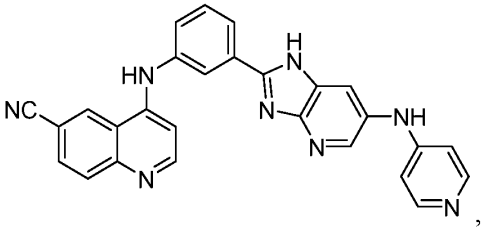
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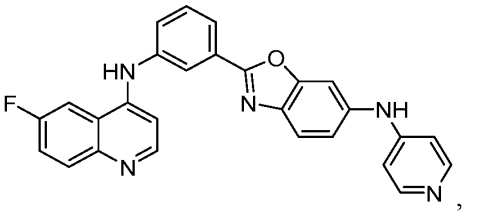
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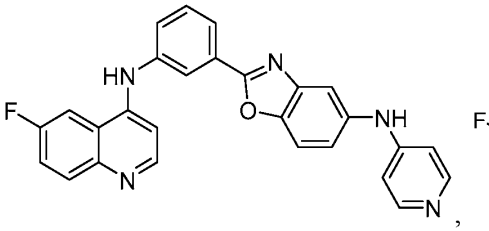
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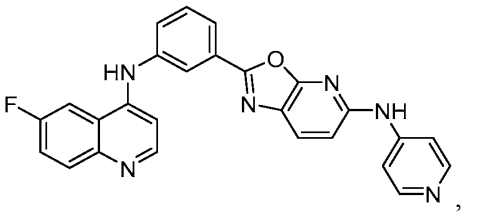
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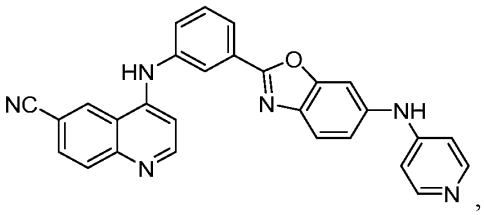
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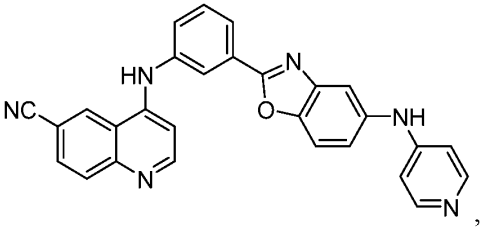
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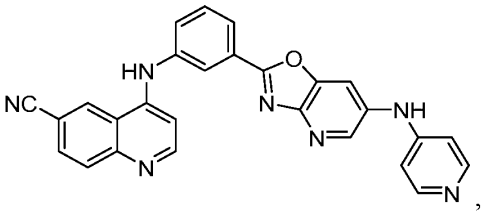
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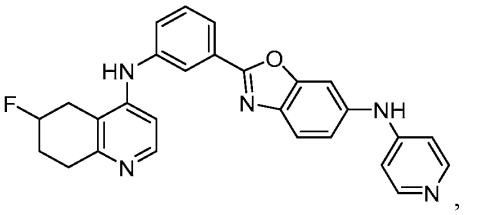
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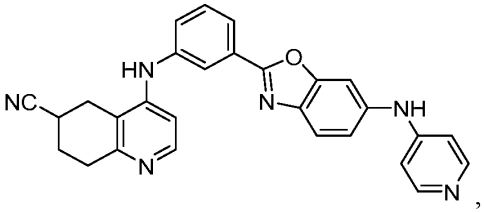
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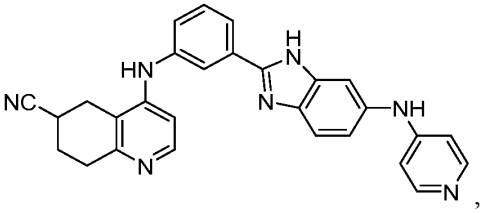
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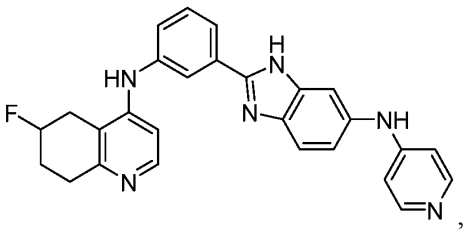
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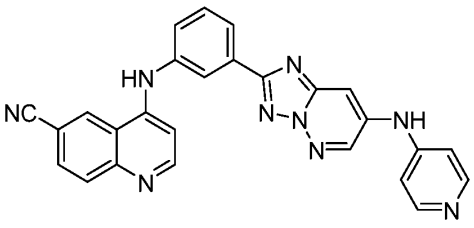
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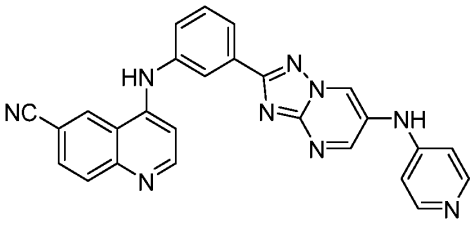
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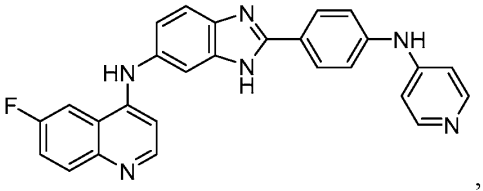
[0088] In any one of the embodiments disclosed herein, the compound of Formula Ic is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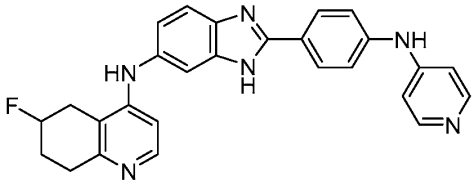
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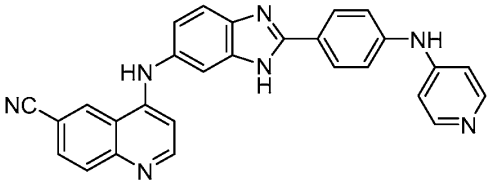
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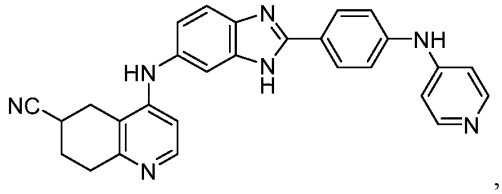
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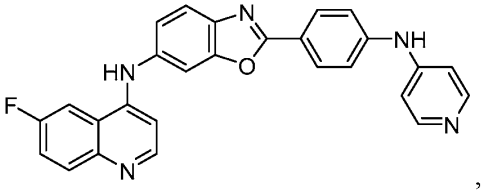
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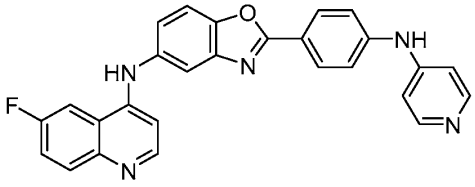
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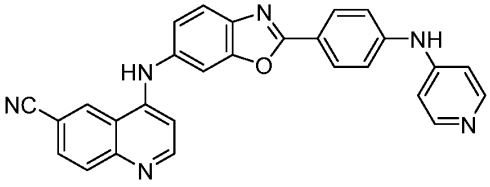
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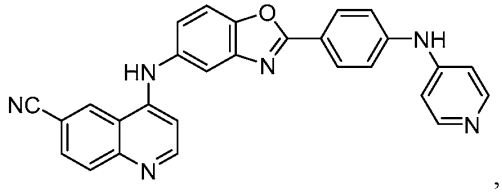
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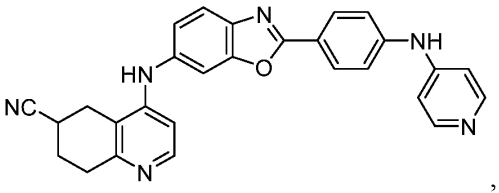
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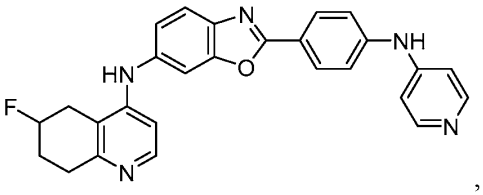
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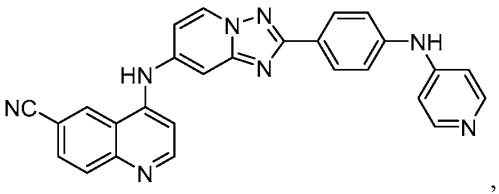
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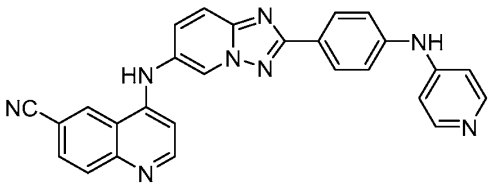
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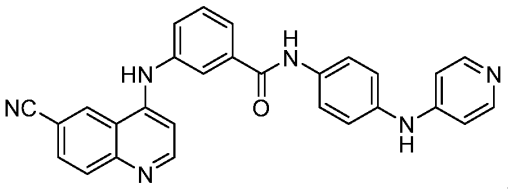
[0089] In any one of the embodiments disclosed herein, the compound is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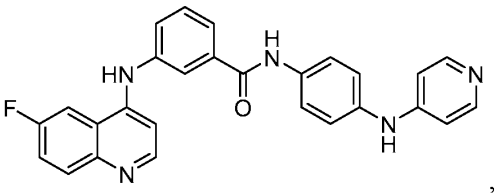
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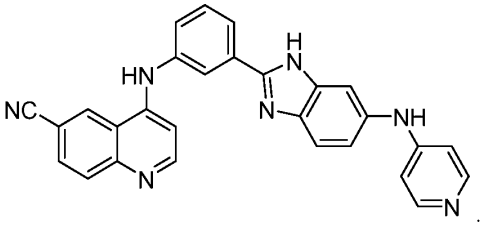
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[0090] In any one of the embodiments disclosed herein, the compound is selected from the group consisting of compounds 2-22 in Examples 2-22, respectively.

[0091] In another aspect, a method of treating a disease in a subject in need thereof is described, including administering to the subject an effective amount of the compound of any one of the embodiments disclosed herein.

[0092] In any one of the embodiments described herein, the disease is selected from the group consisting of neurodegenerative disease, cachexia, anorexia, obesity, obesity's complication, inflammatory disease, viral-induced inflammatory reaction, Gulf War Syndrome, tuberous sclerosis, retinitis pigmentosa, transplant rejection, cancer, an autoimmune disease, ischemic tissue injury, traumatic tissue injury and a combination thereof.

[0093] In any one of the embodiments described herein, the disease is neurodegenerative disease.

[0094] In any one of the embodiments described herein, the neurodegenerative disease is selected from the group consisting of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Motor Neuron Disease, Huntington's disease, HIV-induced neurodegeneration, Lewy Body Disease, spinal muscular atrophy, prion disease, spinocerebellar ataxia, familial amyloid polyneuropathy, multiple sclerosis, and a combination thereof.

[0095] In any one of the embodiments described herein, the disease is cachexia or anorexia.

[0096] In any one of the embodiments described herein, the disease is obesity or obesity's complication.

[0097] In any one of the embodiments described herein, the obesity's complication is selected from the group consisting of glucose intolerance, hepatic steatosis, dyslipidemia, and a combination thereof.

[0098] In any one of the embodiments described herein, the disease is inflammatory disease.

[0099] In any one of the embodiments described herein, the inflammatory disease is selected from the group consisting of atopic dermatitis, allergy, asthma, and a combination thereof.

[0100] In any one of the embodiments described herein, the disease is viral-induced inflammatory reaction.

[0101] In any one of the embodiments described herein, the viral-induced inflammatory reaction is SARS-induced inflammatory pneumonitis, coronavirus disease 2019, or a combination thereof.

[0102] In any one of the embodiments described herein, the disease is Gulf War Syndrome or tuberous sclerosis.

[0103] In any one of the embodiments described herein, the disease is retinitis pigmentosa or transplant rejection.

[0104] In any one of the embodiments described herein, the disease is ischemic tissue injury or traumatic tissue injury.

[0105] In any one of the embodiments described herein, the disease is cancer.

[0106] In any one of the embodiments described herein, the cancer is selected from the group consisting of adult T-cell leukemia/lymphoma, bladder, brain, breast, cervical, colorectal, esophageal, kidney, liver, lung, nasopharyngeal, pancreatic, prostate, skin, stomach, uterine, ovarian, and testicular cancer.

[0107] In any one of the embodiments described herein, the cancer is leukemia.

[0108] In any one of the embodiments described herein, the leukemia is adult T-cell leukemia/lymphoma.

[0109] In any one of the embodiments described herein, the adult T-cell leukemia/lymphoma is caused by human T-cell lymphotropic virus.

[0110] In any one of the embodiments described herein, the disease is autoimmune disease.

[0111] In any one of the embodiments described herein, the autoimmune disease is selected from the group consisting of achalasia, Addison's disease, adult Still's disease, agammaglobulinemia, alopecia areata, amyloidosis, ankylosing spondylitis, anti-glomerular basement membrane disease, anti-tubular basement membrane antibody nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease, autoimmune myocarditis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticaria, axonal and neuronal neuropathy, Baló disease, Behcet's disease, benign mucosal pemphigoid, bullous pemphigoid, Castleman disease, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, chronic recurrent multifocal osteomyelitis, Churg-Strauss syndrome, eosinophilic granulomatosis, cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis, eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura, pemphigoid gestationis, hidradenitis suppurativa (acne inversa), hypogammalglobulinemia, IgA nephropathy, IgG4-related sclerosing disease, immune

thrombocytopenic purpura, inclusion body myositis, interstitial cystitis, juvenile arthritis, juvenile diabetes (type 1 diabetes), juvenile myositis, Kawasaki disease, Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease, lupus, chronic Lyme disease, Meniere's disease, microscopic polyangiitis, mixed connective tissue disease, Mooren's ulcer, Mucha-Habermann disease, multifocal motor neuropathy, multiple sclerosis, myasthenia gravis, myositis, narcolepsy, neonatal lupus, neuromyelitis optica, neutropenia, ocular cicatricial pemphigoid, optic neuritis, palindromic rheumatism, pediatric autoimmune neuropsychiatric disorder, paraneoplastic cerebellar degeneration, paroxysmal nocturnal hemoglobinuria, Parry Romberg syndrome, pars planitis (peripheral uveitis), Parsonage-Turner syndrome, pemphigus, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia, POEMS syndrome, polyarteritis nodosa, polyglandular syndrome type I, polyglandular syndrome type II, polyglandular syndrome type III, polymyalgia rheumatica, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, progesterone dermatitis, psoriasis, psoriatic arthritis, pure red cell aplasia, pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy, relapsing polychondritis, restless legs syndrome, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjögren's syndrome, sperm and testicular autoimmunity, stiff person syndrome, subacute bacterial endocarditis, Susac's syndrome, sympathetic ophthalmia, Takayasu's arteritis, temporal arteritis (giant cell arteritis), thrombocytopenic purpura, Tolosa-Hunt syndrome, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, uveitis, vasculitis, vitiligo, Vogt-Koyanagi-Harada disease, and a combination thereof.

[0112] In any one of the embodiments described herein, the compound modulates Akt3 in immune cells.

[0113] In any one of the embodiments described herein, the immune cells are selected from the group consisting of T cells, B cells, macrophages, and glial cells.

[0114] In any one of the embodiments described herein, the glial cells are astrocytes, microglia, or oligodendrocytes.

[0115] In any one of the embodiments described herein, the T cells are T regulatory cells.

[0116] In any one of the embodiments described herein, the compound activates Akt3 signaling.

[0117] In any one of the embodiments described herein, the compound inhibits Akt3 signaling.

[0118] In any one of the embodiments described herein, the compound increases T regulatory cell activity or production.

[0119] In any one of the embodiments described herein, the compound decreases T regulatory cell activity or production.

[0120] In any one of the embodiments described herein, the method further includes administering a second therapeutic agent to the subject.

[0121] In any one of the embodiments described herein, the second therapeutic agent is selected from the group consisting of a nutrient supplementation, a chemotherapeutic, an anti-inflammatory, an immunosuppressant, a cholinesterase inhibitor, an antidepressant, an anxiolytic, an antipsychotic, riluzole, edavarone, a dopamine agonist, a MAO B inhibitor, a catechol O-methyltransferase inhibitor, an anticholinergic, an anticonvulsant, tetrabenazine, carbidopa-levodopa, an antispastic, an antibody, a fusion protein, an enzyme, a nucleic acid, a ribonucleic acid, an anti-proliferative, a cytotoxic agent, an appetite stimulant, a 5-HT3 antagonist, a Cox-2 inhibitor, and a combination thereof.

[0122] In any one of the embodiments described herein, the method further includes treating the subject with an immune therapeutic agent, an immune modulator, an costimulatory activating agonist, a cytokine, a chemokine, a chemokine factor, an oncolytic virus, a biologics, a vaccine, a small molecule, a targeted therapy, an anti-inflammatory agent, a cell therapy, a chemotherapeutic agent, or radiation therapy.

[0123] Any one of the embodiments disclosed herein may be properly combined with any other embodiment disclosed herein. The combination of any one of the embodiments disclosed herein with any other embodiments disclosed herein is expressly contemplated. Specifically, the selection of one or more embodiments for one substituent group can be properly combined with the selection of one or more particular embodiments for any other substituent group. Such combination can be made in any one or more embodiments of the application described herein or any formula described herein.

DESCRIPTION OF THE DRAWINGS

[0124] The application is described with reference to the following figures, which are presented for the purpose of illustration only and are not intended to be limiting. In the Drawings:

[0125] Figure 1 shows evaluation of iTreg induction (FoxP3) from human CD4 T cells treated with Compound 22 in the presence of anti-CD3/anti-CD28/IL-2/TGFβ, according to one or more embodiments described herein.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0126] It should be appreciated that this disclosure is not limited to the compositions and methods described herein as well as the experimental conditions described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing certain embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

[0127] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Any compositions, methods, and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention.

[0128] The use of the terms "a," "an," "the," and similar referents in the context of describing the presently claimed invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context.

[0129] Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.

[0130] Use of the term "about" is intended to describe values either above or below the stated value in a range of approximately ± 10%. In some embodiments, the values may be either above or below the stated value in a range of approximately ± 5%. In some embodiments, the values may be either above or below the stated value in a range of approximately ± 2%. In other embodiments, the values may be either above or below the stated value in a range of approximately ± 1%. The preceding ranges are intended to be made

clear by context, and no further limitation is implied. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, "exemplary", "such as", "for example", "including, but not limited to") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise indicated.

[0131] The following are definitions of terms used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art.

[0132] The terms "alkyl" and "alk" refer to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms. Exemplary "alkyl" groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. The term "(C_1-C_4)alkyl" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, and isobutyl. "Substituted alkyl" refers to an alkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF_3 or an alkyl group bearing CCl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, bicycloalkyl, spiroalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $-N=S(=O)(R_a)$, $S(=O)(=NR_a)(=N(R_a)_2)$ (linked to the molecule via S or N), $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, where each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle, and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. In some embodiments, groups such as

alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, heterocycle, and aryl can themselves be optionally substituted.

[0133] The term "heteroalkyl" refers to a straight- or branched-chain alkyl group preferably having from 2 to 12 carbons, more preferably 2 to 10 carbons in the chain, one or more of which has been replaced by a heteroatom selected from the group consisting of S, O, P, and N. Exemplary heteroalkyls include, but are not limited to, alkyl ethers, secondary and tertiary alkyl amines, alkyl sulfides, and the like. The group may be a terminal group or a bridging group.

[0134] The term "alkenyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon-carbon double bond. Exemplary such groups include ethenyl or allyl. The term "C_2-C_6 alkenyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 6 carbon atoms and at least one carbon-carbon double bond, such as ethylenyl, propenyl, 2-propenyl, (*E*)-but-2-enyl, (*Z*)-but-2-enyl,
2-methy(*E*)-but-2-enyl, 2-methy(*Z*)-but-2-enyl, 2,3-dimethy-but-2-enyl, (*Z*)-pent-2-enyl, (*E*)-pent-1-enyl, (*Z*)-hex-1-enyl, (*E*)-pent-2-enyl, (*Z*)-hex-2-enyl, (*E*)-hex-2-enyl, (*Z*)-hex-1-enyl, (*E*)-hex-1-enyl, (*Z*)-hex-3-enyl, (*E*)-hex-3-enyl, and (*E*)-hex-1,3-dienyl. "Substituted alkenyl" refers to an alkenyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, halogen, alkyl, halogenated alkyl (*i.e.*, an alkyl group bearing a single halogen substituent or multiple halogen substituents such as CF_3 or CCl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, bicycloalkyl, spiroalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $-N=S(=O)(R_a)$, $-R_aS(=O)(=NR_a)$, $S(=O)(=NR_a)(=N(R_a)_2)$ (linked to the molecule via R_a or N), $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, where each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted.

[0135] The term "alkynyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. Exemplary groups include ethynyl. The term "C_2-C_6 alkynyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 6 carbon atoms and at least one carbon-carbon triple bond, such as ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, pent-1-ynyl, pent-2-ynyl, hex-1-ynyl, hex-2-ynyl, or hex-3-ynyl. "Substituted alkynyl" refers to alkynyl substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF_3 or an alkyl group bearing CCl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, bicycloalkyl, spiroalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $–N=S(=O)(R_a)$, $–R_aS(=O)(=NR_a)$, $S(=O)(=NR_a)(=N(R_a)_2)$ (linked to the molecule via R_a or N), $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, where each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally to form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted.

[0136] The term "cycloalkyl" refers to a fully saturated cyclic hydrocarbon group containing from 1 to 4 rings and 3 to 8 carbons per ring. "C_3-C_7 cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. "Substituted cycloalkyl" refers to a cycloalkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF_3 or an alkyl group bearing CCl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, bicycloalkyl, spiroalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $–N=S(=O)(R_a)$, $–R_aS(=O)(=NR_a)$, $S(=O)(=NR_a)(=N(R_a)_2)$ (linked to the molecule via R_a or N), $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$,

$S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, where each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally to form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0137] The term "bicycloalkyl" or "spiroalkyl" refers to a compound containing at least one cycloalkyl ring that shares one or more ring atoms with at least one other cycloalkyl ring. The term "heterobicycloalkyl" or "heterospiroalkyl" refers to a bicycloalkyl group in which at least one, preferably from 1-3, carbon atoms in at least one ring are replaced with a heteroatom selected from the group consisting of N, S, O, or P. The heteroatom may occupy a terminal position or a bridging position (*i.e.*, a connection point between two rings). Exemplary bicycloalkyl groups include adamantyl, bicyclo[1.1.1]pentyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.1.1]hexyl, octahydropentalenyl, bicyclo[3.2.1]octyl, bicyclo[3.3.3]undecanyl, decahydronaphthalenyl, bicyclo[3.2.0]heptyl, octahydro-1*H*-indenyl, bicyclo[4.2.1]nonanyl, and the like. Exemplary spiro bicycloalkyl groups include spiro[4.4]nonyl, spiro[3.3]heptyl, spiro[5.5]undecyl, spiro[3.5]nonyl, spiro[4.5]decyl, and the like. "Substituted bicycloalkyl", "substituted spiroalkyl", "substituted heterobicycloalkyl", and "substituted heterospiroalkyl" refer to a bicycloalkyl, spiroalkyl, heterobicycloalkyl, or heterospiroalkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF_3 or an alkyl group bearing CCl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, bicycloalkyl, spiroalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $–N=S(=O)(R_a)$, $–R_aS(=O)(=NR_a)$, $S(=O)(=NR_a)(=N(R_a)_2)$

(linked to the molecule via R_a or N), $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, where each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally to form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0138] The term "heterocycloalkyl" or "cycloheteroalkyl" refers to a saturated or partially saturated monocyclic, bicyclic, or polycyclic ring containing at least one heteroatom selected from the group consisting of nitrogen, sulfur, and oxygen, preferably from 1 to 3 heteroatoms in at least one ring. Each ring is preferably from 3 to 10 membered, more preferably 4 to 7 membered. Examples of suitable heterocycloalkyl substituents include, but are not limited to, azetidinyl, oxetanyl, pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morpholino, 1,3-diazepanyl, 1,4-diazepanyl, 1,4-oxazepanyl, and 1,4-oxathiapanyl. The group may be a terminal group or a bridging group.

[0139] The term "cycloalkenyl" refers to a partially unsaturated cyclic hydrocarbon group containing 1 to 4 rings and 3 to 8 carbons per ring. Exemplary such groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, etc. "Substituted cycloalkenyl" refers to a cycloalkenyl group substituted with one more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF_3 or an alkyl group bearing CCl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, bicycloalkyl, spiroalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $-N=S(=O)(R_a)$, $-R_aS(=O)(=NR_a)$, $S(=O)(=NR_a)(=N(R_a)_2)$ (linked to the molecule via R_a or N), $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$,

$S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, where each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c, and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0140] The term "aryl" refers to cyclic, aromatic hydrocarbon groups that have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two or more aromatic rings (bicyclic, *etc.*), the aromatic rings of the aryl group may be joined at a single point (*e.g.*, biphenyl), or fused (*e.g.*, naphthyl, phenanthrenyl and the like). The term "fused aromatic ring" refers to a molecular structure having two or more aromatic rings where two adjacent aromatic rings have two carbon atoms in common. "Substituted aryl" refers to an aryl group substituted by one or more substituents, preferably 1 to 3 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF_3 or an alkyl group bearing CCl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, bicycloalkyl, spiroalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $-N=S(=O)(R_a)$, $-R_aS(=O)(=NR_a)$, $S(=O)(=NR_a)(=N(R_a)_2)$ (linked to the molecule via R_a or N), $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, where each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded

optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted. Exemplary substituents also include fused cyclic groups, especially fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle, and aryl substituents can themselves be optionally substituted.

[0141] The term "biaryl" refers to two aryl groups linked by a single bond. The term "biheteroaryl" refers to two heteroaryl groups linked by a single bond. Similarly, the term "heteroaryl-aryl" refers to a heteroaryl group and an aryl group linked by a single bond and the term "aryl-heteroaryl" refers to an aryl group and a heteroaryl group linked by a single bond. In certain embodiments, the numbers of the ring atoms in the heteroaryl and/or aryl rings are used to specify the sizes of the aryl or heteroaryl ring in the substituents. For example, 5,6-heteroaryl-aryl refers to a substituent in which a 5-membered heteroaryl is linked to a 6-membered aryl group. Other combinations and ring sizes can be similarly specified.

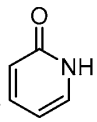
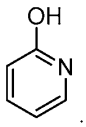
[0142] The term "carbocycle" or "carbon cycle" refers to a fully saturated or partially saturated cyclic hydrocarbon group containing from 1 to 4 rings and 3 to 8 carbons per ring, or cyclic, aromatic hydrocarbon groups that have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as phenyl, biphenyl, or naphthyl. The term "carbocycle" encompasses cycloalkyl, cycloalkenyl, cycloalkynyl, and aryl as defined hereinabove. The term "substituted carbocycle" refers to carbocycle or carbocyclic groups substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, those described above for substituted cycloalkyl, substituted cycloalkenyl, substituted cycloalkynyl, and substituted aryl. Exemplary substituents also include spiro-attached or fused cyclic substituents at any available point or points of attachment, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle, and aryl substituents can themselves be optionally substituted.

[0143] The terms "heterocycle" and "heterocyclic" refer to fully saturated, or partially or fully unsaturated, including aromatic (*i.e.*, "heteroaryl") cyclic groups (for example, 3 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 8 to 16 membered tricyclic ring systems) which have at least one heteroatom in at least one carbon atom-containing ring.

Each ring of the heterocyclic group may independently be saturated, or partially or fully unsaturated. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from the group consisting of nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. (The term "heteroarylium" refers to a heteroaryl group bearing a quaternary nitrogen atom and thus a positive charge.) The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system. Exemplary monocyclic heterocyclic groups include azetidinyl, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, hexahydrodiazepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like. Exemplary bicyclic heterocyclic groups include indolyl, indolinyl, isoindolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, benzo[*d*][1,3]dioxolyl, dihydro-2H-benzo[*b*][1,4]oxazine, 2,3-dihydrobenzo[b][1,4]dioxinyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofurazanyl, dihydrobenzo[*d*]oxazole, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), triazinylazepinyl, tetrahydroquinolinyl, and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl, and the like. The term "partially saturated bicyclic heteroaryl" refers to a bicyclic heteroaryl that is partially saturated, e.g., having a saturated cycloalkyl or heterocyclic alkyl ring.

[0144] "Substituted heterocycle" and "substituted heterocyclic" (such as "substituted heteroaryl") refer to heterocycle or heterocyclic groups substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF_3 or an alkyl group bearing CCl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3,

OCF_3, cycloalkyl, bicycloalkyl, spiroalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $-N=S(=O)(R_a)$, $-R_aS(=O)(=NR_a)$, $S(=O)(=NR_a)(=N(R_a)_2)$ (linked to the molecule via R_a or N), $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, where each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cyclic substituents at any available point or points of attachment, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0145] The term "oxo" refers to  substituent group, which may be attached to a carbon ring atom on a carboncycle or heterocycle. When an oxo substituent group is attached to a carbon ring atom on an aromatic group, *e.g.*, aryl or heteroaryl, the bonds on the aromatic ring may be rearranged to satisfy the valence requirement. For instance, a pyridine with a 2-oxo substituent group may have the structure of  , which also includes its tautomeric form of  .

[0146] The term "alkylamino" refers to a group having the structure –NHR', where R' is hydrogen, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, as defined herein. Examples of alkylamino groups include, but are not limited to, methylamino, ethylamino, n-propylamino, iso-propylamino, cyclopropylamino, n-butylamino, tert-butylamino, neopentylamino, n-pentylamino, hexylamino, cyclohexylamino, and the like.

[0147] The term "dialkylamino" refers to a group having the structure –NRR', where R and R' are each independently alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cyclolalkenyl, aryl or substituted aryl, heterocycle or substituted heterocycle, as defined herein. R and R' may be the same or different in a dialkyamino moiety. Examples of dialkylamino groups include, but are not limited to, dimethylamino, methyl ethylamino, diethylamino, methylpropylamino, di(n-propyl)amino, di(iso-propyl)amino, di(cyclopropyl)amino, di(n-butyl)amino, di(tert-butyl)amino, di(neopentyl)amino, di(n-pentyl)amino, di(hexyl)amino, di(cyclohexyl)amino, and the like. In certain embodiments, R and R' are linked to form a cyclic structure. The resulting cyclic structure may be aromatic or non-aromatic. Examples of the resulting cyclic structure include, but are not limited to, aziridinyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrrolyl, imidazolyl, 1,2,4-triazolyl, and tetrazolyl.

[0148] The terms "halogen" or "halo" refer to chlorine, bromine, fluorine, or iodine.

[0149] The term "substituted" refers to the embodiments in which a molecule, molecular moiety, or substituent group (*e.g.*, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl group or any other group disclosed herein) is substituted with one or more substituents, where valence permits, preferably 1 to 6 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF_3 or an alkyl group bearing CCl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, alkyl, halogen-substituted alkyl, cycloalkyl, bicycloalkyl, spiroalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $–N=S(=O)(R_a)$, $–R_aS(=O)(=NR_a)$, $S(=O)(=NR_a)(=N(R_a)_2)$ (linked to the molecule via R_a or N), $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, where each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. In the aforementioned exemplary substituents, groups such as alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, heterocycle,

and aryl can themselves be optionally substituted. The term "optionally substituted" refers to the embodiments in which a molecule, molecular moiety or substituent group (*e.g.*, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl group or any other group disclosed herein) may or may not be substituted with aforementioned one or more substituents.

[0150] Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

[0151] The compounds of the present invention may form salts which are also within the scope of this invention. Reference to a compound of the present invention is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of the present invention contains both a basic moiety, such as but not limited to a pyridine or imidazole, and an acidic moiety such as but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically-acceptable (*i.e.*, non-toxic, physiologically-acceptable) salts are preferred, although other salts are also useful, *e.g.*, in isolation or purification steps which may be employed during preparation. Salts of the compounds of the present invention may be formed, for example, by reacting a compound described herein with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates, or in an aqueous medium followed by lyophilization.

[0152] The compounds of the present invention which contain a basic moiety, such as but not limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid; for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, hydroxyethanesulfonates (*e.g.*, 2-hydroxyethanesulfonates), lactates, maleates, methanesulfonates, naphthalenesulfonates (*e.g.*, 2-naphthalenesulfonates), nicotinates, nitrates, oxalates, pectinates, persulfates, phenylpropionates (*e.g.*, 3-phenylpropionates), phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those

formed with sulfuric acid), sulfonates, tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

[0153] The compounds of the present invention which contain an acidic moiety, such as but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl) ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glycamides, t-butyl amines, and salts with amino acids such as arginine, lysine, and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.,* methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (*e.g.,* dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.,* decyl, lauryl, myristyl and stearyl chlorides, bromides, and iodides), aralkyl halides (*e.g.,* benzyl and phenethyl bromides), and others.

[0154] Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug" as employed herein denotes a compound that, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the present invention, or a salt and/or solvate thereof. Solvates of the compounds of the present invention include, for example, hydrates.

[0155] Compounds of the present invention, and salts or solvates thereof, may exist in their tautomeric form (for example, as an amide or iminol). All such tautomeric forms are contemplated herein as part of the present invention. As used herein, any depicted structure of the compound includes the tautomeric forms thereof.

[0156] All stereoisomers of the present compounds (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers (*e.g.*, as a pure or substantially pure optical isomer having a specified activity), or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the *S* or *R* configuration as defined by the International Union of Pure and Applied Chemistry (IUPAC) 1974 Recommendations. The racemic forms can be resolved by physical methods, such as, for

example, fractional crystallization, separation or crystallization of diastereomeric derivatives, or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

[0157] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 90%, for example, equal to or greater than 95%, equal to or greater than 99% of the compounds ("substantially pure" compounds), which is then used or formulated as described herein. Such "substantially pure" compounds of the present invention are also contemplated herein as part of the present invention.

[0158] All configurational isomers of the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention embraces both *cis* (*Z*) and *trans* (*E*) alkene isomers, as well as *cis* and *trans* isomers of cyclic hydrocarbon or heterocyclic rings.

[0159] Throughout the specification, groups and substituents thereof may be chosen to provide stable moieties and compounds.

[0160] Definitions of specific functional groups and chemical terms are described in more detail herein. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito (1999), the entire contents of which are incorporated herein by reference.

[0161] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0162] Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

[0163] The present invention also includes isotopically labeled compounds, which are identical to the compounds disclosed 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. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, or an enantiomer, diastereomer, tautomer, or pharmaceutically-acceptable salt or solvate thereof, which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, 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 heavier isotopes such as deuterium, *i.e.*, ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Isotopically-labeled compounds can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily-available isotopically-labeled reagent for a non-isotopically-labeled reagent.

[0164] If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[0165] It will be appreciated that the compounds, as described herein, may be substituted with any number of substituents or functional moieties. In general, the term "substituted" whether preceded by the term "optionally" or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those that result in the formation of stable compounds useful in the treatment, for example, of proliferative disorders. The term "stable," as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

[0166] As used herein, the terms "cancer" and, equivalently, "tumor" refer to a condition in which abnormally replicating cells of host origin are present in a detectable amount in a subject. The cancer can be a malignant or non-malignant cancer. Cancers or tumors include, but are not limited to, adult T-cell leukemia/lymphoma (including that caused by human T-cell lymphotropic virus (HTLV-1)), biliary tract cancer; brain cancer; breast cancer; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric (stomach) cancer; intraepithelial neoplasms; leukemias; lymphomas; liver cancer; lung cancer (*e.g.*, small cell and non-small cell); melanoma; neuroblastomas; oral cancer; ovarian cancer; pancreatic cancer; prostate cancer; rectal cancer; renal (kidney) cancer; sarcomas; skin cancer; testicular cancer; thyroid cancer; as well as other carcinomas and sarcomas. As used herein, the term "lymphoma" refers to cancer of the lymphatic system or a blood cancer that develops from lymphocytes. Cancers can be primary or metastatic. Diseases other than cancers may be associated with mutational alternation of component of Ras signaling

pathways and the compound disclosed herein may be used to treat these non-cancer diseases. Such non-cancer diseases may include: neurofibromatosis; Leopard syndrome; Noonan syndrome; Legius syndrome; Costello syndrome; cardio-facio-cutaneous syndrome; hereditary gingival fibromatosis type 1; autoimmune lymphoproliferative syndrome; and capillary malformation-arterovenous malformation.

[0167] As used herein, "effective amount" refers to any amount that is necessary or sufficient for achieving or promoting a desired outcome. In some instances, an effective amount is a therapeutically effective amount. A therapeutically effective amount is any amount that is necessary or sufficient for promoting or achieving a desired biological response in a subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular agent being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular agent without necessitating undue experimentation.

[0168] As used herein, the term "subject" refers to a vertebrate animal. In one embodiment, the subject is a mammal or a mammalian species. In one embodiment, the subject is a human. In other embodiments, the subject is a non-human vertebrate animal, including, without limitation, non-human primates, laboratory animals, livestock, racehorses, domesticated animals, and non-domesticated animals.

[0169] The term "immune cell" as used herein refers to cells of the innate and acquired immune system including, but not limited to, neutrophils, eosinophils, basophils, glial cells (*e.g.*, astrocytes, microglia, and oligodendrocytes), monocytes, macrophages, dendritic cells, lymphocytes including B cells, T cells, and NK cells.

[0170] As used herein, "conventional T cells" are T lymphocytes that express an αβ T cell receptor ("TCR") as well as a co-receptor CD4 or CD8. Conventional T cells are present in the peripheral blood, lymph nodes, and tissues. *See* Roberts and Girardi, "Conventional and Unconventional T Cells", Clinical and Basic Immunodermatology, pp. 85-104, (Gaspari and Tyring (ed.)), Springer London (2008), herein incorporated by reference in its entirety. As used herein, "unconventional T cells" are lymphocytes that express a γδ TCR and may commonly reside in an epithelial environment, such as the skin, gastrointestinal tract, or genitourinary tract. Another subset of unconventional T cells is the invariant natural killer T ("NKT") cell, which has phenotypic and functional capacities of a conventional T cell, as

well as features of natural killer cells (*e.g.*, cytolytic activity). *See id.* As used herein, regulatory T cells ("Tregs") are a subpopulation of T cells which modulate the immune system, maintain tolerance to self-antigens, abrogate autoimmune disease, and otherwise suppress immune-stimulating or activating responses of other cells. Tregs come in many forms, with the most well-understood being those that express CD4, CD25, and Foxp3. As used herein, "natural Treg" or "nTreg" refer to a Treg or cells that develop in the thymus. As used herein, "induced Treg" or "iTreg" refer to a Treg or cells that develop from mature CD4+ conventional T cells outside of the thymus.

[0171] The "activity" of Akt3 refers to the biological function of the Akt3 protein. Bioactivity can be increased or reduced by increasing or reducing the activity of basal levels of the protein, increasing or reducing the avidity of basal levels of the protein, the quantity of the protein, the ratio of Akt3 relative to one or more other isoforms of Akt (*e.g.*, Akt1 or Akt2) protein, increasing or reducing the expression levels of the protein (including by increasing or decreasing mRNA expression of Akt3), or a combination thereof. For example, bioavailable Akt3 protein is a protein that has kinase activity and can bind to and phosphorylate a substrate of Akt3. Akt3 protein that is not bioavailable includes Akt3 protein that is mis-localized or incapable of binding to and phosphorylating Akt substrates.

[0172] In some embodiments, the disclosed compounds selectively modulate Akt3 compared to Akt1 and Akt2. In some embodiments, any one of the disclosed compounds do not modulate Akt1 and Akt2 to a statistically significant degree. In other embodiments, modulation of Akt3 by the disclosed compounds is about 5, 10, 15, 50, 100, 1000, or 5000-fold greater than their modulations of Akt1 and/or Akt2.

[0173] As used herein, the term "peptide" or "polypeptide" refers to a chain of amino acids of any length, regardless of modification (*e.g.*, phosphorylation or glycosylation). The terms include proteins and fragments thereof. The polypeptides can be "exogenous," meaning that they are "heterologous," *i.e.*, foreign to the host cell being utilized, such as human polypeptide produced by a bacterial cell. Polypeptides are disclosed herein as amino acid residue sequences. Those sequences are written left to right in the direction from the amino to the carboxy terminus. In accordance with standard nomenclature, amino acid residue sequences are denominated by either a three letter or a single letter code as indicated as follows: alanine (Ala, A), arginine (Arg, R), asparagine (Asn, N), aspartic Acid (Asp, D), cysteine (Cys, C), glutamine (Gln, Q), glutamic Acid (Glu, E), glycine (Gly, G), histidine (His, H), isoleucine (Ile, I), leucine (Leu, L), lysine (Lys, K), methionine (Met, M),

phenylalanine (Phe, F), proline (Pro, P), serine (Ser, S), threonine (Thr, T), tryptophan (Trp, W), tyrosine (Tyr, Y), and valine (Val, V).

[0174] The term "stimulate expression of" means to affect expression of, for example, to induce expression or activity, or induce increased/greater expression or activity relative to normal, healthy controls.

[0175] The terms "immune activating response", "activating immune response", and "immune stimulating response" refer to a response that initiates, induces, enhances, or increases the activation or efficiency of innate or adaptive immunity. Such immune responses include, for example, the development of a beneficial humoral (antibody-mediated) and/or a cellular (mediated by antigen-specific T cells or their secretion products) response directed against a peptide in a recipient patient. Such a response can be an active response, induced by administration of immunogen, or a passive response, induced by administration of antibody or primed T-cells. A cellular immune response is elicited by the presentation of polypeptide epitopes in association with class I or class II major histocompatibility complex ("MHC") molecules to activate antigen-specific CD4+ T helper cells and/or CD8+ cytotoxic T cells. The response can also involve activation of monocytes, macrophages, NK cells, basophils, dendritic cells, astrocytes, microglia cells, eosinophils, activation or recruitment of neutrophils, or other components of innate immunity. The presence of a cell-mediated immunological response can be determined by proliferation assays (CD4+ T cells) or cytotoxic T lymphocyte ("CTL") assays. The relative contributions of humoral and cellular responses to the protective or therapeutic effect of an immunogen can be distinguished by separately isolating antibodies and T-cells from an immunized syngeneic animal and measuring protective or therapeutic effect in a second subject.

[0176] The terms "suppressive immune response" and "immune suppressive response" refer to a response that reduces or prevents the activation or efficiency of innate or adaptive immunity.

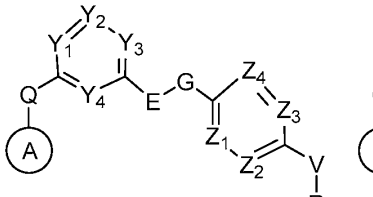
[0177] The term "immune tolerance" refers to any mechanism by which a potentially injurious immune response is prevented, suppressed, or shifted to a non-injurious immune response (*see* Bach, et al., *N. Eng. J. Med.*, 347:911-920 (2002)).

[0178] The terms "immunogenic agent" or "immunogen" refer to an agent capable of inducing an immunological response against itself on administration to a mammal, optionally in conjunction with an adjuvant.

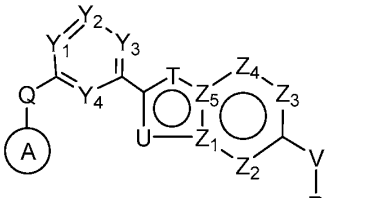
Compounds

[0179] In one aspect, a compound of Formula Ia, Ib, or Ic as an Akt3 modulator is described. Applicants have surprisingly discovered that the compounds disclosed herein modulate Akt3 activity, *e.g.*, activate or inhibit Akt3 activity, and/or a downstream event, depending on the structure and substitutions thereof.

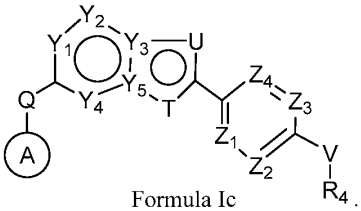
[0180] In one aspect, a compound of Formula Ia, Ib, or Ic is described,



Formula Ia ;



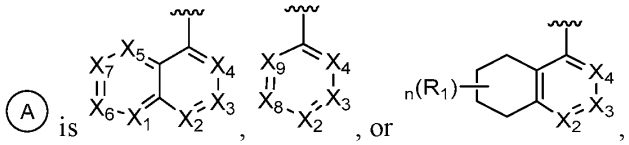
Formula Ib ; or



Formula Ic ;

or a pharmaceutically acceptable salt thereof,

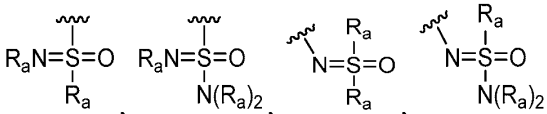
where:



A is , , or ,

each occurrence of X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, and X_9 are independently CR_1 or N;

R_1 is selected from the group consisting of H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, $(C_4$-$C_{10})$heterospiroalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $N(R_a)SO_2R_a$,



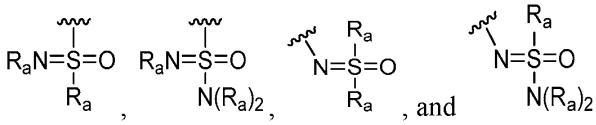
, , , and a partially saturated bicyclic heteroaryl optionally substituted by one or more $(C_1$-$C_6)$alkyl, halogenated $(C_1$-$C_6)$alkyl, $-SO_2R_a$, or $-SO_2N(R_a)_2$;

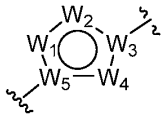
wherein the $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, aryl, and heteroaryl of R_1 are each optionally substituted by one or more $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, $-CN$, or $-N(R_a)_2$;

n is an integer from 0-4 where valence permits;

Q is $C(R_a)_2$, O, NR_a, $N(C=O)R_a$, or NSO_2R_a;

Y_1, Y_2, Y_3, Y_4 and Y_5 are each independently N or CR_2 where valance permits;

R_2 is selected from the group consisting of H, D, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$haloalkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$haloalkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$,  , and ;

–E-G– is $-(C=O)NR_x-$, $-NR_x(C=O)-$, $-N(R_x)(C=O)N(R_x)-$, $-O(C=O)N(R_x)-$, $-N(R_x)(C=O)O-$, $-SO_2NR_x-$, $-NR_xSO_2-$, or  ; where

each occurrence of R_x is independently H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, or heteroaryl; or wherein R_x and Y_3, R_x and Y_4, R_x and Z_1, or R_x and Z_4 taken together form an optionally substituted 5-6-membered heterocycle;

W_1, W_2, W_3, W_4, and W_5 are each independently CR_6, N, or NR_6 where valence permits;

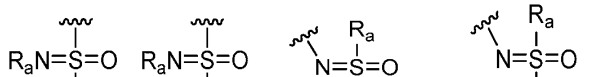
each occurrence of R_6 is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$haloalkyl;

each occurrence of T is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits;

each occurrence of U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits;

each occurrence of R_b is independently H or $(C_1\text{-}C_6)$alkyl;

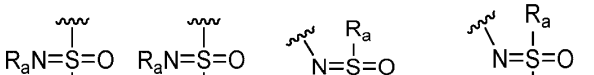
Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently N or CR_3 where valance permits;

R_3 is selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_4-C_{10})heterospiroalkyl, halogenated (C_3-C_7)heterocycloalkyl, aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $N(R_a)SO_2R_a$,  , and ;

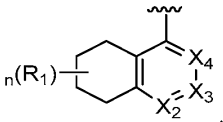
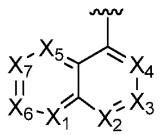
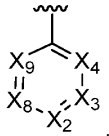
V is absent, $C(R_a)_2$, NR_a, $N(C=O)R_a$, NSO_2R_a or O;

R_4 is selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_4-C_{10})heterospiroalkyl, aryl, heteroaryl, each optionally substituted with one or more R_5;

or alternatively V and R_4 taken together form a (C_3-C_7)heterocycloalkyl or (C_4-C_{10})heterospiroalkyl;

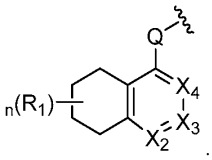
each occurrence of R_5 is independently selected from the group consisting of H, halogen, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_4-C_{10})heterospiroalkyl, halogenated (C_3-C_7)heterocycloalkyl, aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$, $N(R_a)COR_a$,  , and ; and

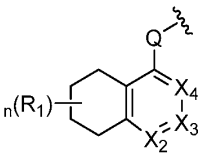
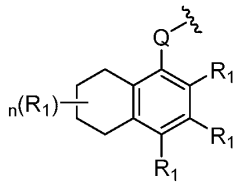
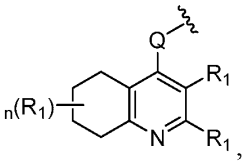
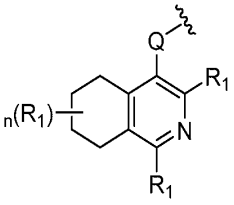
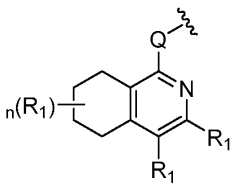
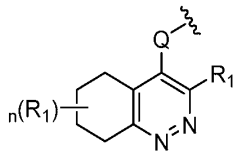
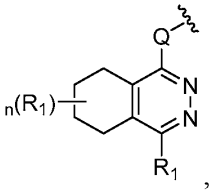
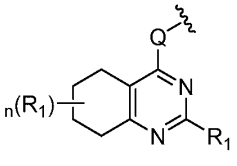
each occurrence of R_a is independently H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, aryl, or heteroaryl, or two R_a taken together form a 4-6-membered ring optionally substituted with halogen or (C_1-C_6)alkyl.

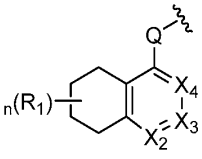
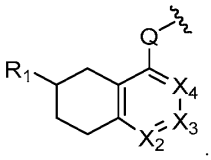
[0181] In some embodiments, Ⓐ is  . In some embodiments, Ⓐ is  . In some embodiments, Ⓐ is  .

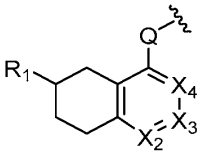
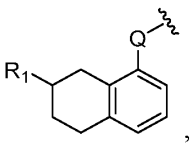
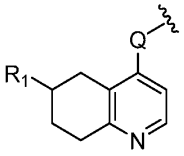
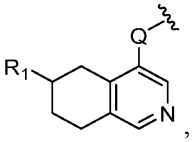
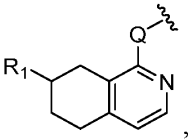
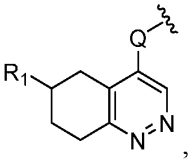
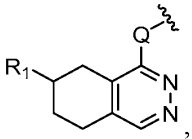
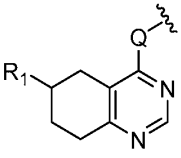
[0182] In some embodiments, Q is $C(R_a)_2$, O, or NR_a. In some embodiments, Q is O. In some embodiments, Q is NR_a. In some embodiments, Q is NH. In some embodiments, Q is NCH_3 or NCH_2CH_3. In some embodiments, Q is $N(C=O)R_a$ or NSO_2R_a. In some embodiments, Q is N(C=O)H. In some embodiments, Q is $N(C=O)CH_3$ or $N(C=O)CH_2CH_3$. In some embodiments, Q is NSO_2H. In some embodiments, Q is NSO_2CH_3 or $NSO_2CH_2CH_3$.

[0183] In some embodiments, n is 0, 1, 2, 3, or 4. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[0184] In some embodiments, Ⓐ is  . In some embodiments, X_2, X_3, and X_4 are each independently CR_1 or N. In some embodiments, X_2, X_3, and X_4 are CR_1. In some embodiments, X_2, X_3, and X_4 are CH. In some embodiments, one of X_2, X_3, and X_4 is N and the rest are CR_1. In some embodiments, one of X_2, X_3, and X_4 is N and the rest are CH. In some embodiments, two of X_2, X_3, and X_4 are N and the rest are CR_1. In some embodiments, two of X_2, X_3, and X_4 are N and the rest are CH.

[0185] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or  .

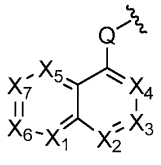
[0186] In some embodiments, the structural moiety  has the structure of  .

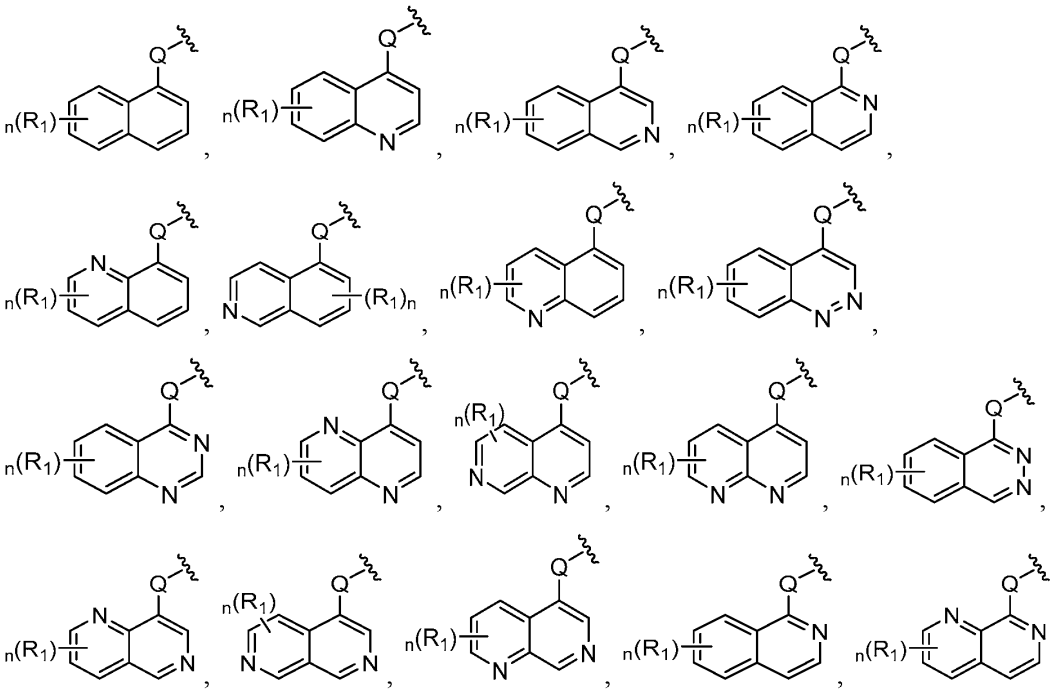
[0187] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  .

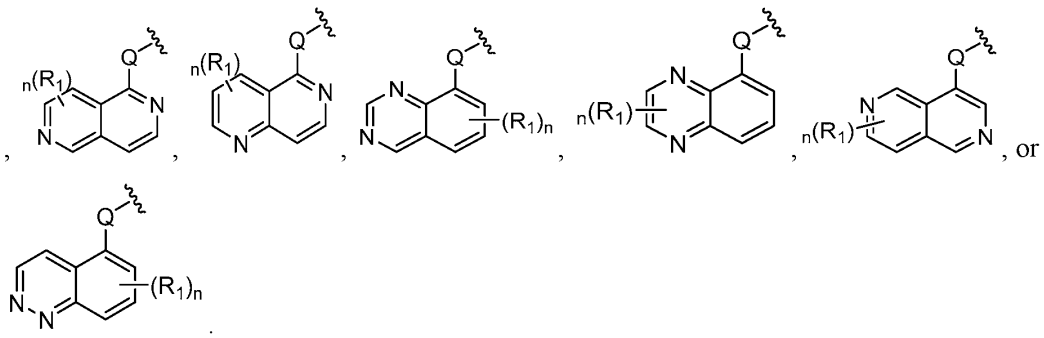
[0188] In some embodiments, X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are each independently CR_1 or N. In some embodiments, X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are CR_1. In some embodiments, X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are each independently CH or CCH_3. In some embodiments, one of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is N and the rest are CR_1. In some embodiments, one of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is N and the rest are each independently CH or CCH_3. In some embodiments, two of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are N and the rest are CR_1. In some embodiments, two of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are N and the rest are each independently CH or CCH_3. In some embodiments, three of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are N and the rest are CR_1. In some embodiments, three of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are N and the rest are each independently CH or CCH_3. In some embodiments, four of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are N and the rest are CR_1. In some embodiments, four of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are N and the rest are each independently CH or CCH_3. In some embodiments, X_2 is N, X_7 is CR_1, and X_1, X_3, X_4, X_5, and X_6 are each independently CH or CCH_3. In some embodiments, X_2 is N, X_7 is CR_1, X_3 is CCH_3, and X_1, X_4, X_5, and X_6 are CH. In some

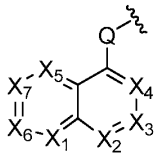
embodiments, X_2 and X_7 are N and X_1, X_3, X_4, X_5, and X_6 are CR_1. In some embodiments, X_2 and X_7 are N and X_1, X_3, X_4, X_5, and X_6 are each independently CH or CCH_3.

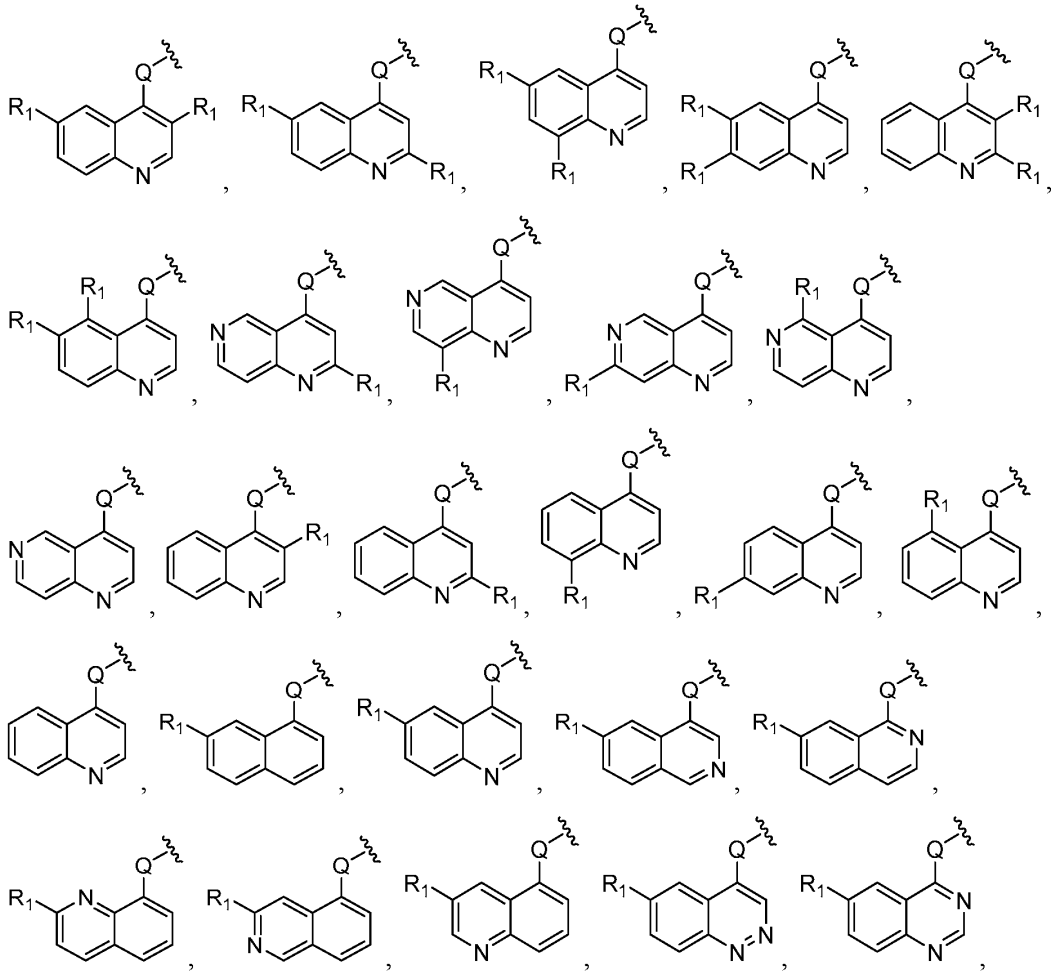
[0189] In some embodiments, X_2, X_3, X_4, X_8, and X_9 are each independently CR_1 or N. In some embodiments, X_2, X_3, X_4, X_8, and X_9 are CR_1. In some embodiments, X_2, X_3, X_4, X_8, and X_9 are each independently CH or CCH_3. In some embodiments, one of X_2, X_3, X_4, X_8, and X_9 is N and the rest are CR_1. In some embodiments, one of X_2, X_3, X_4, X_8, and X_9 is N and the rest are each independently CH or CCH_3. In some embodiments, two of X_2, X_3, X_4, X_8, and X_9 are N and the rest are CR_1. In some embodiments, two of X_2, X_3, X_4, X_8, and X_9 are N and the rest are each independently CH or CCH_3. In some embodiments, three of X_2, X_3, X_4, X_8, and X_9 are N and the rest are CR_1. In some embodiments, three of X_2, X_3, X_4, X_8, and X_9 are N and the rest are each independently CH or CCH_3. In some embodiments, four of X_2, X_3, X_4, X_8, and X_9 are N and one is CR_1. In some embodiments, four of X_2, X_3, X_4, X_8, and X_9 are N and one is CH or CCH_3.

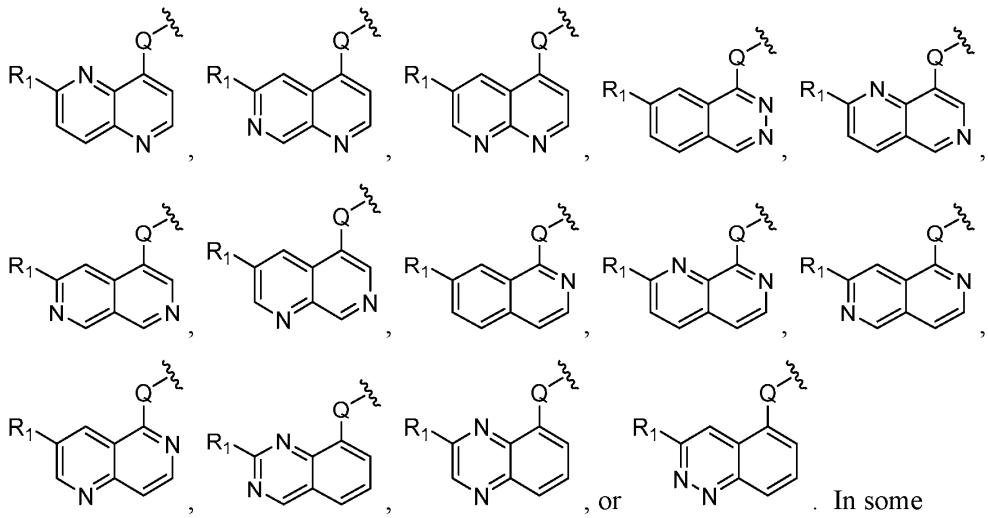
[0190] In some embodiments, the structural moiety  has the structure of



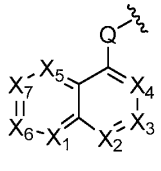


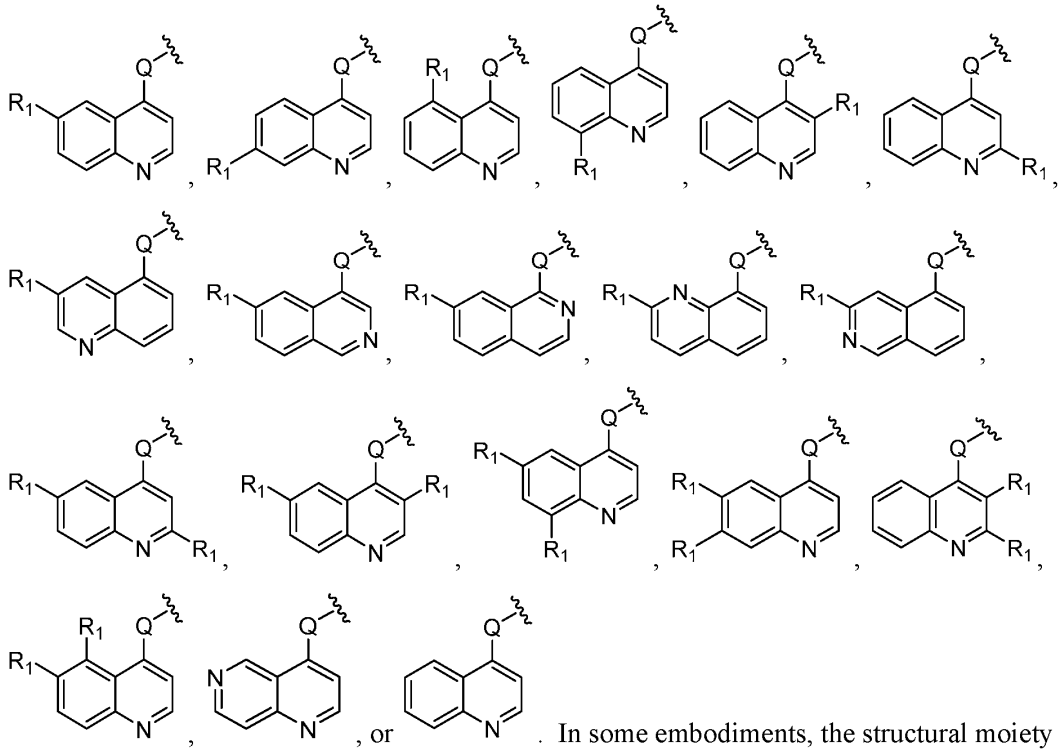
[0191] In some embodiments, the structural moiety  has the structure of



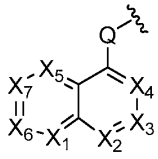
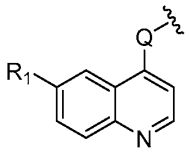
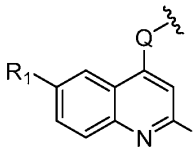


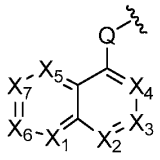
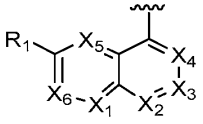
embodiments, Q is O. In some embodiments, Q is NR_a, $N(C=O)R_a$, or NSO_2R_a. In some embodiments, Q is NH. In some embodiments, Q is NCH_3 or NCH_2CH_3.

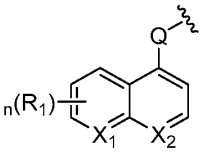
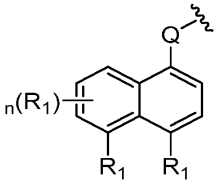
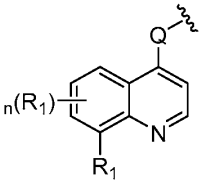
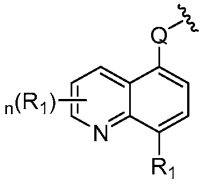
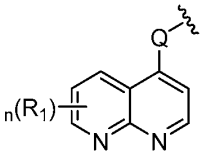
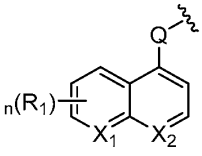
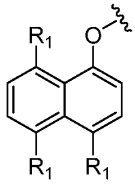
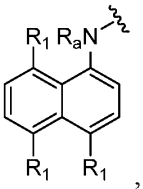
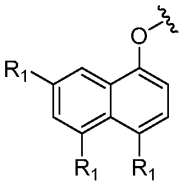
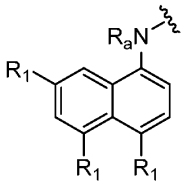
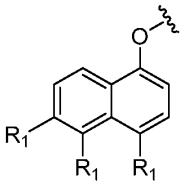
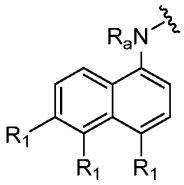
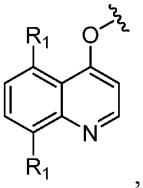
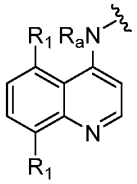
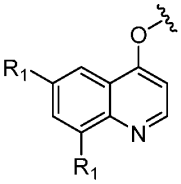
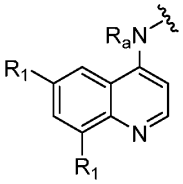
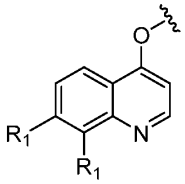
[0192] In some embodiments, the structural moiety  has the structure of

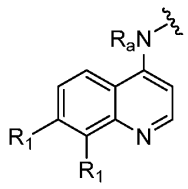
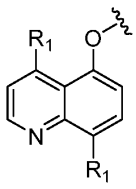
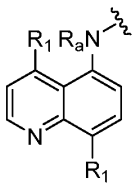
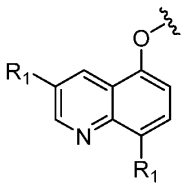
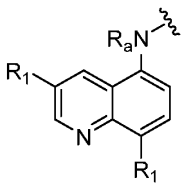
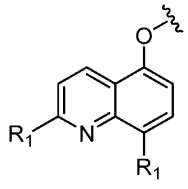
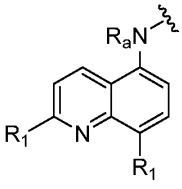
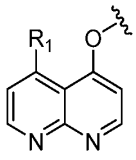
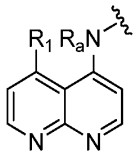
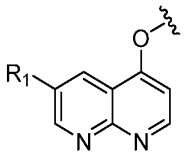
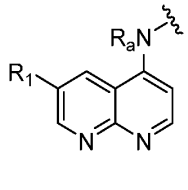
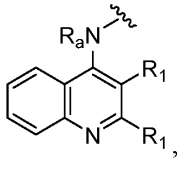
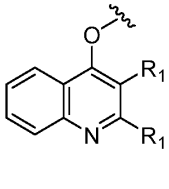
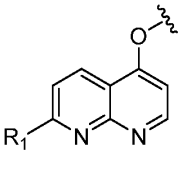
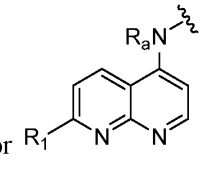


. In some embodiments, the structural moiety

 has the structure of  or  . In some embodiments, Q is O. In some embodiments, Q is NR_a, $N(C=O)R_a$, or NSO_2R_a. In some embodiments, Q is NH. In some embodiments, Q is NCH_3 or NCH_2CH_3.

[0193] In some embodiments, the structural moiety  has the structure of  .

[0194] In some embodiments, the structural moiety  has the structure of  ,  ,  , or  . In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,

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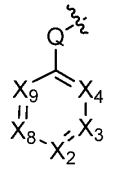
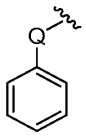
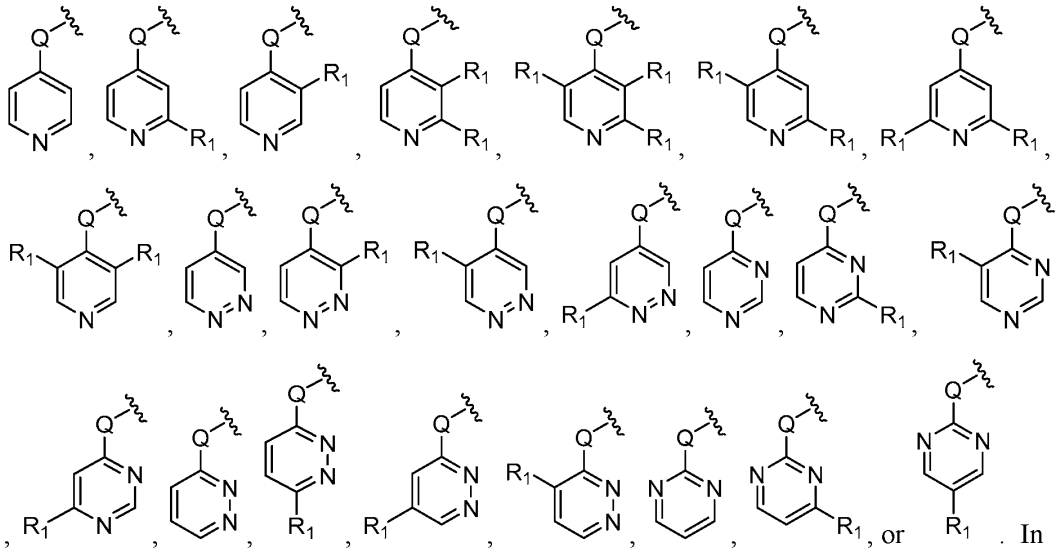
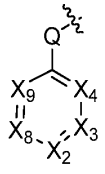
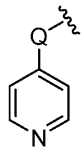
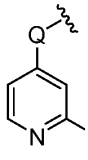
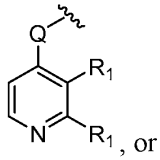
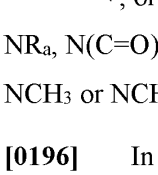
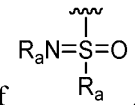
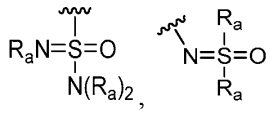
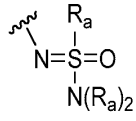
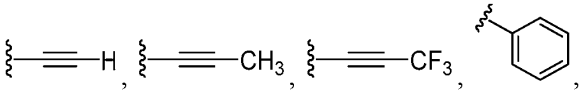
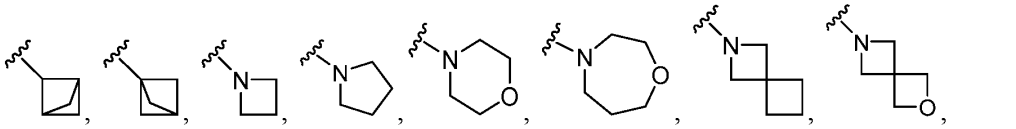
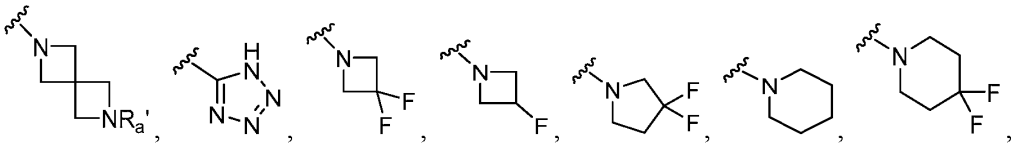
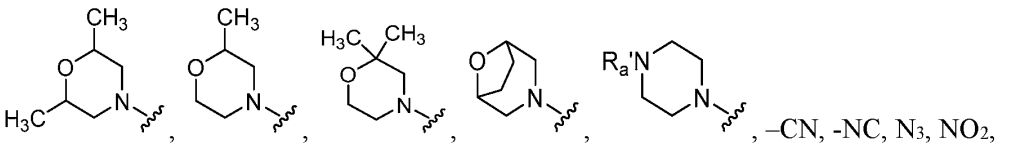
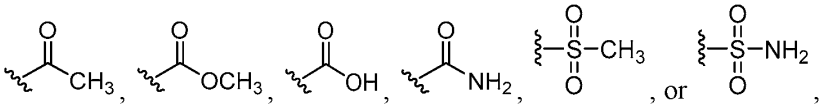
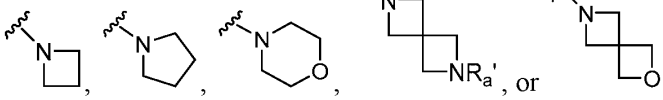
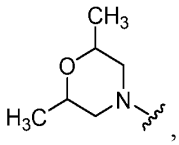
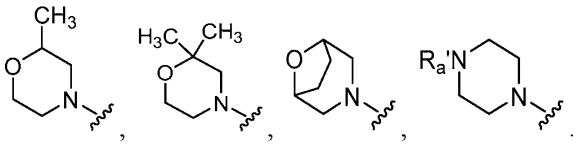
[0195] In some embodiments, the structural moiety  has the structure of  ,  . In some embodiments, the structural moiety  has the structure of  ,  ,  , or  . In some embodiments, Q is O. In some embodiments, Q is NR_a, $N(C{=}O)R_a$, or NSO_2R_a. In some embodiments, Q is NH. In some embodiments, Q is NCH_3 or NCH_2CH_3.

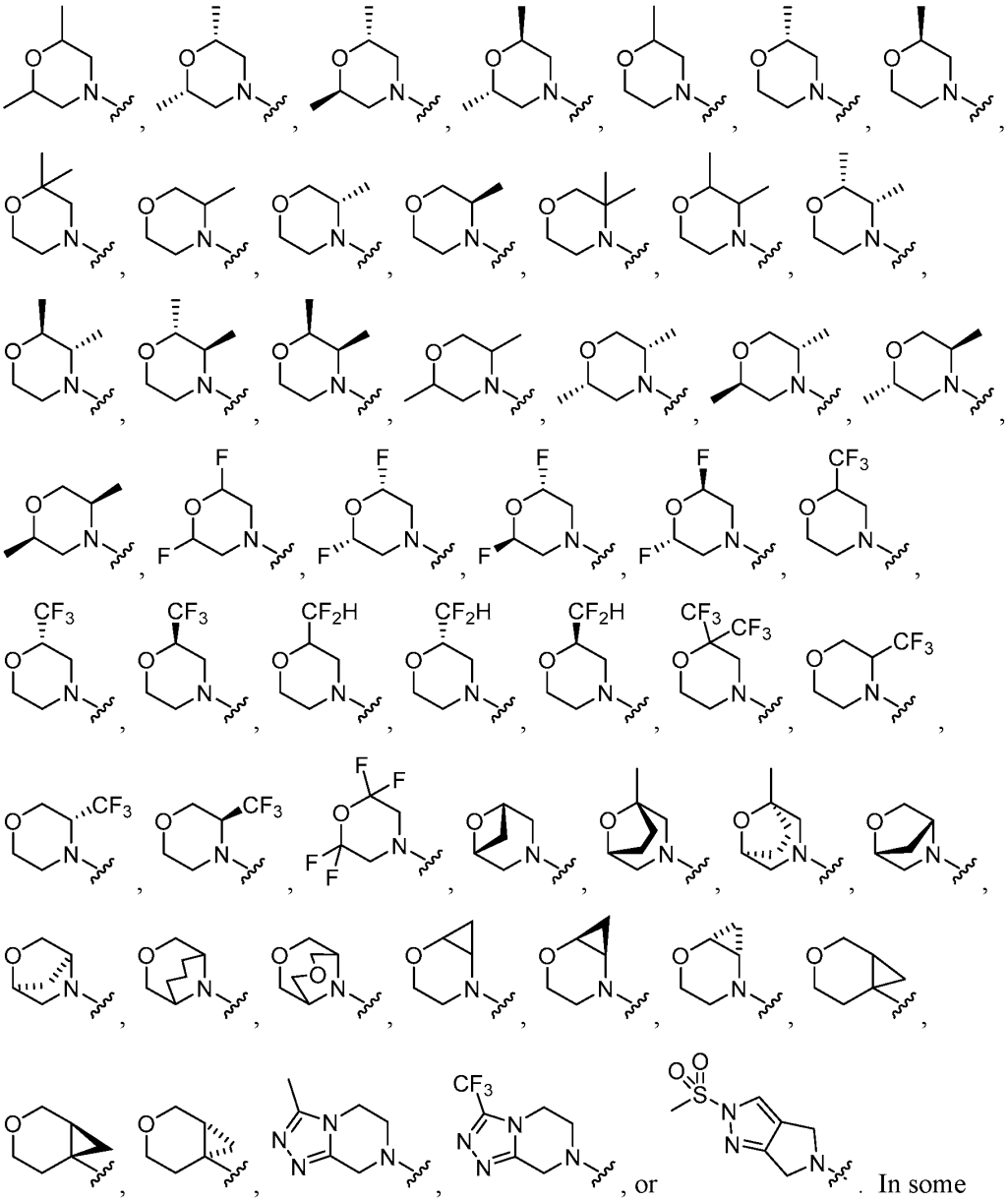
[0196] In some embodiments, each occurrence of R_1 is independently selected from the group consisting of H, D, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$haloalkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$haloalkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, aryl, heteroaryl, $-OR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, –CN, –NC, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, and $-N(R_a)SO_2R_a$; wherein $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, aryl, and heteroaryl are each optionally substituted with one or more $(C_1\text{-}C_6)$alkyl. In some embodiments, each occurrence of R_1 is

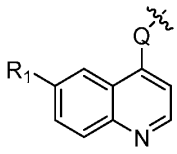
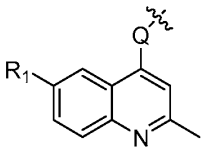
independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, and (C_4-C_{10})heterobicycloalkyl; wherein the (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, and (C_4-C_{10})heterobicycloalkyl are each optionally substituted with one or more (C_1-C_6)alkyl. In some embodiments, each occurrence of R_1 is independently selected from the group consisting of aryl and heteroaryl; wherein the (C_4-C_{10})heterospiroalkyl, aryl, and heteroaryl are each optionally substituted with one or more (C_1-C_6)alkyl. In some embodiments, each occurrence of R_1 is independently selected from the group consisting of $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, and $-N(R_a)SO_2R_a$. In some embodiments, each occurrence of R_1 is independently selected from the group consisting of  ,  , and  . In some embodiments, each occurrence of R_1 is independently H, D, halogen, OR_a, $N(R_a)_2$, (C_1-C_6)alkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterospiroalkyl, halogenated (C_3-C_7)heterocycloalkyl, (C_1-C_6)alkynyl, aryl, (C_4-C_{10})bicycloalkyl, $-CN$, $-NC$, N_3, NO_2, COR_a, CO_2R_a, $CON(R_a)_2$, $-SO_2R_a$, or $-SO_2N(R_a)_2$; wherein the (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterospiroalkyl, aryl, and (C_4-C_{10})bicycloalkyl are each optionally substituted with one or more (C_1-C_6)alkyl. In some embodiments, each occurrence of R_1 is independently H, D, halogen, (C_1-C_6)alkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterospiroalkyl, halogenated (C_3-C_7)heterocycloalkyl, $N(R_a)_2$, or $-CN$; wherein the (C_3-C_7)heterocycloalkyl and (C_4-C_{10})heterospiroalkyl are each optionally substituted with one or more (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_1 is (C_4-C_{10})heterospiroalkyl. In some embodiments, at least one occurrence of R_1 is halogenated (C_3-C_7)heterocycloalkyl. In some embodiments, each occurrence of R_1 is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkynyl, aryl, (C_4-C_{10})bicycloalkyl, $-SO_2R_a$, or $-SO_2N(R_a)_2$; wherein the aryl and (C_4-C_{10})bicycloalkyl are each optionally substituted with one or more (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_1 is (C_4-C_{10})heterospiroalkyl, optionally substituted with one or more (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_1 is halogenated (C_3-C_7)heterocycloalkyl, optionally substituted with one or more (C_1-C_6)alkyl. In some embodiments, each occurrence of R_1 is independently H, D, F, Cl, Br,

CH_3, OCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$,  ,  ,  ,  , –CN, -NC, N_3, NO_2,  , where R_a' is H or (C_1-C_6)alkyl. In some embodiments, each occurrence of R_1 is independently H, D, F, CH_3, $N(CH_3)_2$,  , where R_a' is H or (C_1-C_6)alkyl. In some embodiments, each occurrence of R_1 is independently  ,  .

[0197] In some embodiments, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_4-C_{10})heterospiroalkyl, aryl, and heteroaryl of R_1 are each optionally substituted by one or more halogen, –OR_a, –CN, or –$N(R_a)_2$.

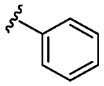
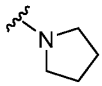
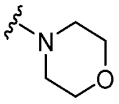
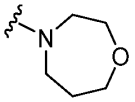
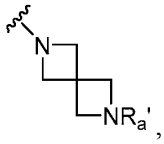
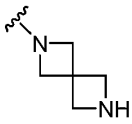
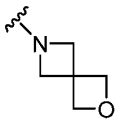
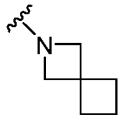
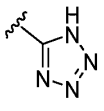
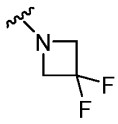
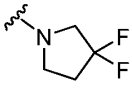
[0198] In some embodiments, at least one occurrence of R_1 is a partially saturated bicyclic heteroaryl optionally substituted by one or more (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, –SO_2R_a, or –$SO_2N(R_a)_2$. In some embodiments, at least one occurrence of R_1 is

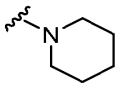
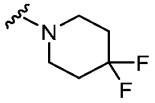
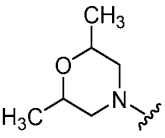
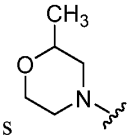
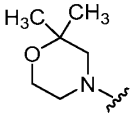
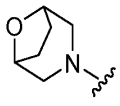
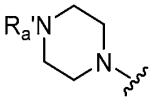
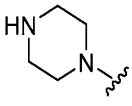
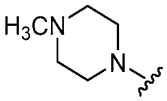
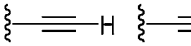
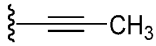
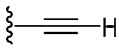
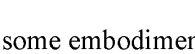
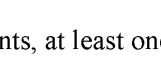
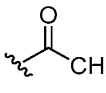
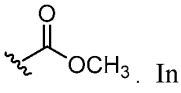
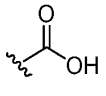
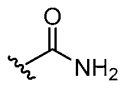


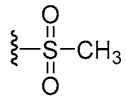
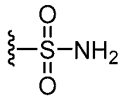
embodiments, Ⓐ is  or  .

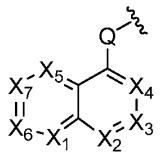
[0199] In some embodiments, at least one occurrence of R_1 is H, D, or halogen. In some embodiments, at least one occurrence of R_1 is H. In some embodiments, at least one occurrence of R_1 is D. In some embodiments, at least one occurrence of R_1 is F. In some embodiments, at least one occurrence of R_1 is CH_3. In some embodiments, at least one

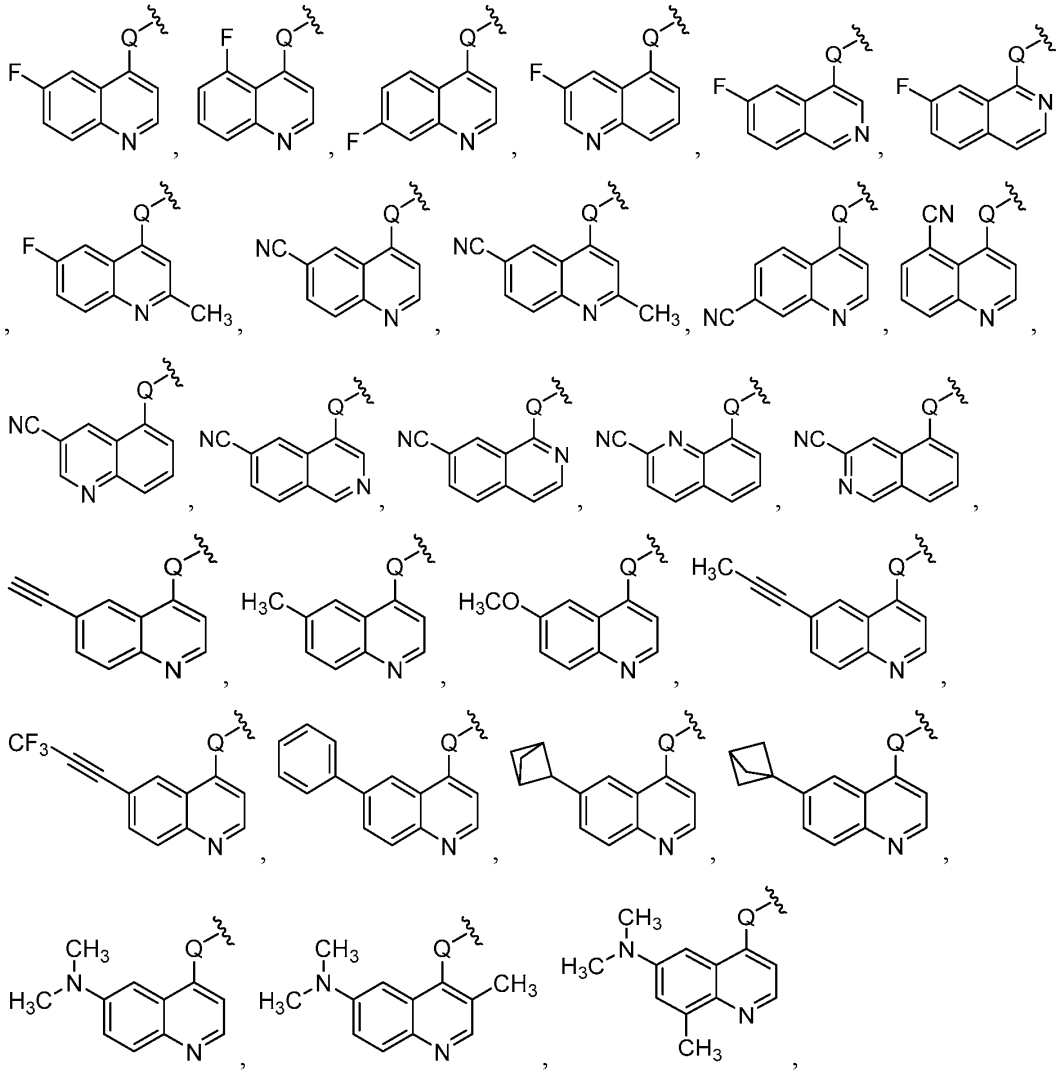
occurrence of R_1 is OCH_3. In some embodiments, at least one occurrence of R_1 is NH_2. In some embodiments, at least one occurrence of R_1 is $NHCH_3$. In some embodiments, at least one occurrence of R_1 is $N(CH_3)_2$. In some embodiments, at least one occurrence of R_1 is F.

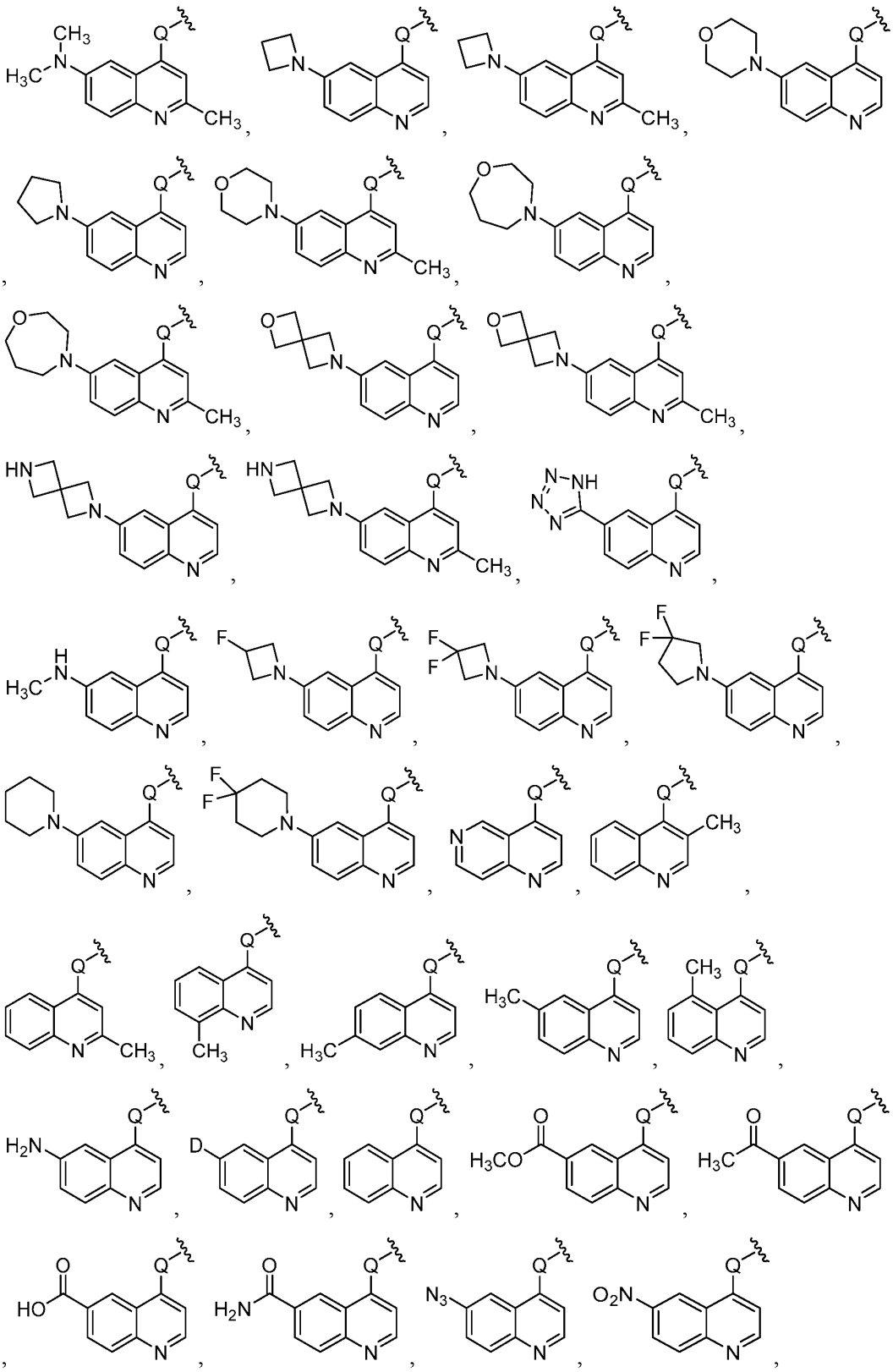
In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  , where R_a' is H or (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is . In some embodiments, at least one occurrence of R_1 is .

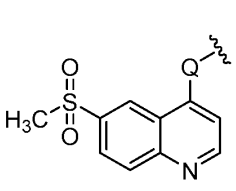
 . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  , wherein R_a' is H or (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  ,  , or . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is –CN. In some embodiments, at least one occurrence of R_1 is –NC. In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is NO_2. In some

embodiments, at least one occurrence of R_1 is N_3. In some embodiments, at least one occurrence of R_1 is  . In some embodiments, at least one occurrence of R_1 is  .

[0200] In some embodiments, the structural moiety  has the structure of



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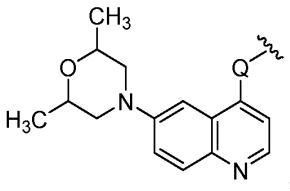
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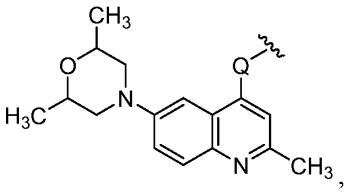
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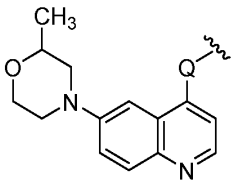
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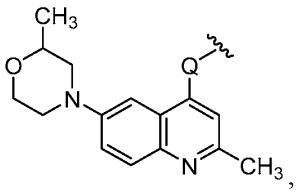
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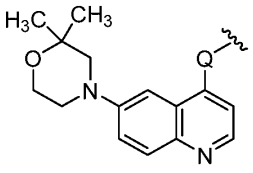
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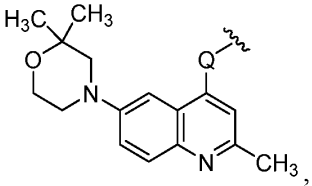
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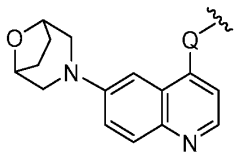
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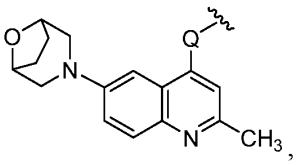
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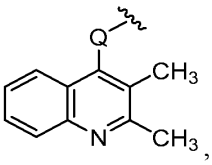
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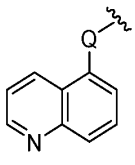
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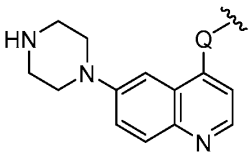
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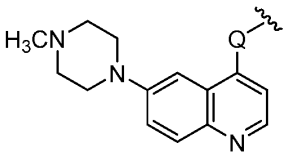
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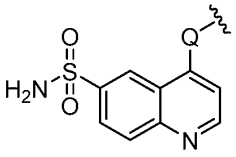
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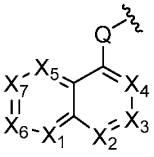
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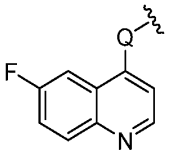
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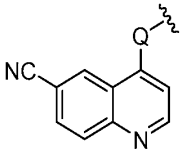
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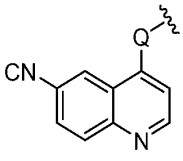
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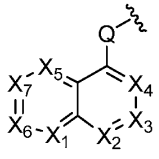
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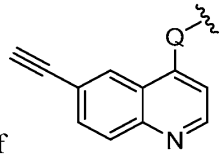
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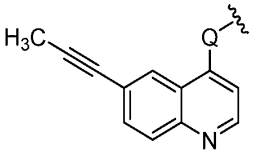
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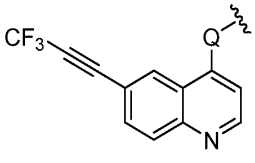
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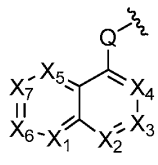
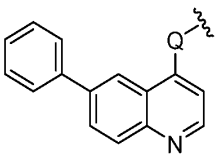
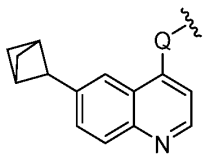
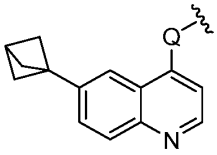
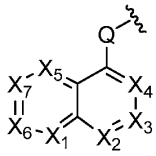
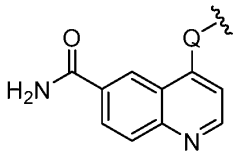
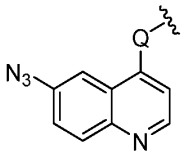
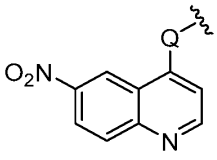
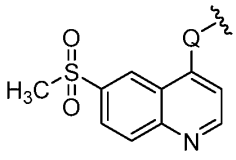
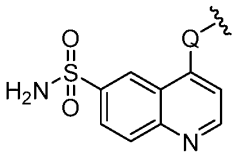
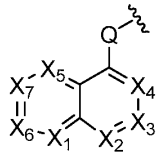
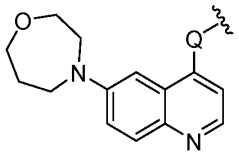
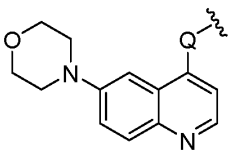
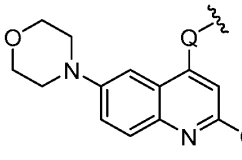
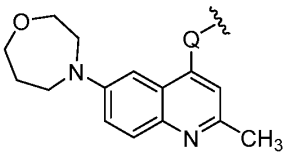
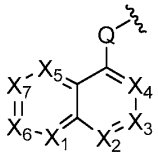
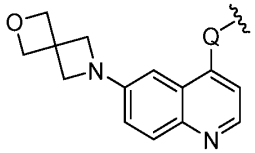
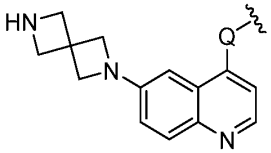
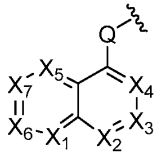
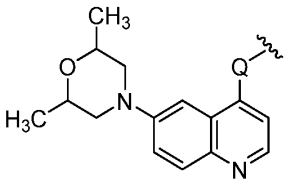
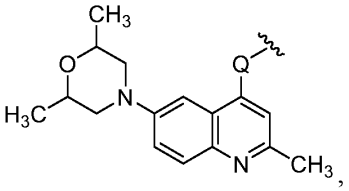
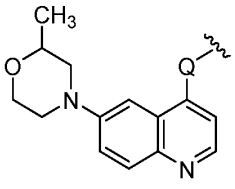
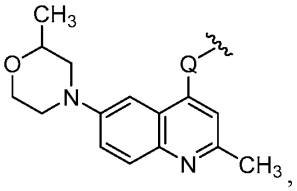
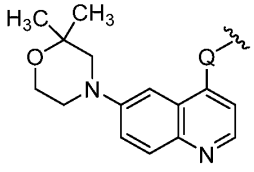
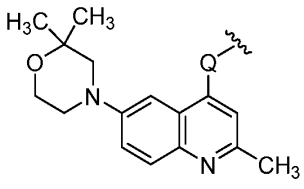
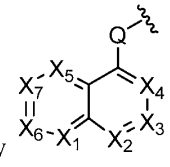
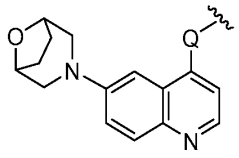
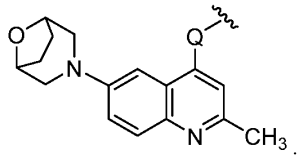
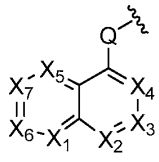
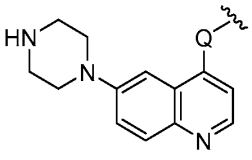
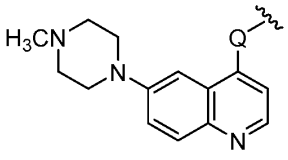
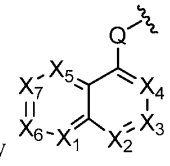
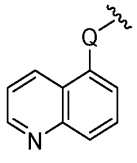
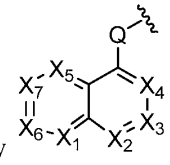
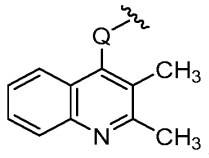
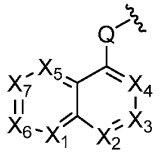
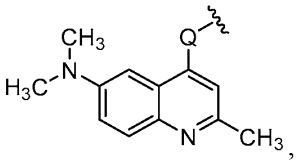
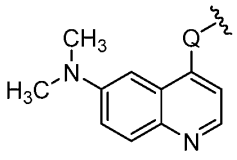
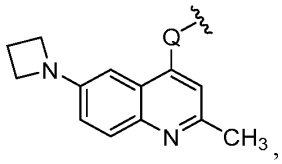
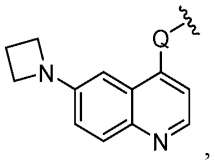
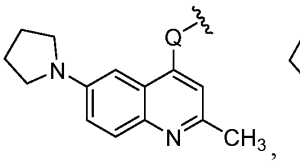
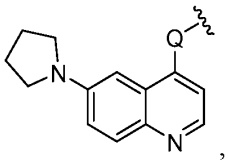
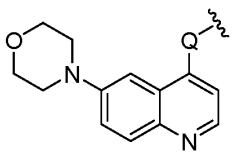
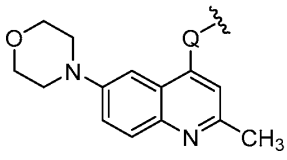
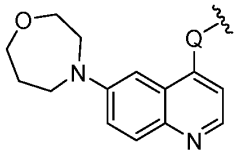
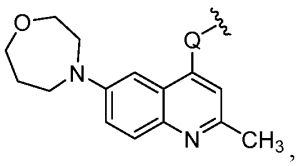
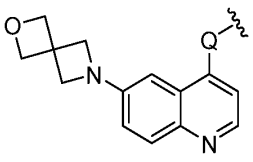
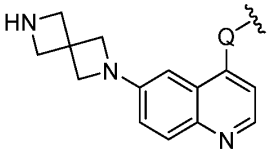
moiety  has the structure of  ,  , or  . In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  , or  . In some embodiments, the structural moiety  ,  ,  , or  . In some embodiments, the structural moiety  has the structure of  or  . In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,

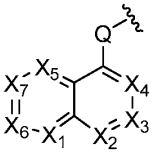
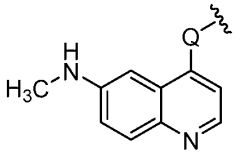
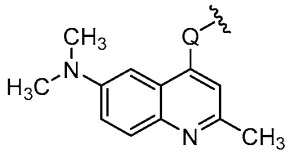

, or  . In some embodiments, the structural moiety  has the structure of  or  .

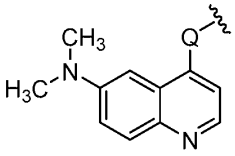
In some embodiments, the structural moiety  has the structure of  or  . In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety  has the structure of  .

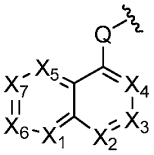
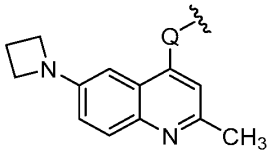
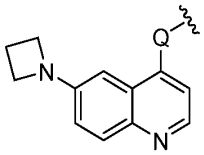
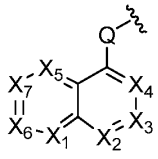
[0201] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  .

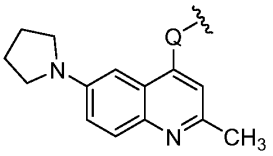
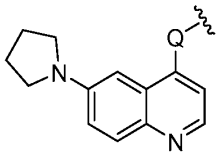
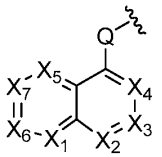
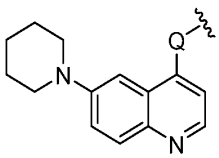
 ,  ,  , or

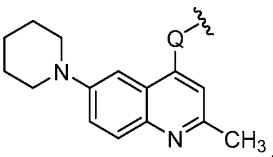
 , where Q is O or NH. In some embodiments, the structural moiety

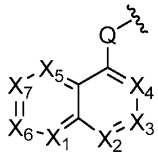
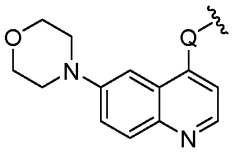
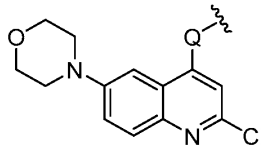
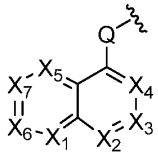
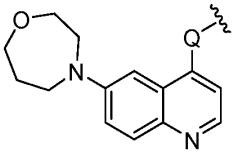
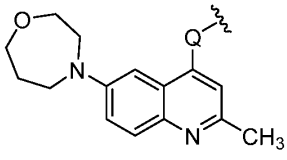
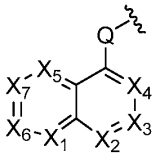
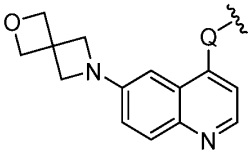
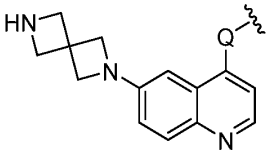
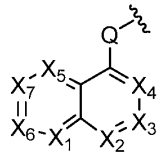
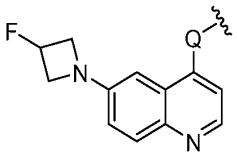
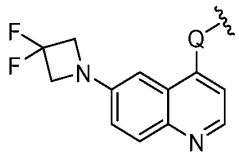
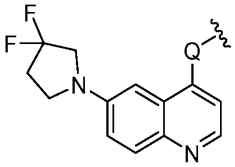
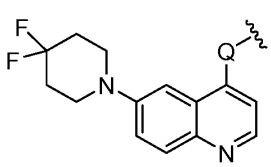
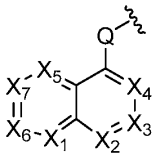
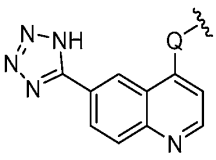
 has the structure of  ,  , or

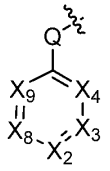
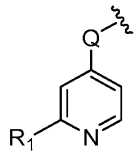
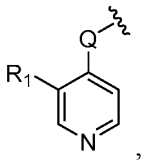
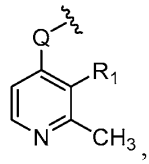
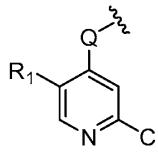
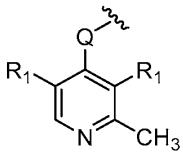
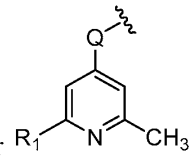
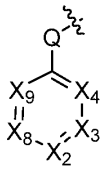
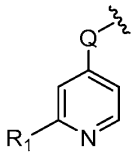
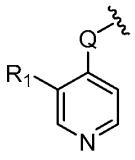
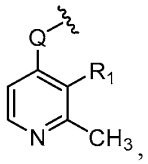
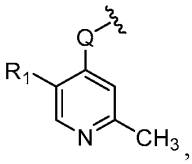
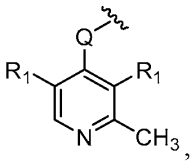
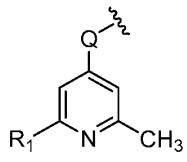
 , where Q is O or NH. In some embodiments, the structural moiety

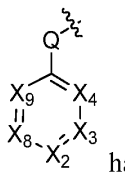
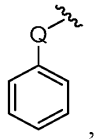
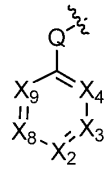
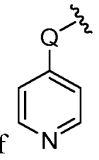
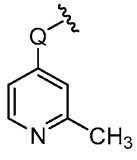
 has the structure of  or  , where Q is O or NH. In some embodiments, the structural moiety  has the structure of

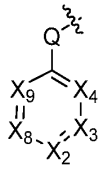
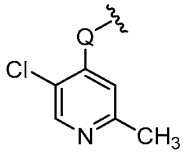
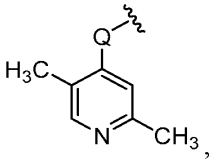
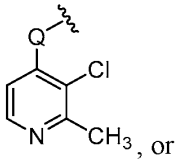
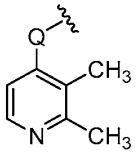
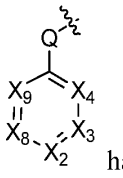
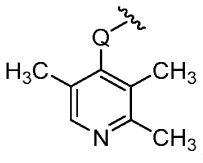
 or  , where Q is O or NH. In some embodiments, the structural moiety  has the structure of  or

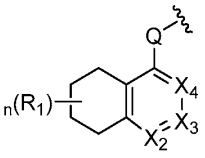
 , where Q is O or NH. In some embodiments, the structural moiety

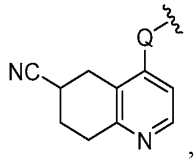
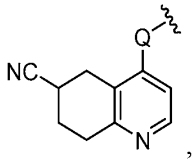
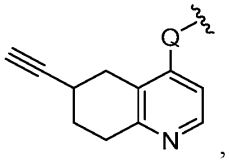
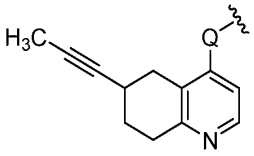
 has the structure of  or  , where Q is O or NH. In some embodiments, the structural moiety  has the structure of  or  , where Q is O or NH. In some embodiments, the structural moiety  has the structure of  or  , where Q is O or NH. In some embodiments, the structural moiety  has the structure of  ,  ,  or  , where Q is O or NH. In some embodiments, the structural moiety  has the structure of  , where Q is O or NH.

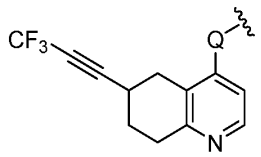
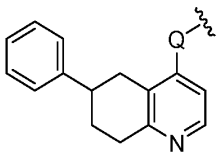
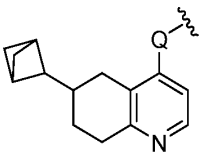
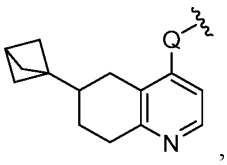
[0202] In some embodiments, the structural moiety  has the structure of       , where Q is O or NH and R_1 is H, D, (C_1-C_6)alkyl, (C_3-C_7)heterocycloalkyl, halogenated (C_3-C_7)heterocycloalkyl, or halogen. In some embodiments, the structural moiety  has the structure of      , or  , where Q is O or NH and R_1 is H, D, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, F, Cl, or Br.

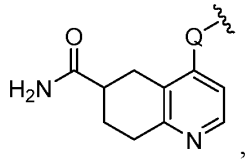
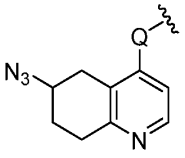
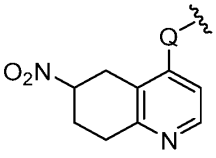
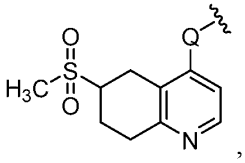
[0203] In some embodiments, the structural moiety  has the structure of  , where Q is O or NH. In some embodiments, the structural moiety  has the structure of  or  , where Q is O or NH. In some embodiments, the structural moiety

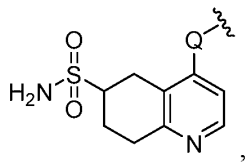
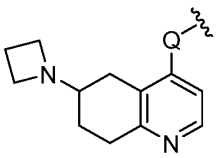
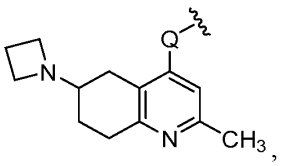
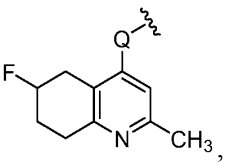
 has the structure of  ,  ,  , or  , where Q is O or NH. In some embodiments, the structural moiety  has the structure of  , where Q is O or NH.

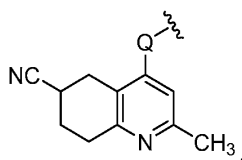
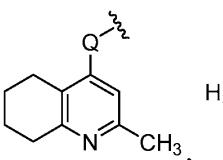
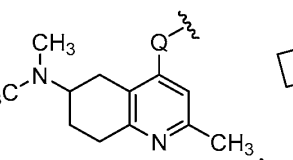
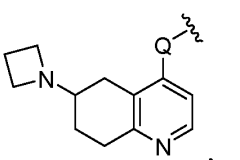
[0204] In some embodiments, the structural moiety  has the structure of

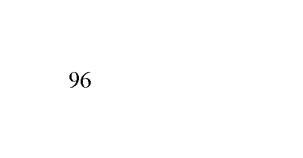
 ,  ,  ,  ,

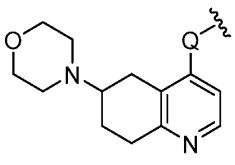
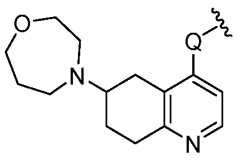
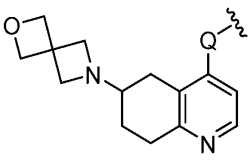
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

, ,  , ,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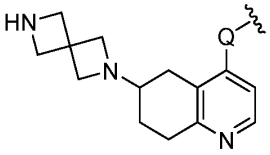
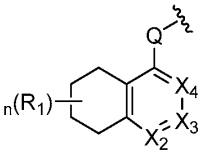
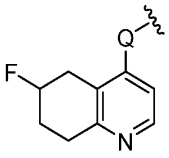
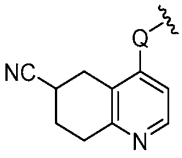
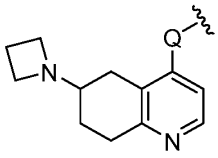
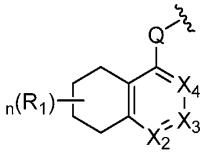
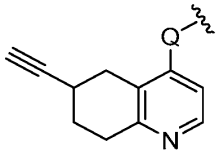
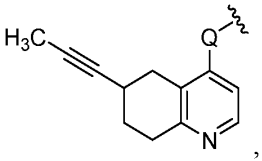
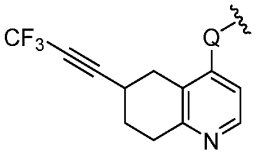
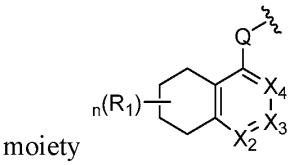
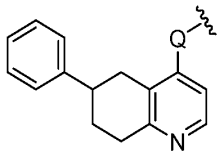
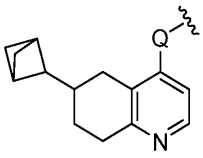
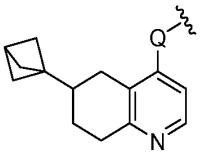
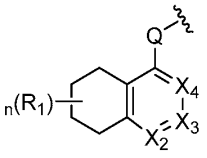
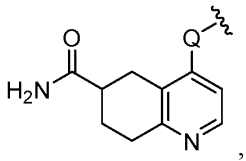
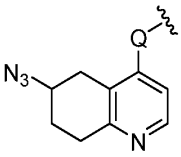
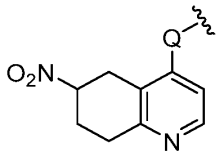
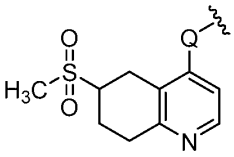
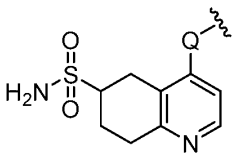
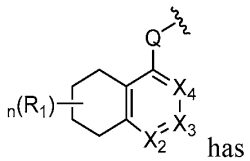
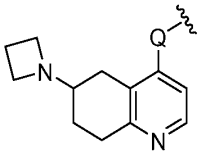
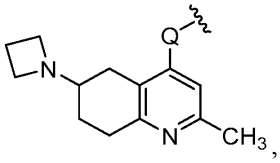
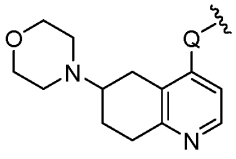
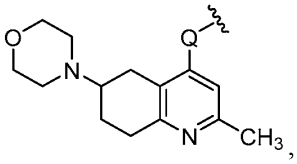
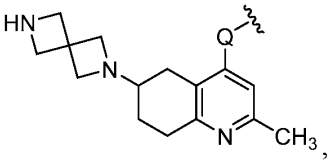
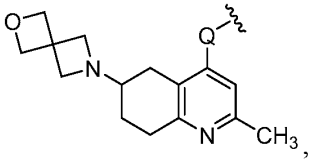
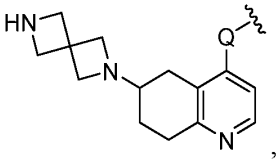
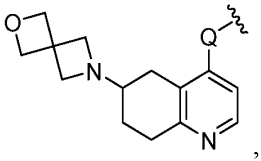
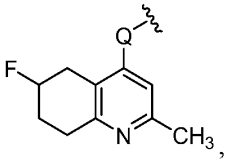
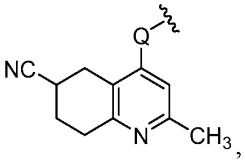
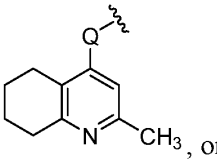
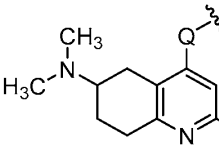
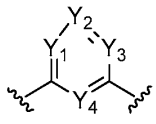
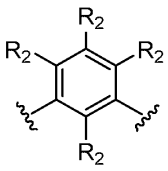
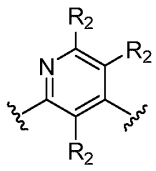
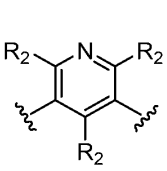
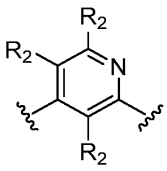
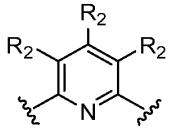
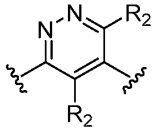
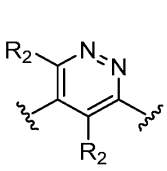
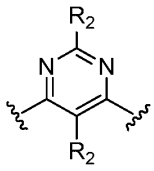
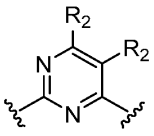
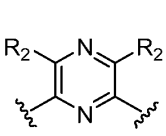
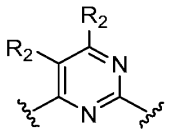
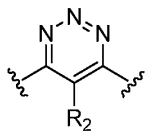
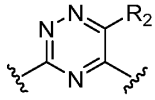
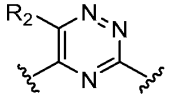
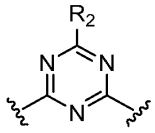
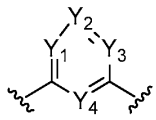
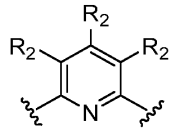
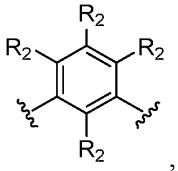
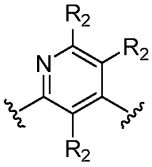
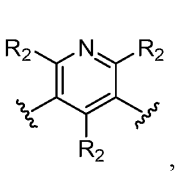
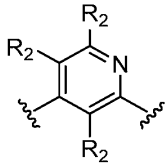

. In some embodiments, the structural moiety  has the structure of  ,  , or  . In some embodiments, the structural moiety  has the structure of  ,  ,  , or  . In some embodiments, the structural moiety has the structure of  ,  , or  . In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  , or  . In some embodiments, the structural moiety has

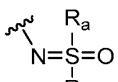
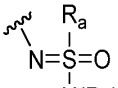
the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , . In some embodiments, Q is O or NH.

[0205] In some embodiments, the compound has the structure of Formula Ia.

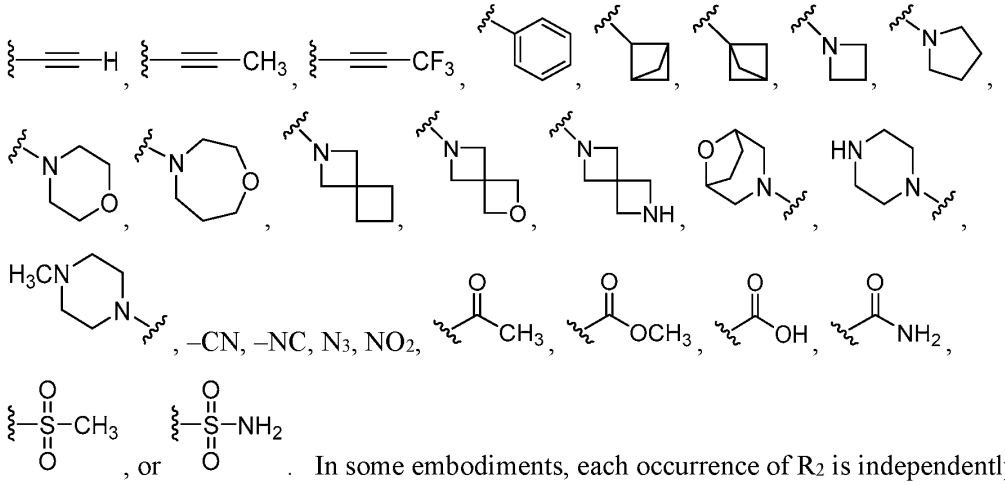
[0206] In some embodiments, Y_1, Y_2, Y_3, Y_4, and Y_5 are each independently CR_2 or N. In some embodiments, Y_1, Y_2, Y_3, Y_4, and Y_5 are each CR_2. In some embodiments, Y_1, Y_2, Y_3, Y_4, and Y_5 are each CH. In some embodiments, Y_1, Y_2, Y_3, Y_4, and Y_5 are each N. In some embodiments, one of Y_1, Y_2, Y_3, Y_4, and Y_5 is CR_2 and the rest are N. In some embodiments, one of Y_1, Y_2, Y_3, Y_4, and Y_5 is CH and the rest are N. In some embodiments, two of Y_1, Y_2, Y_3, Y_4, and Y_5 are CR_2 and the rest are N. In some embodiments, two of Y_1, Y_2, Y_3, Y_4, and Y_5 are CH and the rest are N. In some embodiments, three of Y_1, Y_2, Y_3, Y_4, and Y_5 are CR_2 and two of Y_1, Y_2, Y_3, Y_4, and Y_5 are N. In some embodiments, three of Y_1, Y_2, Y_3, Y_4, and Y_5 are CH and two of Y_1, Y_2, Y_3, Y_4, and Y_5 are N.

[0207] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  , 










, or . In some embodiments, the structural moiety  has the structure of  ,  ,  ,  , or  .

[0208] In some embodiments, each occurrence of R_2 is independently selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, aryl, heteroaryl, $-OR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, –CN, –NC, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, and $-N(R_a)SO_2R_a$. In some embodiments, each occurrence of R_2 is independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, and (C_4-C_{10})heterobicycloalkyl. In some embodiments, each occurrence of R_2 is independently selected from the group consisting of aryl and heteroaryl. In some embodiments, each occurrence of R_2 is independently selected from the group consisting of $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, –CN, –NC, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, and $-N(R_a)SO_2R_a$. In some embodiments, each occurrence of R_2 is independently selected from the group consisting of  ,  ,  ,  , and . In some embodiments, each occurrence of R_2 is independently H, D,

halogen, OR_a, $N(R_a)_2$, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$heterocycloalkyl, $(C_1$-$C_6)$alkynyl, aryl, $(C_4$-$C_{10})$bicycloalkyl, –CN, -NC, N_3, NO_2, COR_a, CO_2R_a, $CON(R_a)_2$, $–SO_2R_a$, or $–SO_2N(R_a)_2$. In some embodiments, each occurrence of R_2 is independently H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$heterocycloalkyl, $N(R_a)_2$, or –CN. In some embodiments, each occurrence of R_2 is independently $(C_4$-$C_{10})$heterospiroalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, aryl, or heteroaryl. In some embodiments, each occurrence of R_2 is independently H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkynyl, aryl, $(C_4$-$C_{10})$bicycloalkyl, $–SO_2R_a$, or $–SO_2N(R_a)_2$. In some embodiments, each occurrence of R_2 is independently H, D, F, Cl, Br, CH_3, OCH_3, NH_2, $N(CH_3)_2$,

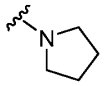


, –CN, –NC, N_3, NO_2,

. In some embodiments, each occurrence of R_2 is independently H, D, F, CH_3, $N(CH_3)_2$,

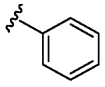


, or



.

[0209] In some embodiments, at least one occurrence of R_2 is H, D, or halogen. In some embodiments, at least one occurrence of R_2 is H. In some embodiments, at least one occurrence of R_2 is D. In some embodiments, at least one occurrence of R_2 is F. In some embodiments, at least one occurrence of R_2 is CH_3. In some embodiments, at least one occurrence of R_2 is OCH_3. In some embodiments, at least one occurrence of R_2 is NH_2. In some embodiments, at least one occurrence of R_2 is $N(CH_3)_2$. In some embodiments, at least one occurrence of R_2 is



. In some embodiments, at least one occurrence of R_2 is



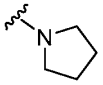
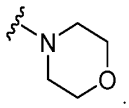
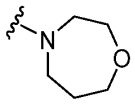
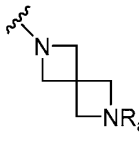
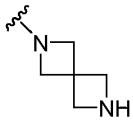
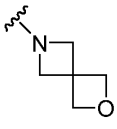
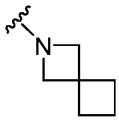
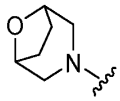
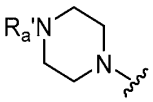
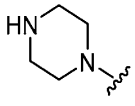
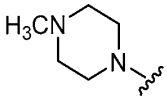
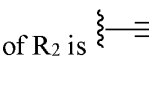
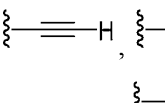
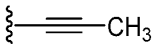
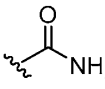
. In some embodiments, at least one occurrence of R_2 is

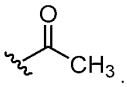
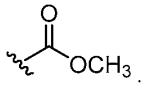
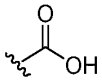
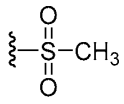
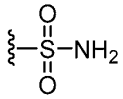


. In some embodiments, at least one occurrence of R_2 is

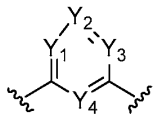
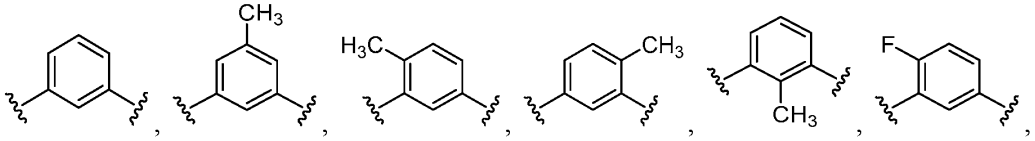


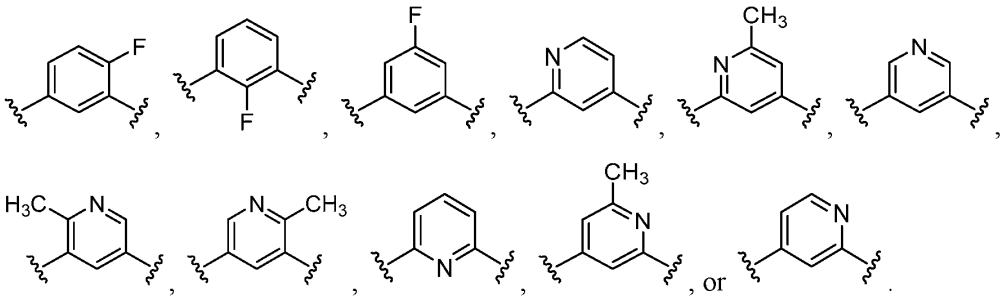
. In some embodiments, at least one

occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  , where R_a' is H or (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  , where R_a' is H or (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  ,  , or . In some embodiments, at least one occurrence of R_2 is . In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is . In some embodiments, at least one occurrence of R_2 is –CN. In some embodiments, at least one occurrence of R_2 is –NC. In some embodiments, at least one occurrence of R_2 is  .

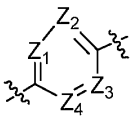
In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is NO_2. In some embodiments, at least one occurrence of R_2 is N_3. In some embodiments, at least one occurrence of R_2 is  . In some embodiments, at least one occurrence of R_2 is  .

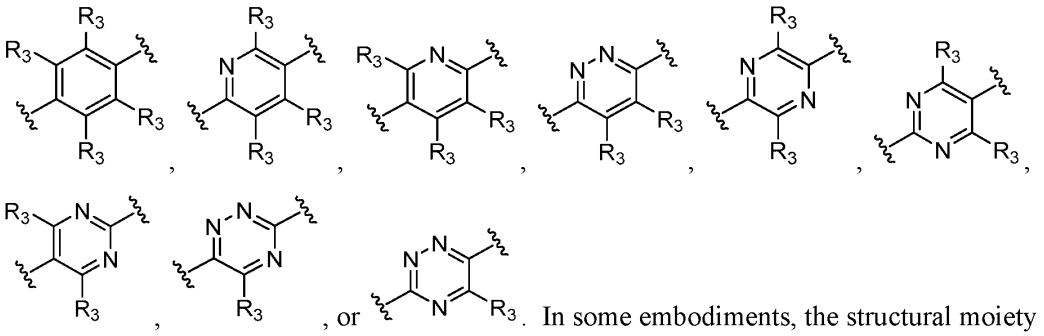
[0210] In some embodiments, each occurrence of R_2 is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $-N(R_a)_2$, NO_2, and $-OR_a$. In some embodiments, each occurrence of R_2 is independently H, halogen, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$. In some embodiments, at least one occurrence of R_2 is H. In some embodiments, at least one occurrence of R_2 is $(C_1\text{-}C_6)$alkyl. In some embodiments, at least one occurrence of R_2 is $-N(R_a)_2$, NO_2, or $-OR_a$. In some embodiments, at least one occurrence of R_2 is H, CH_3, OH, NH_2, or halogen. In some embodiments, at least one occurrence of R_2 is H. In some embodiments, at least one occurrence of R_2 is CF_3. In some embodiments, R_2 is H or CH_3.

[0211] In some embodiments, the structural moiety  has the structure of  .

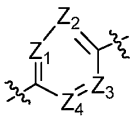
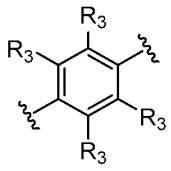
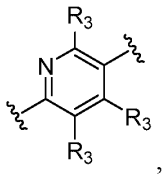
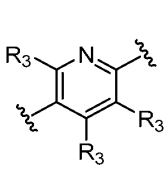
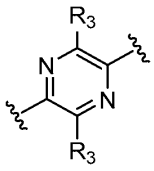
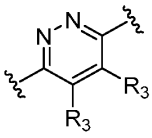
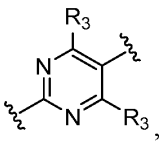
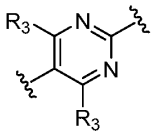


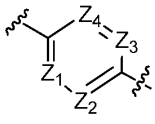
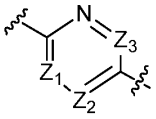
[0212] In some embodiments, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CR_3 or N. In some embodiments, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CR_3. In some embodiments, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CH. In some embodiments, Z_1, Z_2, Z_3, Z_4, and Z_5 are each N. In some embodiments, one of Z_1, Z_2, Z_3, Z_4, and Z_5 is CR_3 and the rest are N. In some embodiments, one of Z_1, Z_2, Z_3, Z_4, and Z_5 is CH and the rest are N. In some embodiments, two of Z_1, Z_2, Z_3, Z_4, and Z_5 are CR_3 and the rest are N. In some embodiments, two of Z_1, Z_2, Z_3, Z_4, and Z_5 are CH and the rest are N. In some embodiments, three of Z_1, Z_2, Z_3, Z_4, and Z_5 are CR_3 and two are N. In some embodiments, three of Z_1, Z_2, Z_3, Z_4, and Z_5 are CH and two are N. In some embodiments, Z_4 is N and Z_1, Z_2, and Z_3, and Z_5 are CR_3.

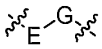
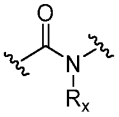
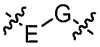
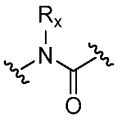
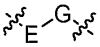
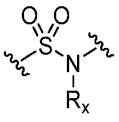
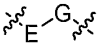
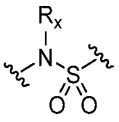
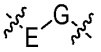
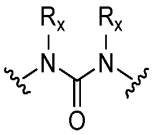
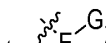
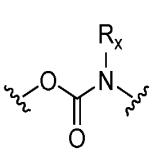
[0213] In some embodiments, the structural moiety  has the structure of

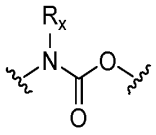
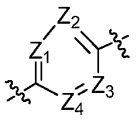


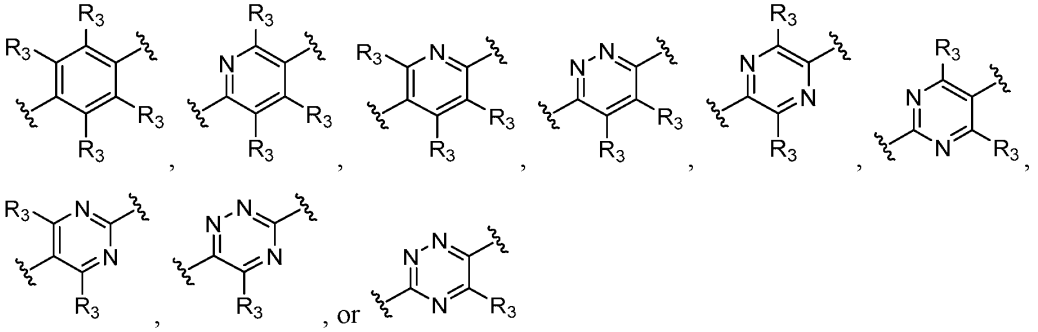
. In some embodiments, the structural moiety

 has the structure of  ,  ,  ,  ,  ,  , or  .

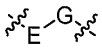
[0214] In some embodiments, the structural moiety  has the structure of  .

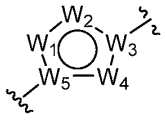
[0215] In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety has the structure of


. In these embodiments, the structural moiety  has the structure of



[0216] In some embodiments, each occurrence of R_x is independently H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, or heteroaryl; or where R_x and Y_3, R_x and Y_4, R_x and Z_1, or R_x and Z_4 taken together form an optionally substituted 5-6-membered heterocycle. In some embodiments, each occurrence of R_x is independently H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, or heteroaryl. In some embodiments, each occurrence of R_x is independently H, CH_3, or CH_2CH_3. In some embodiments, R_x and Y_4 taken together form an optionally substituted 5-6-membered heterocycle. In some embodiments, R_x and Y_3 taken together form an optionally substituted 5-6-membered heterocycle. In some embodiments, R_x and Z_1 taken together form an optionally substituted 5-6-membered heterocycle. In some embodiments, R_x and Z_4 taken together form an optionally substituted 5-6-membered heterocycle.

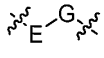
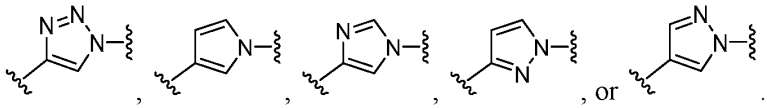
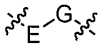
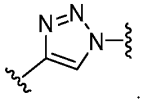
[0217] In some embodiments, the structural moiety  has the structure of

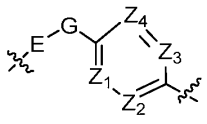
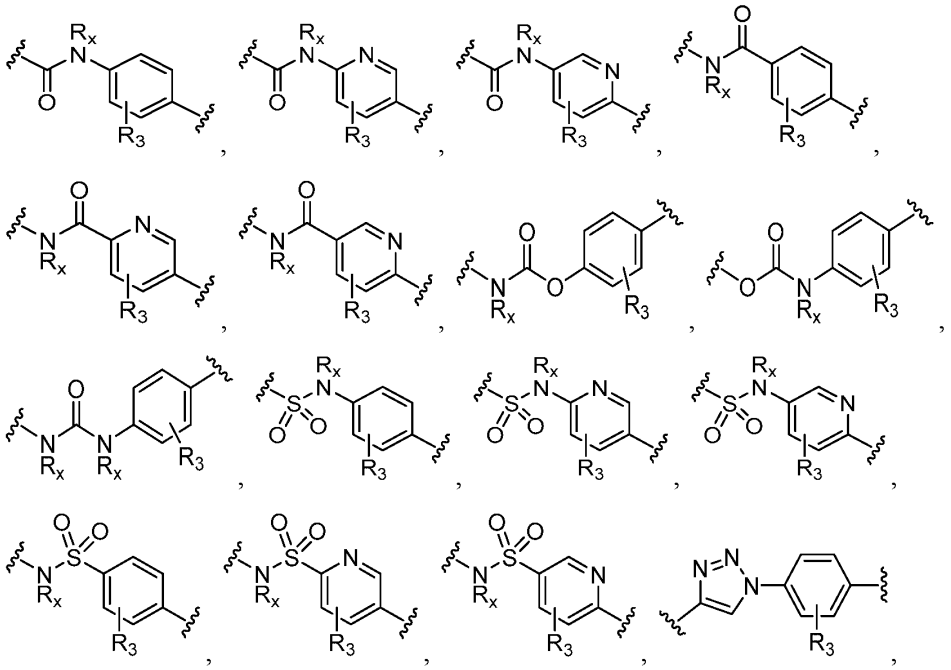

.

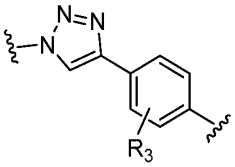
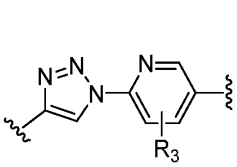
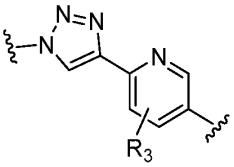
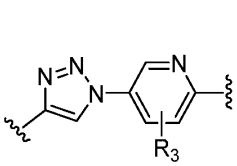
[0218] In some embodiments, W_1, W_2, W_3, W_4, and W_5 are each independently CR_6, N, or NR_6 where valence permits. In some embodiments, one of W_1, W_2, W_3, W_4, and W_5 are N or NR_6 and the rest are C or CR_6 where valence permits. In some embodiments, two of W_1, W_2, W_3, W_4, and W_5 are N or NR_6 and the rest are C or CR_6 where valence permits. In some embodiments, three of W_1, W_2, W_3, W_4, and W_5 are N or NR_6 and two are C or CR_6 where valence permits. In some embodiments, one of W_1, W_2, W_3, W_4, and W_5 are N and the rest are C or CR_6 where valence permits. In some embodiments, two of W_1, W_2, W_3, W_4, and W_5

are N and the rest are C or CR_6 where valence permits. In some embodiments, three of W_1, W_2, W_3, W_4, and W_5 are N and two are C or CR_6 where valence permits.

[0219] In some embodiments, each occurrence of R_6 is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$haloalkyl. In some embodiments, each occurrence of R_6 is independently selected from the group consisting of H, F, CH_3, and CH_2CH_3.

[0220] In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety  has the structure of  .

[0221] In some embodiments, the structural moiety  has the structure of  .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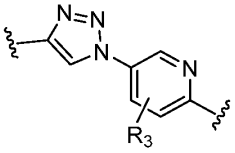
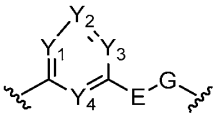
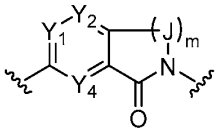
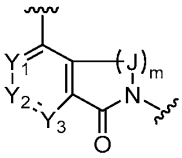
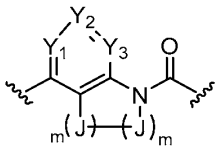
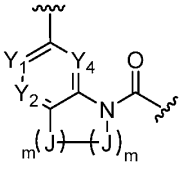
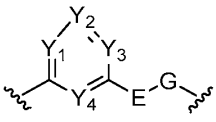
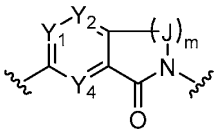
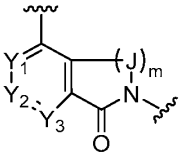
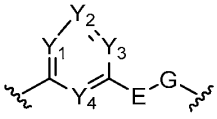
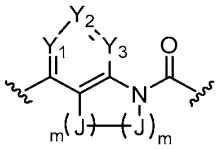
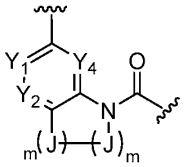
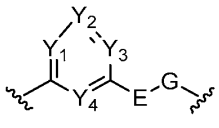
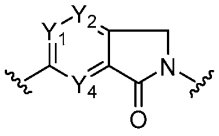
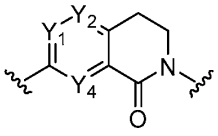
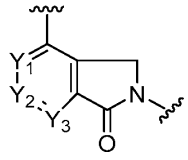
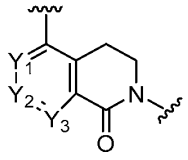
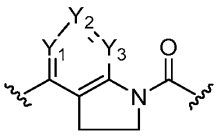
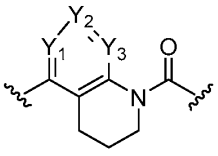
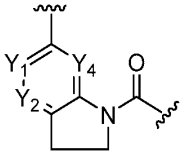
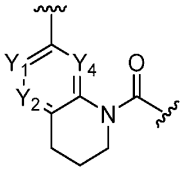
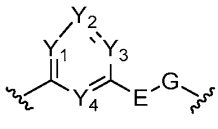
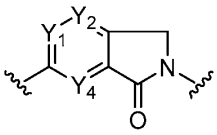
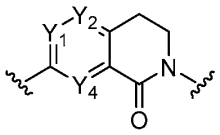
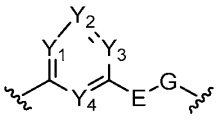
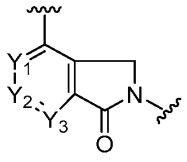
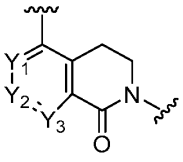
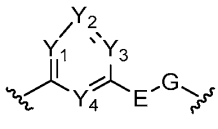
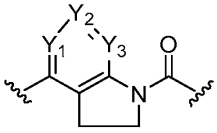
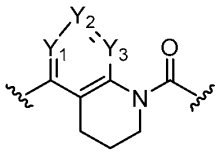
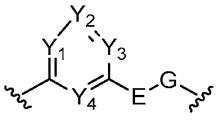
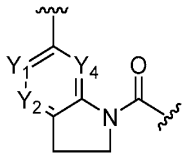
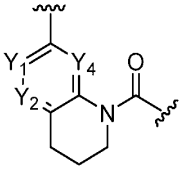
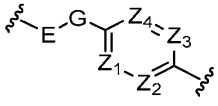
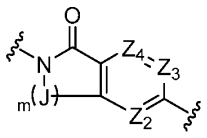
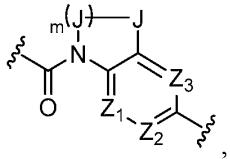
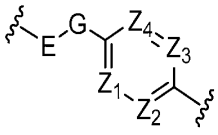
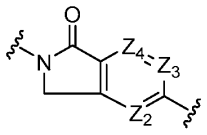
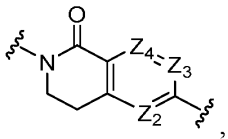
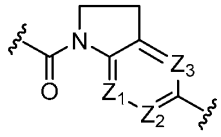
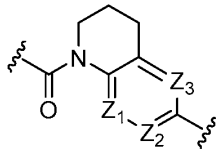
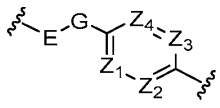
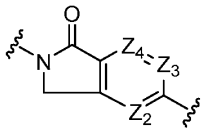
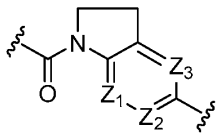
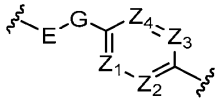
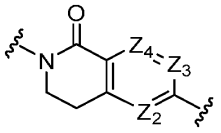
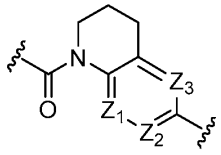

. In some embodiments, R_3 is H, CH_3, OH, halogen, or NH_2. In some embodiments, R_x is H, CH_3, or CH_2CH_3.

[0222] In some embodiments, the structural moiety  has the structure of  ,  ,  , or  . In some embodiments, the structural moiety  has the structure of  or  . In some embodiments, the structural moiety  has the structure of  or  . In these embodiments, each occurrence of m is independently 1 or 2, J is $C(R_y)_2$, and each occurrence of R_y is independently H, $(C_1\text{-}C_6)$alkyl, OH, $O(C_1\text{-}C_6)$alkyl, or halogen. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, each occurrence of R_y is independently H or $(C_1\text{-}C_6)$alkyl. In some embodiments each occurrence of R_y is independently OH, $O(C_1\text{-}C_6)$alkyl, or halogen. In some embodiments each occurrence of R_y is H.

[0223] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, the structural moiety  has the structure of  or  . In some embodiments, the structural moiety  has the structure of  or  . In some embodiments, the structural moiety  has the structure of  or  . In some embodiments, the structural moiety  has the structure of  or  . In some embodiments, Y_1, Y_2, Y_3, and Y_4 are each independently N, CH, CCH_3, or CF. In some embodiments, Y_1, Y_2, Y_3, and Y_4 are each independently N or CH.

[0224] In some embodiments, the structural moiety  has the structure of  or  , wherein each occurrence of m is independently 1 or 2, J is $C(R_z)_2$, and each occurrence of R_z is independently H, $(C_1\text{-}C_6)$alkyl, OH, $O(C_1\text{-}C_6)$alkyl, or halogen. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments each occurrence of R_z is independently H or $(C_1\text{-}C_6)$alkyl. In some embodiments each occurrence of R_z is independently OH, $O(C_1\text{-}C_6)$alkyl, or halogen. In some embodiments each occurrence of R_z is H.

[0225] In some embodiments, the structural moiety  has the structure of  ,  ,  , or  . In some embodiments, the structural moiety  has the structure of  or  . In some embodiments, the structural moiety  has the structure of  or  . In some embodiments, Z_1, Z_2, Z_3, and Z_4 are each independently N, CH, CCH_3, or CF. In some embodiments, Z_1, Z_2, Z_3, and Z_4 are each independently N or CH.

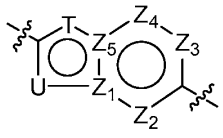
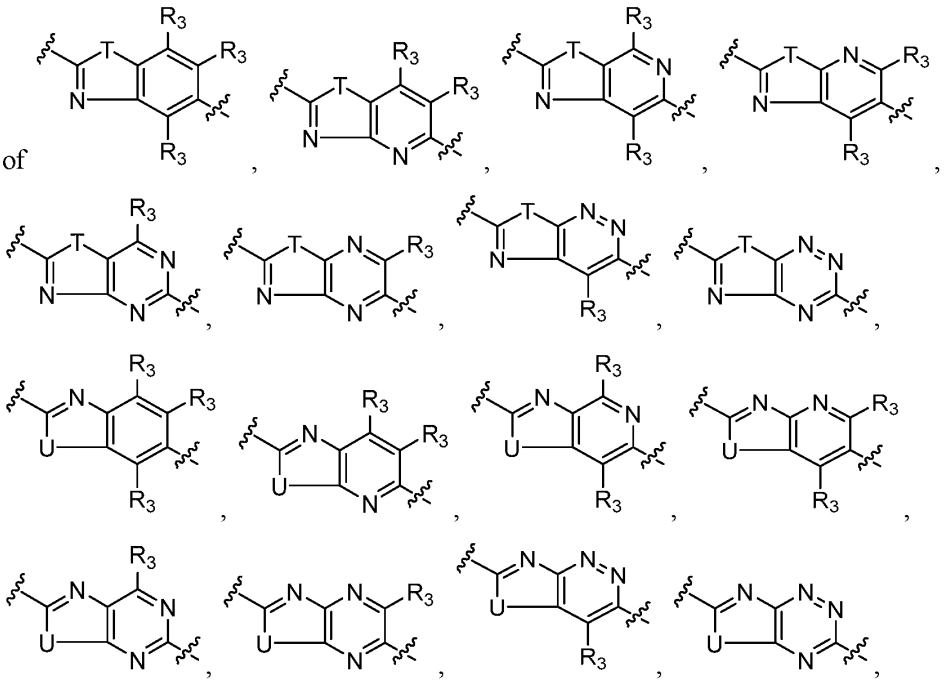
[0226] In some embodiments, the compound has the structure of Formula Ib.

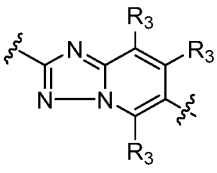
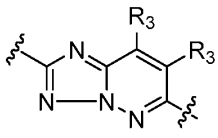
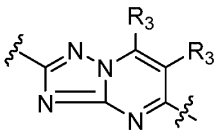
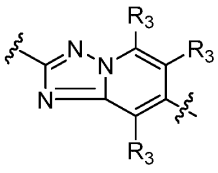
[0227] In some embodiments, T is $N(C{=}O)R_a$ or NSO_2R_a. In some embodiments, T is N(C=O)Me or N(C=O)Et. In some embodiments, T is NSO_2Me or NSO_2Et. In some

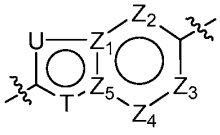
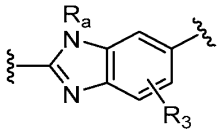
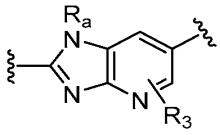
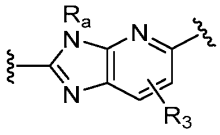
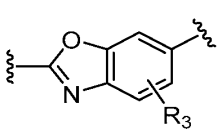
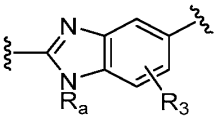
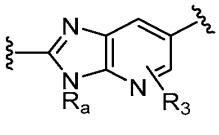
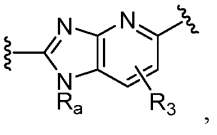
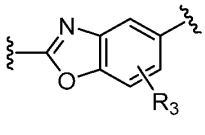
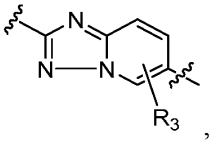
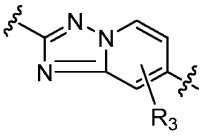
embodiments, T is O or NR_a. In some embodiments, T is O. In some embodiments, T is NR_a. In some embodiments, T is NH. In some embodiments, T is NCH_3 or NCH_2CH_3. In some embodiments, T is $NC(R_b)_2OP(=O)(OR_b)_2$.

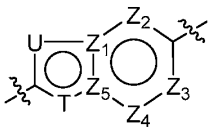
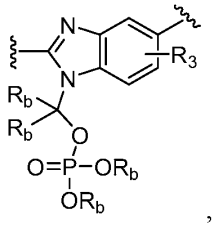
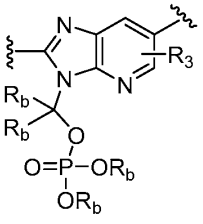
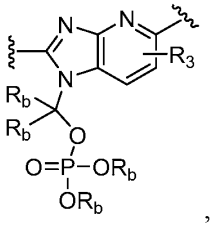
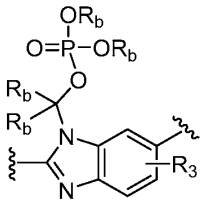
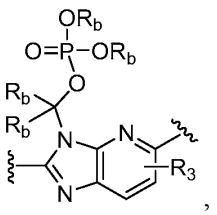
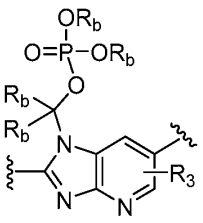
[0228] In some embodiments, U is $N(C=O)R_a$ or NSO_2R_a. In some embodiments, U is N(C=O)Me or N(C=O)Et. In some embodiments, U is NSO_2Me or NSO_2Et. In some embodiments, U is O or NR_a. In some embodiments, U is O. In some embodiments, U is NR_a. In some embodiments, U is NH. In some embodiments, U is NCH_3 or NCH_2CH_3. In some embodiments, U is $NC(R_b)_2OP(=O)(OR_b)_2$.

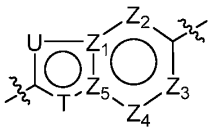
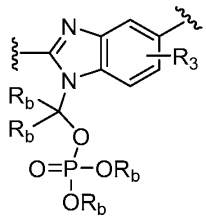
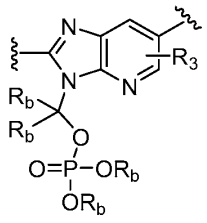
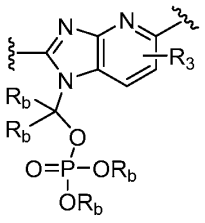
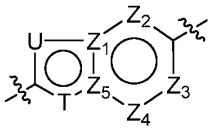
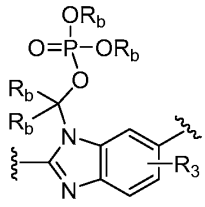
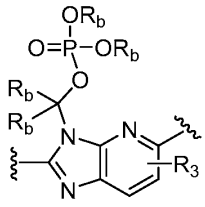
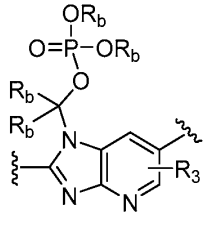
[0229] In some embodiments, each occurrence of R_b is independently H or $(C_1$-$C_6)$alkyl. In some embodiments, each occurrence of R_b is independently H, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, or *tert*-butyl. In some embodiments, each occurrence of R_b is independently H or CH_3. In some embodiments, each occurrence of R_b is H.

[0230] In some embodiments, the structural moiety  has the structure of 

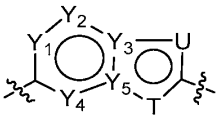
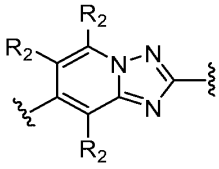
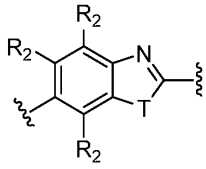
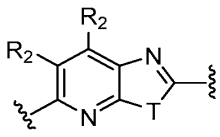
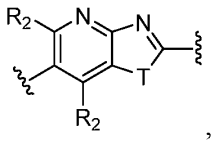
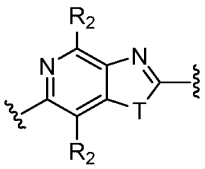
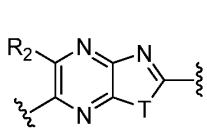
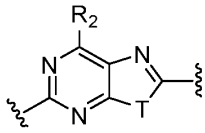
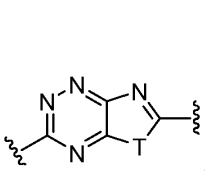
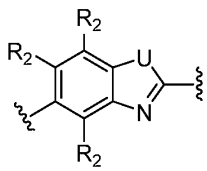
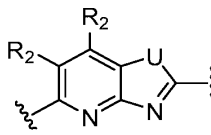
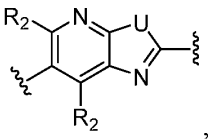



, or  , where each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

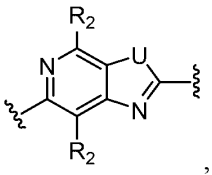
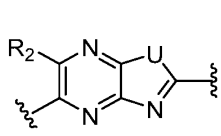
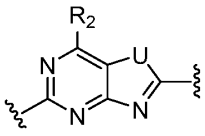
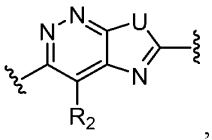
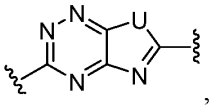
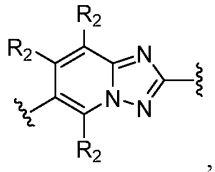
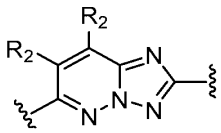
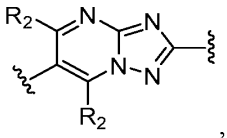
[0231] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or .

[0232] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  , or  , where each occurrence of R_b is independently H or

CH_3. In some embodiments, the structural moiety  has the structure of  ,  , or  , where each occurrence of R_b is independently H or CH_3. In some embodiments, the structural moiety  has the structure of  ,  , or  , where each occurrence of R_b is independently H or CH_3.

[0233] In some embodiments, the compound has the structure of Formula Ic.

[0234] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .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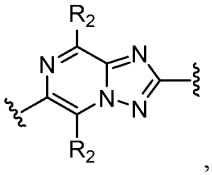
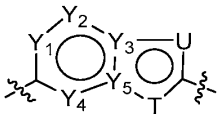
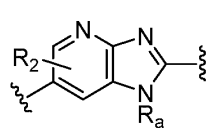
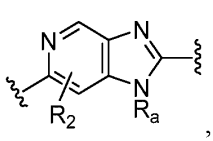
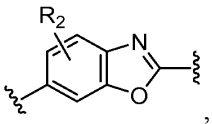
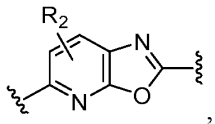
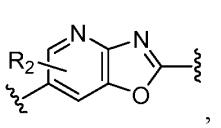
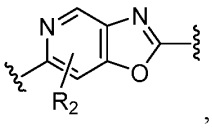
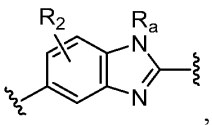
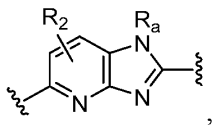
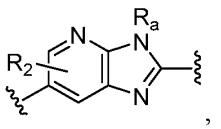
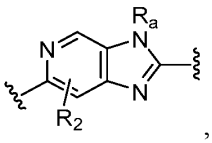
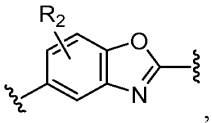
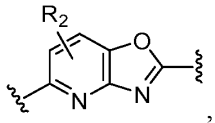
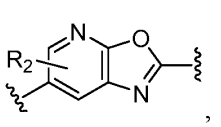
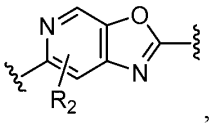
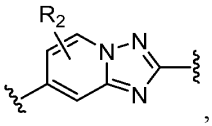
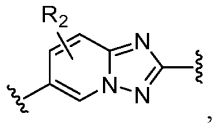
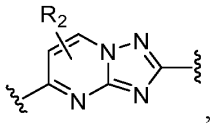
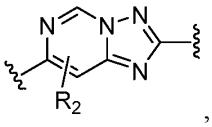
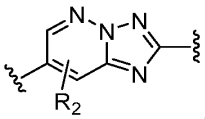
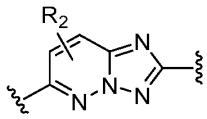
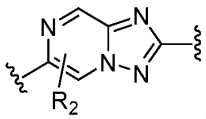
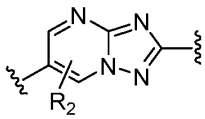
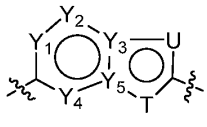
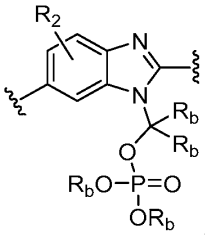
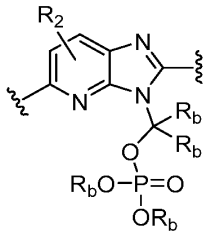
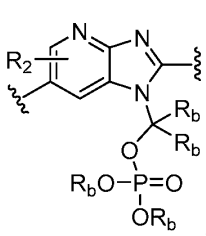
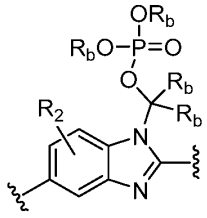
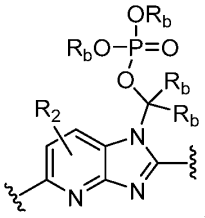
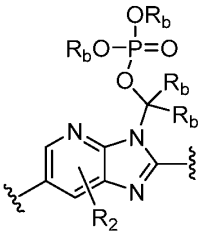
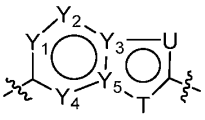
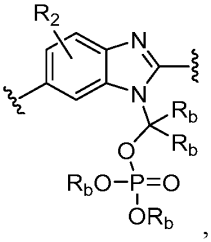
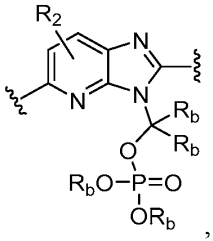
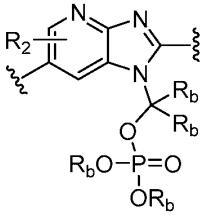
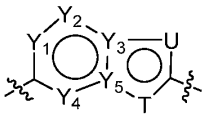
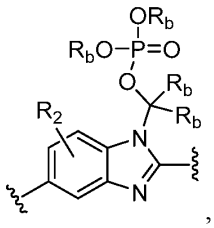
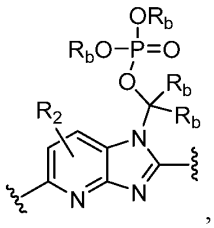
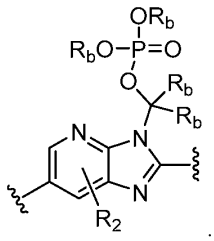

, where each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

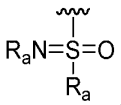
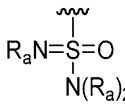
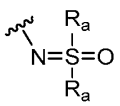
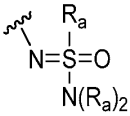
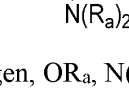
[0235] In some embodiments, the structural moiety  has the structure of

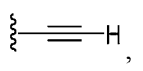
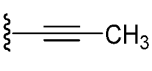
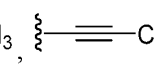
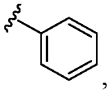
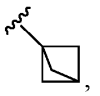
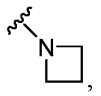
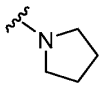
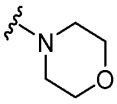
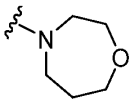
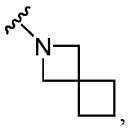
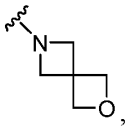
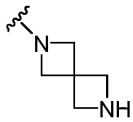
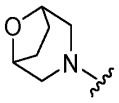
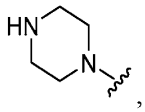
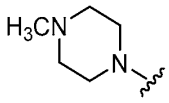
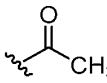
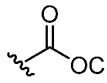
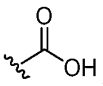
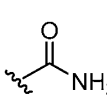
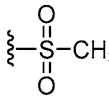
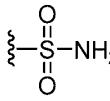
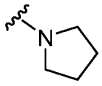




















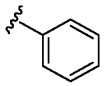
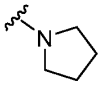
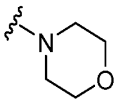
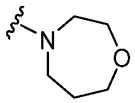
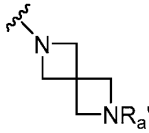
 ,  ,  , or  , where R_2 is H, CH_3, OH, halogen, or NH_2; and wherein R_a is H, CH_3, or CH_2CH_3. In some embodiments, R_2 is H, CH_3, OH, halogen, or NH_2. In some embodiments, R_a is H, CH_3, or CH_2CH_3.

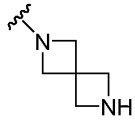
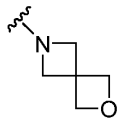
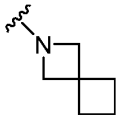
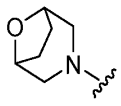
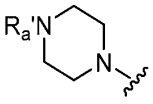
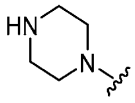
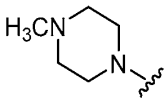
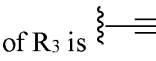
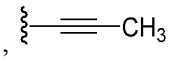
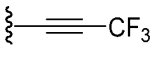
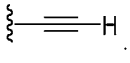
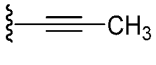
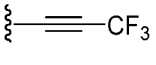
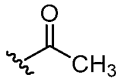
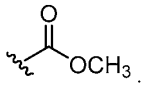
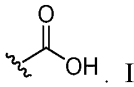
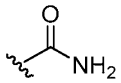
[0236] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  , or  . In some embodiments, the structural moiety  has the structure of  ,  , or  . In some embodiments, the structural moiety  has the

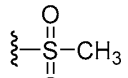
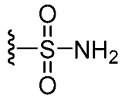
structure of  ,  , or  . In some embodiments, each occurrence of R_b is independently H or CH_3.

[0237] In some embodiments, each occurrence of R_3 is independently selected from the group consisting of H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, aryl, heteroaryl, $–OR_a$, $–N(R_a)_2$, $–COR_a$, $–CO_2R_a$, $CON(R_a)_2$, –CN, –NC, NO_2, N_3, $–SO_2R_a$, $–SO_2N(R_a)_2$, and $–N(R_a)SO_2R_a$. In some embodiments, each occurrence of R_3 is independently $(C_4$-$C_{10})$heterospiroalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, aryl, or heteroaryl. In some embodiments, each occurrence of R_3 is independently selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, and $(C_4$-$C_{10})$heterobicycloalkyl. In some embodiments, each occurrence of R_3 is independently selected from the group consisting of aryl and heteroaryl. In some embodiments, each occurrence of R_3 is independently selected from the group consisting of $–OR_a$, $–SR_a$, $–N(R_a)_2$, $–COR_a$, $–CO_2R_a$, $CON(R_a)_2$, –CN, –NC, NO_2, N_3, $–SO_2R_a$, $–SO_2N(R_a)_2$, and $–N(R_a)SO_2R_a$. In some embodiments, each occurrence of R_3 is independently selected from the group consisting of  ,  ,  ,  , and  . In some embodiments, each occurrence of R_3 is independently H, D, halogen, OR_a, $N(R_a)_2$, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$heterocycloalkyl, $(C_1$-$C_6)$alkynyl, aryl, $(C_4$-$C_{10})$bicycloalkyl, –CN, –NC, N_3, NO_2, COR_a, CO_2R_a, $CON(R_a)_2$, $–SO_2R_a$, or $–SO_2N(R_a)_2$. In some embodiments, each occurrence of R_3 is independently H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$heterocycloalkyl, $N(R_a)_2$, or –CN. In some embodiments, each occurrence of R_3 is independently H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkynyl, aryl, $(C_4$-$C_{10})$bicycloalkyl, $–SO_2R_a$, or $–SO_2N(R_a)_2$. In some embodiments, each occurrence of R_3 is independently H, D, F, Cl, Br,

CH_3, OCH_3, NH_2, $N(CH_3)_2$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , –CN, –NC, N_3, NO_2,  ,  ,  ,  ,  ,  . In some embodiments, each occurrence of R_3 is independently H, D, F, CH_3, $N(CH_3)_2$,  , or  .

[0238] In some embodiments, at least one occurrence of R_3 is H, D, or halogen. In some embodiments, at least one occurrence of R_3 is H. In some embodiments, at least one occurrence of R_3 is D. In some embodiments, at least one occurrence of R_3 is F. In some embodiments, at least one occurrence of R_3 is CH_3. In some embodiments, at least one occurrence of R_3 is OCH_3. In some embodiments, at least one occurrence of R_3 is NH_2. In some embodiments, at least one occurrence of R_3 is $N(CH_3)_2$. In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  , where R_a' is H or (C_1-C_6)alkyl.

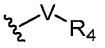
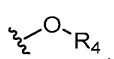
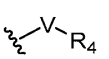
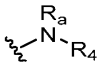
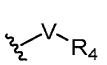
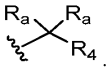
In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  , where R_a' is H or (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  ,  , or  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is –CN. In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is –NC. In some embodiments, at least one occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is NO_2. In some embodiments, at least one occurrence of R_3 is N_3. In some embodiments, at least one

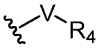
occurrence of R_3 is  . In some embodiments, at least one occurrence of R_3 is  .

[0239] In some embodiments, each occurrence of R_3 is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $-N(R_a)_2$, NO_2, and $-OR_a$. In some embodiments, at least one occurrence of R_3 is H, CH_3, OH, NH_2, or halogen. In some embodiments, at least one occurrence of R_3 is H or CH_3. In some embodiments, at least one occurrence of R_3 is OH or NH_2. In some embodiments, at least one occurrence of R_3 is halogen. In some embodiments, at least one occurrence of R_3 is H. In some embodiments, at least one occurrence of R_3 is CF_3. In some embodiments, R_3 is H or CH_3.

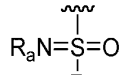
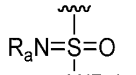
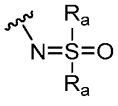
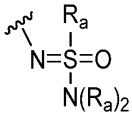
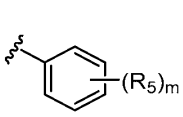
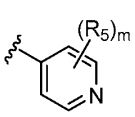
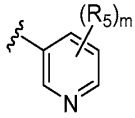
[0240] In some embodiments, V is absent, O, or NR_a. In some embodiments, V is absent. In some embodiments, V is O. In some embodiments, V is NR_a. In some embodiments, V is NH. In some embodiments, V is NCH_3 or NCH_2CH_3.

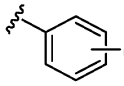
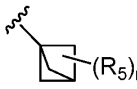
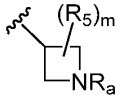
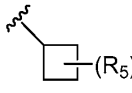
[0241] In some embodiments, V is $N(C{=}O)R_a$ or NSO_2R_a. In some embodiments, V is $N(C{=}O)H$. In some embodiments, V is $N(C{=}O)CH_3$ or $N(C{=}O)CH_2CH_3$. In some embodiments, V is NSO_2H. In some embodiments, V is NSO_2CH_3 or $NSO_2CH_2CH_3$.

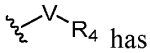
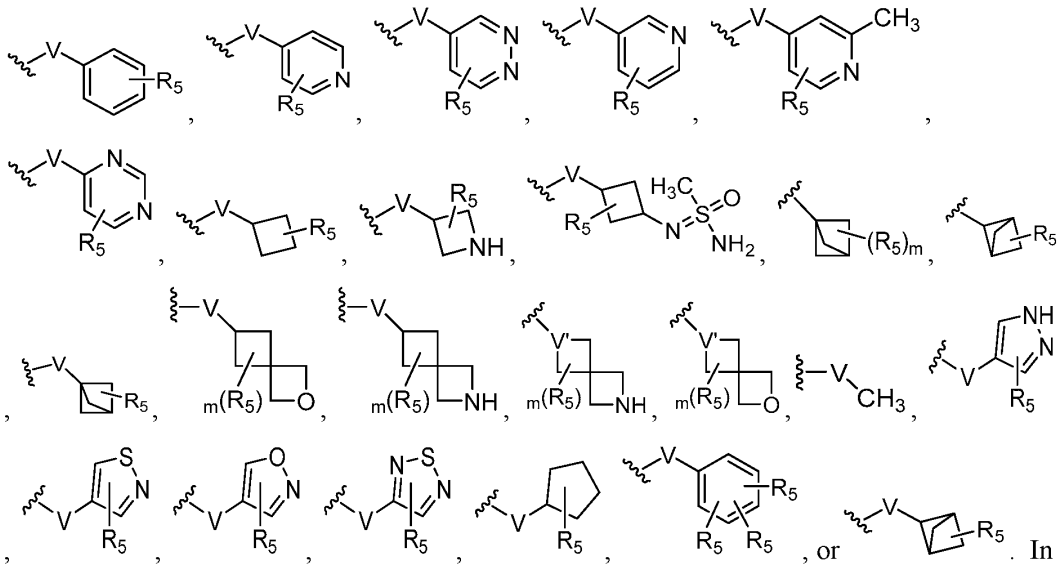
[0242] In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety  has the structure of  . In some embodiments, the structural moiety  has the structure of  .

[0243] In some embodiments, the V and R_4 of the structural moiety  taken together form a $(C_4\text{-}C_{10})$heterospiroalkyl.

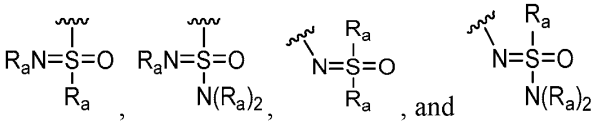
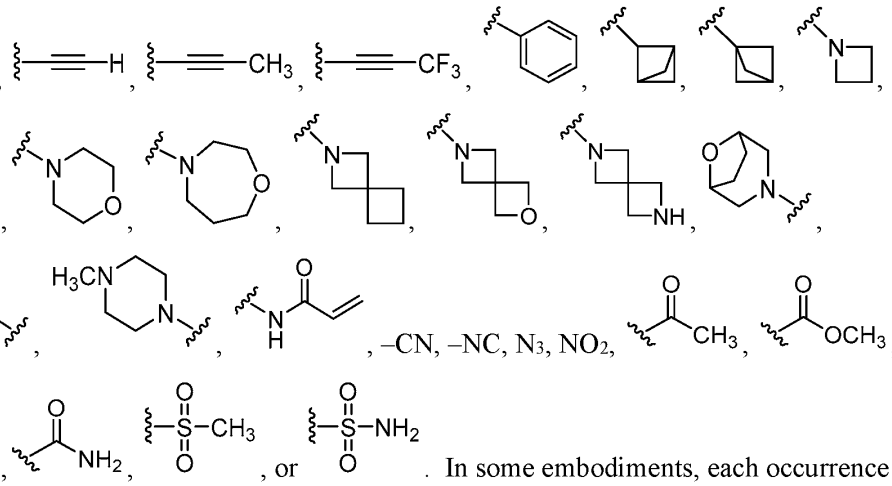
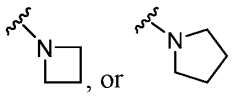
[0244] In some embodiments, R_4 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, aryl, and heteroaryl, each optionally substituted with one or more R_5. In some embodiments, R_4 is substituted by 0, 1, 2, 3, 4, 5 or 6 R_5 substituents, wherein each R_5 is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$haloalkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$haloalkynyl, $(C_3\text{-}$

C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl,aryl, heteroaryl, $-OR_a$, $-SR_a$, $-N(R_a)_2$, $N(R_a)COR_a$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$,  ,  ,  , and  . In some embodiments, each occurrence of R_5 is independently (C_4-C_{10})heterospiroalkyl, halogenated (C_3-C_7)heterocycloalkyl, aryl, or heteroaryl. In some embodiments, R_4 is  ,  ,  ,

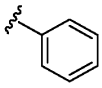
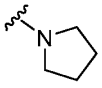
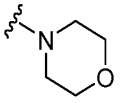
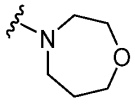
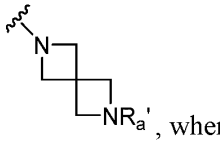
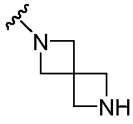
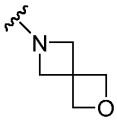
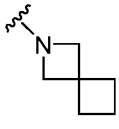
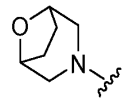
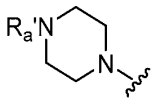
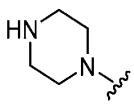
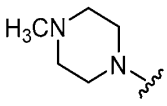
embodiments, R_4 is  . In some embodiments, R_4 is  . In some embodiments, R_4 is  . In some embodiments, R_4 is  . In some embodiments, R_4 is  . In some embodiments, m is an integer from 0-3. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

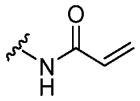
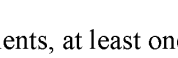
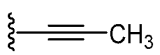
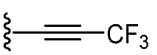
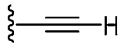
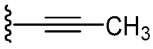
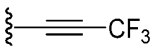
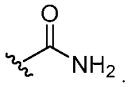
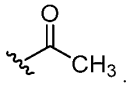
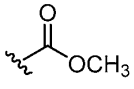
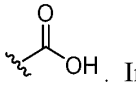
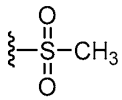
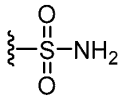
[0245] In some embodiments, the structural moiety  has the structure of  . In some embodiments, V is $C(R_a)_2$, O, NR_a, $N(C{=}O)R_a$, or NSO_2R_a. In some embodiments, V' is CR_a or N.

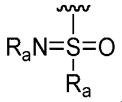
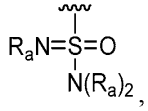
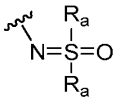
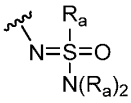
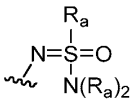
[0246] In some embodiments, each occurrence of R_5 is independently selected from the group consisting of H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, aryl, heteroaryl, $-OR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $N(R_a)COR_a$, $CON(R_a)_2$, –CN, –NC, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, and $-N(R_a)SO_2R_a$. In some embodiments, each occurrence of R_5 is independently selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-

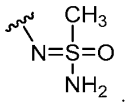
C_7)heterocycloalkyl, and (C_4-C_{10})heterobicycloalkyl. In some embodiments, each occurrence of R_5 is independently selected from the group consisting of (C_4-C_{10})heterospiroalkyl, halogenated (C_3-C_7)heterocycloalkyl, aryl and heteroaryl. In some embodiments, each occurrence of R_5 is independently selected from the group consisting of $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $N(R_a)COR_a$, $-SO_2N(R_a)_2$, and $-N(R_a)SO_2R_a$. In some embodiments, each occurrence of R_5 is independently selected from the group consisting of  . In some embodiments, each occurrence of R_5 is independently H, D, halogen, OR_a, $N(R_a)_2$, (C_1-C_6)alkyl, (C_3-C_7)heterocycloalkyl, (C_1-C_6)alkynyl, aryl, (C_4-C_{10})bicycloalkyl, $-CN$, $-NC$, N_3, NO_2, COR_a, CO_2R_a, $CON(R_a)_2$, $-SO_2R_a$, $N(R_a)COR_a$, or $-SO_2N(R_a)_2$. In some embodiments, each occurrence of R_5 is independently H, D, halogen, (C_1-C_6)alkyl, (C_3-C_7)heterocycloalkyl, $N(R_a)COR_a$, $N(R_a)_2$, or $-CN$. In some embodiments, each occurrence of R_5 is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkynyl, aryl, (C_4-C_{10})bicycloalkyl, $-SO_2R_a$, or $-SO_2N(R_a)_2$. In some embodiments, each occurrence of R_5 is independently H, D, F, Cl, Br, CH_3, CF_3, OCH_3, NH_2, $N(CH_3)_2$,  , $-CN$, $-NC$, N_3, NO_2, . In some embodiments, each occurrence of R_5 is independently H, D, F, CH_3, $N(CH_3)_2$,  .

[0247] In some embodiments, at least one occurrence of R_5 is H, D, or halogen. In some embodiments, at least one occurrence of R_5 is H. In some embodiments, at least one occurrence of R_5 is D. In some embodiments, at least one occurrence of R_5 is F. In some embodiments, at least one occurrence of R_5 is CH_3. In some embodiments, at least one occurrence of R_5 is OCH_3. In some embodiments, at least one occurrence of R_5 is NH_2. In

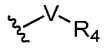
some embodiments, at least one occurrence of R_5 is $N(CH_3)_2$. In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  , where R_a' is H or $(C_1$-$C_6)$alkyl. In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  , where R_a' is H or $(C_1$-$C_6)$alkyl. In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence

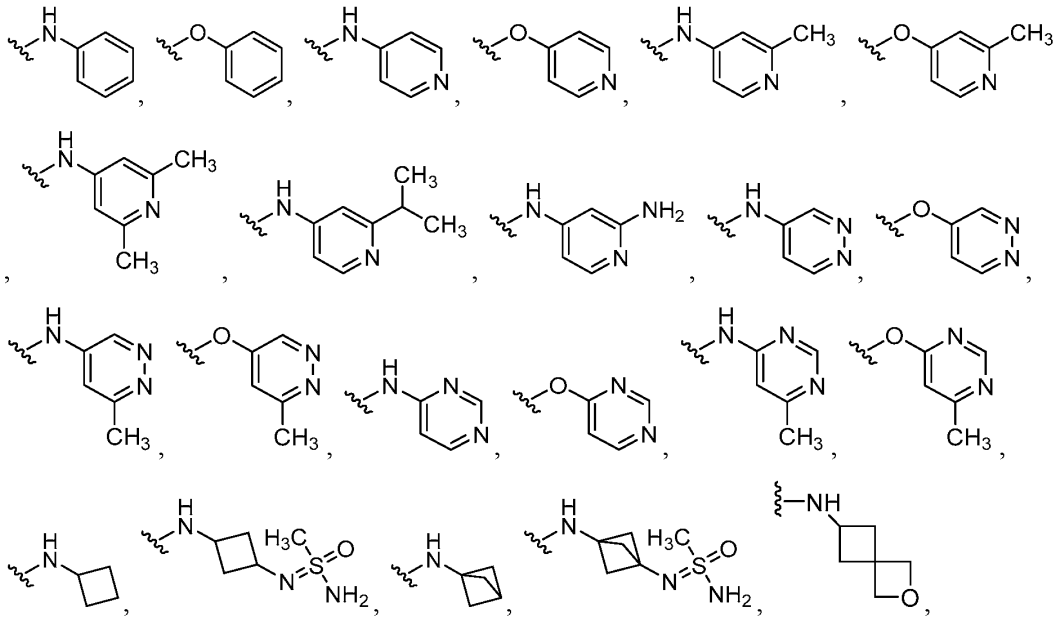
of R_5 is  . In some embodiments, at least one occurrence of R_5 is  ,  , or  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is –CN. In some embodiments, at least one occurrence of R_5 is –NC. In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is NO_2. In some embodiments, at least one occurrence of R_5 is N_3. In some embodiments, at least one occurrence of R_5 is  . In some embodiments, at least one occurrence of R_5 is  .

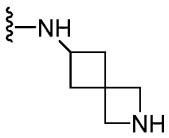
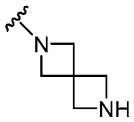
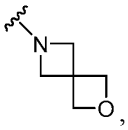
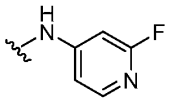
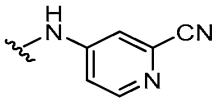
[0248] In some embodiments, each occurrence of R_5 is independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, OR_a, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $N(R_a)COR_a$, –CN, NO_2, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$,  ,  ,  , and  . In some embodiments, at least one occurrence of R_5 is $(C_1\text{-}C_6)$alkyl, halogen, OH, NH_2, or  . In some embodiments, at least one occurrence of R_5 is CH_3, halogen, OH, or NH_2. In some embodiments, at least one

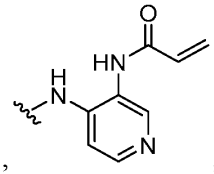
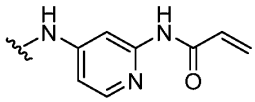
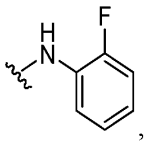
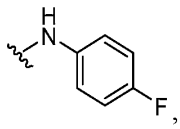
occurrence of R_5 is OH. In some embodiments, at least one occurrence of R_5 is CH_3. In some embodiments, at least one occurrence of R_5 is  .

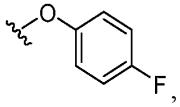
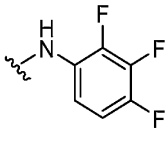
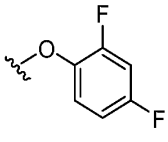
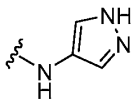
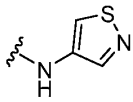
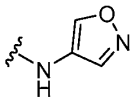
[0249] In any one of embodiments described herein, each occurrence of R_a is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, aryl, or heteroaryl. In any one of embodiments described herein, at least one occurrence of R_a is aryl, or heteroaryl. In any one of embodiments described herein, each occurrence of R_a is independently H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_3-C_7)cycloalkyl, or two R_a taken together form a 5- or 6-membered ring optionally substituted with halogen or (C_1-C_6)alkyl. In some embodiments, each occurrence of R_a is independently H or (C_1-C_6)alkyl. In some embodiments, each occurrence of R_a is independently (C_2-C_6)alkenyl. In some embodiments, each occurrence of R_a is independently H, CH_3, or CH_2CH_3. In some embodiments, at least one occurrence of R_a is H or CH_3. In some embodiments, each occurrence of R_a is H. In some embodiments, each occurrence of R_a is CH_3. In some embodiments, at least one occurrence of R_a is (C_3-C_7)cycloalkyl, optionally substituted with halogen or (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_a is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, optionally substituted with halogen or (C_1-C_6)alkyl.

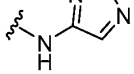
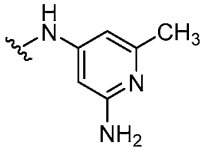
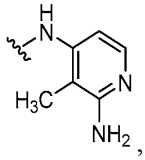
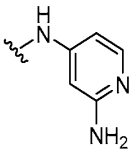
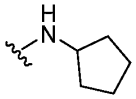
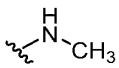
[0250] In some embodiments, the structural moiety  has the structure of

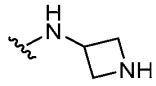
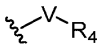


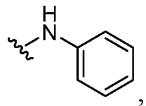
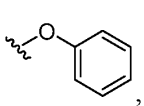
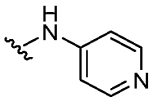
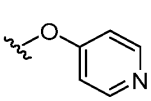
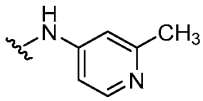
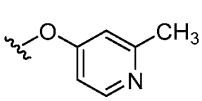
 ,  ,  ,  ,  ,

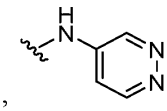
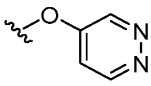
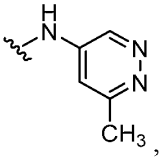
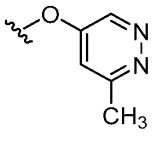
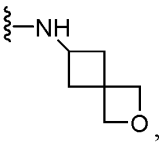
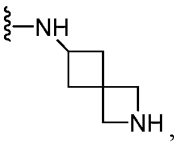
 ,  ,  ,  ,  ,

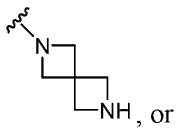
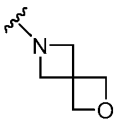
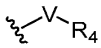
 ,  ,  ,  ,  ,  ,

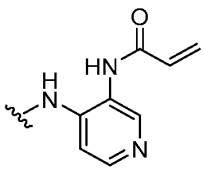
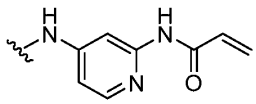
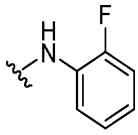
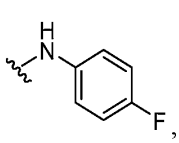
 ,  ,  ,  ,  ,  , or

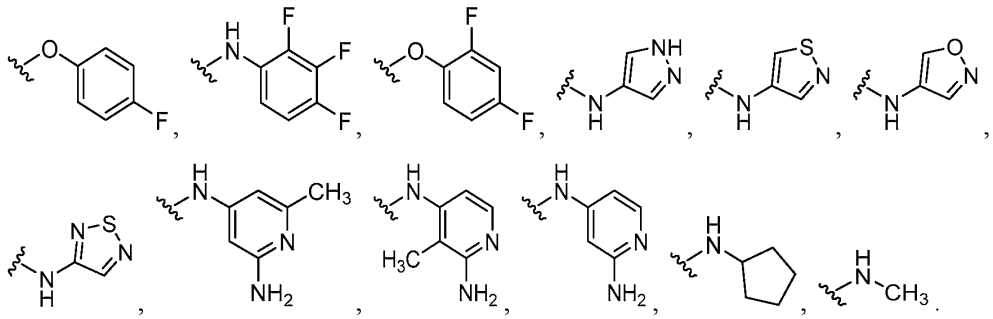
 . In some embodiments, the structural moiety  has the structure of

 ,  ,  ,  ,  ,  ,

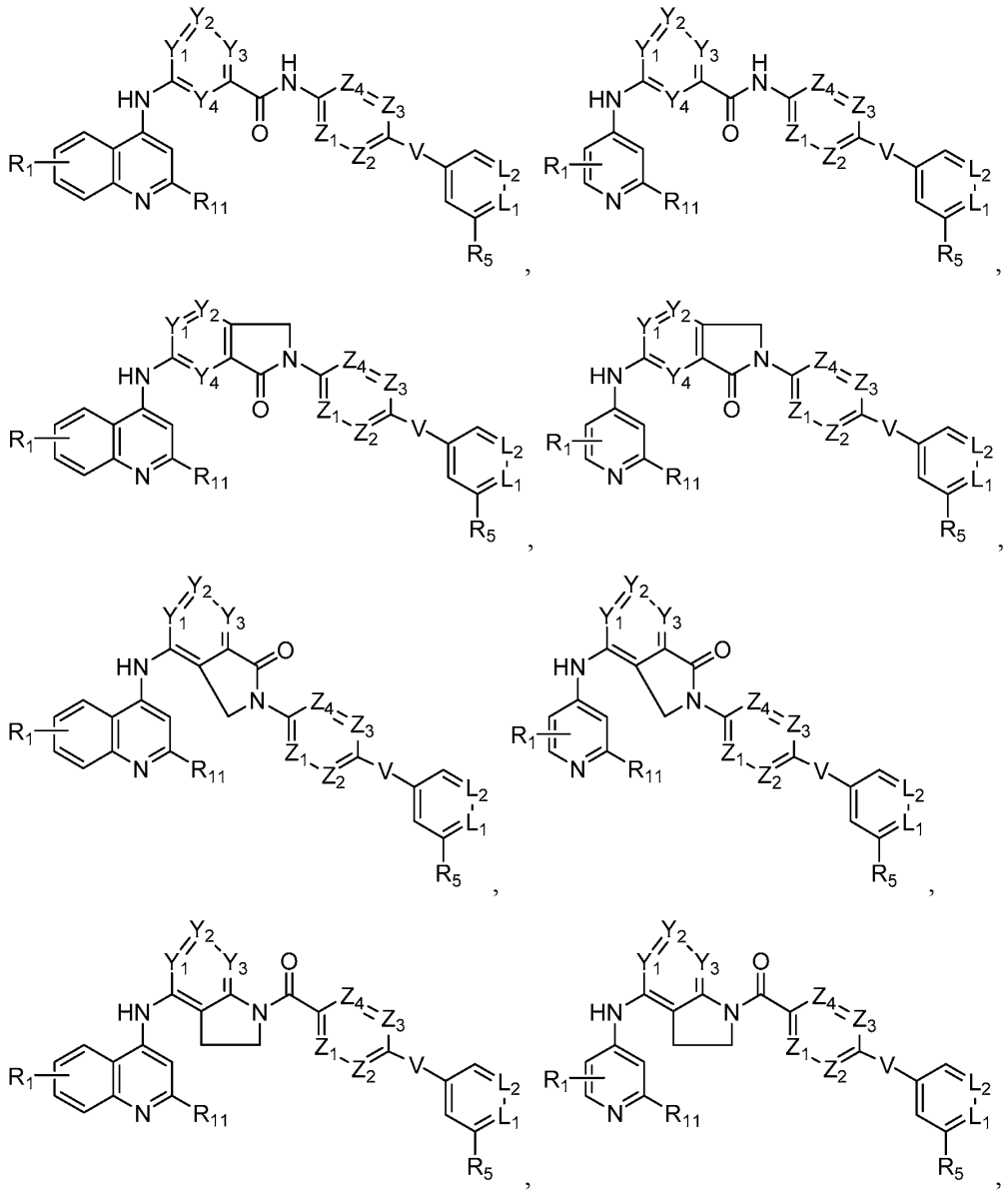
 ,  ,  ,  ,  ,  ,

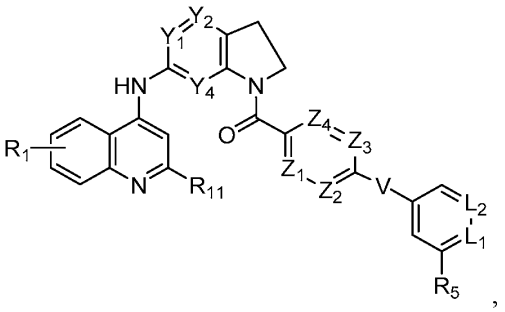
 , or  . In some embodiments, the structural moiety  has the structure of

 ,  ,  ,  ,



[0251] In some embodiments, the compound of Formula Ia has the structure of

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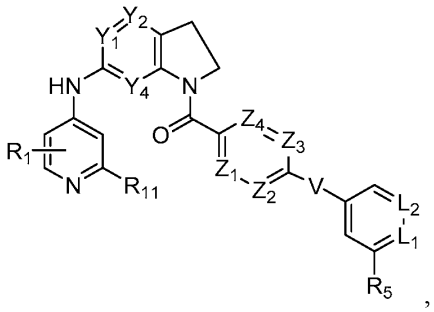
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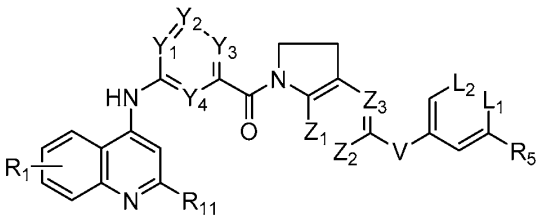
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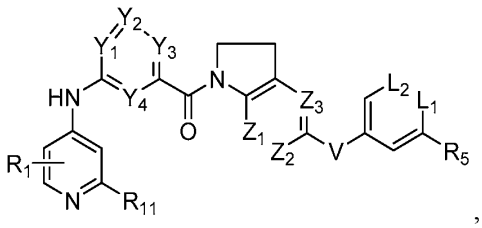
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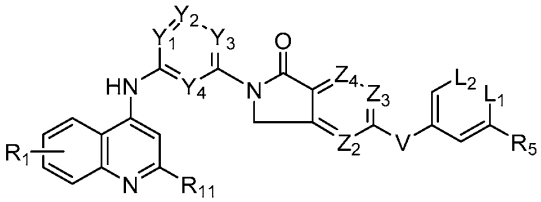
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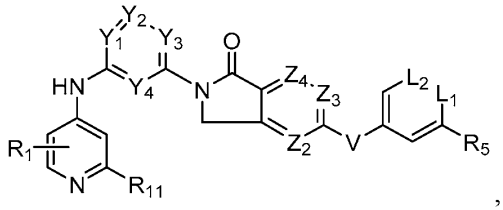
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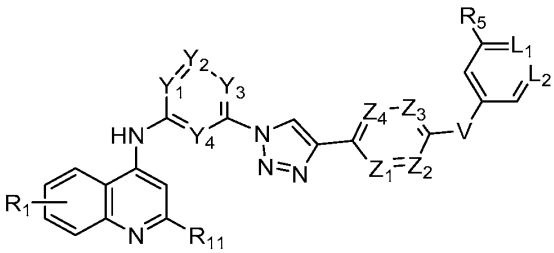
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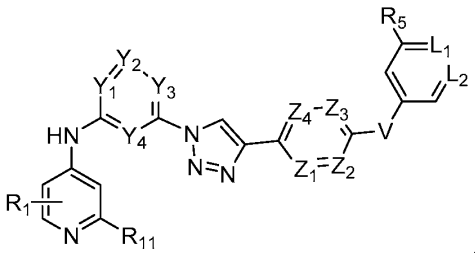
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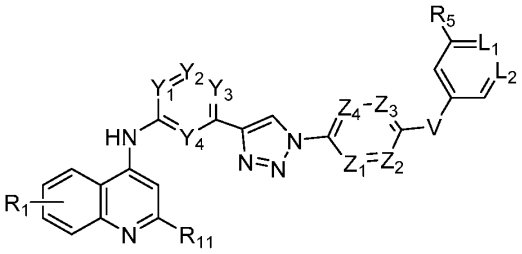
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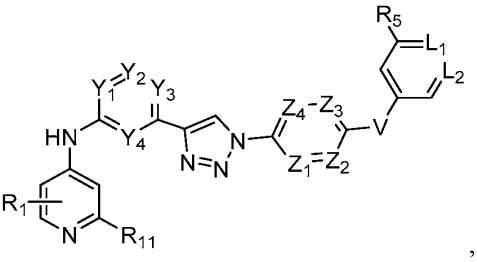
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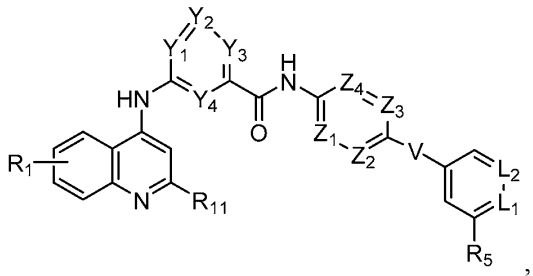
where R_1 is H, $(C_1\text{-}C_6)$alkyl, $N(R_a)_2$, $(C_3\text{-}C_7)$heterocycloalkyl, or halogen; R_5 and R_{11} are each independently H or CH_3; Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, Z_3, Z_4, L_1, and L_2 are each independently CH or N; and V is NH or O. In some embodiments, the compound of Formula Ia has the



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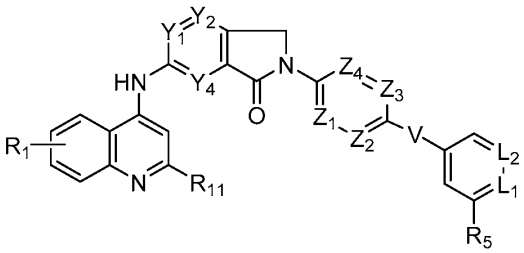

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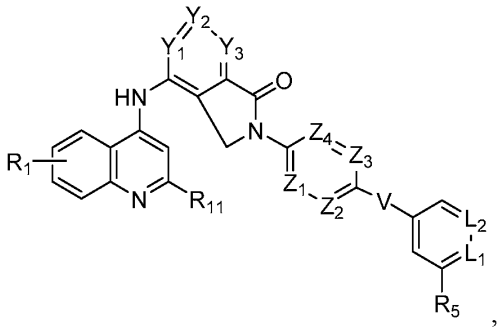

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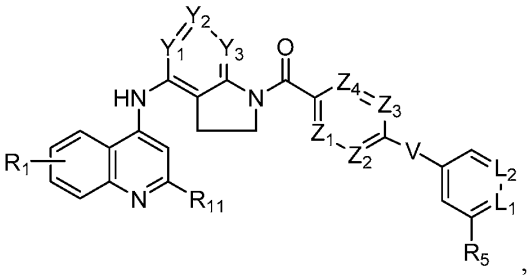

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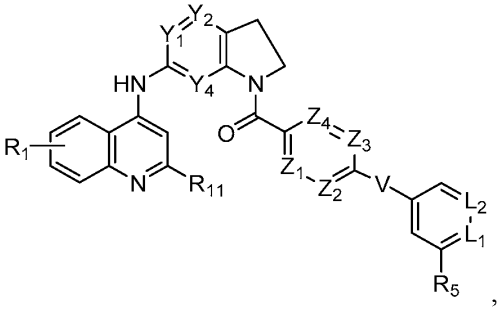

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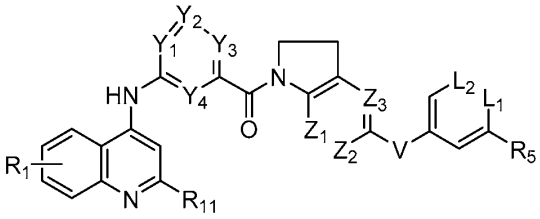

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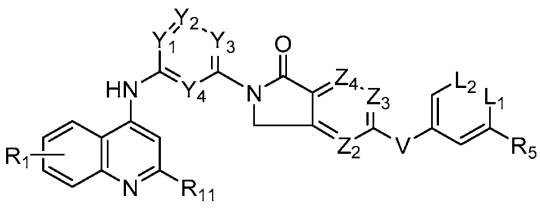

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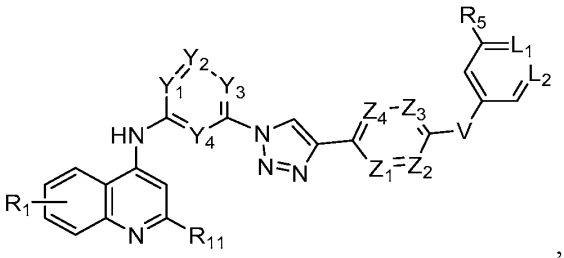

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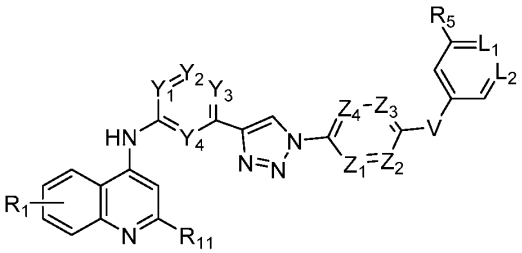
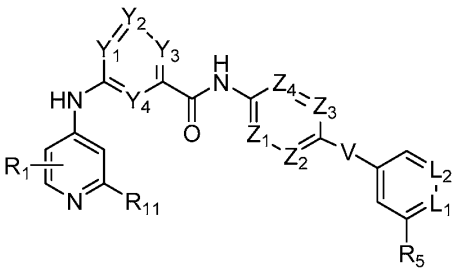


, where R_1 is H, (C_1-C_6)alkyl, $N(R_a)_2$, (C_3-C_7)heterocycloalkyl, or halogen; R_5 and R_{11} are each independently H or CH_3; Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, Z_3, Z_4, L_1, and L_2 are each independently CH or N; and V is NH or O. In some embodiments, the compound of Formula Ia has the structure of



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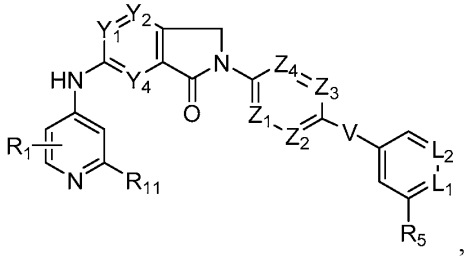

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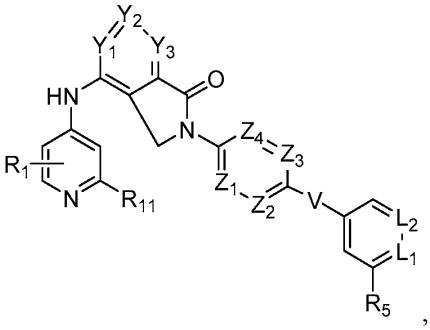

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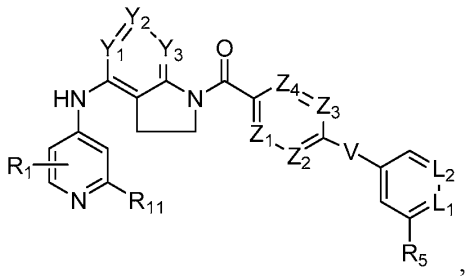

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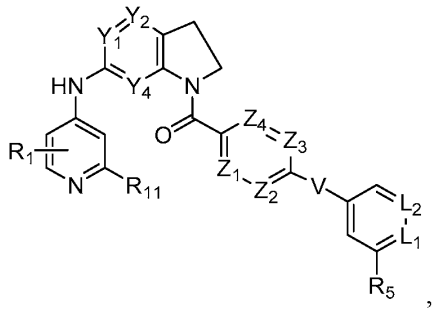
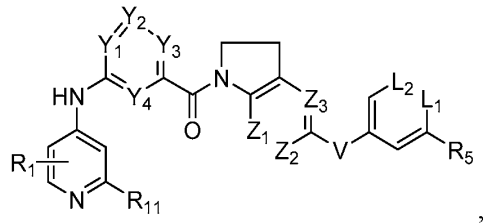
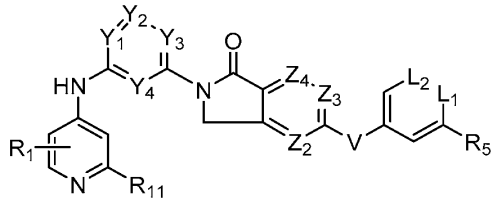
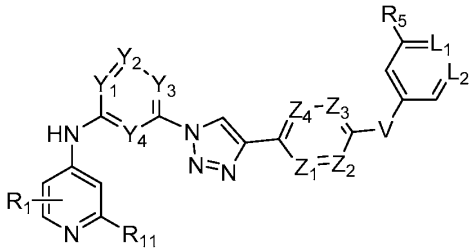
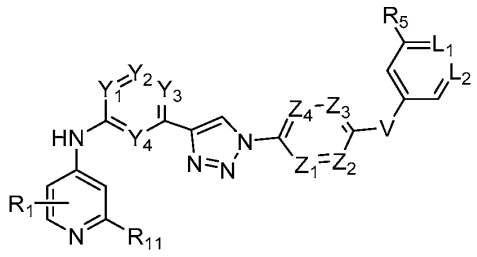
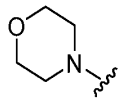
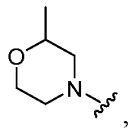
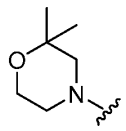
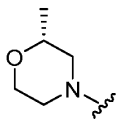
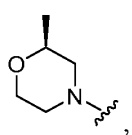
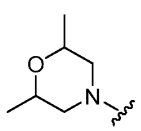
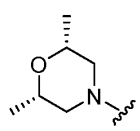
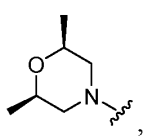
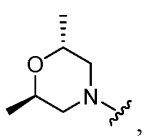
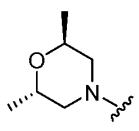
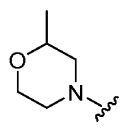
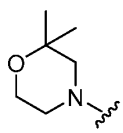
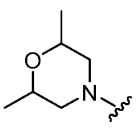
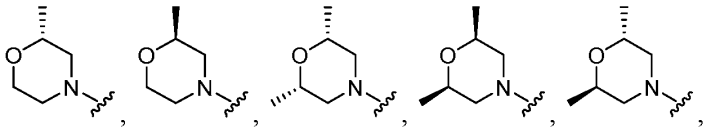
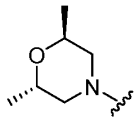
 ,  ,

 ,  , or

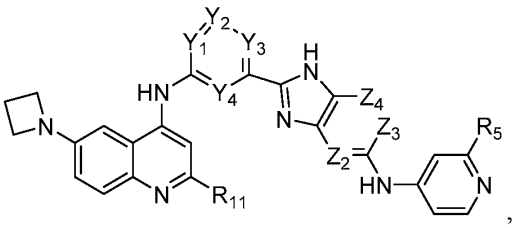
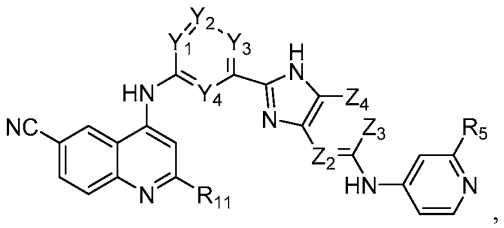
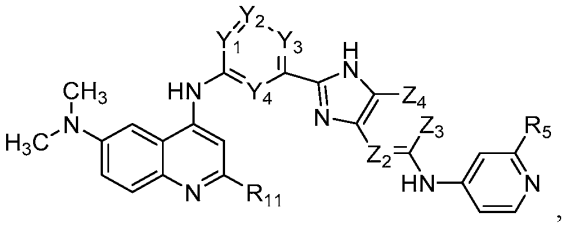
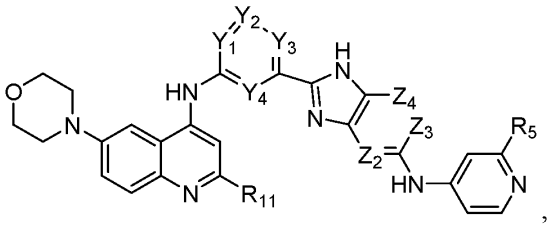
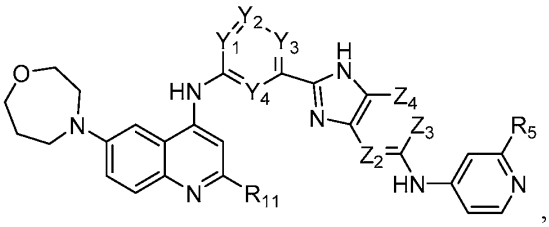
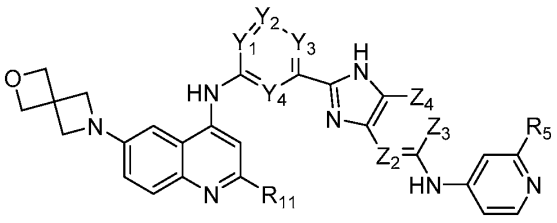
 , where R_1 is H, $(C_1\text{-}C_6)$alkyl, $N(R_a)_2$, $(C_3\text{-}C_7)$heterocycloalkyl, or halogen; R_5 and R_{11} are each independently H or CH_3; Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, Z_3, Z_4, L_1, and L_2 are each independently CH or N; and V is NH or O. In some embodiments, R_1 is H, F, Cl, Br, CH_3, CH_2CH_3, or $CH(CH_3)_2$,  ,  ,

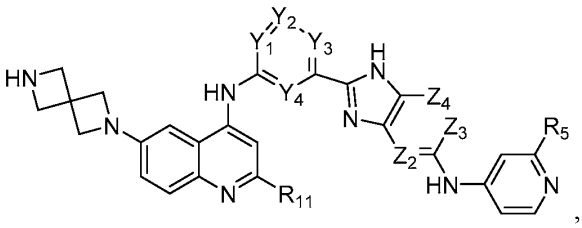
 ,  ,  ,  ,  ,  ,  ,

 or  . In some embodiments, R_1 is  ,  or  .

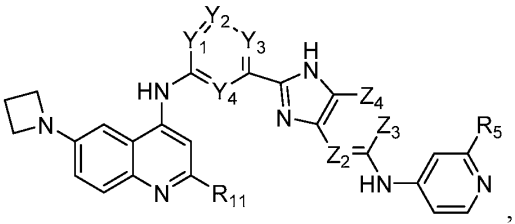
In some embodiments, R_1 is  ,  .

[0252] In some embodiments, the compound of Formula Ib has the structure of

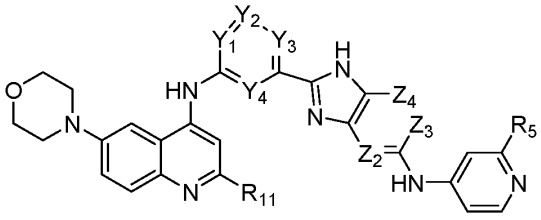
 ,
 ,
 ,
 ,
 ,
 , or



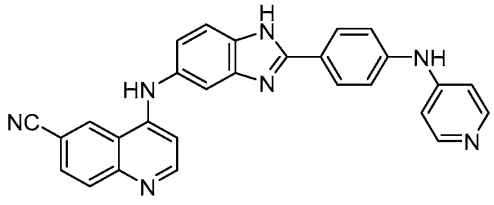
, where R_{11} and R_5 are each independently H or CH_3; and Y_1, Y_2, Y_3, Y_4, Z_2, Z_3, and Z_4 are each independently CH or N. In some embodiments, the compound of Formula Ib has the structure of

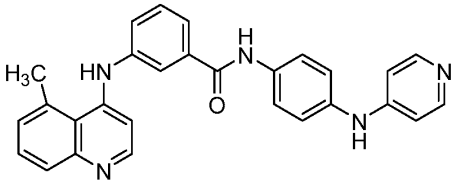


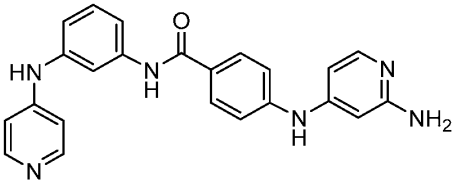
, where R_{11} and R_5 are each independently H or CH_3; and Y_1, Y_2, Y_3, Y_4, Z_2, Z_3, and Z_4 are each independently CH or N. In some embodiments, the compound of Formula Ib has the structure of



, where R_{11} and R_5 are each independently H or CH_3; and Y_1, Y_2, Y_3, Y_4, Z_2, Z_3, and Z_4 are each independently CH or N.

[0253] In some embodiments, the compound of Formula Ia, Ib, or Ic activates Akt3 and is the compound  . In some embodiments, the compound of Formula Ia, Ib, or Ic activates Akt3 and is Compound 2 as shown in Table 2.

[0254] In some embodiments, the compound of Formula Ia, Ib, or Ic inhibits Akt3 and is selected from the group consisting of  ,



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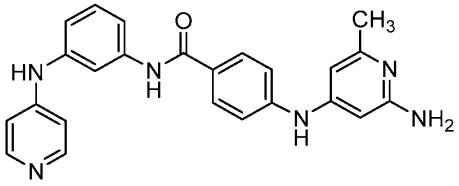

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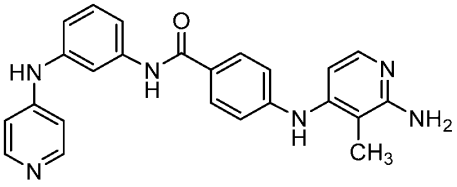
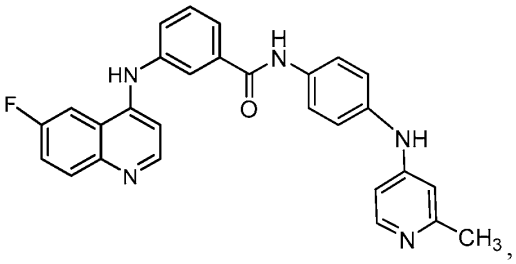


. In some embodiments, the compound of Formula Ia, Ib, or Ic inhibits Akt3 and is selected from the group consisting of Compounds 3 and 18-21 as shown in Table 1.

[0255] In some embodiments, the compound of Formula Ia is



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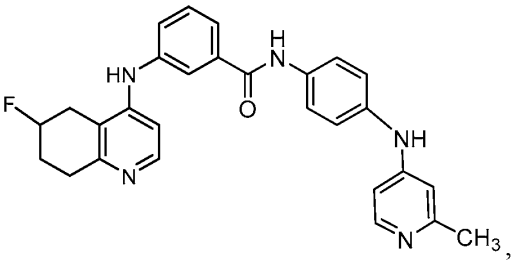

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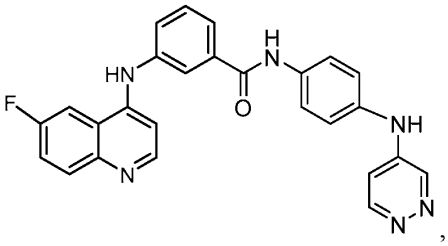

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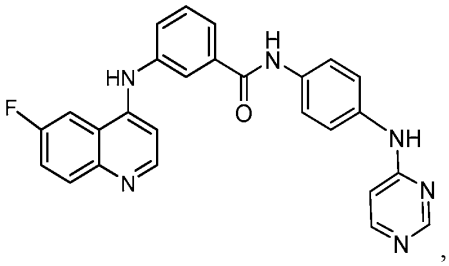

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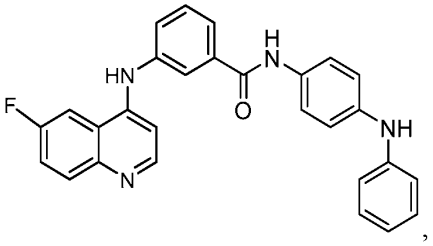

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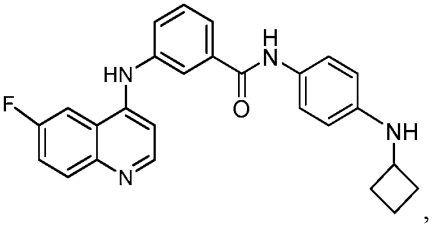

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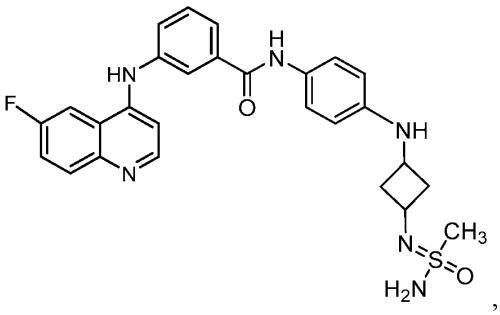
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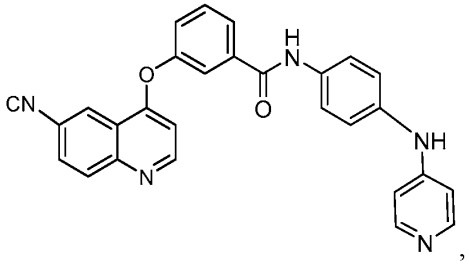
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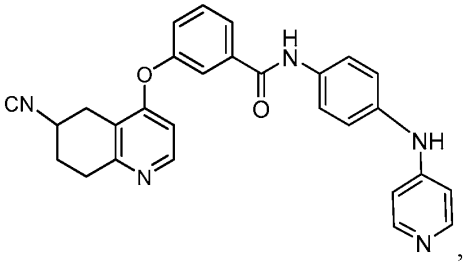
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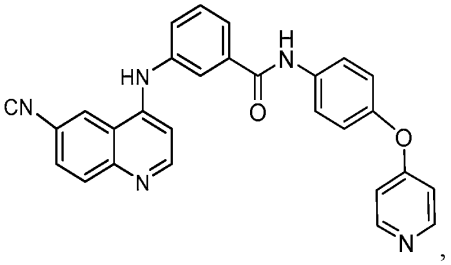
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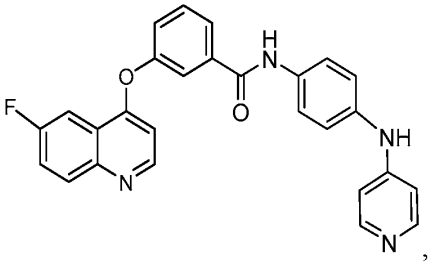
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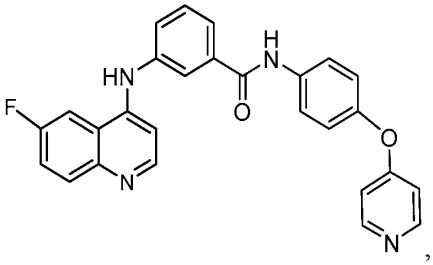
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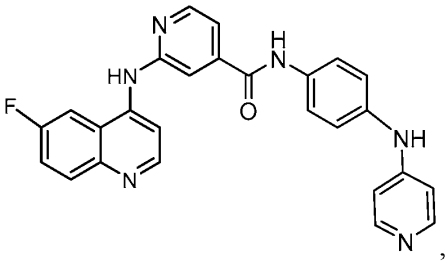
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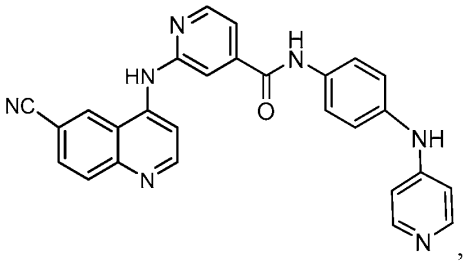
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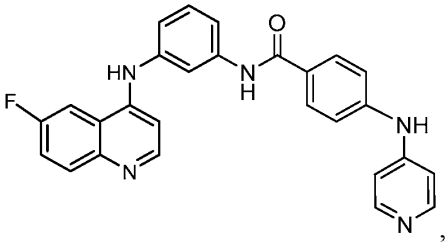
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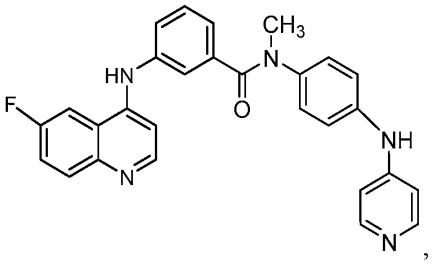
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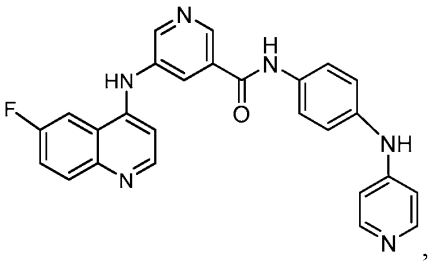
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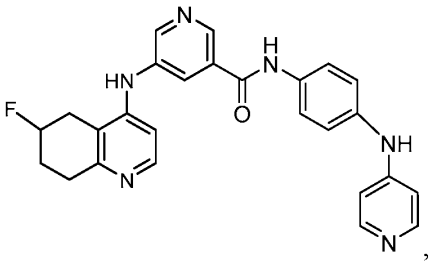
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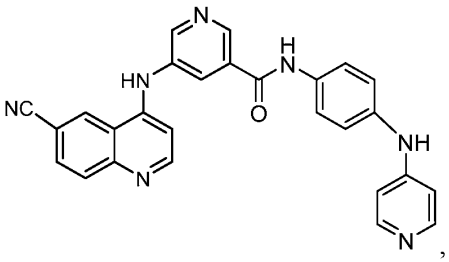
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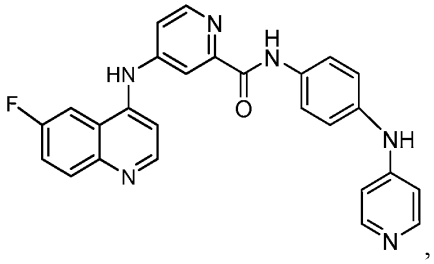
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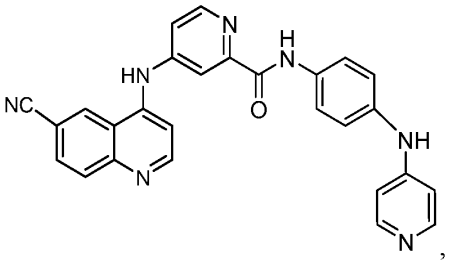
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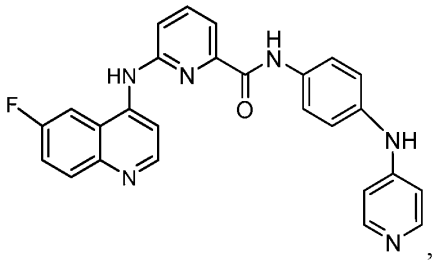
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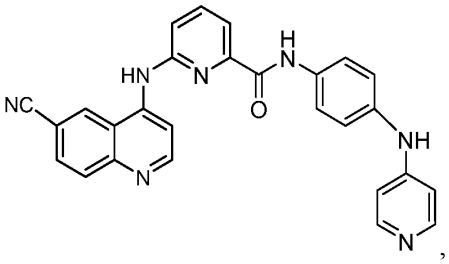
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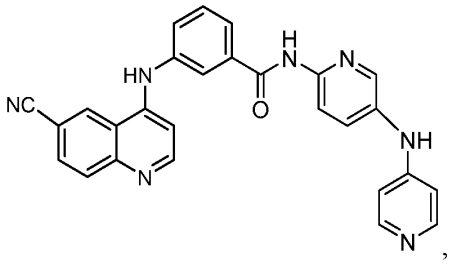
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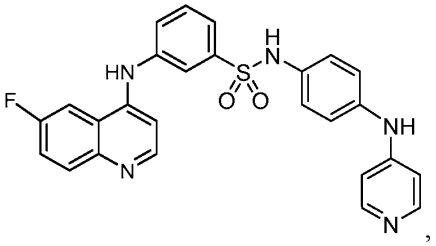
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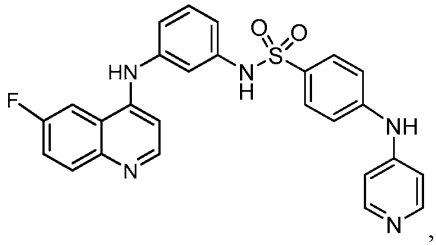
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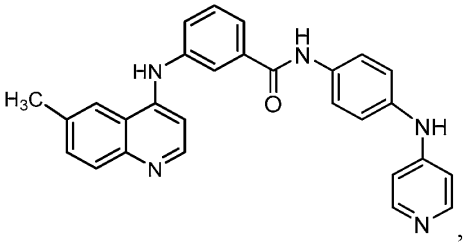
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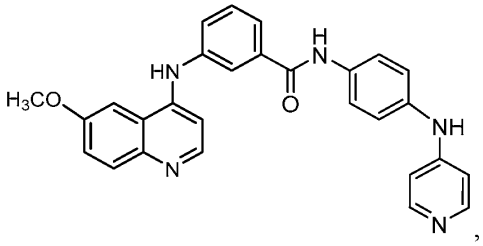
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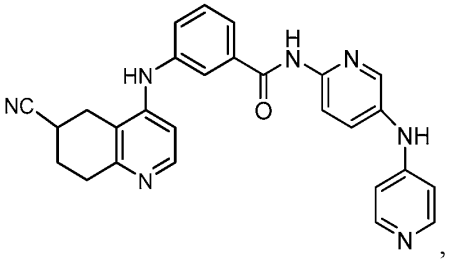
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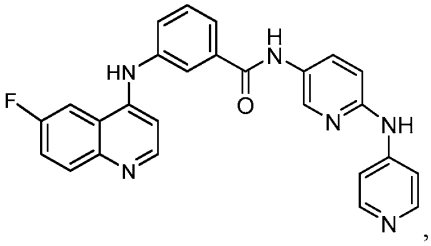
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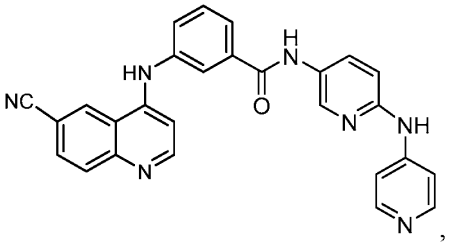
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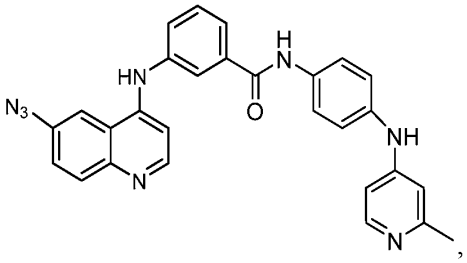
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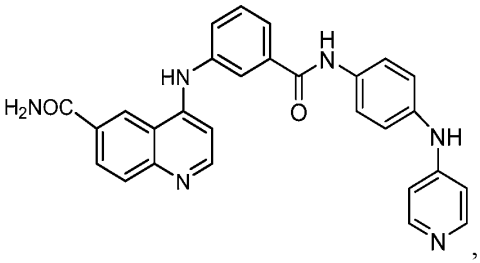
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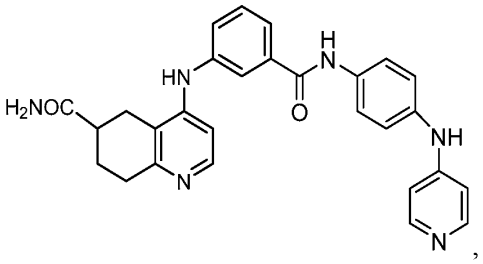
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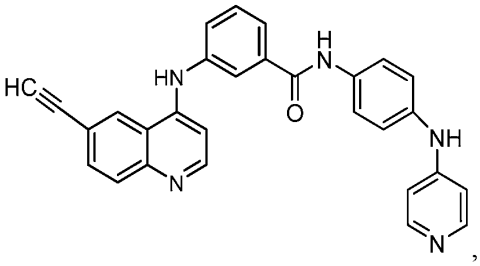
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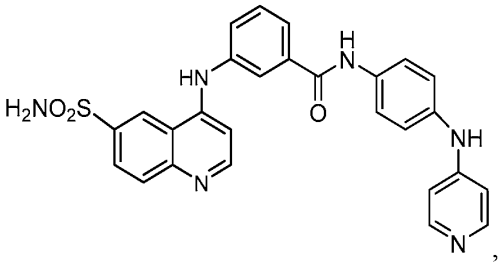
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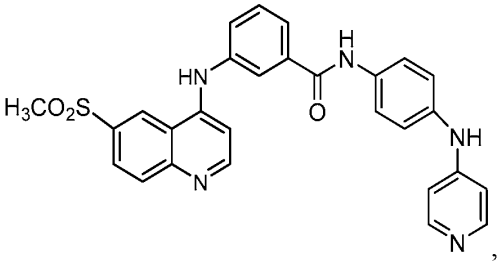
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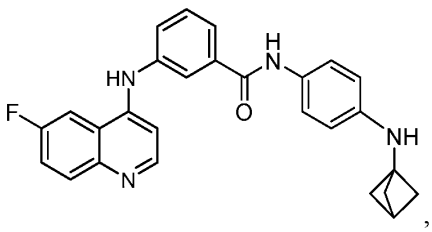
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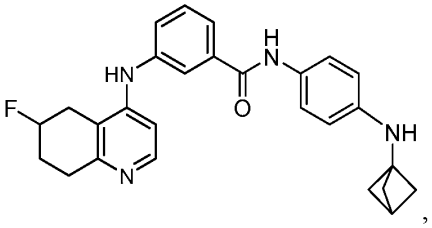
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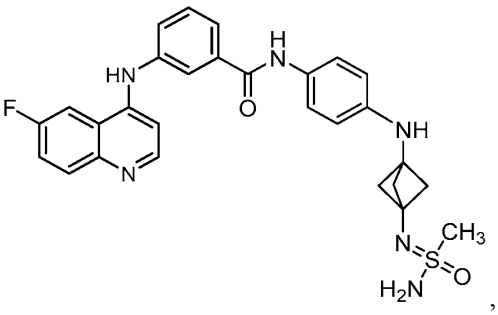
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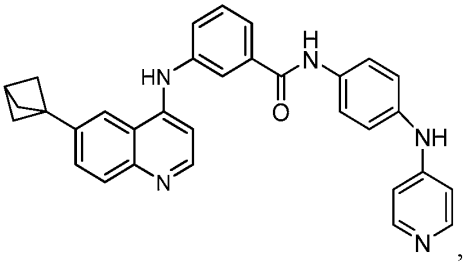
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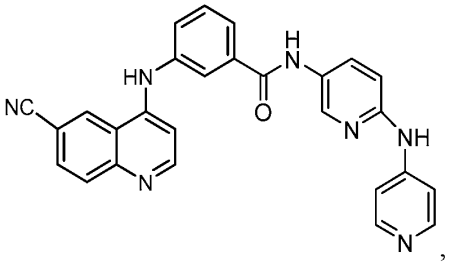
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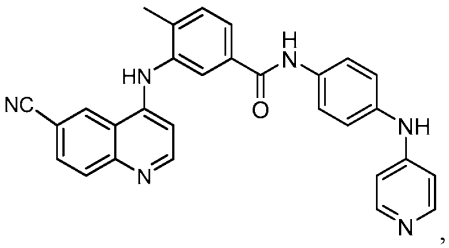
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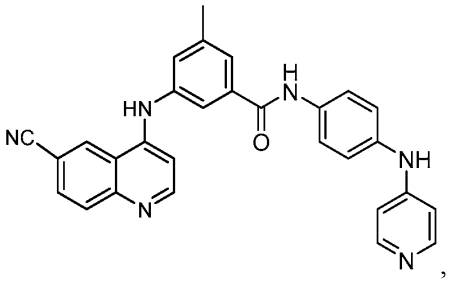
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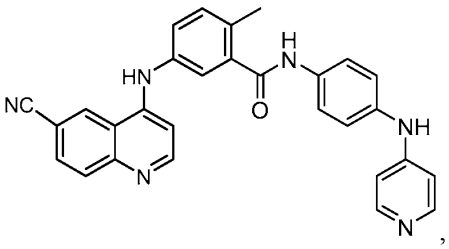
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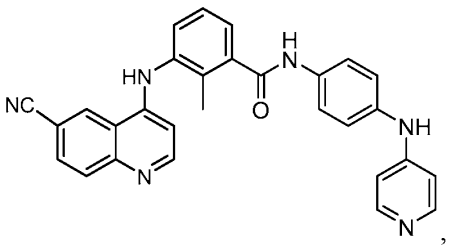
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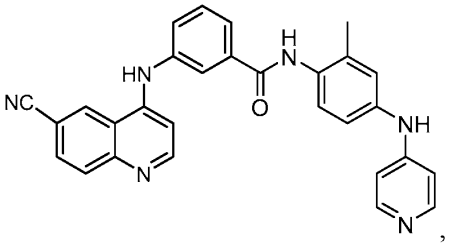
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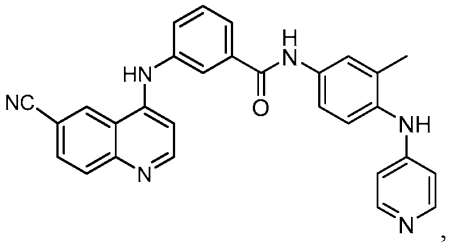
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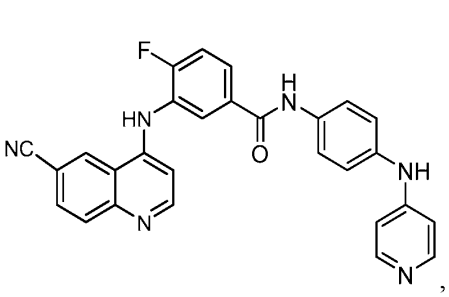
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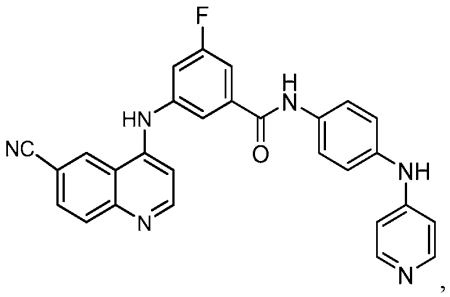
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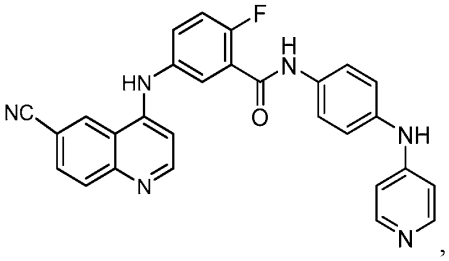
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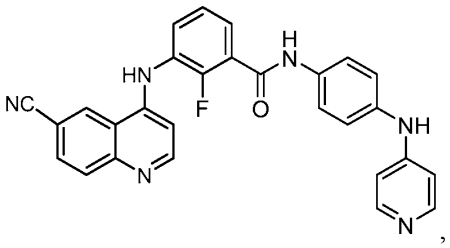
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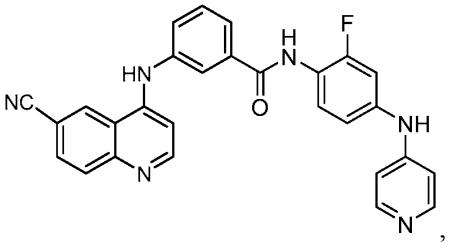
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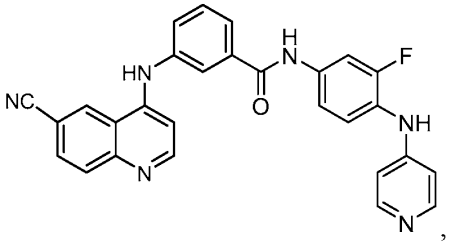
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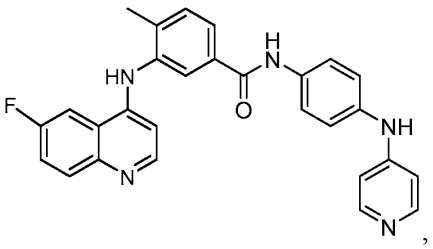
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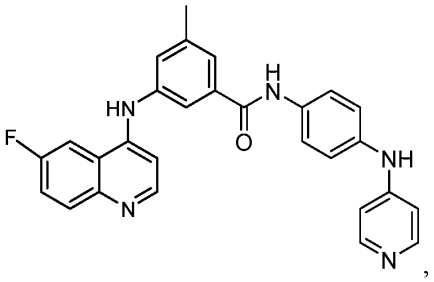
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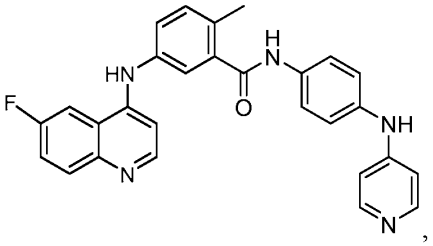
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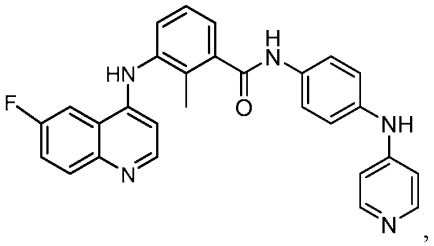
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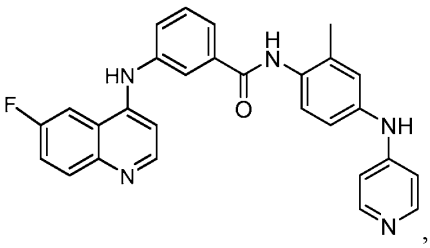
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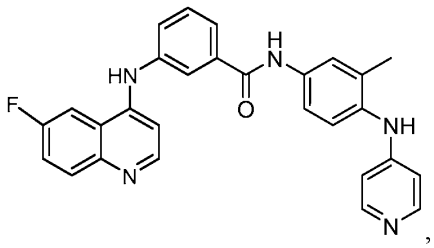
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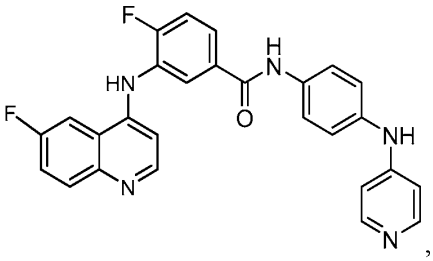
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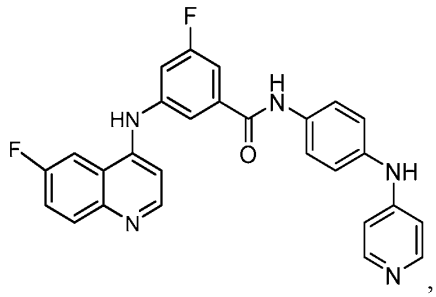
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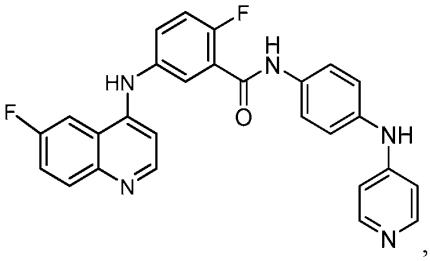
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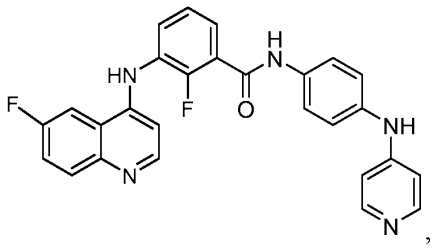
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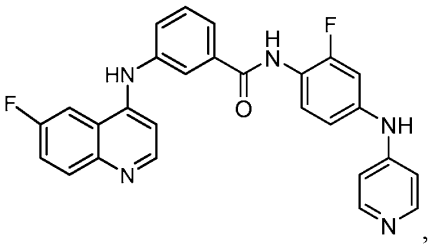
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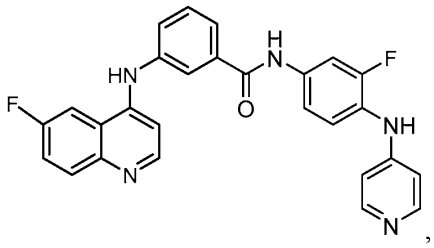
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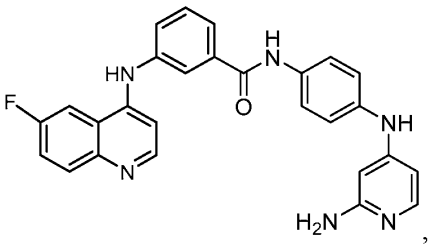
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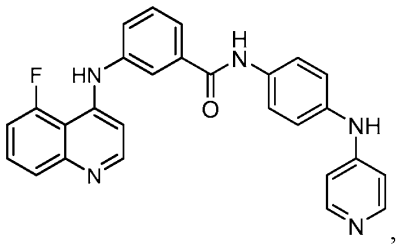
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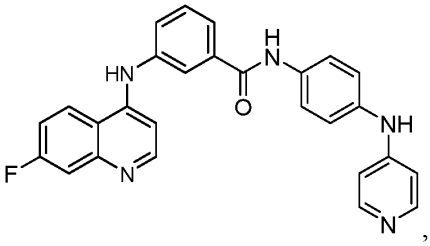
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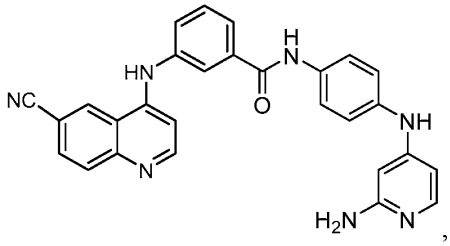
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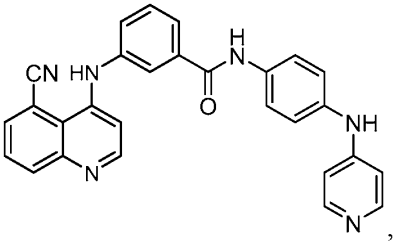
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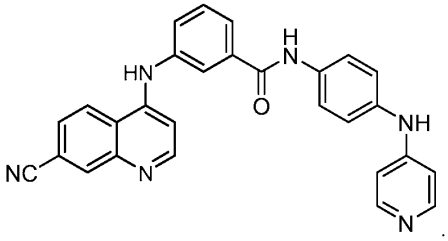
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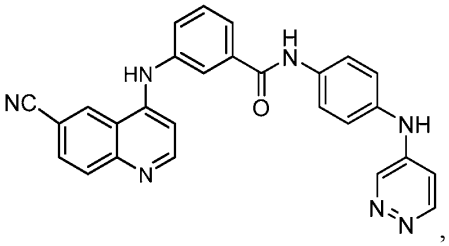
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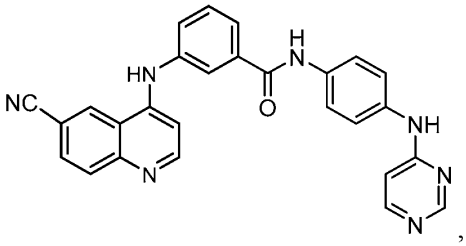
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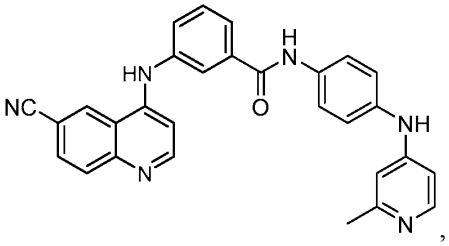
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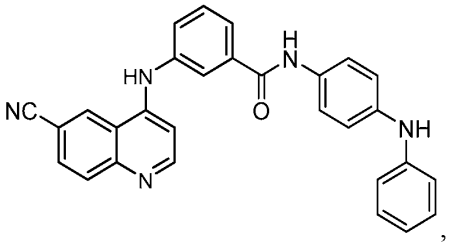
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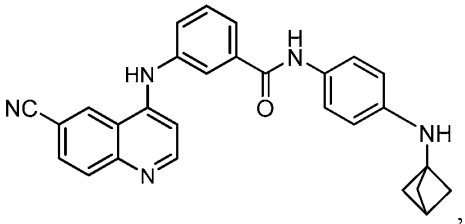
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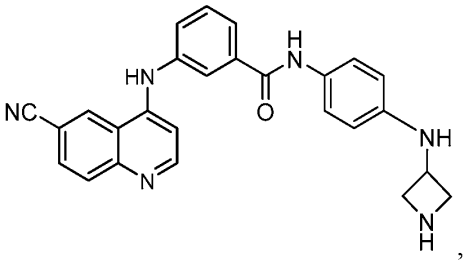
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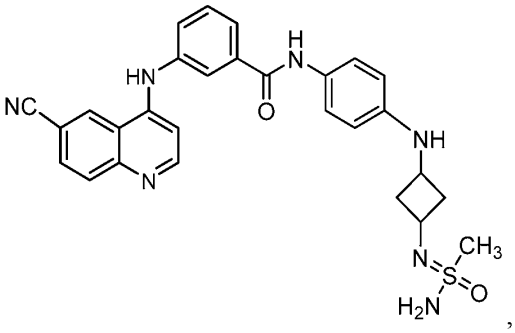
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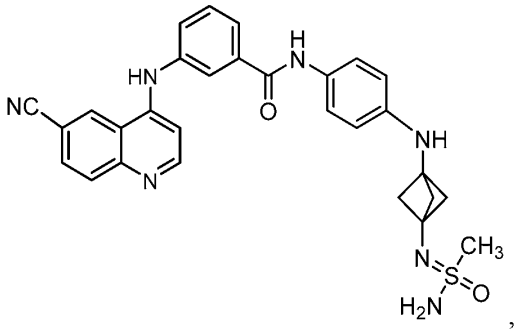
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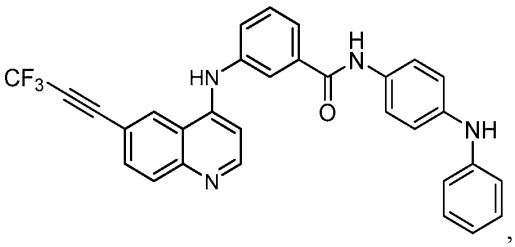

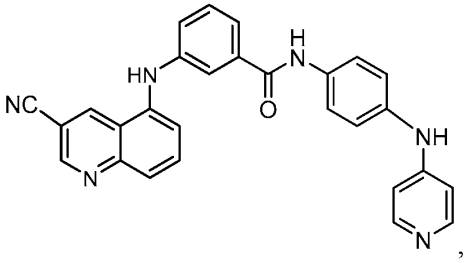

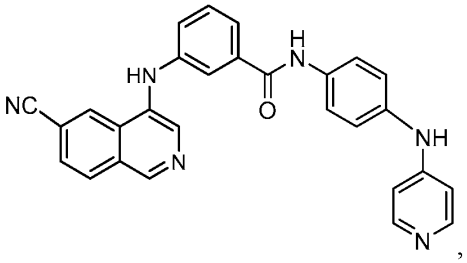

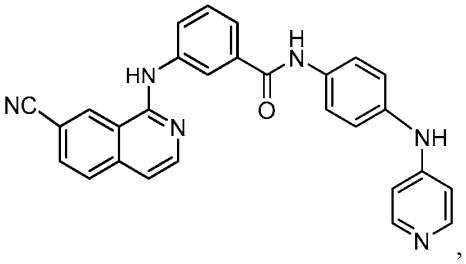

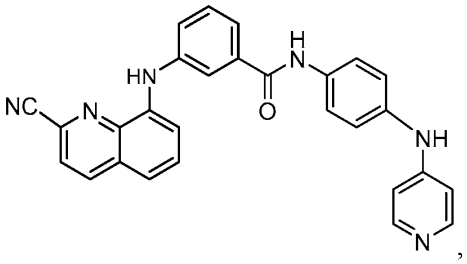

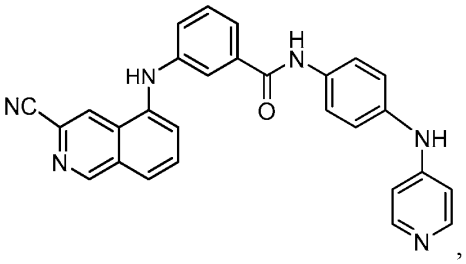

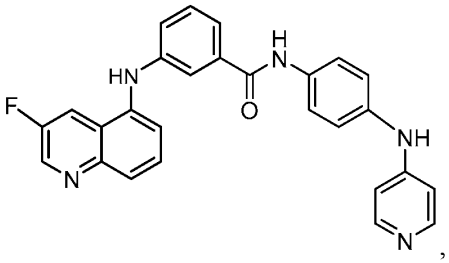

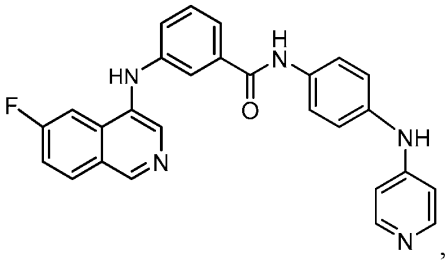

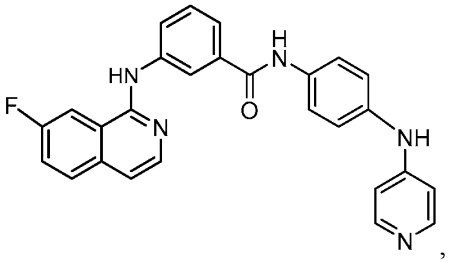

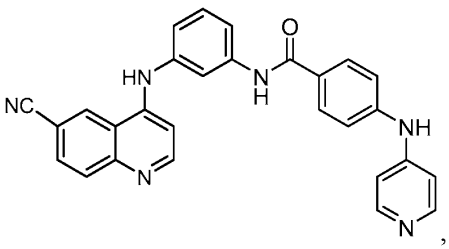

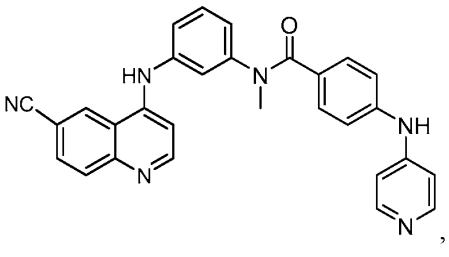

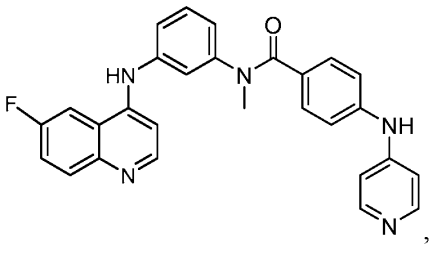

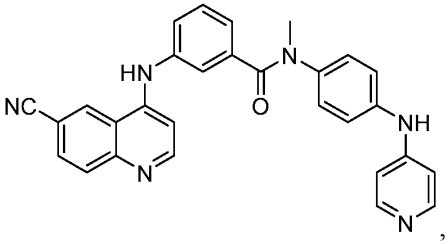
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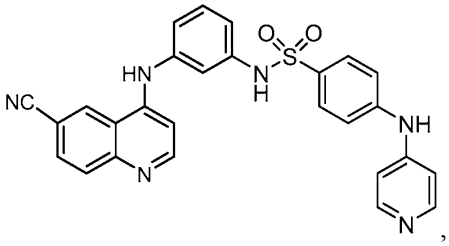
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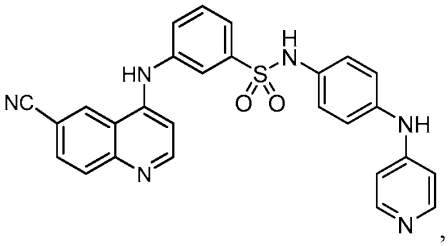
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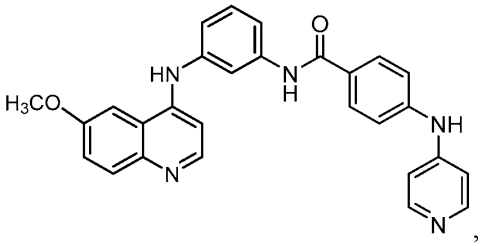
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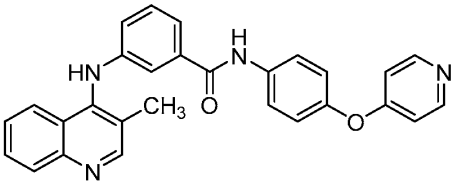
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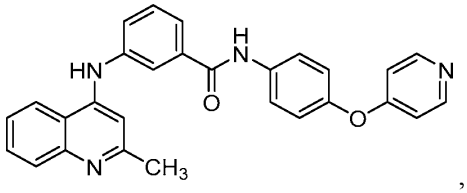
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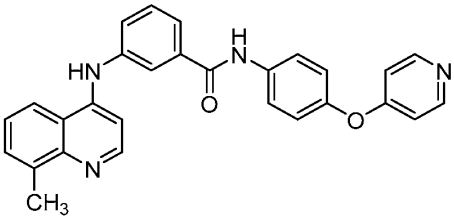
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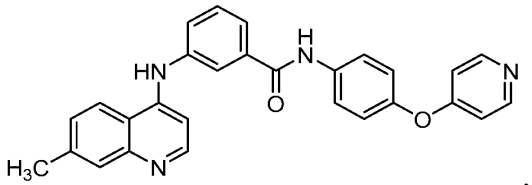
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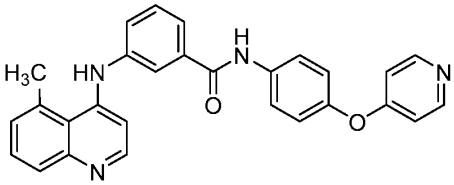
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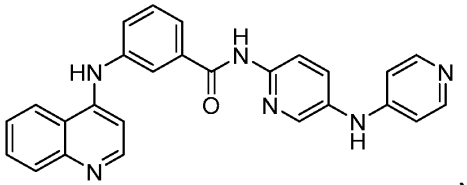
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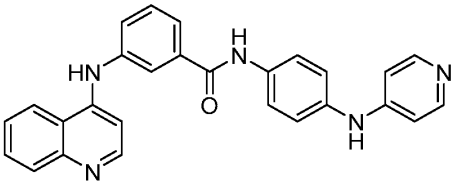
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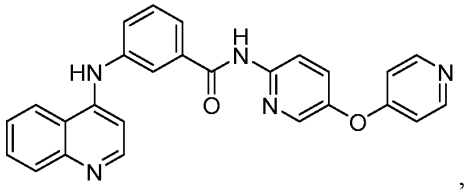
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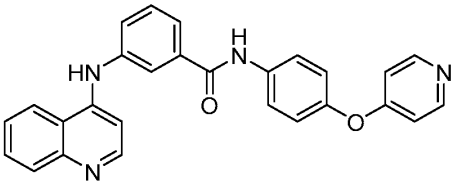
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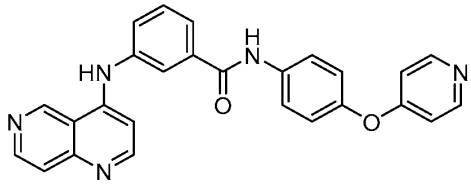
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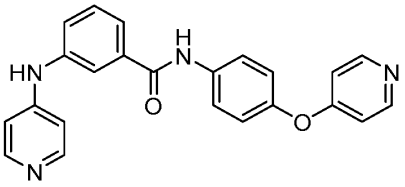
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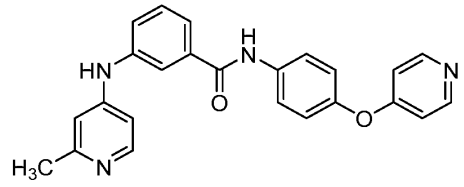
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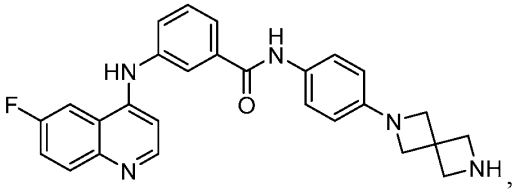
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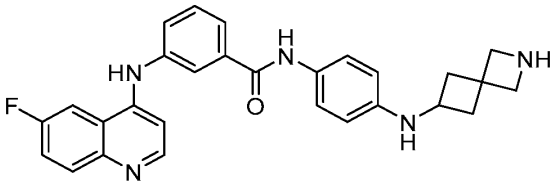
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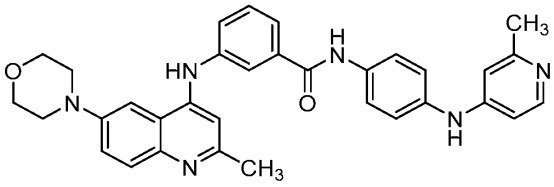
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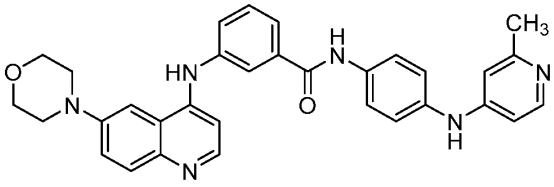
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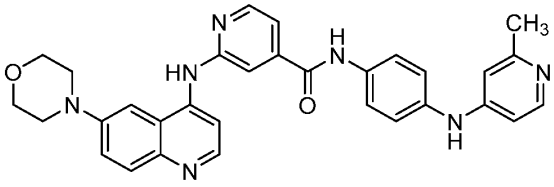
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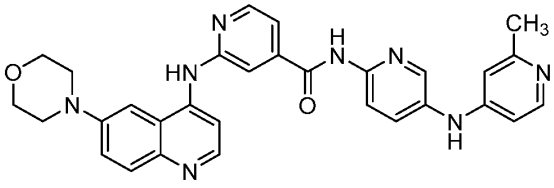
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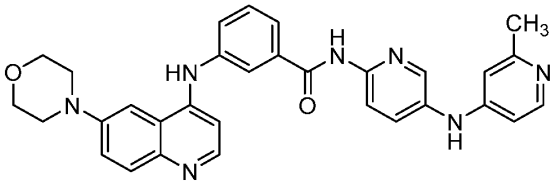
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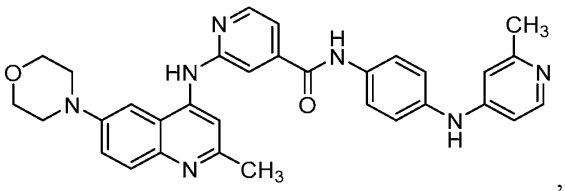
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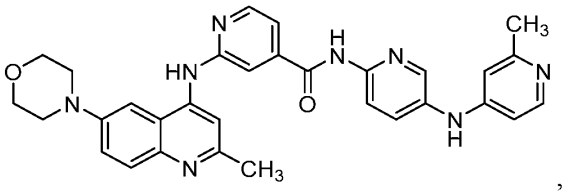
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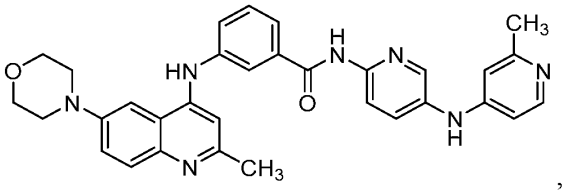
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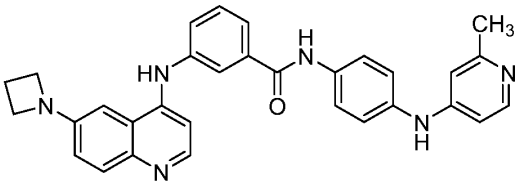
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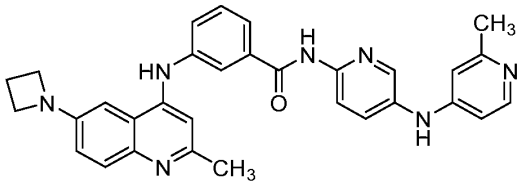
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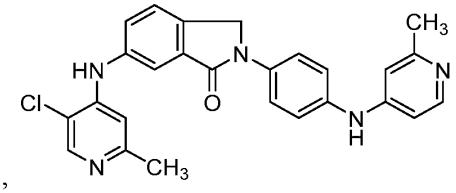
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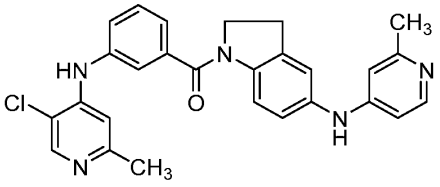
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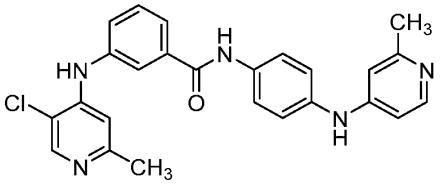
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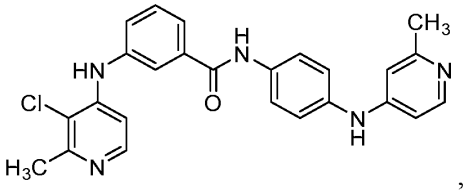
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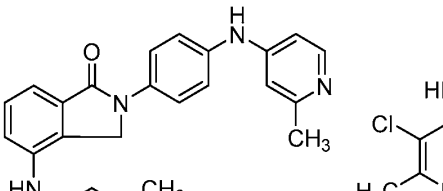
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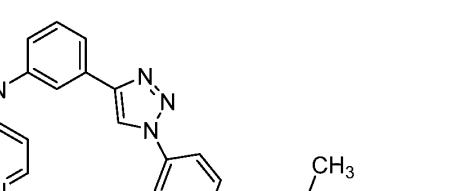
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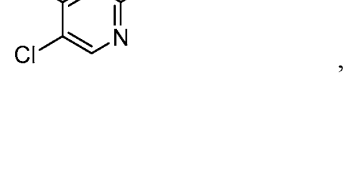
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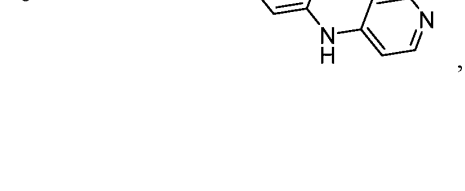
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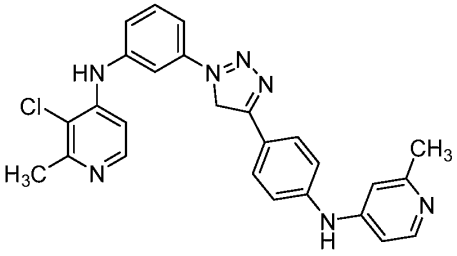
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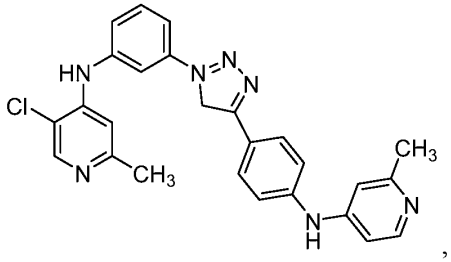
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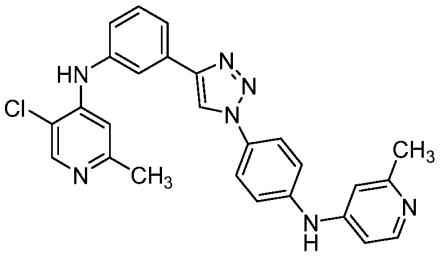
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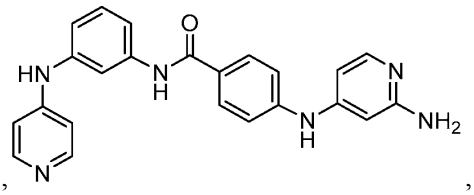
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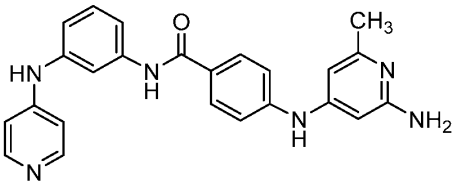
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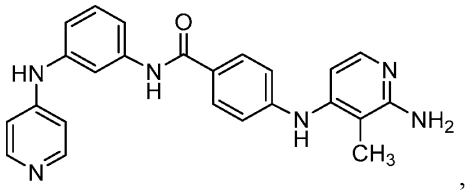
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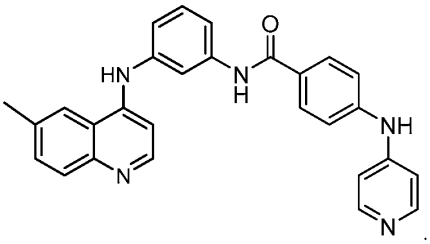
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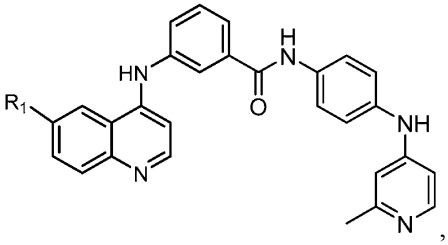
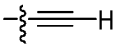
[0256] In some embodiments, the compound of Formula Ia is


, where R_1 is $–CONH_2$, $–SO_2NH_2$, $–SO_2CH_3$, or

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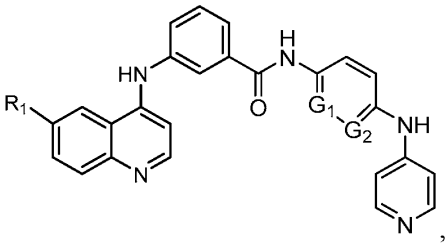
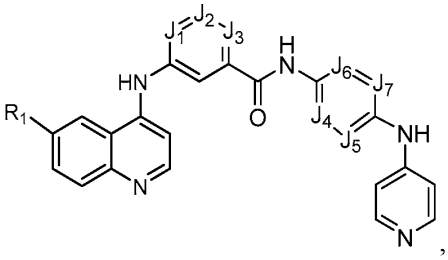
[0257] In some embodiments, the compound of Formula Ia is

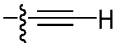


, where R_1 is –CN or –F, and G_1 and G_2 are either –N– and –CH–, or –CH– and –N–.

[0258] In some embodiments, the compound of Formula Ia is

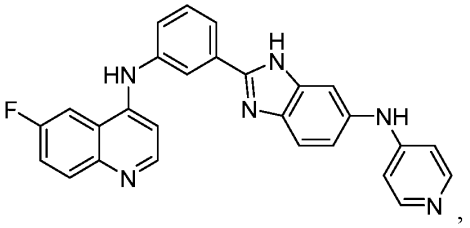


, where R_1 is $–CONH_2$, $–SO_2NH_2$, $–SO_2CH_3$, or



, and each of J_1, J_2, J_3, J_4, J_5, J_6, and J_7 is independently –N– or –CF.

[0259] In some embodiments, the compound of Formula Ib is



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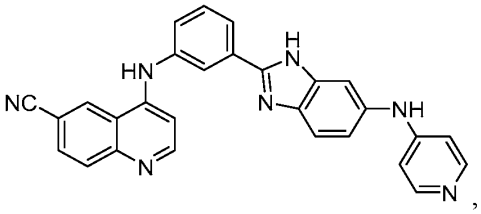

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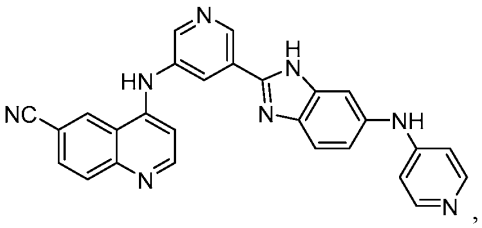

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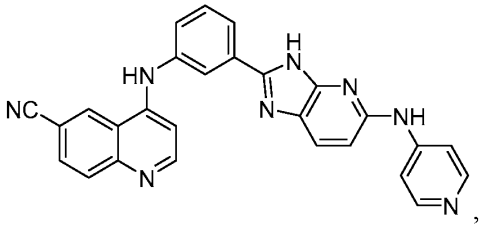

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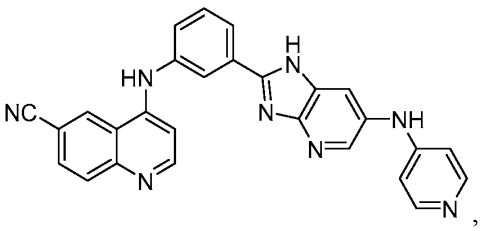

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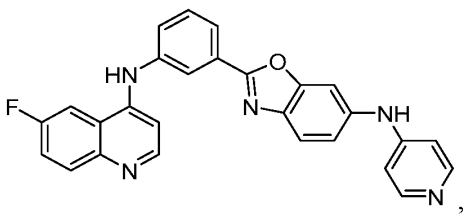

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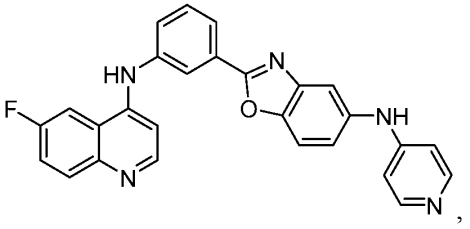

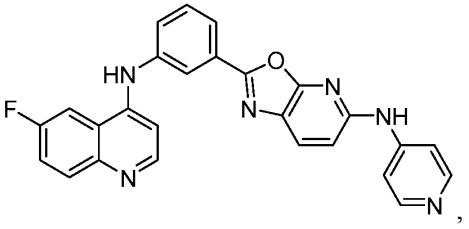

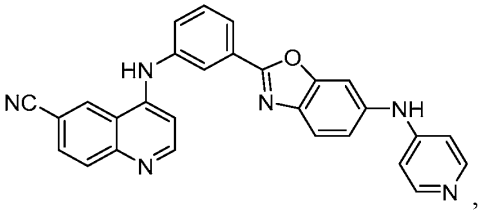

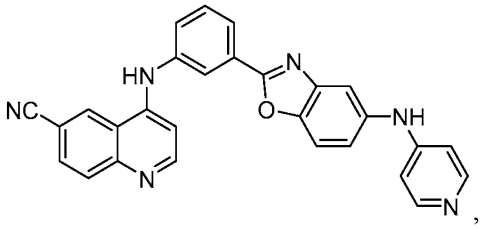

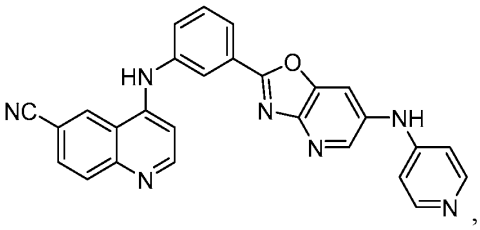

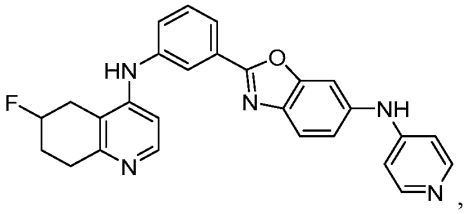

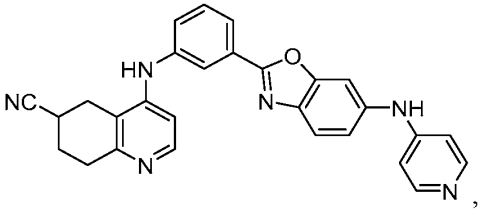

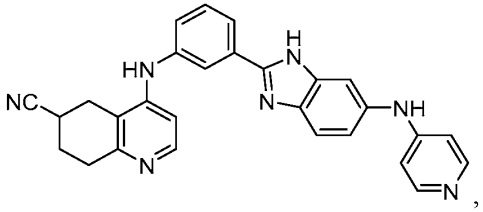

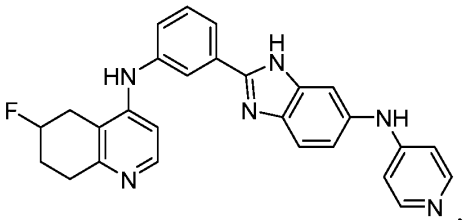

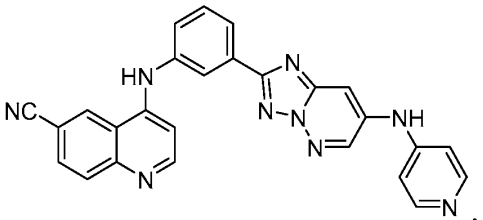

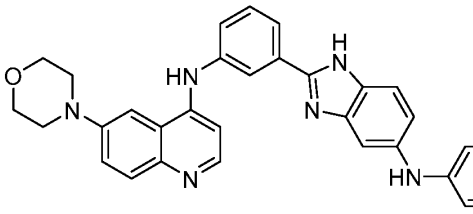



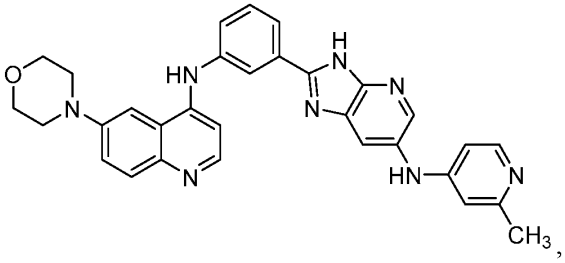

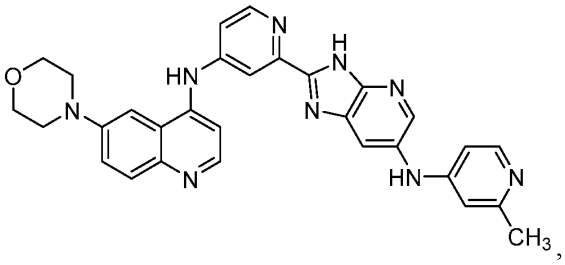

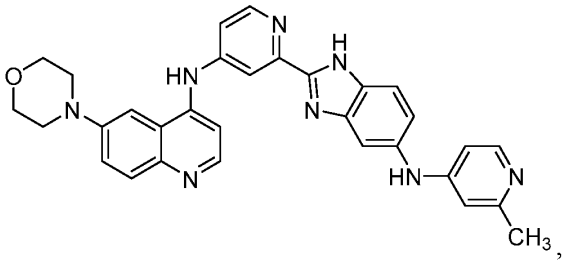

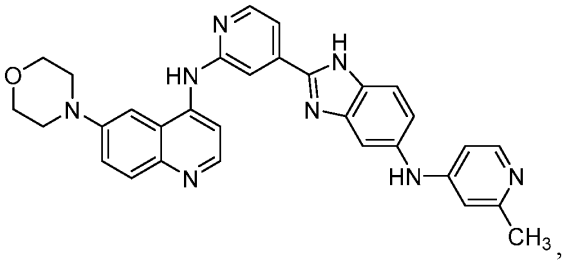

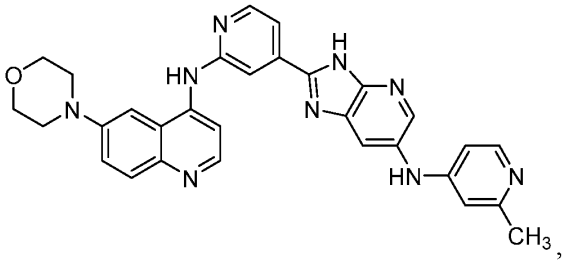

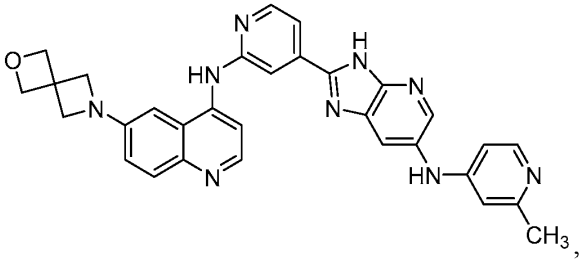

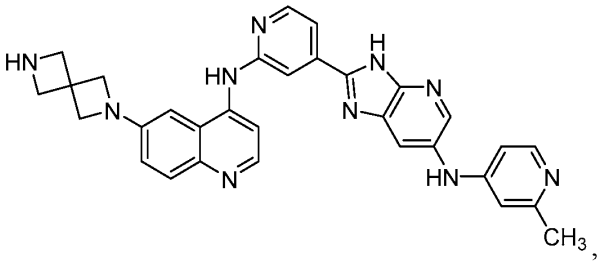

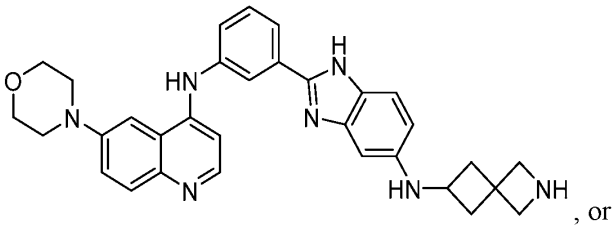
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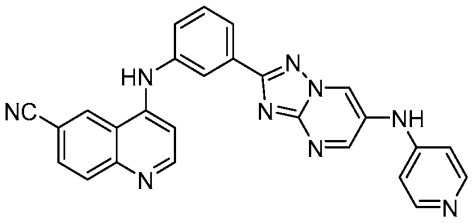
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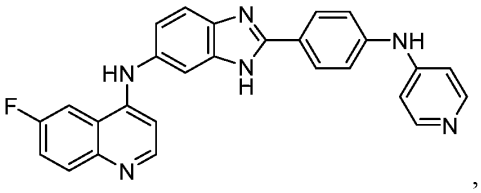
[0260] In some embodiments, the compound of Formula Ic is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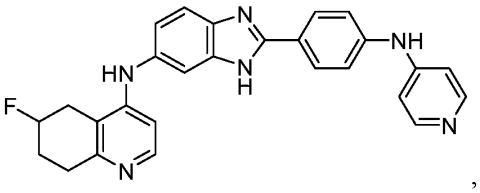
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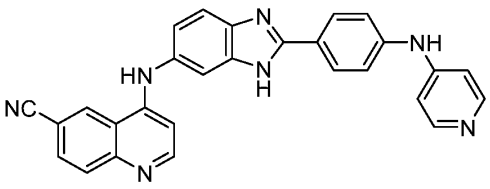
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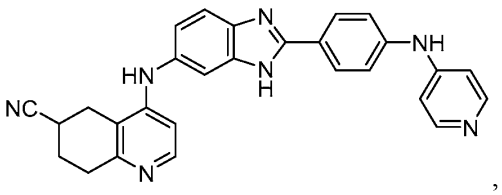
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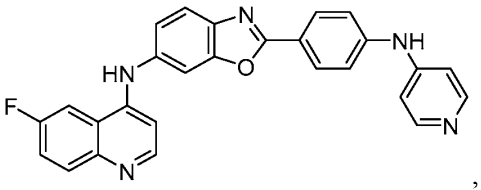
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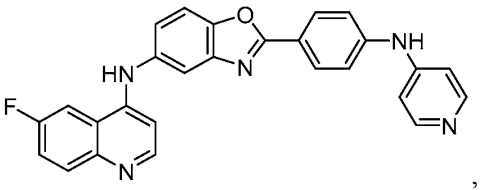
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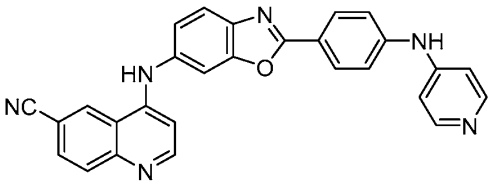
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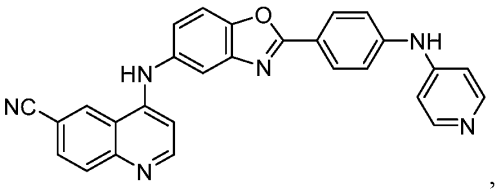
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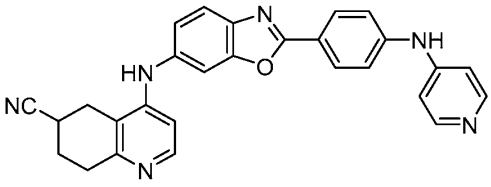
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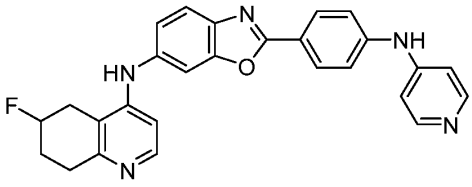
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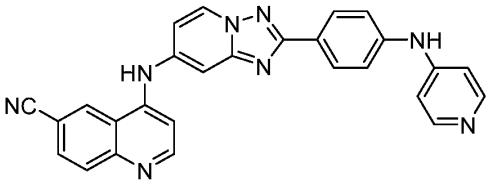
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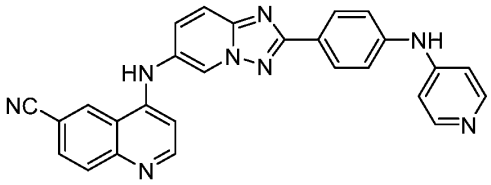
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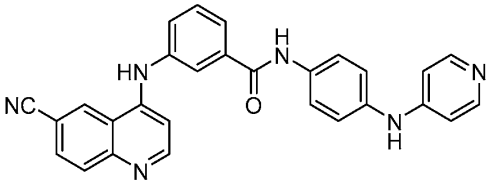
[0261] In some embodiments, the compound is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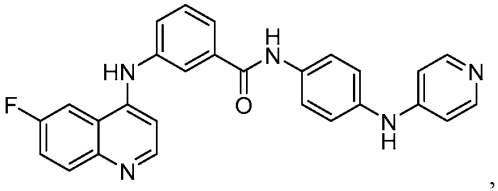
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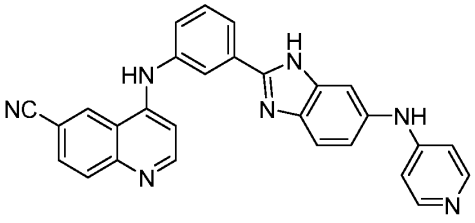

.

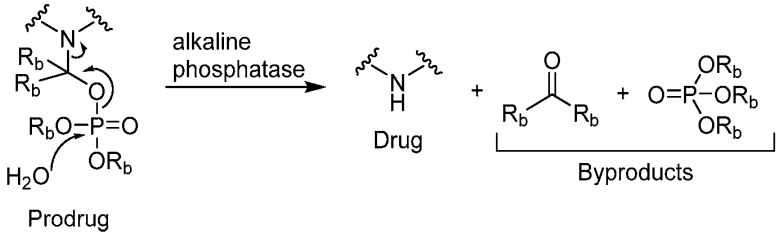
[0262] In any one of the embodiments disclosed herein, the compound is selected from the group consisting of Compounds 2-22 in Examples 2-22, respectively.

[0263] In any one of the embodiments disclosed herein, the compound is selected from the group consisting of Compounds 3 and 18-21 as shown in Table 1.

[0264] In any one of the embodiments disclosed herein, the compound is Compound 2 as shown in Table 2.

Prodrugs

[0265] In some embodiments, any one of the compounds described herein may be made into a prodrug by attaching to one or more functional groups therein a cleavable moiety. *See*, *e.g.*, *J. Med. Chem.*, Vol. 61, pp. 62-80 (2018); *J. Med. Chem.*, Vol. 61, pp. 6308-6327 (2018); and *J. Med. Chem.*, Vol. 61, pp. 3918-3929 (2018). In some embodiments, the moiety is cleavable upon exposure to a stimulus. Non-limiting examples of such a stimulus include temperature, electromagnetic radiation, sonic vibrations, pH, solvents, and substances and processes found on or in living organisms. In some embodiments, the cleavable moiety is removed upon contact with a living organism. In some embodiments, the cleavable moiety is removed upon contact with an enzyme. In some, embodiments, the cleavable moiety is removed upon contact with alkaline phosphatase. In some embodiments, the cleavable moiety is a phosphonooxymethyl moiety that is cleaved as illustrated in Scheme A below.



Scheme A

Methods of Modulating Akt3

[0266] Akt3, also referred to as RAC-gamma serine/threonine-protein kinase, is an enzyme that, in humans, is encoded by the *Akt3* gene. Akt kinases are known to be regulators of cell signaling in response to insulin and growth factors and are associated with a broad range of biological processes, including, but not limited to, cell proliferation, differentiation, apoptosis, and tumorigenesis, as well as glycogen synthesis and glucose uptake. Akt3 has been shown to be stimulated by platelet-derived growth factor ("PDGF"), insulin, and insulin-like growth factor 1 ("IGF1").

[0267] Akt3 kinase activity mediates serine and/or threonine phosphorylation of a range of downstream substrates. Nucleic acid sequences for Akt3 are known in the art. *See*, for example, Genbank accession no. AF124141.1: *Homo sapiens protein kinase B gamma*

mRNA, complete cds, which is specifically incorporated by reference in its entirety, and provides the following nucleic acid sequence:

AGGGGAGTCATCATGAGCGATGTTACCATTGTGAAGGAAGGTTGGGTTCAGAAGAGGGGA
GAATATATAAAAAACTGGAGGCCAAGATACTTCCTTTTGAAGACAGATGGCTCATTCATA
GGATATAAAGAGAAACCTCAAGATGTGGATTTACCTTATCCCCTCAACAACTTTTCAGTG
GCAAAATGCCAGTTAATGAAAACAGAACGACCAAAGCCAAACACATTTATAATCAGATGT
CTCCAGTGGACTACTGTTATAGAGAGAACATTTCATGTAGATACTCCAGAGGAAAGGGAA
GAATGGACAGAAGCTATCCAGGCTGTAGCAGACAGACTGCAGAGGCAAGAAGAGGAGAGA
ATGAATTGTAGTCCAACTTCACAAATTGATAATATAGGAGAGGAAGAGATGGATGCCTCT
ACAACCCATCATAAAAGAAAGACAATGAATGATTTTGACTATTTGAAACTACTAGGTAAA
GGCACTTTTGGGAAAGTTATTTTGGTTCGAGAGAAGGCAAGTGGAAAATACTATGCTATG
AAGATTCTGAAGAAAGAAGTCATTATTGCAAAGGATGAAGTGGCACACACTCTAACTGAA
AGCAGAGTATTAAAGAACACTAGACATCCCTTTTTAACATCCTTGAAATATTCCTTCCAG
ACAAAAGACCGTTTGTGTTTTGTGATGGAATATGTTAATGGGGGCGAGCTGTTTTTCCAT
TTGTCGAGAGAGCGGGTGTTCTCTGAGGACCGCACACGTTTCTATGGTGCAGAAATTGTC
TCTGCCTTGGACTATCTACATTCCGGAAAGATTGTGTACCGTGATCTCAAGTTGGAGAAT
CTAATGCTGGACAAAGATGGCCACATAAAAATTACAGATTTTGGACTTTGCAAAGAAGGG
ATCACAGATGCAGCCACCATGAAGACATTCTGTGGCACTCCAGAATATCTGGCACCAGAG
GTGTTAGAAGATAATGACTATGGCCGAGCAGTAGACTGGTGGGGCCTAGGGGTTGTCATG
TATGAAATGATGTGTGGGAGGTTACCTTTCTACAACCAGGACCATGAGAAACTTTTTGAA
TTAATATTAATGGAAGACATTAAATTTCCTCGAACACTCTCTTCAGATGCAAAATCATTG
CTTTCAGGGCTCTTGATAAAGGATCCAAATAAACGCCTTGGTGGAGGACCAGATGATGCA
AAAGAAATTATGAGACACAGTTTCTTCTCTGGAGTAAACTGGCAAGATGTATATGATAAA
AAGCTTGTACCTCCTTTTAAACCTCAAGTAACATCTGAGACAGATACTAGATATTTTGAT
GAAGAATTTACAGCTCAGACTATTACAATAACACCACCTGAAAAATATGATGAGGATGGT
ATGGACTGCATGGACAATGAGAGGCGGCCGCATTTCCCTCAATTTTCCTACTCTGCAAGT
GGACGAGAATAAGTCTCTTTCATTCTGCTACTTCACTGTCATCTTCAATTTATTACTGAA
AATGATTCCTGGACATCACCAGTCCTAGCTCTTACACATAGCAGGGGCACCTTCCGACAT
CCCAGACCAGCCAAGGGTCCTCACCCCTCGCCACCTTTCACCCTCATGAAAACACACATA
CACGCAAATACACTCCAGTTTTTGTTTTTGCATGAAATTGTATCTCAGTCTAAGGTCTCA
TGCTGTTGCTGCTACTGTCTTACTATTA

(SEQ ID NO:1).

[0268] Amino acid sequences for Akt3 are also known in the art. *See*, for example, UniProtKB/Swiss-Prot accession no. Q9Y243 (Akt3_HUMAN), which is specifically incorporated by reference in its entirety and provides the following amino acid sequence:

MSDVTIVKEGWVQKRGEYIKNWRPRYFLLKTDGSFIGYKEKPQDVDLPYPLNNFSVAKCQ
LMKTERPKPNTFIIRCLQWTTVIERTFHVDTPEEREEWTEAIQAVADRLQRQEEERMNCS
PTSQIDNIGEEEMDASTTHHKRKTMNDFDYLKLLGKGTFGKVILVREKASGKYYAMKILK
KEVIIAKDEVAHTLTESRVLKNTRHPFLTSLKYSFQTKDRLCFVMEYVNGGELFFHLSRE

RVFSEDRTRFYGAEIVSALDYLHSGKIVYRDLKLENLMLDKDGHIKITDFGLCKEGITDA
ATMKTFCGTPEYLAPEVLEDNDYGRAVDWWGLGVVMYEMMCGRLPFYNQDHEKLFELILM
EDIKFPRTLSSDAKSLLSGLLIKDPNKRLGGGPDDAKEIMRHSFFSGVNWQDVYDKKLVP
PFKPQVTSETDTRYFDEEFTAQTITITPPEKYDEDGMDCMDNERRPHFPQFSYSASGRE

(SEQ ID NO:2).

[0269] The domain structure of Akt3 is reviewed in Romano, *Scientifica*, Volume 2013 (2013), Article ID 317186, 12 pages, and includes an N-terminal pleckstrin homology domain ("PH"), followed by a catalytic kinase domain ("KD"), and the C-terminal regulatory hydrophobic region. The KD and regulatory domain are both important for the biological actions mediated by Akt protein kinases and exhibit the maximum degree of homology among the three Akt isoforms. The PH domain binds lipid substrates, such as phosphatidylinositol (3,4) diphosphate ("PIP2") and phosphatidylinositol (3,4,5) triphosphate ("PIP3"). The ATP binding site is situated approximately in the middle of the catalytic kinase domain, which has a substantial degree of homology with the other components of the AGC kinases family, such as p70 S6 kinase ("S6K") and p90 ribosomal S6 kinase ("RSK"), protein kinase A ("PKA"), and protein kinase B ("PKB"). The hydrophobic regulatory moiety is a typical feature of the AGC kinases family. With reference to SEQ ID NO:2, Akt 3 is generally considered to have the molecule processing and domain structure outlined as follows.

Molecule Processing:

Feature key	**Position(s)**	**Length**	**Description**
Initiator methionine	1	1	Removed
Chain	2-479	478	Akt3

Regions:

Feature key	**Position(s)**	**Length**	**Description**
Domain	5-107	103	PH
Domain	148-405	258	Protein kinase
Domain	406-479	74	AGC-kinase, C-terminal
Nucleotide binding	154-162	9	ATP

Sites:

Feature key	**Position(s)**	**Length**	**Description**

Active site	271	1	Proton acceptor
Binding site	177	1	ATP

[0270] The initiator methionine of SEQ ID NO:2 is disposable for Akt3 function. Therefore, in some embodiments, the compound directly or indirectly modulates expression or bioavailability of an Akt3 having the following amino acid sequence:

SDVTIVKEGWVQKRGEYIKNWRPRYFLLKTDGSFIGYKEKPQDVDLPYPLNNFSVAKCQ
LMKTERPKPNTFIIRCLQWTTVIERTFHVDTPEEREEWTEAIQAVADRLQRQEEERMNCS
PTSQIDNIGEEEMDASTTHHKRKTMNDFDYLKLLGKGTFGKVILVREKASGKYYAMKILK
KEVIIAKDEVAHTLTESRVLKNTRHPFLTSLKYSFQTKDRLCFVMEYVNGGELFFHLSRE
RVFSEDRTRFYGAEIVSALDYLHSGKIVYRDLKLENLMLDKDGHIKITDFGLCKEGITDA
ATMKTFCGTPEYLAPEVLEDNDYGRAVDWWGLGVVMYEMMCGRLPFYNQDHEKLFELILM
EDIKFPRTLSSDAKSLLSGLLIKDPNKRLGGGPDDAKEIMRHSFFSGVNWQDVYDKKLVP
PFKPQVTSETDTRYFDEEFTAQTITITPPEKYDEDGMDCMDNERRPHFPQFSYSASGRE

(SEQ ID NO:3).

[0271] Two specific sites, one in the kinase domain (Thr-305 with reference to SEQ ID NO:2) and the other in the C-terminal regulatory region (Ser-472 with reference to SEQ ID NO:2), need to be phosphorylated for full activation of Akt3. Interaction between the PH domain of Akt3 and TCL1A enhances Akt3 phosphorylation and activation. IGF-1 leads to the activation of Akt3, which may play a role in regulating cell survival.

[0272] In some embodiments, a compound of Formula Ia, Ib, or Ic as described herein is an inhibitor of Akt3. In other embodiments, a compound of Formula Ia, Ib, or Ic as described herein is an activator of Akt3.

Pharmaceutical Compositions

[0273] Some aspects of the invention involve administering an effective amount of a composition to a subject to achieve a specific outcome. The small molecule compositions useful according to the methods of the present invention thus can be formulated in any manner suitable for pharmaceutical use.

[0274] The formulations of the invention are administered in pharmaceutically-acceptable solutions, which may routinely contain pharmaceutically-acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

[0275] For use in therapy, an effective amount of the compound can be administered to a subject by any mode allowing the compound to be taken up by the appropriate target cells.

"Administering" the pharmaceutical composition of the present invention can be accomplished by any means known to the skilled artisan. Specific routes of administration include, but are not limited to, oral, transdermal (*e.g.*, via a patch), parenteral injection (subcutaneous, intradermal, intramuscular, intravenous, intraperitoneal, intrathecal, etc.), or mucosal (intranasal, intratracheal, inhalation, intrarectal, intravaginal, etc.). An injection can be in a bolus or a continuous infusion.

[0276] For example the pharmaceutical compositions according to the invention are often administered by intravenous, intramuscular, or other parenteral means. They can also be administered by intranasal application, inhalation, topically, orally, or as implants; even rectal or vaginal use is possible. Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for injection or inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops, or preparations with protracted release of active compounds in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of present methods for drug delivery, *see* Langer R (1990) *Science* 249:1527-33.

[0277] The concentration of compounds included in compositions used in the methods of the invention can range from about 1 nM to about 100 μM. Effective doses are believed to range from about 10 picomole/kg to about 100 micromole/kg.

[0278] The pharmaceutical compositions are preferably prepared and administered in dose units. Liquid dose units are vials or ampoules for injection or other parenteral administration. Solid dose units are tablets, capsules, powders, and suppositories. For treatment of a patient, different doses may be necessary depending on activity of the compound, manner of administration, purpose of the administration (*i.e.*, prophylactic or therapeutic), nature and severity of the disorder, age and body weight of the patient. The administration of a given dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units. Repeated and multiple

administration of doses at specific intervals of days, weeks, or months apart are also contemplated by the invention.

[0279] The compositions can be administered *per se* (neat) or in the form of a pharmaceutically-acceptable salt. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically-acceptable salts can conveniently be used to prepare pharmaceutically-acceptable salts thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, TsOH (p-toluene sulphonic acid), tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic acids. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

[0280] Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v); and thimerosal (0.004-0.02% w/v).

[0281] Compositions suitable for parenteral administration conveniently include sterile aqueous preparations, which can be isotonic with the blood of the recipient. Among the acceptable vehicles and solvents are water, Ringer's solution, phosphate buffered saline, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed mineral or non-mineral oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Carrier formulations suitable for subcutaneous, intramuscular, intraperitoneal, intravenous, etc. administrations can be found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, PA.

[0282] The compounds useful in the invention can be delivered in mixtures of more than two such compounds. A mixture can further include one or more adjuvants in addition to the combination of compounds.

[0283] A variety of administration routes is available. The particular mode selected will depend, of course, upon the particular compound selected, the age and general health status of the subject, the particular condition being treated, and the dosage required for therapeutic efficacy. The methods of this invention can be practiced using any mode of administration

that is medically acceptable, meaning any mode that produces effective levels of response without causing clinically unacceptable adverse effects. Preferred modes of administration are discussed above.

[0284] The compositions can conveniently be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the compounds into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

[0285] Other delivery systems can include time-release, delayed release, or sustained-release delivery systems. Such systems can avoid repeated administrations of the compounds, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Pat. No. 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids, or neutral fats such as mono-di-and tri-glycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which an agent of the invention is contained in a form within a matrix such as those described in U.S. Pat. Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Pat. Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

Methods of Treating Disease

[0286] In another aspect, a method of treating a disease in a subject in need thereof includes administering to the subject an effective amount of a compound of Formula Ia, Ib, or Ic as described herein.

[0287] In some embodiments, the disease is selected from the group consisting of neurodegenerative disease, cachexia, anorexia, obesity, obesity's complication, inflammatory disease, viral-induced inflammatory reaction, Gulf War Syndrome, tuberous sclerosis, retinitis pigmentosa, transplant rejection, cancer, an autoimmune disease, ischemic tissue injury, traumatic tissue injury, and a combination thereof.

[0288] In some embodiments, the compound of Formula Ia, Ib, or Ic modulates Akt3 in immune cells. Non-limiting examples of immune cells include T cells (*e.g.*, T regulatory cells ("Tregs")), B cells, macrophages, and glial cells (*e.g.*, astrocytes, microglia, or oligodendrocytes). In some embodiments, the immune cells are Tregs. In some embodiments, the compound of Formula Ia, Ib, or Ic activates Akt3 signaling. In other embodiments, the compound of Formula Ia, Ib, or Ic inhibits Akt3 signaling. In some embodiments, the compound of Formula Ia, Ib, or Ic modulates Akt3 in Tregs. The inventors surprisingly found that, in some embodiments, the compound of Formula Ia, Ib, or Ic increases Treg activity or production while, in other embodiments, the compound decreases Treg activity or production. The inventors also surprisingly found that, in some embodiments, the compound of Formula Ia, Ib, or Ic activates Akt3 signaling while, in other embodiments, the compound inhibits Akt3 signaling.

Neurodegenerative Disease

[0289] In some embodiments, a method of treating or preventing neurodegenerative diseases in a subject in need thereof is described, including modulating Akt3 signaling through administering to the subject an effective amount of a compound of Formula Ia, Ib, or Ic as described herein. In some embodiments, the neurodegenerative disease is selected from the group consisting of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Motor Neuron Disease, Huntington's disease, HIV-induced neurodegeneration, Lewy Body Disease, spinal muscular atrophy, prion disease, spinocerebellar ataxia, familial amyloid polyneuropathy, multiple sclerosis, and a combination thereof.

[0290] Neurodegenerative diseases occur when nerve cells in the brain or peripheral nervous system lose function over time and ultimately die. In many of the neurodegenerative diseases, chronic neuroinflammation contributes to disease progression. Although current treatments may help relieve some of the physical or mental symptoms associated with neurodegenerative diseases, there are currently no ways to slow disease progression and no known cures.

[0291] While the mechanisms causing neurodegenerative processes are unknown, growing evidence suggests a critical role of immunity and the immune system in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, spinal muscular atrophy, familial amyloid polyneuropathy, and ALS. Tregs are a subset of $CD4^+$ T cells that suppress immune responses and are essential mediators of self-tolerance and immune homeostasis (*see* Sakaguchi, et al., *Cell*, 133, 775-787 (2008)). Evidence suggest that Tregs play an important role in the progression of neurodegenerative diseases. For example, Akt3 can modulate the suppressive function of natural Tregs and the polarization of induced Tregs and, therefore, modulating Akt3 in immune cells can modulate immune responses. More specifically, activating Akt3 in immune cells can lead to increased immune suppressive responses, while inhibiting Akt3 in immune cells can lead to decreased immune suppressive responses. Without being bound by any one theory, it is believed that modulating Akt3 signaling in immune cells can be used for the treatment and prevention of neurodegenerative diseases.

[0292] In some embodiments, a method of treating or preventing neurodegenerative diseases in a subject in need thereof is described, including administering to the subject an Akt3 activator of a compound of Formula Ia, Ib, or Ic as described herein in an amount effective to induce an immune suppressive response and treat or delay the progression of the disease. In some embodiments, the Akt3 activator modulates an immune response by increasing a suppressive function of immune suppressive cells. In some embodiments, Akt3 is selectively activated in immune cells. Exemplary immune cells include, but are not limited to, T cells, B cells, macrophages, and glial cells, such as astrocytes, microglia, and oligodendrocytes. In a preferred embodiment, Akt3 is activated in Tregs. In some embodiments, the Akt3 activators can also be used to increase or promote the activity or production of Tregs, increase the production of cytokines, such as IL-10, from Tregs, increase the differentiation of Tregs, increase the number of Tregs, or increase the survival of Tregs.

[0293] In some embodiments, a method of treating or preventing neurodegenerative diseases in a subject in need thereof is described, including administering to the subject an Akt3 inhibitor of a compound of Formula Ia, Ib, or Ic as described herein in an amount effective to inhibit an immune suppressive response and treat or prevent the progression of the disease. In some embodiments, the Akt3 inhibitor of a compound of Formula Ia, Ib, or Ic as described herein modulates an immune response by decreasing an immune suppressive

response or increasing an immune stimulatory response. In some embodiments, Akt3 is selectively inhibited in immune cells. Exemplary immune cells include but are not limited to T cells, B cells, macrophages, and glial cells, such as astrocytes, microglia, and oligodendrocytes. In a preferred embodiment, Akt3 is inhibited in Tregs.

[0294] In one embodiment, the compounds of Formula Ia, Ib, or Ic can treat or prevent ALS. ALS, also called Lou Gehrig's disease, is a progressive neurodegenerative disease that affects motor neurons in the brain and spinal cord. Symptoms of ALS include, but are not limited to, difficulty speaking, swallowing, walking, moving, and breathing. ALS usually affects men and women between the ages of 40 and 70. There are two different types of ALS, sporadic and familial. Sporadic, which is the most common form of the disease in the U.S., accounts for 90 to 95 percent of all cases. Familial ALS has been associated with mutations in Cu/Zn superoxide dismutase (SOD1). Oxidative stress, mitochondrial dysfunction, excitotoxicity, protein aggregation, endoplasmic reticulum stress, impairment of axonal transport, dysregulation of neuronal-glial interactions, and apoptosis have all been demonstrated to contribute to motor neuron injury in the presence of mutant SOD1. Without being bound by any one theory, it is believed that Treg dysfunction plays a role in the development of ALS and that administration of an Akt3 modulator can treat or prevent the progression of ALS. Some subjects with rapidly progressing ALS have a deficiency of the Treg master transcription factor FOXP3 which leads to impairment of Treg suppressive function. One embodiment provides a method of treating ALS in a subject in need thereof by administering an Akt3 activator to a subject in need thereof in an amount effective to activate Akt3 in immune cells and induce immune suppressive responses. In a preferred embodiment, Akt3 is activated in Tregs.

[0295] In some embodiments, administration of Akt3 activators of Formula Ia, Ib, or Ic as described herein to a subject having ALS slows disease progression and prolongs the subject's survival.

[0296] Other motor neuron diseases may be treated or prevented using the disclosed Akt3 modulators including, for example, progressive bulbar palsy, pseudobulbar palsy, primary lateral sclerosis, spinal muscular atrophy, and post-polio syndrome.

[0297] Parkinson's disease is a neurodegenerative disorder that predominantly affects dopamine-producing neurons in a specific area of the brain called substantia nigra. Parkinson's disease is a progressive disease that worsens over time as more neurons become

impaired or die. The cause of neuronal death in Parkinson's is not known. Symptoms of Parkinson's disease include, but are not limited to, tremors in hands, arms, legs, jaw, or head, stiffness of the limbs and trunk, slowness of movement, and impaired balance and coordination.

[0298] One embodiment provides a method of treating Parkinson's disease by administering an Akt3 modulator to a subject in need thereof in an amount effective to activate or inhibit Akt3 in immune cells and induce an immune suppressive response. In some embodiments, administration of Akt3 activators to a subject having Parkinson's disease will slow or stop disease progression to unaffected areas of the brain.

[0299] In some embodiments, the disclosed Akt3 activators of Formula Ia, Ib, or Ic as described herein can be administered to a subject prophylactically if the subject has a family history of Parkinson's disease or other neurodegenerative diseases. In some embodiments, the Akt3 activators can protect neurons from disease induction or slow down the induction of the disease.

[0300] Huntington's disease is a progressive neurodegenerative disease. The disease is characterized by the progressive breakdown of nerve cells in the brain. Symptoms of Huntington's disease include, but are not limited to, involuntary movement problems and impairments in voluntary movement, such as involuntary jerking, muscle rigidity, slow or abnormal eye movements, impaired gait, posture, and balance, difficulty with the physical production of speech or swallowing; cognitive impairments, such as difficulty organizing, prioritizing, or focusing on tasks, lack of flexibility or the tendency to get stuck on a thought, behavior, or action, lack of impulse control, lack of awareness of one's own behaviors and abilities, slowness in processing thoughts or finding words, and difficulty in learning new information; and psychiatric disorders, such as depression. In one embodiment, the disclosed Akt3 modulators can lessen or slow the progression of symptoms of Huntington's disease.

[0301] One embodiment provides a method of treating Huntington's disease in a subject in need thereof by administering an Akt3 modulator to the subject in an amount effective to activate or inhibit Akt3 in immune cells and induce an immune suppressive response. In some embodiments, Akt3 modulators can slow down or stop the progression of disease symptoms in subjects with Huntington's disease. In another embodiments, Akt3 modulators can alter the Treg/Th17 balance.

[0302] Huntington's disease is largely genetic; every child of a parent with Huntington's disease has a 50/50 chance of inheriting the disease. In one embodiment, subjects with a familial history of Huntington's disease can be prophylactically administered one of the disclosed Akt3 modulators before symptoms of the disease appear to prevent or slow down the manifestation of disease symptoms.

[0303] Alzheimer's disease is a progressive disorder that causes brain cells to degenerate and eventually die. Alzheimer's disease is the most common cause of dementia and is hallmarked by a continuous decline in thinking, behavioral, and social skills that disrupts a person's ability to function independently. Symptoms of Alzheimer's disease include, but are not limited to, memory loss, impairment in thinking and reasoning abilities, difficulty in making judgments and decisions, and changes in personality and behavior. While the exact cause of Alzheimer's disease is not fully understood, it is believed that the core problem is dysfunctionality in brain proteins which disrupt neuronal function and unleash a series of toxic events. The damage most often starts in the region of the brain that controls memory, but the process begins years before the first symptoms. The loss of neurons spreads in a somewhat predictable pattern to other regions of the brain. By the late stage of the disease, the brain has shrunk significantly. Beta-amyloid plaques and tau protein tangles are most often attributed with the bulk of the damage and dysfunctionality of neurons in Alzheimer's disease.

[0304] One embodiment provides a method of treating Alzheimer's disease in a subject by administering an Akt3 activator to the subject in an amount effective to activate Akt3 in Tregs and activate downstream neuroprotective pathways in the brain. In another embodiment, subjects are administered an effective amount of an Akt3 activator to reduce or eliminate symptoms of Alzheimer's disease or to slow down disease progression.

[0305] Another embodiment provides a method of treating or preventing the progression of Alzheimer's disease in a subject by administering an Akt3 inhibitor of Formula Ia, Ib, or Ic as described herein to the subject in an amount effective to inhibit Akt3 in Tregs and induce an immune response or decrease an immune suppressive response. In some embodiments, inhibition of Akt3 in Tregs leads to beta-amyloid plaque clearance, mitigation of neuroinflammatory response, and reversal of cognitive decline.

[0306] Spinal muscular atrophy ("SMA") is a group of chronic neuromuscular disorders that are characterized by progressive loss of motor neurons and muscle wasting. SMA is

commonly classified in four types that vary in severity and the life stage during which the disease manifests. These types are:

SMA1 or Werdnig-Hoffmann disease, which manifests during age 0-6 months ("infantile" SMA);

SMA2 or Dubowitz disease, which manifests during age 6-18 months ("intermediate" SMA);

SMA3 or Kugelberg-Welander disease, which manifests after age 1 year ("juvenile" SMA); and

SMA4, which manifests during adulthood ("adult-onset" SMA).

The most severe form of SMA1 is sometimes termed SMA0 ("severe infantile" SMA). Signs and symptoms of SMA vary according to type, but the most common include, but are not limited to, limpness or tendency to flop, difficulty sitting, standing, or walking, loss of strength in respiratory muscles, twitching, and difficulty eating and swallowing. All types of SMA have been linked to exonal deletion and/or point mutations in the *SMN1* gene, preventing expression of the SMN protein. Depending on the type, SMA can be treated with various gene therapies, assisted nutrition and respiration, orthopedics, and combinations thereof. Neuroprotective drugs are promising as a way to stabilize motor neuron loss, but currently available candidates have yet to successfully advance through clinical trials. Therefore, more candidate neuroprotective drugs are needed for treatment of SMA.

[0307] One embodiment provides a method of treating SMA in a subject by administering an Akt3 modulator of Formula Ia, Ib, or Ic as described herein to the subject in an amount effective to enable survival of motor neurons. In another embodiment, subjects are administered an effective amount of an Akt3 modulator to reduce or eliminate symptoms of SMA or to slow down disease progression.

[0308] Multiple sclerosis ("MS") is a disease in which nerve cells in the brain and spinal cord become demyelinated, leading to nerve cell damage and disrupting signal transmission throughout the nervous system. Persons suffering MS can experience almost any neurological sign/symptom, with autonomic, visual, motor, and sensory impairment being most common. The precise cause of MS is unknown but is thought to be a combination of genetic, such as chromosomal aberrations in the major histocompatibility complex, and environmental factors, such as exposure to infectious agents and toxins. Treatments for MS, including, but not limited to, drugs and physical therapy, attempt to restore function in the affected area after an acute attack and prevent new attacks from occurring. There is no

known cure for MS and many current drugs, while moderately effective, can have severe side effects and be poorly tolerated. Therefore, new drugs are needed for safe, effective restorative and preventative treatment of MS.

[0309] One embodiment provides a method of treating MS in a subject by administering an Akt3 modulator of Formula Ia, Ib, or Ic as described herein to the subject in an amount effective to restore loss of function after an attack and/or prevent attacks from occurring. In another embodiment, subjects are administered an effective amount of an Akt3 modulator to reduce or eliminate symptoms of MS or to slow down disease progression.

Weight Loss

[0310] In some embodiments, a method of treating or preventing extreme weight loss is disclosed herein, including administering a compound disclosed here to a subject in need thereof. Non-limiting examples of weight loss disorders include cachexia, anorexia, and anorexia nervosa. An exemplary method includes inhibiting Akt3 in subjects in need thereof by administering a compound of Formula Ia, Ib, or Ic as described herein. Without being bound by any one theory, it is believed that Akt3 plays an important role in adipogenesis. White adipogenesis requires activation of a transcriptional cascade involving the sequential induction of a number of transcription factors including, but not limited to, FOXO1, several members of the C/EBP family, and PPARγ. FOXO1 is an essential negative regulator of adipogenesis and is primarily controlled through phosphorylation/acetylation on multiple residues by enzymes including Akt. FOXO1 can also be controlled by the serine/threonine protein kinase SGK1. SGK1 is downstream of PI3K and can inhibit FOXO1 upon phosphorylation. SGK1 is regulated by the serine/threonine protein kinase WNK1, which can also be regulated by Akt and SGK1. Akt3 suppresses adipogenesis through phosphorylation of WNK1, leading to downregulation of SGK1 activity and SGK-1-mediated inhibition of FOXO1. In one embodiment, inhibition of Akt3 in Tregs can promote adipogenesis and reverse disease-induced weight loss.

[0311] Cachexia, or wasting syndrome, is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Cachexia is so destructive that it taps into other sources of energy, namely skeletal muscle and adipose tissue, when the body senses lack of nutrition. It affects the majority of patients with advanced cancer and is associated with a reduction in ability to fight infection, treatment tolerance, response to

therapy, quality of life, and duration of survival. In one embodiment, the cachexia is caused by a chronic disease such as, but not limited to, cancer, inflammatory disease, neurodegenerative disease, pathogenic infection, immunodeficiency disorder, weight gain disorder, weight loss disorder, hormone imbalance, tuberous sclerosis, retinitis pigmentosa, congestive heart failure, and a combination thereof. One embodiment provides a method of treating cachexia in a subject in need thereof by administering an Akt3 inhibitor of a compound of Formula Ia, Ib, or Ic as described herein to the subject in an amount effective to reduce symptoms of cachexia. Another embodiment provides a method of promoting weight gain in a subject in need thereof by administering an Akt3 inhibitor of a compound of Formula Ia, Ib, or Ic as described herein to the subject in an amount effective to promote adipogenesis in the subject. In one embodiment, a subject suspected of being susceptible for cachexia (for example, subjects who have been diagnosed with cancer or other diseases) can be prophylactically administered an Akt3 inhibitor to prevent or slow down the manifestation of cachexia syndrome. In some embodiments, the compound disclosed herein is used for treating cachexia by modulating Akt3 and not by modulating T regulatory cells.

[0312] Anorexia nervosa is an eating disorder characterized by weight loss or the lack of weight gain in growing children, difficulties maintaining an appropriate body weight for height, age, and stature, and, often, distorted body image. One of the first goals of treatment for anorexia is the restoration of a normal body weight. In some embodiments, the compound of Formula Ia, Ib, or Ic disclosed herein inhibits Akt3, which has been overactivated by estradiol, the levels of which are increased in subjects with anorexia. In some embodiments, the compound of Formula Ia, Ib, or Ic disclosed herein can be used to treat anorexia. In one embodiment, the disclosed Akt3 inhibitors of a compound of Formula Ia, Ib, or Ic can be administered to a subject diagnosed with anorexia in an amount effective to promote adipogenesis and reverse extreme weight loss.

Obesity and Obesity's Complications

[0313] Diseases hallmarked by weight gain (*e.g.*, obesity) are estimated to effect 40% of adults and 20% of children and adolescents in the United States alone, with those numbers trending upward. *See* "Overweight & Obesity: Data & Statistics", U.S. Centers for Disease Control and Prevention, accessed April 3, 2020. Obesity, which is characterized by a body mass index of > 30 kg/m^2, increases the likelihood of various diseases (*e.g.*, cardiovascular diseases and type 2 diabetes). Akt3 activation has been shown to be protective against obesity. In one embodiment, a method of treating obesity includes administering to a subject

having obesity or at risk of developing obesity an Akt3 activator in an amount effective to reverse or prevent the effects of the disease.

[0314] In some embodiments, the compound disclosed herein modulating Akt3 is used for treating obesity and/or obesity's complications. In some embodiments, the obesity's complication is selected from the group consisting of glucose intolerance, hepatic steatosis, dyslipidemia, and a combination thereof. In some embodiments, the compound disclosed herein is used for treating Obesity and/or Obesity's complications by modulating Akt3 and not by modulating T regulatory cells.

Inflammatory Diseases

[0315] Akt3 signaling has been linked to the chronic or acute inflammation that contributes to inflammatory diseases. One embodiment provides a method of treating or preventing an inflammatory disease in a subject in need thereof including administering to the subject a composition comprising an Akt3 modulator in an amount effective to modulate Akt3 signaling and treat or delay the progression of the disease. In some embodiments, the Akt3 modulator activates Akt3 signaling and/or increases Treg activity or production, resulting in an immunosuppressive effect.

[0316] Non-limiting examples of inflammatory disease include atopic dermatitis, allergy, asthma, and a combination thereof.

Viral-Induced Inflammatory Reaction

[0317] Akt3 signaling has been linked to the acute immune responses that contribute to viral-induced inflammatory diseases, such as severe acute respiratory syndrome ("SARS") and coronavirus disease 2019 ("COVID-19"). Therefore, in one embodiment, a method of treating a viral-induced inflammatory disease in a subject in need thereof includes administering to the subject an Akt3 modulator in an amount effective to reverse or slow down the progression of the disease.

Cancer

[0318] In some embodiments, a method of treating or preventing cancer in a subject in need thereof is provided, including modulating Akt3 signaling through administering to the subject an effective amount of a compound of Formula Ia, Ib, or Ic as described herein. In some embodiments, the compound of Formula Ia, Ib, or Ic inhibits Akt3 signaling and/or decreases Treg activity or production, resulting in an immune response-activating effect.

[0319] In some embodiments, the cancer is selected from the group consisting of bladder cancer, brain cancer, breast cancer, cervical cancer, colorectal cancer, esophageal cancer, kidney cancer, liver cancer, lung cancer, nasopharyngeal cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, uterine cancer, ovarian cancer, testicular cancer, adult T-cell leukemia/lymphoma, and a combination thereof.

[0320] In some embodiments, the compounds and compositions disclosed herein are useful for treating leukemia. In some embodiments, the compounds and compositions disclosed herein that inhibit Akt3 are useful for treating leukemia. In these embodiments, the compounds and compositions disclosed herein that inhibit Akt3 are useful *in vivo* and *ex vivo* as immune response-stimulating therapeutics. The ability to inhibit Akt3 and thereby inhibit or reduce Treg-mediated immune suppression enables a more robust immune response. In some embodiments, the compounds and compositions disclosed herein are also useful to stimulate or enhance immune-stimulating or -activating responses involving T cells. In some embodiments, the compounds and compositions disclosed herein are useful for stimulating or enhancing an immune response in a host for treating leukemia by selectively inhibiting Akt3. In these embodiments, the compounds and compositions disclosed herein can be administered to a subject in an amount effective to stimulate T cells in the subject. The types of leukemia that can be treated with the compounds and compositions as disclosed herein include, but are not limited to, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), adult T-cell leukemia/lymphoma (ATLL) and chronic myelomonocytic leukemia (CMML).

[0321] In some embodiments, ATLL is almost exclusively diagnosed in adults, with a median age in the mid-60s. In some embodiments, there are four types of ATLL: (1) acute, (2) chronic, (3) smouldering, and (4) lymphomatous. In some embodiments, acute ATLL is the most common form, and is characterized by high white blood cell count, hypercalcemia, organomegaly, and high lactose dehydrogenase. In some embodiments, lymphomatous ATLL manifests in the lymph nodes with less than 1% circulating lymphocytes. In some embodiments, chronic and smouldering ATLL are characterized by a less aggressive clinical course and allow for long-term survival. In some embodiments, the four-year survival rate for acute and lymphomatous ATLL is less than 5%. In some embodiments, chronic and smouldering forms of ATLL have four-year survival rates of 26.9% and 62%, respectively. In some embodiments, the adult T-cell leukemia/lymphoma is caused by human T-cell lymphotropic virus (HTLV-1).

[0322] In some embodiments, the compounds and compositions disclosed herein are useful for treating ATLL. In some embodiments, the compounds and compositions disclosed herein that inhibit Akt3 are useful for treating ATLL. In some embodiments, Tregs expressing CD25 and FoxP3 may transform into ATLL cells. In some embodiments, ATLL cells display an activated helper/inducer T-cell phenotype but exhibit strong immunosuppressive activity. In some embodiments, the compounds and compositions disclosed herein that inhibit Akt3 reduce the immunosuppressive response of the ATLL cells. In other embodiments, the compounds and compositions disclosed herein that inhibit Akt3 increase an immune stimulatory response to overcome the strong immunosuppressive activity of ATLL cells.

[0323] In some embodiments, the compounds and compositions disclosed herein that are useful for treating leukemia or ATLL reduce or inhibit an immune suppressive response, such as, but not limited to an immune suppressive function of natural Treg (nTreg) cells and induction of conventional T cells into induced Treg (iTreg). In these embodiments, the immune suppressive function of nTreg cells that is reduced or inhibited is the secretion of one or more anti-inflammatory cytokines, such as, but not limited to IL10, TGFβ, or a combination thereof. In some embodiments, methods for treating leukemia or adult T-cell leukemia/lymphoma include administering to a subject a second active agent, such as, but not limited to, an anti-nausea drug, a chemotherapeutic drug, or a potentiating agent (*e.g.*, cyclophosphamide).

Autoimmune Disease

[0324] In some embodiments, the disease is an autoimmune disease. Non-limiting examples of autoimmune disease include achalasia, Addison's disease, adult Still's disease, agammaglobulinemia, alopecia areata, amyloidosis, ankylosing spondylitis, anti-glomerular basement membrane disease, anti-tubular basement membrane antibody nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease, autoimmune myocarditis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticaria, axonal and neuronal neuropathy, Baló disease, Behcet's disease, benign mucosal pemphigoid, bullous pemphigoid, Castleman disease, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, chronic recurrent multifocal osteomyelitis, Churg-Strauss syndrome, eosinophilic granulomatosis, cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease,

congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis, eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura, pemphigoid gestationis, hidradenitis suppurativa (acne inversa), hypogammalglobulinemia, IgA nephropathy, IgG4-related sclerosing disease, immune thrombocytopenic purpura, inclusion body myositis, interstitial cystitis, juvenile arthritis, juvenile diabetes (type 1 diabetes), juvenile myositis, Kawasaki disease, Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease, lupus, chronic Lyme disease, Meniere's disease, microscopic polyangiitis, mixed connective tissue disease, Mooren's ulcer, Mucha-Habermann disease, multifocal motor neuropathy, multiple sclerosis, myasthenia gravis, myositis, narcolepsy, neonatal lupus, neuromyelitis optica, neutropenia, ocular cicatricial pemphigoid, optic neuritis, palindromic rheumatism, pediatric autoimmune neuropsychiatric disorder, paraneoplastic cerebellar degeneration, paroxysmal nocturnal hemoglobinuria, Parry Romberg syndrome, pars planitis (peripheral uveitis), Parsonage-Turner syndrome, pemphigus, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia, POEMS syndrome, polyarteritis nodosa, polyglandular syndrome type I, polyglandular syndrome type II, polyglandular syndrome type III, polymyalgia rheumatica, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, progesterone dermatitis, psoriasis, psoriatic arthritis, pure red cell aplasia, pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy, relapsing polychondritis, restless legs syndrome, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjögren's syndrome, sperm and testicular autoimmunity, stiff person syndrome, subacute bacterial endocarditis, Susac's syndrome, sympathetic ophthalmia, Takayasu's arteritis, temporal arteritis (giant cell arteritis), thrombocytopenic purpura, Tolosa-Hunt syndrome, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, uveitis, vasculitis, vitiligo, and Vogt-Koyanagi-Harada disease.

Other Indications

[0325] In some embodiments, a compound disclosed herein modulates Akt3 and is used for treating Gulf War Syndrome, tuberous sclerosis, retinitis pigmentosa, transplant rejection, ischemic tissue injury, or traumatic tissue injury. In some embodiments, the transplant rejection is Graft-versus-Host disease. In some embodiments, the compound disclosed herein is used for treating retinitis pigmentosa by modulating Akt3 and not by modulating T regulatory cells. In some embodiments, the compound disclosed herein is used for treating ischemic tissue injury or traumatic tissue injury. In some embodiments, the ischemic tissue injury or traumatic tissue injury is the ischemic tissue injury or traumatic tissue injury of the brain.

Methods of Combination Therapy

[0326] In some embodiments, the disclosed compounds can be administered to a subject in need thereof alone or in combination with one or more additional therapeutic agents. In some embodiments, the compounds and the additional therapeutic agent are administered separately, but simultaneously. In some embodiments, the compound and the additional therapeutic agent are administered as part of the same composition. In other embodiments, the compound and the second therapeutic agent are administered separately and at different times, but as part of the same treatment regime.

[0327] In some embodiments, the subject can be administered a first therapeutic agent 1, 2, 3, 4, 5, 6, or more hours, or 1, 2, 3, 4, 5, 6, 7, or more days, before administration of a second therapeutic agent. In some embodiments, the subject can be administered one or more doses of the first agent every 1, 2, 3, 4, 5, 6 7, 14, 21, 28, 35, or 48 days prior to a first administration of second agent. The compounds disclosed herein can be the first or the second therapeutic agent.

[0328] In some embodiments, the compounds and the additional therapeutic agent can be administered as part of a therapeutic regimen. For example, if a first therapeutic agent can be administered to a subject every fourth day, the second therapeutic agent can be administered on the first, second, third, or fourth day, or combinations thereof. The first therapeutic agent or second therapeutic agent may be repeatedly administered throughout the entire treatment regimen.

[0329] Exemplary additional therapeutic agents include, but are not limited to, cytokines, chemotherapeutic agents, radionuclides, other immunotherapeutics, enzymes, antibiotics, antivirals (*e.g.*, protease inhibitors alone or in combination with nucleosides for treatment of

HIV or Hepatitis B or C), anti-parasites (*e.g.*, helminths or protozoans), growth factors, growth inhibitors, hormones, hormone antagonists, antibodies and bioactive fragments thereof (including humanized, single chain, and chimeric antibodies), antigen and vaccine formulations (including adjuvants), peptide drugs, anti-inflammatories, ligands that bind to Toll-like receptors (including, but not limited to, CpG oligonucleotides) to activate the innate immune system, molecules that mobilize and optimize the adaptive immune system, other molecules that activate or up-regulate the action of cytotoxic T lymphocytes, NK cells and helper T-cells, and other molecules that deactivate or down-regulate suppressor or regulatory T-cells.

[0330] The additional therapeutic agents are selected based on the condition, disorder or disease to be treated. For example, the compounds of the invention can be co-administered with one or more additional agents that function to enhance or promote an immune response or reduce or inhibit an immune response.

Chemotherapeutic Agents

[0331] In some embodiments, the compounds of the invention can be combined with one or more chemotherapeutic agents or pro-apoptotic agents. Representative chemotherapeutic agents include, but are not limited to, amsacrine, bleomycin, busulfan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clofarabine, crisantaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gemcitabine, hydroxycarbamide, idarubicin, ifosfamide, irinotecan, leucovorin, liposomal doxorubicin, liposomal daunorubicin, lomustine, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitoxantrone, oxaliplatin, paclitaxel, pemetrexed, pentostatin, procarbazine, raltitrexed, satraplatin, streptozocin, tegafur-uracil, temozolomide, teniposide, thiotepa, tioguanine, topotecan, treosulfan, vinblastine, vincristine, vindesine, vinorelbine, or a combination thereof. Representative pro-apoptotic agents include, but are not limited to fludarabinetaurosporine, cycloheximide, actinomycin D, lactosylceramide, 15d-PGJ(2), and combinations thereof.

Anti-Inflammatories

[0332] Other suitable additional therapeutic agents include, but are not limited to, anti-inflammatory agents. In some embodiments, the anti-inflammatory agent can be non-steroidal, steroidal, or a combination thereof. One embodiment provides oral compositions

containing about 1% (w/w) to about 5% (w/w), typically about 2.5 % (w/w), of an anti-inflammatory agent. Representative examples of non-steroidal anti-inflammatory agents include, without limitation, oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam; salicylates, such as aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal; acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, and ketorolac; fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids; propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indopropfen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; pyrazoles, such as phenylbutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone. In some embodiments, mixtures of these non-steroidal anti-inflammatory agents may also be employed.

[0333] Representative examples of steroidal anti-inflammatory drugs include, without limitation, corticosteroids, such as hydrocortisone, hydroxyl-triamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionates, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylesters, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone, fludrocortisone, diflurosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, diflurprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof.

Immunosuppressive Agents

[0334] In some embodiments, the compound disclosed herein decreases Treg activity or production. In some embodiments, the compound disclosed herein is used in induction therapy for cancer. In some embodiments, the compound disclosed herein is used in

combination with other immune therapeutic agents, immune modulators, costimulatory activating agonists, other cytokines and chemokines and factors, vaccines, oncolytic viruses, cell therapy, small molecules and targeted therapy, chemotherapy and radiation therapy. In some embodiments, the immune modulators include check point inhibitors such as anti-PD1, anti-CTLA4, anti-TIM3, anti-LAG3. In some embodiments, the costimulatory activating agonists including anti-OX40, anti-GITR, and the like. In some embodiments, the cell therapy includes engineered T cells, CAR-T, TCR-Tcells and others.

[0335] In some embodiments, the compound disclosed herein is used in combination with other immune therapeutic agents, immune modulators, biologics (e.g., antibodies), vaccines, small molecules and targeted therapy, anti-inflammatory, cell therapy (*e.g.*, engineered Tregs and other type of cells, chemotherapy and radiation therapy.

[0336] In some embodiments, the compound disclosed herein, either used alone or in combination with other agents, is administered *in vivo* to a patient by intravenous, intramuscular, or other parenteral means. They can also be administered by intranasal application, inhalation, rectally, vaginally, topically, orally, or as implants. In other embodiments, the compound disclosed herein, either used alone or in combination with other agents, is applied *ex vivo* to enhance the function of suppressive Tregs, including natural tregs, induce-Tregs, engineered Tregs and other type of suppressive T cells, which optionally can then be used to treat a patient.

[0337] In some embodiments, the additional therapeutic agent is an immune suppressant. Immunosuppressive agents include, but are not limited to, antibodies against other lymphocyte surface markers (*e.g.*, CD40, alpha-4 integrin) or against cytokines, fusion proteins (*e.g.*, CTLA-4-Ig (Orencia®), TNFR-Ig (Enbrel®)), TNF-α blockers, such as Enbrel, Remicade, Cimzia, and Humira, cyclophosphamide ("CTX") (*e.g.*, Endoxan®, Cytoxan®, Neosar®, Procytox®, and Revimmune™), methotrexate ("MTX") (*e.g*, Rheumatrex® and Trexall®), belimumab (*e.g*, Benlysta®), other immunosuppressive drugs (*e.g.*, cyclosporin A, FK506-like compounds, rapamycin compounds, and steroids), anti-proliferatives, cytotoxic agents, and other compounds that may assist in immunosuppression.

[0338] In some embodiments, the additional therapeutic agent can be a checkpoint inhibitor. In some embodiments, the additional therapeutic agent can be a CTLA-4 fusion protein, such as CTLA-4-Ig (abatacept). CTLA-4-Ig fusion proteins can compete with the co-stimulatory receptor, CD28, on T-cells for binding to CD80/CD86 (B7-1/B7-2) on antigen

presenting cells, and thus function to inhibit T-cell activation. In another embodiment, the additional therapeutic agent is a CTLA-4-Ig fusion protein known as belatacept. Belatacept contains two amino acid substitutions (L104E and A29Y) that can markedly increase its avidity to CD86 *in vivo*. In another embodiment, the additional therapeutic agent is Maxy-4.

[0339] In another embodiment, the additional therapeutic agent is CTX. CTX (the generic name for Endoxan®, Cytoxan®, Neosar®, Procytox®, and Revimmune™), also known as cytophosphane, is a nitrogen mustard alkylating agent from the oxazophorines group. It can be used to treat various types of cancer and some autoimmune disorders. CTX is the primary drug used for diffuse proliferative glomerulonephritis in patients with renal lupus.

[0340] In some embodiments, the additional therapeutic agent can be administered in an effective amount to reduce the blood or serum levels of anti-double-stranded DNA ("anti-ds DNA") auto antibodies and/or to reduce proteinuria in a patient in need thereof.

[0341] In another embodiment, the additional therapeutic agent can increase the amount of adenosine in the serum (*see*, for example, WO 08/147482). For example, the second therapeutic agent can be CD73-Ig, recombinant CD73, or another agent (*e.g.*, a cytokine, monoclonal antibody, or small molecule) that increases the expression of CD73 (*see*, for example WO 04/084933). In another embodiment, the additional therapeutic agent is Interferon-beta.

[0342] In some embodiments, the additional therapeutic agent can be a small molecule that inhibits or reduces differentiation, proliferation, activity, cytokine production, and/or cytokine secretion by Th1, Th17, Th22, and/or other cells that secrete, or cause other cells to secrete, inflammatory molecules, including, but not limited to, IL-1β, TNF-α, TGF-beta, IFN-γ, IL-18 IL-17, IL-6, IL-23, IL-22, IL-21, and MMPs. In another embodiment, the additional therapeutic agent is a small molecule that interacts with Tregs, enhances Treg activity, promotes or enhances IL-10 secretion by Tregs, increases the number of Tregs, increases the suppressive capacity of Tregs, or combinations thereof.

[0343] In some embodiments, the composition increases Treg activity or production. Exemplary Treg enhancing agents include, but are not limited to, glucocorticoid fluticasone, salmeteroal, antibodies to IL-12, IFN-γ, and IL-4; vitamin D3, and dexamethasone, and combinations thereof.

[0344] In some embodiments, the additional therapeutic agent is an antibody, for example, a function-blocking antibody against a proinflammatory molecule such as IL-6, IL-23, IL-22, or IL-21.

[0345] In some embodiments, the additional therapeutic agent includes a nucleic acid. In some embodiments, the additional therapeutic agent includes a ribonucleic acid.

Combination Treatments for Neurodegenerative Diseases

[0346] In some embodiments, the compounds disclosed herein can be administered with a second therapeutic that is selected based on the subject's disease state. In some embodiments, the second therapeutic can be a treatment for Alzheimer's disease. Current treatments for Alzheimer's disease include, but are not limited to, cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine; memantine; antidepressants, such as citalopram, fluoxetine, paroxetine, sertraline, and trazadone; anxiolytics, such as lorazepam and oxazepam; and antipsychotics, such as aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone.

[0347] In another embodiment, the additional therapeutic agent can be a treatment for ALS. There are currently two U.S. FDA-approved treatments for ALS: riluzole and edavarone. Both drugs have been shown to slow down the progression of ALS. In addition to riluzole and edavarone, subjects with ALS can also be treated with drugs that target a specific symptom of the disease. Exemplary such drugs include, but are not limited to, drugs to reduce spasticity such, as antispastics (*e.g.*, baclofen, dantrolene, and diazepam); drugs to help control nerve pain, such as amitriptyline, carbamazepine, duloxetine, gabapentin, lamotrigine, milnacipran, nortriptyline, pregabalin and venlafaxine; and drugs to help patients swallow, such as trihexyphenidyl or amitriptyline.

[0348] In one embodiment, the additional therapeutic agent can be a treatment for Parkinson's disease. Current treatments for Parkinson's disease include, but are not limited to, carbidopa-levodopa; dopamine agonists, such as pramipexole, ropinirole, and rotigotine; MAO B inhibitors, such as selegiline, rasagiline, and safinamide; catechol O-methyltransferase inhibitors, such as entacapone and tolcapone; anticholinergics, such as bentztropine and trihexyphenidyl; and amantadine.

[0349] In some embodiments, the second therapeutic agent can be a treatment for Huntington's disease. Current treatments for Huntington's disease include, but are not limited to, tetrabenazine; antipsychotics, such as haloperidol, chlorpromazine, risperidone,

and quetiapine; amantadine; levetiracetam; clonazepam; antidepressants, such as citalopram, escitalopram, fluoxetine, and sertraline; and anticonvulsants, such as valproate, carbamazepine, and lamotrigine.

Combination Treatments for Weight Loss

[0350] In some embodiments, the compounds disclosed herein can be administered to a subject with an additional therapeutic agent that is used to treat cachexia or extreme weight loss. The current strategy for treating cachexia and extreme weight loss is to improve appetite by using appetite stimulants to ensure adequate intake of nutrients. Pharmacological interventions with appetite stimulants, nutrient supplementation, 5-HT3 antagonists, and Cox-2 inhibitor have been used to treat cancer cachexia.

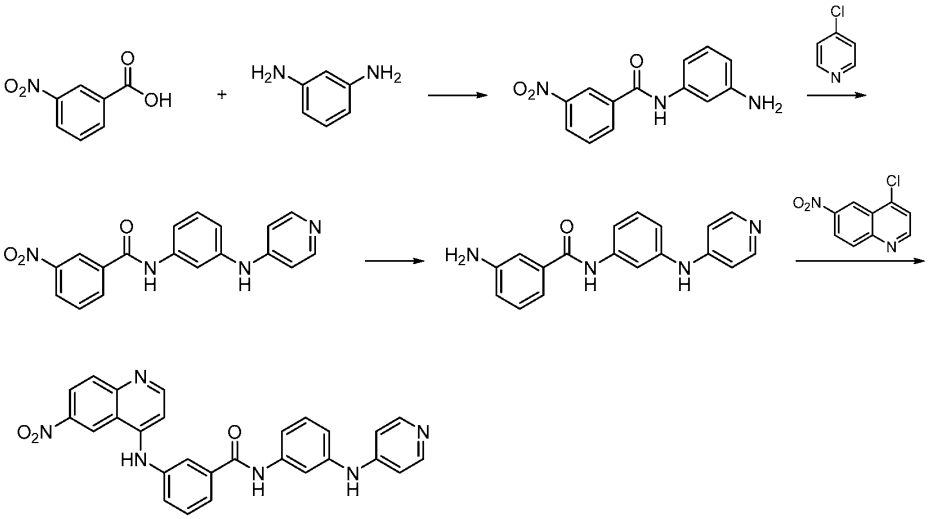
[0351] In some embodiments, appetite stimulants are, for example, vitamins, minerals, or herbs including, but not limited to, zinc, thiamine, or fish oil. In another embodiment, the appetite stimulant is a medication including, but not limited to, dronabinol, megesterol, and oxandrolone.

Equivalents

[0352] The representative examples which follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. It should further be appreciated that the contents of those cited references are incorporated herein by reference to help illustrate the state of the art. The following examples contain important additional information, exemplification, and guidance which can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

EXAMPLES

Example 1: Compound 1 (3-((6-nitroquinolin-4-yl)amino)-N-(3-(pyridin-4-ylamino)phenyl)benzamide)



1

Scheme 1

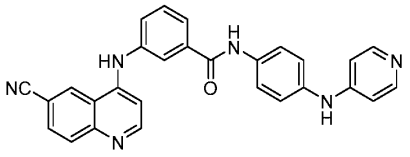
[0353] As shown in Scheme 1, *meta*-nitrobenzoic acid was coupled with 1,3-phenylenediamine using EDCI in the presence of HOBt and DIPEA. The resulting intermediate was coupled with 4-chloro-pyridine followed by reduction of the nitro group into an amino group using Sn/HCl. The resulting amino-intermediate was then reacted with 4-chloro-6-nitro-quinoline in EtOH under reflux for 3 hours with the addition of 2-3 drops of TEA to give meta-substituted product Compound 1. The final product was precipitated from the reaction mixture soon after it reached room temperature and then filtered off and purified via recrystallization from EtOH: diethyl ether 1:1.

[0354] The compounds shown in the following examples were made in an analogous manner based on the experimental procedure described in Example 1, and/or as described below, and/or by a method known in the art.

[0355] The following abbreviations as used in the following examples have the following definitions: DCE = dichloroethane; DCM = dichloromethane; DIEPA or DIPEA = N,N-diisopropylethylamine; DMAP = 4-dimethylaminopyridine; DMF = dimethylformamide; EA or EtOAc = ethyl acetate; EDC or EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; HPLC = high-performance liquid chromatography; PE = petroleum

ether; RT = retention time (*e.g.*, HPLC retention time); TEA = triethylamine; TFA = trifluoroacetic acid; THF = tetrahydrofuran; and TsOH or TosOH = p-toluenesulfonic acid. These abbreviations and definitions are not intended to be limiting of other abbreviations and definitions in the application.

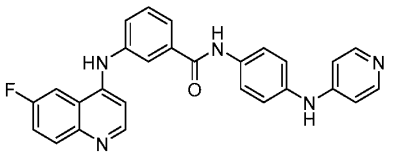
Example 2: **Compound 2 (3-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)**



2

[0356] **Compound 2** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 2** (3-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide): $C_{28}H_{20}N_6O$; 456.51 g/mol; 26 mg; yellow solid; ESI-LCMS m/z = 457 $[M+H]^+$; LCMS RT = 1.594 min, 100% (214 nm).

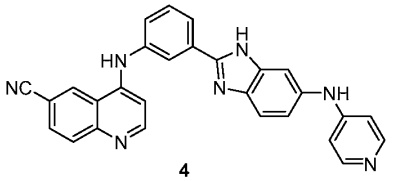
Example 3: **Compound 3 (3-((6-fluoroquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)**



3

[0357] **Compound 3** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 3** (3-((6-fluoroquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide): $C_{27}H_{20}FN_5O$; 449.49 g/mol; 34 mg; white solid; ESI-LCMS m/z = 450 $[M+H]^+$; LCMS RT = 1.614 min, 99% (214 nm).

Example 4: **Compound 4 (4-((3-(6-(pyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)amino)quinoline-6-carbonitrile)**

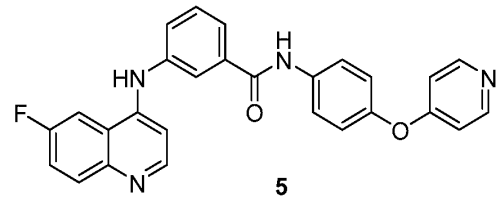


4

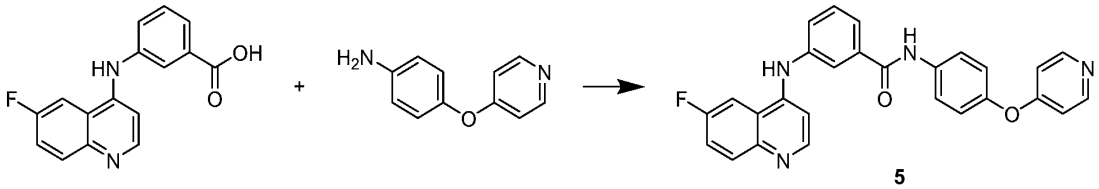
[0358] **Compound 4** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 4** (4-((3-(6-(pyridin-4-ylamino)-1H-

benzo[d]imidazol-2-yl)phenyl)amino)quinoline-6-carbonitrile): $C_{28}H_{19}N_7$; 453.51 g/mol; 22 mg; yellow solid; ESI-LCMS m/z = 454 $[M+H]^+$; LCMS RT = 1.634 min, 100% (214 nm).

Example 5: **Compound 5 (3-((6-fluoroquinolin-4-yl)amino)-N-(4-(pyridin-4-yloxy)phenyl)benzamide)**



5

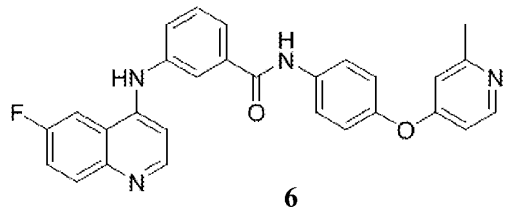


5

Scheme 2

[0359] **Compound 5** was prepared by the method shown in Scheme 2. **Compound 5** (3-((6-fluoroquinolin-4-yl)amino)-N-(4-(pyridin-4-yloxy)phenyl)benzamide) was prepared as shown in Scheme 2: $C_{27}H_{19}FN_4O_2$; 450.47 g/mol; 13 mg; white solid; ESI-LCMS m/z = 451 $[M+H]^+$; LCMS RT = 0.99 min, >95.00% (214 nm).

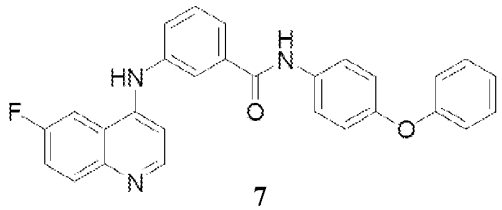
Example 6: **Compound 6 (3-((6-fluoroquinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)oxy)phenyl)benzamide)**



6

[0360] **Compound 6** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 6** (3-((6-fluoroquinolin-4-yl)amino)-N-(4-((2-methylpyridin-4- yl)oxy)phenyl)benzamide): $C_{28}H_{21}FN_4O_2$; 464.50 g/mol; 18 mg; pale yellow solid; ESI-LCMS m/z = 456 $[M+H]^+$; LCMS RT = 1.43 min, >95.00% (214 nm).

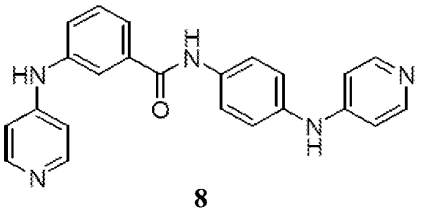
Example 7: **Compound 7 (4-((6-fluoroquinolin-4-yl)amino)-N-(3-phenoxyphenyl)benzamide)**



7

[0361] **Compound 7** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 7** (4-((6-fluoroquinolin-4-yl)amino)-N-(3-phenoxyphenyl)benzamide): $C_{28}H_{20}FN_3O_2$; 449.49 g/mol; 13 mg; white solid; ESI-LCMS m/z = 450 $[M+H]^+$; LCMS RT = 1.74 min, >95.00% (214 nm).

Example 8: **Compound 8 (3-(pyridin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)**



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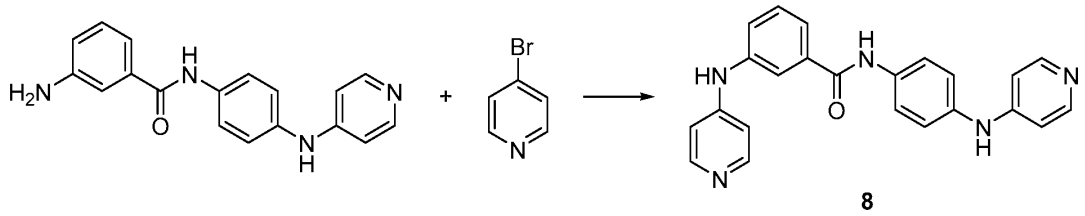

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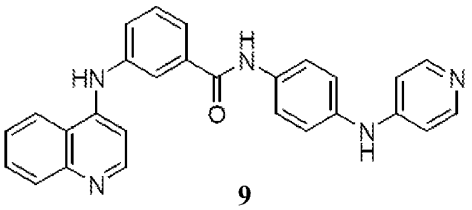
Scheme 3

[0362] **Compound 8** was prepared by the method shown in Scheme 3. **Compound 8** (3-(pyridin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Scheme 3: $C_{23}H_{19}N_5O$; 381.44 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 382 $[M+H]^+$; LCMS RT = 1.30 min, >95.00% (214 nm).

Example 9: **Compound 9 (N-(4-(pyridin-4-ylamino)phenyl)-3-(quinolin-4-ylamino)benzamide)**



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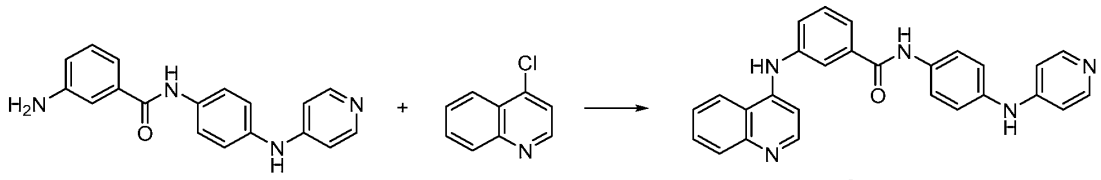
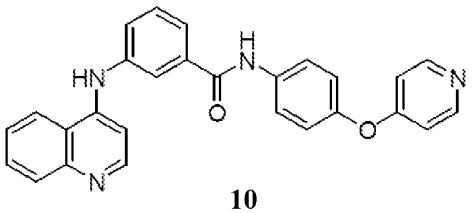


Scheme 4

[0363] **Compound 9** was prepared by the method shown in Scheme 4. **Compound 9** (N-(4-(pyridin-4-ylamino)phenyl)-3-(quinolin-4-ylamino)benzamide) was prepared as shown in Scheme 4: $C_{27}H_{21}N_5O$; 431.50 g/mol; 24 mg; pale yellow solid; ESI-LCMS m/z = 432 $[M+H]^+$; LCMS RT = 1.46 min, >95.00% (214 nm).

Example 10: **Compound 10 (N-(4-(pyridin-4-yloxy)phenyl)-3-(quinolin-4-ylamino)benzamide)**



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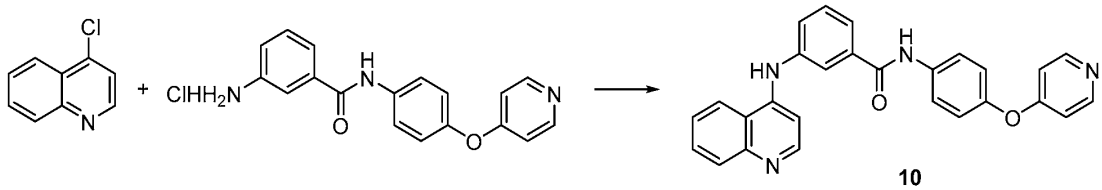
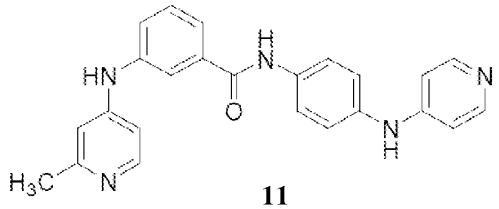


Scheme 5

[0364] **Compound 10** was prepared by the method shown in Scheme 5. **Compound 10** (N-(4-(pyridin-4-yloxy)phenyl)-3-(quinolin-4-ylamino)benzamide) was prepared as shown in Scheme 5: $C_{27}H_{20}N_4O_2$; 432.48 g/mol; 29 mg; pale yellow solid; ESI-LCMS m/z = 433 $[M+H]^+$; LCMS RT = 1.43 min, >95.00% (214 nm).

Example 11: **Compound 11 (3-((2-methylpyridin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)**



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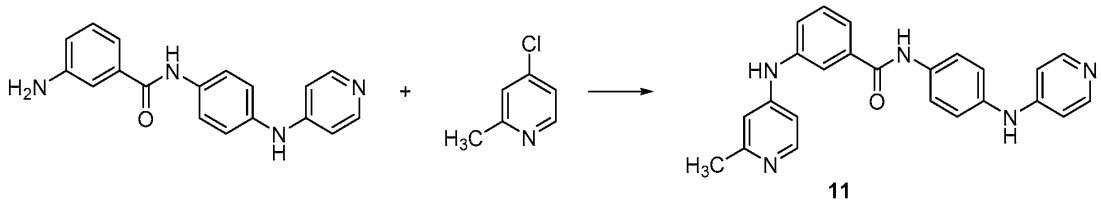
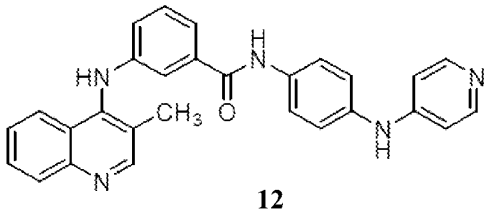


11

Scheme 6

[0365] **Compound 11** was prepared by the method shown in Scheme 6. **Compound 11** (3-((2-methylpyridin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Scheme 6: $C_{24}H_{21}N_5O$; 395.47 g/mol; 16 mg; pale yellow solid; ESI-LCMS m/z = 396 $[M+H]^+$; LCMS RT = 1.32 min, >95.00% (214 nm).

Example 12: **Compound 12 (3-((3-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide)**



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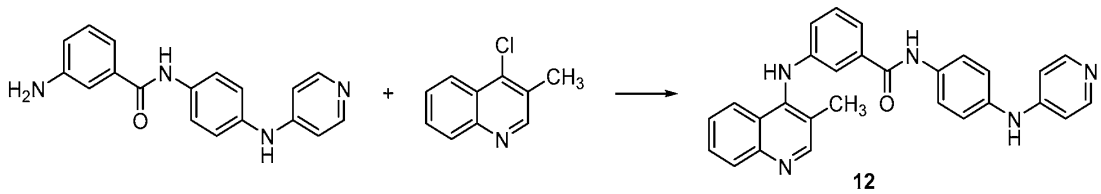

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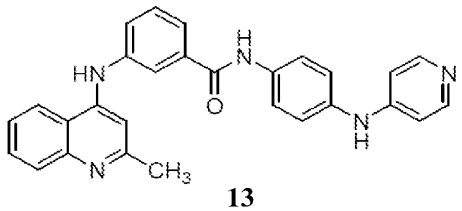
Scheme 7

[0366] **Compound 12** was prepared by the method shown in Scheme 7. **Compound 12** (3-((3-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide) was prepared as shown in Scheme 7: $C_{28}H_{23}N_5O$; 445.53 g/mol; 19 mg; pale yellow solid; ESI-LCMS m/z = 446 $[M+H]^+$; LCMS RT = 1.48 min, >95.00% (214 nm).

Example 13: **Compound 13 (3-((2-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide)**



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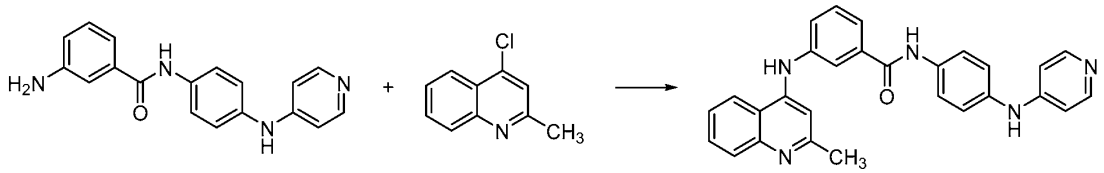
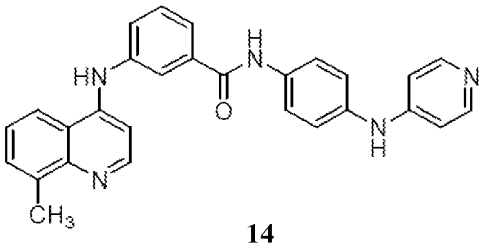


Scheme 8

[0367] **Compound 13** was prepared by the method shown in Scheme 8. **Compound 13** (3-((2-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide) was prepared as shown in Scheme 8: $C_{28}H_{23}N_5O$; 445.53 g/mol; 20 mg; pale yellow solid; ESI-LCMS m/z = 446 $[M+H]^+$; LCMS RT = 1.46 min, >95.00% (214 nm).

Example 14: **Compound 14 (3-((8-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide)**



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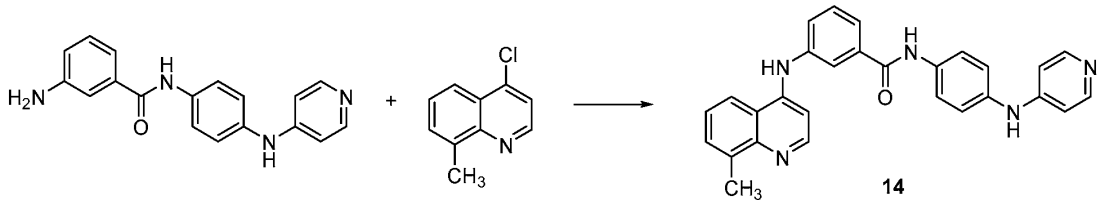
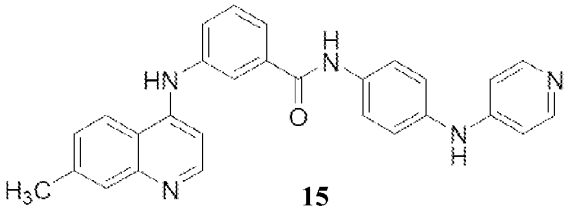


Scheme 9

[0368] **Compound 14** was prepared by the method shown in Scheme 9. **Compound 14** (3-((8-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide) was prepared as shown in Scheme 9: $C_{28}H_{23}N_5O$; 445.53 g/mol; 29 mg; pale yellow solid; ESI-LCMS m/z = 446 $[M+H]^+$; LCMS RT = 1.54 min, >95.00% (214 nm).

Example 15: **Compound 15 (3-((7-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide)**



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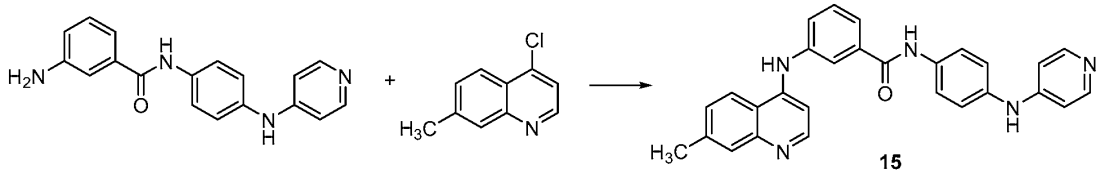
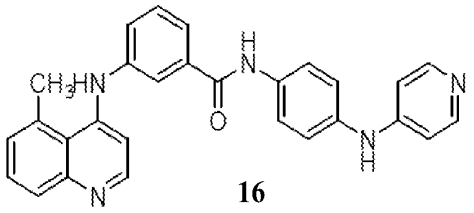


Scheme 10

[0369] **Compound 15** was prepared by the method shown in Scheme 10. **Compound 15** (3-((7-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide) was prepared as shown in Scheme 10: $C_{28}H_{23}N_5O$; 445.53 g/mol; 24 mg; pale yellow solid; ESI-LCMS m/z = 446 $[M+H]^+$; LCMS RT = 1.48 min, >95.00% (214 nm).

Example 16: **Compound 16 (3-((5-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide)**



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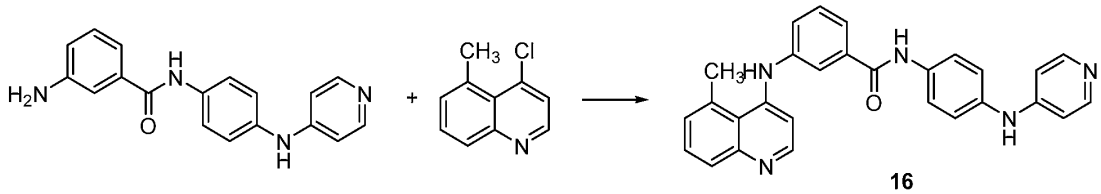
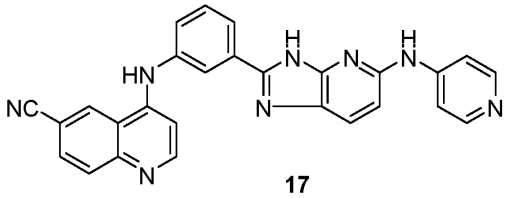


Scheme 11

[0370] **Compound 16** was prepared by the method shown in Scheme 11. **Compound 16** (3-((5-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide) was prepared as shown in Scheme 11: $C_{28}H_{23}N_5O$; 445.53 g/mol; 17 mg; pale yellow solid; ESI-LCMS m/z = 446 $[M+H]^+$; LCMS RT = 1.49 min, >95.00% (214 nm).

Example 17: Compound 17 (4-((3-(5-(pyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)phenyl)amino)quinoline-6-carbonitrile)



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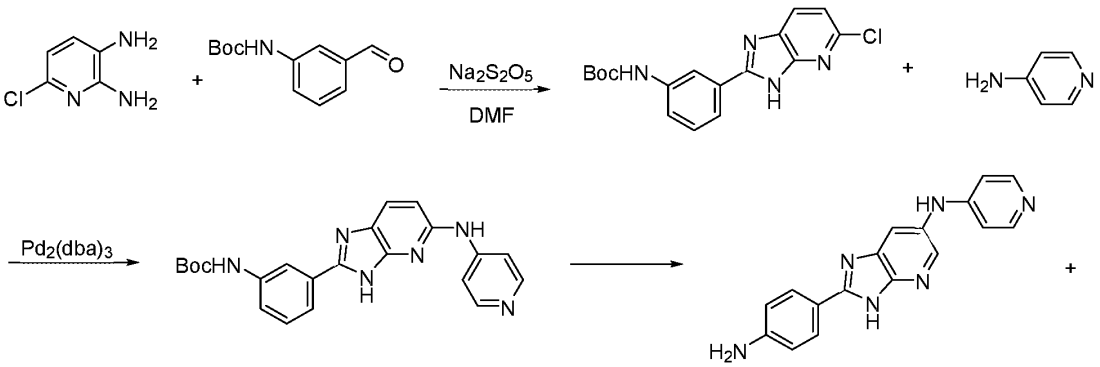

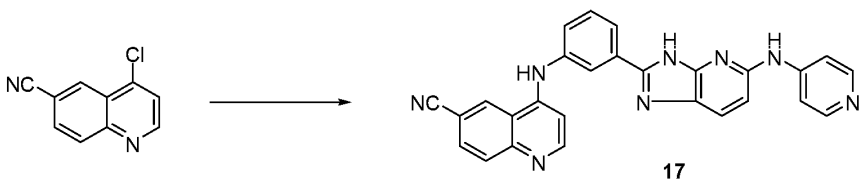

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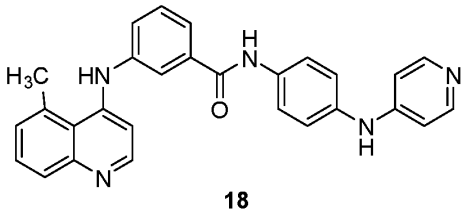
Scheme 12

[0371] **Compound 17** was prepared by the method shown in Scheme 12. **Compound 17** (4-((3-(5-(pyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)phenyl)amino)quinoline-6-carbonitrile) was prepared as shown in Scheme 12; $C_{27}H_{18}N_8$; 454.50 g/mol; 13 mg; yellow solid; ESI-LCMS m/z = 455 $[M+H]^+$; RT = 1.44 min, >95.00% (214 nm).

Example 18: Compound 18 (3-((5-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide)



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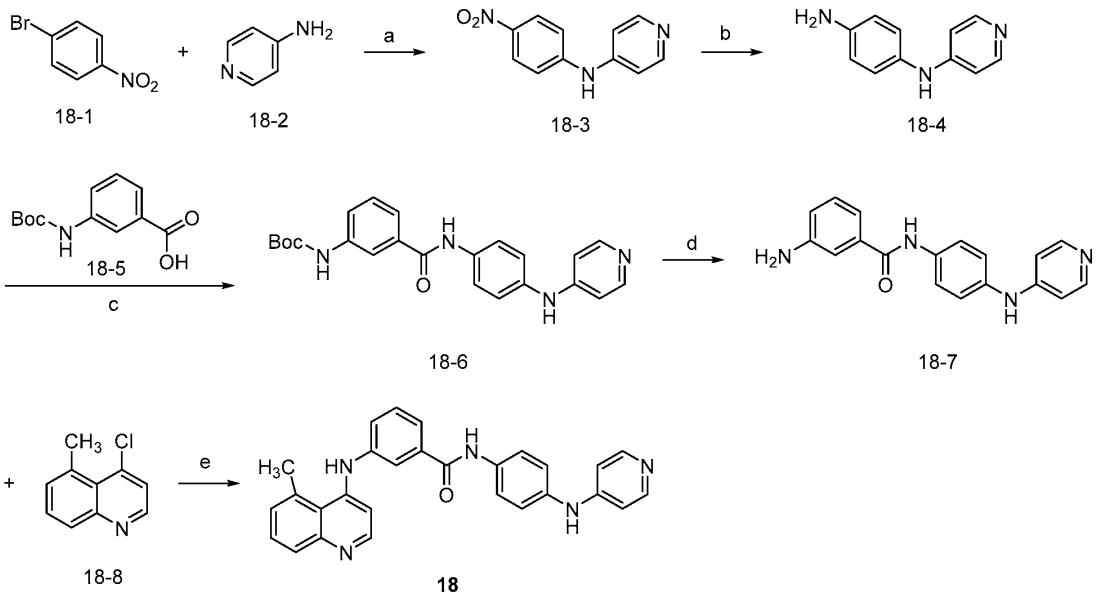


Scheme 13

[0372] Step a: To a stirred mixture of Compound 18-1 (20 g, 0.1 mol) in 1,4-dioxane (500 mL) was added pyridin-4-amine (Compound 18-2) (9.4 g, 0.1 mol), Cs_2CO_3 (65 g, 0.2 mol), $Pd_2(dba)_3$ (457 mg, 0.5 mmol), and Xantphos (457 mg, 0.8 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 100 °C for 2 hours. The reaction was then quenched with water (500 mL) and extracted with EA (3 × 500 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (0-50% EA in PE) to afford Compound 18-3 (19.8 g, 93%) as a yellow solid.

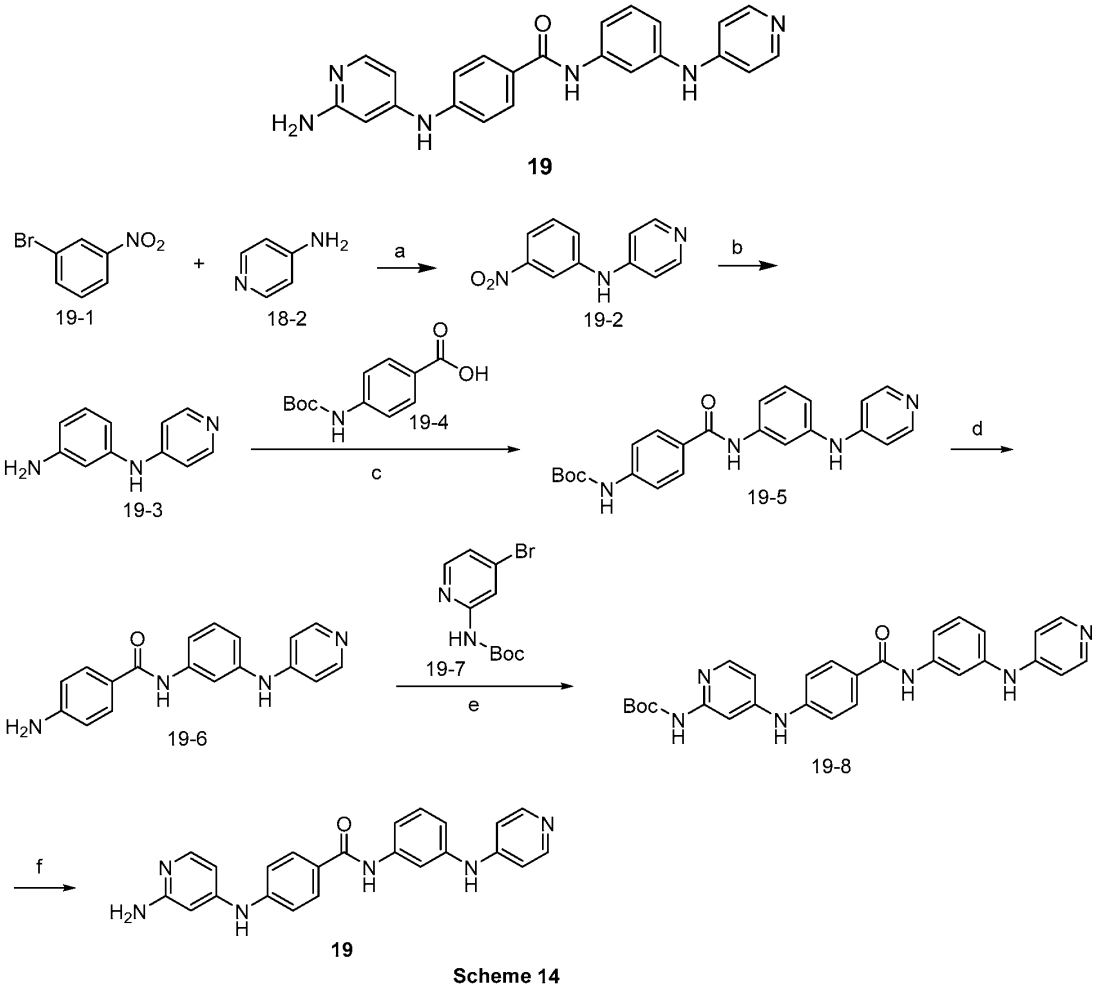
[0373] Step b: To a mixture of Compound 18-3 (19.8 g, 93 mmol) in MeOH (1000 mL) was added Pd/C (986 mg, 0.93mmol), and the mixture was stirred at room temperature for 4 hours under H_2. The combined organic phase was filtered by diatomite to give Compound 18-4 as yellow solid (16.9 g, 98.5%).

[0374] Step c: To a mixture of Compound 18-4 (16.9 g, 92 mmol) in DMF (250 mL) was added 3-((tert-butoxycarbonyl)amino)benzoic acid (Compound 18-5) (21.8 g, 92 mmol), EDCI (9.1 mg, 0.01 mmol), and DMAP (22.4 g, 184 mmol), and the mixture was stirred at room temperature for 16 hours. The reaction was then quenched with water (1000 mL) and extracted with EA (3 × 600 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (0-50% EA in PE) to afford Compound 18-6 (30.2 g, 81.2%) as a white solid.

[0375] Step d: A mixture of Compound 18-6 (30.2 g, 74 mmol) in dioxane hydrochloride (1000 mL, 4 M) was stirred at room temperature for 4 hours. The combined organic phase was concentrated to give Compound 18-7 as white solid (20.2 g, 90%).

[0376] Step e: To a mixture of Compound 18-7 (50 mg, 0.16 mmol) in DMSO (2 mL) was added 4-chloro-3-methylquinoline (Compound 18-8) (29 mg, 0.16 mmol), and a drop of hydrochloric acid. The mixture was stirred at 100 °C for 1 hour. The crude residue was purified by prep-HPLC to give **Compound 18** (3-((5-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide) as a pale yellow solid (11 mg, 15.0%): $C_{28}H_{23}N_5O$; 445.53 g/mol; ESI-LCMS m/z = 446 $[M+H]^+$; RT = 1.49 min, >95.00% (214 nm).

Example 19: Compound 19 (4-(2-aminopyridin-4-ylamino)-N-(3-(pyridin-4-ylamino)phenyl)benzamide)



Scheme 14

[0377] Step a: To a stirred mixture of 1-bromo-3-nitrobenzene (Compound 19-1) (20 g, 0.1 mol) in 1,4-dioxane (500 mL) was added pyridin-4-amine (Compound 18-2) (9.4 g, 0.1 mol), Cs_2CO_3 (65 g, 0.2 mol), $Pd_2(dba)_3$ (457mg, 0.5 mmol), and Xantphos (457 mg, 0.8 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 100 °C for 2 hours. The reaction was then quenched with water (500 mL) and extracted with EA (3 × 500 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (0-50% EA in PE) to afford Compound 19-2 (20 g, 93%) as a yellow solid.

[0378] Step b: To a mixture of Compound 19-2 (20 g, 93 mmol) in MeOH (1000 mL) was added Pd/C (986 mg, 0.93mmol), and the mixture was stirred at room temperature for 4 hours under H_2. The combined organic phase was filtered by diatomite to give Compound 19-3 as yellow solid (17.0 g, 98.7%).

[0379] Step c: To a mixture of Compound 19-3 (17.0 g, 92 mmol) in DMF (250 mL) was added 4-((tert-butoxycarbonyl)amino)benzoic acid (Compound 19-4) (21.8 g, 92 mmol), EDCI (9.1 mg, 0.01 mmol), and DMAP (22.4 g, 184 mmol), and the mixture was stirred at room temperature for 16 hours. The reaction was then quenched with water (1000 mL) and extracted with EA (3 × 600 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (0-50% EA in PE) to afford Compound 19-5 (30 g, 81%) as a white solid.

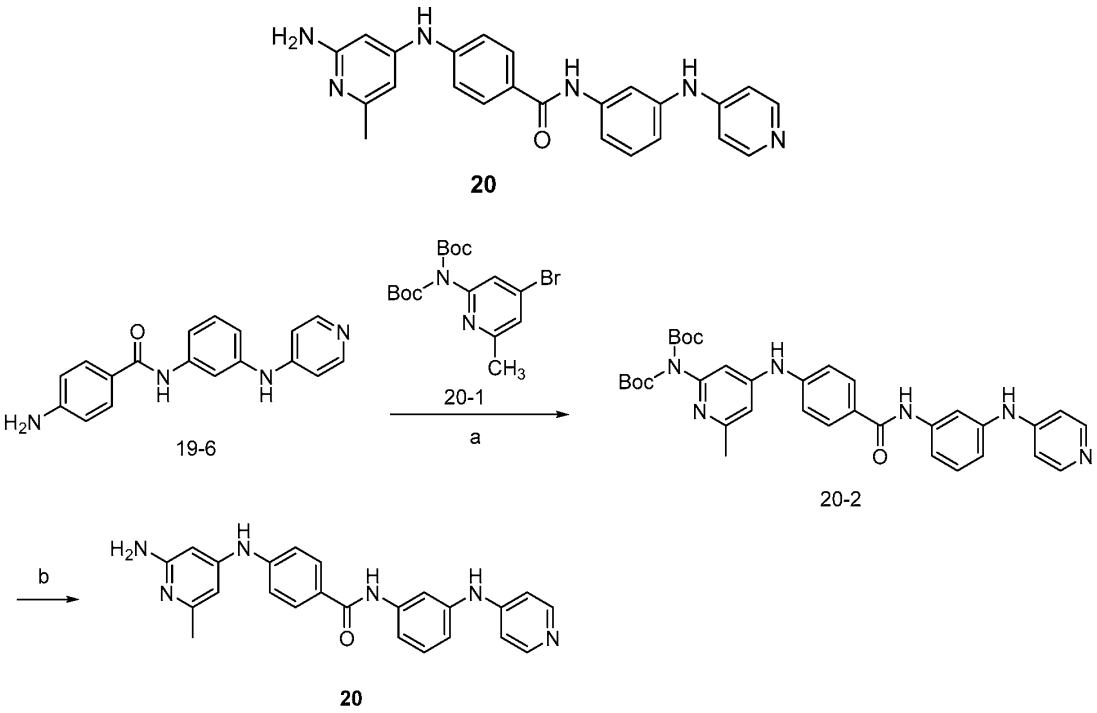
[0380] Step d: A mixture of Compound 19-5 (30 g, 74 mmol) in dioxane hydrochloride (1000 mL, 4 M) was stirred at room temperature for 4 hours. The combined organic phase was concentrated to give compound 19-6 as white solid (20.2 g, 90%).

[0381] Step e: To a mixture of Compound 19-6 (50 mg, 0.164 mmol) in 1,4-dioxane (2 mL) was added tert-butyl (4-bromopyridin-2-yl)carbamate (Compound 19-7) (45 mg, 0.164 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), and Cs_2CO_3 (102 mg, 0.32 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2 . The mixture was concentrated to give Compound 19-8, which was used directly in the next step without further purification.

[0382] Step f: A solution of Compound 19-8 in TFA (3mL) was stirred at room temperature for 1 hour. The mixture was concentrated and the crude residue was purified by prep-HPLC to give **Compound 19** (4-(2-aminopyridin-4-ylamino)-N-(3-(pyridin-4-

ylamino)phenyl)benzamide) as a white solid (12 mg, 18.5%): $C_{23}H_{20}N_6O$; 396.44 g/mol; ESI-LCMS m/z = 397 $[M+H]^+$; RT = 1.44 min, >95.00% (214 nm).

Example 20: Compound 20 (4-(2-amino-6-methylpyridin-4-ylamino)-N-(3-(pyridin-4-ylamino)phenyl)benzamide)



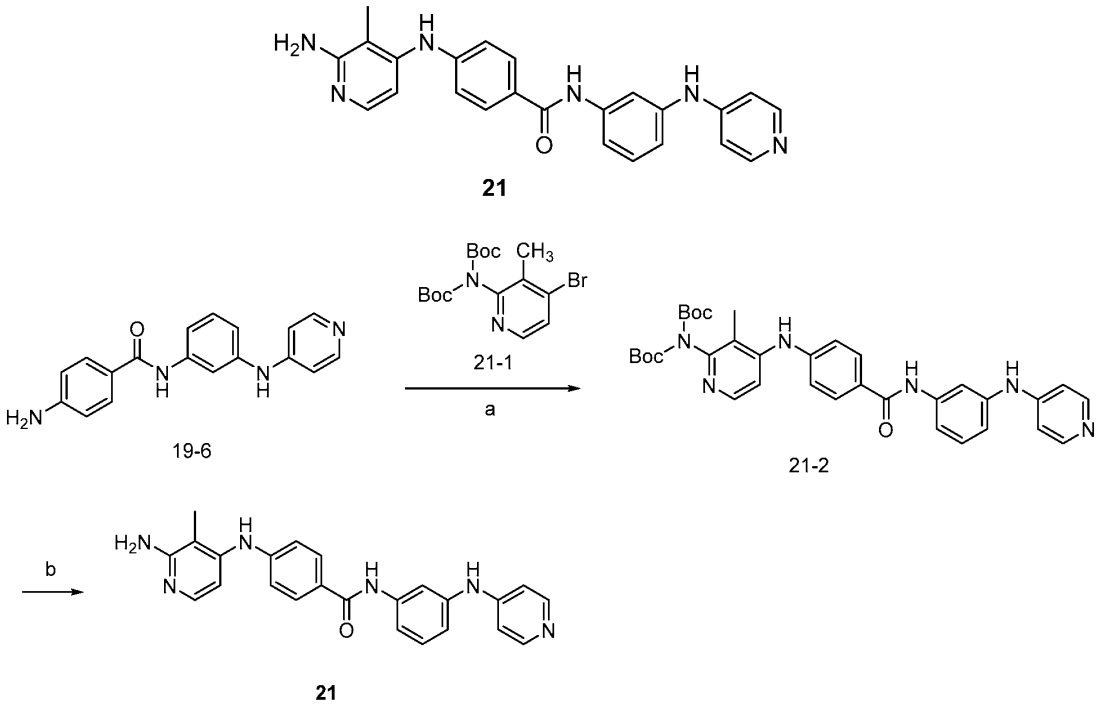
Scheme 15

[0383] Compound 19-6 was prepared in an analogous fashion to the procedure described in Example 19.

[0384] Step a: To a mixture of Compound 19-6 (50 mg, 0.164 mmol) in 1,4-dioxane (2 mL) was added tert-butyl (4-bromopyridin-2-yl)carbamate (Compound 20-1) (45 mg, 0.164 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), and Cs_2CO_3 (102 mg, 0.32 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated to give Compound 20-2, which was used directly in the next step without further purification.

[0385] Step b: A solution of Compound 20-2 in TFA (3mL) was stirred at room temperature for 1 hour. The mixture was concentrated and the crude residue was purified by prep-HPLC to give **Compound 20** (4-(2-amino-6-methylpyridin-4-ylamino)-N-(3-(pyridin-4-ylamino)phenyl)benzamide) as a white solid (12 mg, 18.5%): $C_{24}H_{22}N_6O$; 410.47 g/mol; ESI-LCMS m/z = 411 $[M+H]^+$; RT = 1.47 min, >95.00% (214 nm).

Example 21: Compound 21 (4-(2-amino-3-methylpyridin-4-ylamino)-N-(3-(pyridin-4-ylamino)phenyl)benzamide)



Scheme 16

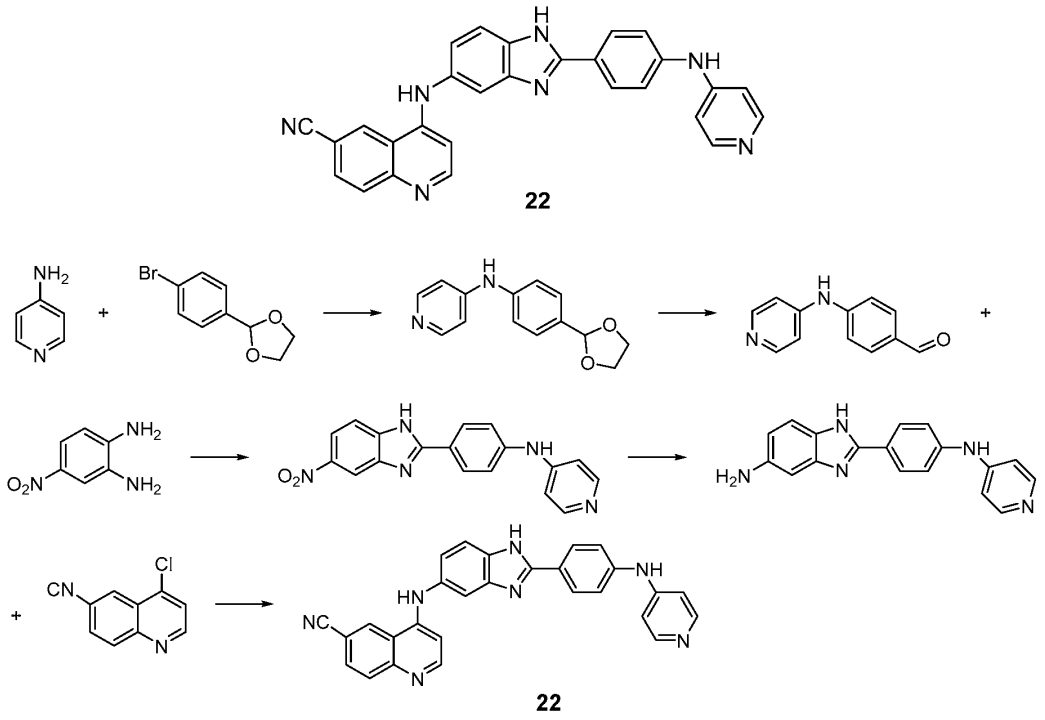
[0386] Compound 19-6 was prepared in an analogous fashion to the procedure described in Example 19.

[0387] Step a: To a mixture of Compound 19-6 (50 mg, 0.164 mmol) in 1,4-dioxane (2 mL) was added Compound 21-1 (45 mg, 0.164 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), and Cs_2CO_3 (102 mg, 0.32 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated give Compound 20-2, which was used directly in the next step without further purification.

[0388] Step b: A solution of Compound 21-2 in TFA (3mL) was stirred at room temperature for 1 hour. The mixture was concentrated and the crude residue was purified by prep-HPLC to give **Compound 21** (4-(2-amino-3-methylpyridin-4-ylamino)-N-(3-(pyridin-4-

ylamino)phenyl)benzamide) as a white solid (12 mg, 18.5%): $C_{24}H_{22}N_6O$; 410.47 g/mol; ESI-LCMS m/z = 411 $[M+H]^+$; RT = 1.42 min, >95.00% (214 nm).

Example 22: Compound 22 (4-((2-(4-(pyridin-4-ylamino)phenyl)-1H-benzo[d]imidazol-5-yl)amino)quinoline-6-carbonitrile)



Scheme 17

[0389] **Compound 22** was prepared by the method shown in Scheme 17. **Compound 22** (4-((2-(4-(pyridin-4-ylamino)phenyl)-1H-benzo[d]imidazol- 5-yl)amino)quinoline-6-carbonitrile) was prepared as shown in Scheme 32: $C_{28}H_{19}N_7$; 453.51 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 454 $[M+H]^+$; LCMS RT = 1.35 min, >95.00% (214 nm).

Example 23. Biological Assays

Foxp3 induction assay

[0390] Sorted or enriched (Miltenyi magnetic separation) CD4 conventional T cells (Tconvs -CD4+/CD25) from C57/Bl6 mice were used for the induction of iTregs. A 10μg/mL plate-bound anti-CD3 antibody (50ul per well for 96-well plate), 2.5μg/mL of soluble anti-CD28 antibody, 100 IU/mL of IL2 and 5ng/mL of TGF-β in absence or presence of different concentrations of drug (usually titrating from 0.01uM to 10uM) were used. As negative control for induction, samples without TGF-β were used.

[0391] After 3 days of culture in presence of stimulation, TGF-β and drug, cells were stained with fixable live/dead cell stain (Life Technologies, NY) for gating and exclusion of toxic doses. The mouse Foxp3 buffer kit was used to fix and permeabilize cells according to the manufacturer's instructions (BD Bioscience, San Jose, CA). The anti-CD4 antibody and anti-Foxp3 antibody were used to stain the cells. After staining, cells were acquired using flow cytometer.

Jurkat-FoxP3 Reporter assay (according to BPS Bioscience, Cat # 60628)

[0392] **Cells Culture Process:** Prepare a 50 ml conical tube and a T-25 culture flask with 5 ml of pre-warmed Thaw Medium 2 (no G418). Quickly thaw cells in a 37°C water bath with constant and slow agitation. Immediately transfer the entire contents to the conical tube with Thaw Medium 2 (no G418) and centrifuge the cells at 200 x g for 3 minutes. Re-suspend the cells in 6 ml of pre-warmed Thaw Medium 2 (no G418) and transfer the entire content to the T25 culture flask containing Thaw Medium 2 (no G418). Incubate the cells in a humidified 37°C incubator with 5% CO2. Forty-eight hours after incubation, centrifuge cells at 250 x g for 5 minutes and re-suspend to fresh Thaw Medium 2 (no G418). Continue to monitor growth for 2-3 days and change medium to remove dead debris. Switch to Growth Medium 2B (containing G418) after multiple cell colonies (in clumps) start to appear (indicative of healthy cell division)

After Assay Protocol: (CD3/CD28)

[0393] 1. In a white opaque 384-well plate, Jurkat-FoxP3-luciferase reporter cells at ~2.5 x103 cells/well (10 µL per well) in Assay Medium (RPMI 1640 medium (Thermo Fisher, Cat. #A1049101) supplemented with 1% Penicillin/Streptomycin) were cultured in absence and presence of (ratio: 1:5) of Human T-Activator CD3/CD28 Dynabead (Thermo Fisher, Cat. No. 11161D).

[0394] 2. Make drugs serial dilution range 1-60,000nM and add 10 µL of drugs, which will yield a range of 1-30,000nM, and mix with gentle sacking. In some experiments, the range is from 10-20,000 nM. Cells were cultured in presence and absence of drugs for 12 hours at 37°C with 5% CO_2.

[0395] 3. Add ONE-Step™ Luciferase Assay System (BPS Bioscience, Cat. #60690) to each well, according to the protocol. Add equal volume of luciferase assay working solution (Component A + Component B) to the culture medium in each well. As an example, a 384

well plate with 20 µl of culture medium requires 20 µl of luciferase assay working solution per well.

[0396] 4. Gently rock the plates for ≥15 minutes at room temperature. Measure firefly luminescence using a luminometer.

Phospho-Akt Isoform Specificity Assay

[0397] Human CD4+/CD45RA+/CD25-naïve T cells were plated under induction conditions (IL-2/ anti-CD3/anti-CD28 + TGFβ) in the absence or presence of compounds for 72 hours. To determine the compounds' specificity for each phospho-AKT isoform, phospho-AKT cellular HTRF kits (Cisbio catalogue numbers 63ADK078PEG (pAKT1), 63ADK080PEG (p-AKT2), and 63ADK082PEG (pAKT3)) were used according to manufacturer specifications. Briefly, after removal of the supernatant, cells were lysed, and total protein concentration measured and normalized for all samples. The cell lysates were transferred into 384-well plates and Eu Cryptate antibody + d2 antibody mixture was added. This process was the same for each isoform but utilized the corresponding isoform antibodies from each respective kit. Positive and negative controls (supplied with the kit) were incorporated into each experiment. The plates were incubated overnight. Data acquisition was performed on the Varioskan Lux reader utilizing the settings for the TRF fluorescence protocol. Data was presented as percent change over DMSO-treated controls. Each test condition was run in duplicate, and the assay was performed at least twice.

IL-10 ELISA Assay

[0398] Human CD4+/CD25+ natural Treg cells were plated under stimulating conditions (IL-2/ anti-CD3/anti-CD28) in the absence or presence of compounds. 24 and 48 hours after incubation, the supernatants were collected, and IL-10 concentrations were determined using the Human IL-10 ELISA kit according to manufacturer specifications (Invitrogen BMS215-2). Briefly, supernatants were added to pre-coated 96-well ELISA plates and incubated, followed by addition of biotin-conjugated detection antibodies and Streptavidin-HRP. After incubation, substrate was added, and the reaction was stopped by addition of acid. Absorbance was measured at 450 nm using the Varioskan Lux reader. Known concentrations of IL-10 (provided in the kit) were used to generate the calibration curves and calculate the concentration of IL-10 in supernatants. Data was presented as percent change over untreated stimulated cell controls. Each test condition was run in triplicate, and the assay was performed at least twice.

FoxP3 ELISA Assay

[0399] Human CD4+/CD45RA+/CD25-naïve T cells were plated under induction conditions (IL-2/ anti-CD3/anti-CD28 + TGFβ) in absence or presence of compounds for 72 hours. After incubation, cells were lysed and FoxP3 protein was measured in lysates using the Human FoxP3 ELISA kit according to manufacturer specifications (LSBio, LS-F5047). Briefly, lysates were added to pre-coated 96-well ELISA plates and incubated, followed by biotin-conjugated detection antibodies and Streptavidin-HRP. After incubation, substrate was added, and the reaction was stopped by addition of acid. Absorbance was measured at 450 nm using the Varioskan Lux reader. Known concentrations of FoxP3 (provided in the kit) were used to generate the calibration curves and calculate the concentration of FoxP3 in lysates. Data was presented as percent change over cells induced in the absence of compounds. Each test condition was run in duplicate, and the assay was performed at least twice.

iTreg Induction Assay

[0400] Sorted human CD4 T cells were used for the induction of iTregs. Human T cell activation beads (Gibco Dynabeads CD3/CD28), 100 IU/mL of IL2 and 5 ng/mL of TGF-β, in absence or presence of different concentrations of drug, were used. As negative control for induction, samples without TGF-β were used. After 3 days of culture in the presence of stimulation with TGF-β and drug, cells were stained with fixable live/dead cell stain (Life Technologies) for gating and exclusion of toxic doses, fixed and permeabilized using the Foxp3 buffer kit according to the manufacturer specifications (BD Bioscience), and stained with anti-Foxp3 antibody. After staining, cells were acquired using flow cytometer. Each test condition was run in duplicate, and the assay was performed at least twice.

[0401] Data illustrated by Figure 1 was obtained at least partially using this assay protocol. Figure 1 shows evaluation of iTreg induction (FoxP3) from human CD4 T cells treated with Compound 22 in the presence of anti-CD3/anti-CD28/IL-2/TGFβ.

[0402] The Akt3 inhibition and activation activities of selected compounds disclosed herein are shown in Tables 1 and 2, respectively.

Table 1. Akt3 inhibition activity of selected compound.

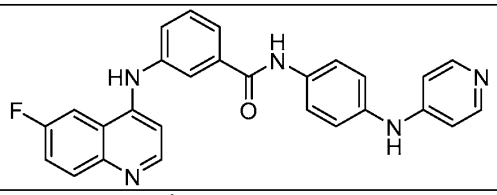
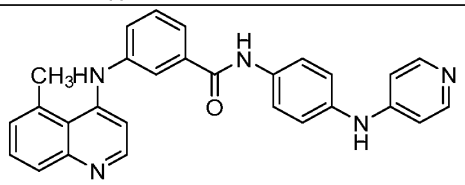
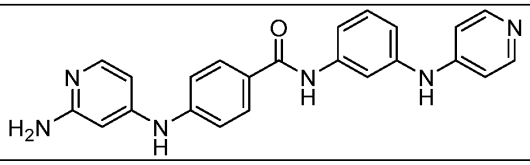
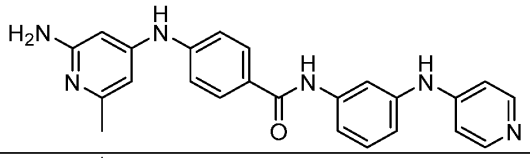
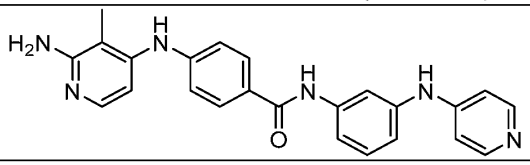
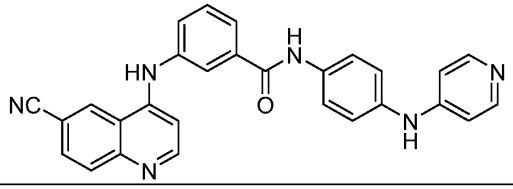
Compound No.	Structure	IC_{50} (μM)
3		< 2
18		< 2
19		< 5
20		< 5
21		< 2

Table 2. Akt3 activation activity of selected compound.

Compound No.	Structure	EC_{50} (μM)
2		< 5