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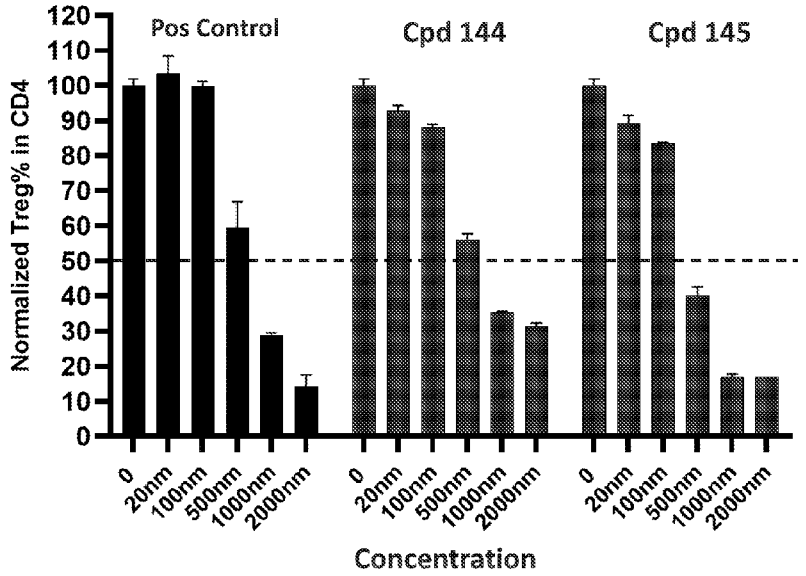


Figure 16

(57) Abstract: Compounds of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc, or, are described, where the various substituents are defined herein. The compounds can modulate a property or effect of Akt3 in vitro or in vivo, and can also be used, individually or in combination with other agents, in the prevention or treatment of a variety of conditions. Methods for synthesizing the compounds are described. Pharmaceutical compositions and methods of using these compounds or compositions, individually or in combination with other agents or compositions, in the prevention or treatment of a variety of conditions are also described.

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[Continued on next page]

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AKT3 MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit and priority of U.S. Provisional Application No. 63/276,338, filed on November 5, 2021, the content of which is incorporated herein by reference in its entirety. This application is related to International Patent Application No. PCT/US2021/031297, filed on May 7, 2021, International Patent Application No. PCT/US2021/031325, filed on May 7, 2021, International Patent Application No. PCT/US2021/031381, filed on May 7, 2021, and International Patent Application No. PCT/US2021/031386, filed on May 7, 2021, the contents of all 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.

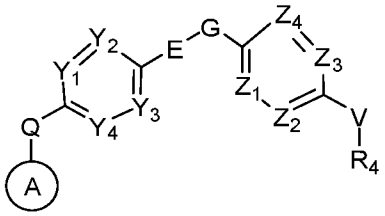
[0005] Neurodegenerative diseases are debilitating conditions that are characterized by the progressive degeneration and death of nerve cells, also called neurons. Neurons are the building blocks of the nervous system and do not usually self-replenish following damage or death. The loss or dysfunction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

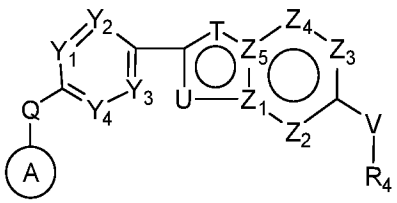
SUMMARY OF THE INVENTION

[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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc (



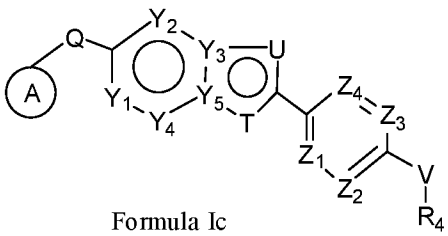
Formula Ia

,



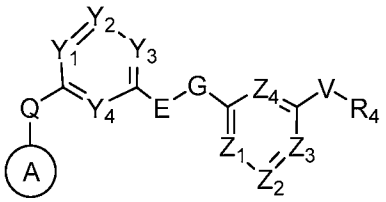
Formula Ib

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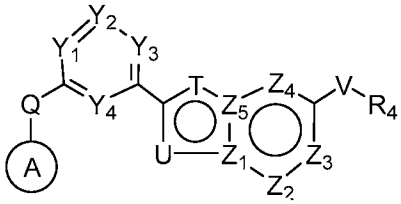
Formula Ic

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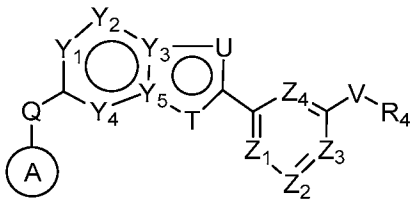
Formula IIa

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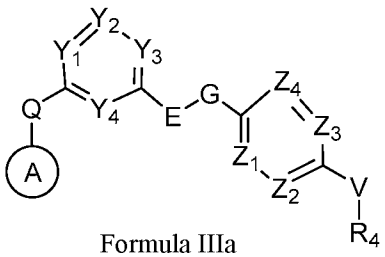
Formula IIb

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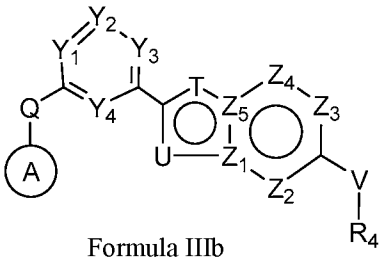
Formula IIc

;



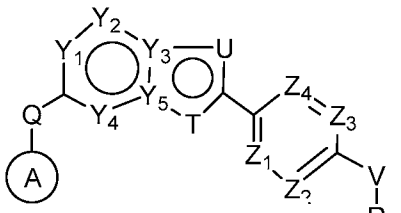
Formula IIIa

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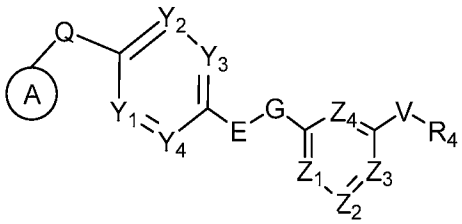
Formula IIIb

;



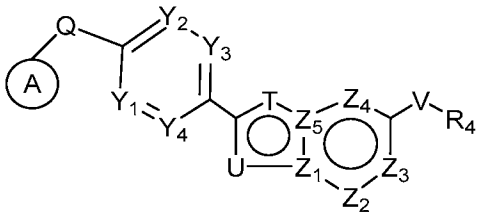
Formula IIIc

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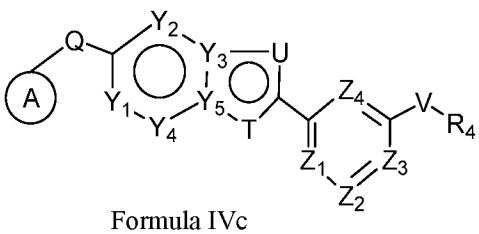
Formula IVa

;



Formula IVb

; or

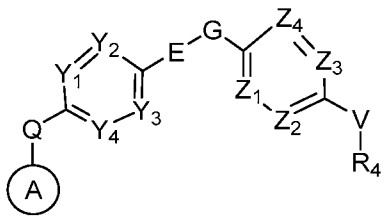


Formula IVc

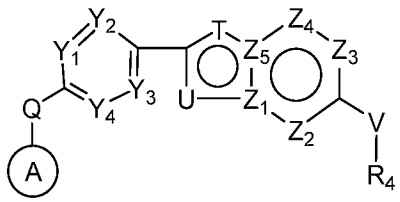
), or a salt thereof, is described, where the various substituents are defined herein. In certain

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.

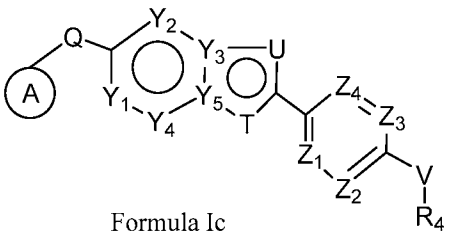
[0009] In one aspect, a compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc,



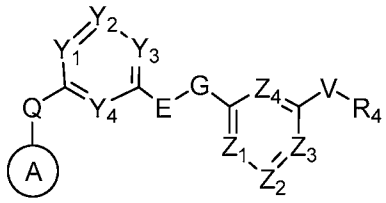
Formula Ia ;



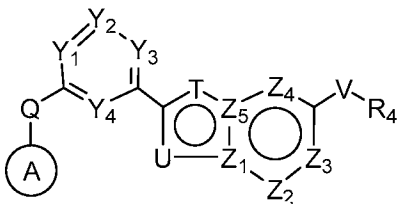
Formula Ib ;



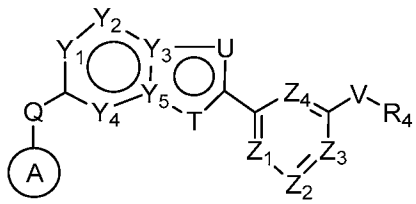
Formula Ic ;



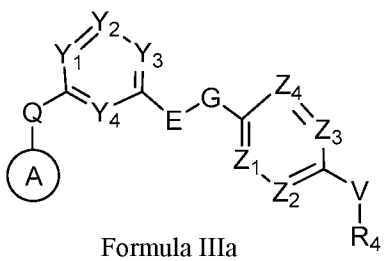
Formula IIa ;



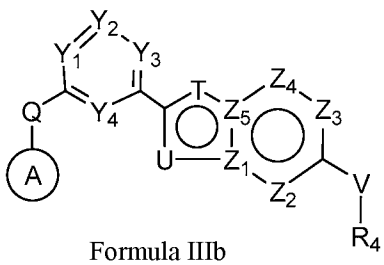
Formula IIb ;



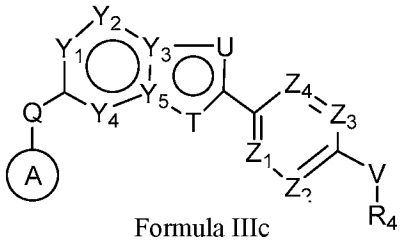
Formula IIc ;



Formula IIIa ;

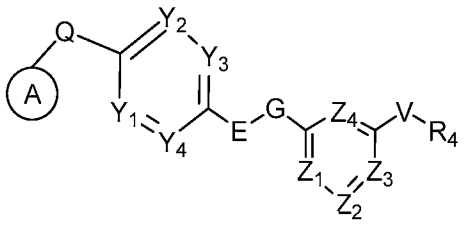


Formula IIIb ;



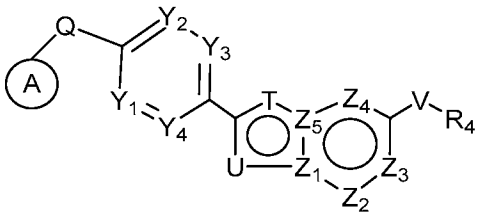
Formula IIIc

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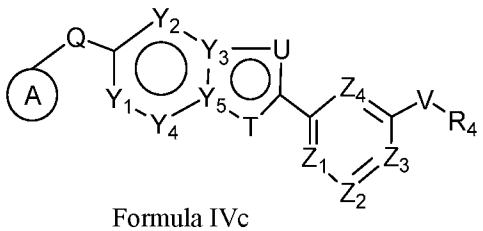
Formula IVa

;



Formula IVb

; or

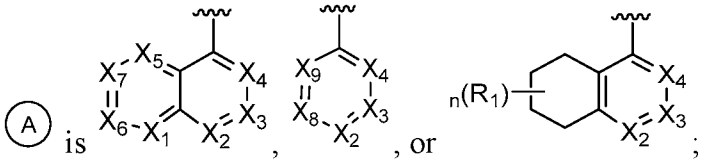


Formula IVc

;

or a pharmaceutically acceptable salt thereof;

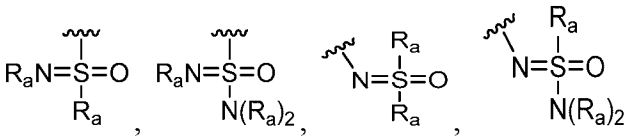
wherein:



is , , or ;

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

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, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, $(C_4\text{-}C_{14})$heterotricycloalkenyl, 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 $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, $-SO_2R_a$, or $-SO_2N(R_a)_2$;

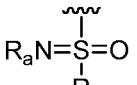
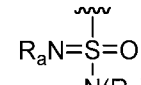
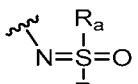
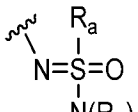
wherein the $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}$

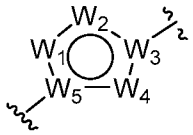
C_7)heterocycloalkenyl, (C_4-C_{10})bicycloalkenyl, (C_4-C_{10})heterobicycloalkenyl, (C_4-C_{14})tricycloalkenyl, (C_4-C_{14})heterotricycloalkenyl, aryl, and heteroaryl of R_1 are each optionally substituted by one or more (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, $-OR_a$, $-CN$, or $-N(R_a)_2$;

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, 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 ;

–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 ; wherein

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_2, R_x and Y_3, 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;

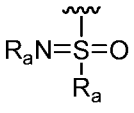
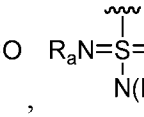
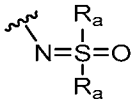
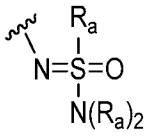
each occurrence of R_6 is independently selected from the group consisting of H, halogen, (C_1-C_6)alkyl, and (C_1-C_6)haloalkyl;

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-C_6)alkyl;

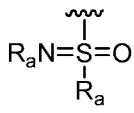
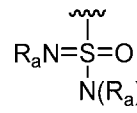
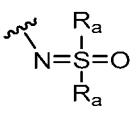
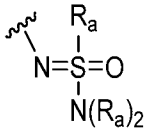
Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently N or CR_3 where valance permits;

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;

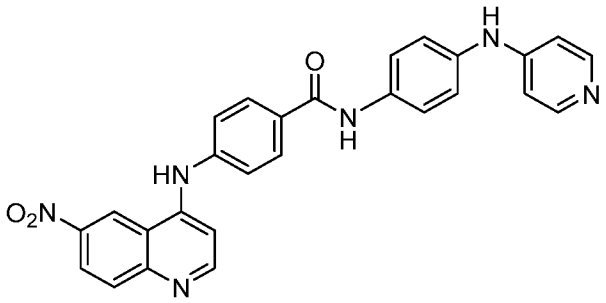
R_4 is selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_4-C_{10})heterospiroalkyl, aryl, and heteroaryl, each optionally substituted with one or more R_5;

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

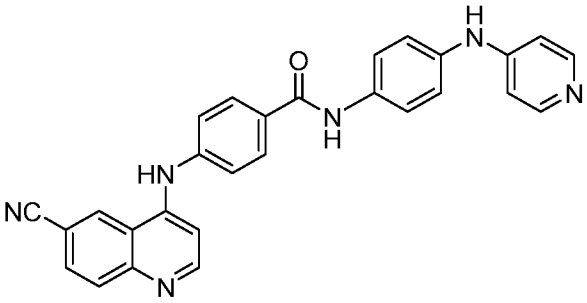
each occurrence of R_5 is independently selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (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, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$, $N(R_a)COR_a$, , , , 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;

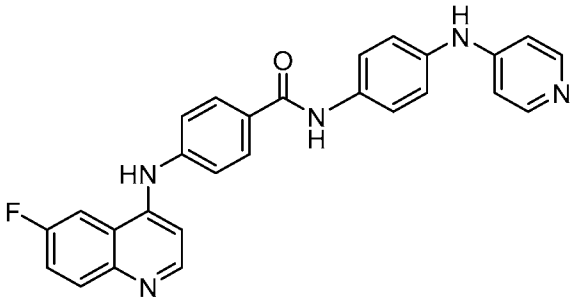
with the proviso that the compound is not



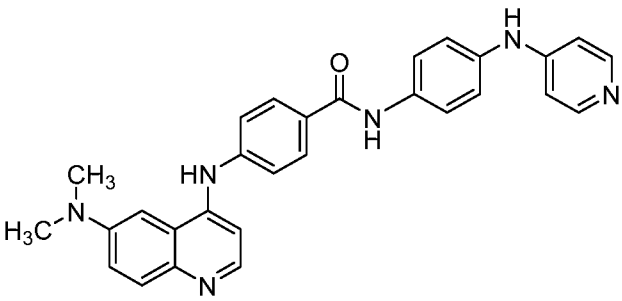
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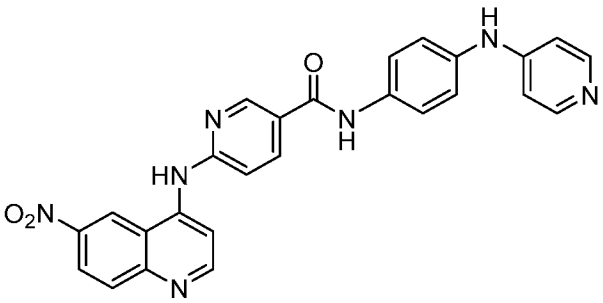
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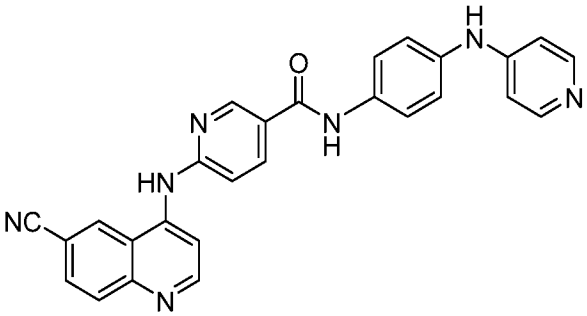
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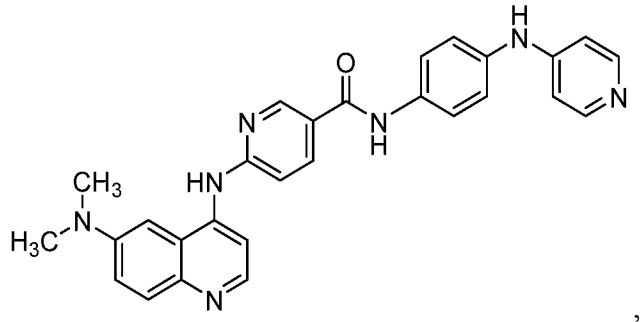
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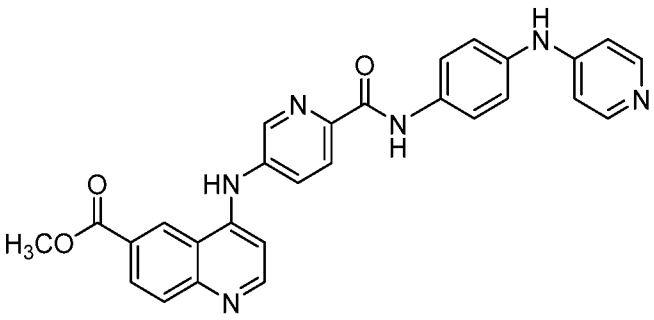
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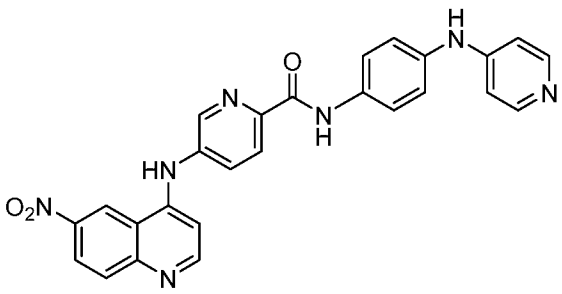
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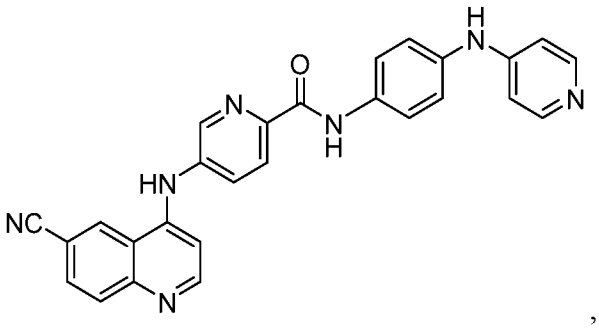
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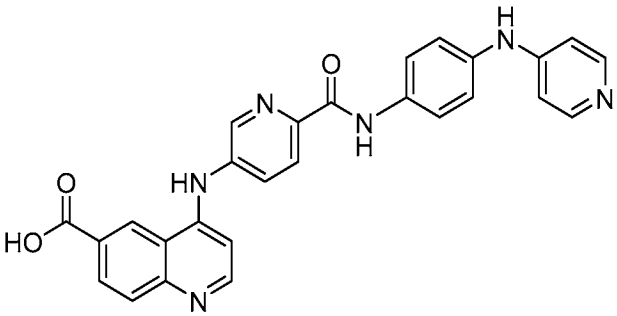
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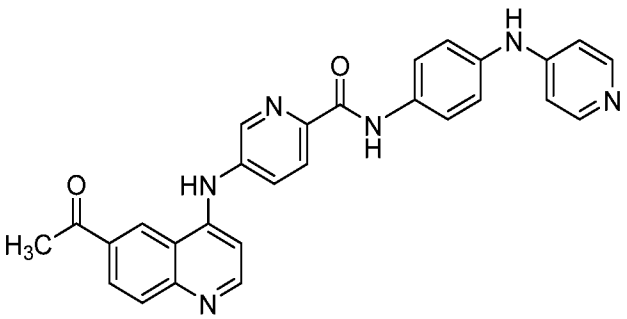
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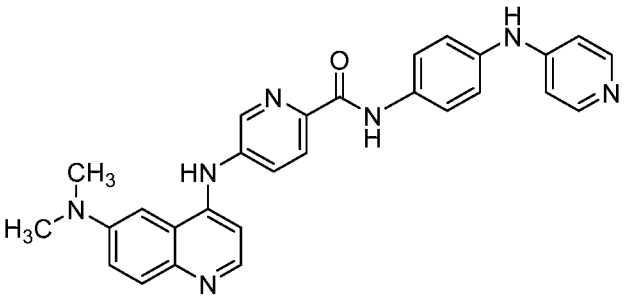
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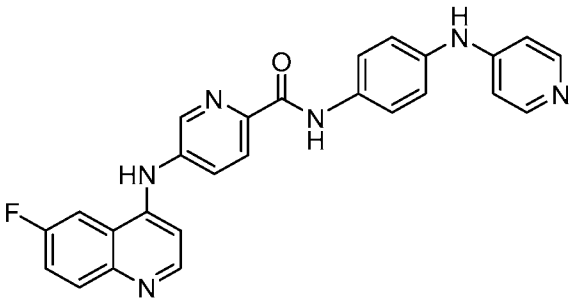
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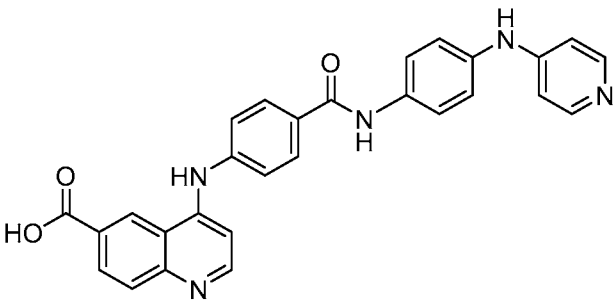
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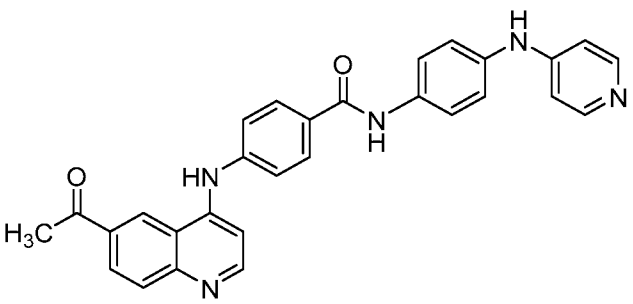
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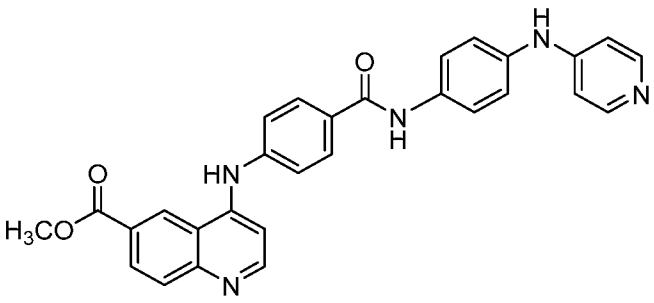
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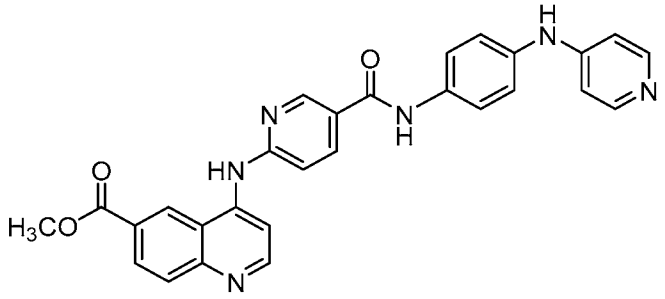
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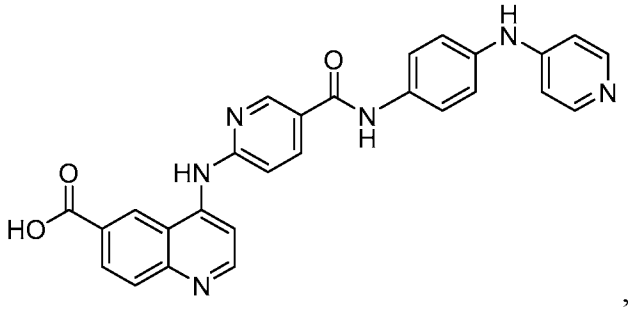
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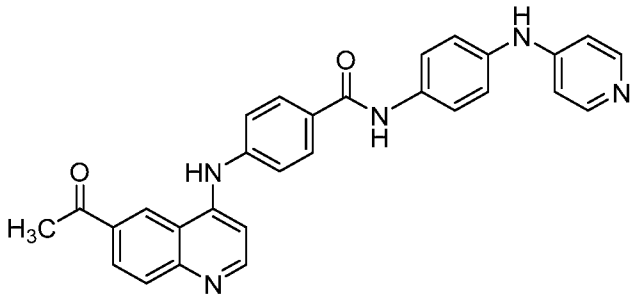
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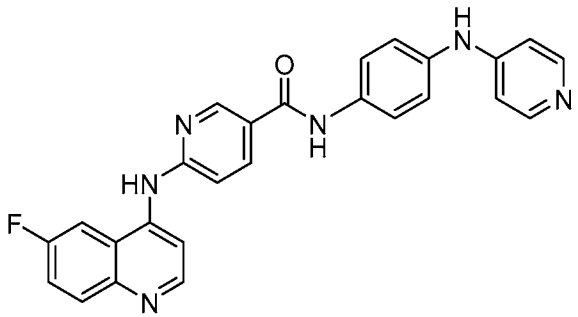
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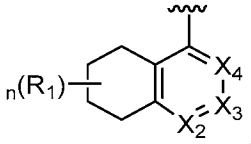
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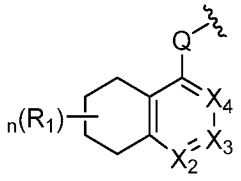
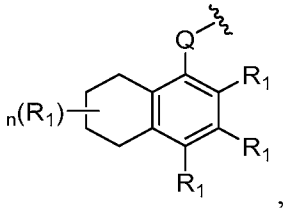
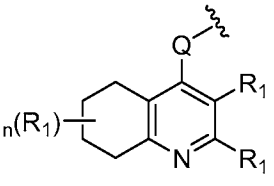
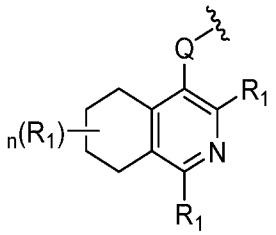
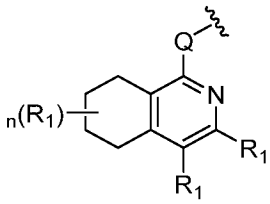
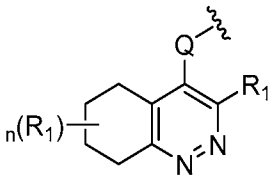
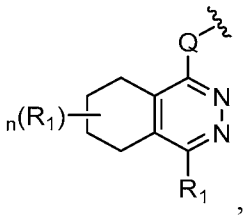
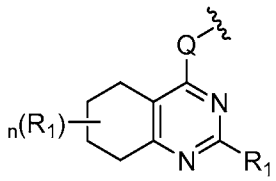


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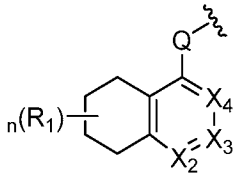
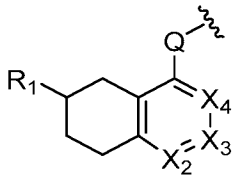
[0010] In any one of the embodiments disclosed herein, Q, T, and U are each independently O, NH, NCH_3, N(C=O)H, $N(C=O)CH_3$, $N(C=O)CH_2CH_3$, NSO_2CH_3, or $NSO_2CH_2CH_3$, where valence permits. In any one of the embodiments disclosed herein, T and U are each independently O, N, NH, NCH_3, N(C=O)H,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

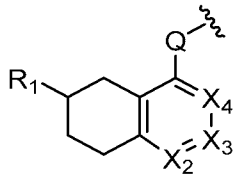
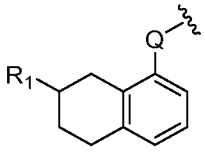
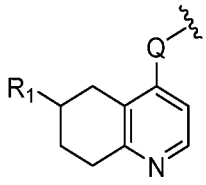
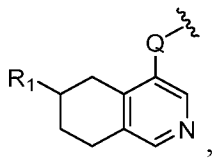
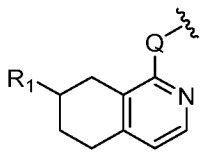
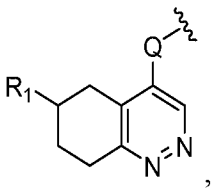
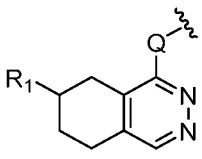
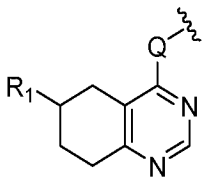
[0011] In any one of the embodiments disclosed herein, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, Y_1, Y_2, Y_3, Y_4, Y_5, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CH, C(halogen), or N.

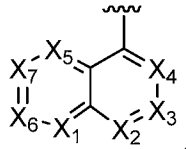
[0012] In any one of the embodiments disclosed herein, Ⓐ is .

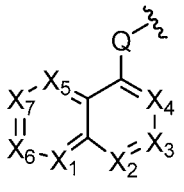
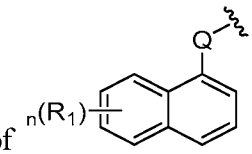
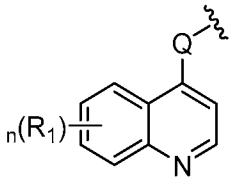
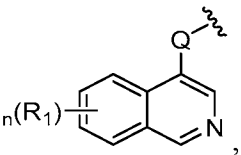
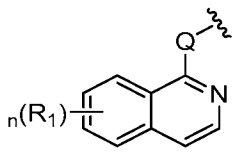
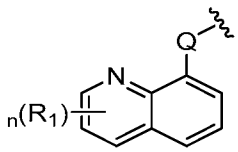
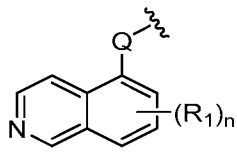
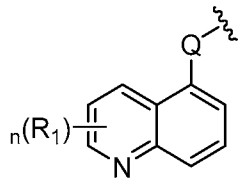
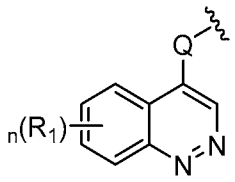
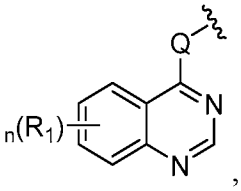
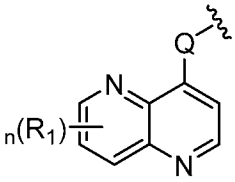
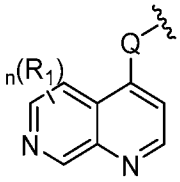
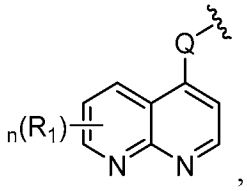
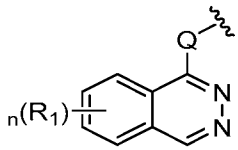
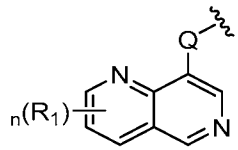
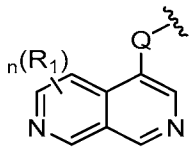
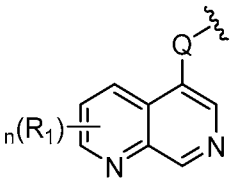
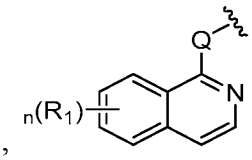
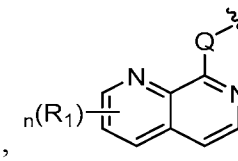
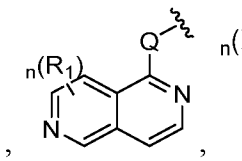
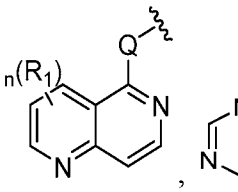
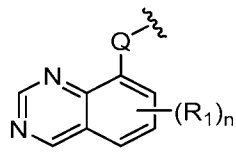
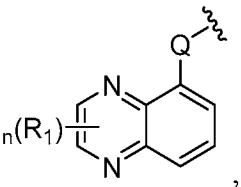
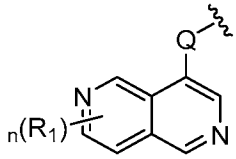
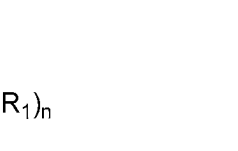
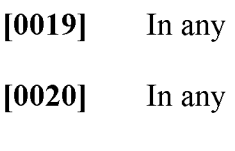
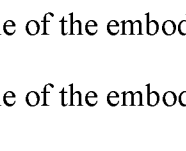
[0013] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , or .

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

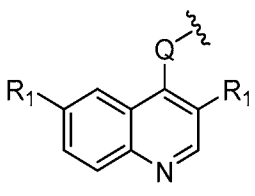
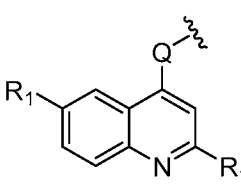
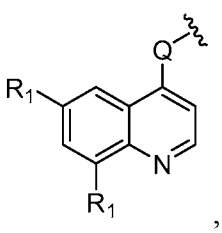
[0015] In any one of the embodiments disclosed herein, the structural moiety  has the structure of .

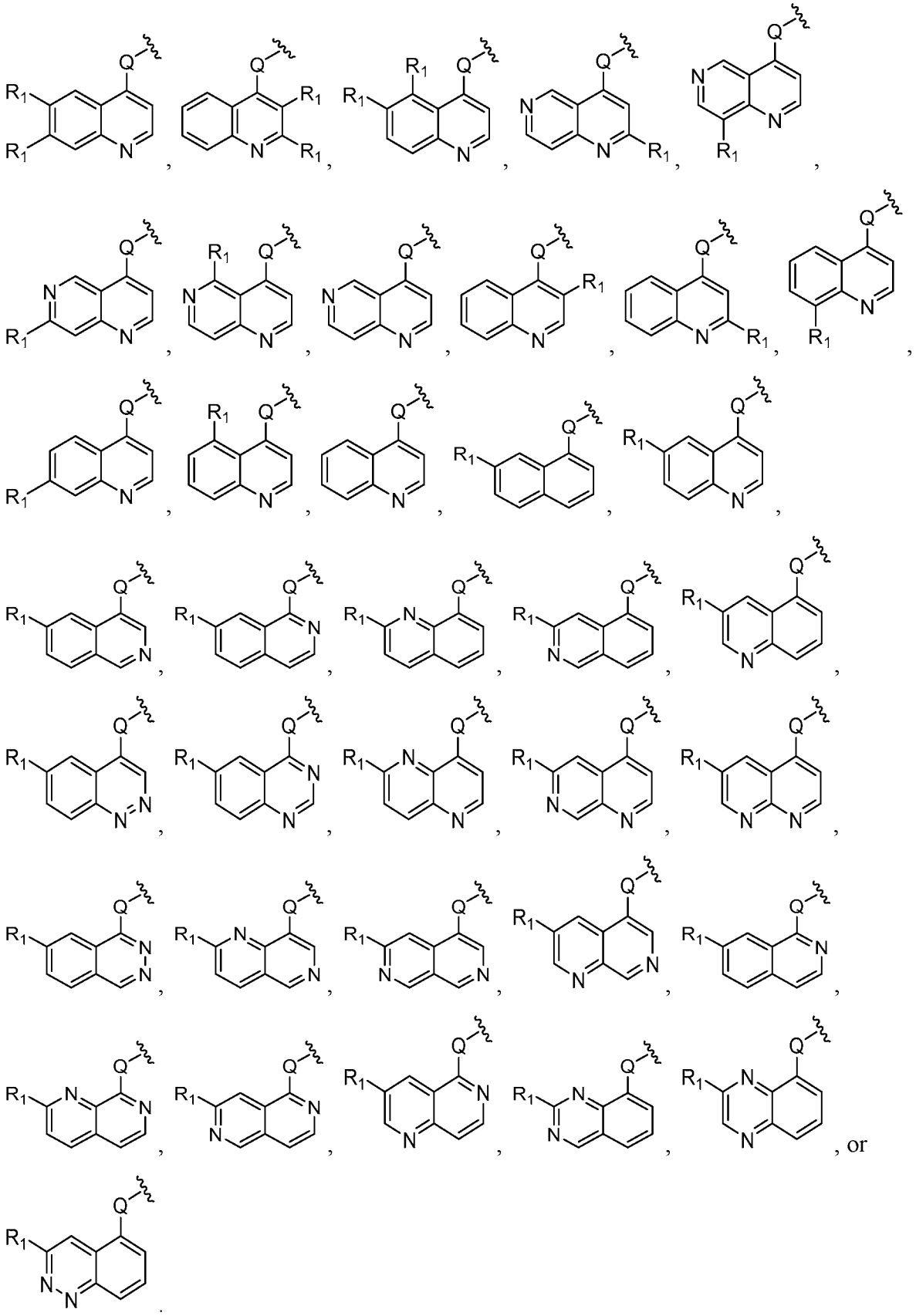
[0016] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , or .

[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 , , , , , , , , , , , , , , , , , , , , , , , , , , , , , or .

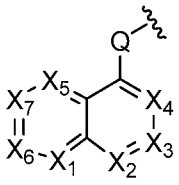
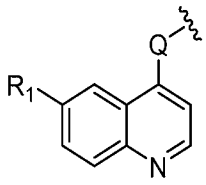
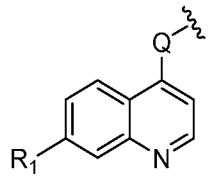
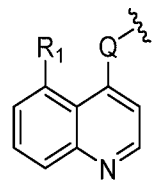
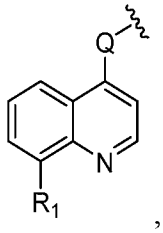
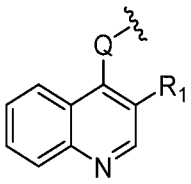
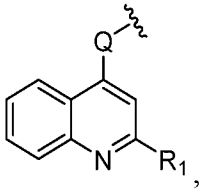
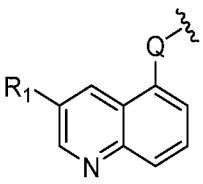
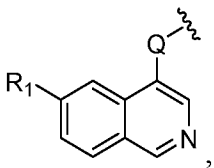
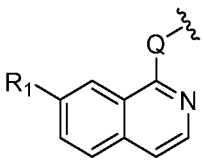
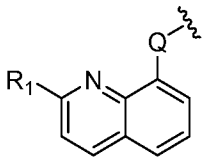
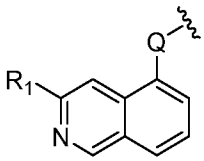
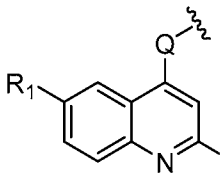
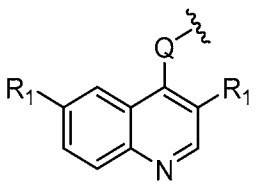
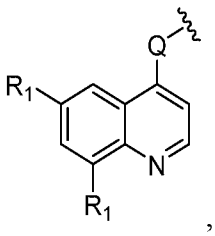
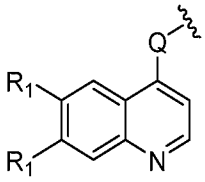
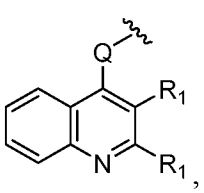
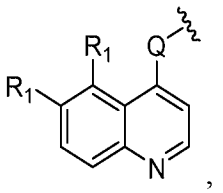
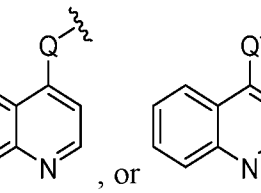
[0019] In any one of the embodiments disclosed herein, n is 0, 1, or 2.

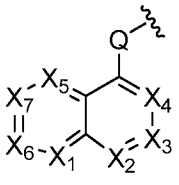
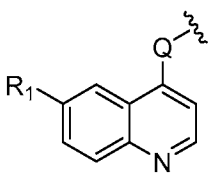
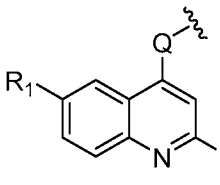
[0020] In any one of the embodiments disclosed herein, the structural moiety has the structure of , , ,

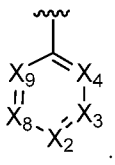


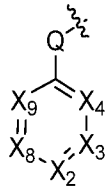
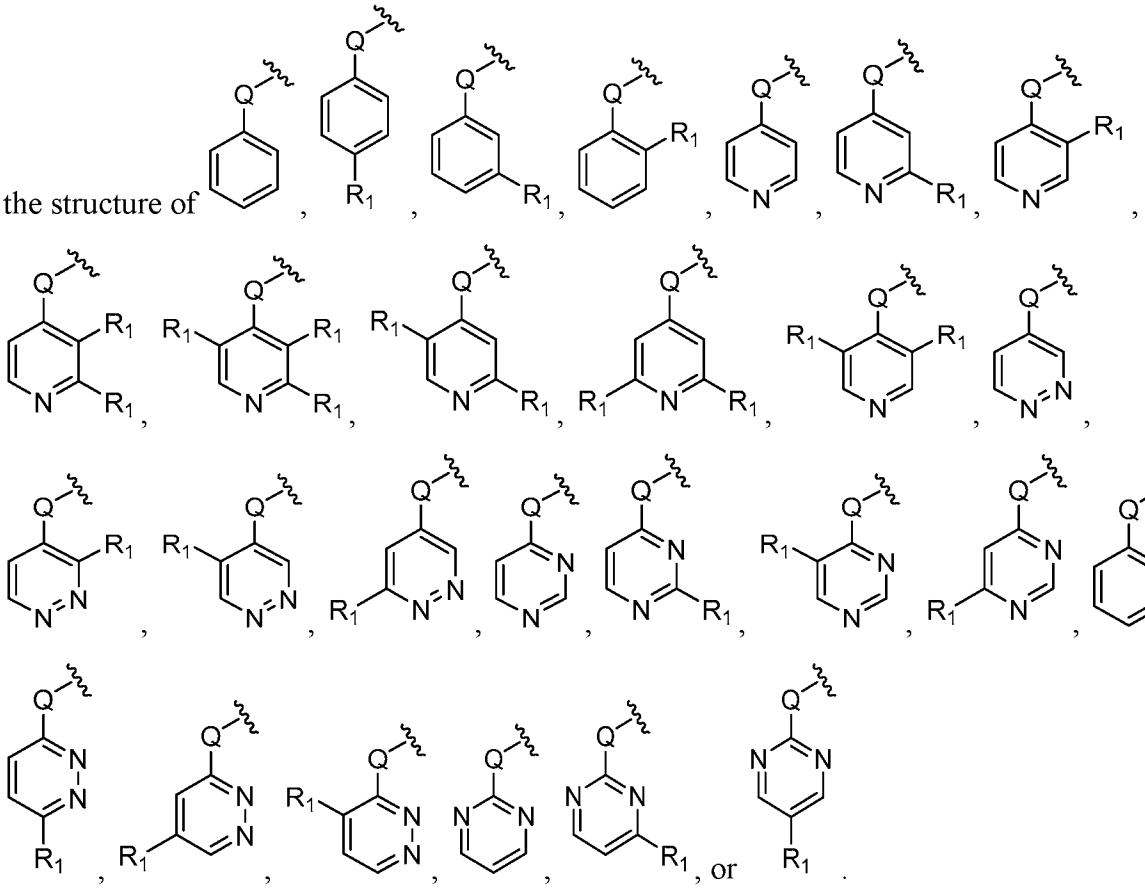
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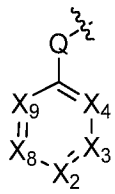
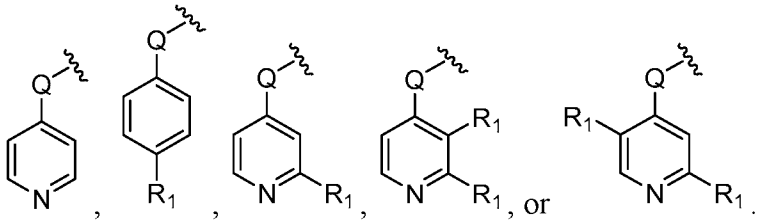
.

[0021] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , , , , , , , , , , , , , , , , , , or .

[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, (A) is .

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

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

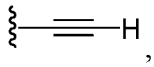
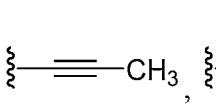
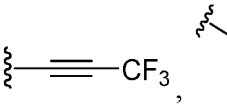
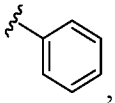
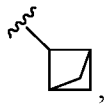
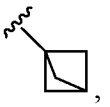
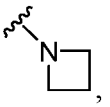
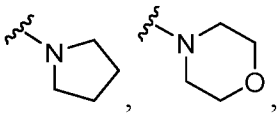
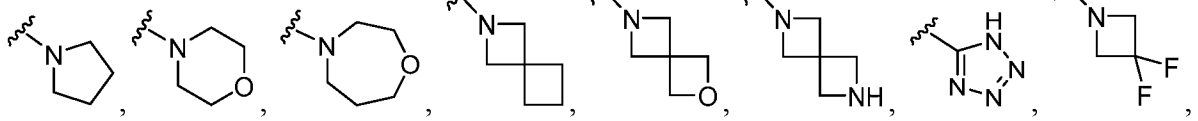
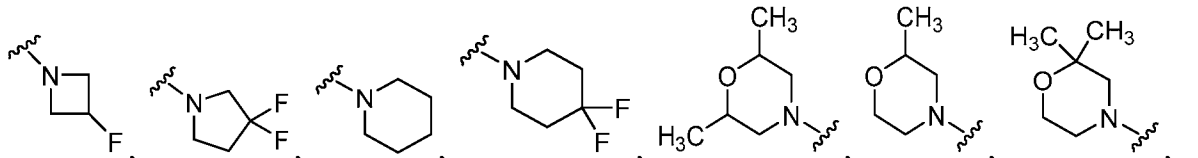
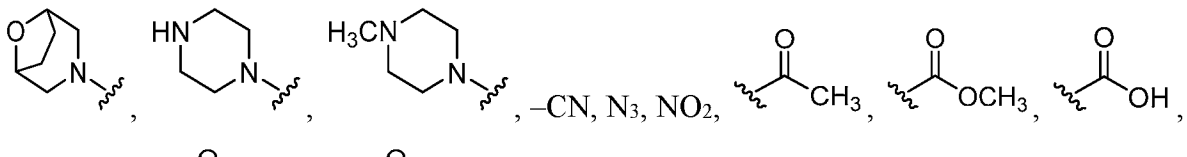
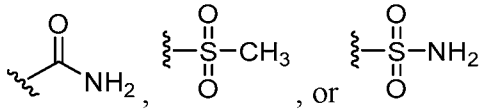
[0026] In any one of the embodiments disclosed herein, Q is O.

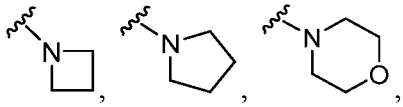
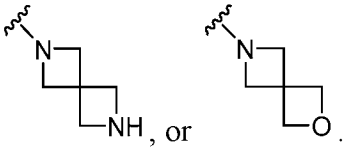
[0027] In any one of the embodiments disclosed herein, Q is NR_a, $N(C=O)R_a$, or NSO_2R_a.

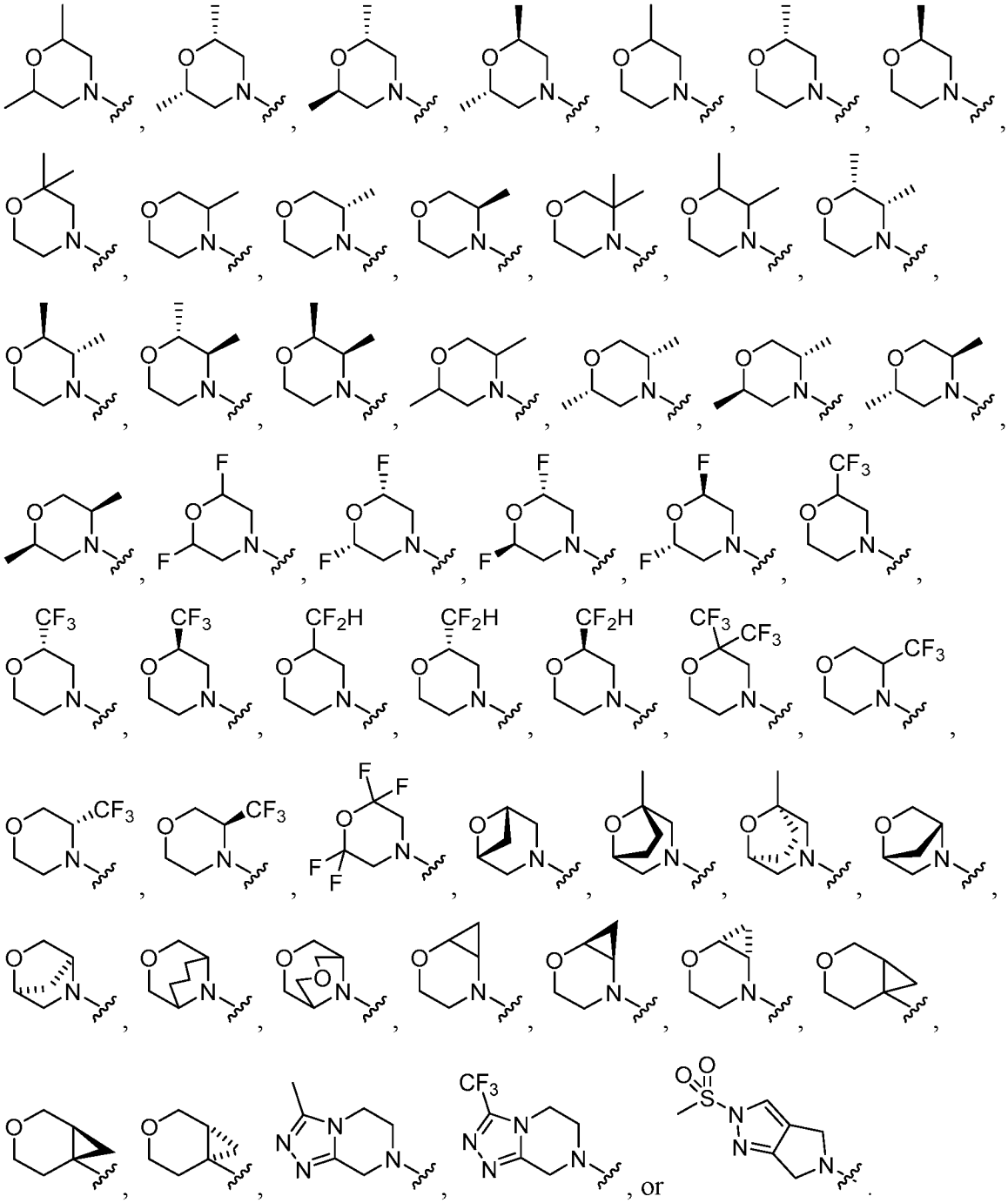
[0028] In any one of the embodiments disclosed herein, each occurrence of R_1 is independently H, D, halogen, OR_a, $N(R_a)_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, aryl, $(C_4\text{-}C_{10})$bicycloalkyl, –CN, 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.

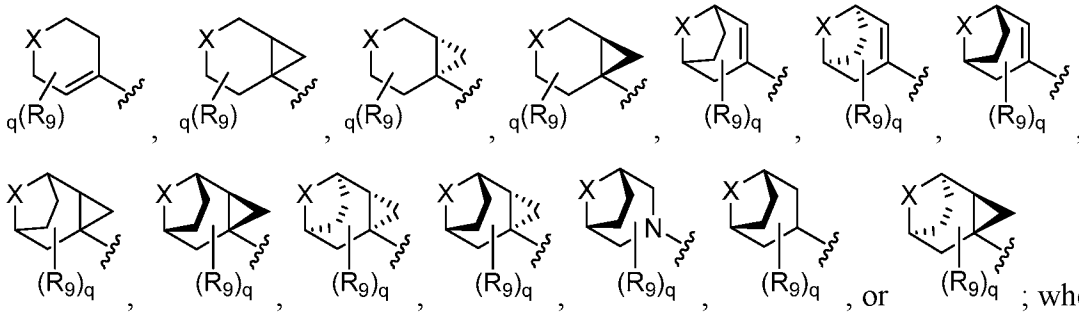
[0029] In any one of the embodiments disclosed herein, each occurrence of R_1 is independently H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $N(R_a)_2$, or –CN; wherein the $(C_3\text{-}C_7)$heterocycloalkyl 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, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$heterocyclohaloalkyl, 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, $NHCH_3$, $N(CH_3)_2$, , , , , , , , , , , , –CN, N_3, NO_2, , or .

[0032] 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 .

[0033] In any one of the embodiments disclosed herein, at least one occurrence of R_1 is , or .

[0034] In any one of the embodiments disclosed herein, at least one occurrence of R_1 is  ; wherein X is CR_{15} O, NR_{14}, or S; each occurrence of R_9 is independently H, (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; R_{14} is H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, aryl, or heteroaryl; each occurrence of R_{15} is independently H, (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; and q is 0, 1, 2, or 3.

[0035] In any one of the embodiments disclosed herein, X is O.

[0036] In any one of the embodiments disclosed herein, each occurrence of R_9 is independently H, (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, or halogen.

[0037] In any one of the embodiments disclosed herein, each occurrence of R_9 is independently H, F, Cl, Br, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$.

[0038] In any one of the embodiments disclosed herein, each occurrence of R_9 is independently H, F, Cl, Br, or CH_3.

[0039] In any one of the embodiments disclosed herein, each occurrence of R_{15} is independently H, (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, or halogen.

[0040] In any one of the embodiments disclosed herein, each occurrence of R_{15} is independently H, F, Cl, Br or CH_3.

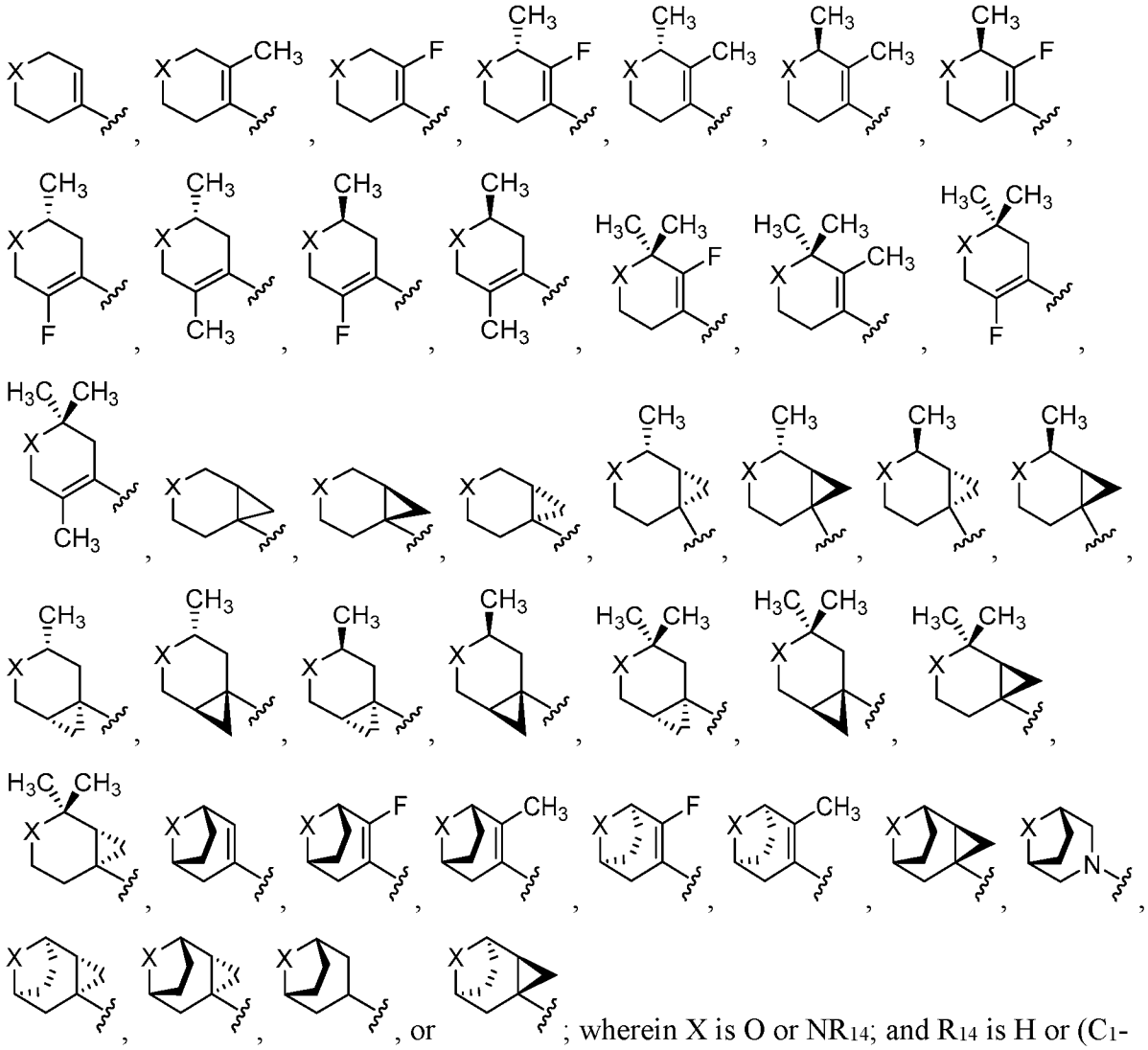
[0041] In any one of the embodiments disclosed herein, q is 0.

[0042] In any one of the embodiments disclosed herein, q is 1.

[0043] In any one of the embodiments disclosed herein, q is 2 or 3.

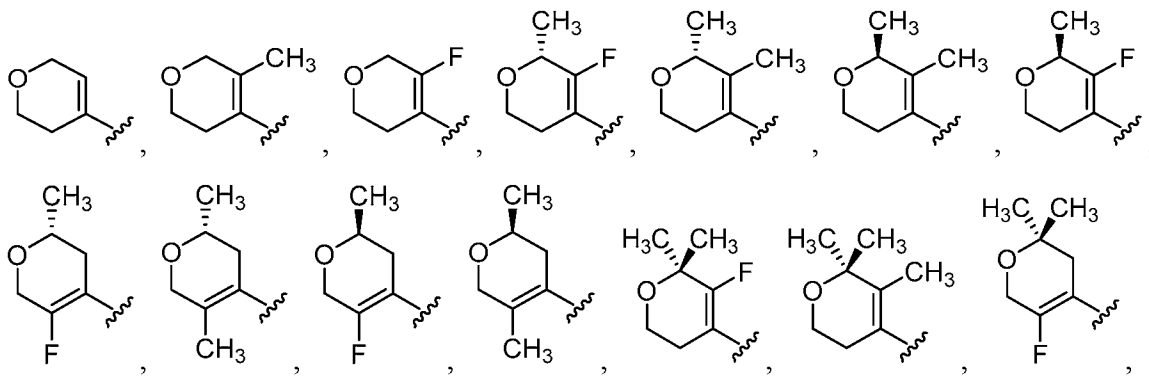
[0044] In any one of the embodiments disclosed herein, X is NR_{14} and R_{14} is H or (C_1-C_6)alkyl.

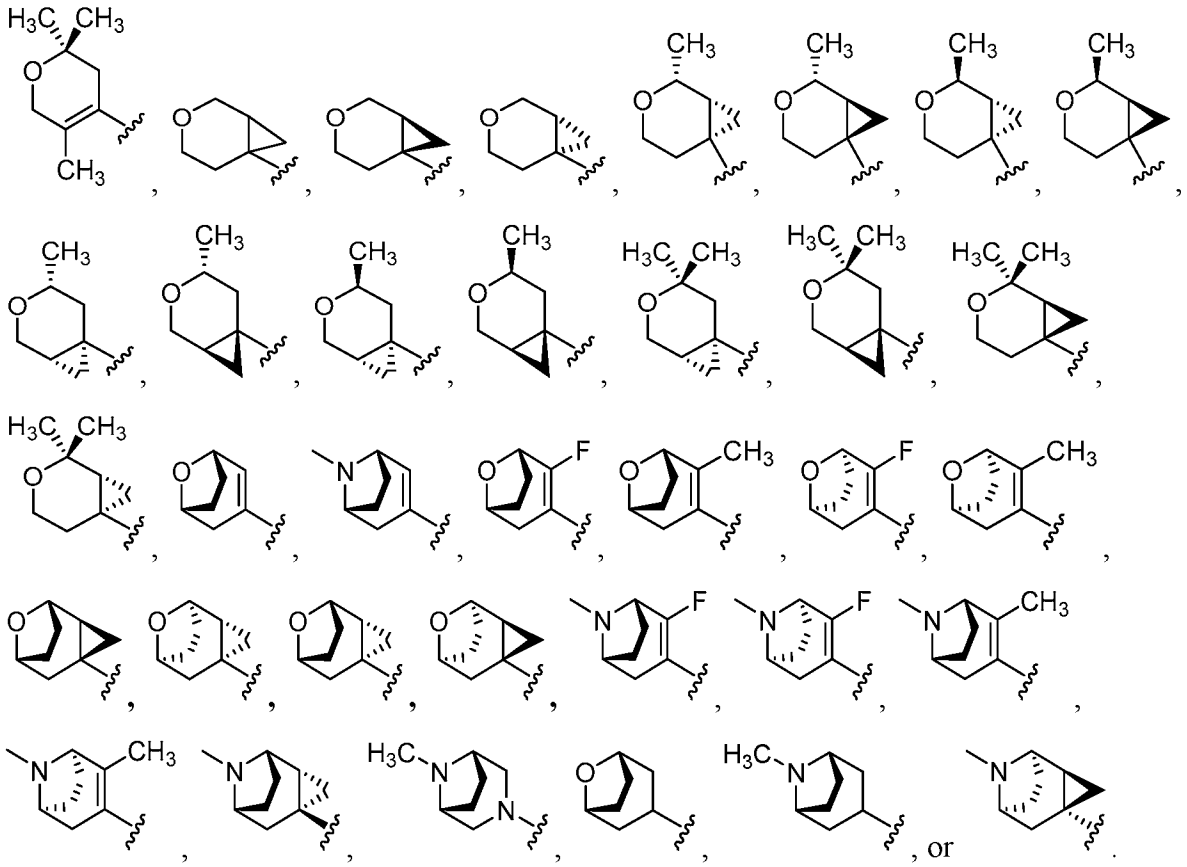
[0045] In any one of the embodiments disclosed herein, at least one occurrence of R_1 is

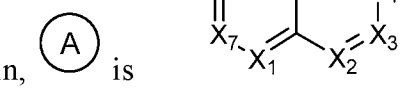


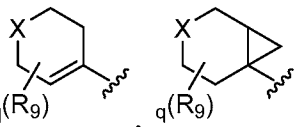
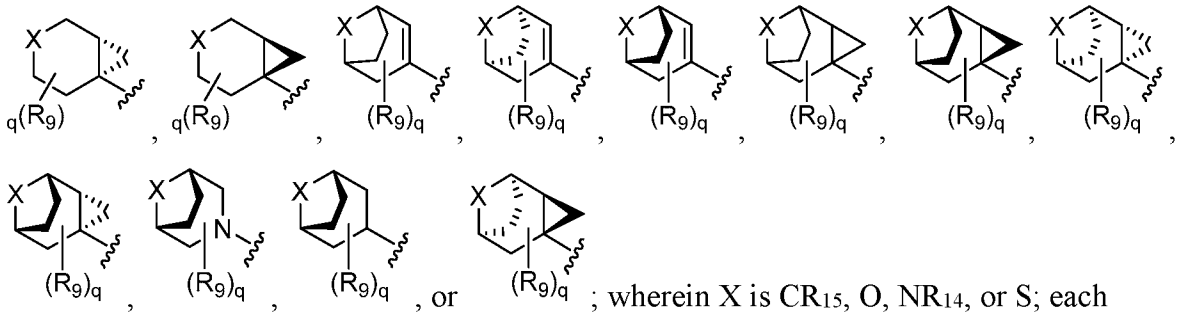
; wherein X is O or NR_{14}; and R_{14} is H or (C_1-C_6)alkyl.

[0046] In any one of the embodiments disclosed herein, at least one occurrence of R_1 is

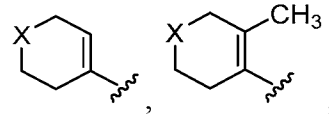
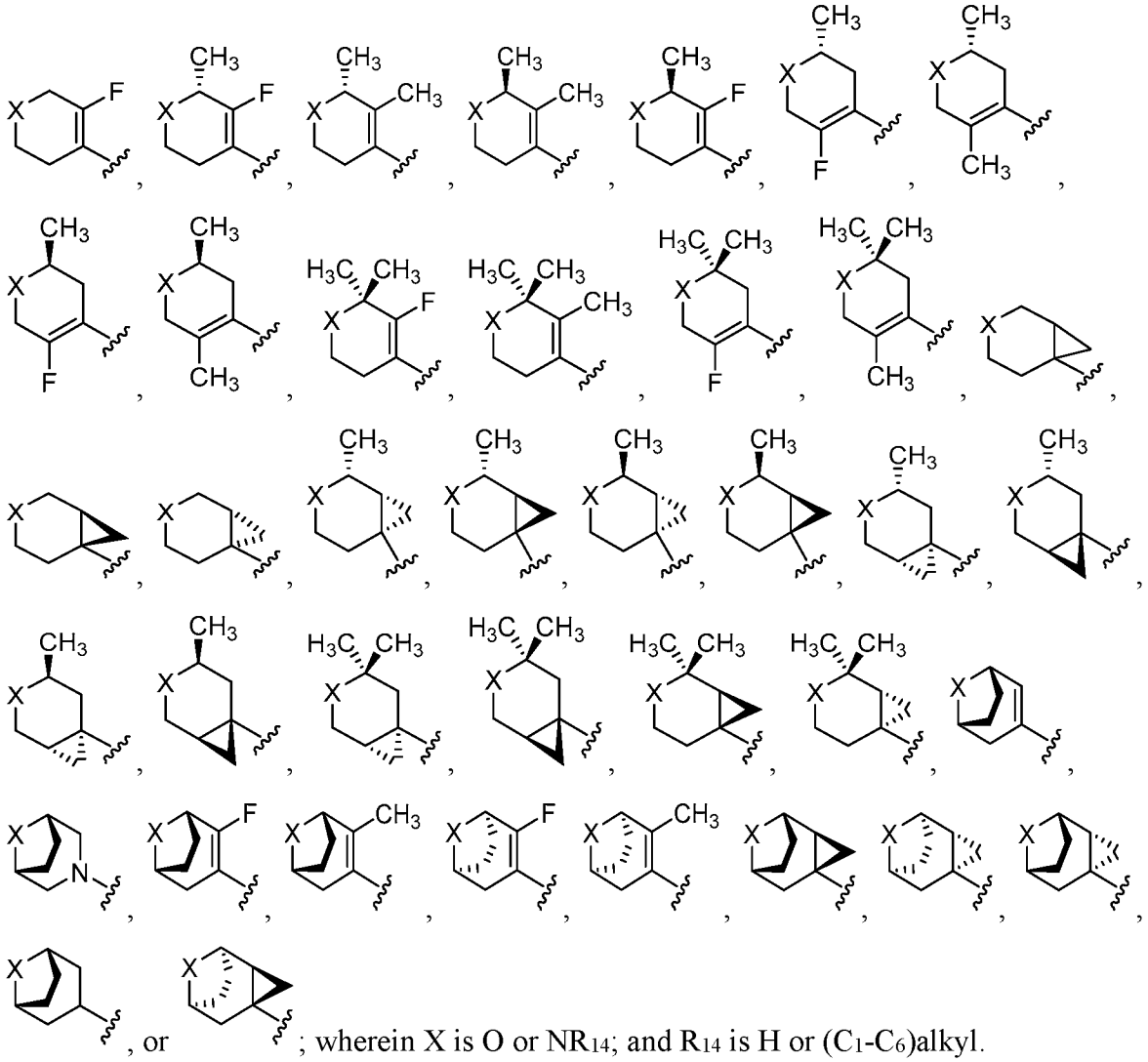


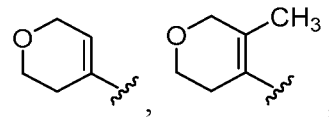
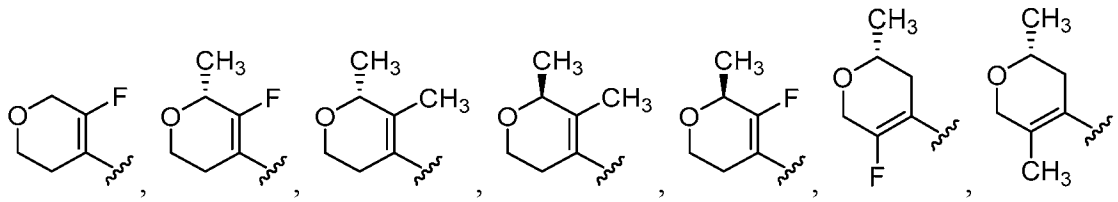


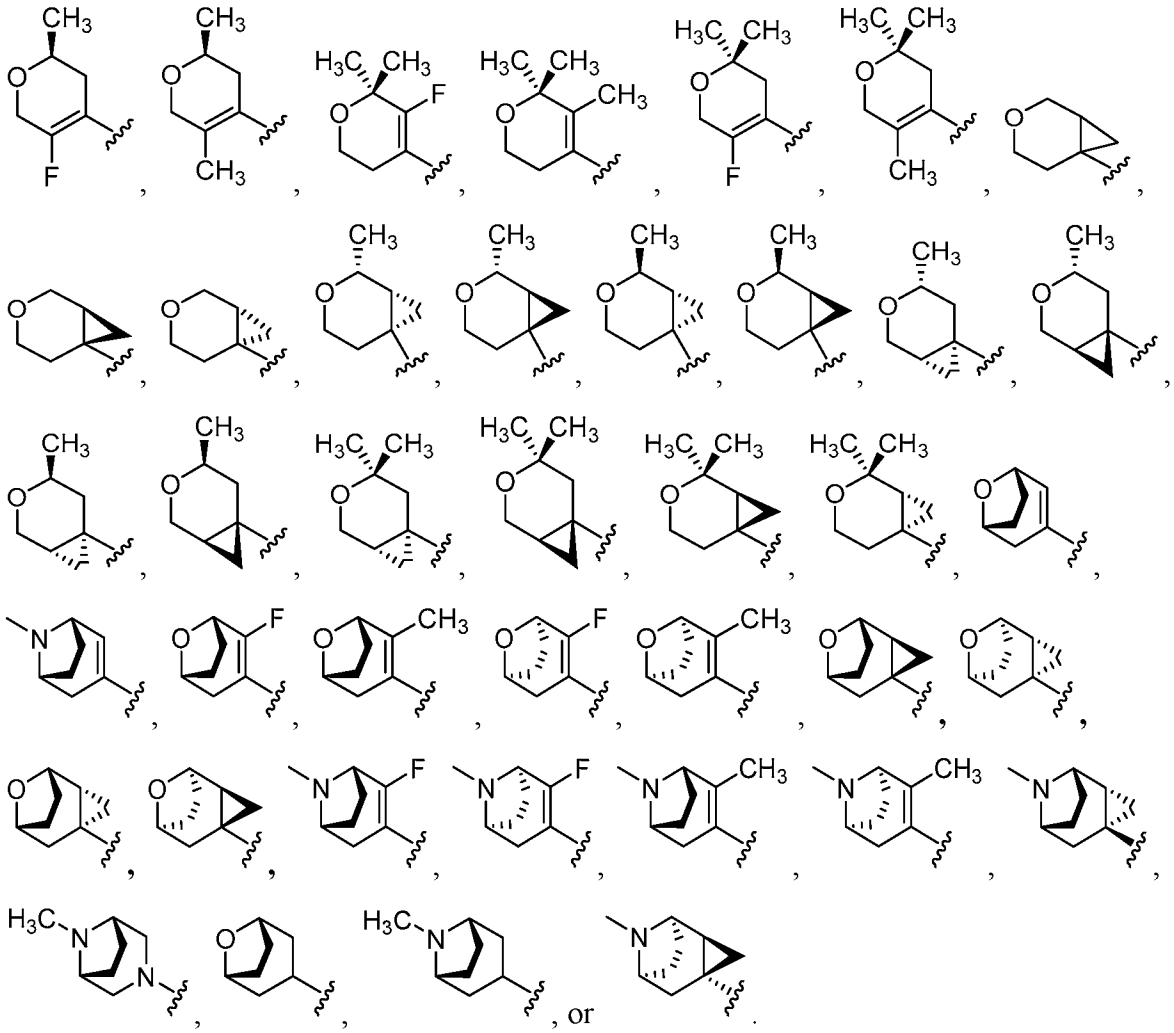
[0047] In any one of the embodiments disclosed herein,  is wherein R_{12} is (C_3-C_7)cycloalkenyl, (C_3-C_7)heterocycloalkenyl, (C_4-C_{10})bicycloalkenyl, (C_4-C_{10})heterobicycloalkenyl, (C_4-C_{14})tricycloalkenyl, or (C_4-C_{14})heterotricycloalkenyl, each of which is optionally substituted by one or more (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, $-OR_a$, $-CN$, or $-N(R_a)_2$.

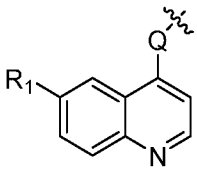
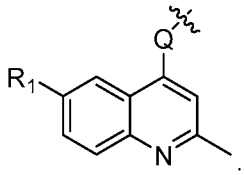
[0048] In any one of the embodiments disclosed herein, R_{12} is   ; wherein X is CR_{15}, O, NR_{14}, or S; each occurrence of R_9 is independently H, (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, $-OR_a$,

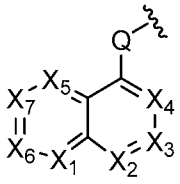
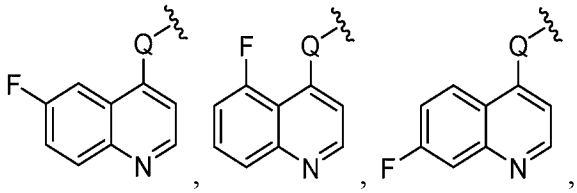
–CN, or –N(R_a)$_2$; R_{14} is H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, aryl, or heteroaryl; each occurrence of R_{15} is independently H, (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, –OR_a, –CN, or –N(R_a)$_2$; and q is 0, 1, 2, or 3.

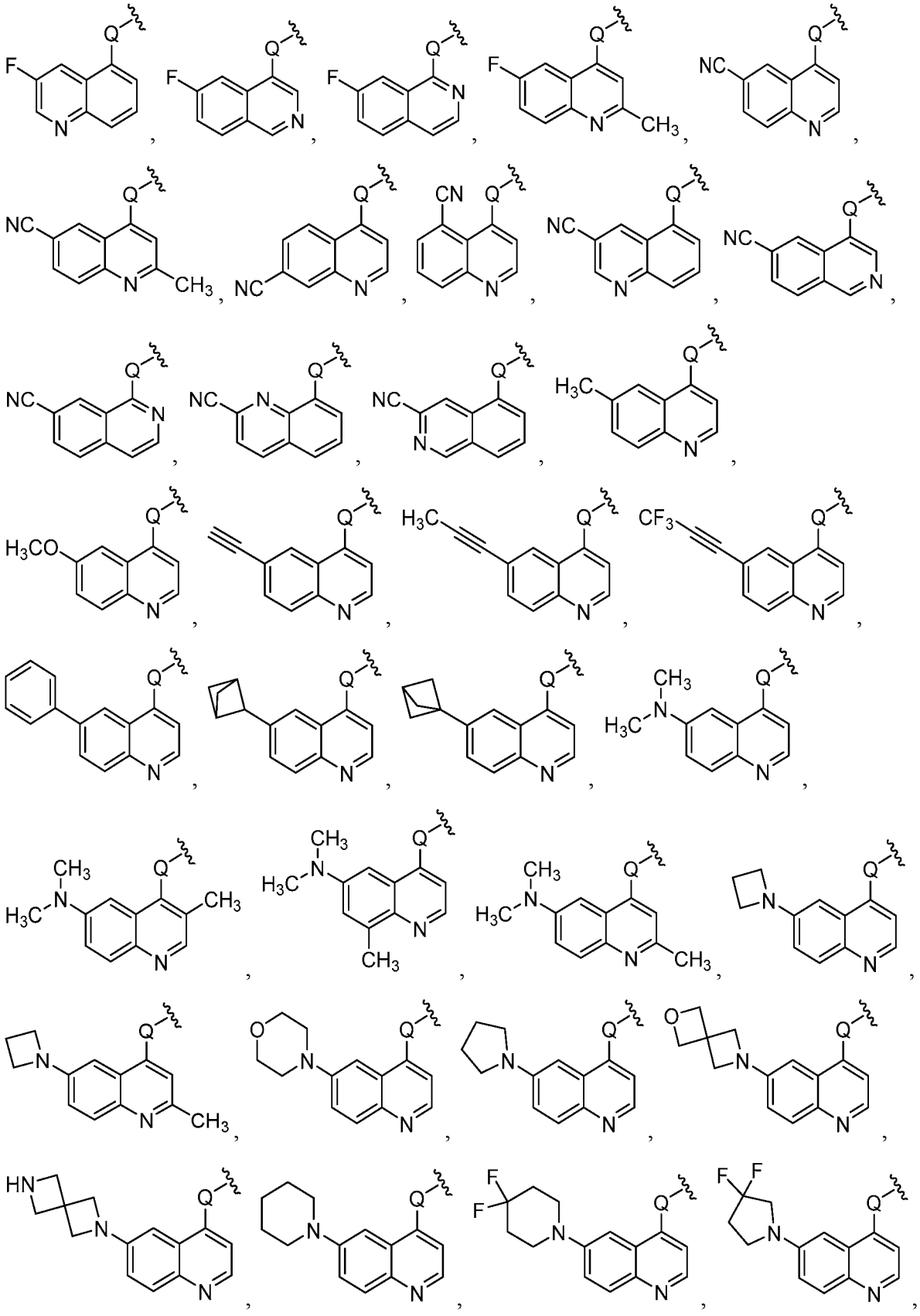
[0049] In any one of the embodiments disclosed herein, R_{12} is , , or ; wherein X is O or NR_{14}; and R_{14} is H or (C_1-C_6)alkyl.

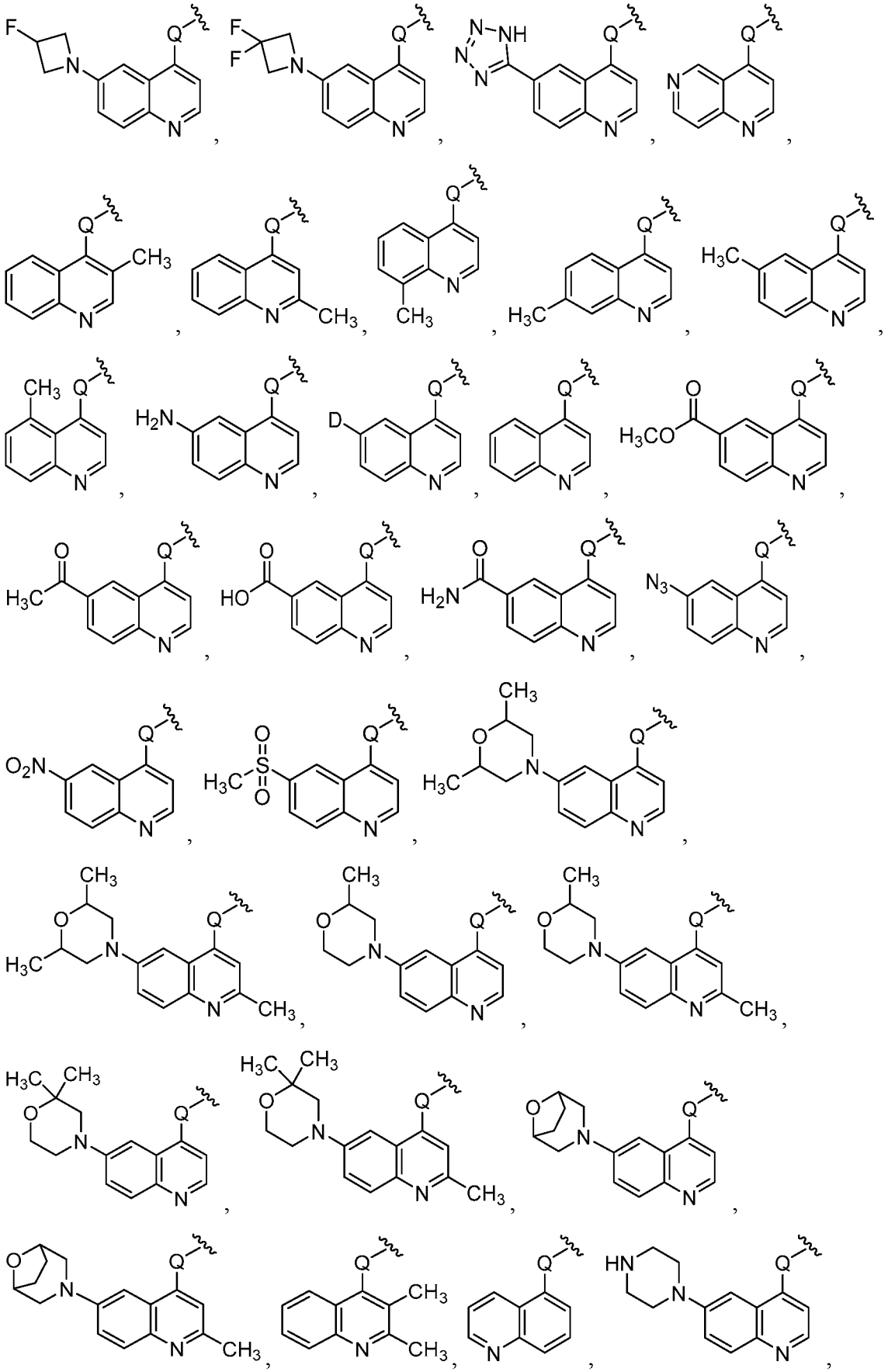
[0050] In any one of the embodiments disclosed herein, R_{12} is , .

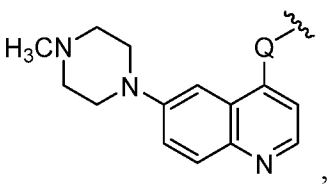
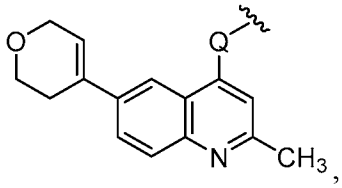
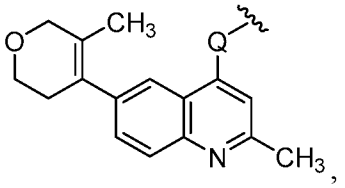
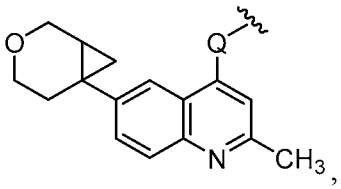
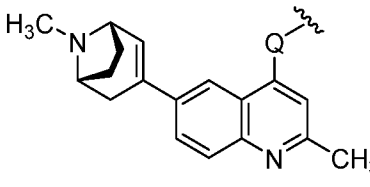
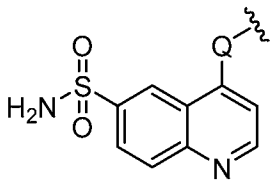


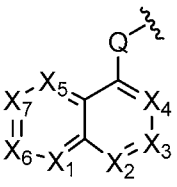
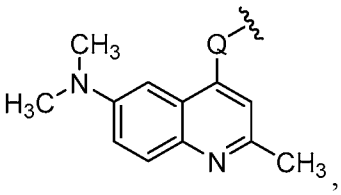
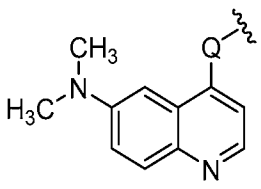
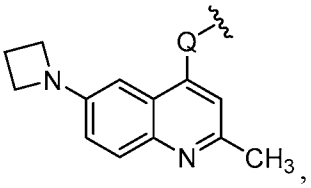
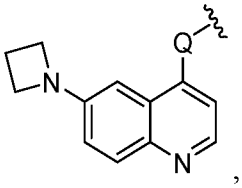
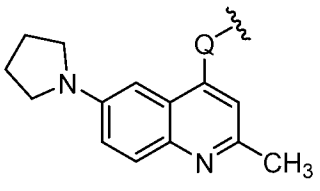
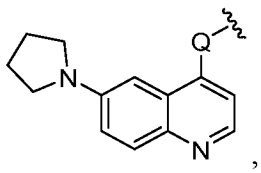
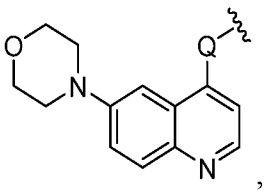
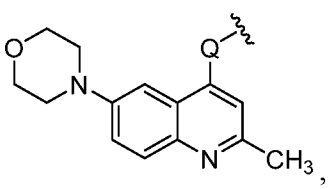
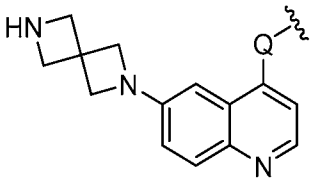
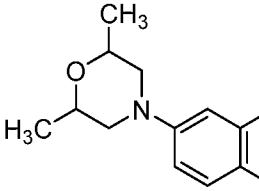
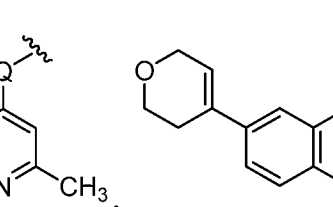
[0051] In any one of the embodiments disclosed herein, Ⓐ is  or .

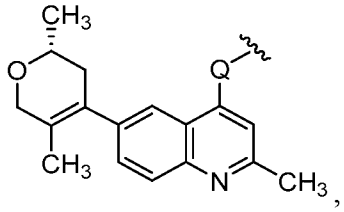
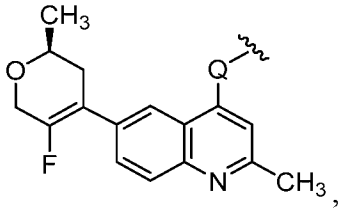
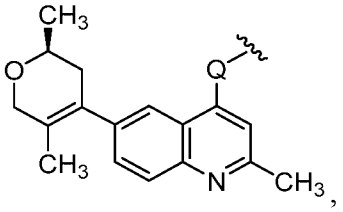
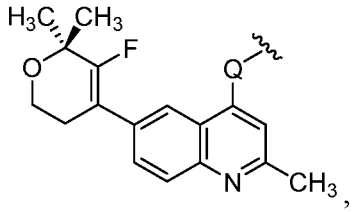
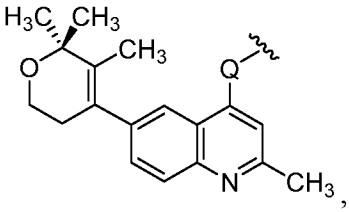
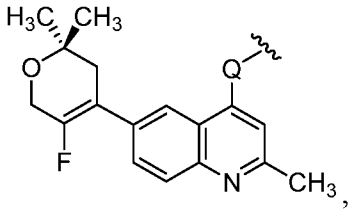
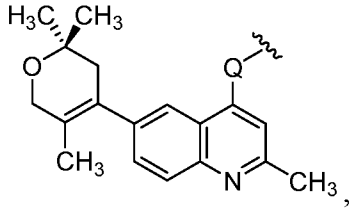
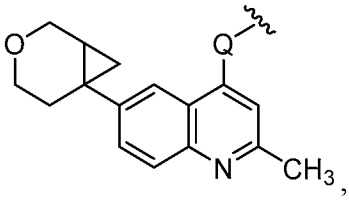
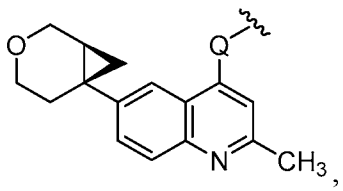
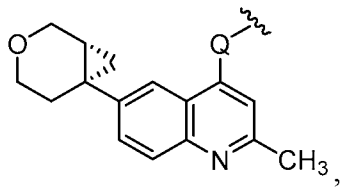
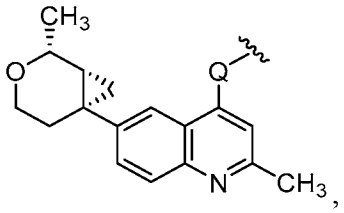
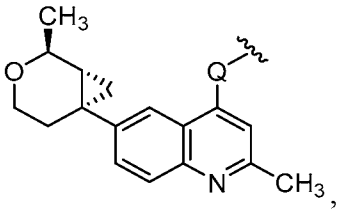
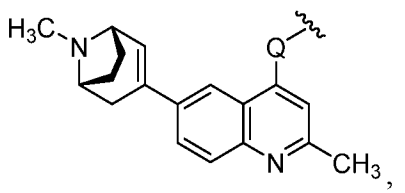
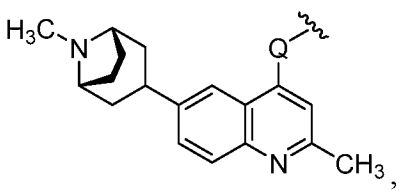
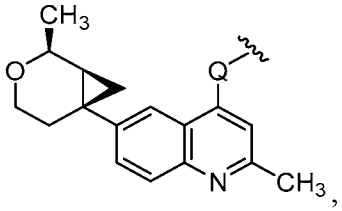
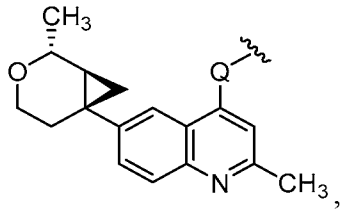
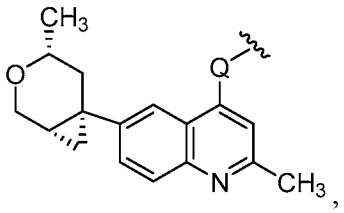
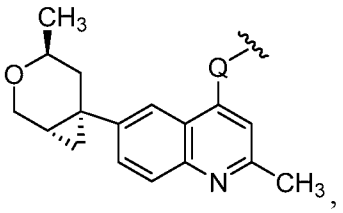
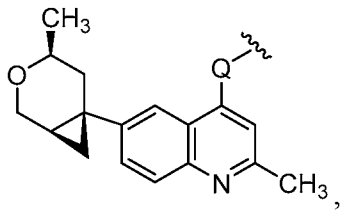
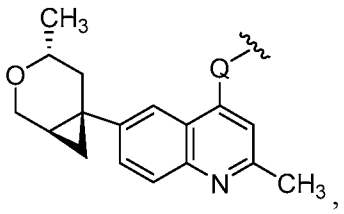
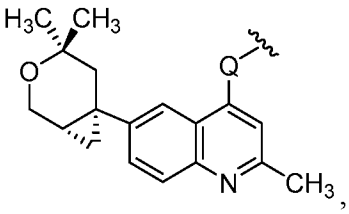
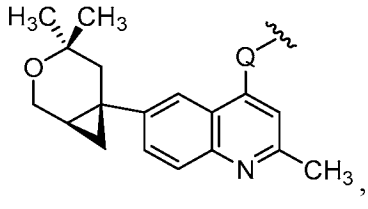
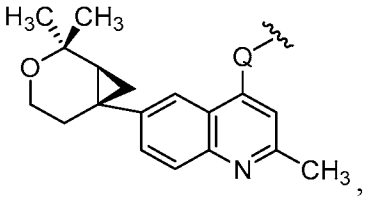
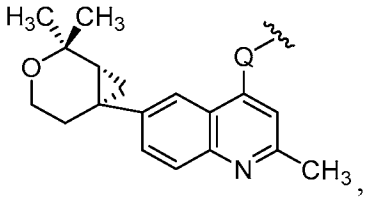
[0052] In any one of the embodiments disclosed herein, the structural moiety  has the structure of ,

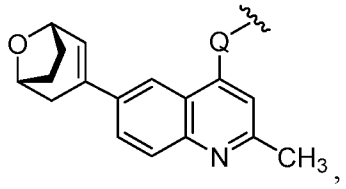
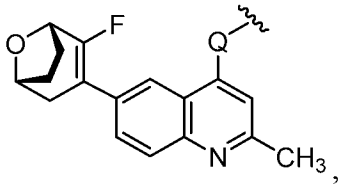
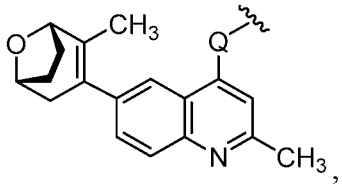
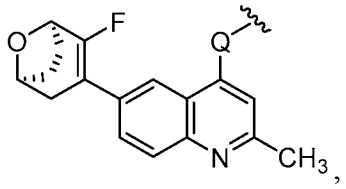
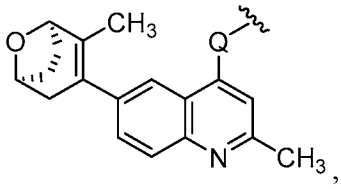
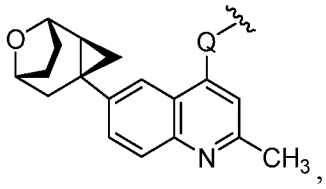
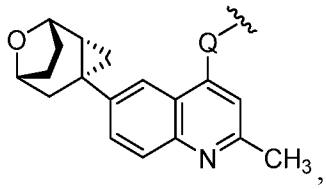
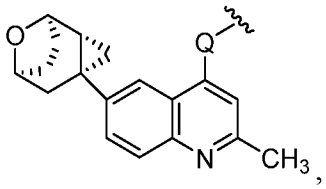
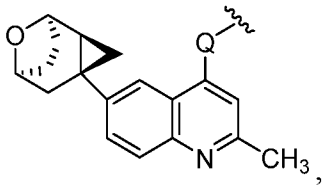
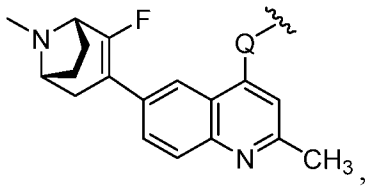
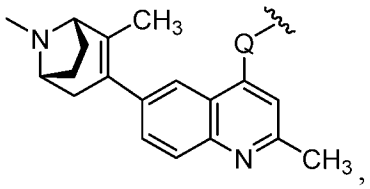
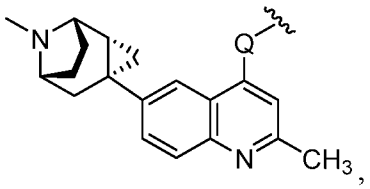
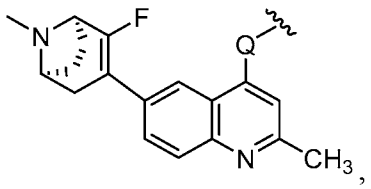
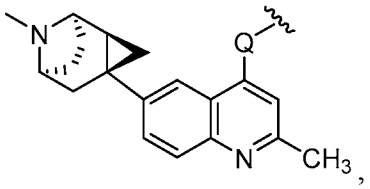
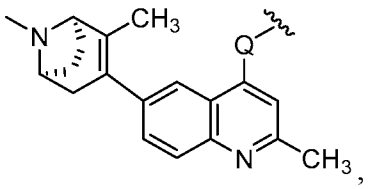
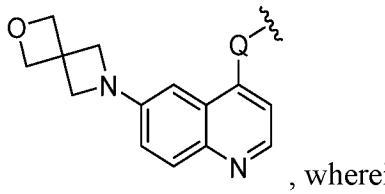
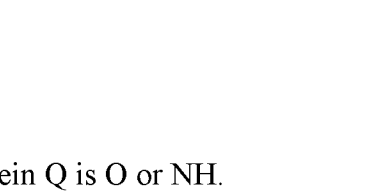




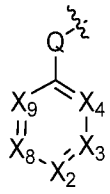
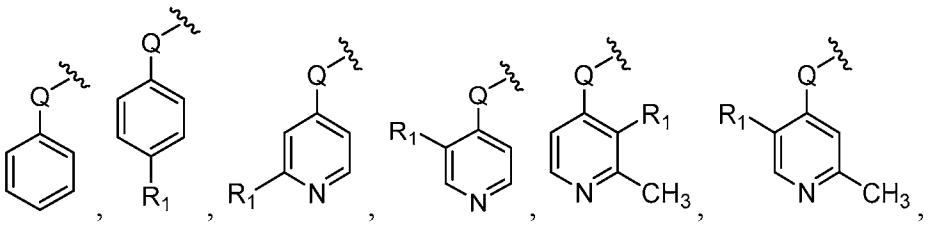





, or

, wherein Q is O or NH.

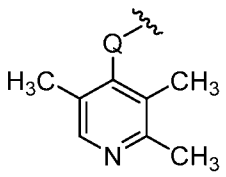
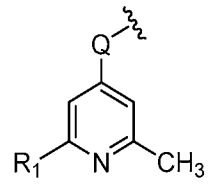
[0053] In any one of the embodiments disclosed herein, the structural moiety

has the structure of












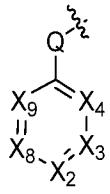
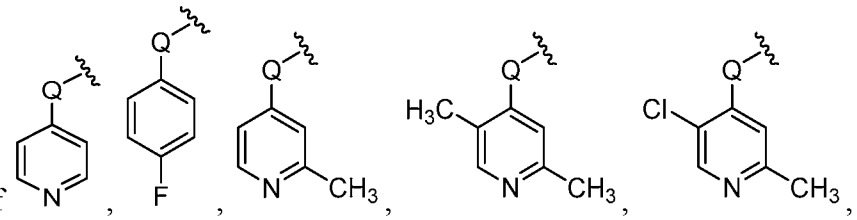
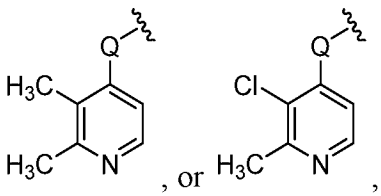

























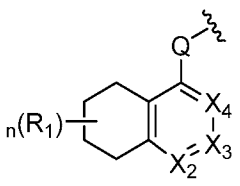


















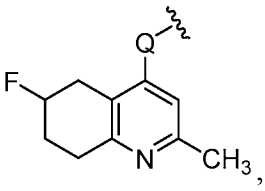
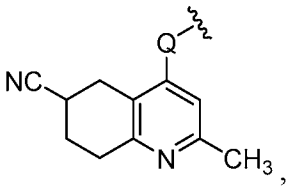
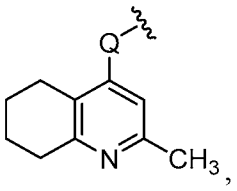
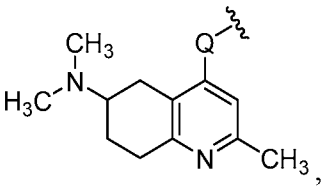
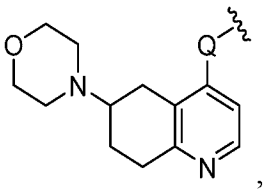
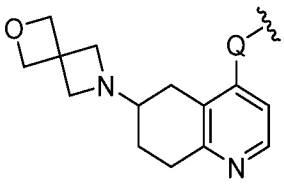
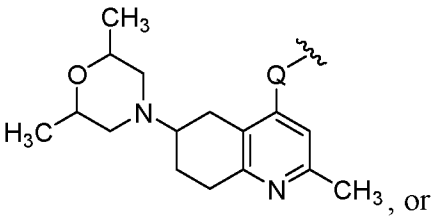
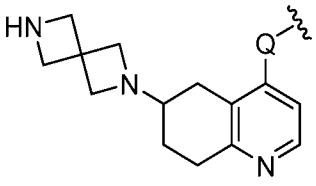
, wherein Q is O or NH.

[0054] In any one of the embodiments disclosed herein, the structural moiety  has the structure of 



, wherein 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.

[0055] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , or , wherein Q is O or NH.

[0056] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , or .

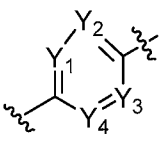
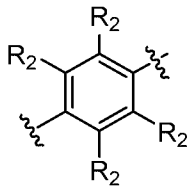
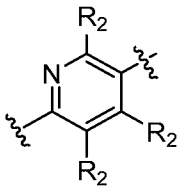
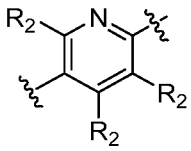
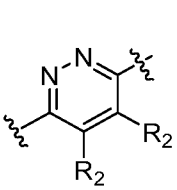
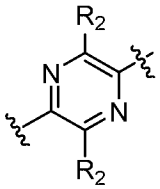
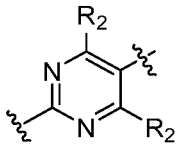
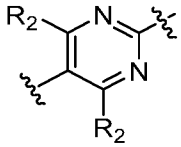
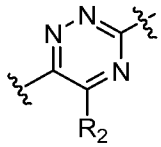
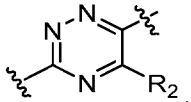







, or

, wherein Q is O or NH.

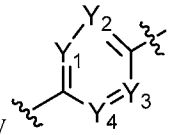
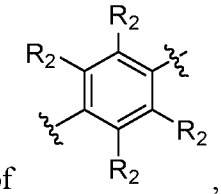
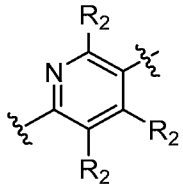
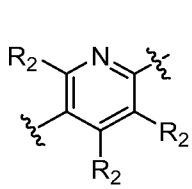
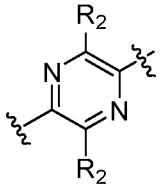
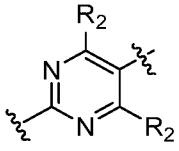
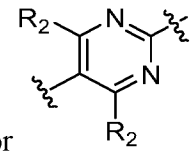
[0057] In any one of the embodiments disclosed herein, the compound has the formula of Formula Ia.

[0058] In any one of the embodiments disclosed herein, the compound has the formula of Formula IIa.

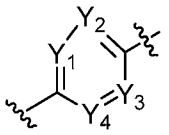
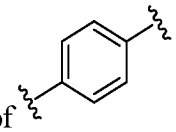
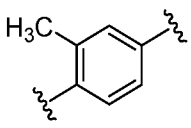
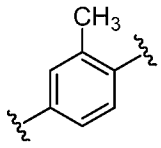
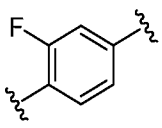
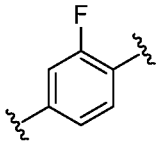
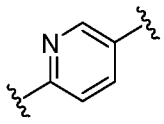
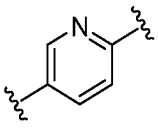
[0059] In any one of the embodiments disclosed herein, the compound has the formula of Formula IIIa.

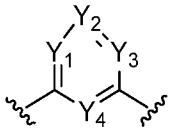
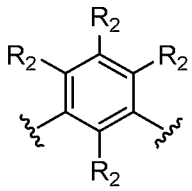
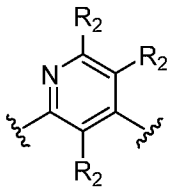
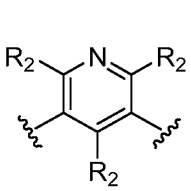
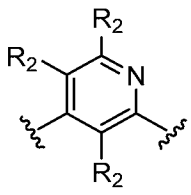
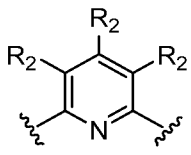
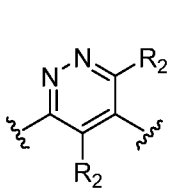
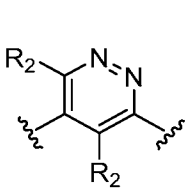
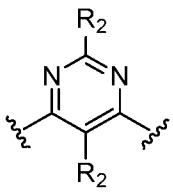
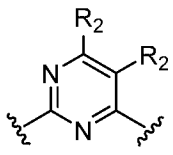
[0060] In any one of the embodiments disclosed herein, the compound has the formula of Formula IVa.

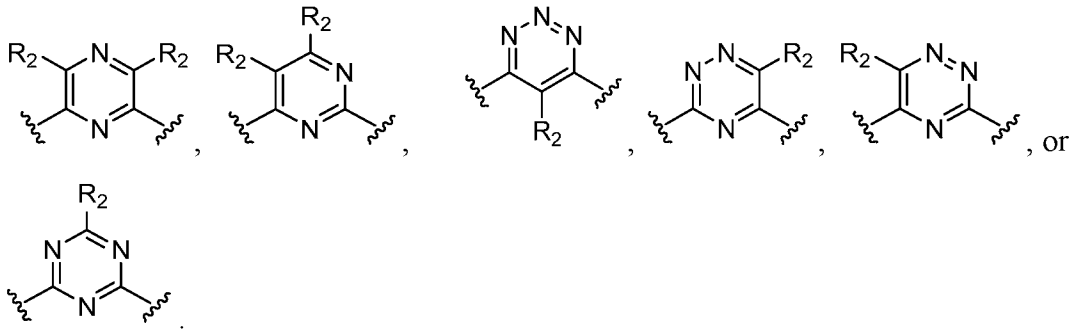
[0061] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , , , or .

[0062] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  ,  ,  , or  .

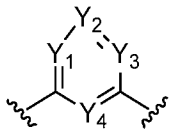
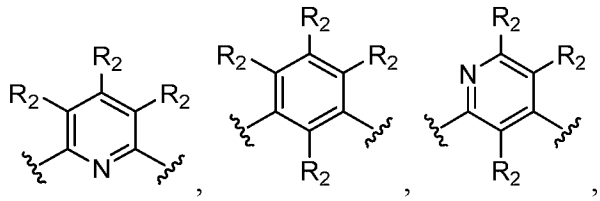
[0063] In any one of the embodiments disclosed herein, each occurrence of R_2 is independently H, halogen, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$.

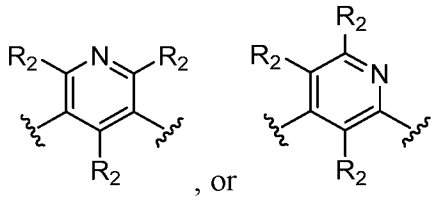
[0064] In any one of the embodiments disclosed herein, the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or  .

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

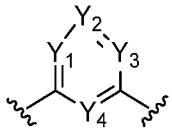
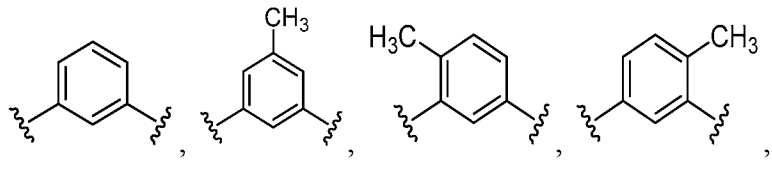


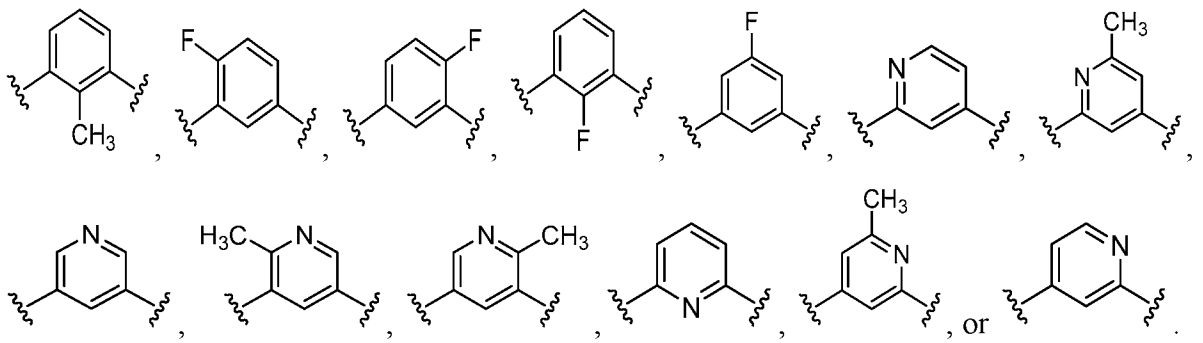
[0066] In any one of the embodiments disclosed herein, the structural moiety

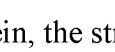
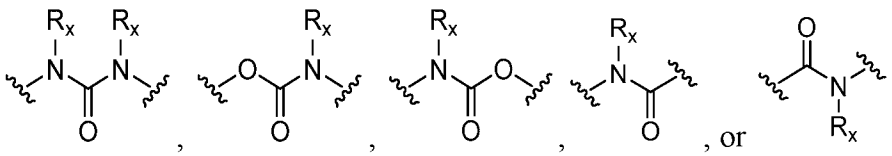
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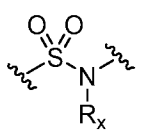
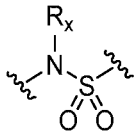


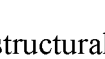
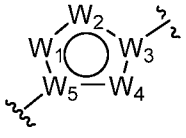
[0067] In any one of the embodiments disclosed herein, the structural moiety

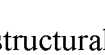
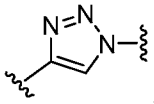
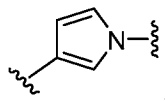
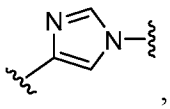
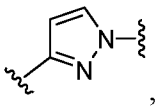
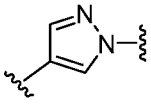
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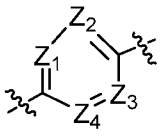
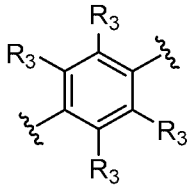
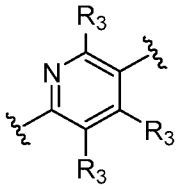
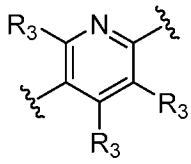
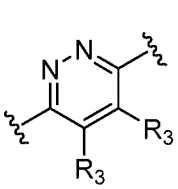
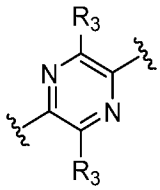
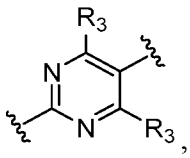
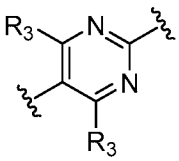
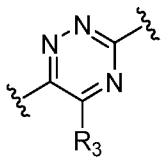
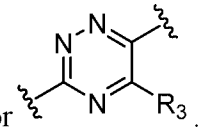


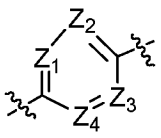
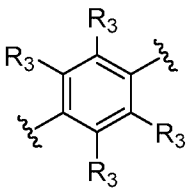
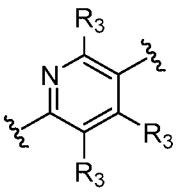
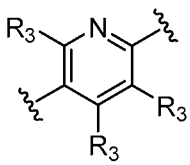
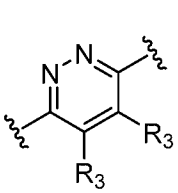
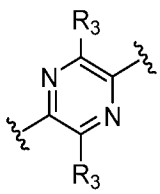
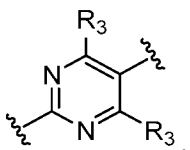
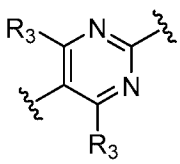
[0068] In any one of the embodiments disclosed herein, the structural moiety  has the structure of 

[0069] In any one of the embodiments disclosed herein, the structural moiety has the structure of  or .

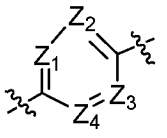
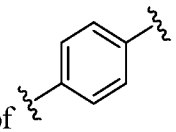
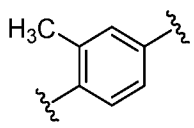
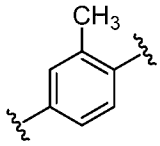
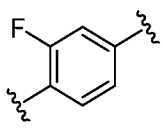
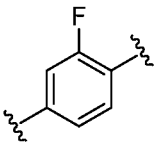
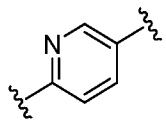
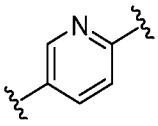
[0070] In any one of the embodiments disclosed herein, the structural moiety  has the structure of .

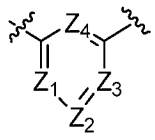
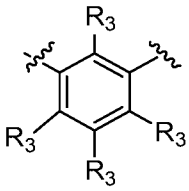
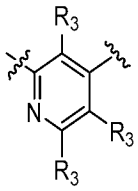
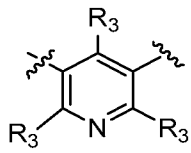
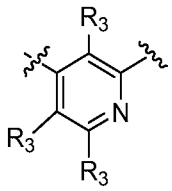
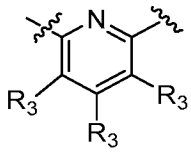
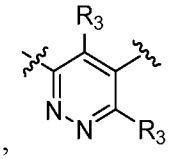
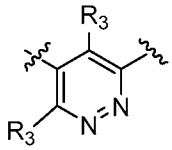
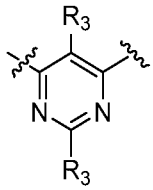
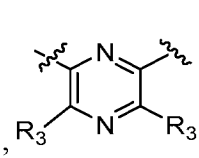
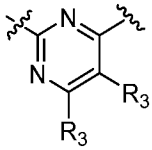
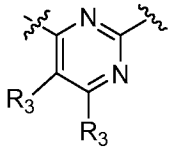
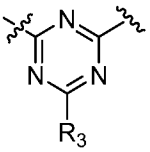
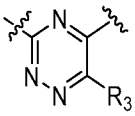
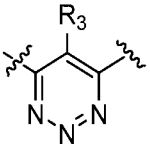
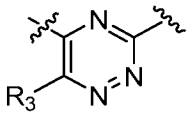
[0071] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , or .

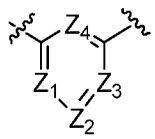
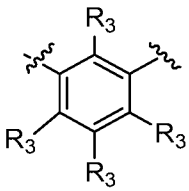
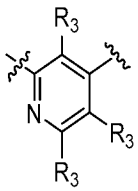
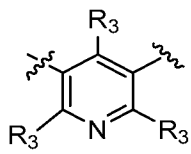
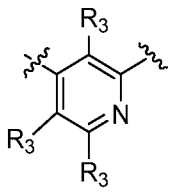
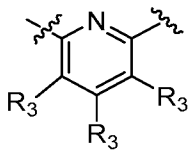
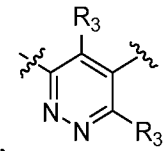
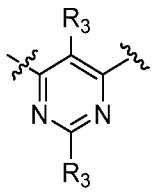
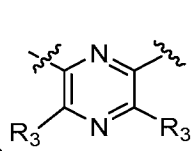
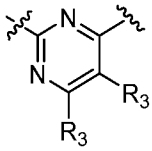
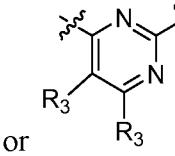
[0072] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , , , or .

[0073] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , or .

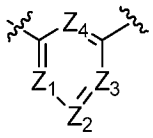
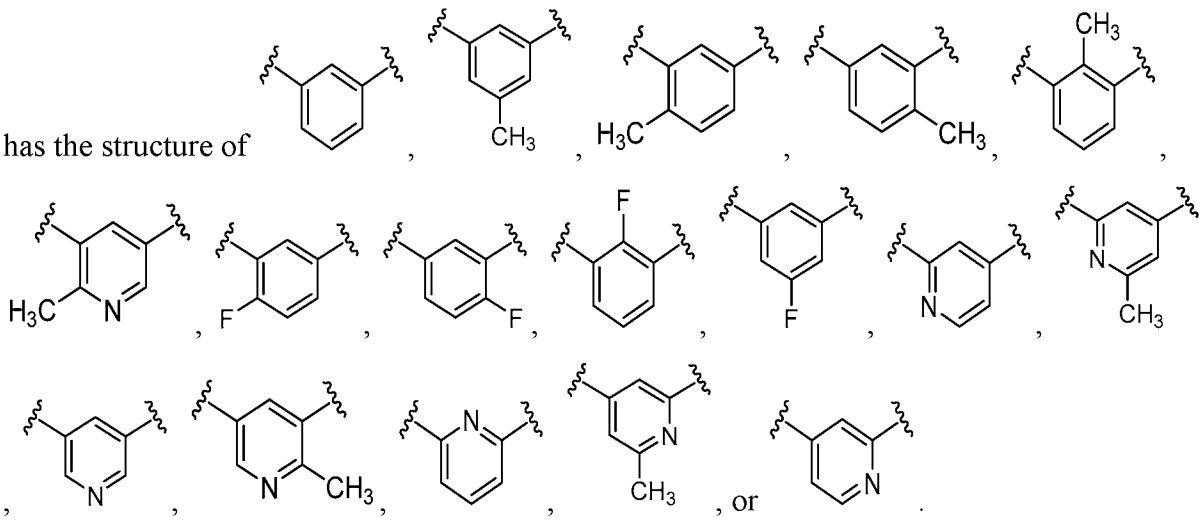
[0074] In any one of the embodiments disclosed herein, each occurrence of R_3 is H, halogen, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$.

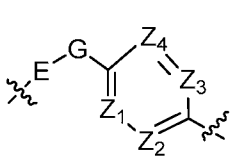
[0075] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , or .

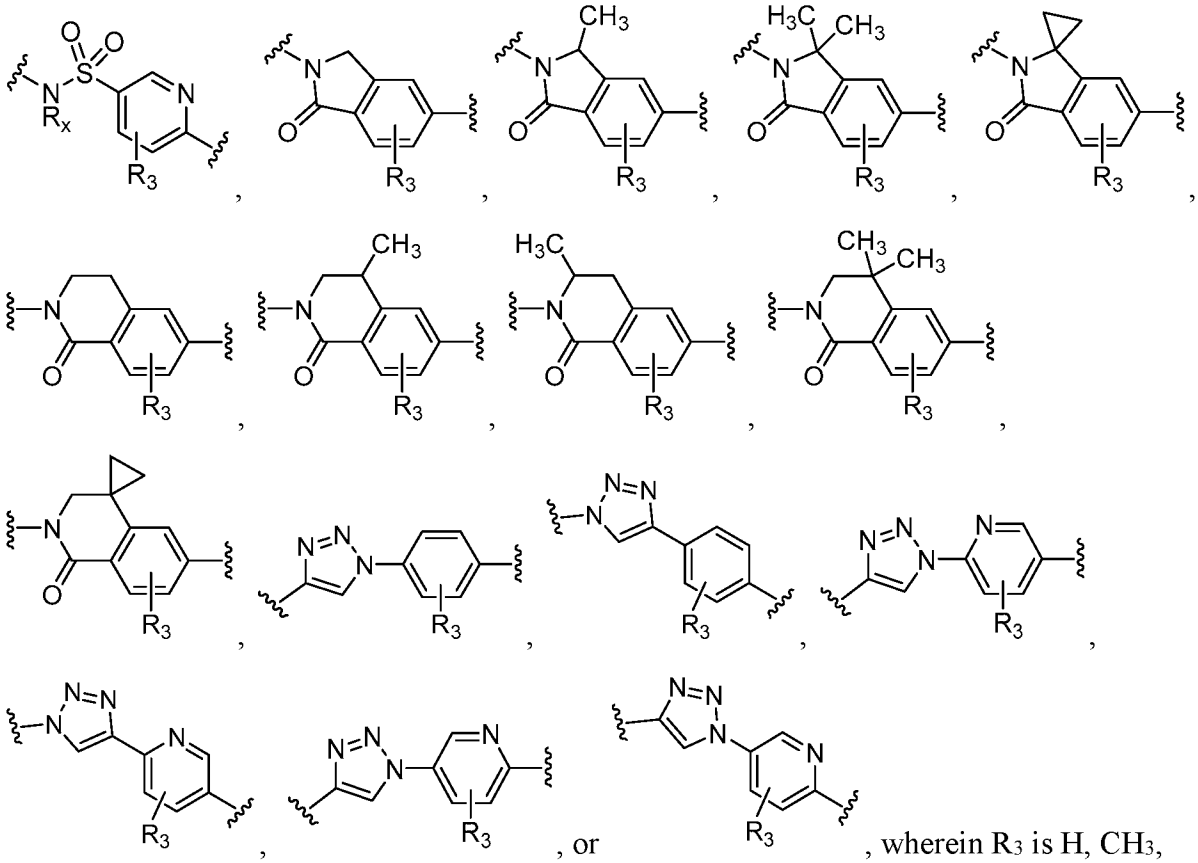
[0076] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , , , , , , , , , or .

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

[0078] 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 $-N(CH_3)_2$.

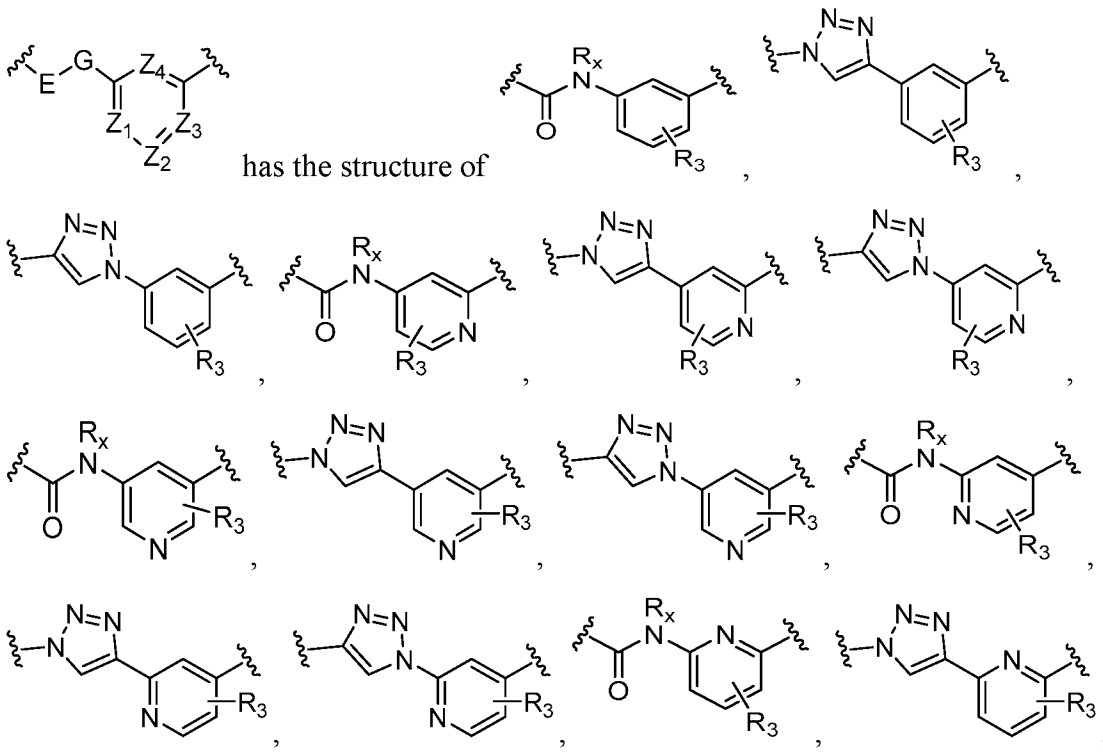
[0079] In any one of the embodiments disclosed herein, the structural moiety  has the structure of .

[0080] In any one of the embodiments disclosed herein, the structural moiety  has the structure of .

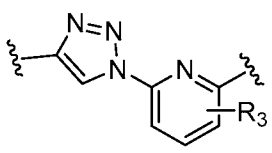
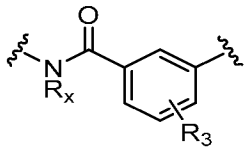
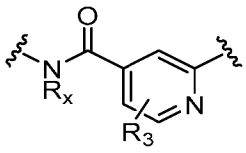
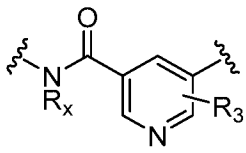
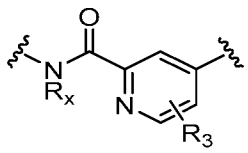
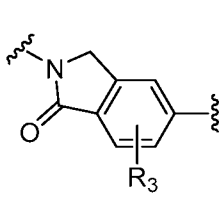
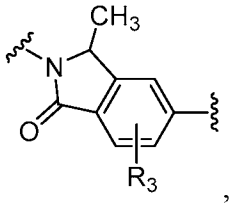
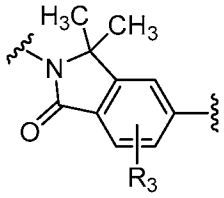
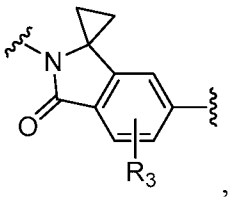
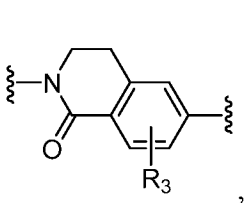
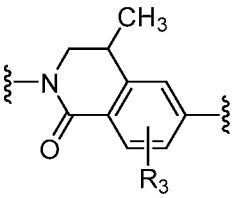
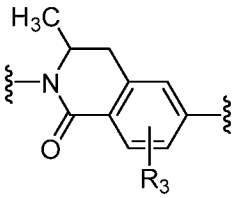
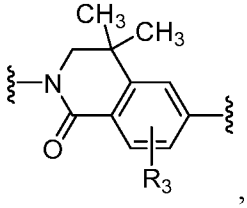


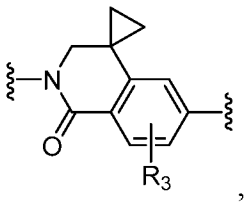
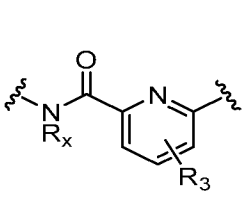
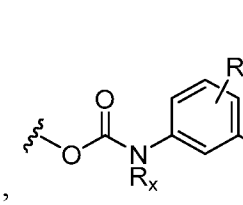
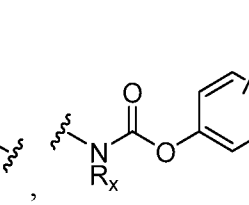
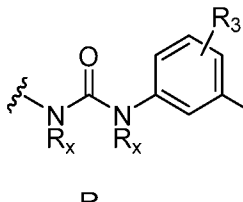
, wherein R_3 is H, CH_3, OH, halogen, or NH_2; and wherein R_x is H, CH_3, or CH_2CH_3.

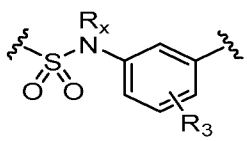
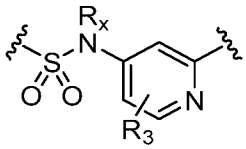
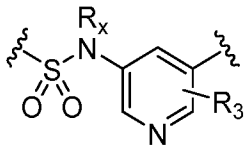
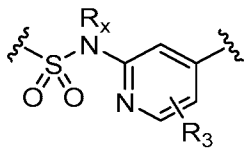
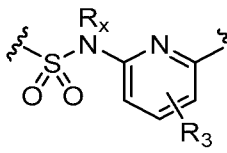
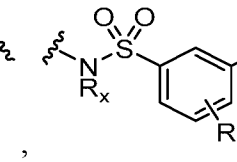
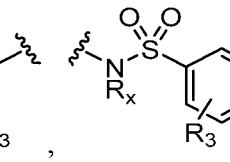
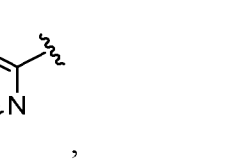
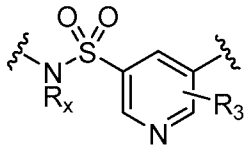
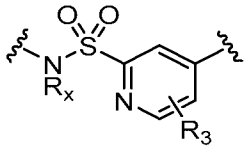
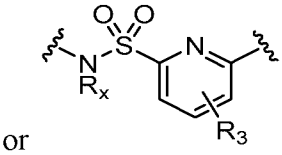
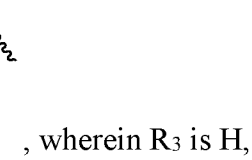
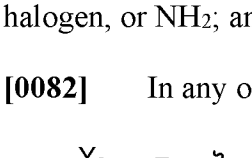
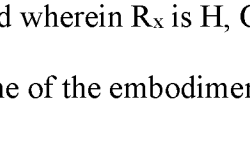
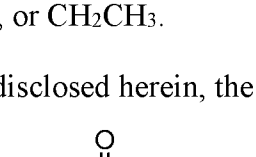
[0081] In any one of the embodiments disclosed herein, the structural moiety



has the structure of

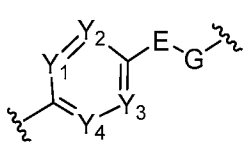














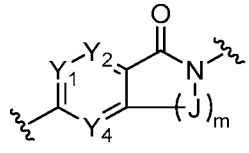
















, or , wherein R_3 is H, CH_3, OH, halogen, or NH_2; and wherein R_x is H, CH_3, or CH_2CH_3.

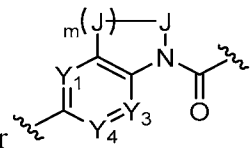
[0082] In any one of the embodiments disclosed herein, the structural moiety



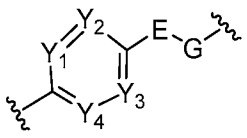
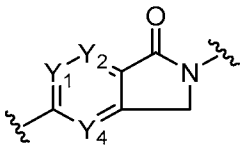
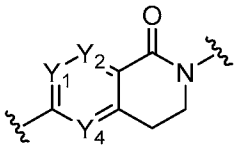
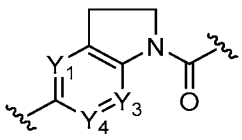
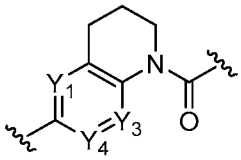
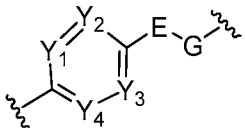
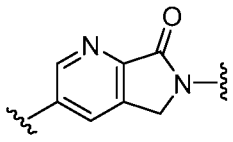
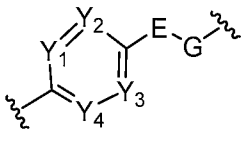
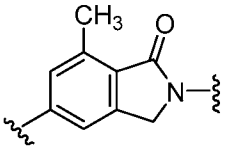
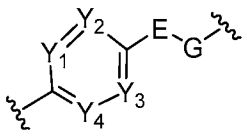
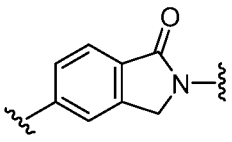
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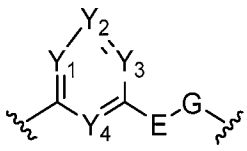
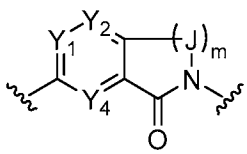
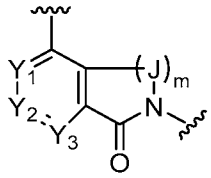
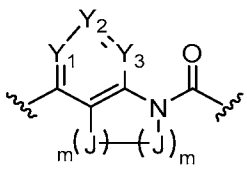
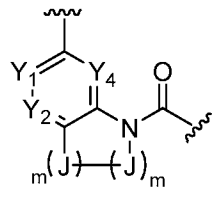


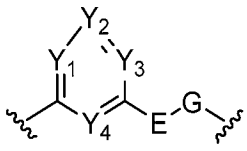
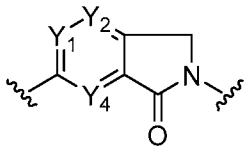
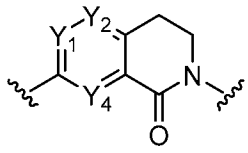
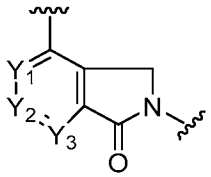
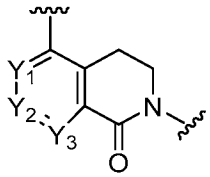
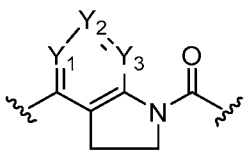
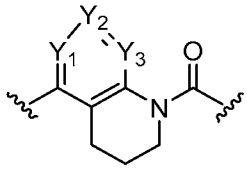
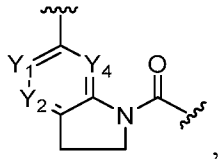
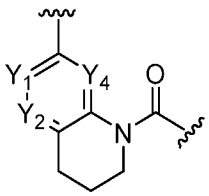
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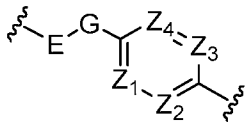
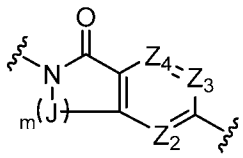
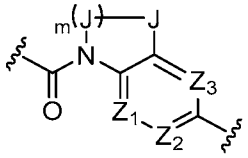


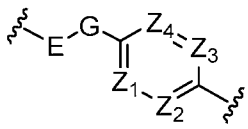
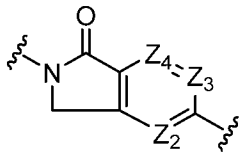
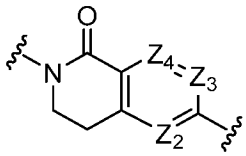
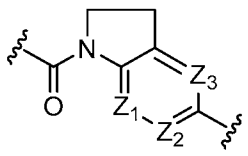
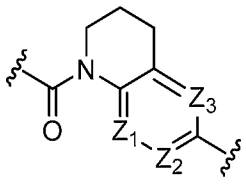
, wherein each occurrence of m is independently 1 or 2, J is $C(R_y)_2$, and each occurrence of R_y is independently H, $(C_1\text{-}C_6)$alkyl, OH, $O(C_1\text{-}C_6)$alkyl, or halogen.

[0083] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , or , wherein Y_1, Y_2, Y_3, and Y_4 are each independently N, CH, CCH_3, or CF. In any one of the embodiments disclosed herein, the structural moiety  has the structure of . In any one of the embodiments disclosed herein, the structural moiety  has the structure of . In any one of the embodiments disclosed herein, the structural moiety  has the structure of .

[0084] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , or , wherein 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.

[0085] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , ,  or , wherein Y_1, Y_2, Y_3, and Y_4 are each independently N, CH, CCH_3, or CF.

[0086] In any one of the embodiments disclosed herein, 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.

[0087] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , or , wherein Z_1, Z_2, Z_3, and Z_4 are each independently N, CH, CCH_3, or CF.

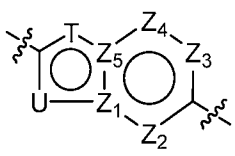
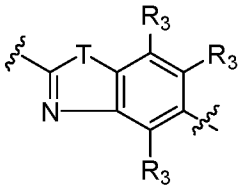
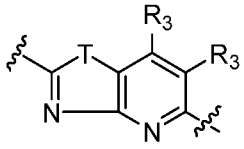
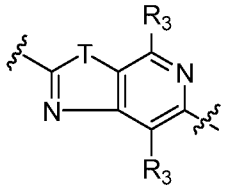
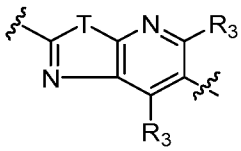
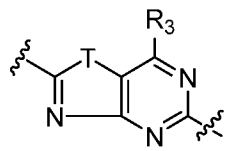
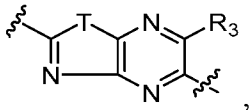
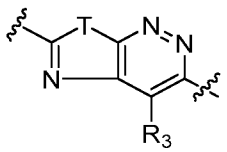
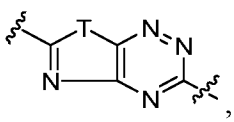
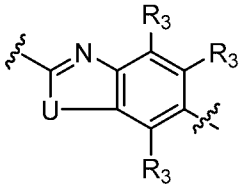
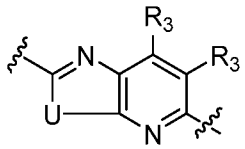
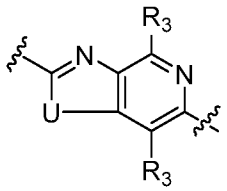
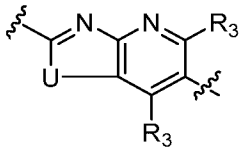
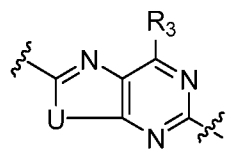
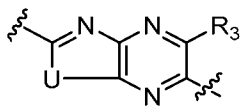
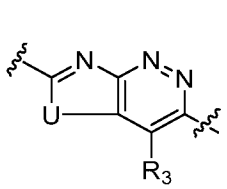
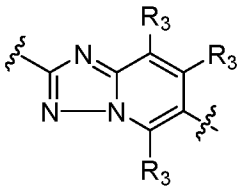
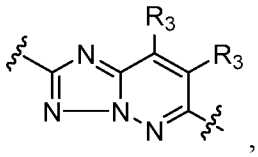
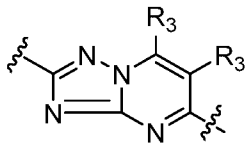
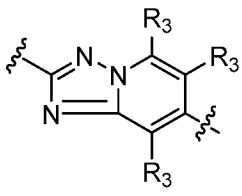
[0088] In any one of the embodiments disclosed herein, the compound has the formula of Formula Ib.

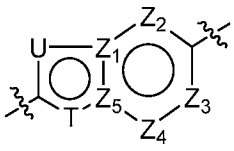
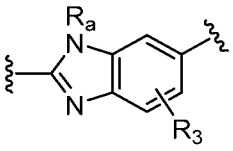
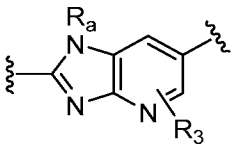
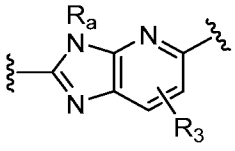
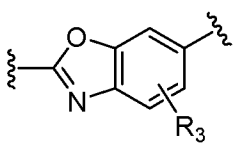
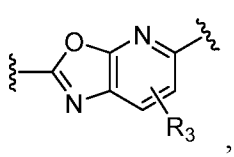
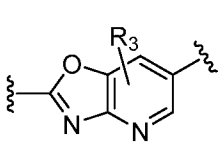
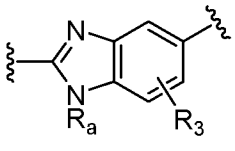
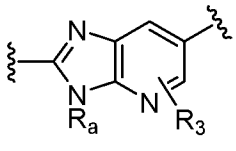
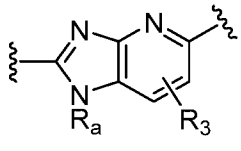
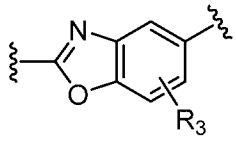
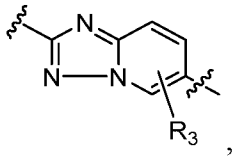
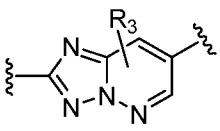
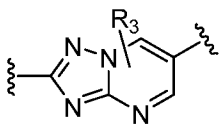
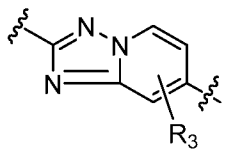
[0089] In any one of the embodiments disclosed herein, the compound has the formula of Formula IIb.

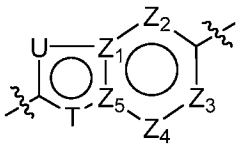
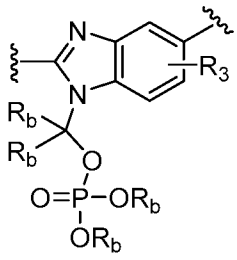
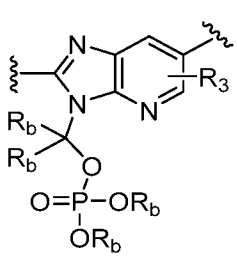
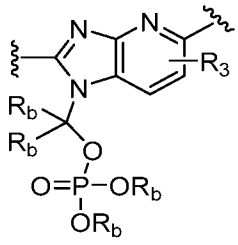
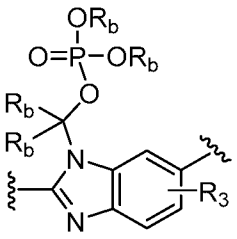
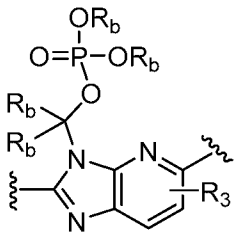
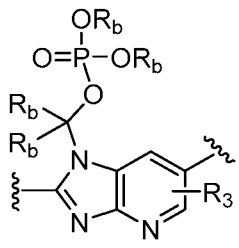
[0090] In any one of the embodiments disclosed herein, the compound has the formula of Formula IIIb.

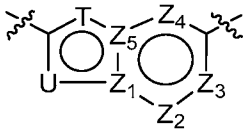
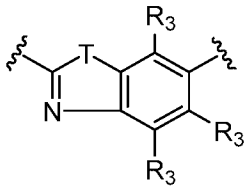
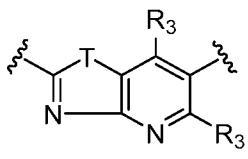
[0091] In any one of the embodiments disclosed herein, the compound has the formula of Formula IVb.

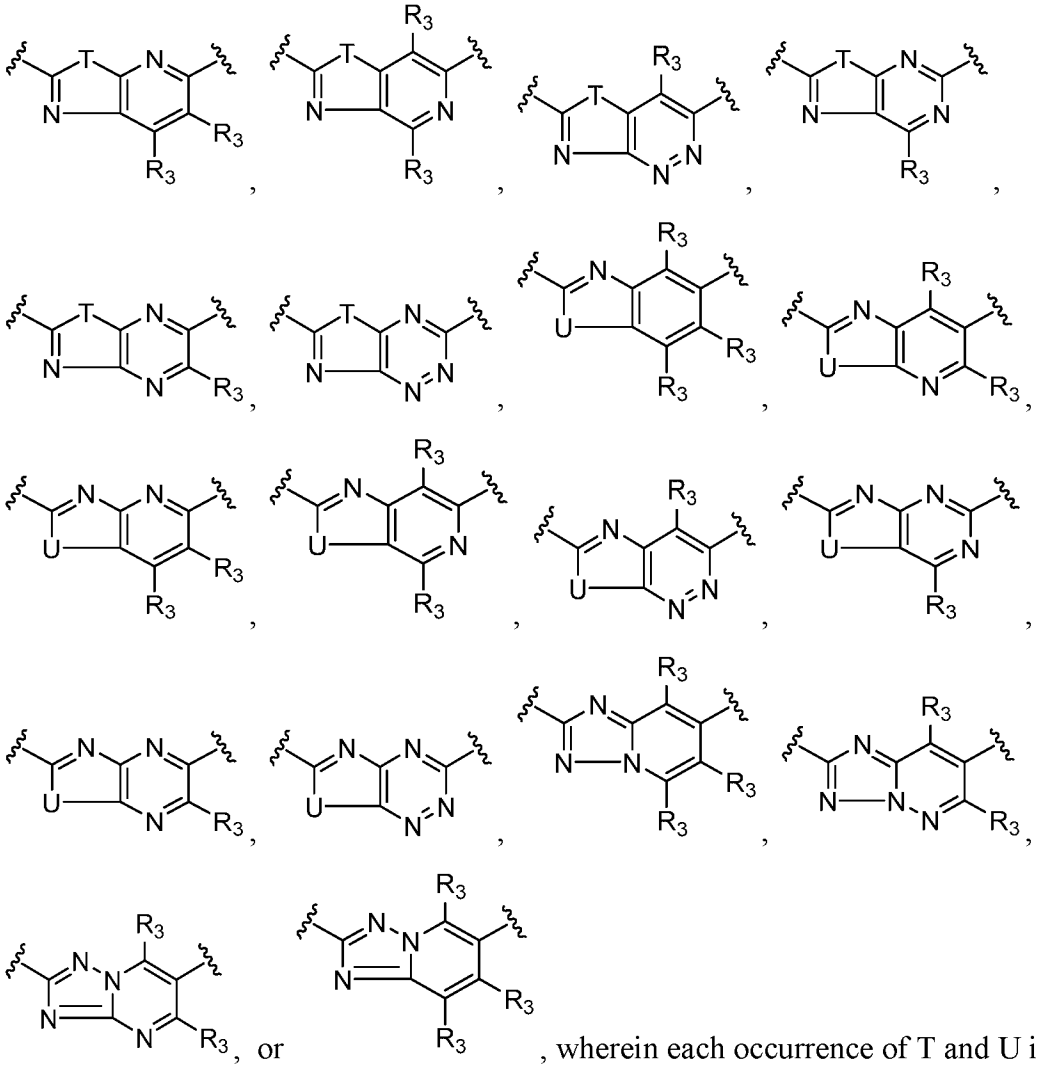
[0092] In any one of the embodiments disclosed herein, the structural moiety


has the structure of

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, or

, wherein 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.

[0093] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , , , , , , , , or , wherein R_3 is H, CH_3, OH, halogen, or NH_2; and wherein R_a is H, CH_3, or CH_2CH_3.

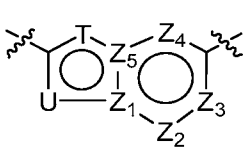
[0094] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , or .

[0095] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , ,

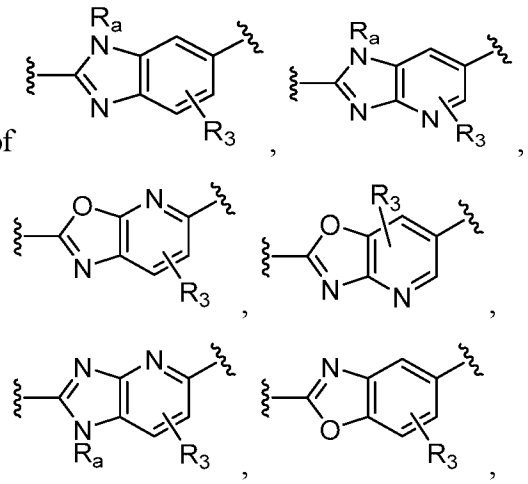


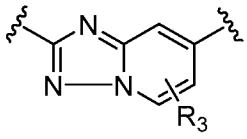
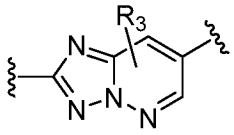
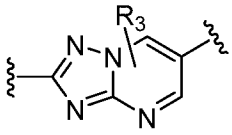
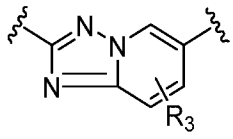
, wherein each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

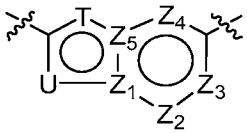
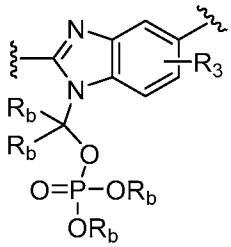
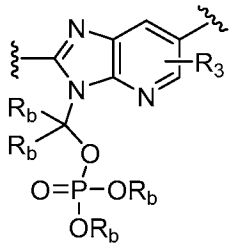
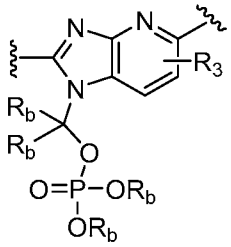
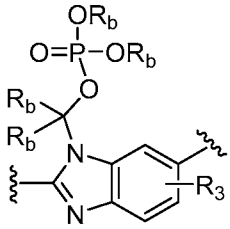
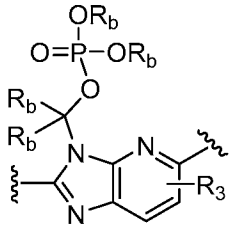
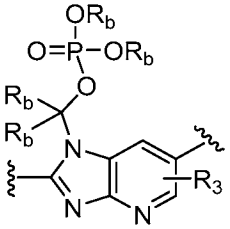
[0096] In any one of the embodiments disclosed herein, the structural moiety



has the structure of






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

[0097] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , or .

[0098] In any one of the embodiments disclosed herein, each occurrence of R_b is independently H or $(C_1\text{-}C_6)$alkyl.

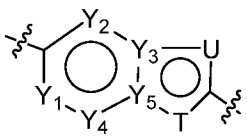
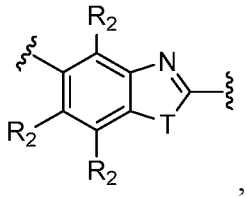
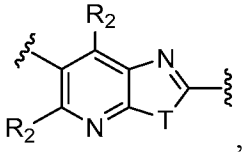
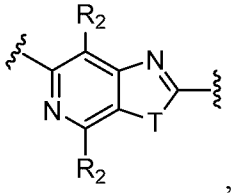
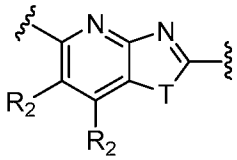
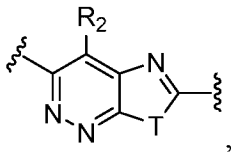
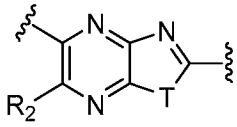
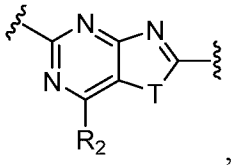
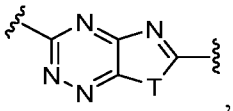
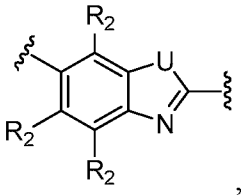
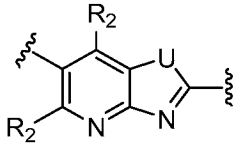
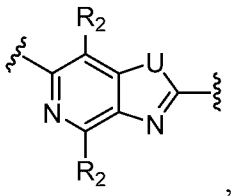
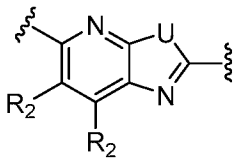
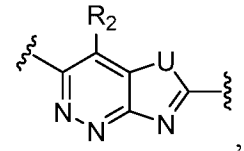
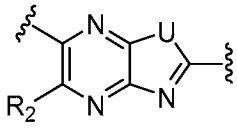
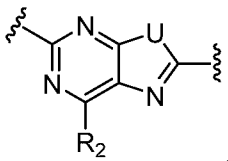
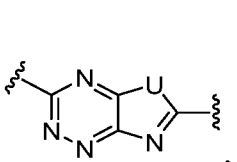
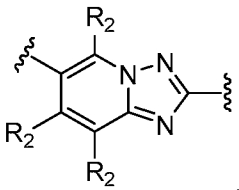
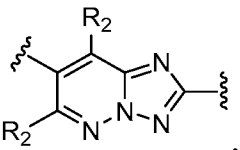
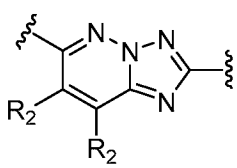
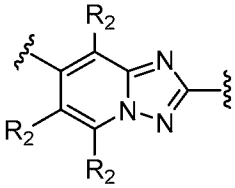
[0099] In any one of the embodiments disclosed herein, each occurrence of R_b is independently H, CH_3, CH_2CH_3, or $CH(CH_3)_2$.

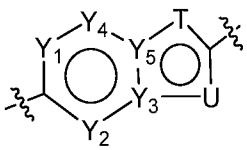
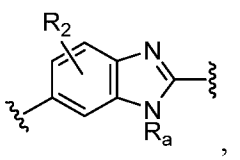
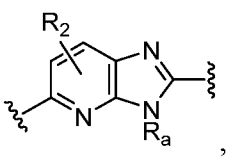
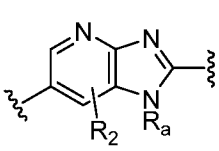
[0100] In any one of the embodiments disclosed herein, the compound has the formula of Formula Ic.

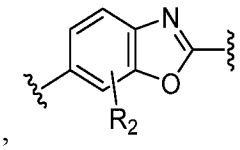
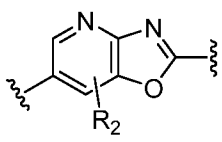
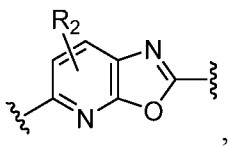
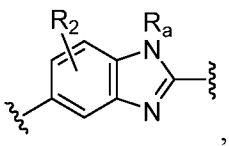
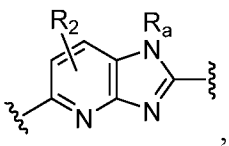
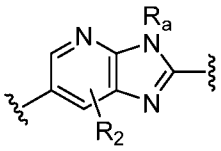
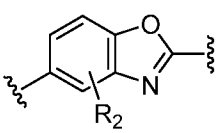
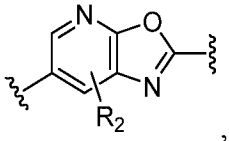
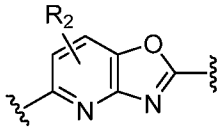
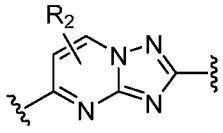
[0101] In any one of the embodiments disclosed herein, the compound has the formula of Formula IIc.

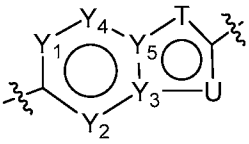
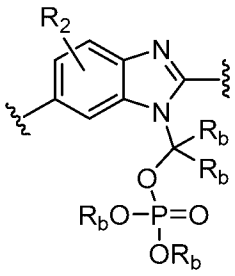
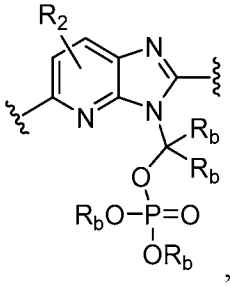
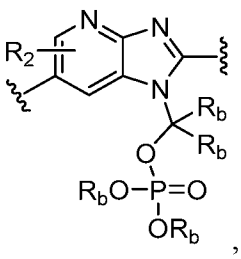
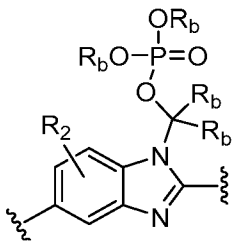
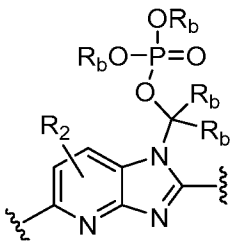
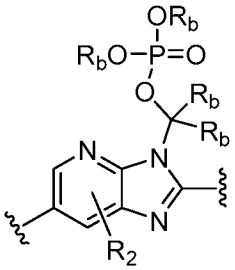
[0102] In any one of the embodiments disclosed herein, the compound has the formula of Formula IIIc.

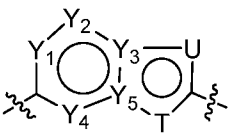
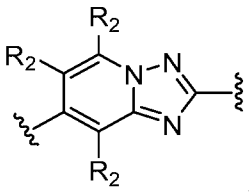
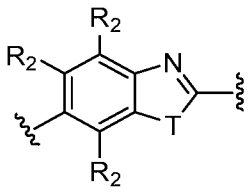
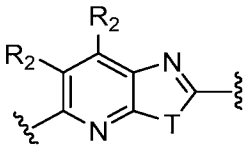
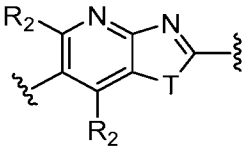
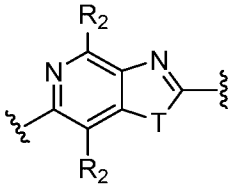
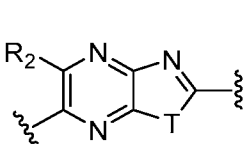
[0103] In any one of the embodiments disclosed herein, the compound has the formula of Formula IVc.

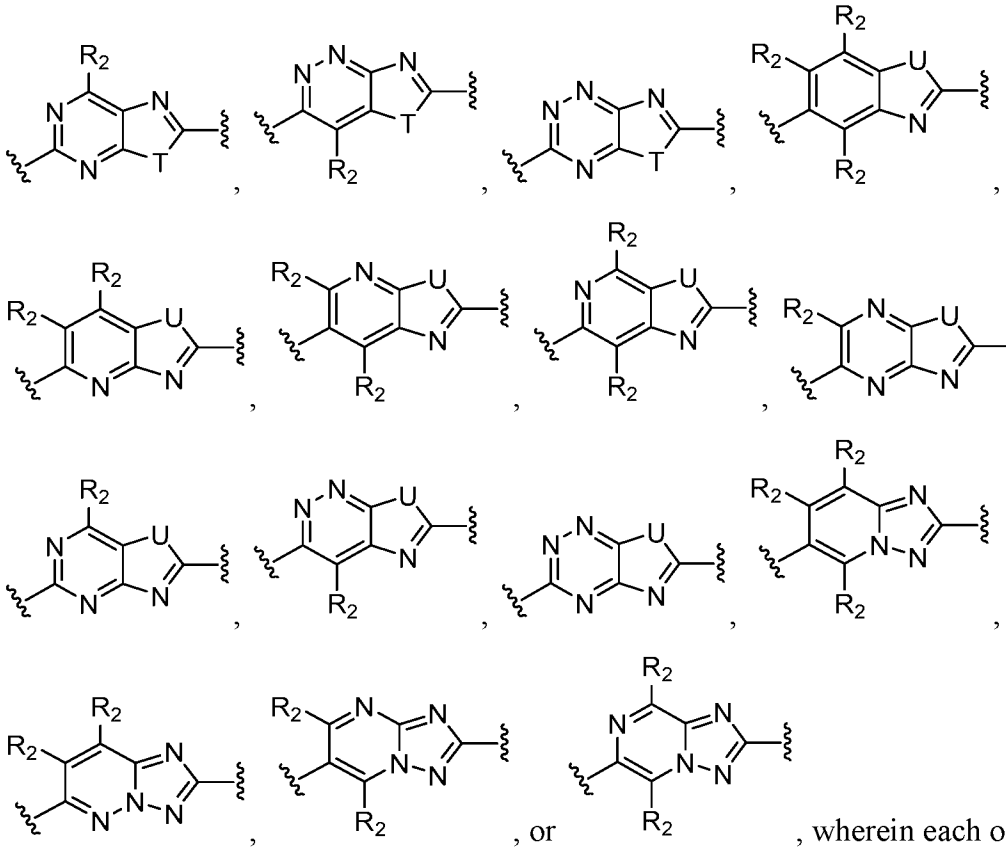
[0104] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , , , , , , , , , , , , , , , , , , , , or , wherein each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

[0105] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , 

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

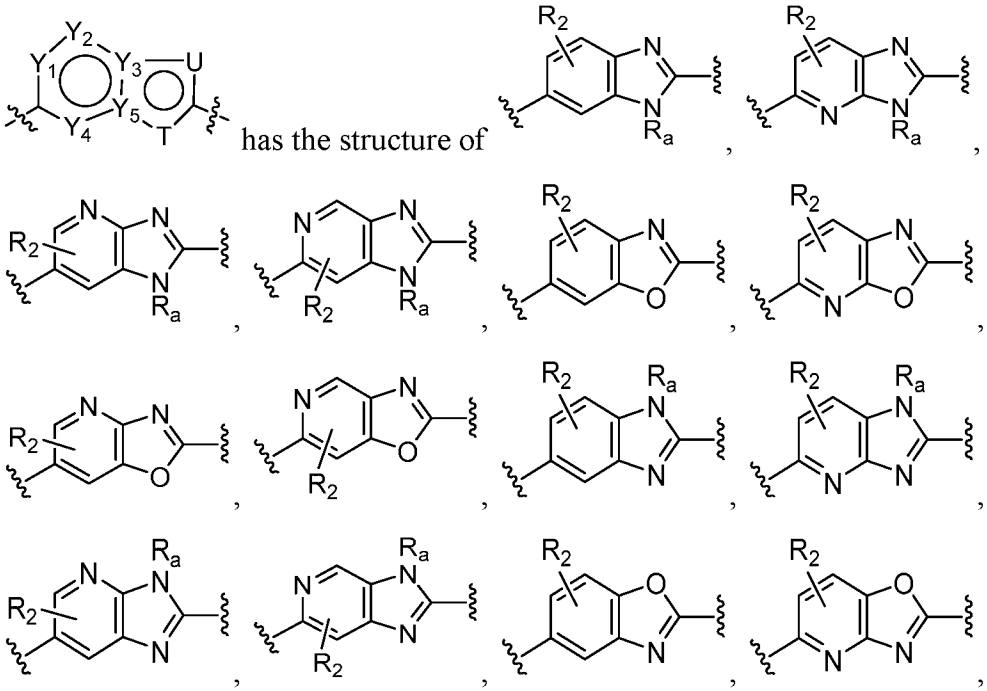
[0106] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , or .

[0107] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , , , , , .

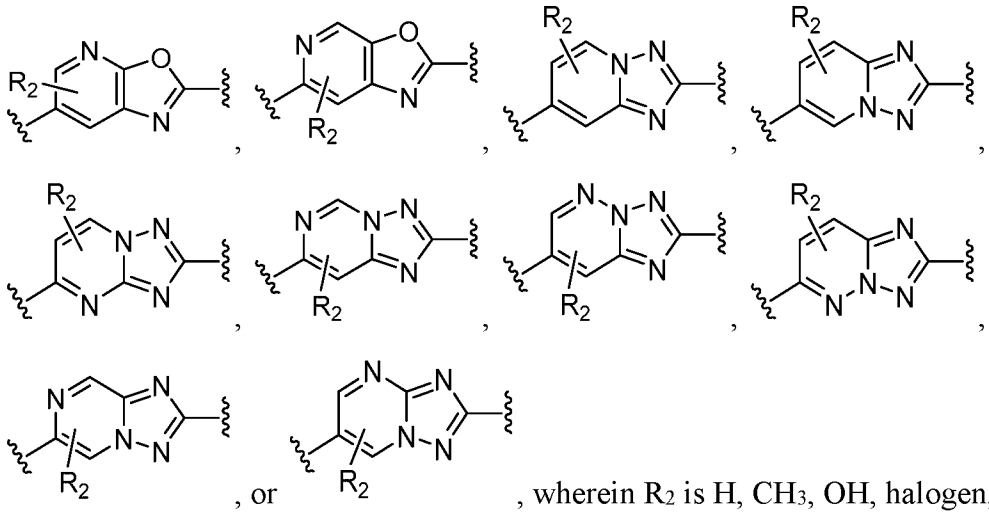


, wherein each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

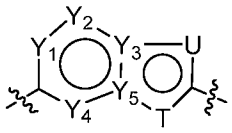
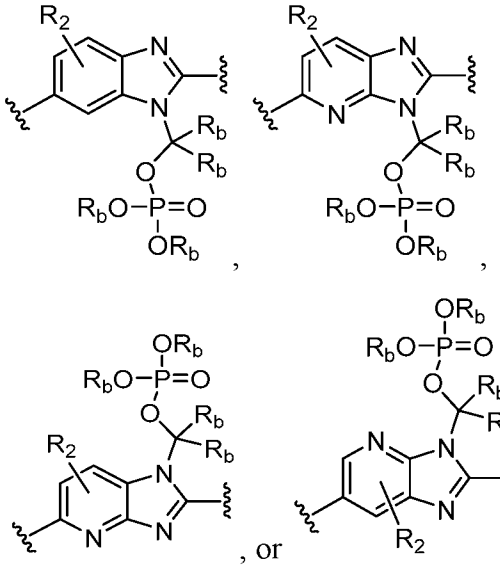
[0108] In any one of the embodiments disclosed herein, the structural moiety



has the structure of



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

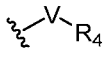
[0109] In any one of the embodiments disclosed herein, the structural moiety  has the structure of .

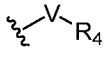
[0110] In any one of the embodiments disclosed herein, each occurrence of R_b is independently H or (C_1-C_6)alkyl.

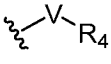
[0111] In any one of the embodiments disclosed herein, each occurrence of R_b is independently H, CH_3, CH_2CH_3, or $CH(CH_3)_2$.

[0112] In any one of the embodiments disclosed herein, each occurrence of R_2 is independently H, CH_3, OH, NH_2, or halogen.

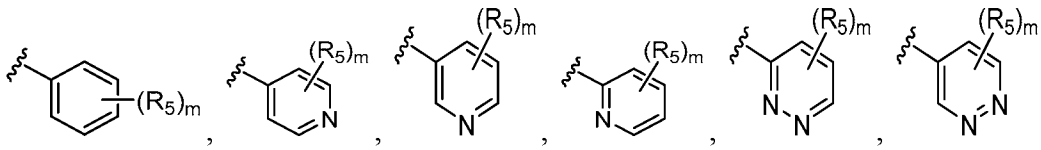
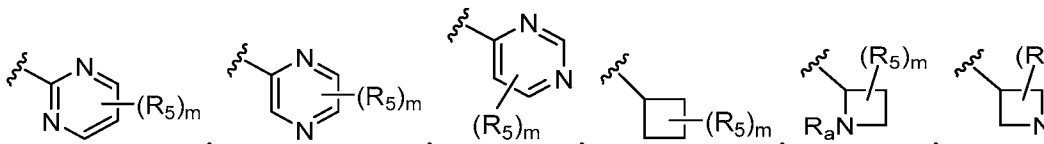
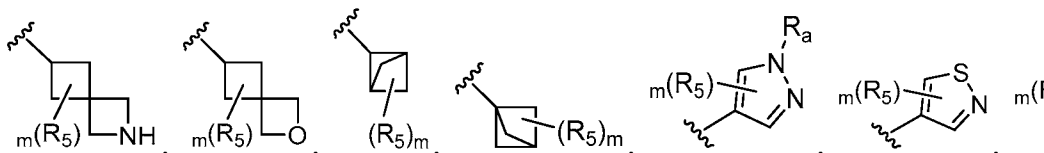
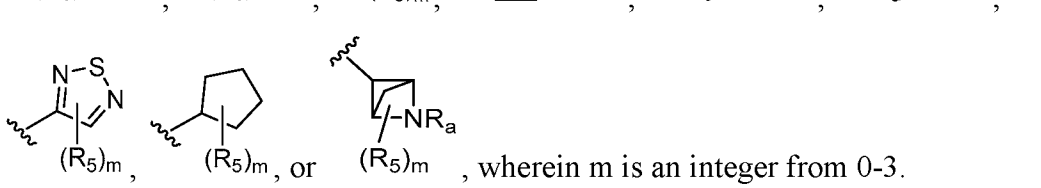
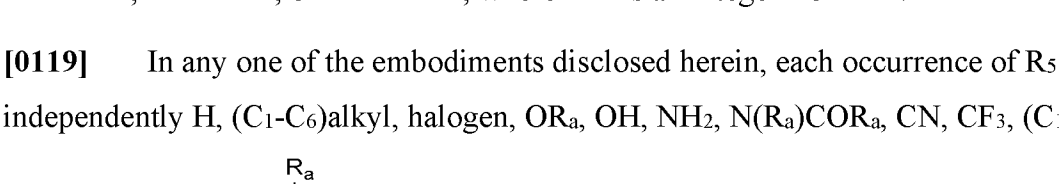
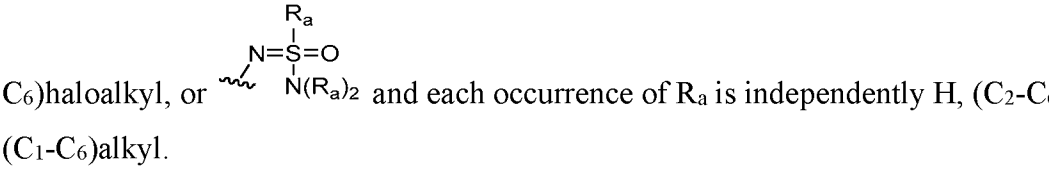
[0113] In any one of the embodiments disclosed herein, the structural moiety  has the structure of .

[0114] In any one of the embodiments disclosed herein, the structural moiety  has the structure of .

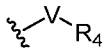
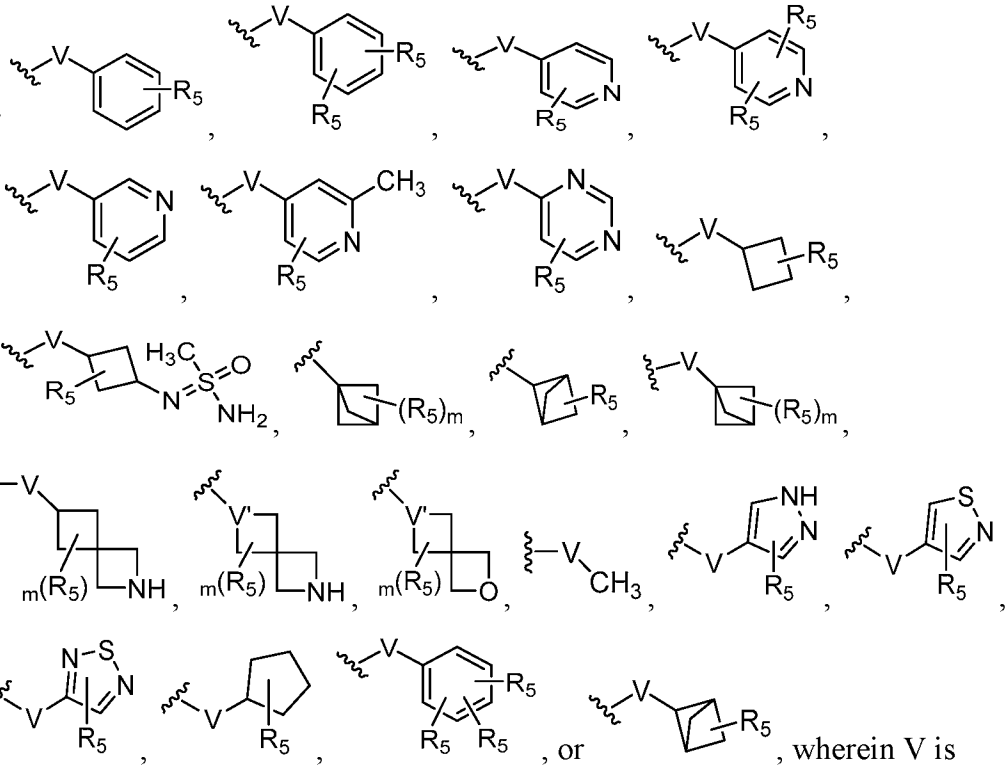
[0115] In any one of the embodiments disclosed herein, the structural moiety  has the structure of .

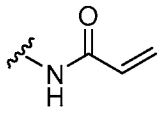
[0116] In any one of the embodiments disclosed herein, the V and R_4 of the structural moiety  taken together form a (C_4-C_{10})heterospiroalkyl.

[0117] In any one of the embodiments disclosed herein, V is absent.

[0118] In any one of the embodiments disclosed herein, R_4 is (C_1-C_6)alkyl, , , , , , , , wherein m is an integer from 0-3.

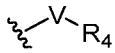
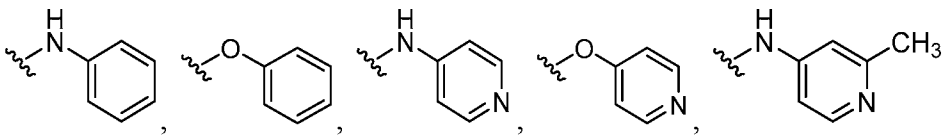
[0119] In any one of the embodiments disclosed herein, each occurrence of R_5 is independently H, (C_1-C_6)alkyl, halogen, OR_a, OH, NH_2, $N(R_a)COR_a$, CN, CF_3, (C_1-C_6)haloalkyl, or and each occurrence of R_a is independently H, (C_2-C_6)alkenyl, or (C_1-C_6)alkyl.

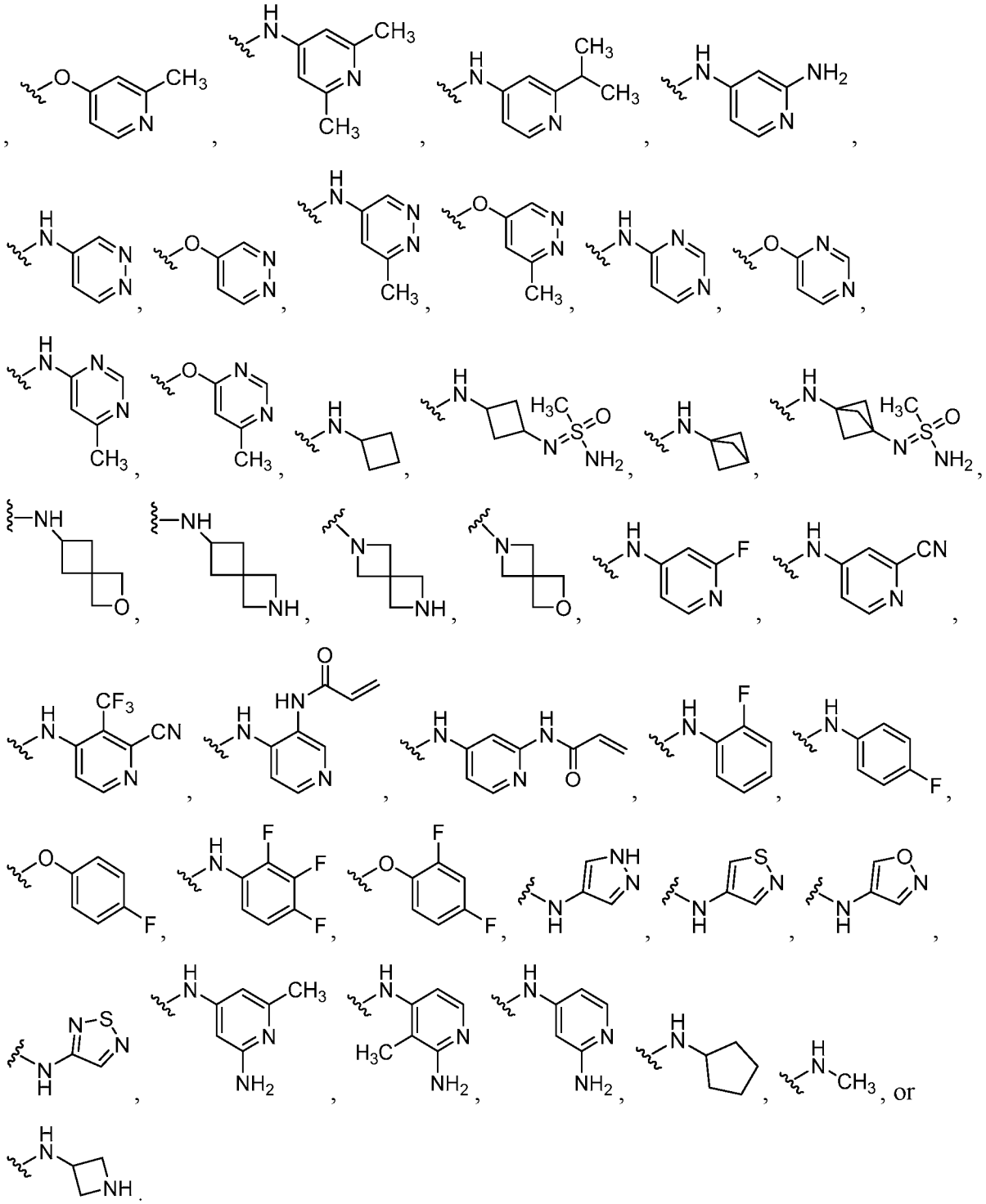
[0120] In any one of the embodiments disclosed herein, the structural moiety  has the structure of , wherein V is $C(R_a)_2$, O, NR_a, $N(C{=}O)R_a$, or NSO_2R_a and V' is CR_a or N.

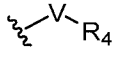
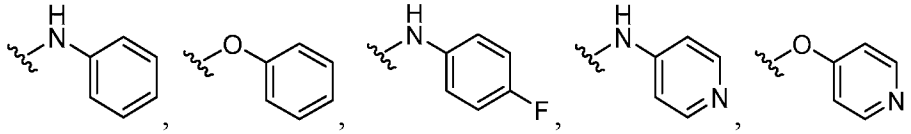
[0121] In any one of the embodiments disclosed herein, each occurrence of R_5 is independently H, CH_3, isopropyl, halogen, OH, CN, , CF_3, $(C_1\text{-}C_6)$haloalkyl, or NH_2.

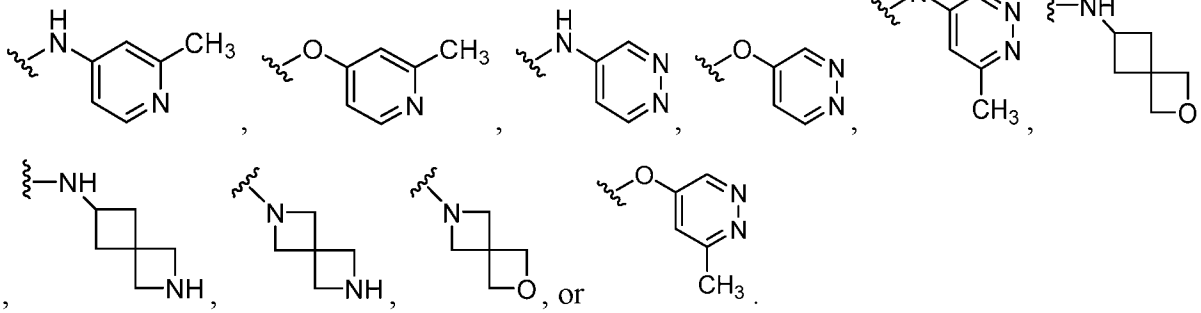
[0122] In any one of the embodiments disclosed herein, each occurrence of R_a is independently H, $(C_2\text{-}C_6)$alkenyl, or $(C_1\text{-}C_6)$alkyl.

[0123] In any one of the embodiments disclosed herein, each occurrence of R_a is H, CH_3, or CH_2CH_3.

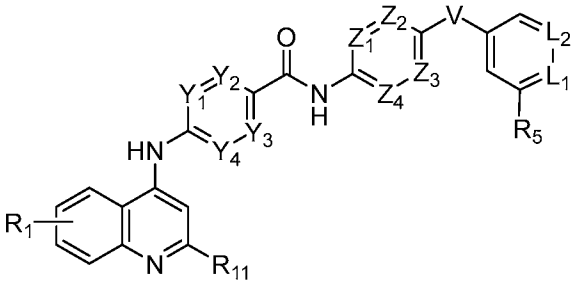
[0124] In any one of the embodiments disclosed herein, the structural moiety  has the structure of 



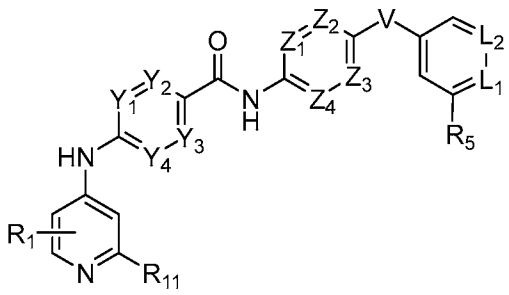
[0125] In any one of the embodiments disclosed herein, the structural moiety  has the structure of 



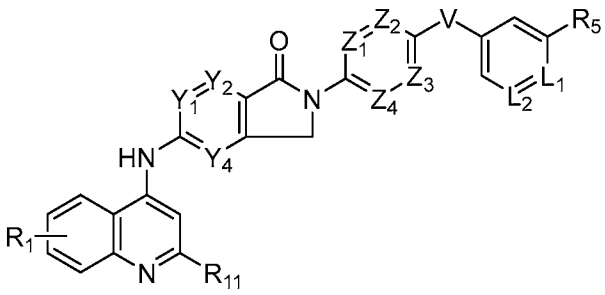
[0126] In any one of the embodiments disclosed herein, the compound of Formula Ia has the structure of



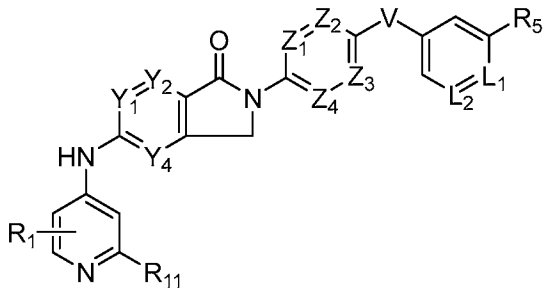
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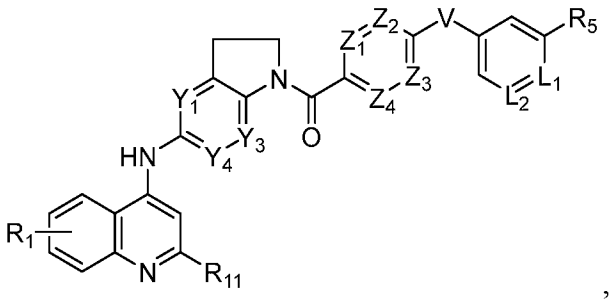
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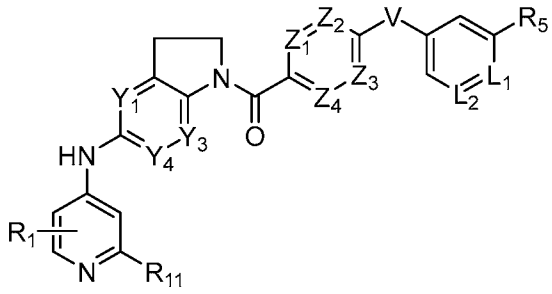
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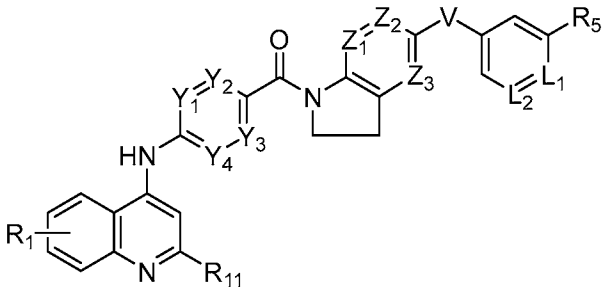
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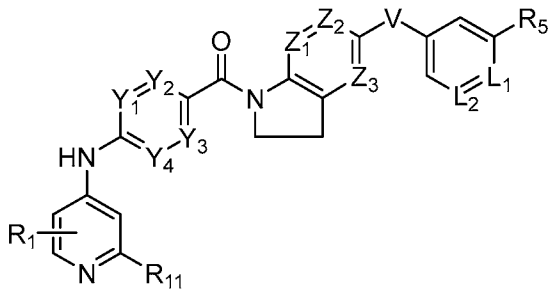
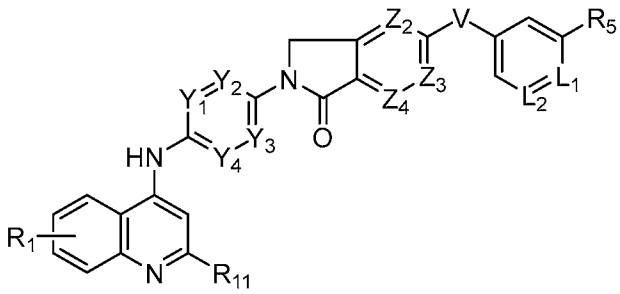
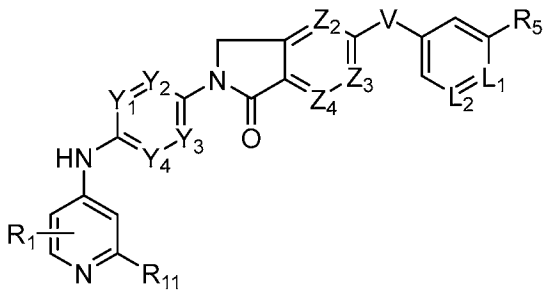
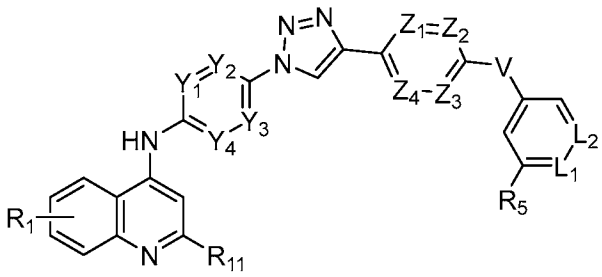
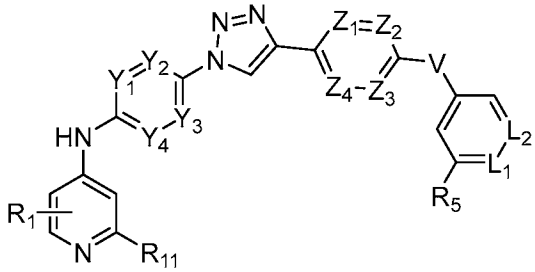
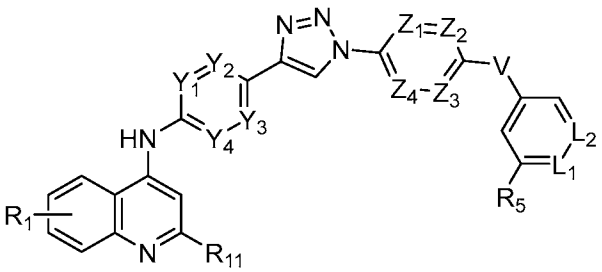
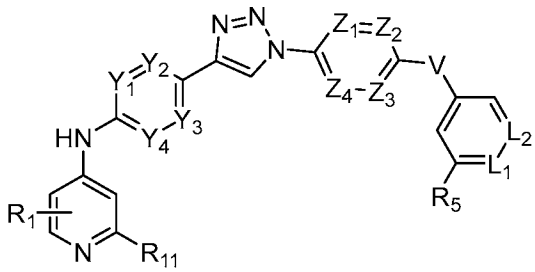
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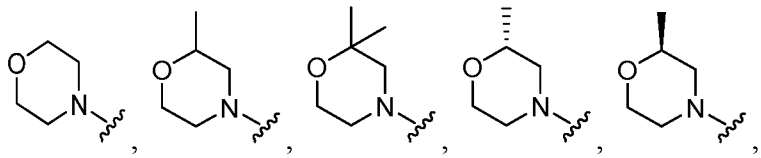
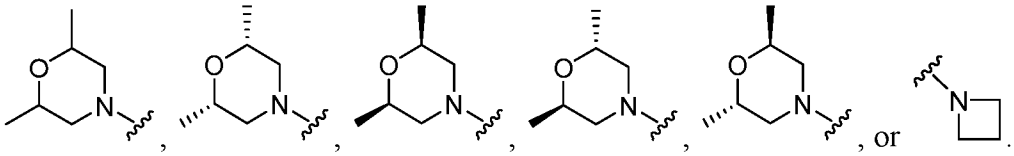


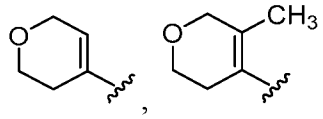
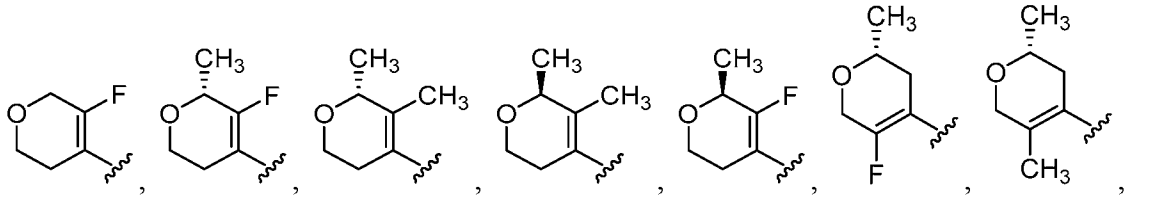
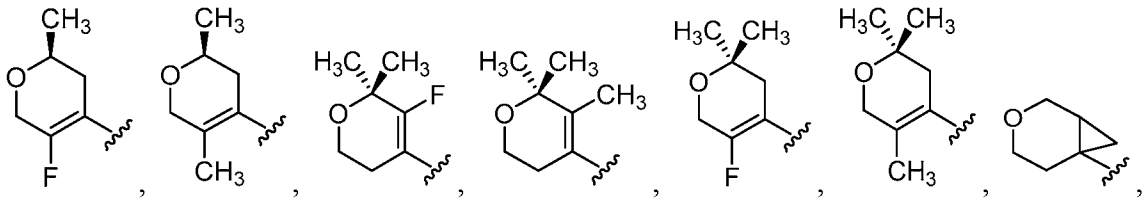
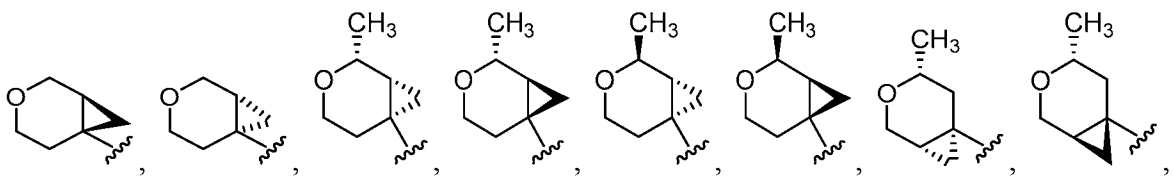
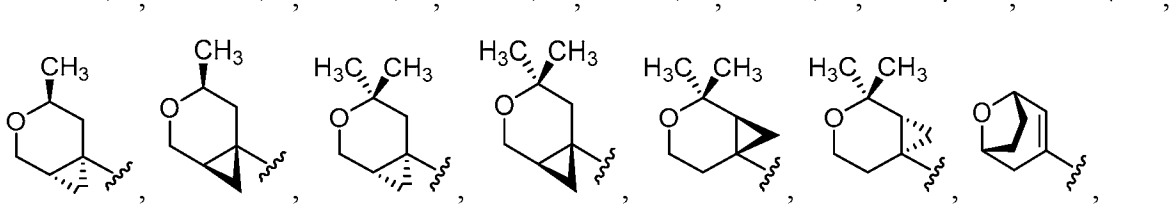
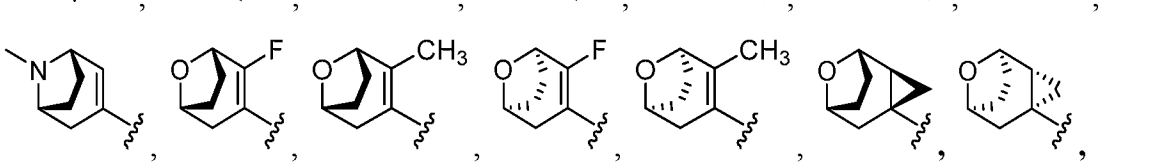
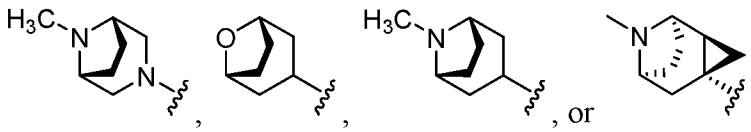
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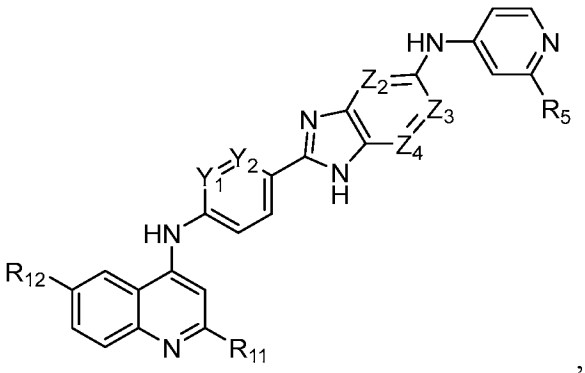
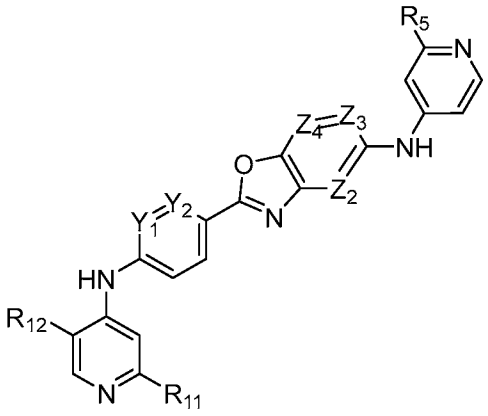
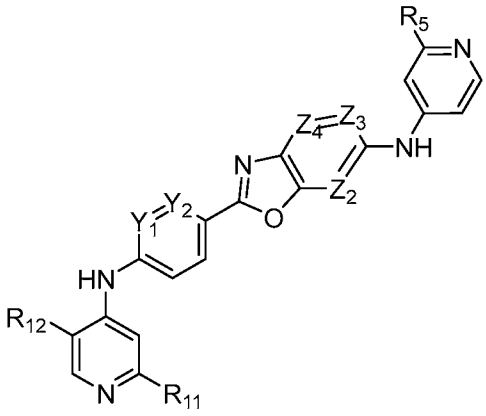
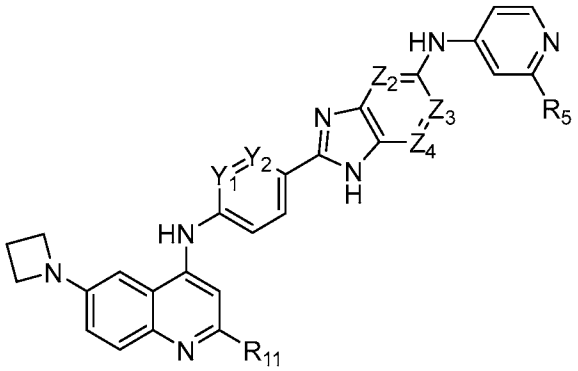
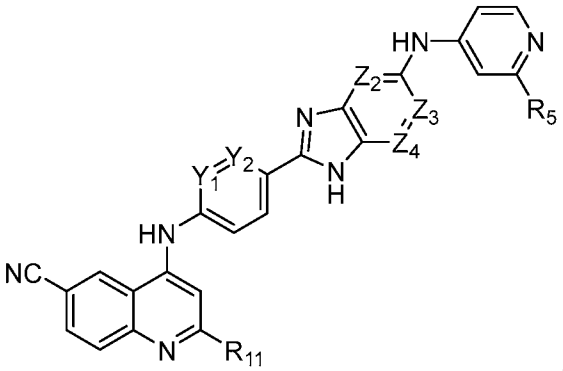
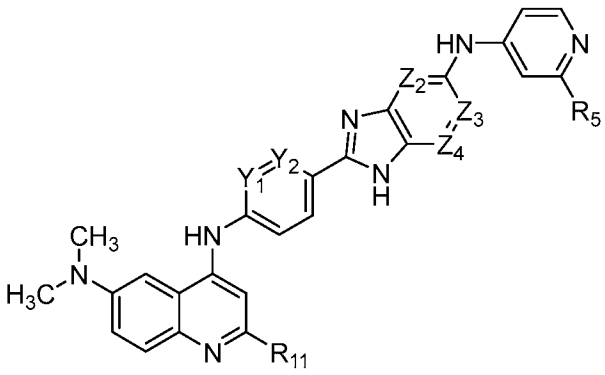


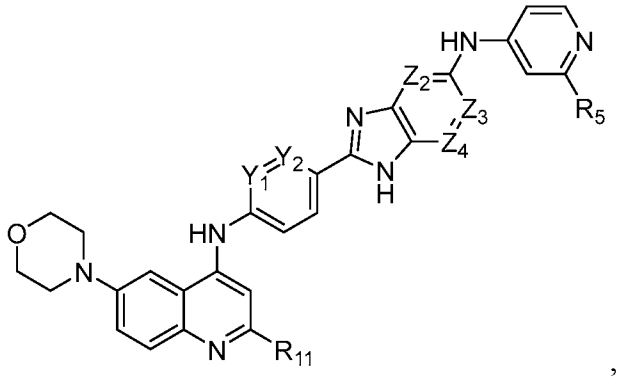
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, or

, wherein R_1 is H, $(C_1\text{-}C_6)$alkyl, $N(R_a)_2$, $(C_3\text{-}C_7)$heterocycloalkyl, halogen, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, or $(C_4\text{-}C_{14})$heterotricycloalkenyl; R_5 and R_{11} are each independently H, halogen, 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.

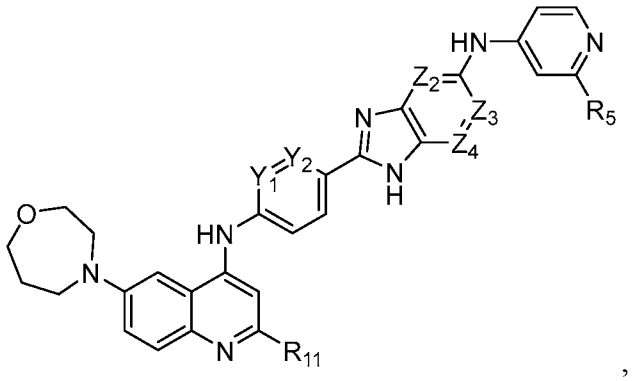
[0127] In any one of the embodiments disclosed herein, R_1 is H, F, Cl, Br, CH_3, CH_2CH_3, $CH(CH_3)_2$, NH_2, NMe_2, , , or .

[0128] In any one of the embodiments disclosed herein, R_1 is , , , , , , or .

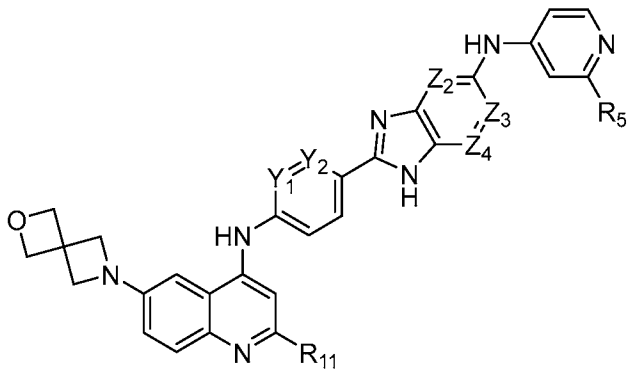
[0129] In any one of the embodiments disclosed herein, the compound of Formula Ib has the structure of , , , , , .



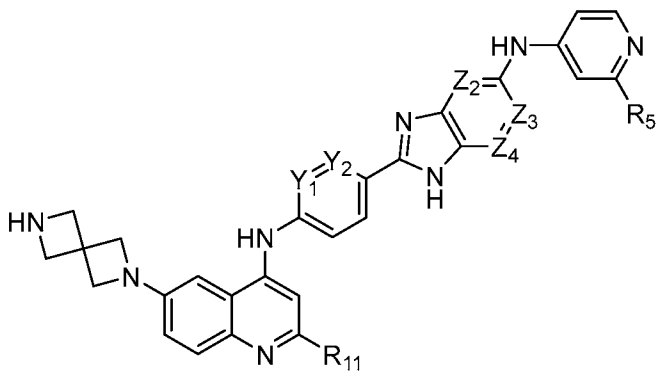
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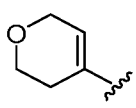
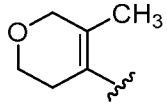


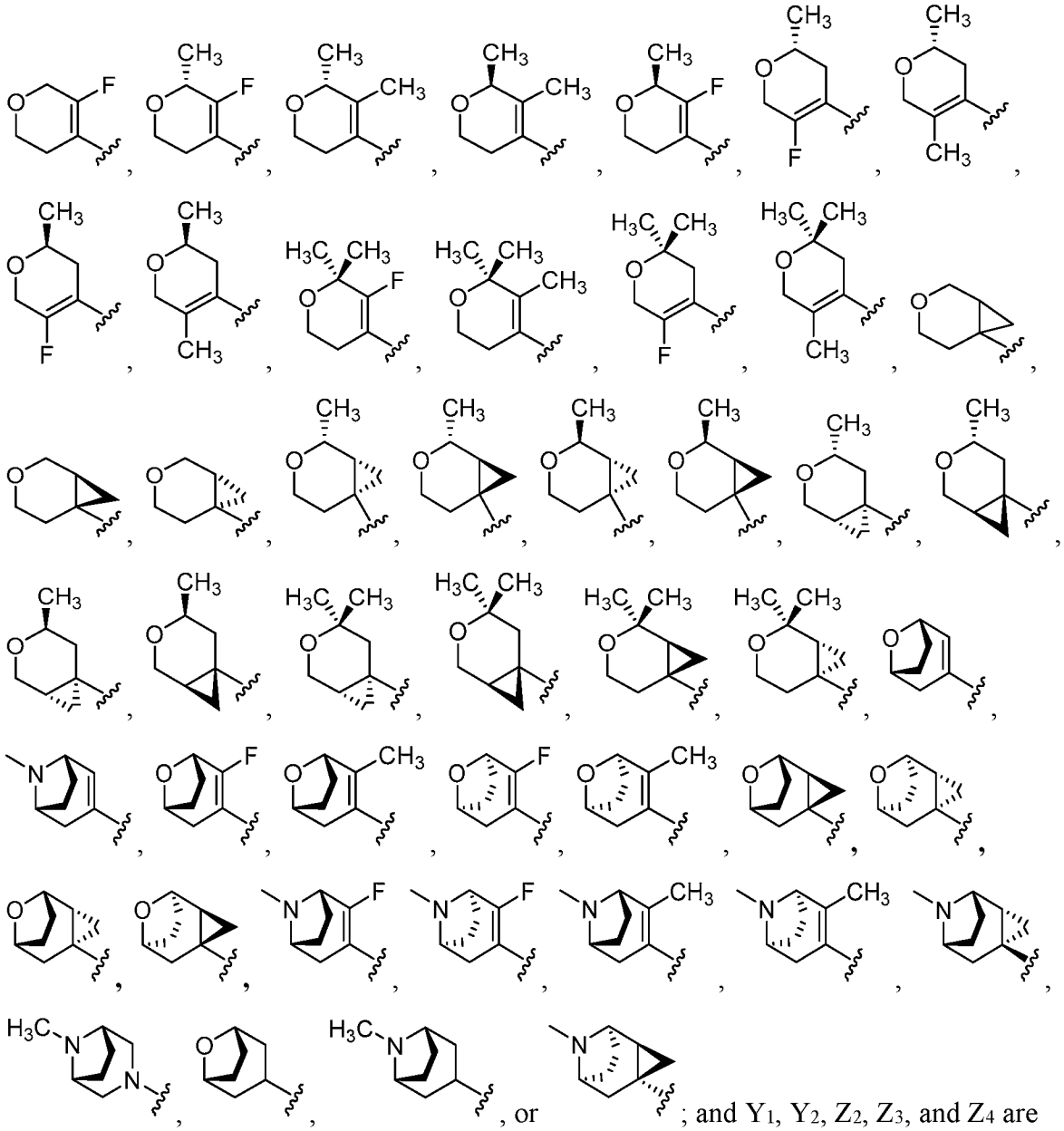
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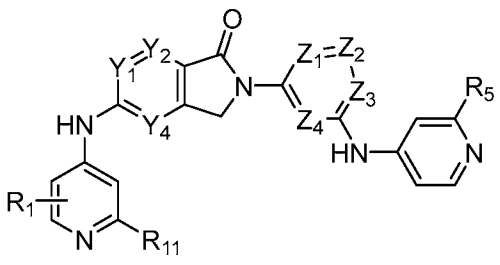
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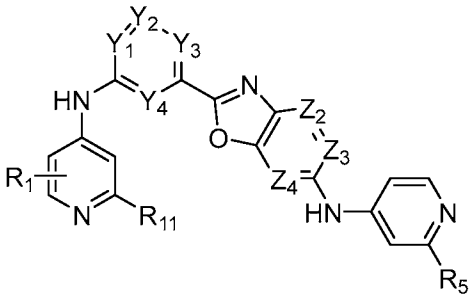
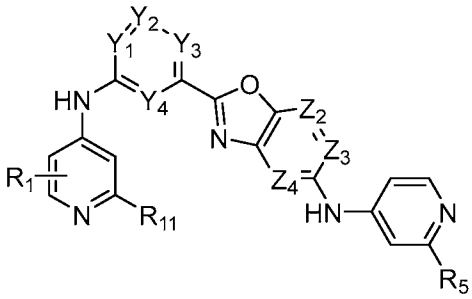


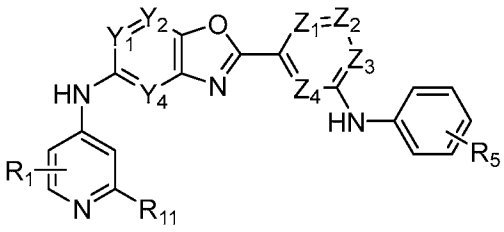
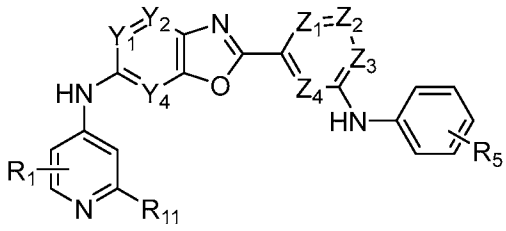
, wherein R_{11} and R_5 are each independently H, halogen, or CH_3; R_{12} is H, halogen, CH_3, , ,

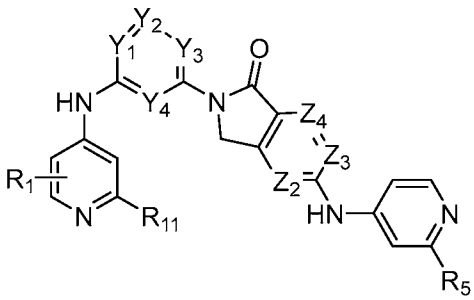


; and Y_1, Y_2, Z_2, Z_3, and Z_4 are each independently CH or N.

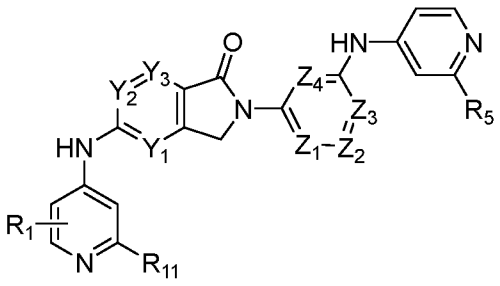
[0130] In any one of the embodiments disclosed herein, the compound of Formula IIa has the structure of , wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_4, Z_1, Z_2, Z_3, and Z_4 are each independently CH or N.

[0131] In any one of the embodiments disclosed herein, the compound of Formula IIb has the structure of  or , wherein R_1, R_5, and R_{11} are each independently H, halogen, 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.

[0132] In any one of the embodiments disclosed herein, the compound of Formula IIc has the structure of  or , wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_4, Z_1, Z_2, Z_3, and Z_4 are each independently CH or N.

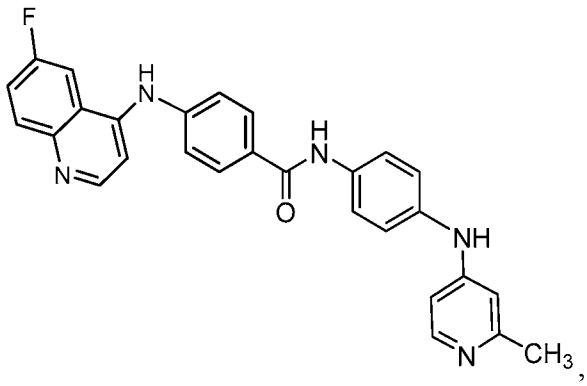
[0133] In any one of the embodiments disclosed herein, the compound of Formula IIIa has the structure of , wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_3, Y_4, Z_2, Z_3, and Z_4 are each independently CH or N.

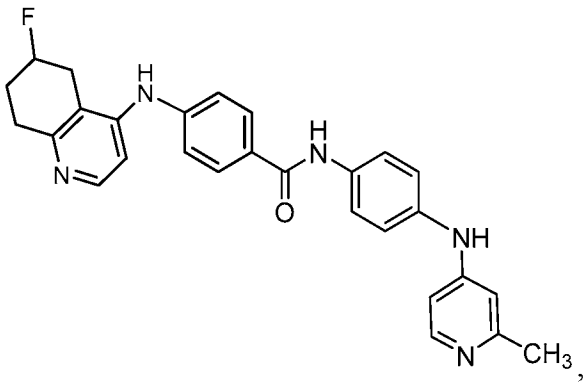
[0134] In any one of the embodiments disclosed herein, the compound of Formula IVa

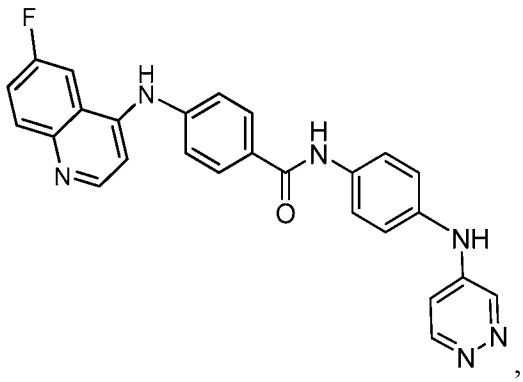


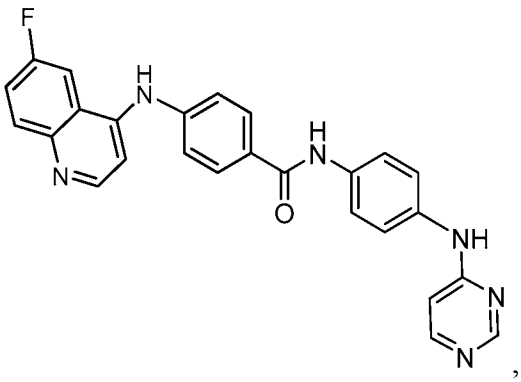
has the structure of , wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_3, Z_1, Z_2, Z_3, and Z_4 are each independently CH or N.

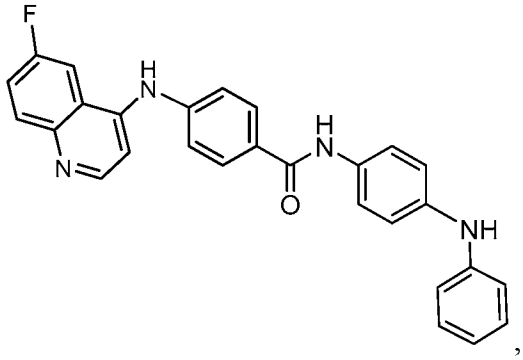
[0135] In any one of the embodiments disclosed herein, the compound of Formula Ia is

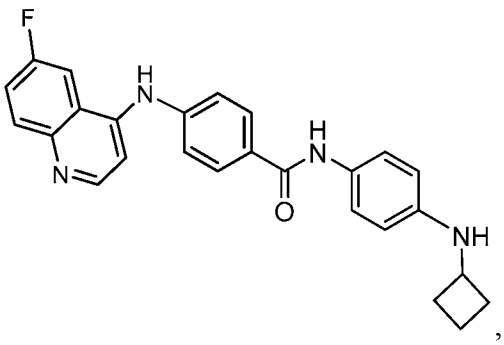


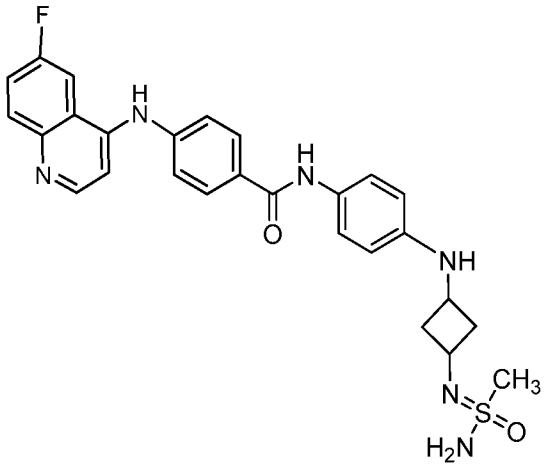


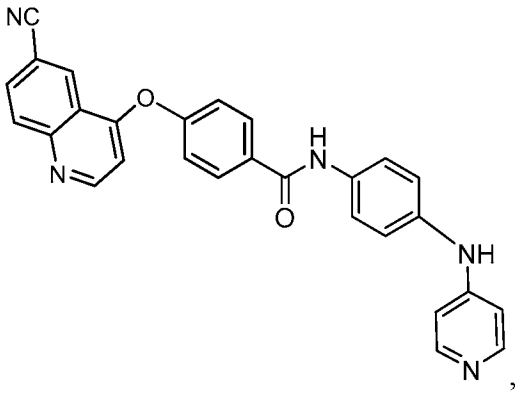


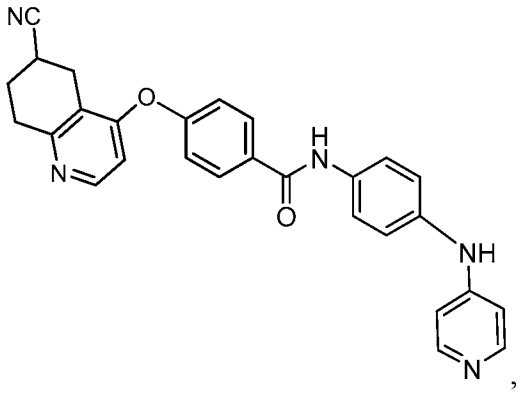


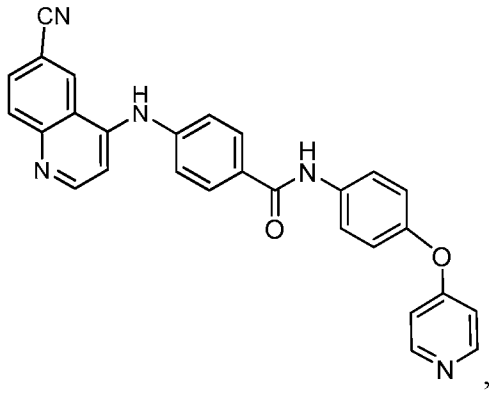


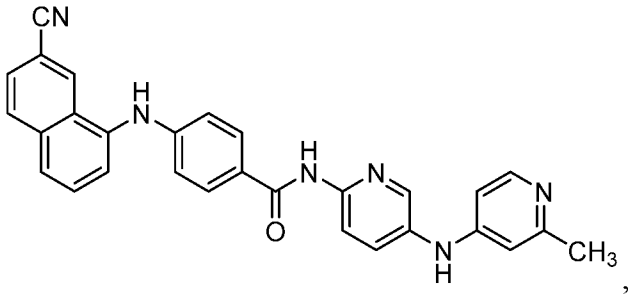


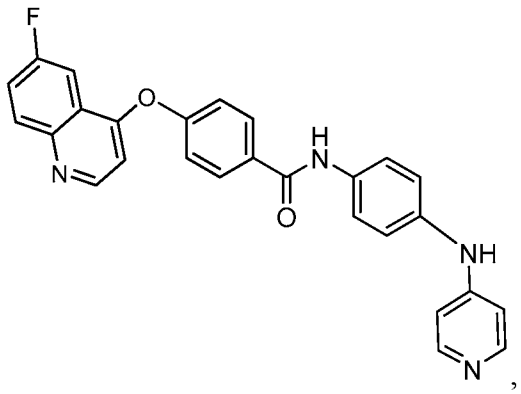


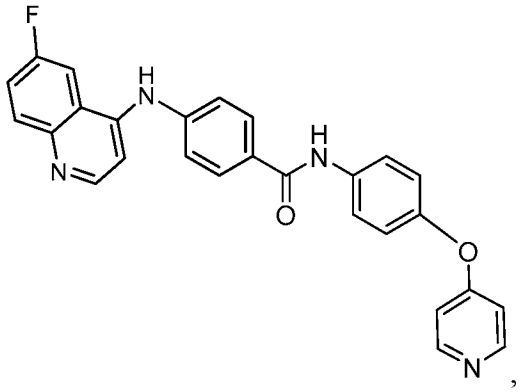


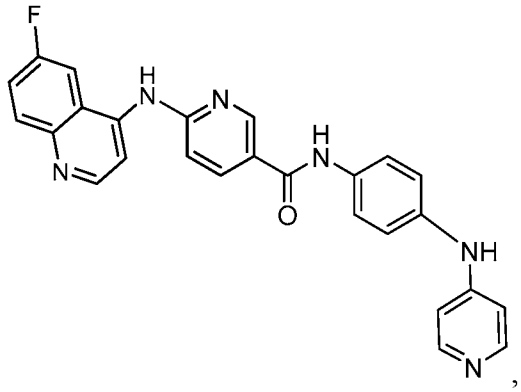


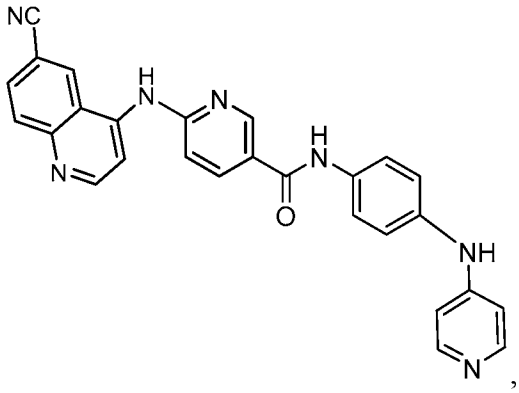




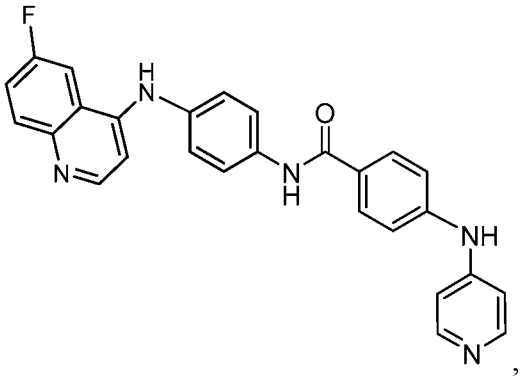




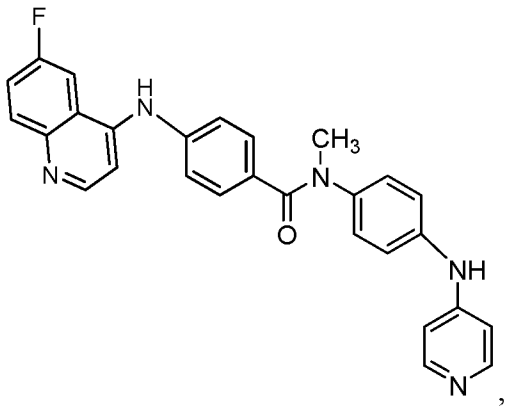




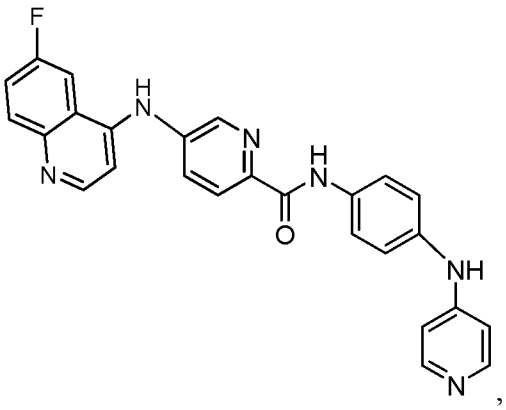
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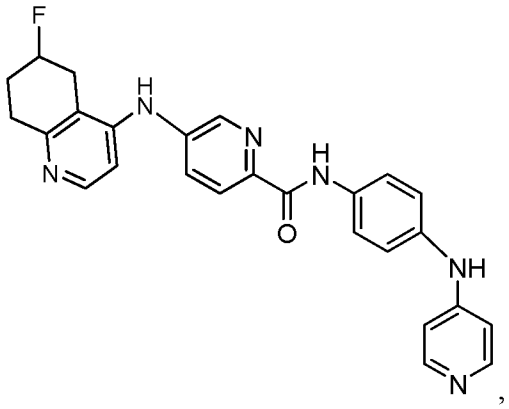
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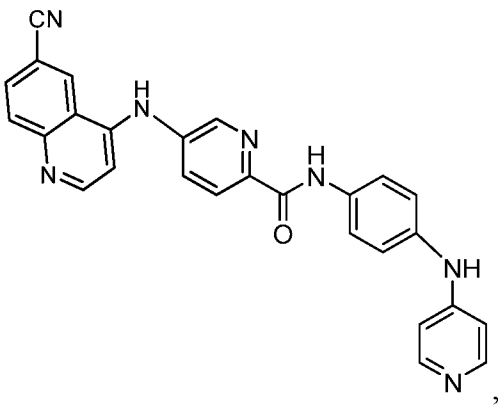
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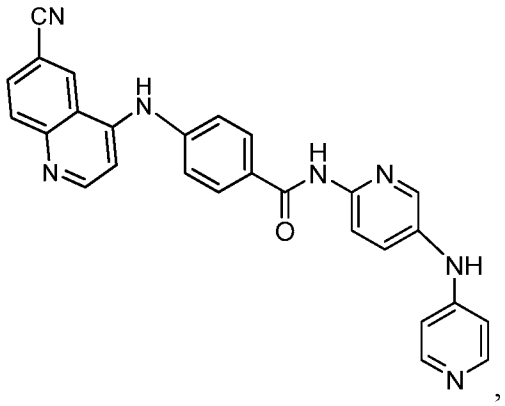
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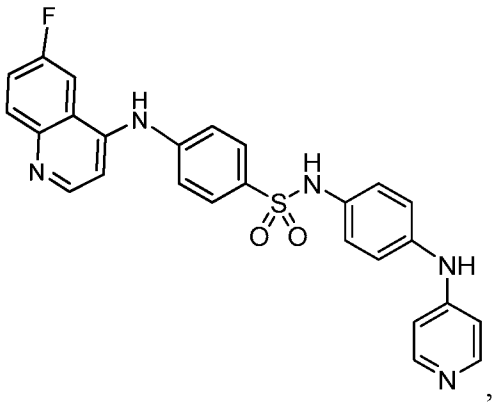
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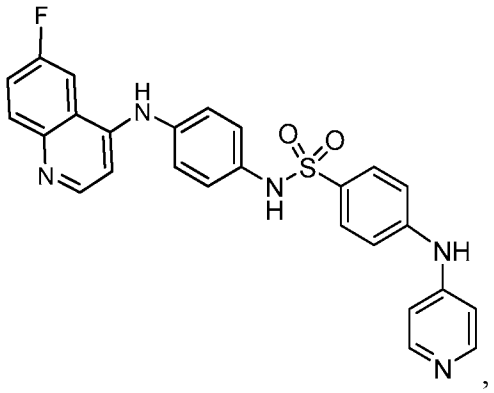
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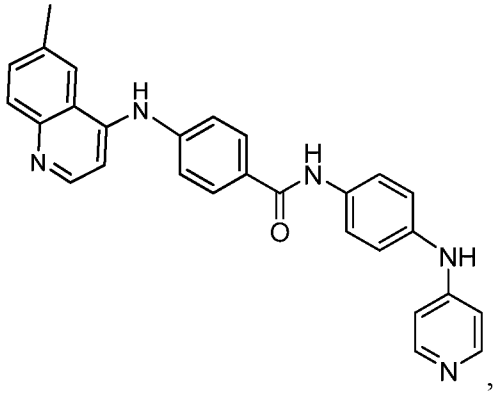
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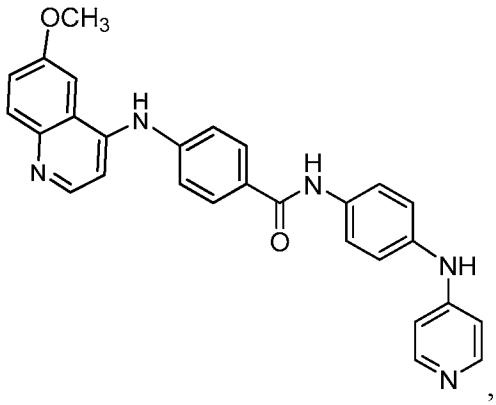
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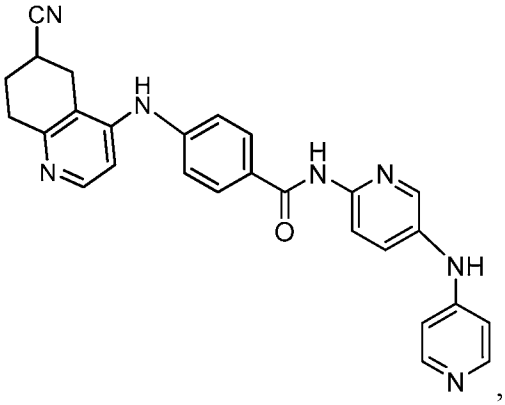
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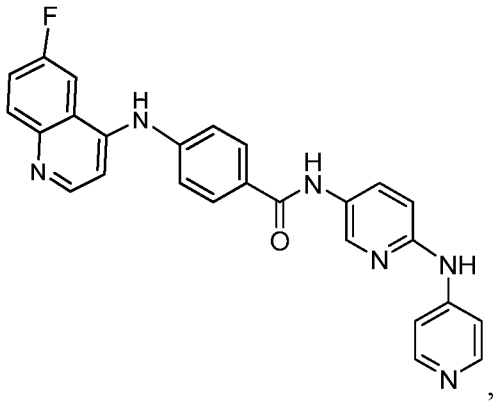
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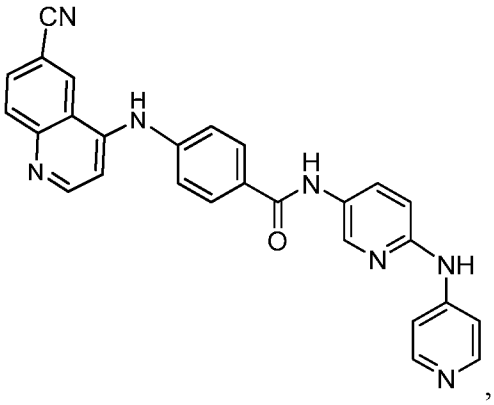
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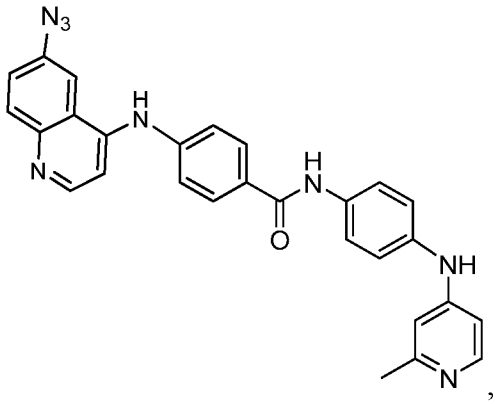
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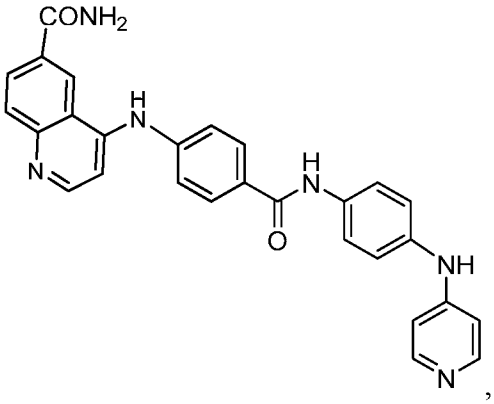
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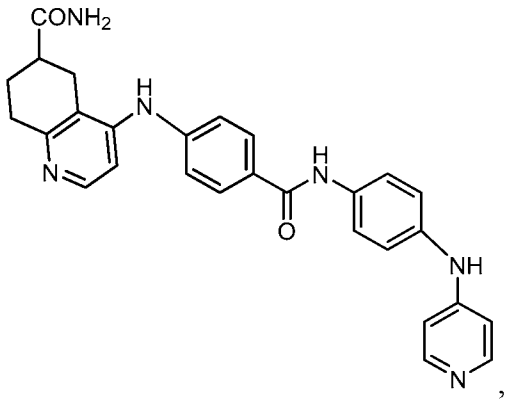
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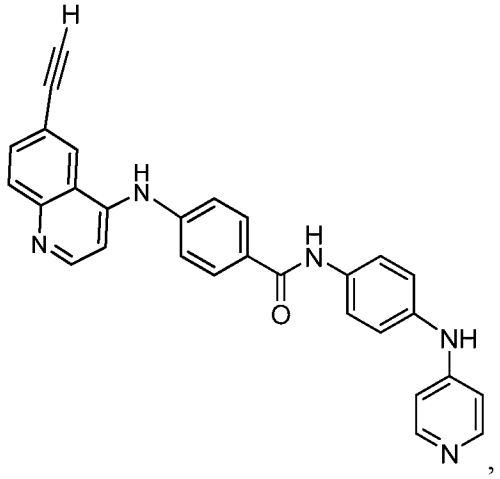
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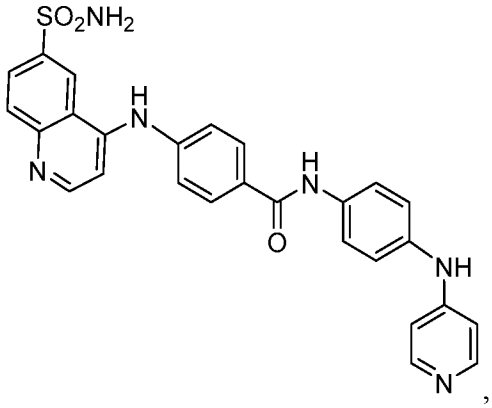
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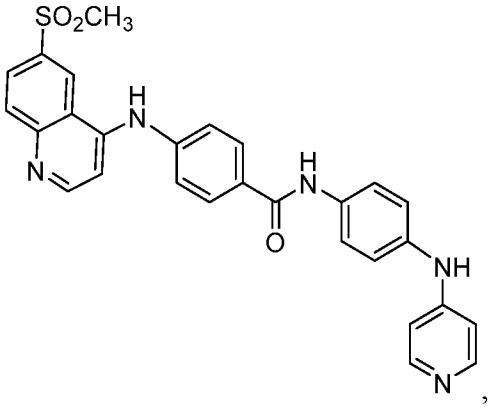
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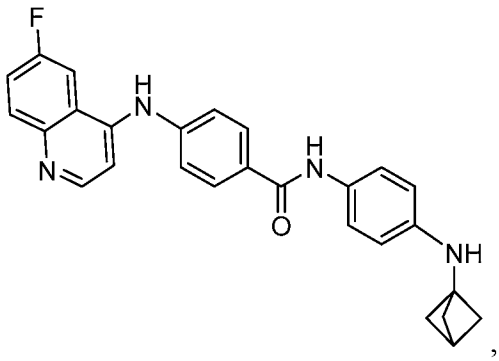
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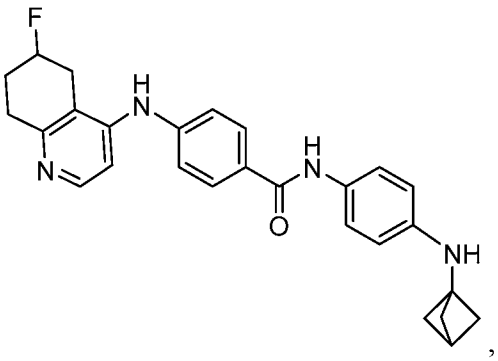
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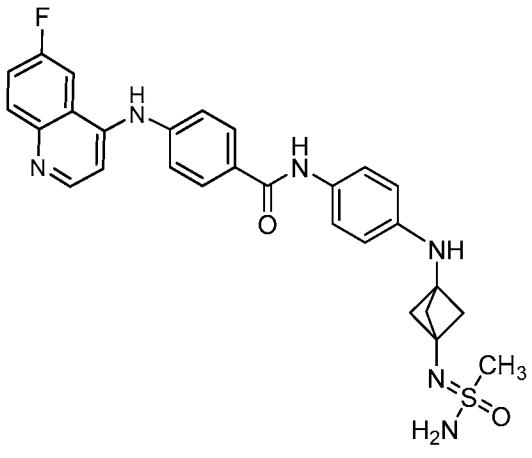
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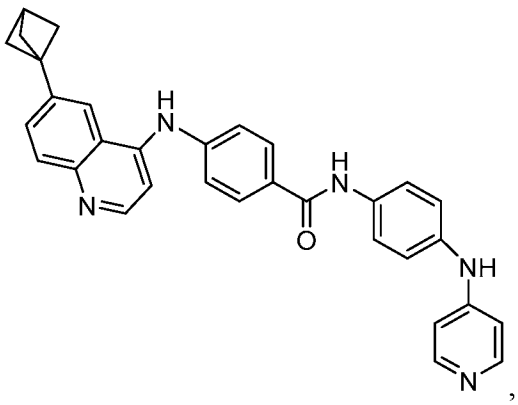
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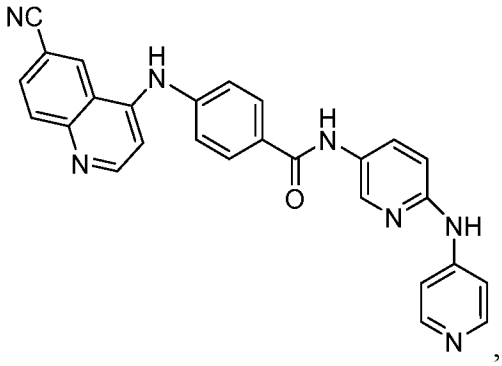
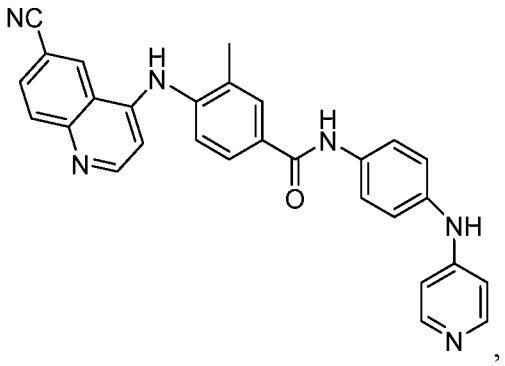
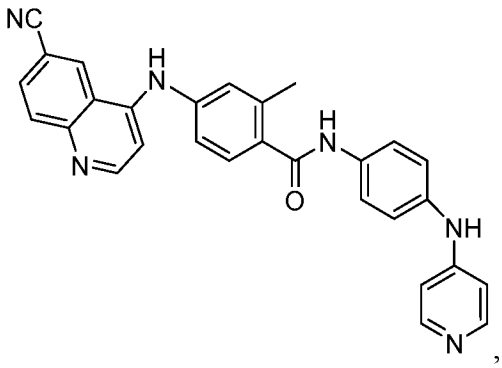
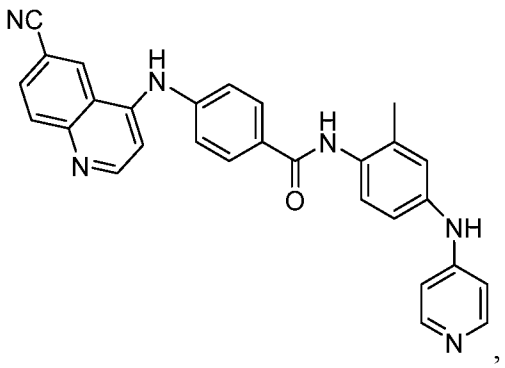
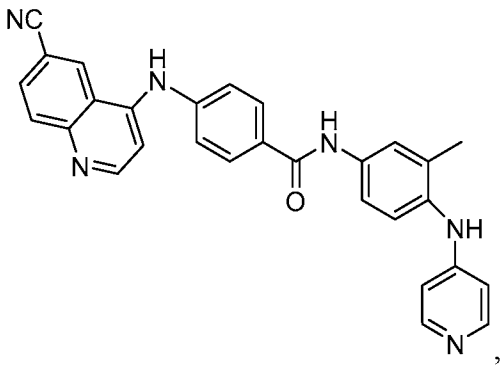
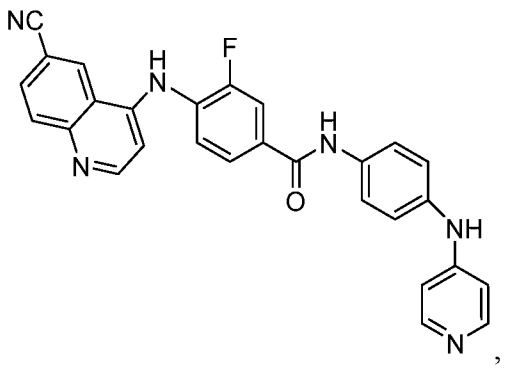
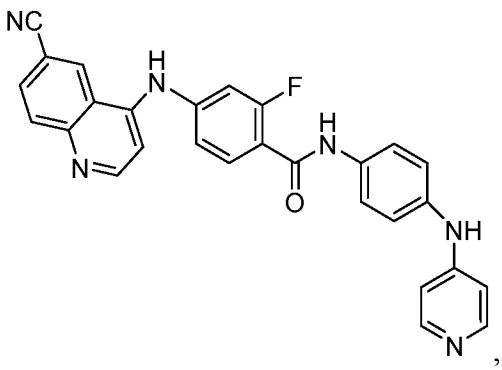
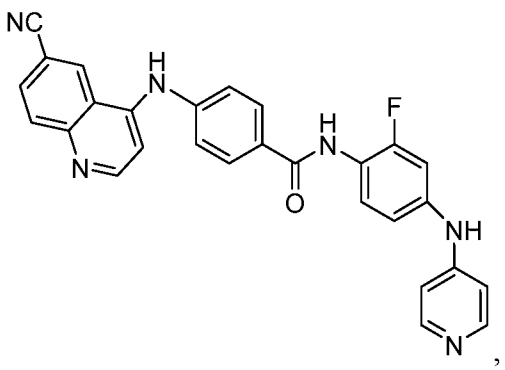
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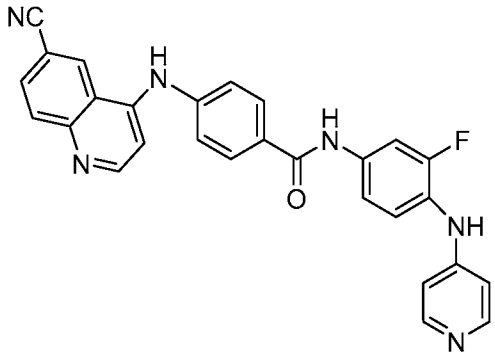
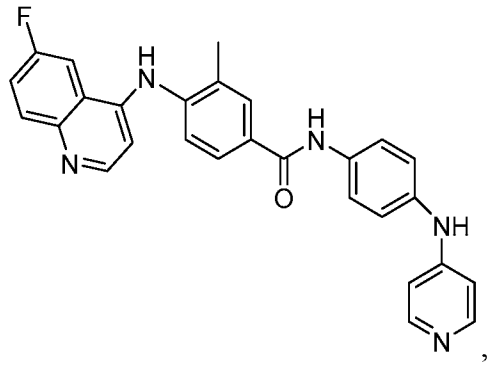
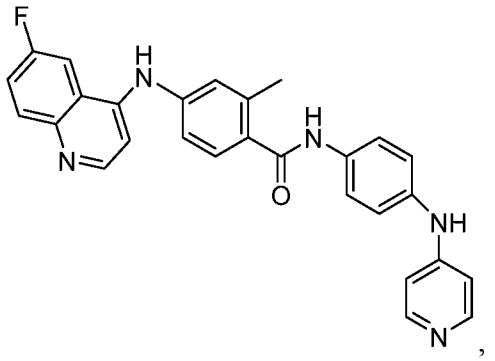
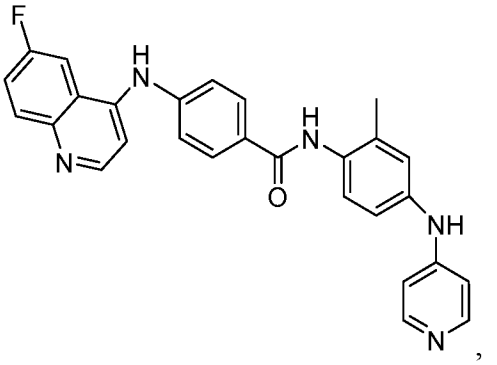
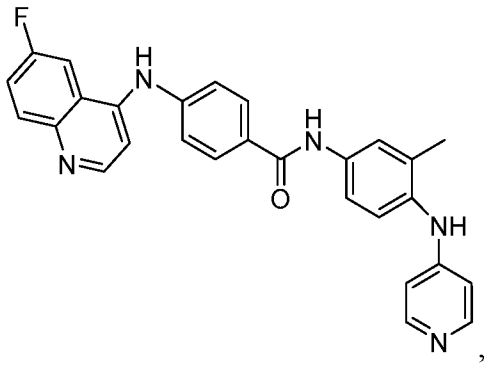
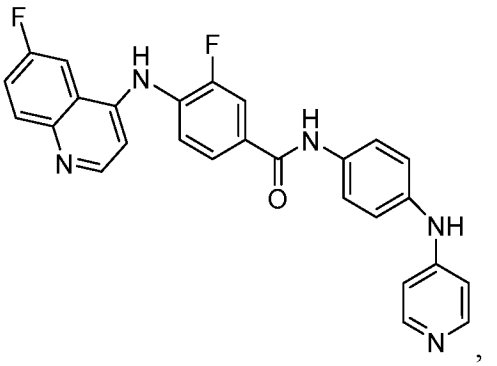
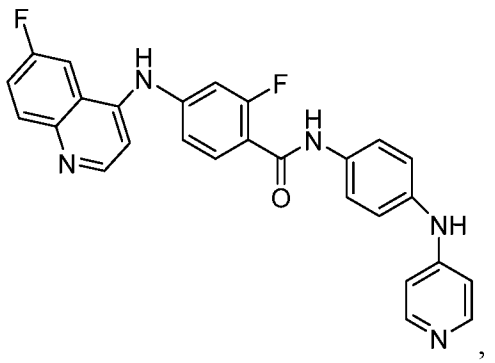
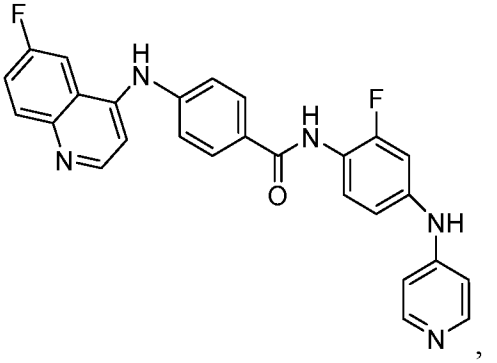


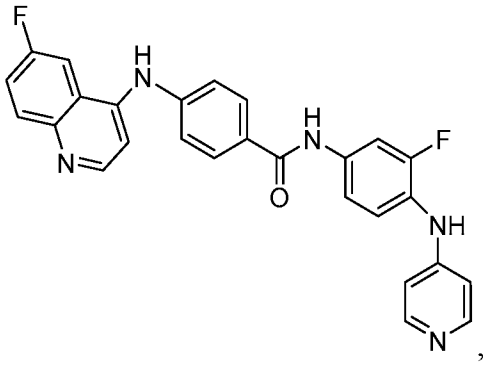
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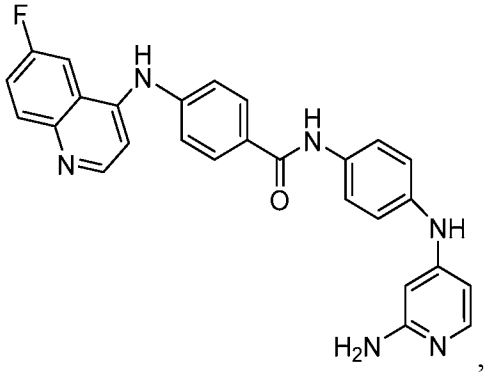


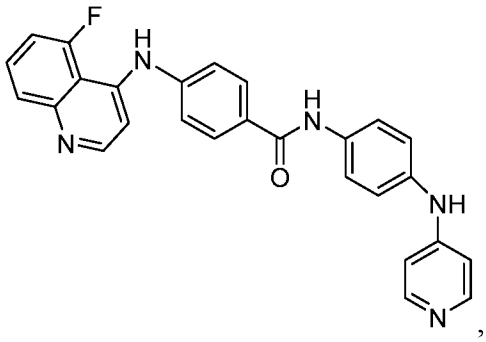
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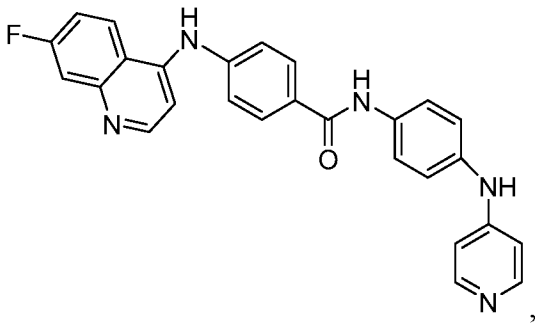

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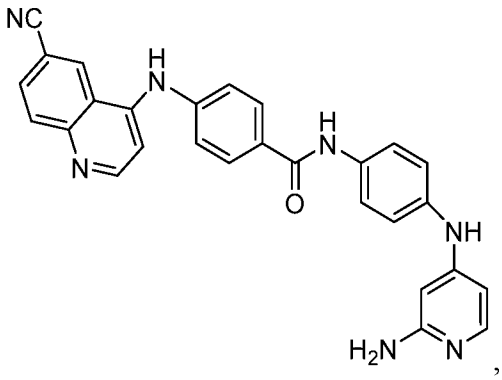

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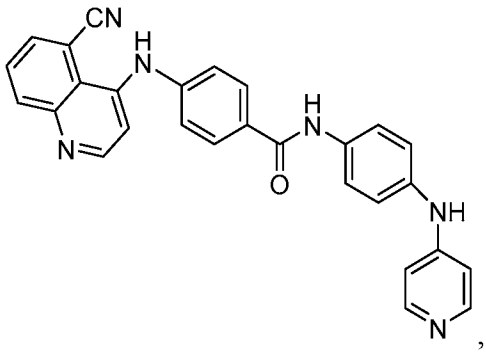


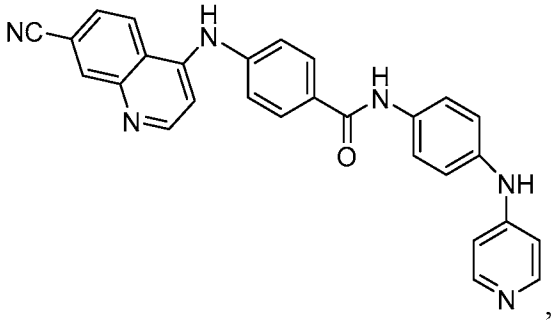


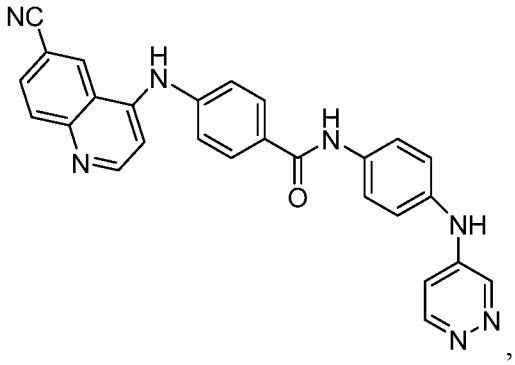


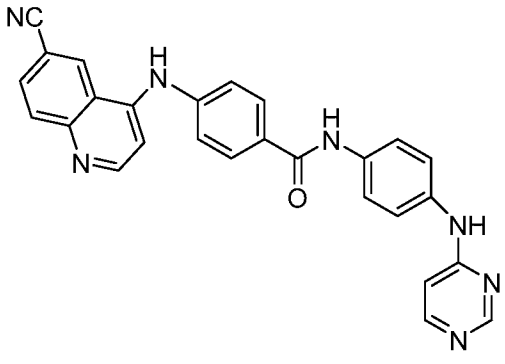


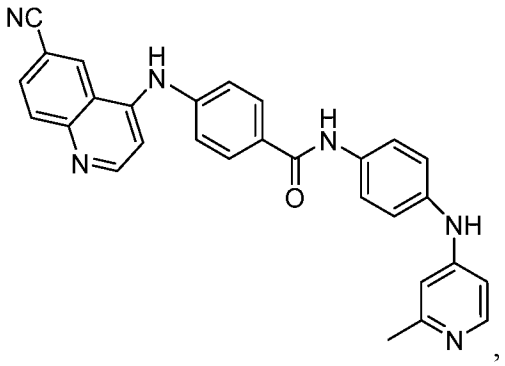


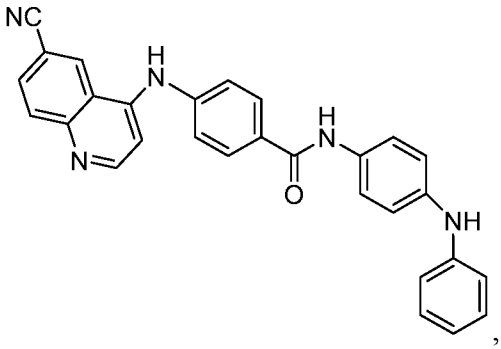


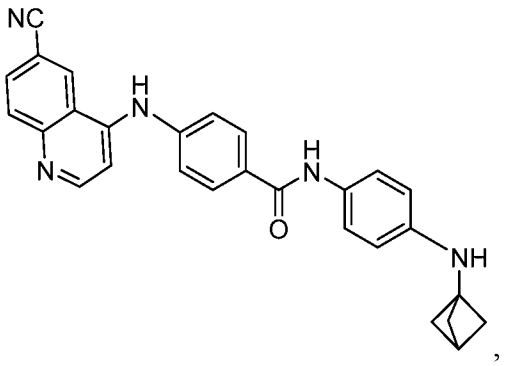

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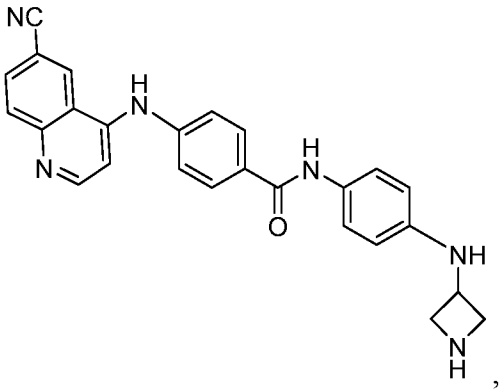

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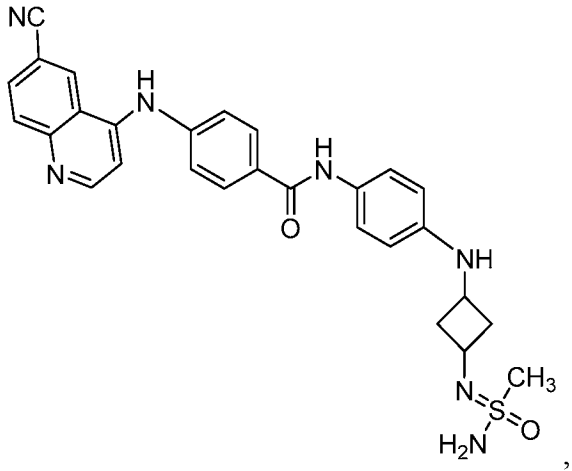

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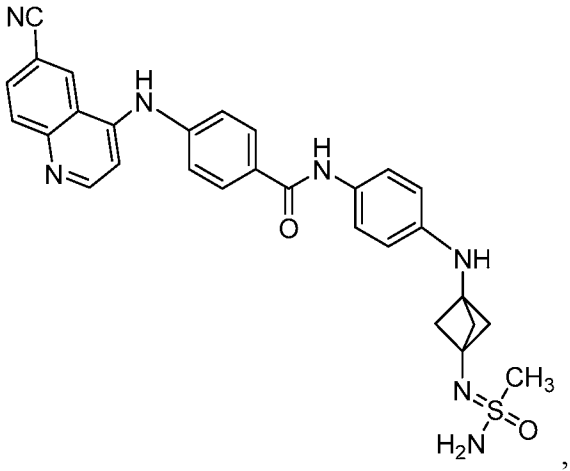

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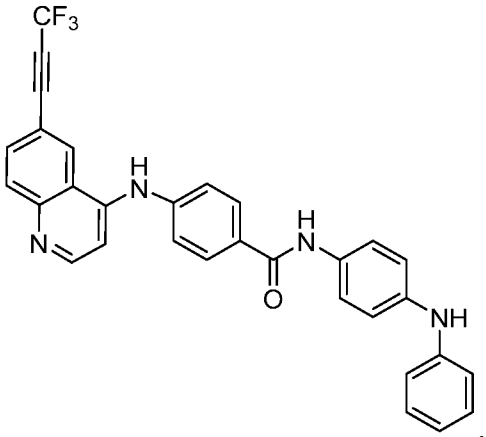

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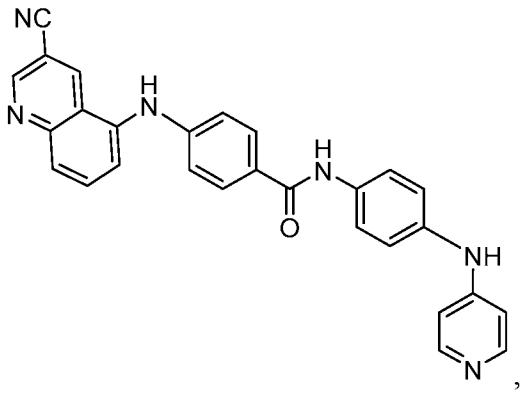
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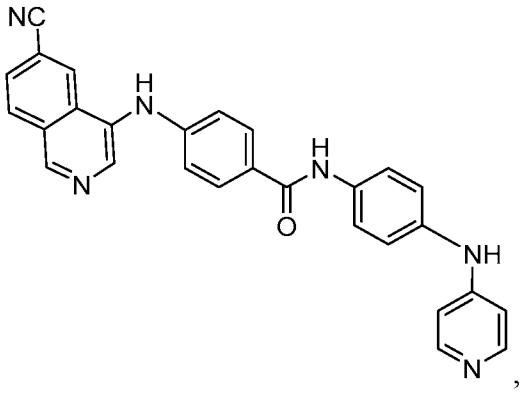
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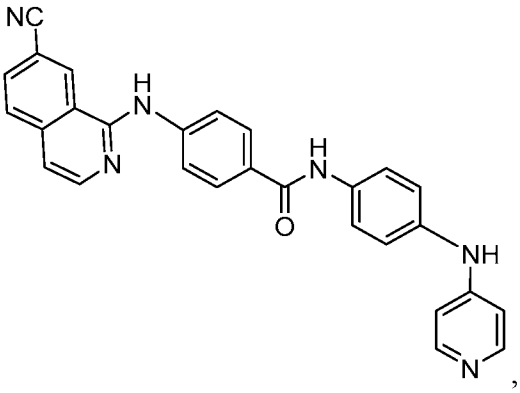
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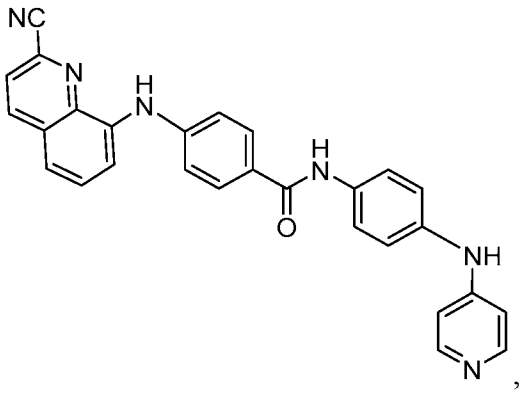
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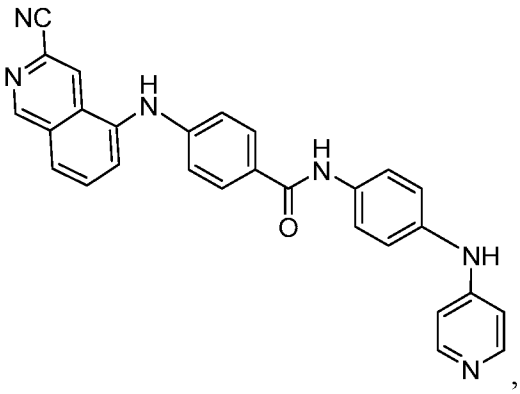
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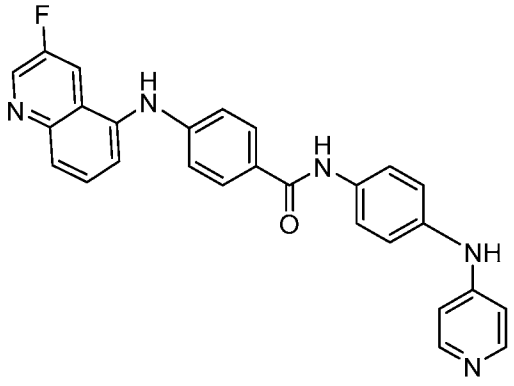
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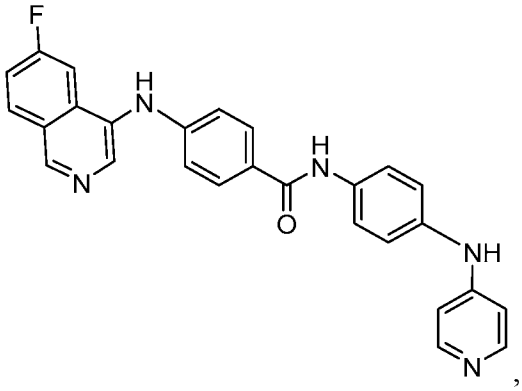


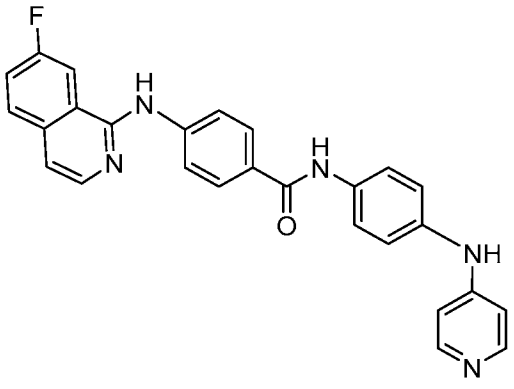
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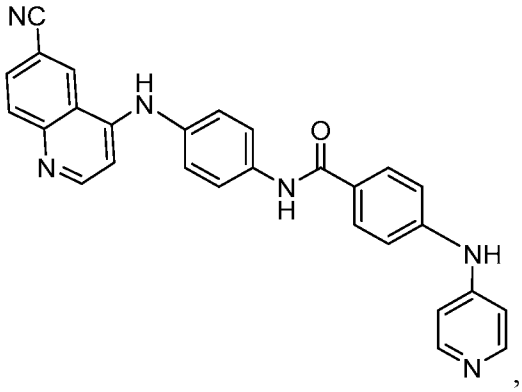


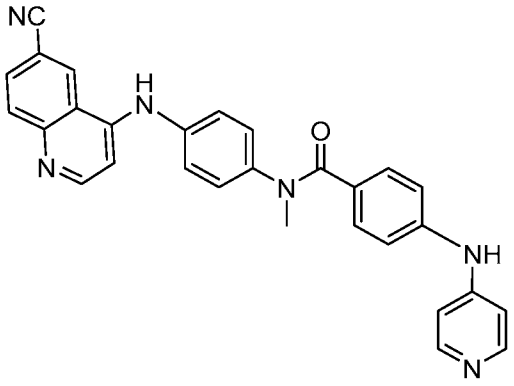
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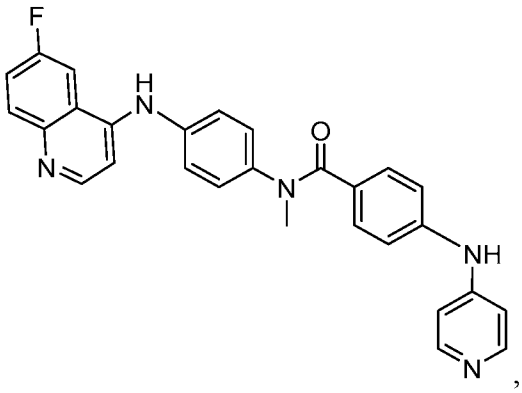


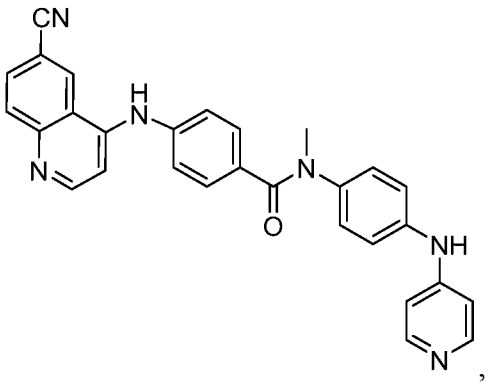


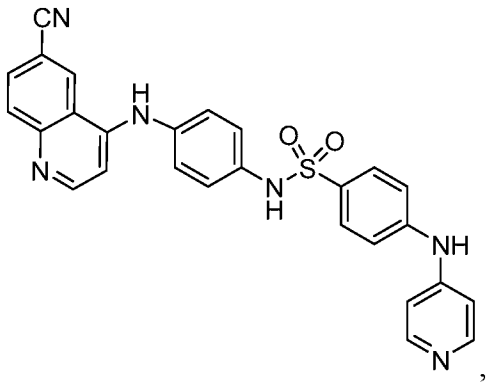


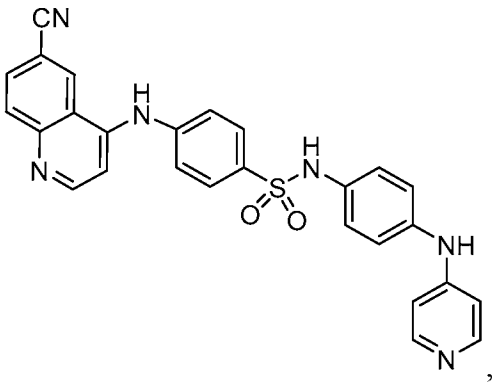


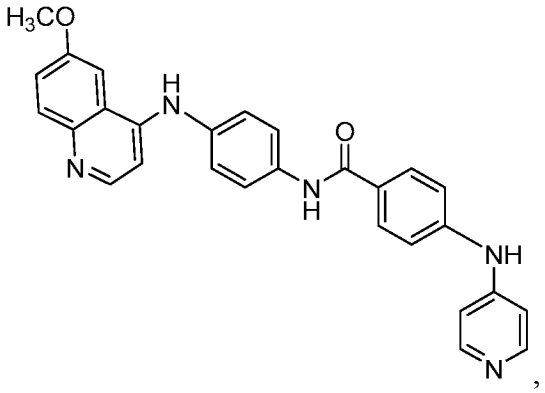


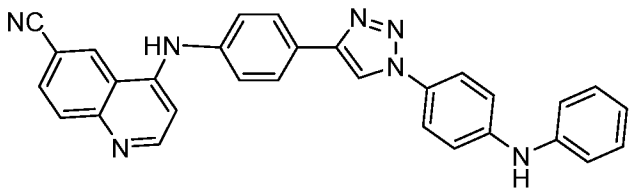


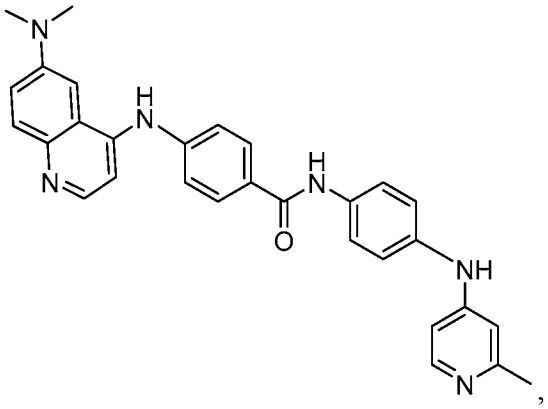


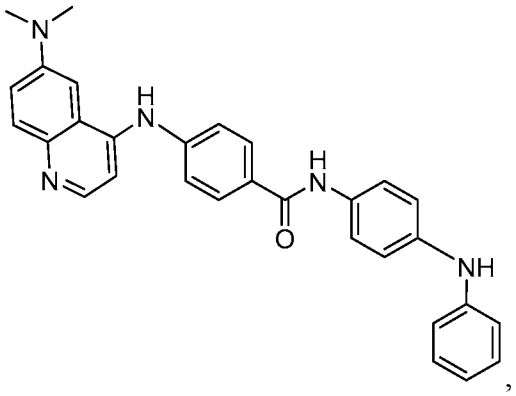


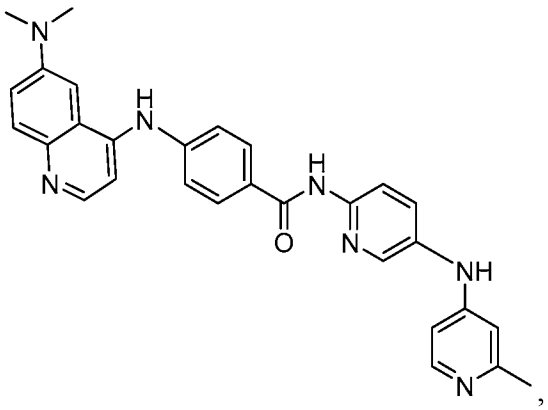


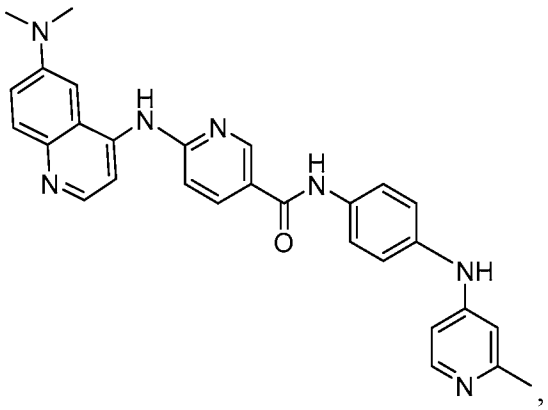


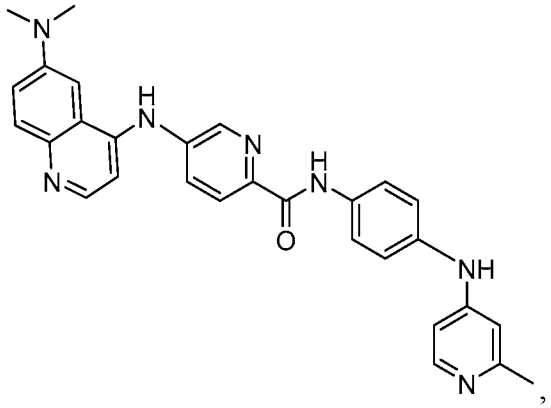


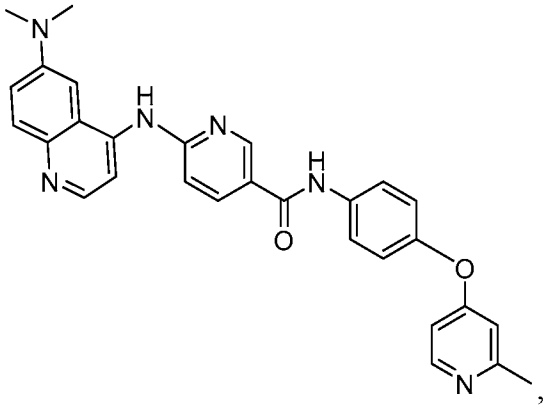


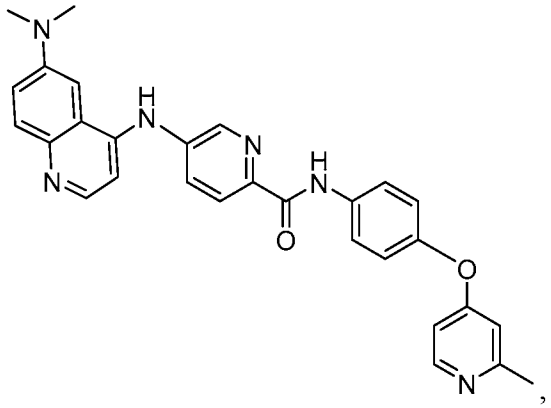


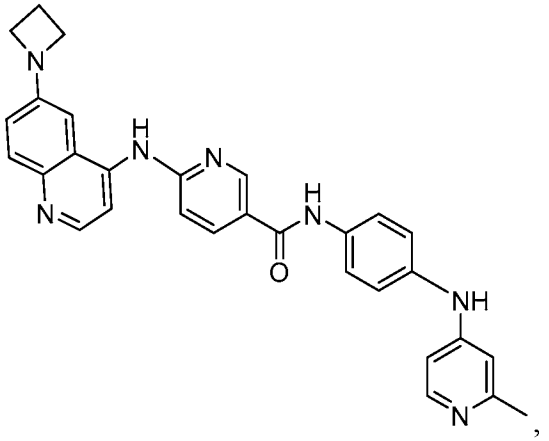


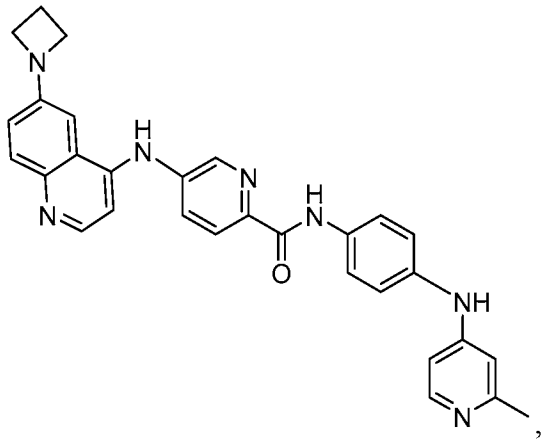


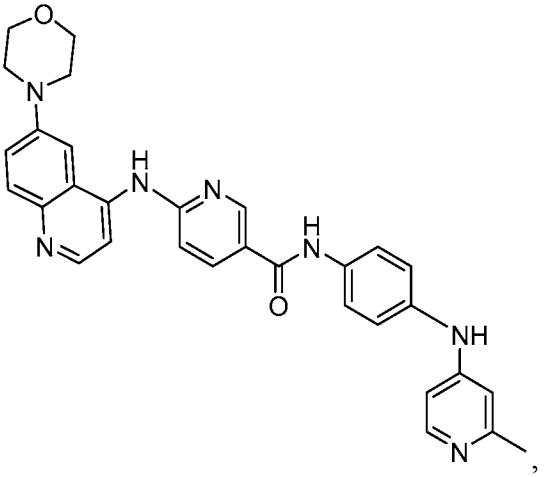


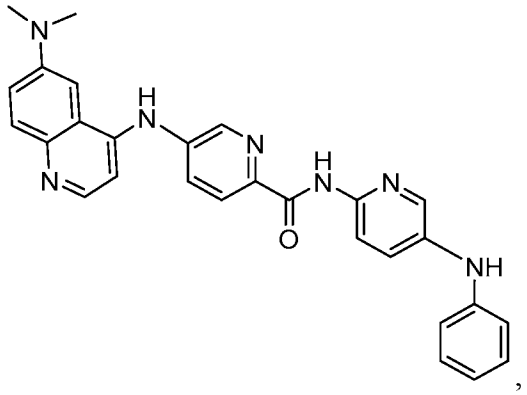


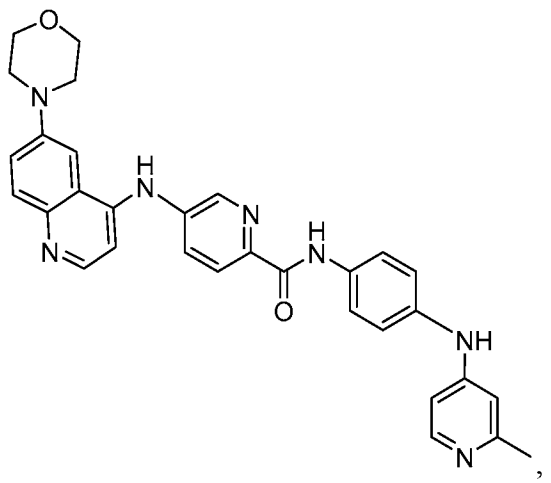


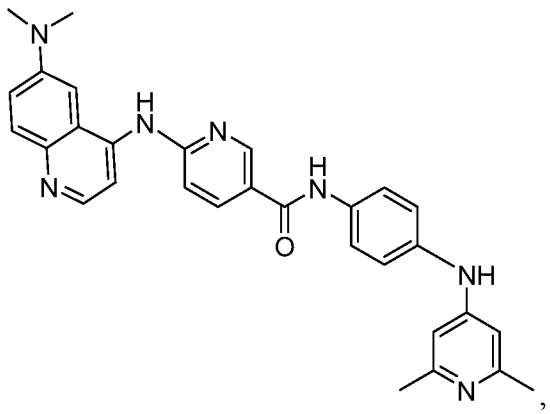


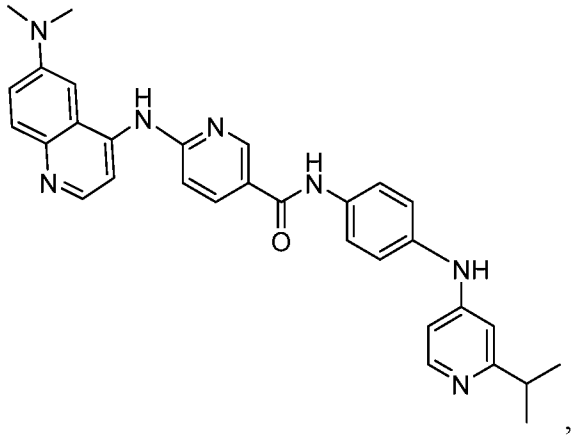


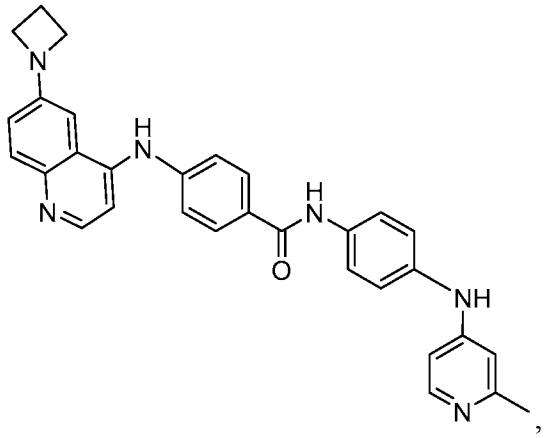


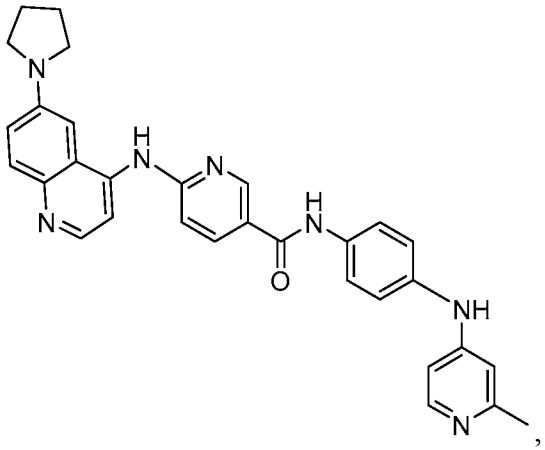


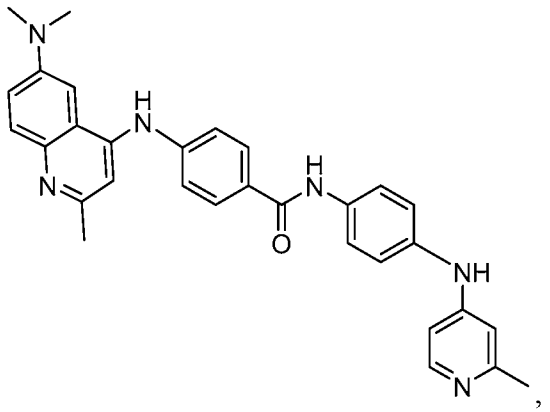


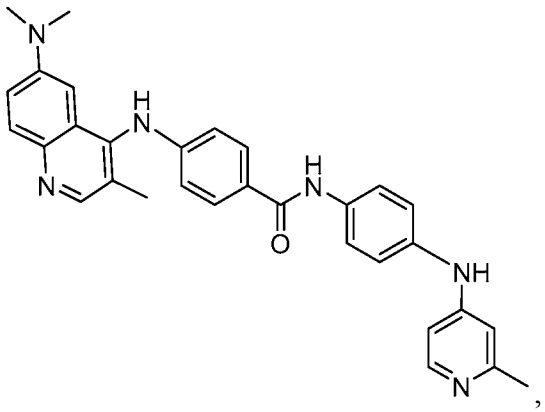


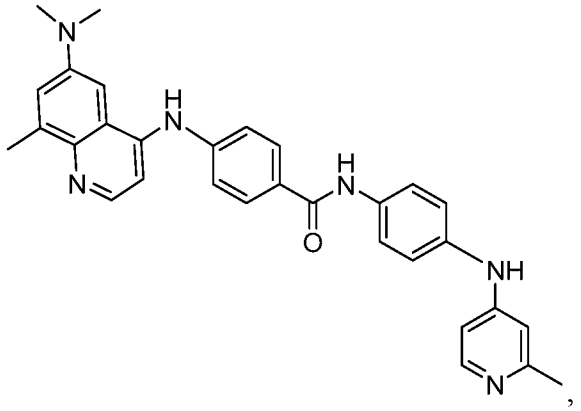


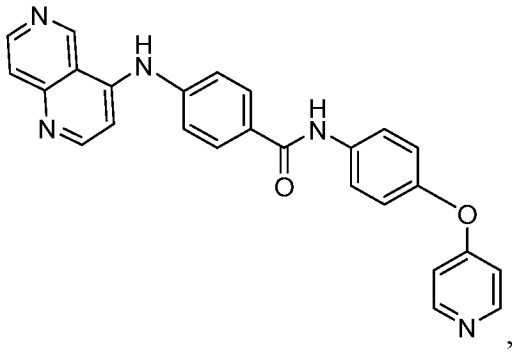


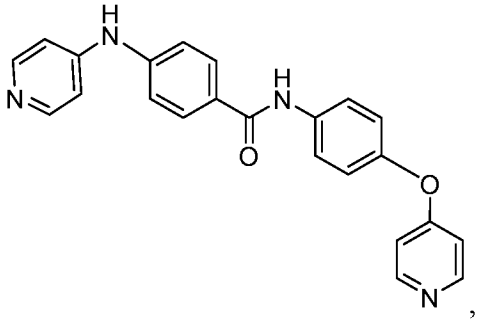


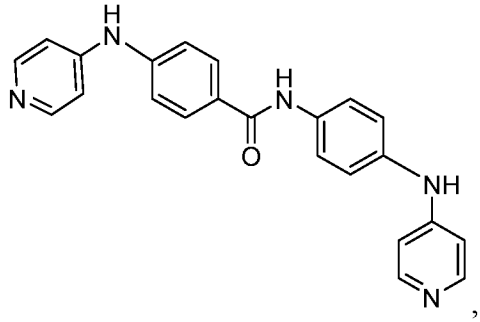


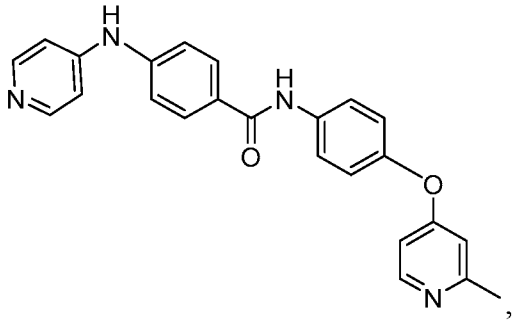


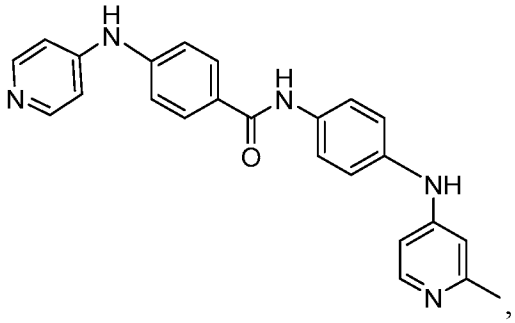


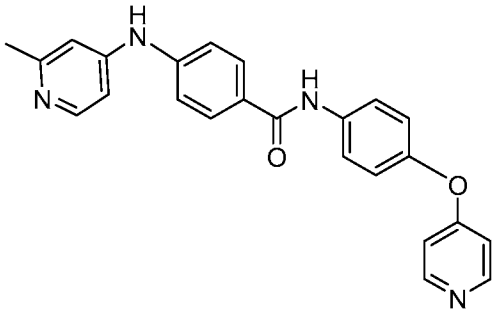


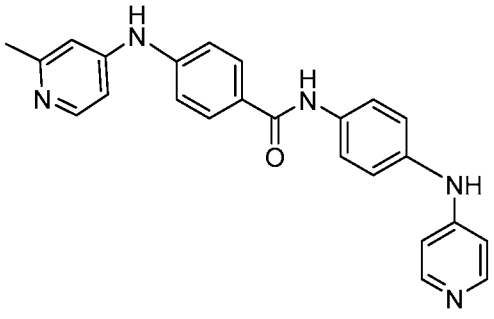


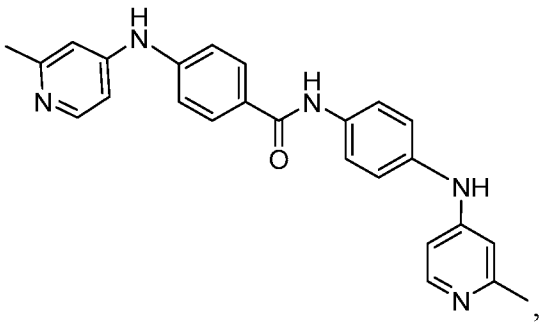


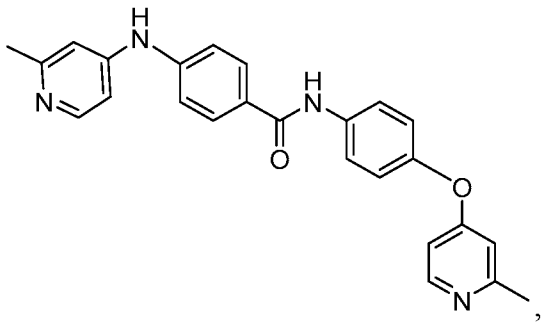


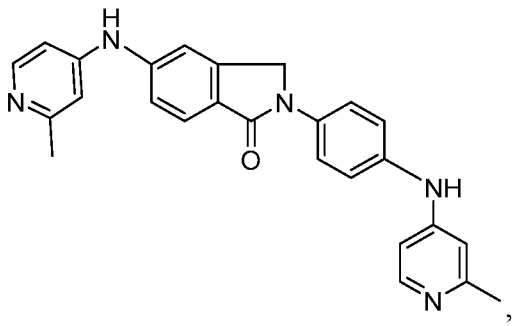


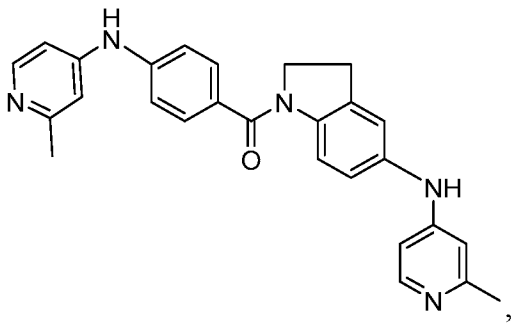


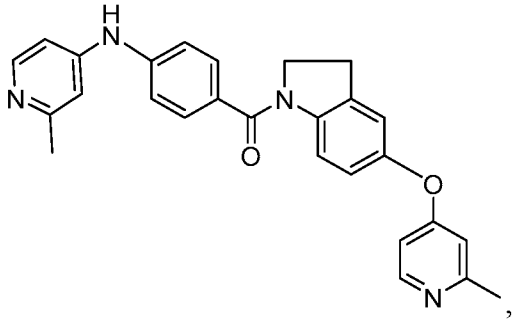


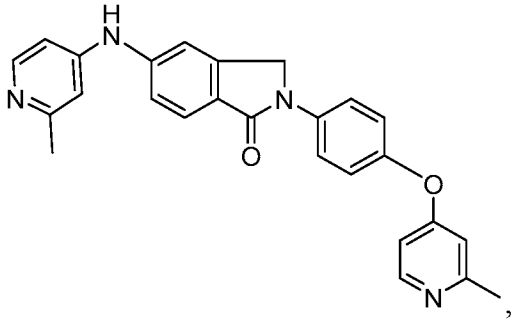


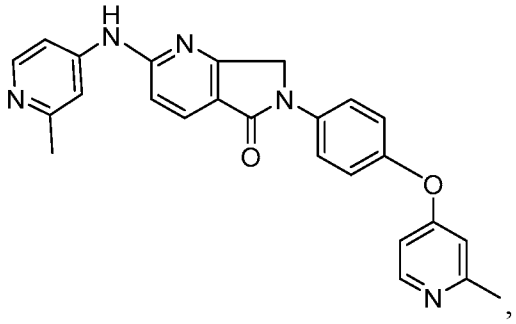


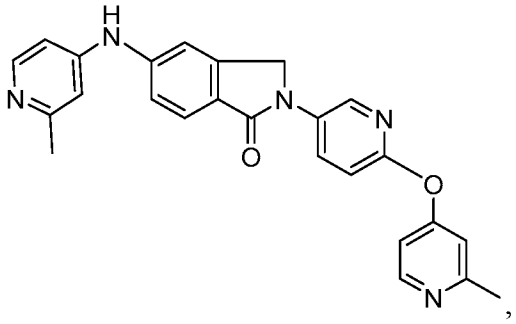


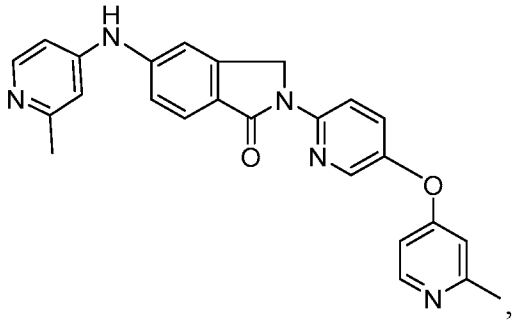


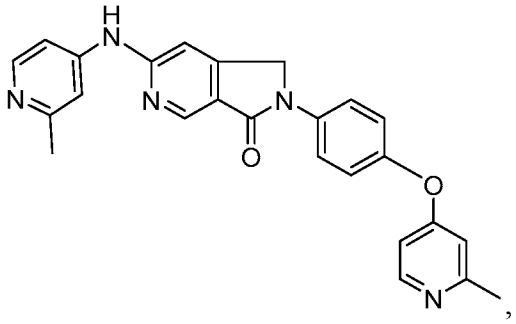


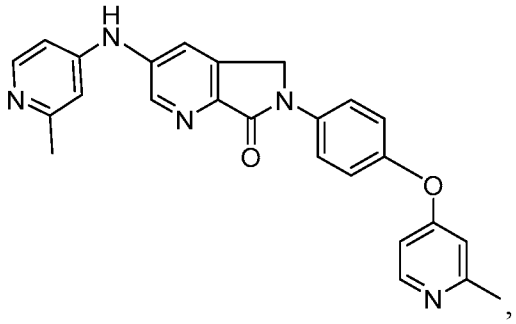


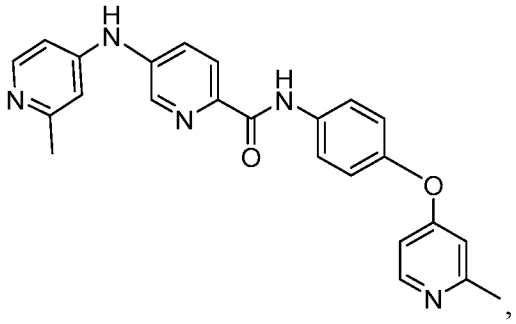


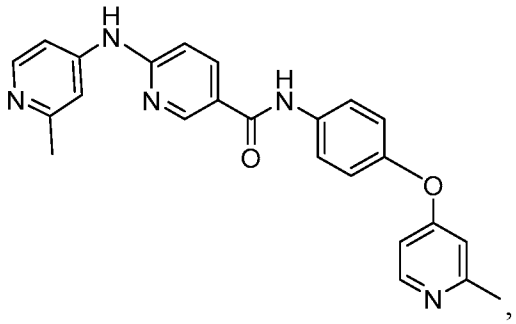


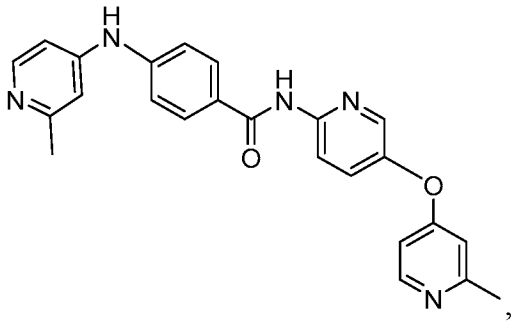


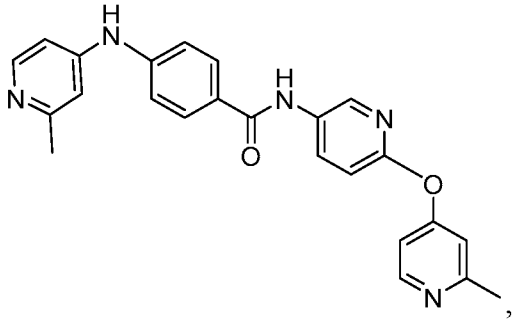


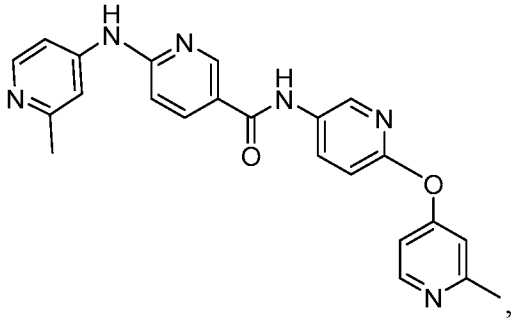


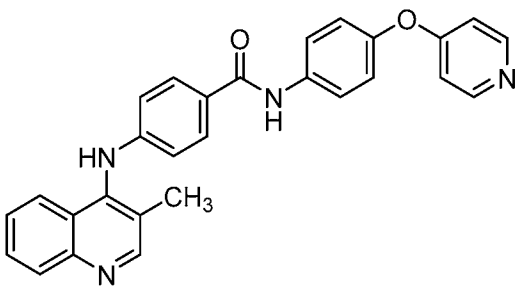


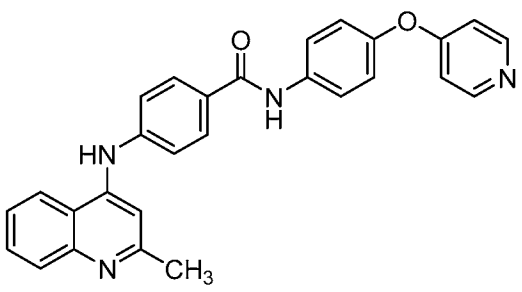


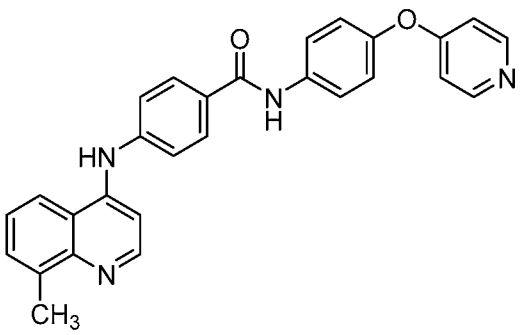


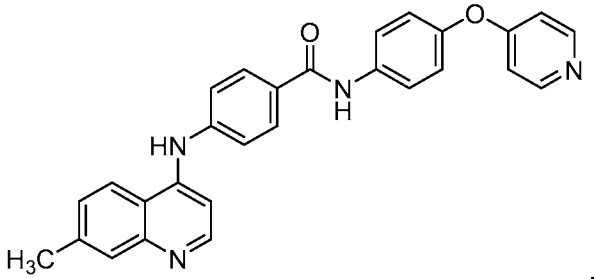


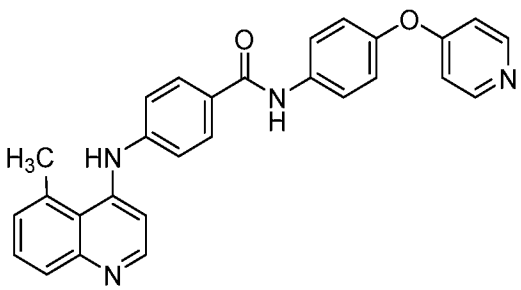


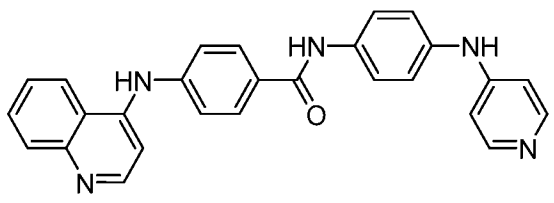


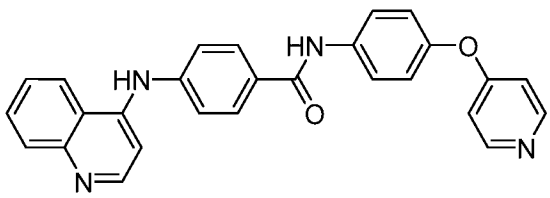


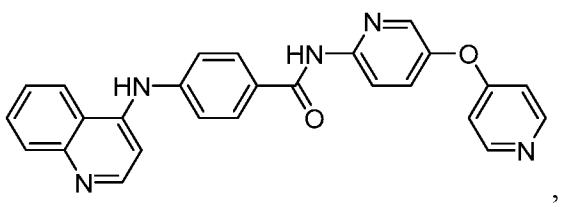


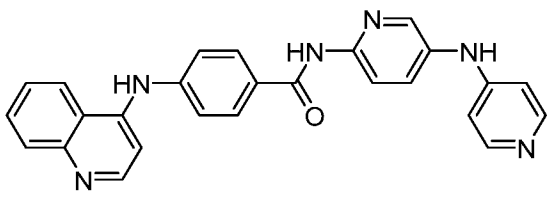


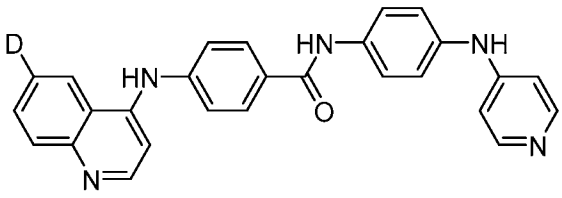


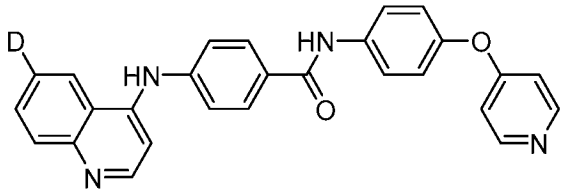
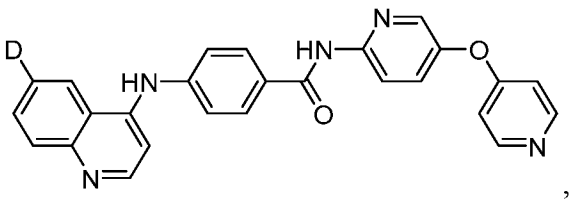
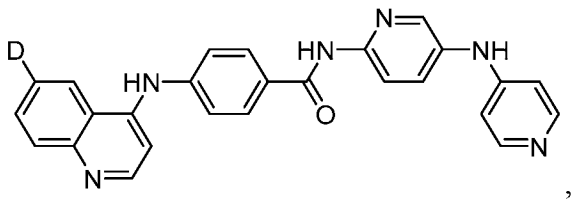
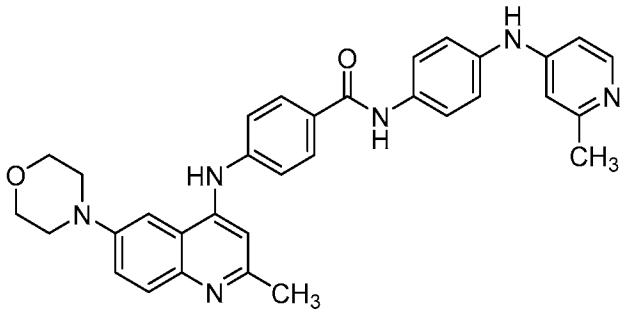
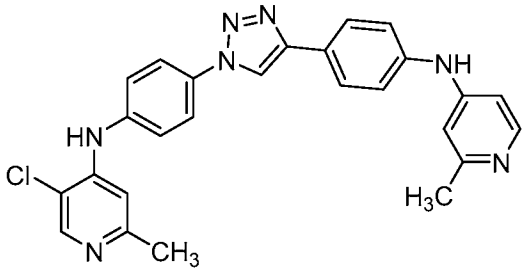
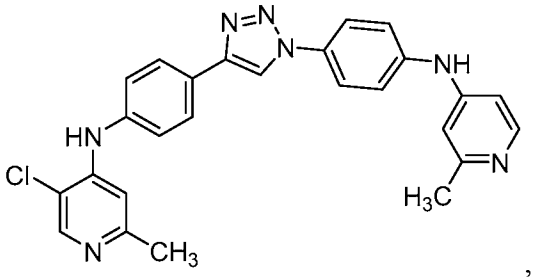
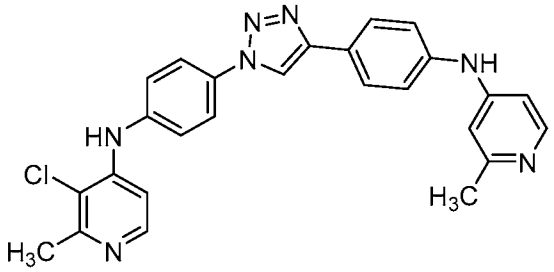
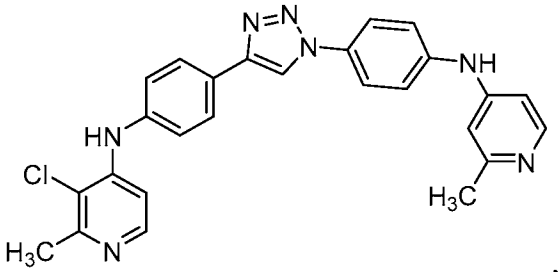
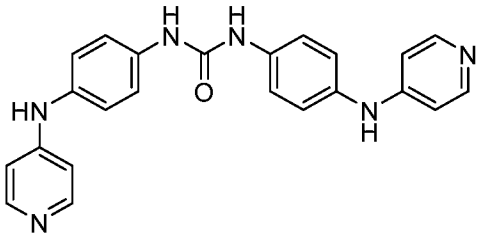
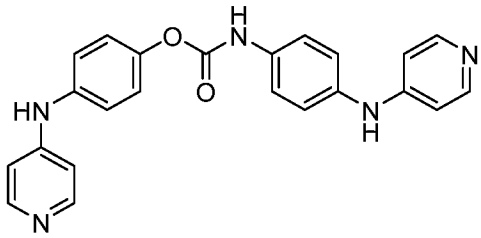


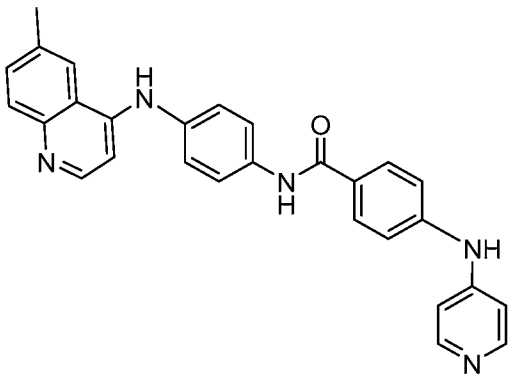




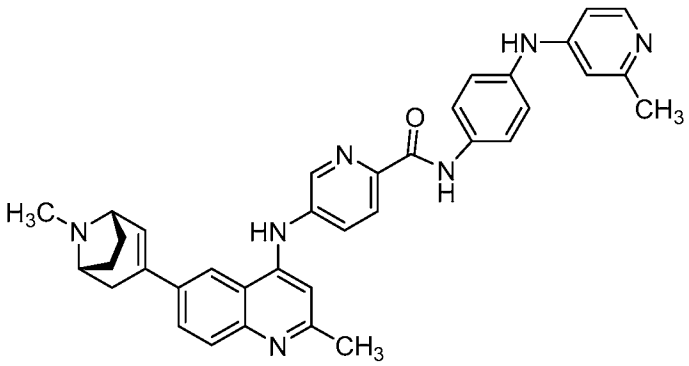




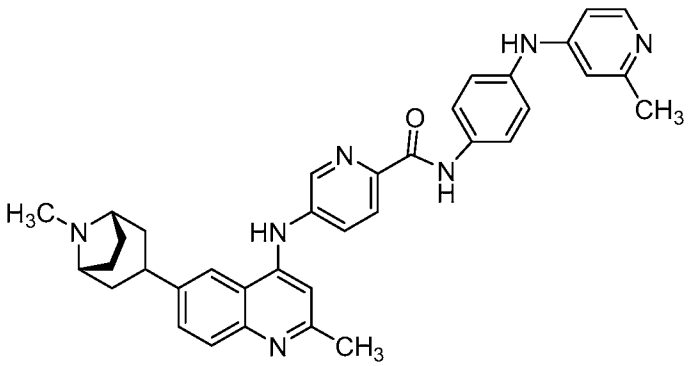

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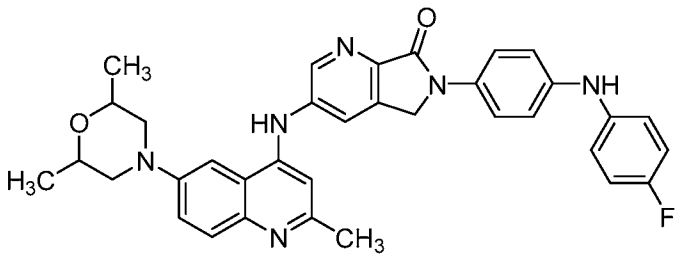
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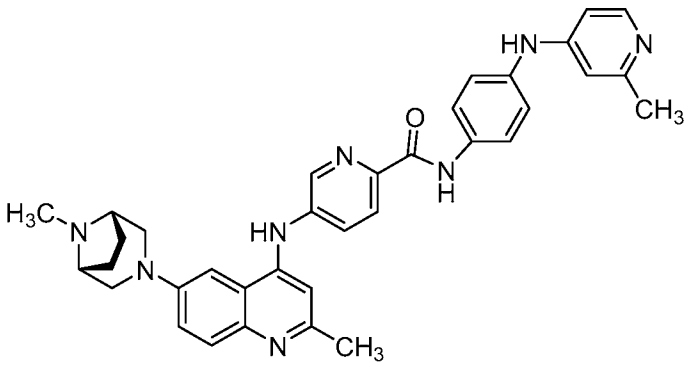
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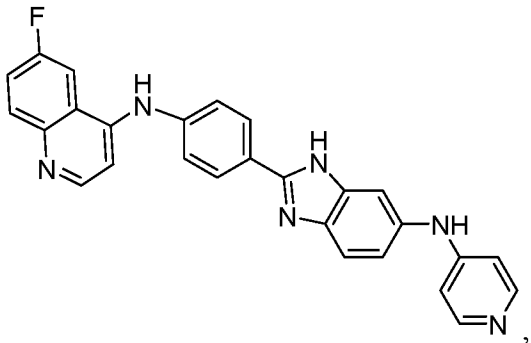


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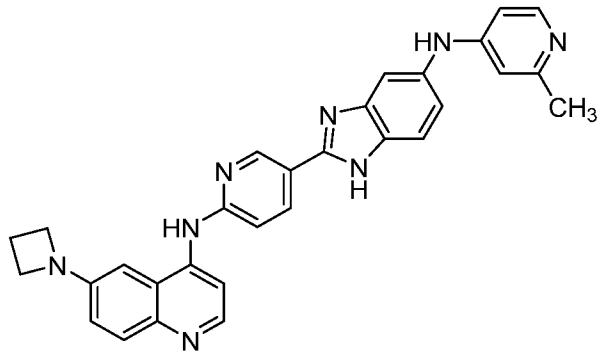


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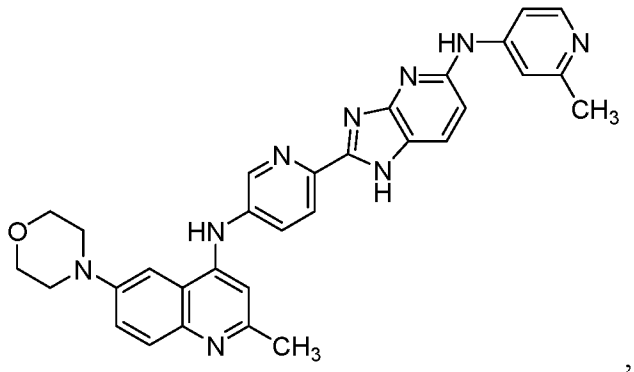
[0136] In any one of the embodiments disclosed herein, the compound of Formula Ib is



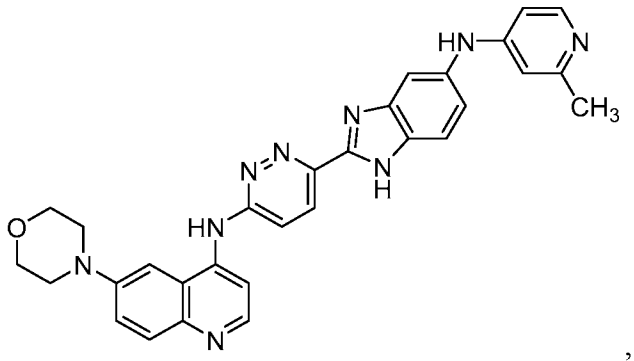
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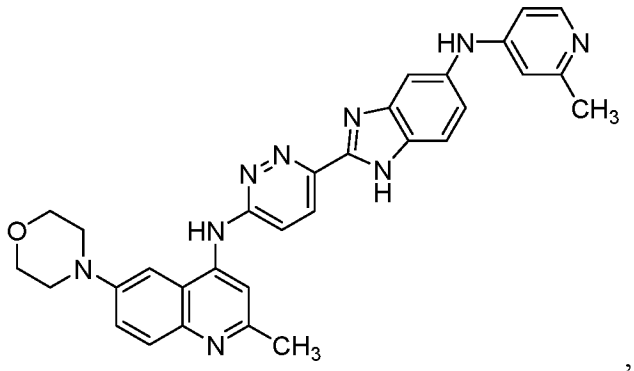
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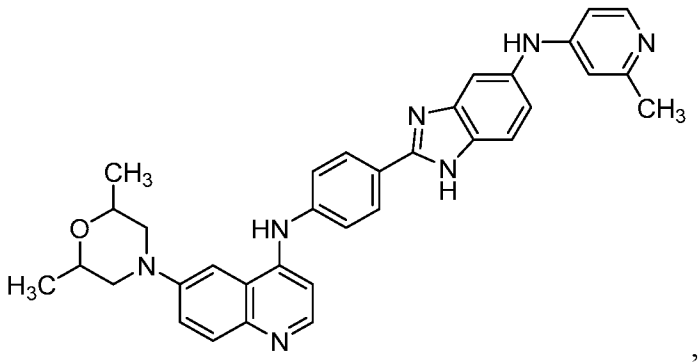
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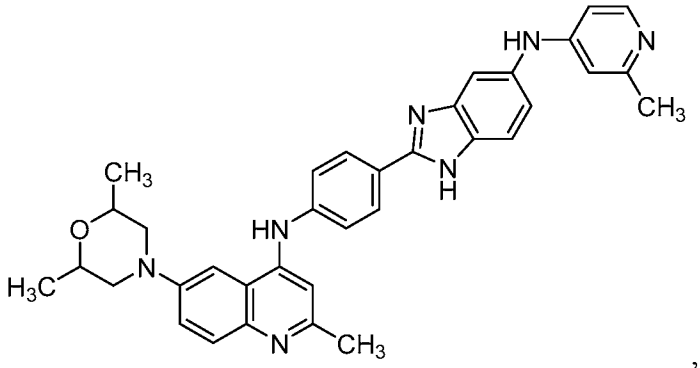
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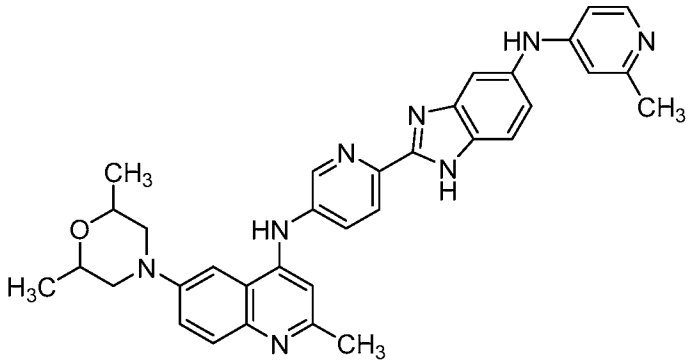
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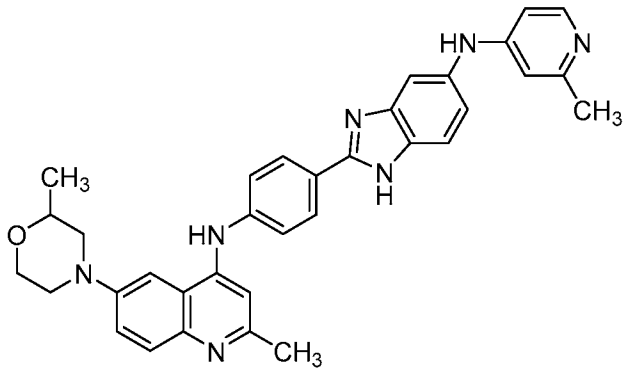
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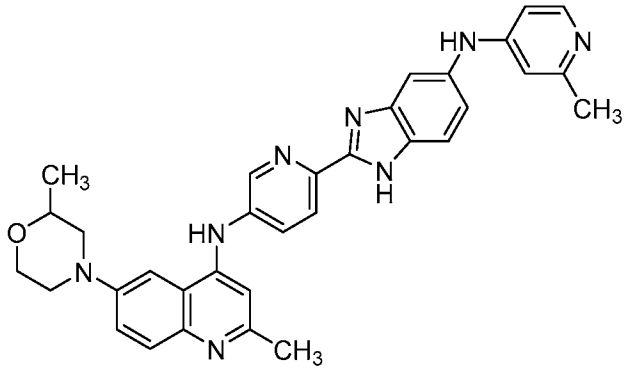
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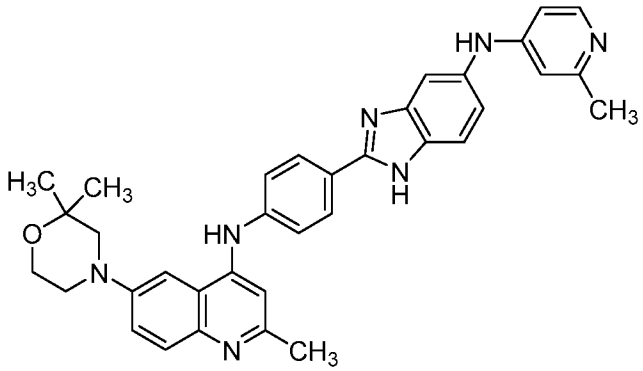
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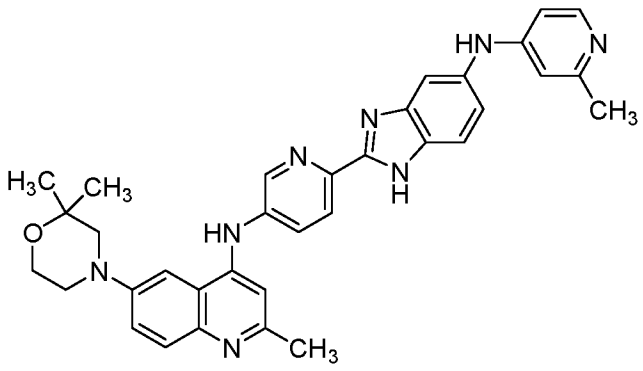
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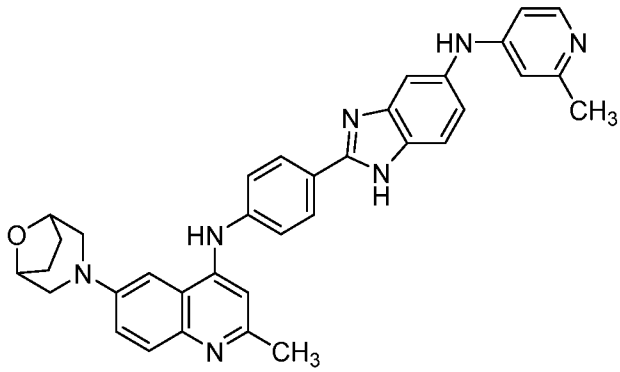
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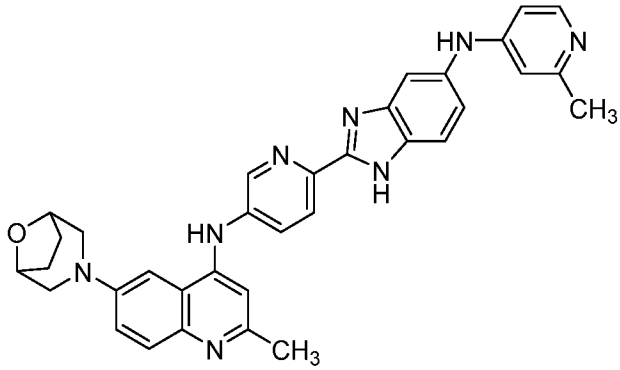
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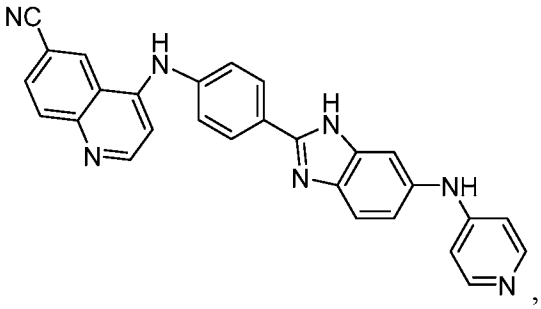


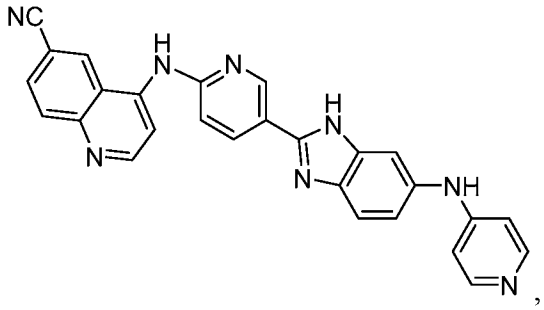
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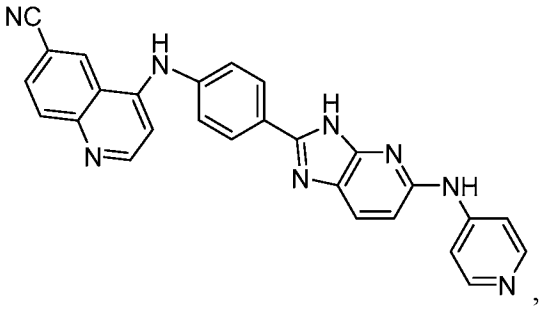


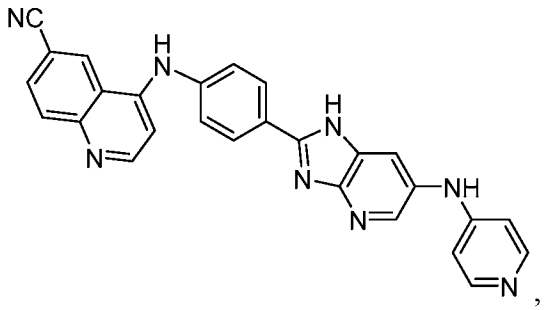
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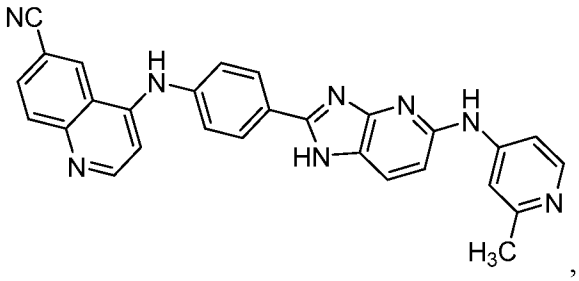


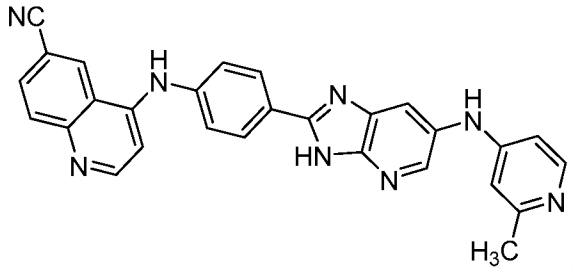


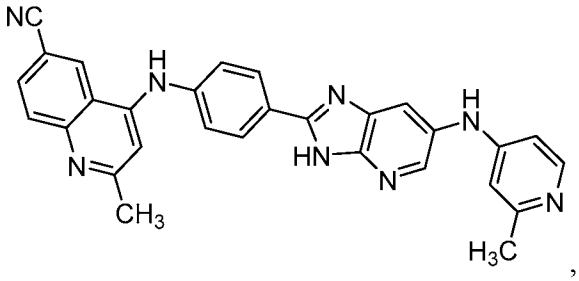


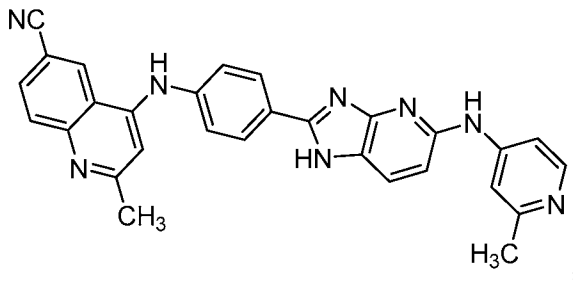


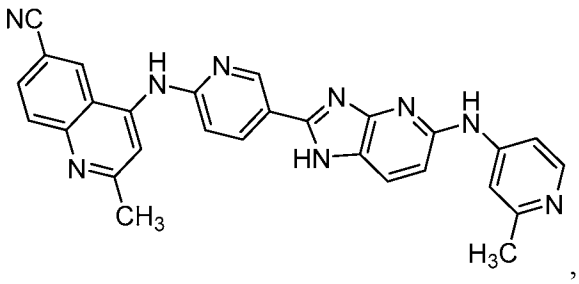


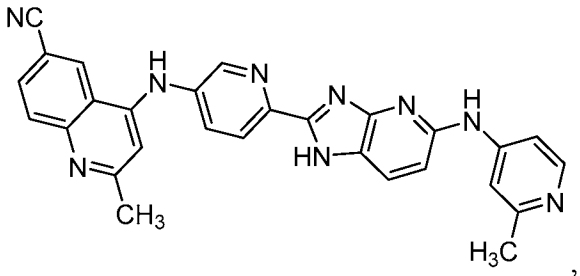


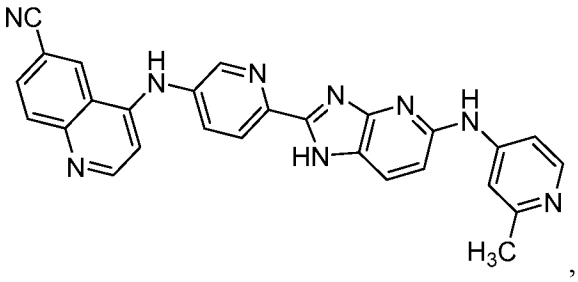


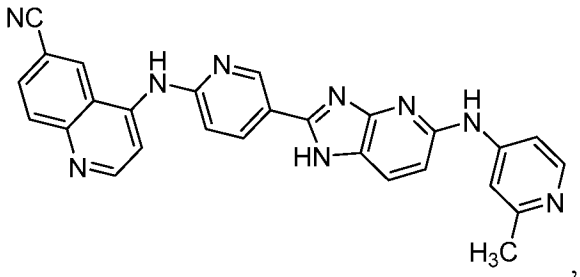


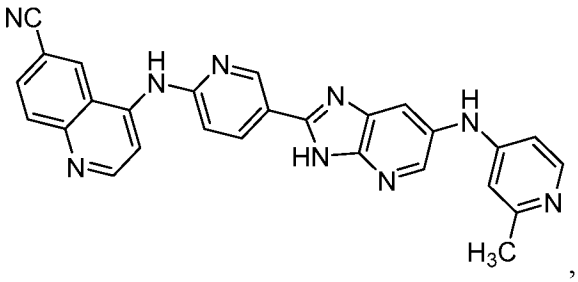


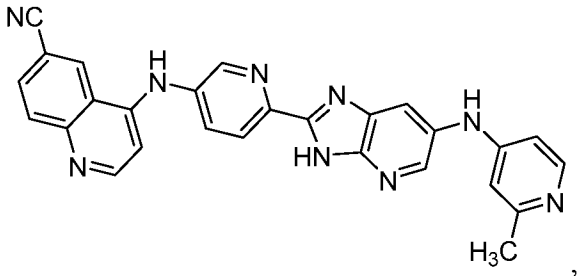


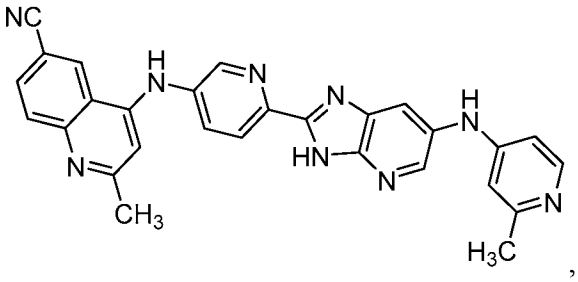


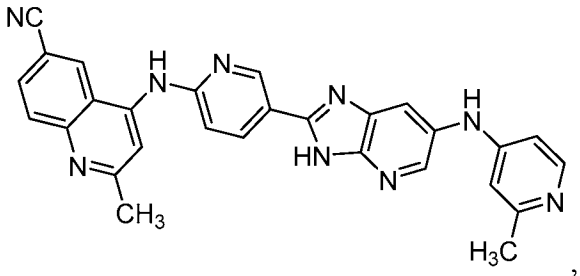


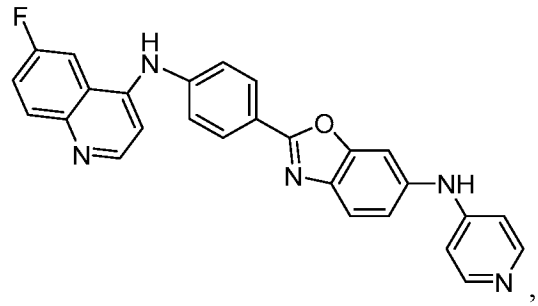


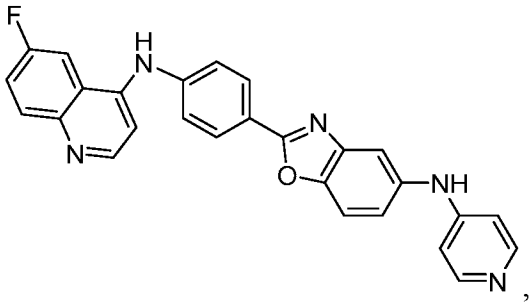


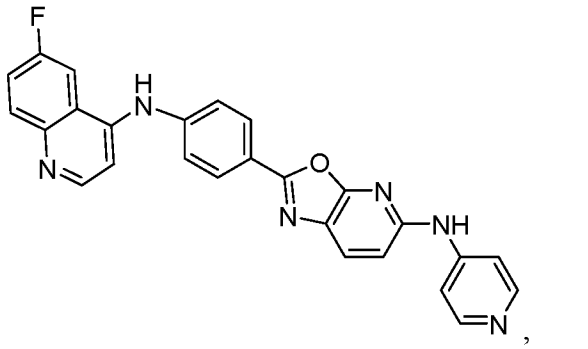


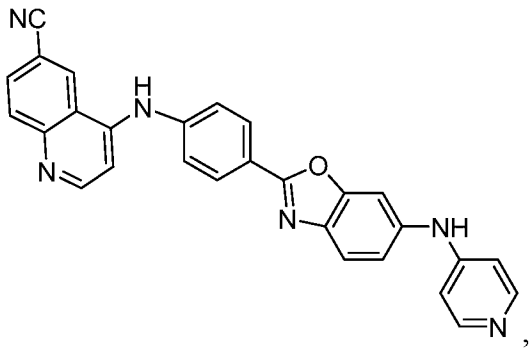


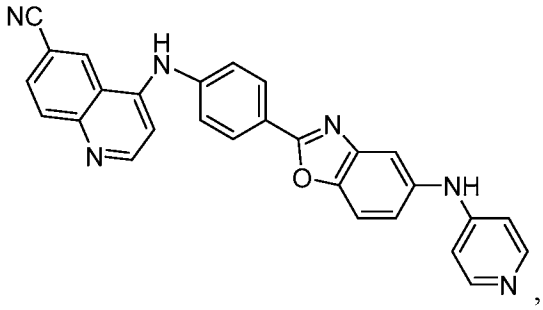


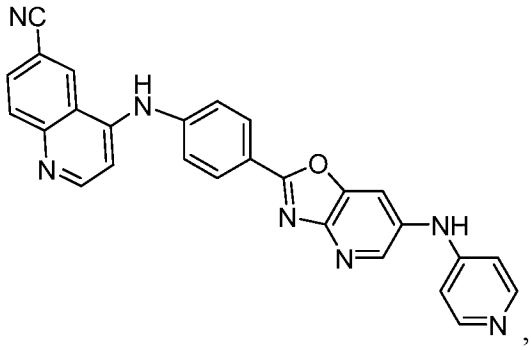


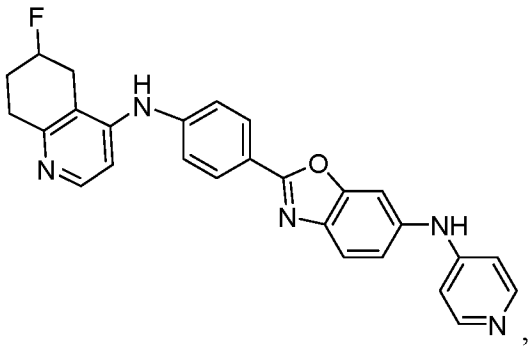


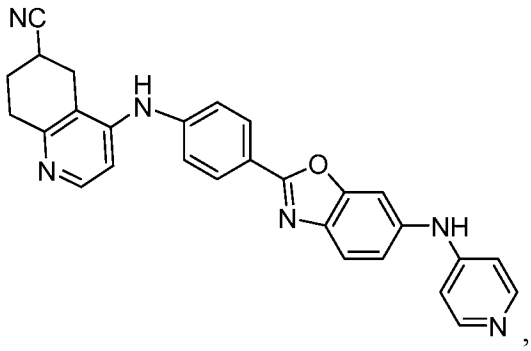


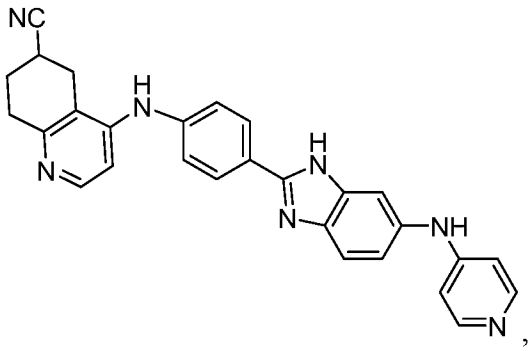


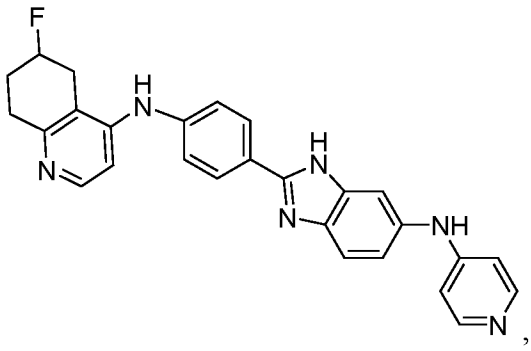


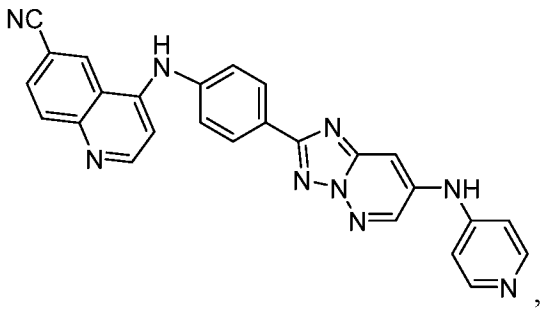


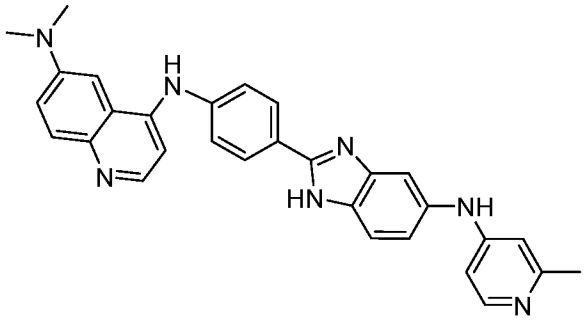


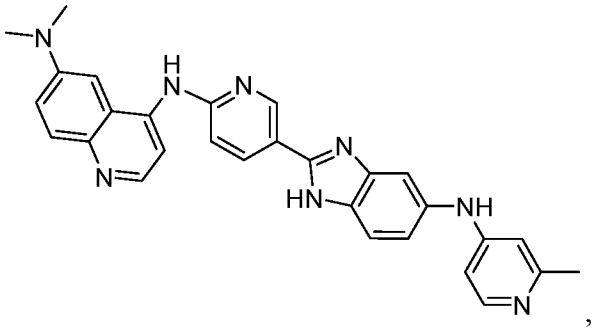


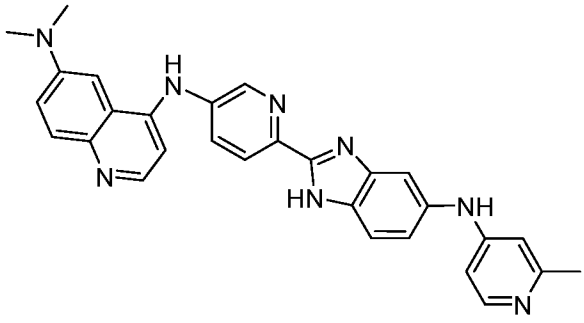
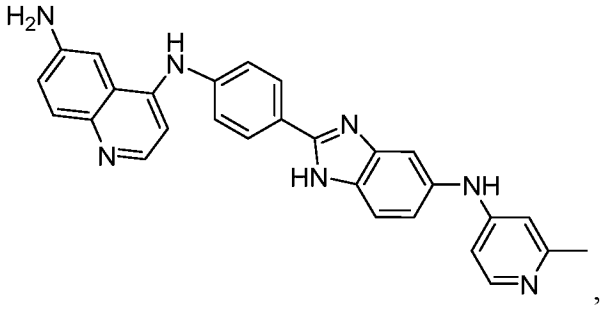
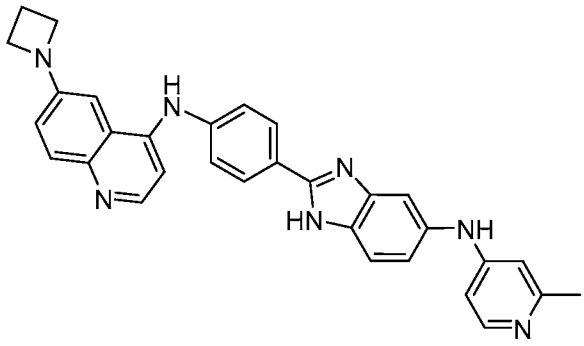
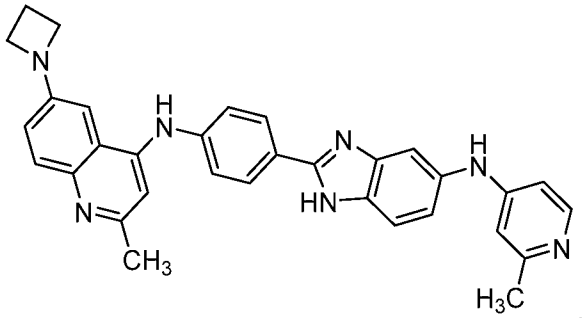
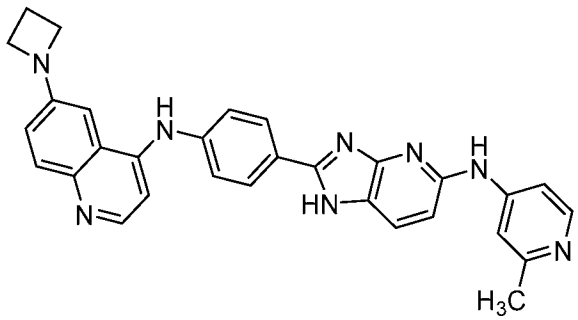
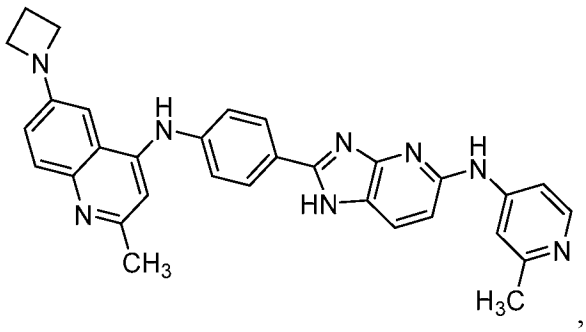
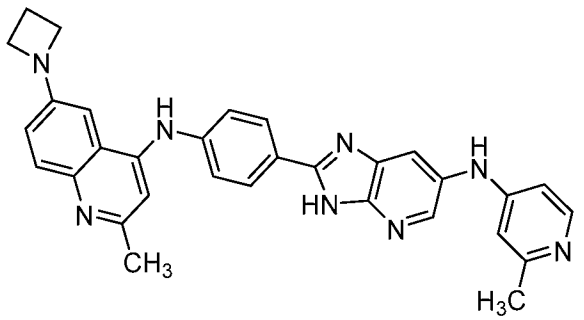
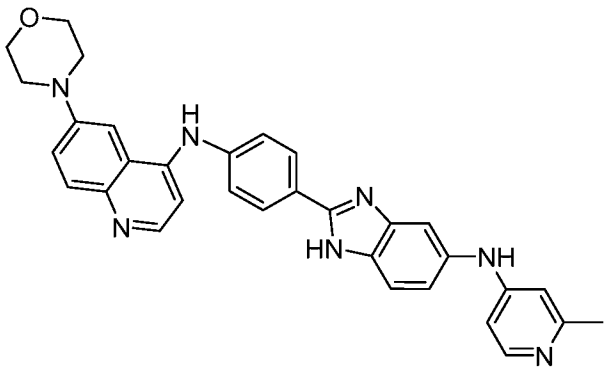
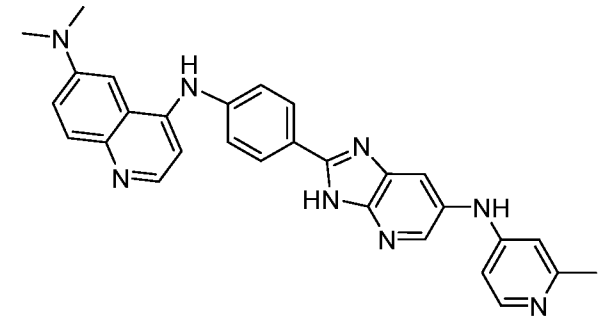
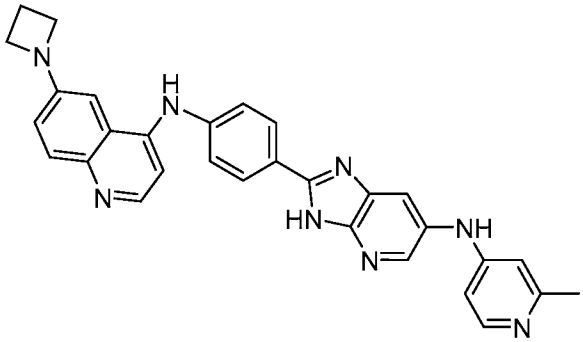


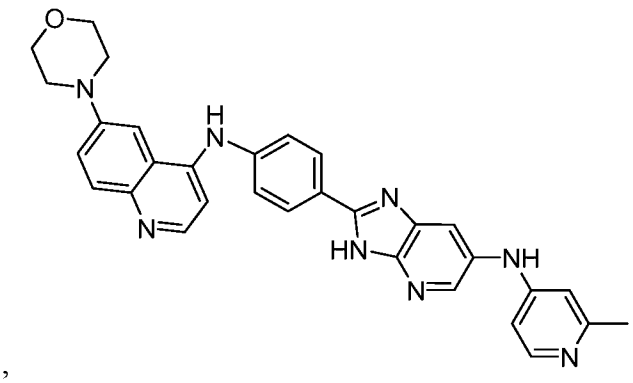




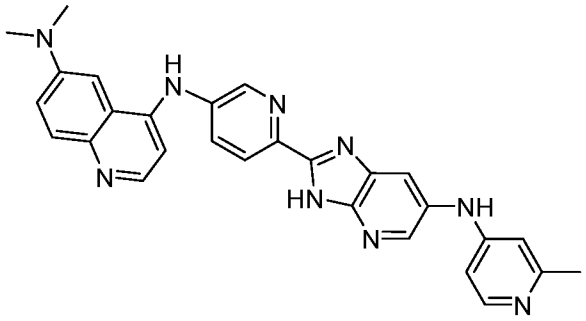




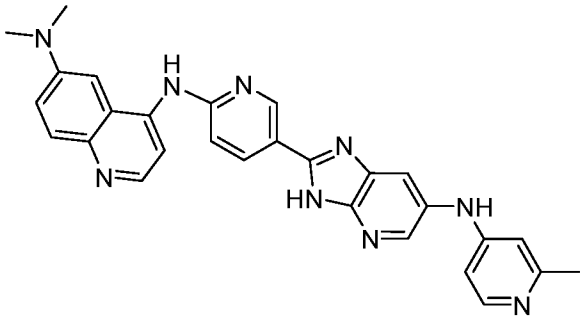

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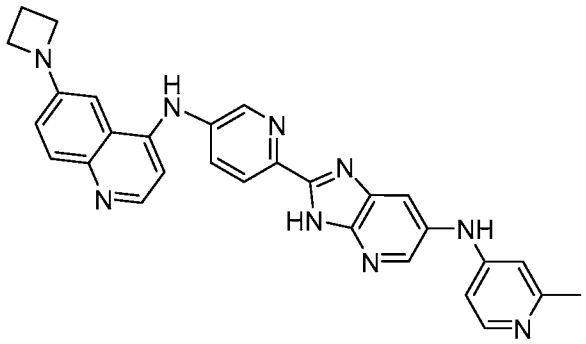
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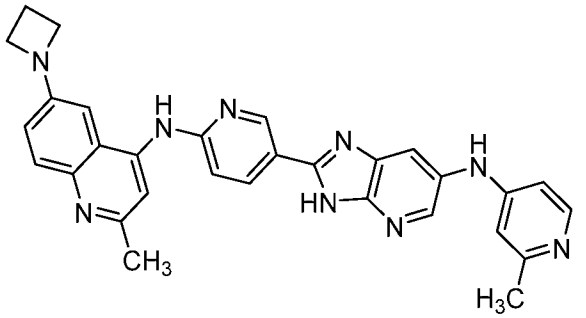
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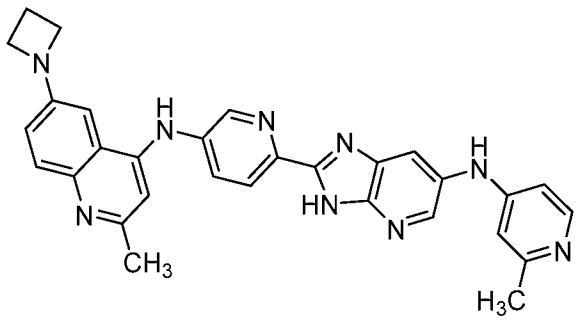
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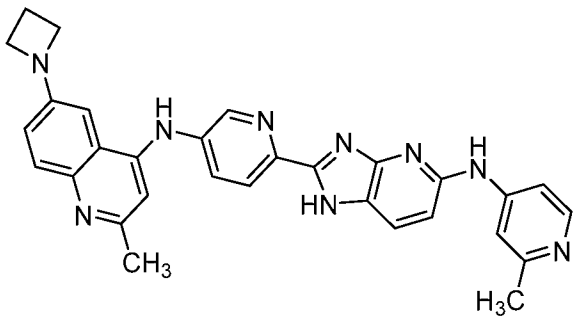
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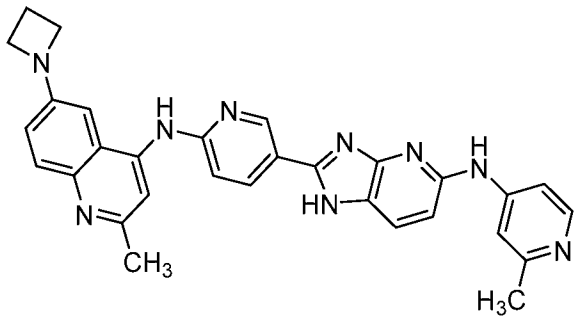
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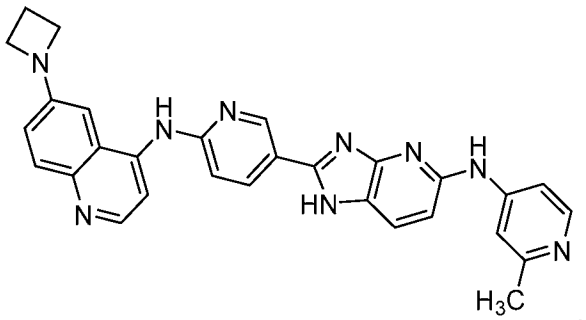
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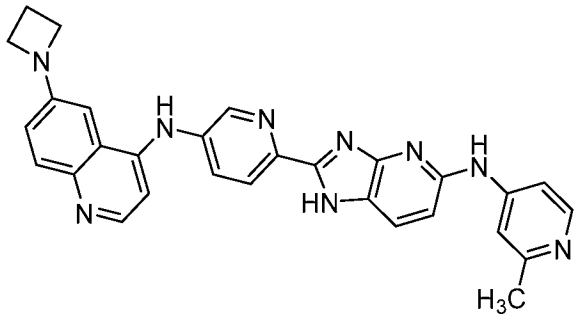
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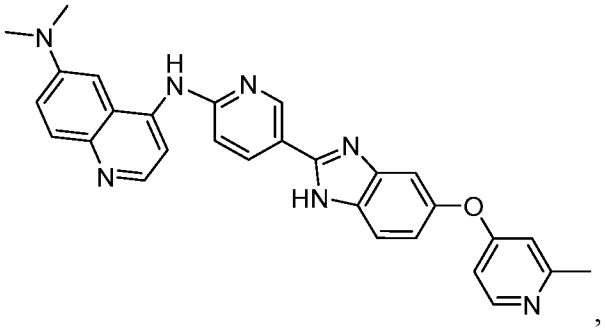
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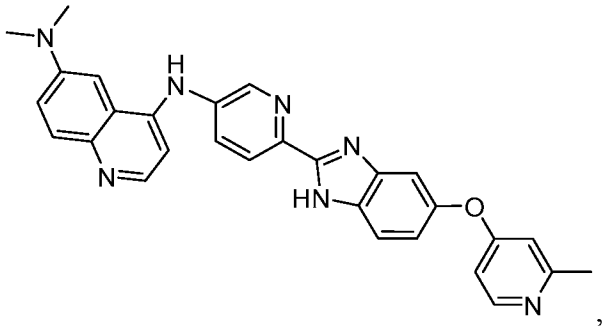
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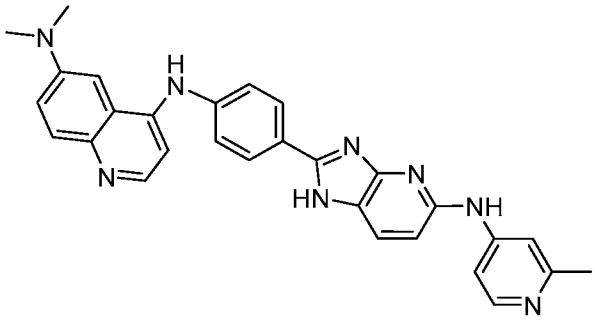
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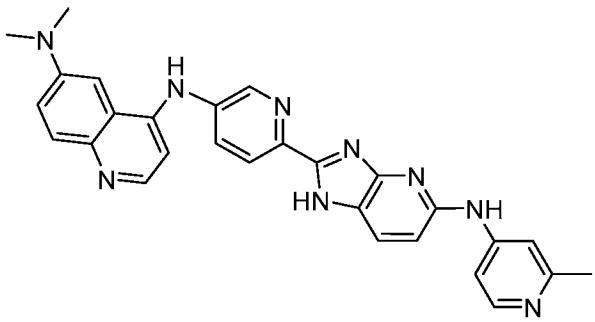
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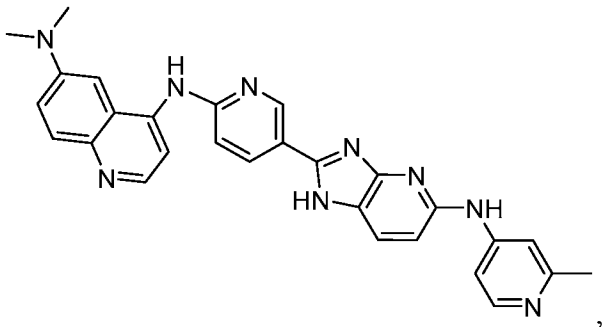


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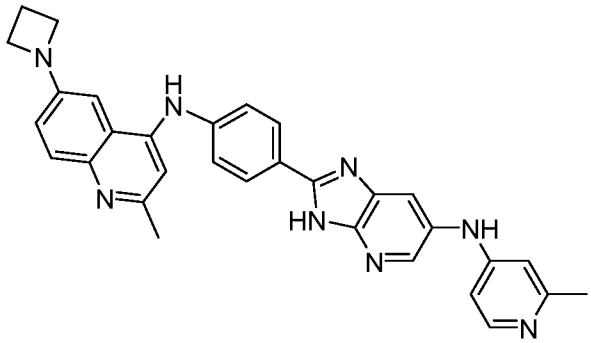


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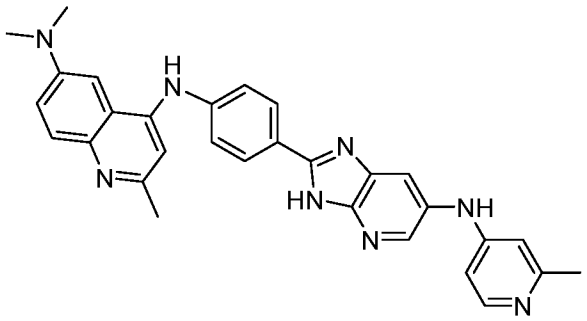
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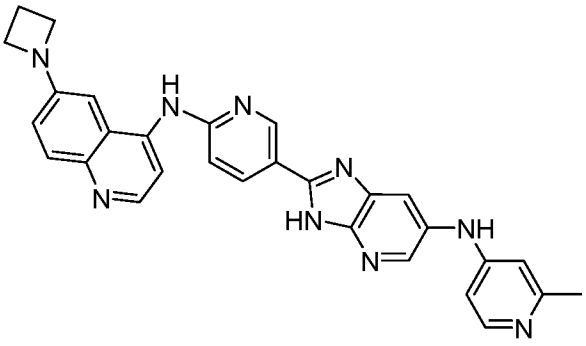


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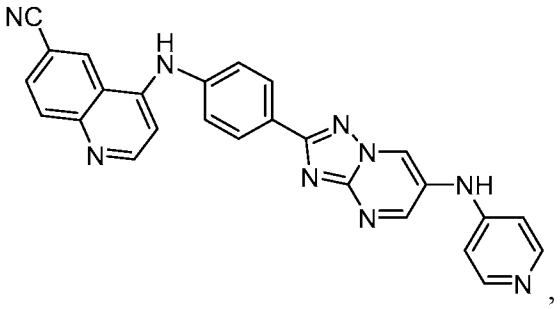


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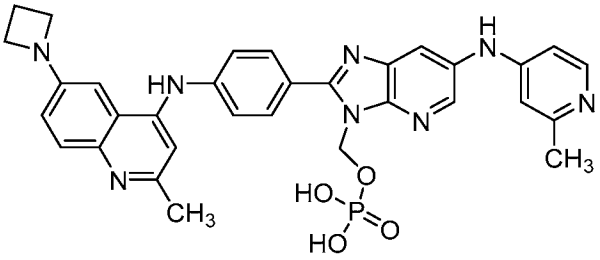
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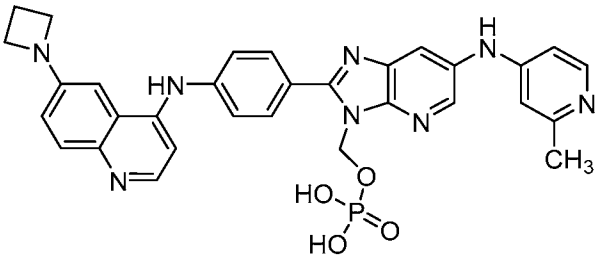
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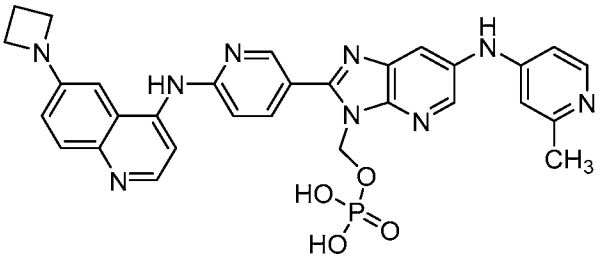
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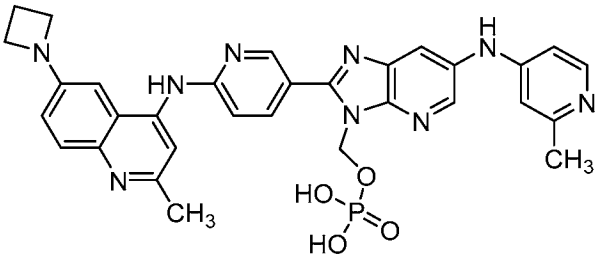
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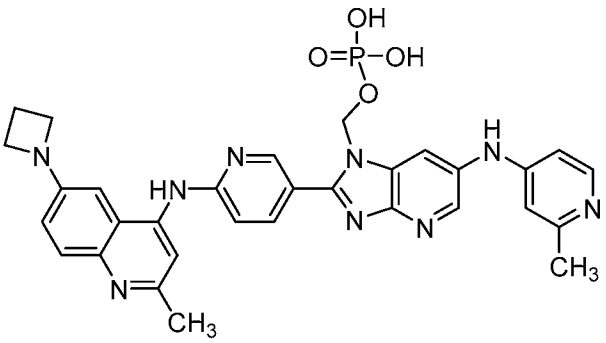
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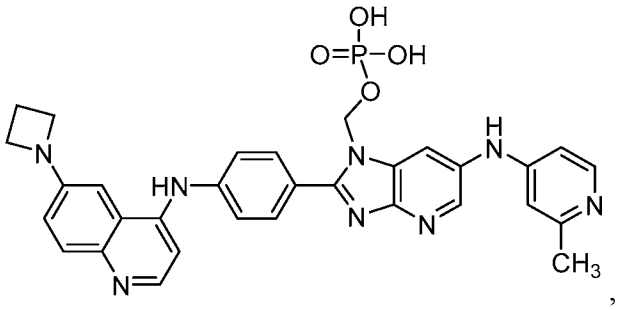
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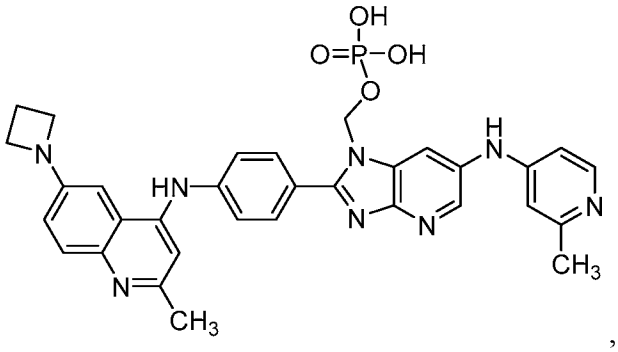
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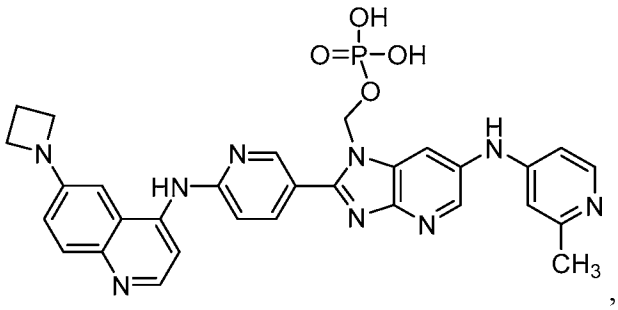
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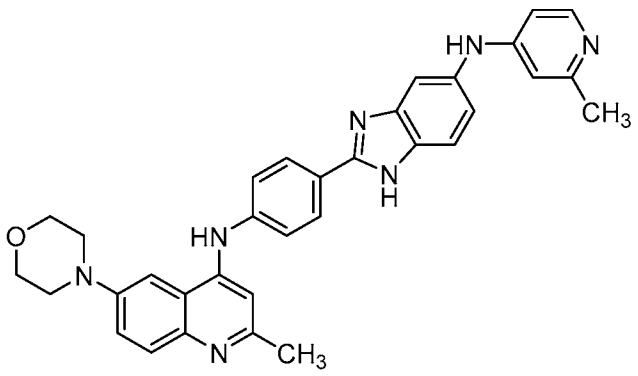
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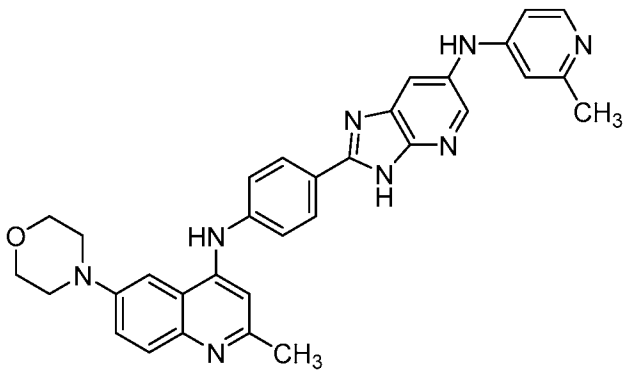
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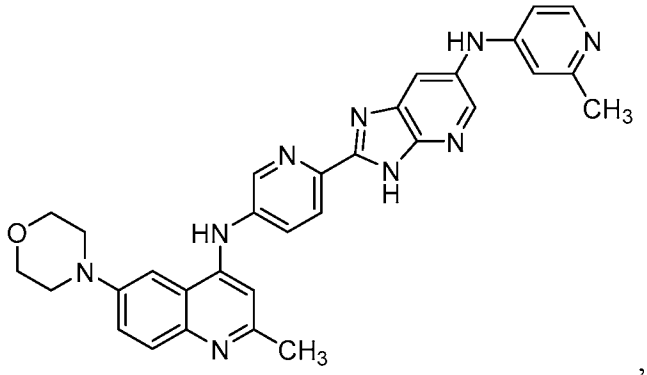
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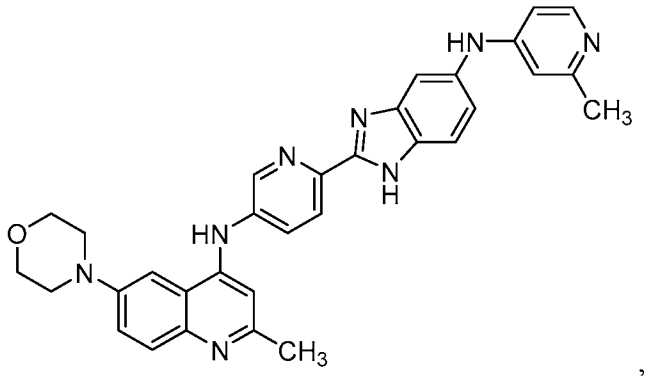


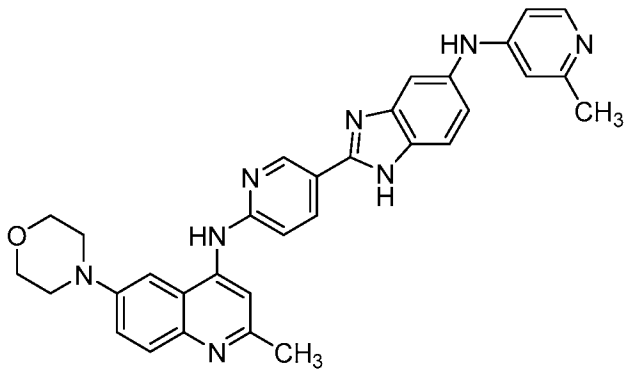
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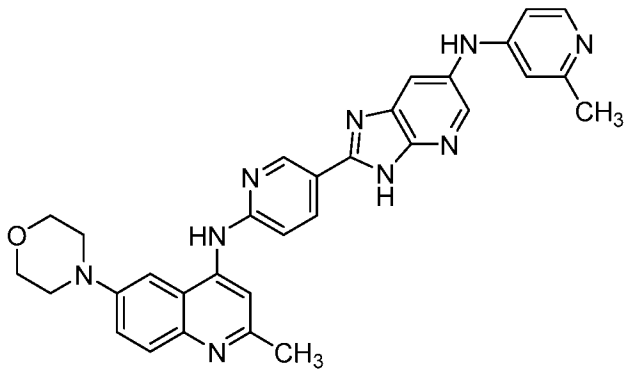


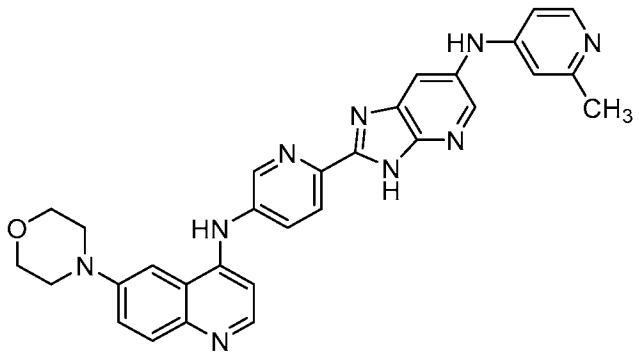
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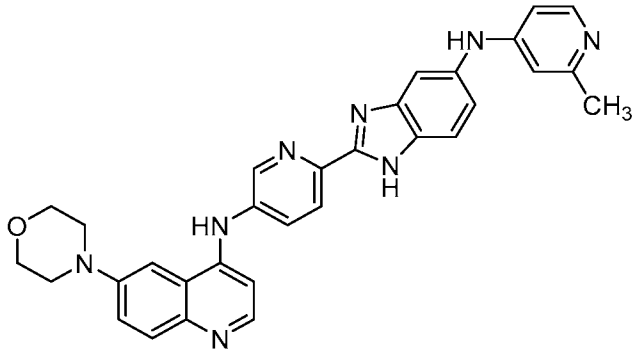

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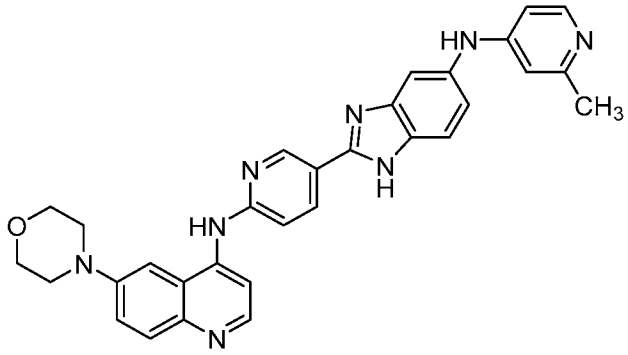

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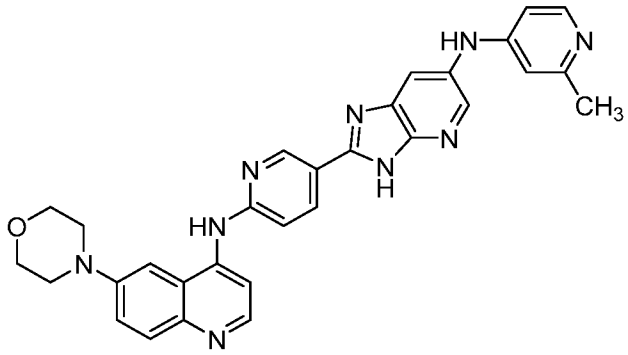
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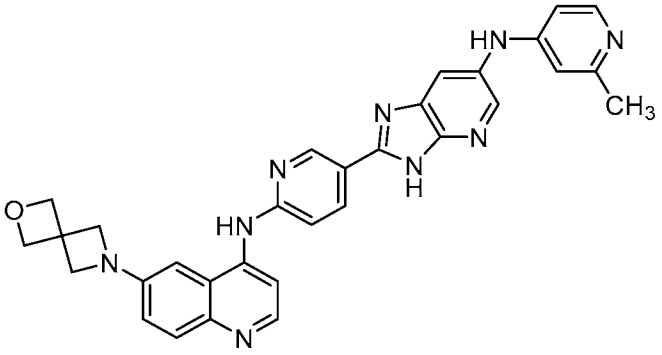
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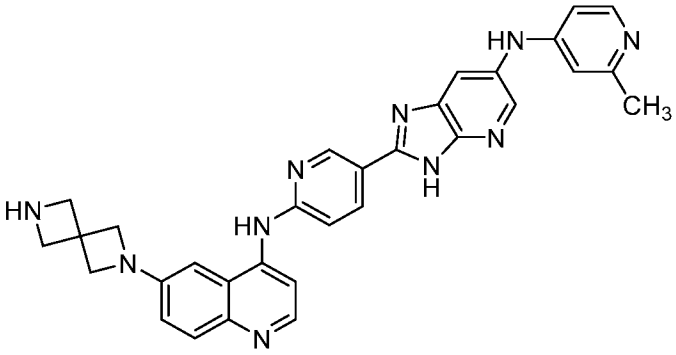
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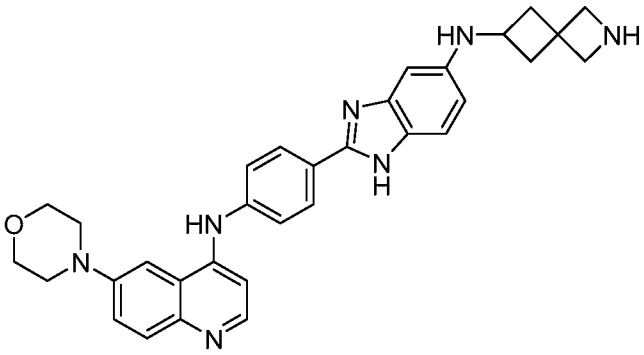
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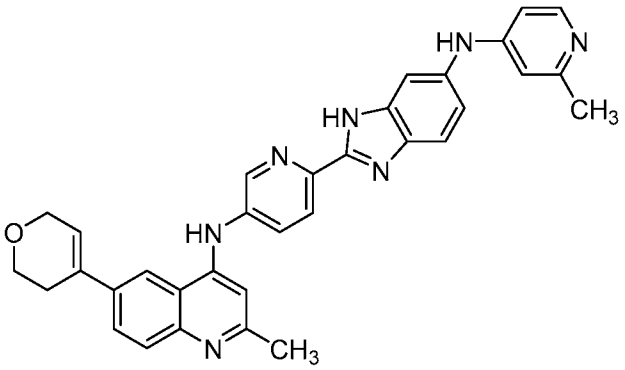
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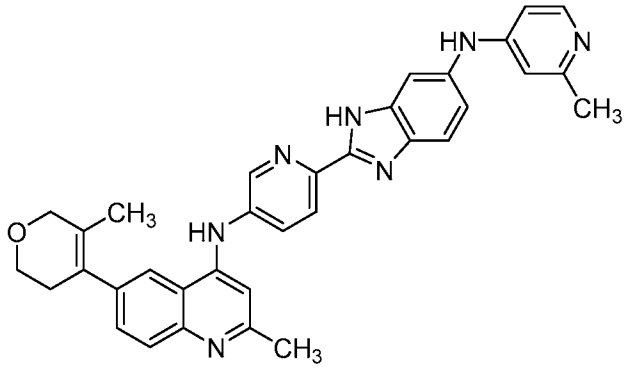
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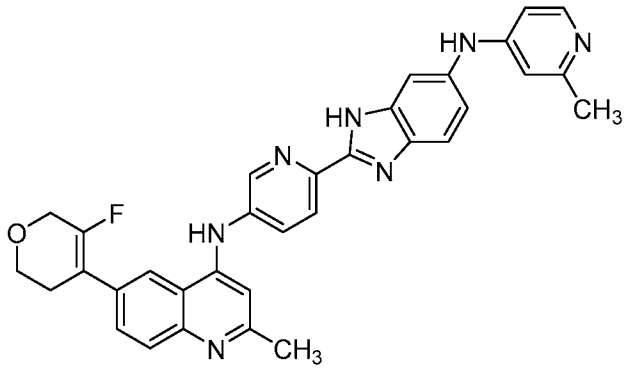
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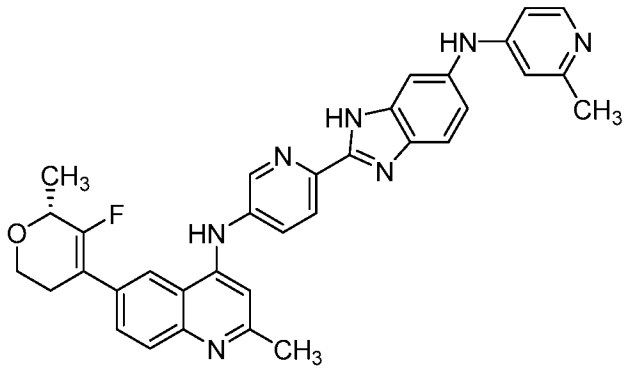
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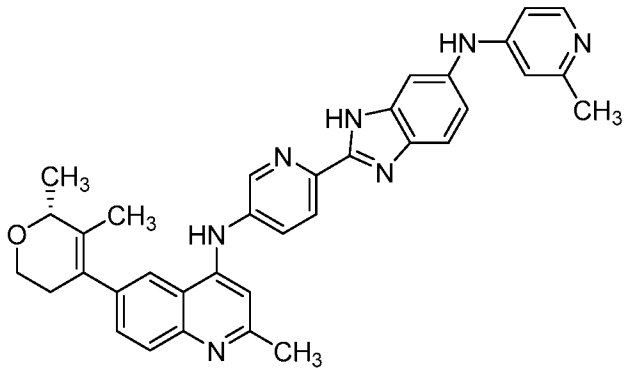
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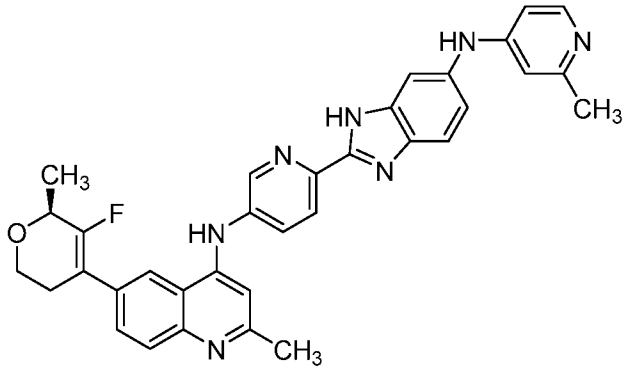
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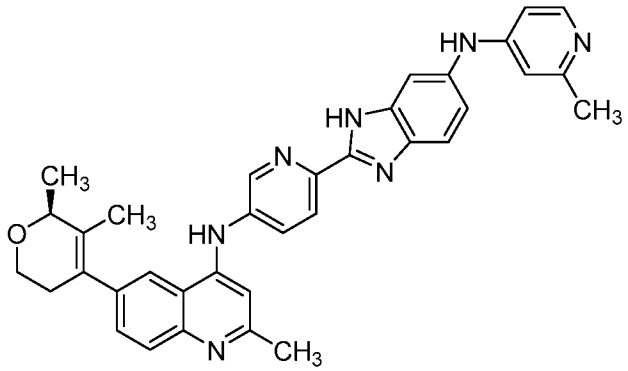
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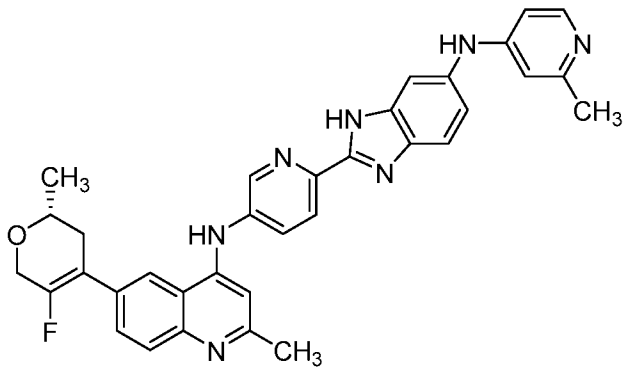
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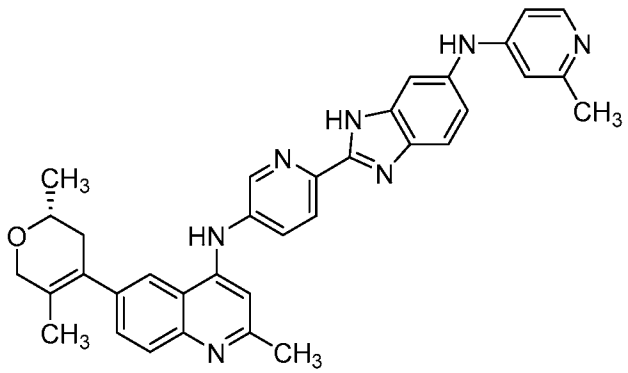
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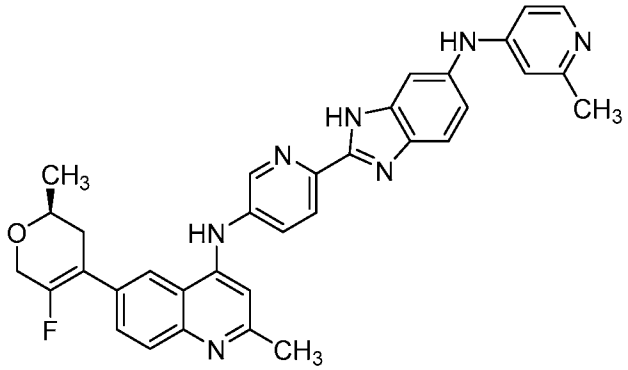
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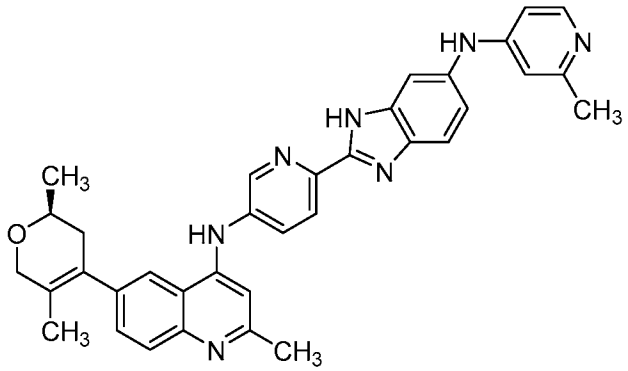
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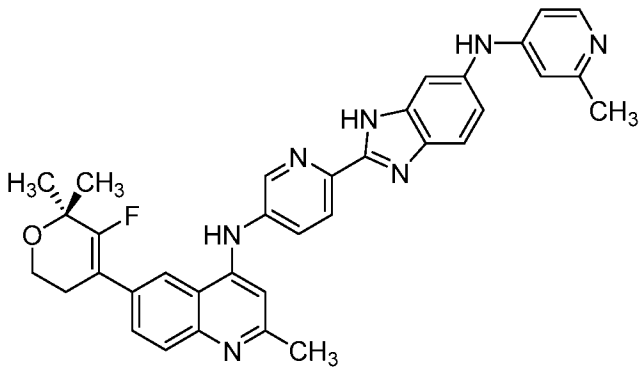
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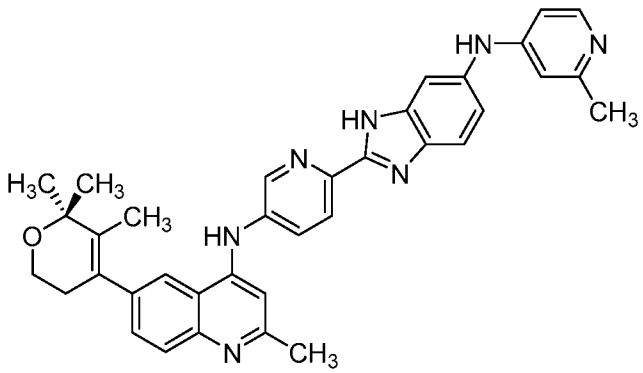
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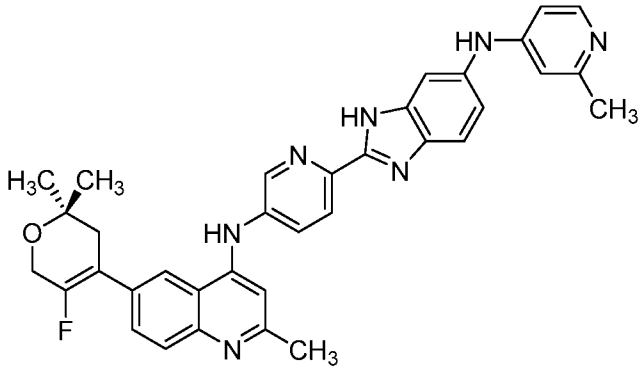
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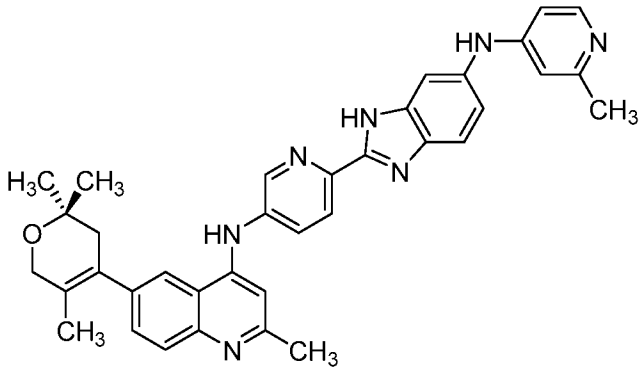
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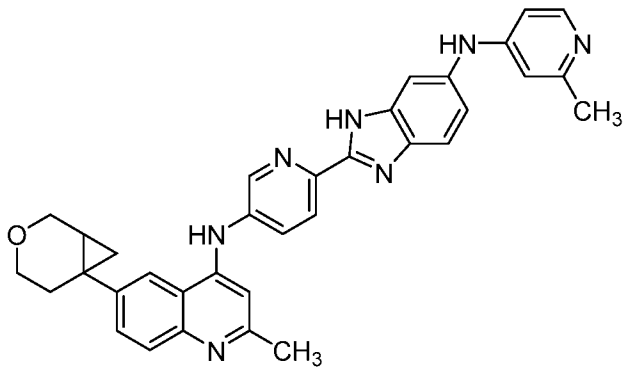
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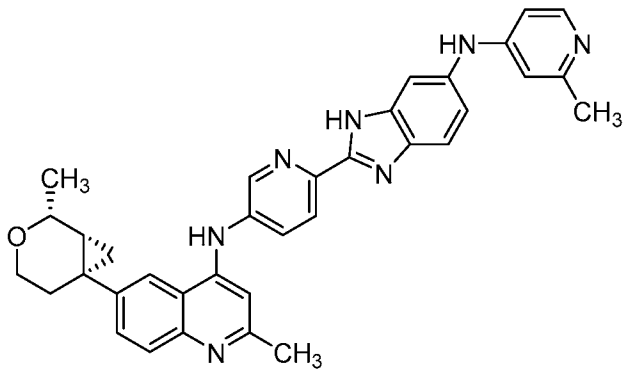
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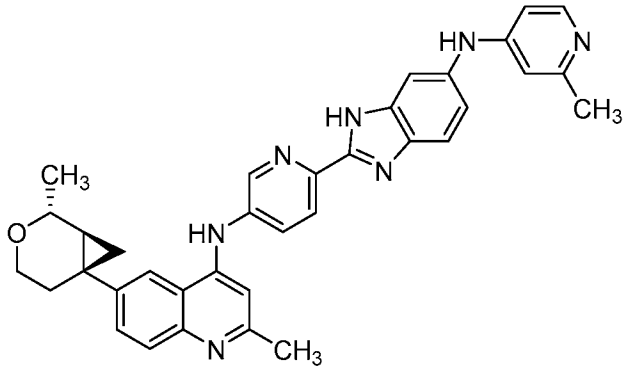
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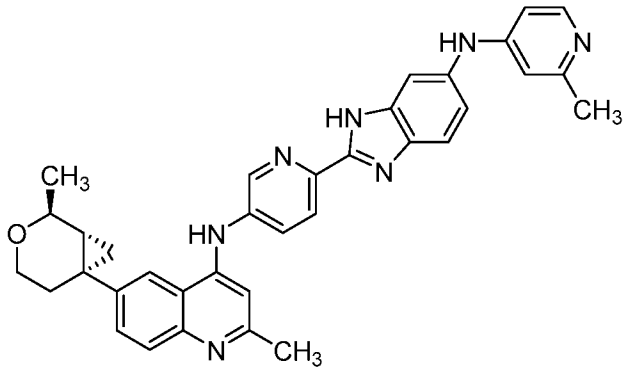
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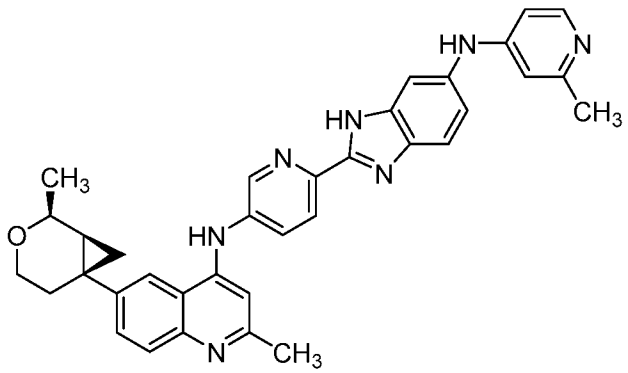
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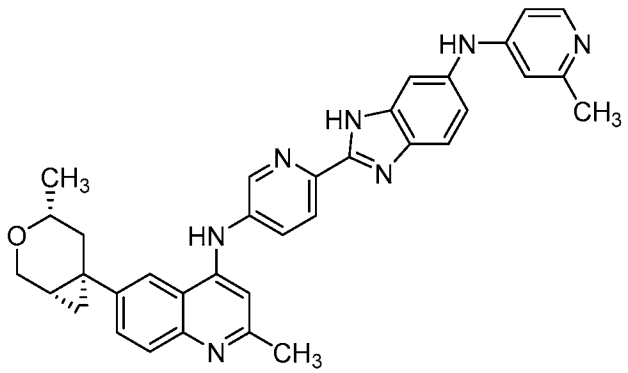
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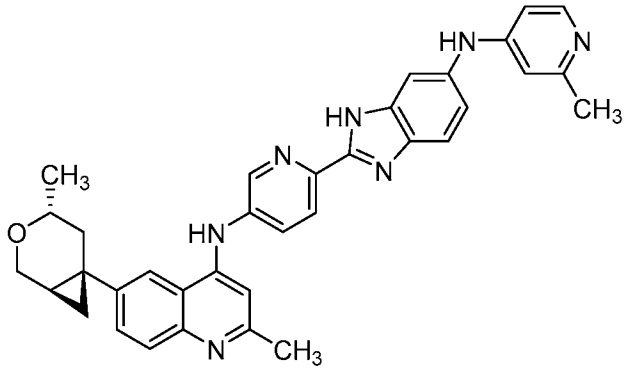
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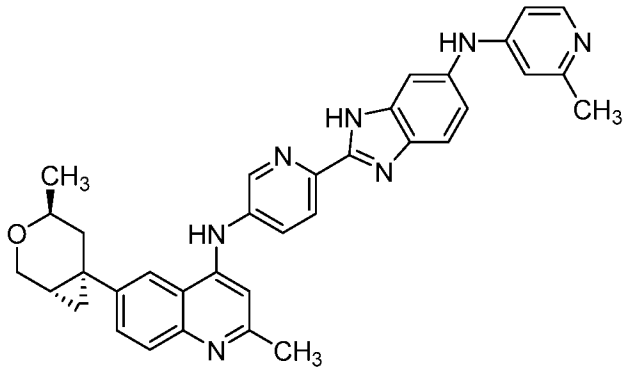

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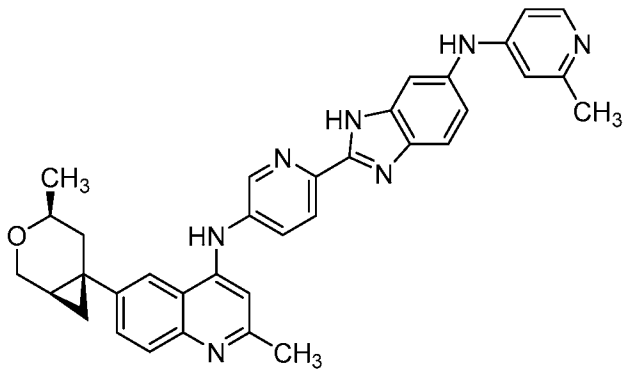
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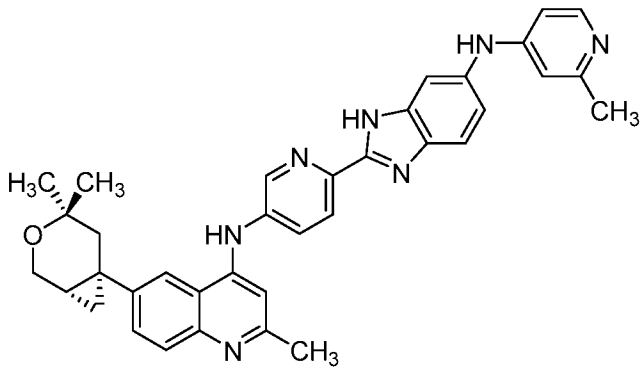

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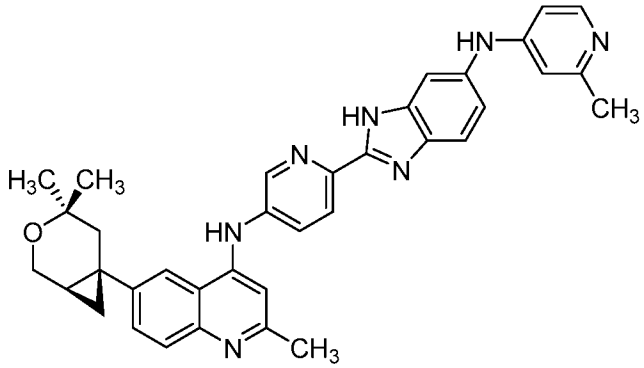
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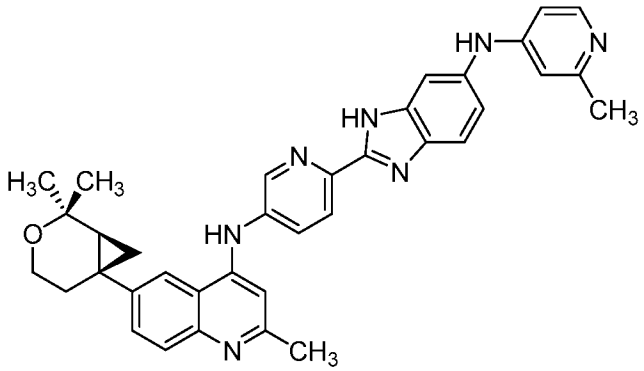

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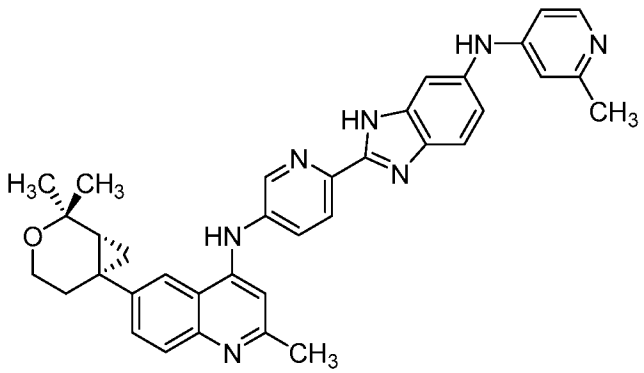

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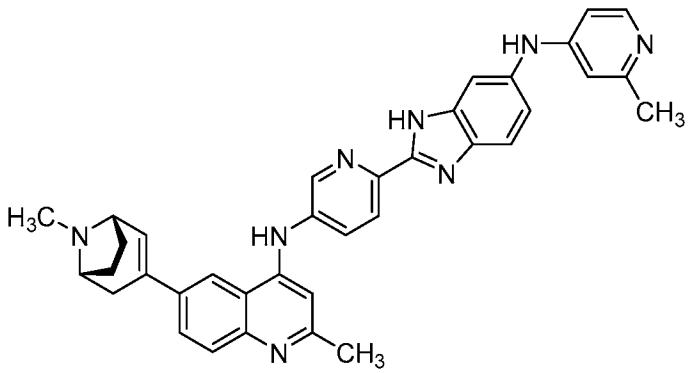
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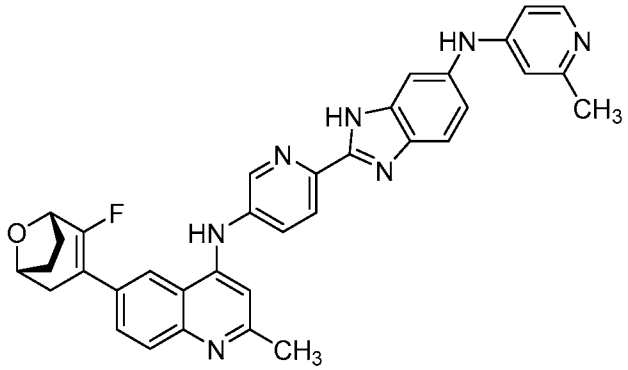
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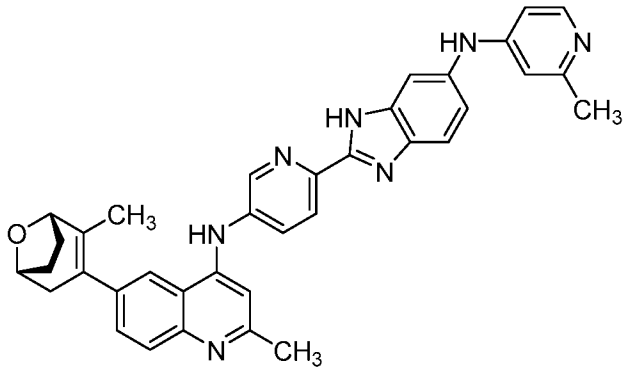
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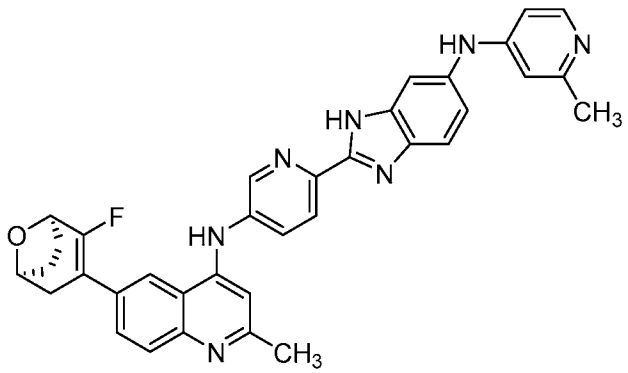
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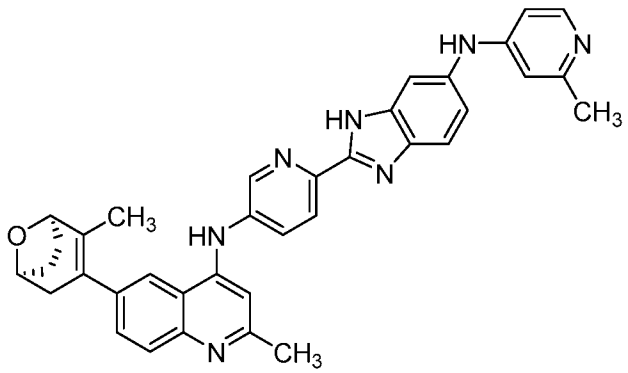
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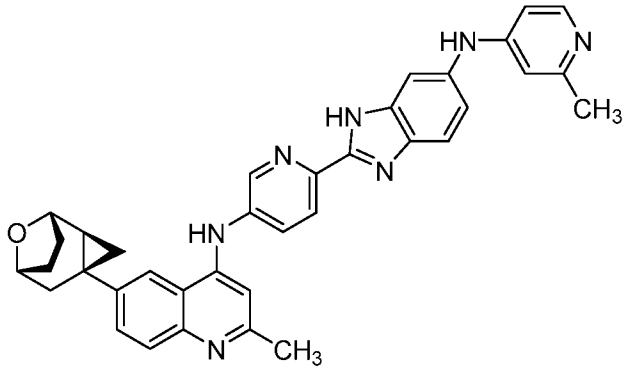
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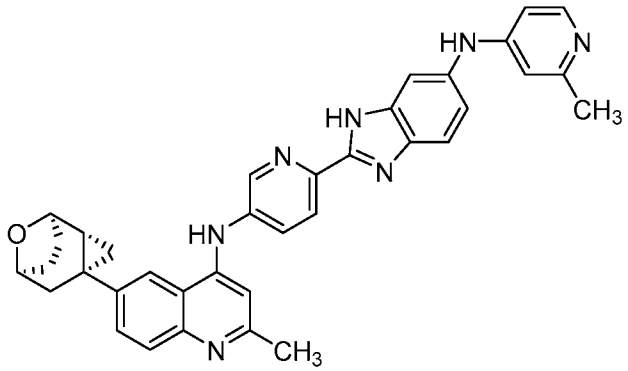


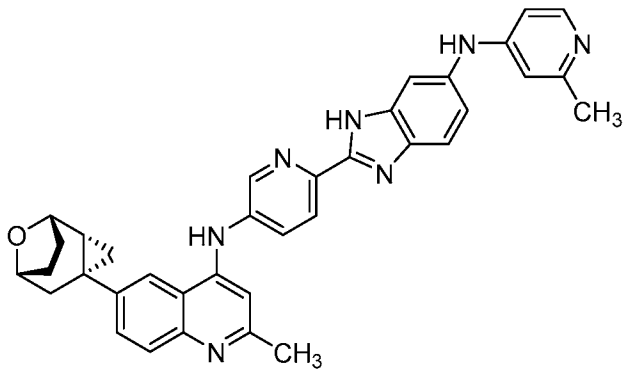
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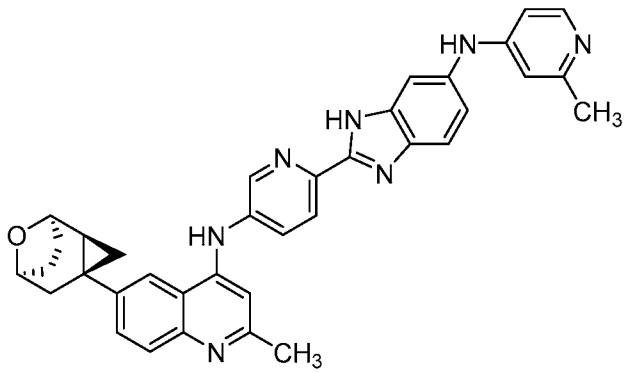


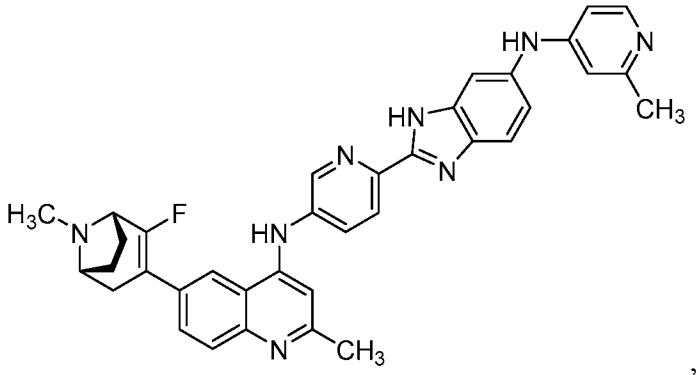
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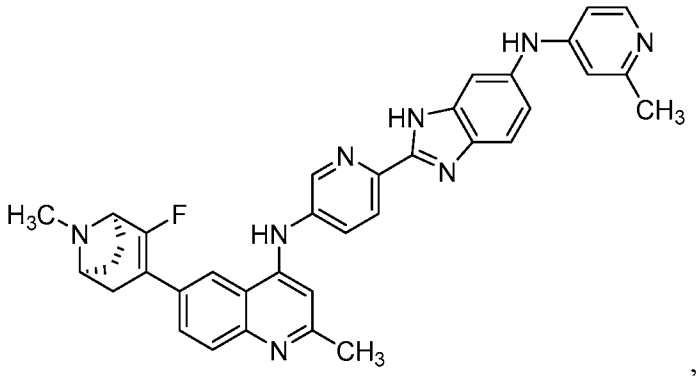

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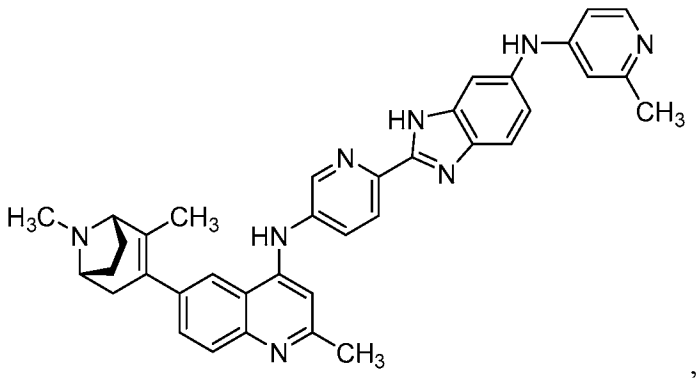

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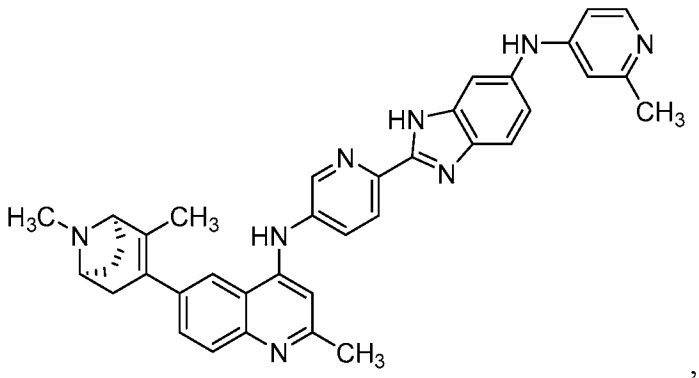

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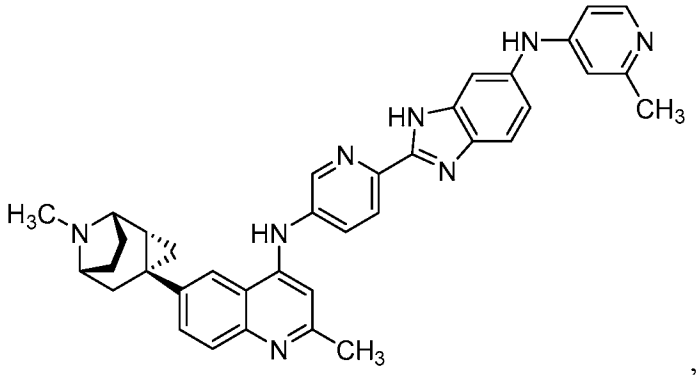

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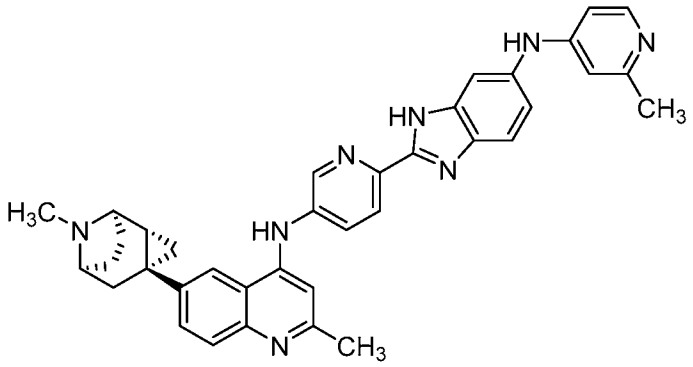

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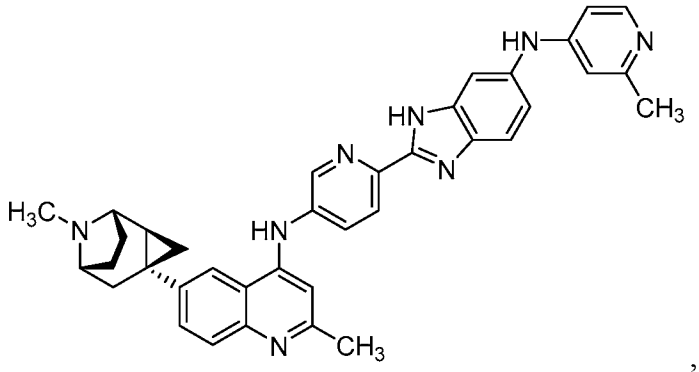

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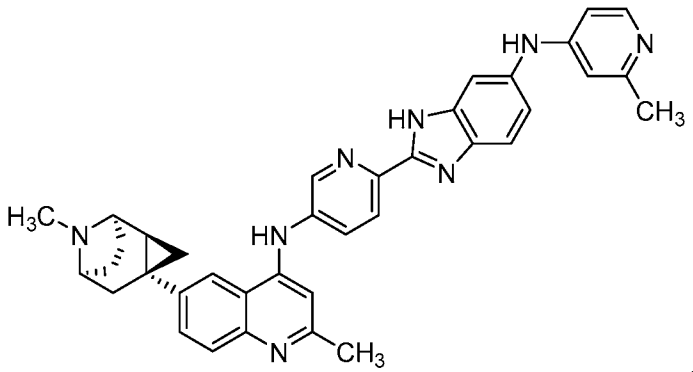

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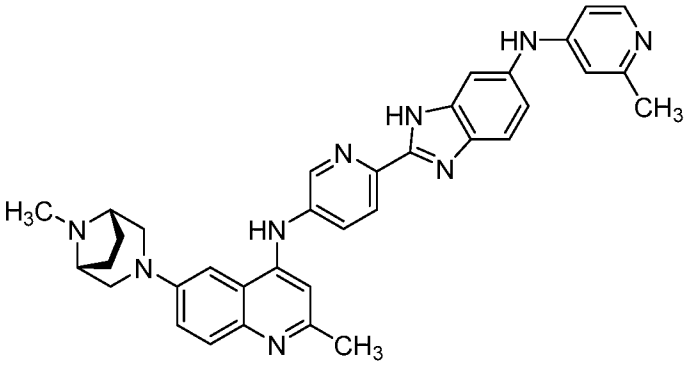

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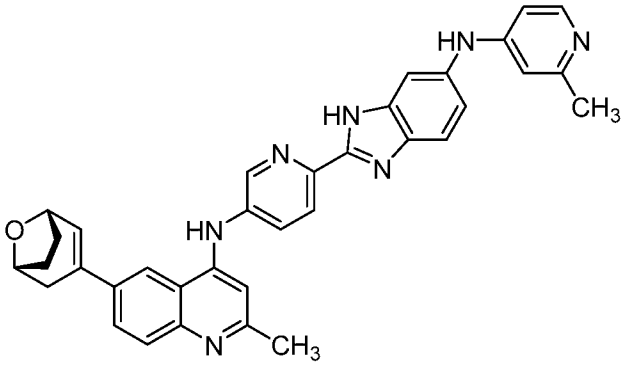

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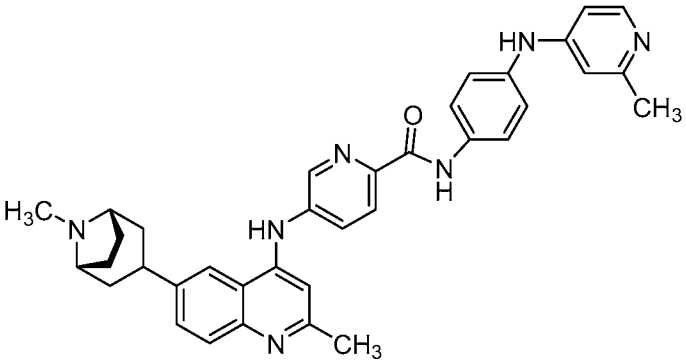

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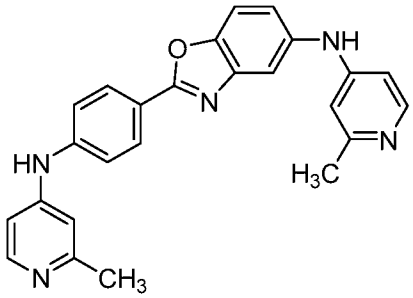
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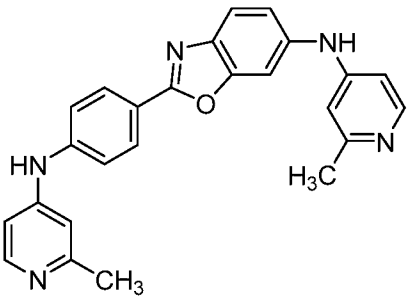
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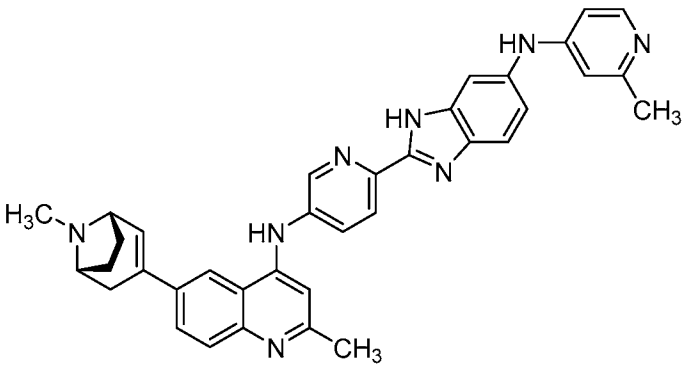
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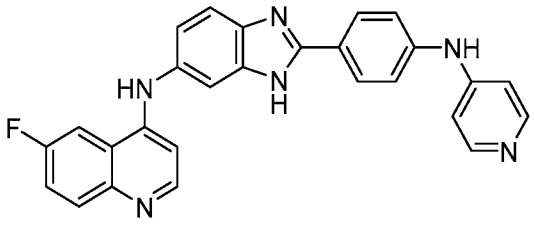
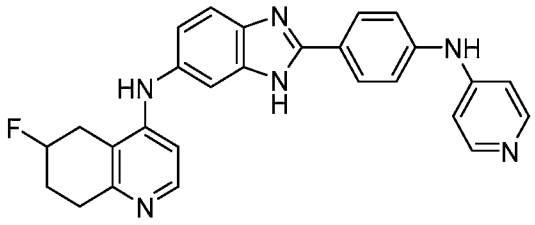
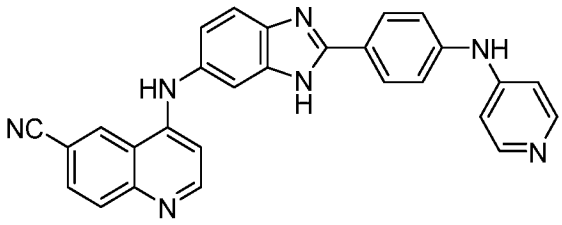
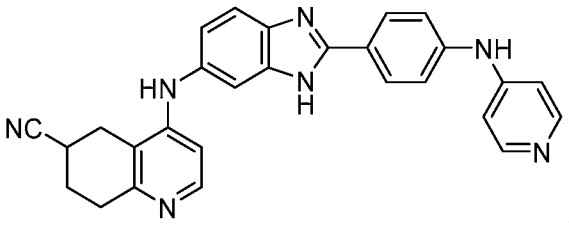
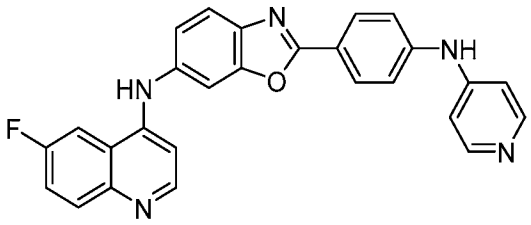
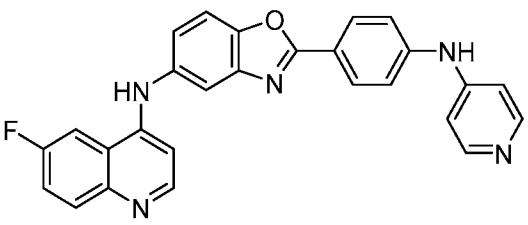
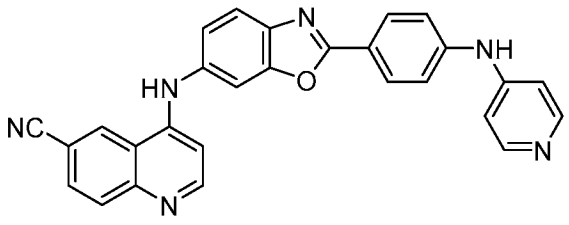
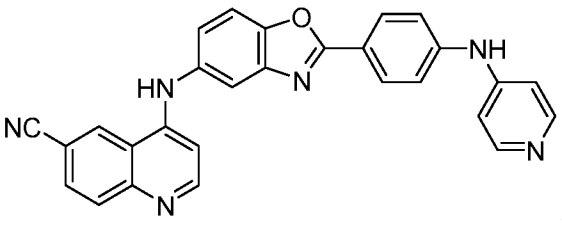
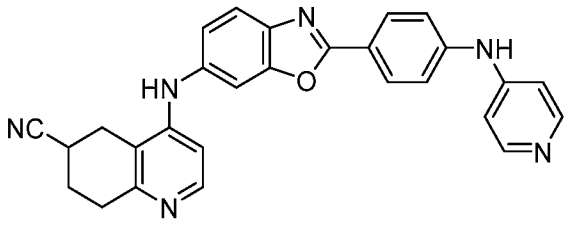
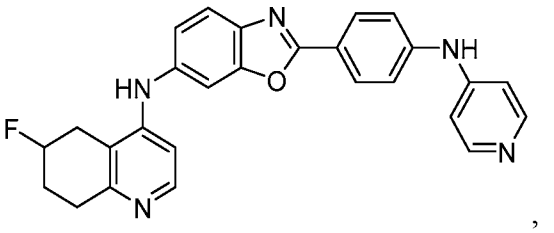
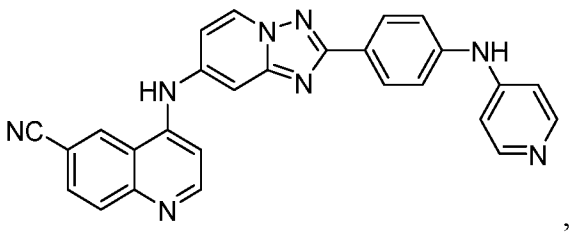
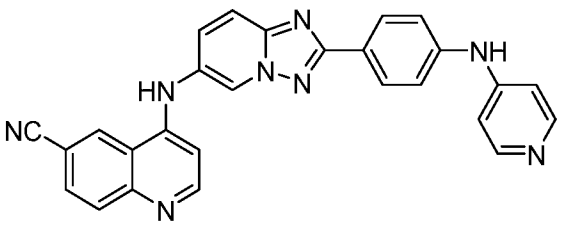


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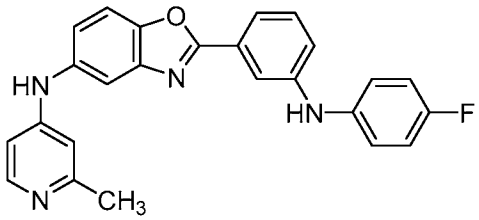


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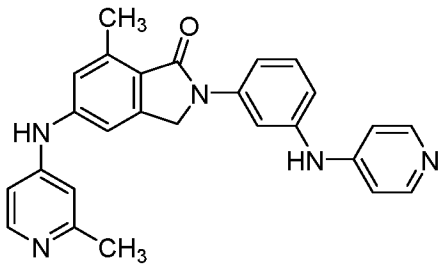
[0137] In any one of the embodiments disclosed herein, the compound of Formula Ic is


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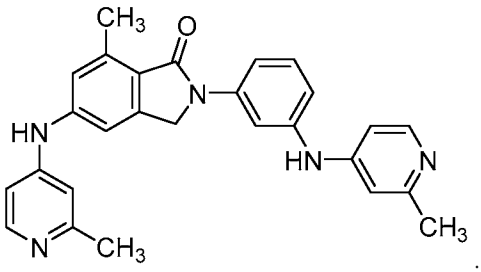
[0138] In any one of the embodiments disclosed herein, the compound of Formula IIc is



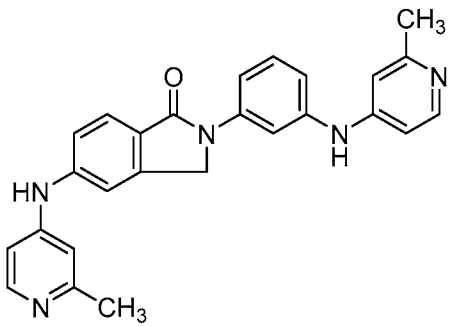
[0139] In any one of the embodiments disclosed herein, the compound of Formula IVa is



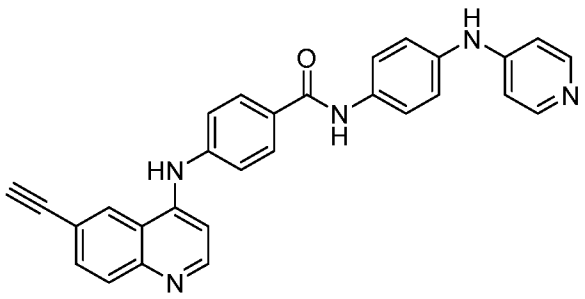
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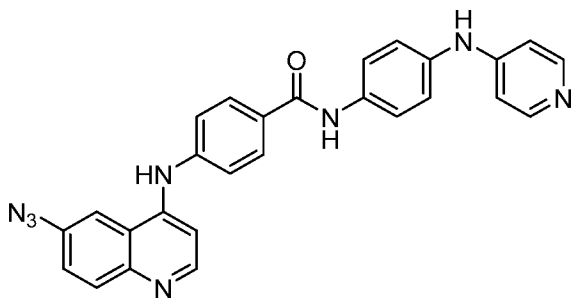
[0140] In any one of the embodiments disclosed herein, the compound is



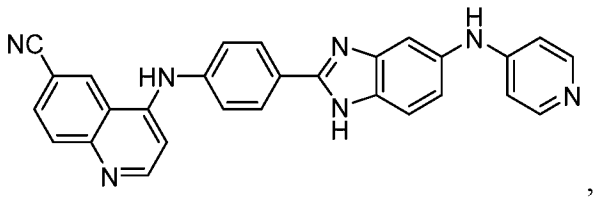
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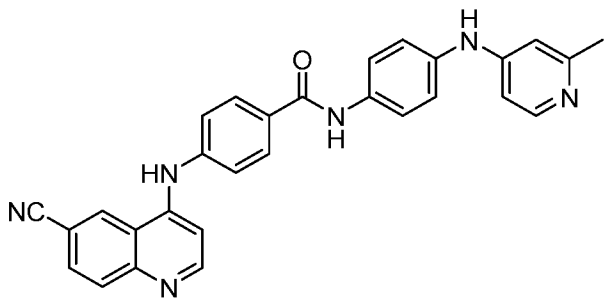
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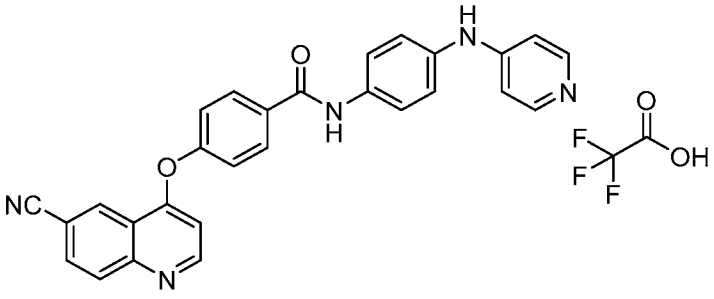
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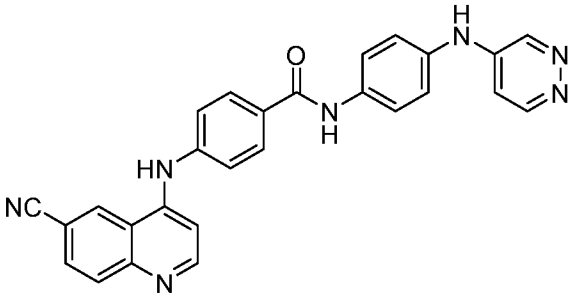
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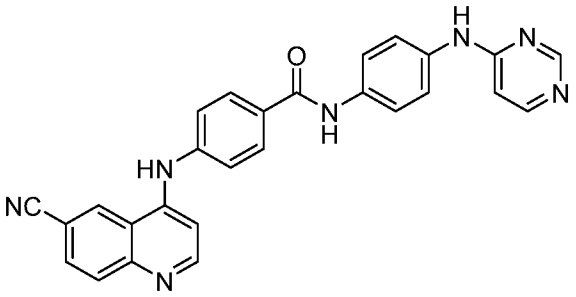
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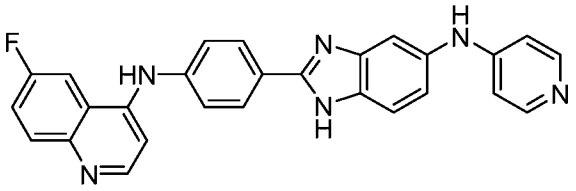
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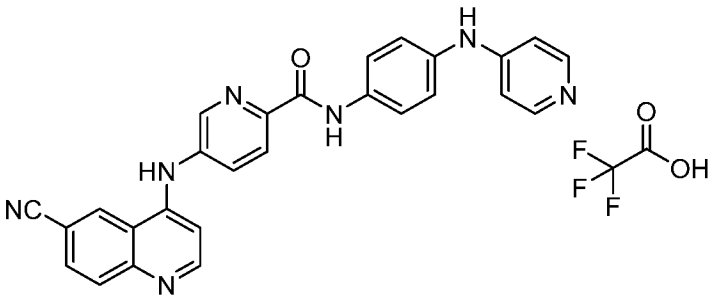
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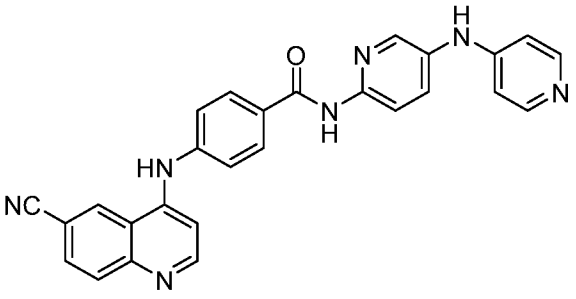
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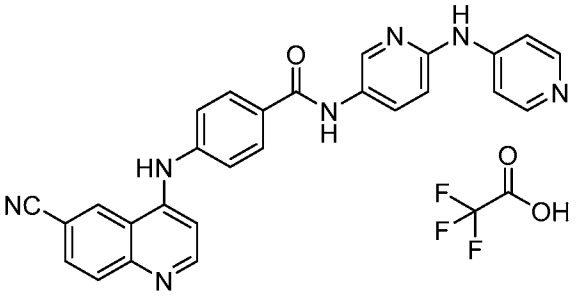
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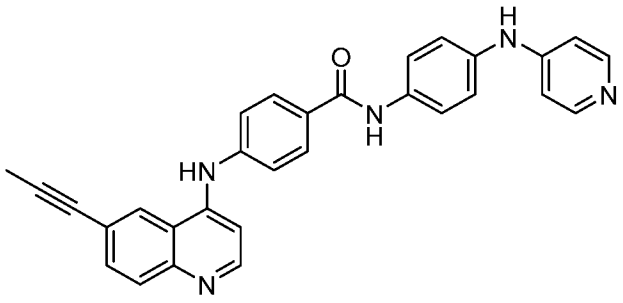
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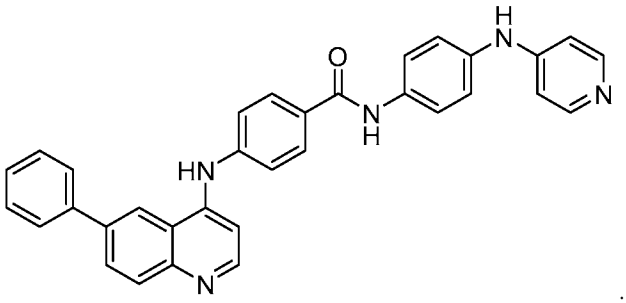
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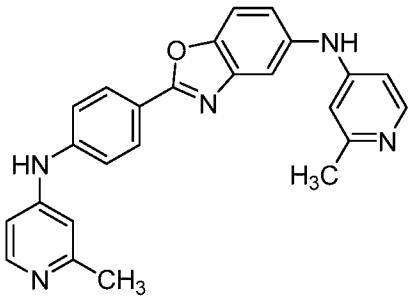


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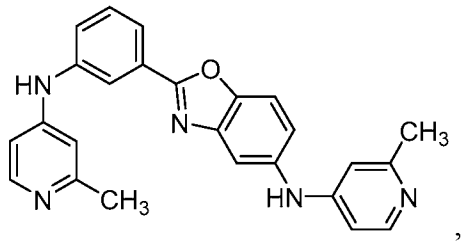


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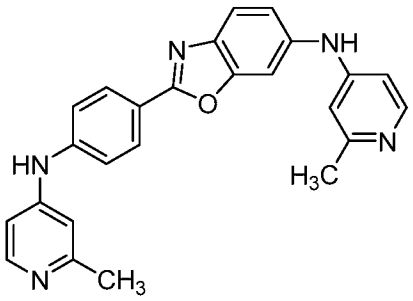
[0141] In any one of the embodiments disclosed herein, the compound is



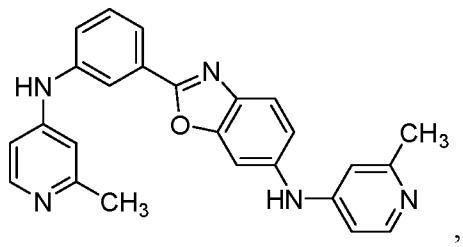
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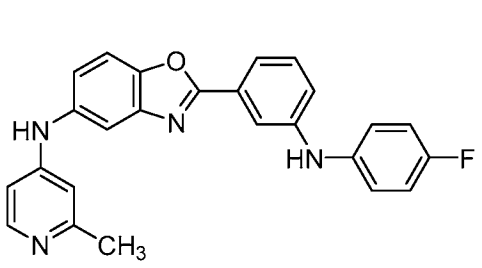
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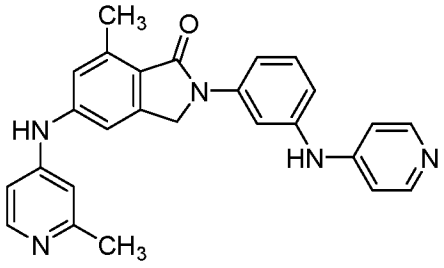
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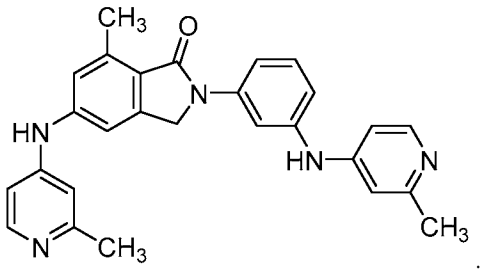
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[0142] In any one of the embodiments disclosed herein, the compound is selected from the group consisting of Compounds 2-9, 11-14, 30, and 32-145 in Examples 2-9, 11-14, 30, and 32-145, respectively.

[0143] 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.

[0144] 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.

[0145] In any one of the embodiments described herein, the disease is neurodegenerative disease.

[0146] 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.

[0147] In any one of the embodiments described herein, the disease is cachexia or anorexia.

[0148] In any one of the embodiments described herein, the disease is obesity or obesity's complication.

[0149] 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.

[0150] In any one of the embodiments described herein, the disease is inflammatory disease.

[0151] 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.

[0152] In any one of the embodiments described herein, the disease is viral-induced inflammatory reaction.

[0153] 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.

[0154] In any one of the embodiments described herein, the disease is Gulf War Syndrome or tuberous sclerosis.

[0155] In any one of the embodiments described herein, the disease is retinitis pigmentosa or transplant rejection.

[0156] In any one of the embodiments described herein, the disease is ischemic tissue injury or traumatic tissue injury.

[0157] In any one of the embodiments described herein, the disease is cancer.

[0158] 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.

[0159] In any one of the embodiments described herein, the cancer is leukemia.

[0160] In any one of the embodiments described herein, the leukemia is adult T-cell leukemia/lymphoma.

[0161] In any one of the embodiments described herein, the adult T-cell leukemia/lymphoma is caused by human T-cell lymphotropic virus.

[0162] In any one of the embodiments described herein, the disease is autoimmune disease.

[0163] 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.

[0164] In any one of the embodiments described herein, the compound modulates Akt3 in immune cells.

[0165] 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.

[0166] In any one of the embodiments described herein, the glial cells are astrocytes, microglia, or oligodendrocytes.

[0167] In any one of the embodiments described herein, the T cells are T regulatory cells.

[0168] In any one of the embodiments described herein, the compound activates Akt3 signaling.

[0169] In any one of the embodiments described herein, the compound inhibits Akt3 signaling.

[0170] In any one of the embodiments described herein, the compound increases T regulatory cell activity or production.

[0171] In any one of the embodiments described herein, the compound decreases T regulatory cell activity or production.

[0172] In any one of the embodiments described herein, the method further includes administering a second therapeutic agent to the subject.

[0173] 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.

[0174] 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.

[0175] 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

[0176] 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:

[0177] Figure 1 shows evaluation of iTreg induction (FoxP3) from human CD4 T cells treated with Compounds 131, 51, 42, 56, 50, 55, 53, 57, 5, 15, 18, 19, and 24 in the presence of anti-CD3/anti-CD28/IL-2/TGFβ, according to one or more embodiments described herein.

Compound 15 was evaluated at concentrations of 20 nM, 100 nM, 500 nM, and 1000 nM. Compounds 18 and 24 were evaluated at concentrations of 20 nM, 100 nM, and 500 nM.

[0178] Figure 2 shows evaluation of iTreg induction (FoxP3) from human CD4 T cells treated with Compounds 131, 72, 65, 63, 67, 70, 68, 77, 69, 84, 62, 83, 78, and 79 in the presence of anti-CD3/anti-CD28/IL-2/TGFβ, according to one or more embodiments described herein. Compound 77 was evaluated at concentrations of 20 nM, 100 nM, 500 nM, and 1000 nM. Compounds 84 and 83 were evaluated at concentrations of 20 nM, 100 nM, and 500 nM.

[0179] Figure 3 shows evaluation of iTreg induction (FoxP3) from human CD4 T cells treated with Compounds 131, 103, 89, 104, 93, 94, 92, 102, 90, 110, 87, 88, 91, 111, 96, and 97 in the presence of anti-CD3/anti-CD28/IL-2/TGFβ, according to one or more embodiments described herein. Compounds 93, 94, 92, 102, and 97 were evaluated at concentrations of 20 nM, 100 nM, 500 nM, and 1000 nM. Compounds 110, 87 and 91 were evaluated at concentrations of 20 nM, 100 nM, and 500 nM. Compound 88 was evaluated at concentrations of 20 nM and 100 nM.

[0180] Figure 4 shows evaluation of iTreg induction in human CD4 T cells treated with Compounds 131, 24, 69, 70, 87, 90, 97, and 102, according to one or more embodiments described herein. Compounds 97 and 102 were evaluated at concentrations of 20 nM, 100 nM, 500 nM, and 1000 nM. Compounds 24, 87, and 90 were evaluated at concentrations of 20 nM, 100 nM, and 500 nM.

[0181] Figure 5 shows evaluation of FoxP3 protein level in human CD4 T cells treated with Compounds 131, 24, 69, 70, 87, 90, 97, and 102, according to one or more embodiments described herein.

[0182] Figure 6 shows evaluation of Akt isoform specificity of Compounds 131, 24, 69, 87, 90, 97, and 102, according to one or more embodiments described herein.

[0183] Figure 7 shows evaluation of IL-10 in supernatants from human nTreg cells treated with Compounds 131, 24, 69, 70, 87, 90, 97, and 102 for 24 hours in the presence of anti-CD3/anti-CD28/IL-2 stimulation, according to one or more embodiments described herein.

[0184] Figure 8 shows evaluation of IL-10 in supernatants from human nTreg cells treated with Compounds 131, 24, 69, 70, 87, 90, 97, and 102 for 48 hours in the presence of

anti-CD3/anti-CD28/IL-2 stimulation, according to one or more embodiments described herein.

[0185] Figure 9 shows in vivo changes in Tregs in the spleen of mice on day 0 through day 4 post-PO treatment (10 mg/kg) with Compounds 131, 24, 69, 70, 87, 90, 97, and 102, according to one or more embodiments described herein.

[0186] Figure 10 shows in vivo changes in Tregs in the spleen of mice on day 0 through day 3 post-IV treatment (1 mg/kg) with Compounds 131, 24, 69, 70, 87, 90, 97, and 102, according to one or more embodiments described herein.

[0187] Figure 11 shows evaluation of Treg activation (normalized to untreated control; measured by flow cytometry) in isolated spleen of C57/Bl6 mice at two days post-treatment by single oral gavage with Compounds 131, 132, 133, and 134, according to one or more embodiments described herein.

[0188] Figure 12 shows evaluation of Treg activation (normalized to untreated control; measured by flow cytometry) in isolated spleen of C57/Bl6 mice at two days post-treatment by single oral gavage with Compounds 131, 121, and 127, according to one or more embodiments described herein.

[0189] Figure 13 shows evaluation of Treg activation (normalized to untreated control; measured by flow cytometry) in isolated spleen of C57/Bl6 mice at two days post-treatment (PO with Compounds 131, 123, 126, and 129, according to one or more embodiments described herein.

[0190] Figure 14 shows evaluation of Treg activation in response to treatment with Compound 138, according to one or more embodiments described herein.

[0191] Figure 15 shows evaluation of iTreg induction (FoxP3) from human CD4 T cells treated with Compounds 139-143, according to one or more embodiments described herein.

[0192] Figure 16 shows evaluation of iTreg induction from human CD4 T cells treated with Compounds 144-145, according to one or more embodiments described herein.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0193] 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.

[0194] 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.

[0195] 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.

[0196] 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.

[0197] 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.

[0198] 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.

[0199] 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.

[0200] 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. In some embodiments, heteroalkyl is optionally substituted.

[0201] 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.

[0202] 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.

[0203] 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, 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

substituents, such as cycloalkyl, cycloalkenyl, heterocycle and aryl substituents, can themselves be optionally substituted.

[0204] The term "bicycloalkyl" or "spiroalkyl" refers to a group 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 substituents, such as cycloalkyl, cycloalkenyl, heterocycle and aryl substituents, can themselves be optionally substituted.

[0205] 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. In some embodiments, heterocycloalkyl or cycloheteroalkyl is optionally substituted. 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.

[0206] 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 substituents, such as cycloalkyl, cycloalkenyl, heterocycle and aryl substituents, can themselves be optionally substituted.

[0207] 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 substituents, such as cycloalkyl, cycloalkenyl, heterocycle, and aryl substituents, can themselves be optionally substituted.

[0208] 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.

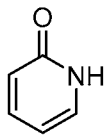
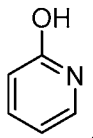
[0209] The term "carbocycle" or "carbon cycle" refers to a fully saturated or partially saturated cyclic hydrocarbon group containing from 1 to 4 rings and 3 to 8 carbons per ring, or cyclic, aromatic hydrocarbon groups that have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as 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 substituents, such as cycloalkyl, cycloalkenyl, heterocycle, and aryl substituents, can themselves be optionally substituted.

[0210] 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.

[0211] "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 substituents, such as cycloalkyl, cycloalkenyl, heterocycle and aryl substituents, can themselves be optionally substituted.

[0212] 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 .

[0213] 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.

[0214] 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.

[0215] The terms "halogen" or "halo" refer to chlorine, bromine, fluorine, or iodine.

[0216] 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.

[0217] Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

[0218] 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.

[0219] 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.

[0220] 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.

[0221] 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.

[0222] 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.

[0223] All stereoisomers of the compounds described herein (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.

[0224] 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.

[0225] 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.

[0226] Throughout the specification, groups and substituents thereof may be chosen to provide stable moieties and compounds.

[0227] 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).

[0228] 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.

[0229] 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.

[0230] 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 (or D), ^{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.

[0231] 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.

[0232] 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.

[0233] 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.

[0234] 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.

[0235] 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.

[0236] 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.

[0237] 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). 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.

[0238] 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.

[0239] 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, about 10, about 15, about 50, about 100, about 1000, or about 5000-fold greater than their modulations of Akt1 and/or Akt2.

[0240] 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).

[0241] 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.

[0242] 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.

[0243] 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.

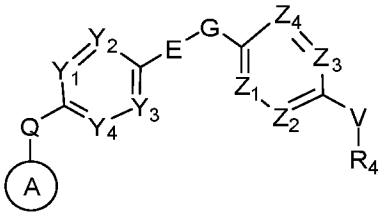
[0244] The term "immune tolerance" refers to any mechanism by which a potentially injurious immune response is prevented, suppressed, or shifted to a non-injurious immune response (*see* Bach, et al., *N. Eng. J. Med.*, 347:911-920 (2002)).

[0245] 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.

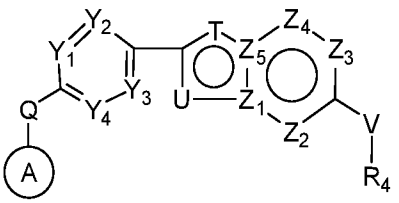
Compounds

[0246] In one aspect, a compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

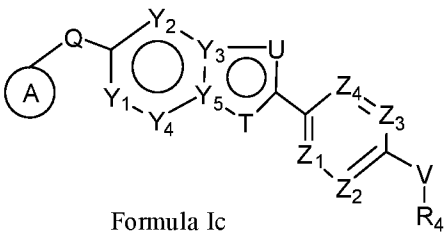
[0247] In one aspect, a compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc is described,



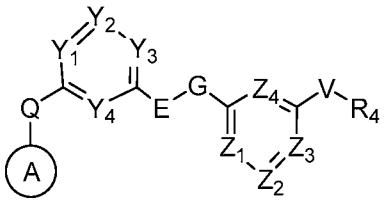
Formula Ia ;



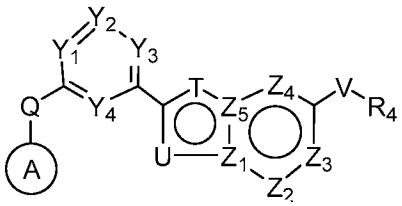
Formula Ib ;



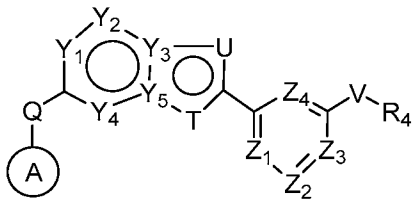
Formula Ic ;



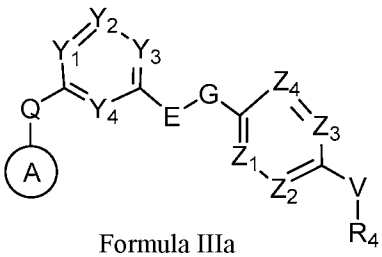
Formula IIa ;



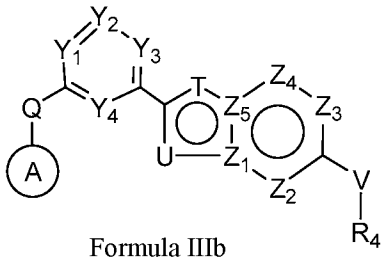
Formula IIb ;



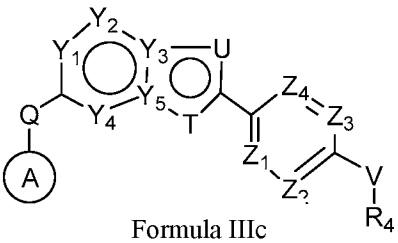
Formula IIc ;



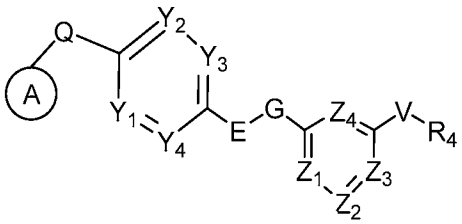
Formula IIIa ;



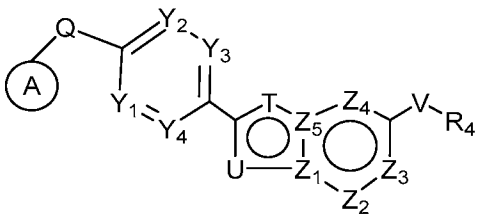
Formula IIIb ;



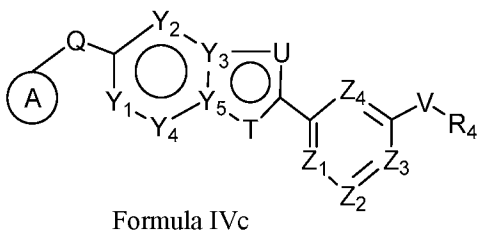
Formula IIIc ;



Formula IVa ;



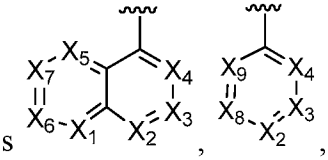
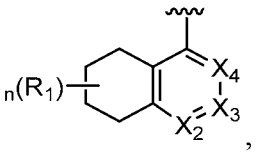
Formula IVb ; or



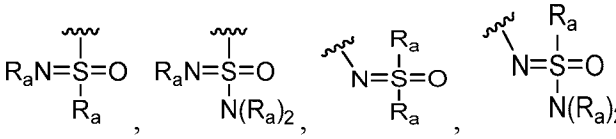
Formula IVc ;

or a pharmaceutically acceptable salt thereof,

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 is independently CR_1 or N;

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, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, $(C_4\text{-}C_{14})$heterotricycloalkenyl, 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 $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, $-SO_2R_a$, or $-SO_2N(R_a)_2$;

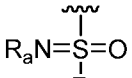
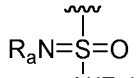
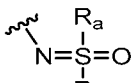
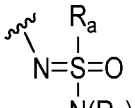
wherein the $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, $(C_4\text{-}C_{14})$heterotricycloalkenyl, 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 $-N(R_a)_2$;

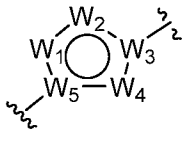
n is an integer from 0-4 where valence permits;

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  ;

$-E\text{-}G-$ 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 where R_x and Y_2, R_x and Y_3, 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;

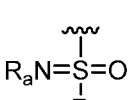
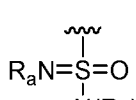
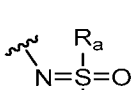
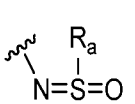
each occurrence of R_6 is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$haloalkyl;

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;

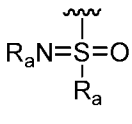
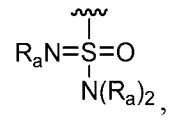
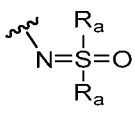
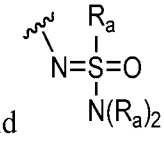
Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently N or CR_3 where valance permits;

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, $(C_4\text{-}C_{10})$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  ;

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

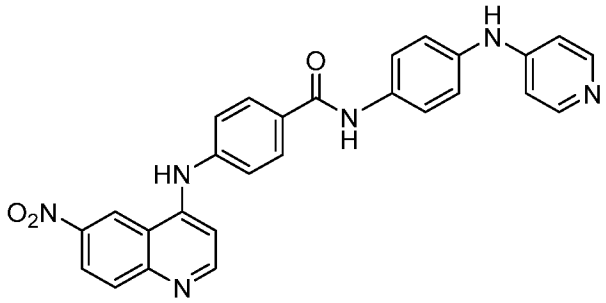
R_4 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, aryl, and heteroaryl, each optionally substituted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

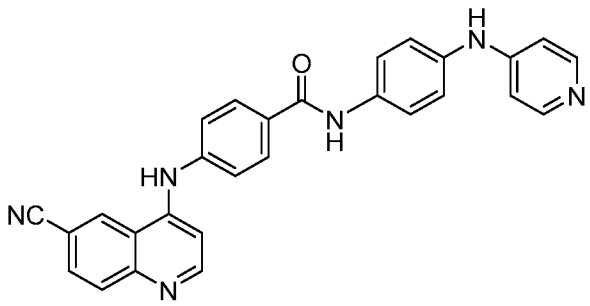
or alternatively V and R_4 taken together form a (C_3-C_7)heterocycloalkyl or (C_4-C_{10})heterospiroalkyl;

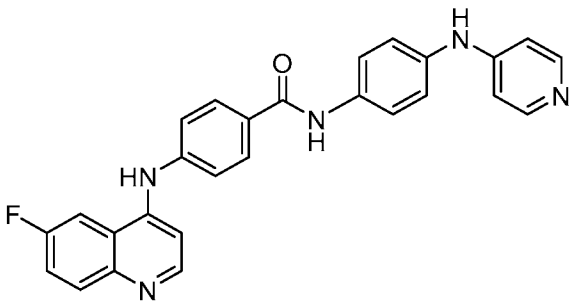
each occurrence of R_5 is independently selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (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

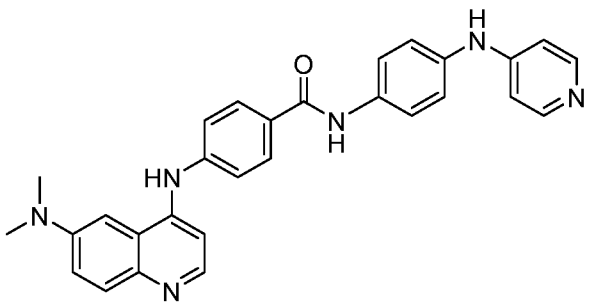
each occurrence of R_a is independently H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, aryl, or heteroaryl, or two R_a taken together form a 4-6-membered ring optionally substituted with halogen or (C_1-C_6)alkyl;

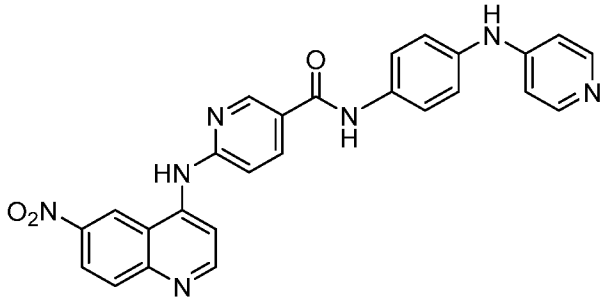
with the proviso that the compound is not

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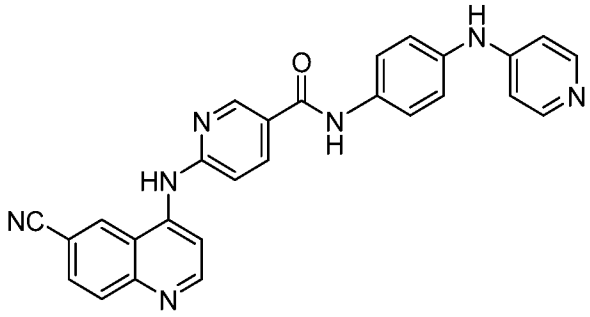
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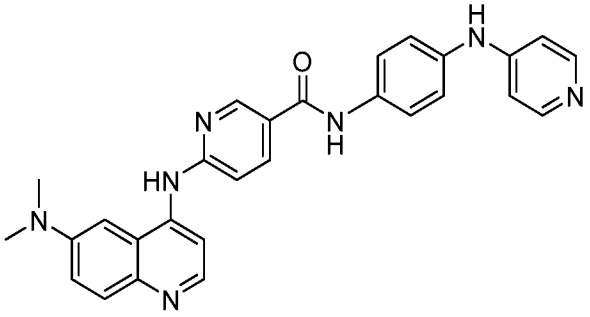
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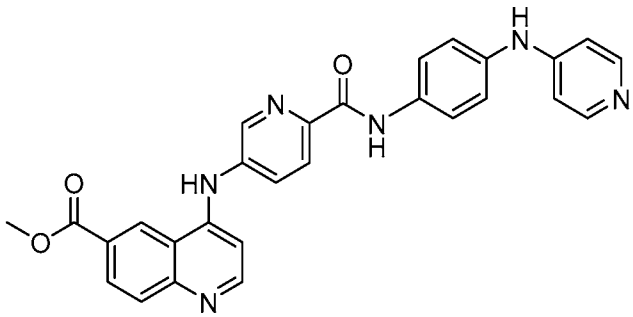
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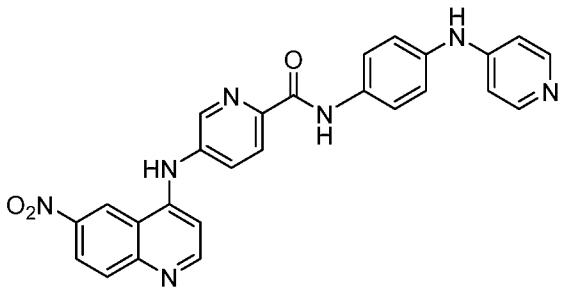
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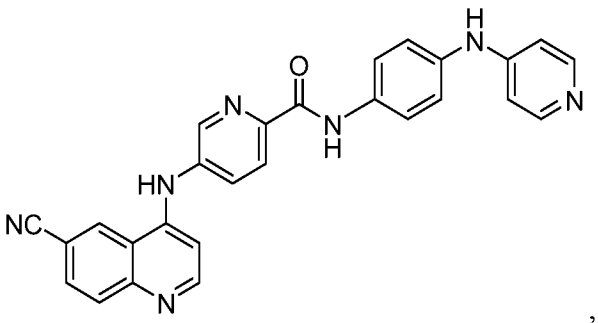
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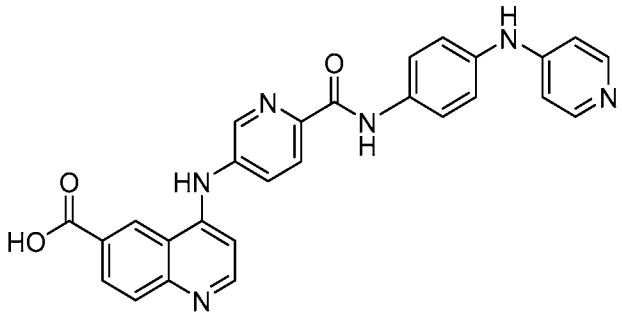
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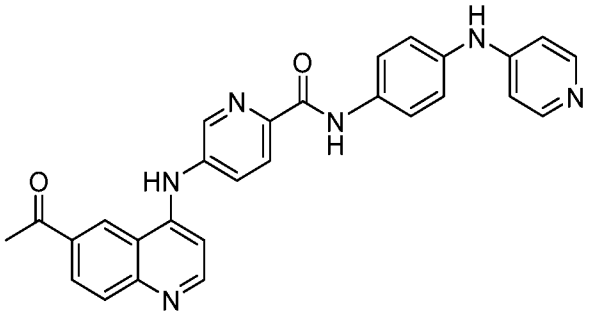
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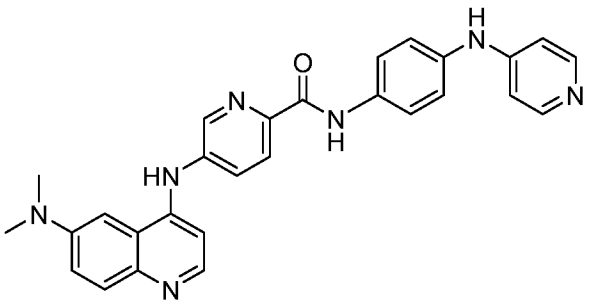
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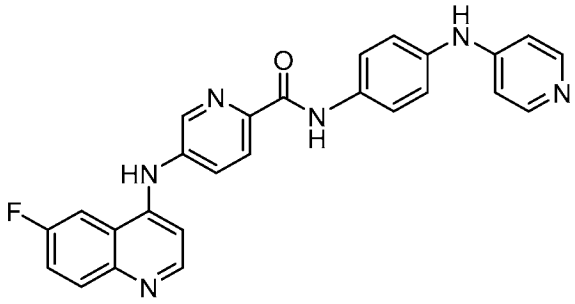
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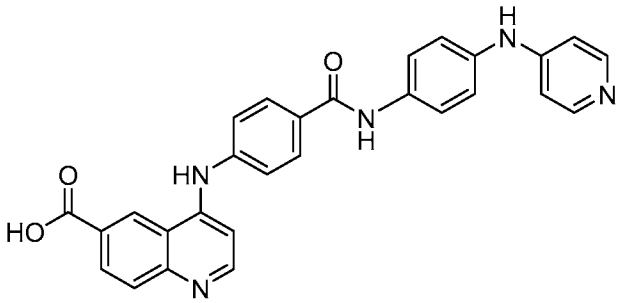
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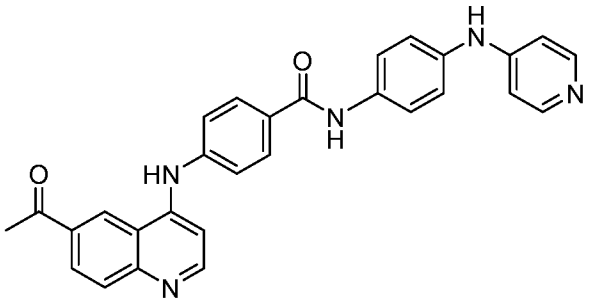
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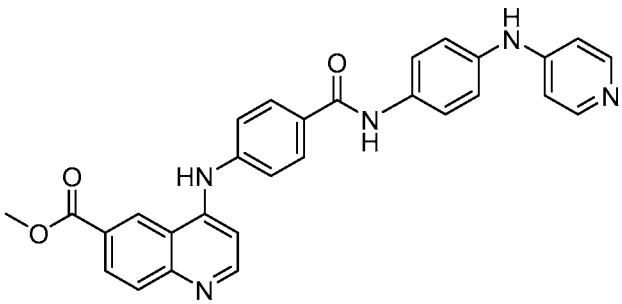
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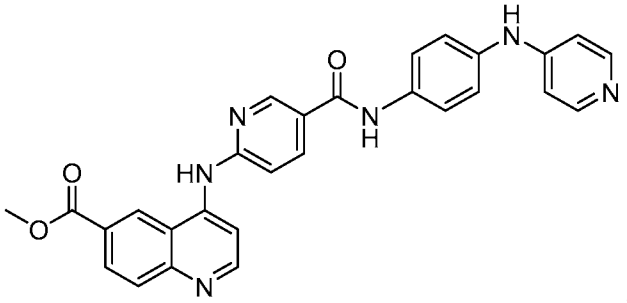
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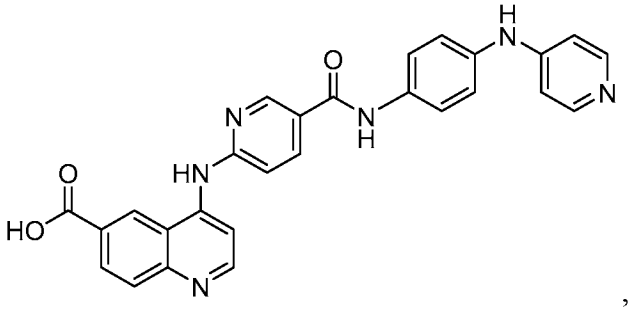
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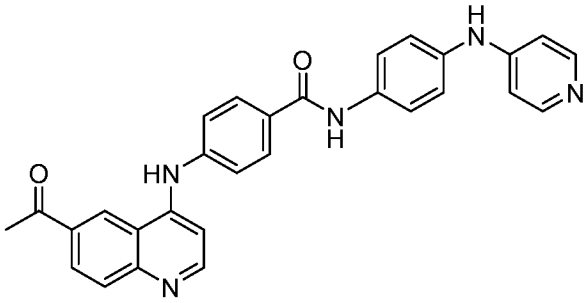
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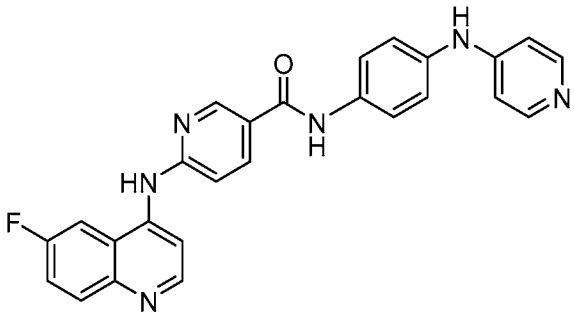
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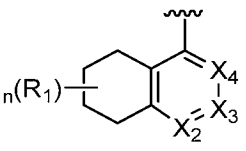
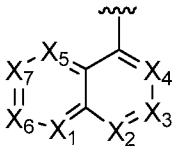
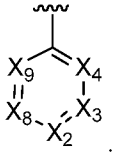
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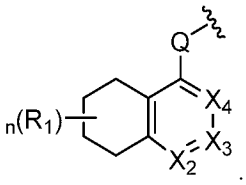
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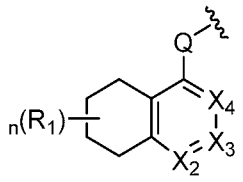
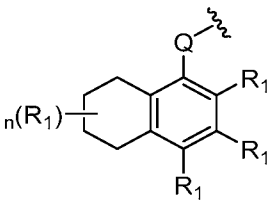
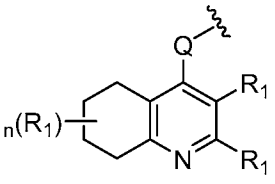
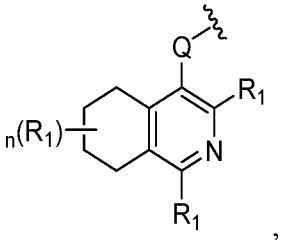
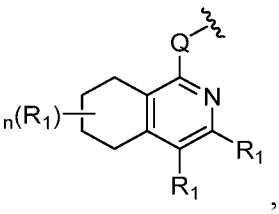
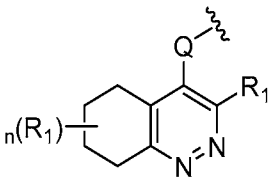
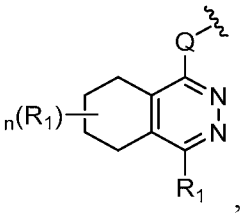
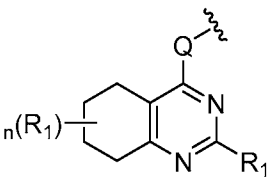
[0248] In some embodiments, Ⓐ is . In some embodiments, Ⓐ is . In some embodiments, Ⓐ is .

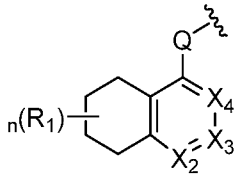
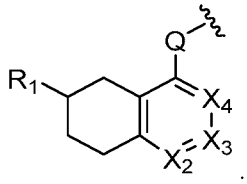
[0249] In some embodiments, Q is $C(R_a)_2$, O, or NR_a. In some embodiments, Q is O. In some embodiments, Q is NR_a. In some embodiments, Q is NH. In some embodiments, Q is

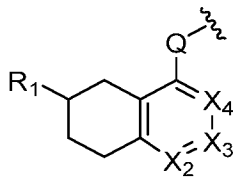
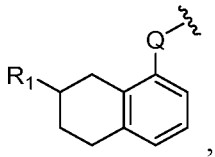
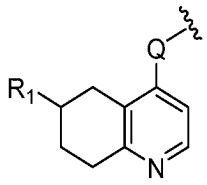
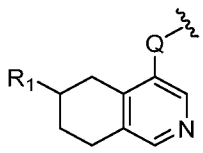
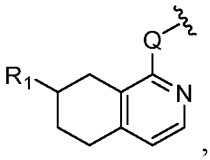
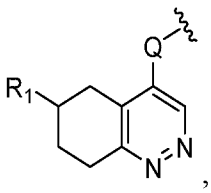
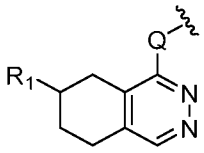
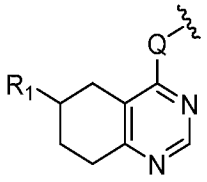
NCH_3 or NCH_2CH_3. In some embodiments, Q is $N(C=O)R_a$ or NSO_2R_a. In some embodiments, Q is N(C=O)H. In some embodiments, Q is $N(C=O)CH_3$ or $N(C=O)CH_2CH_3$. In some embodiments, Q is NSO_2H. In some embodiments, Q is NSO_2CH_3 or $NSO_2CH_2CH_3$.

[0250] 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.

[0251] 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.

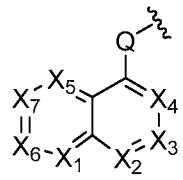
[0252] In some embodiments, the structural moiety  has the structure of , , , , , , or .

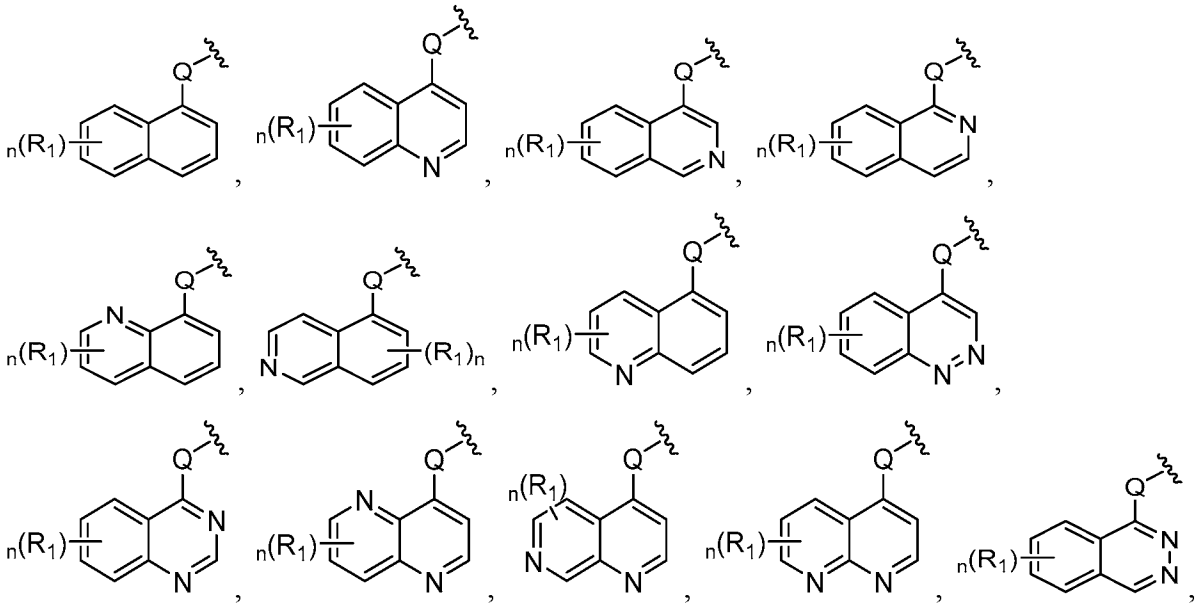
[0253] In some embodiments, the structural moiety  has the structure of .

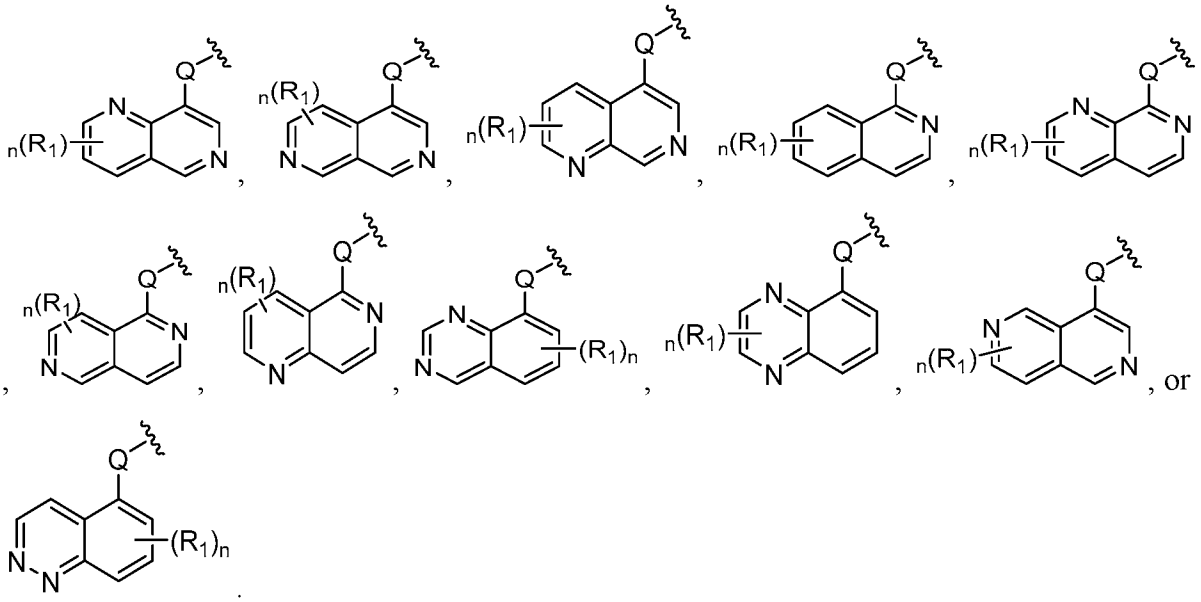
[0254] In some embodiments, the structural moiety  has the structure of , , , , , , or .

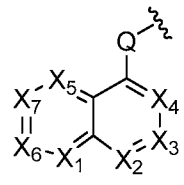
[0255] In some embodiments, X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are each independently CR_1 or N. In some embodiments, X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are CR_1. In some embodiments, X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are each independently CH, C(halogen), or CCH_3. In some embodiments, one 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, C(halogen), 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, C(halogen), 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, C(halogen), 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, C(halogen), 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, C(halogen), or CCH_3. In some

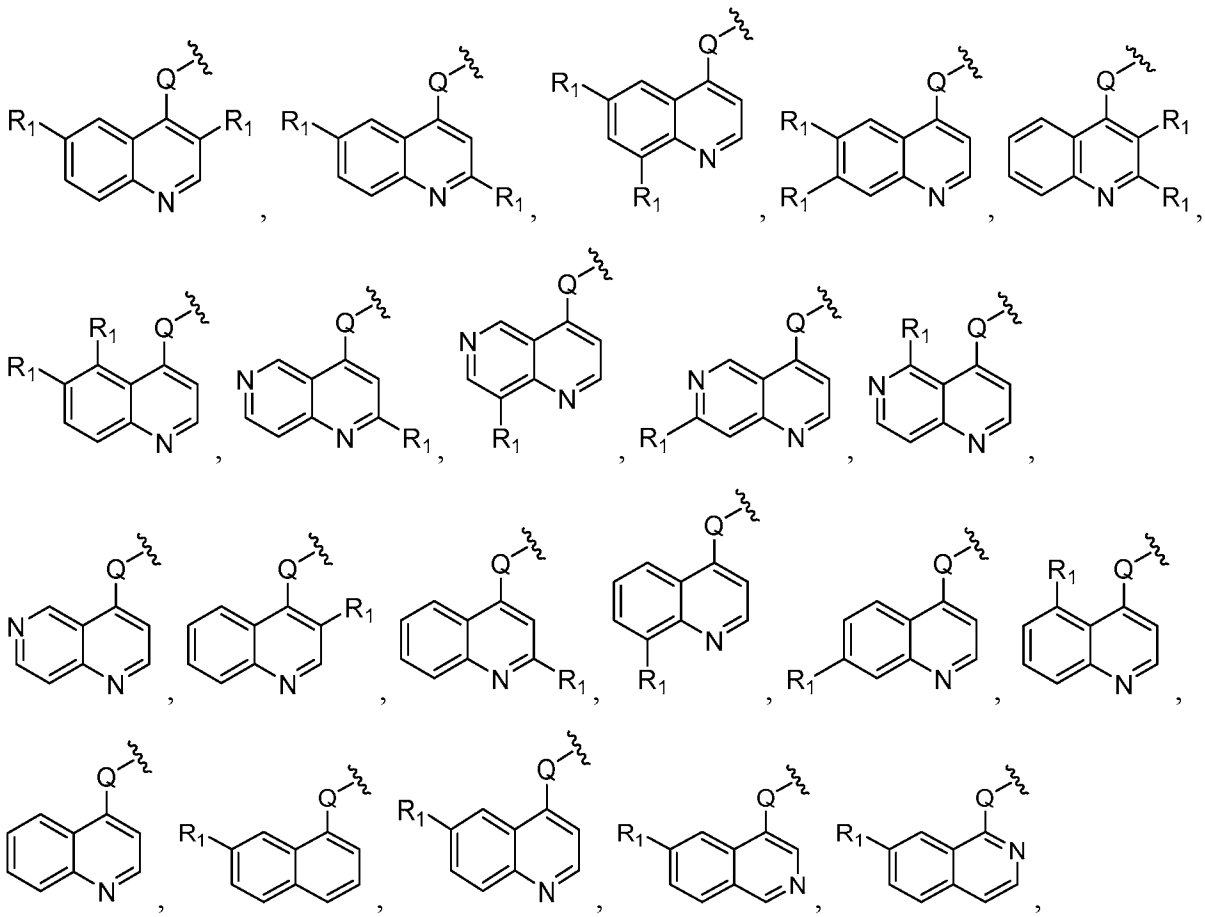
embodiments, X_2 is N, X_7 is CR_1, X_3 is C(halogen) or CCH_3, and X_1, X_4, X_5, and X_6 are CH. In some embodiments, X_2 and X_7 are N and X_1, X_3, X_4, X_5, and X_6 are CR_1. In some embodiments, X_2 and X_7 are N and X_1, X_3, X_4, X_5, and X_6 are each independently CH, C(halogen), or CCH_3. In 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, C(halogen), 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, C(halogen), 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, C(halogen), 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, C(halogen), 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, C(halogen), or CCH_3. In some embodiments, the halogen is F, Cl, Br, or I. In some embodiments, the halogen is F.

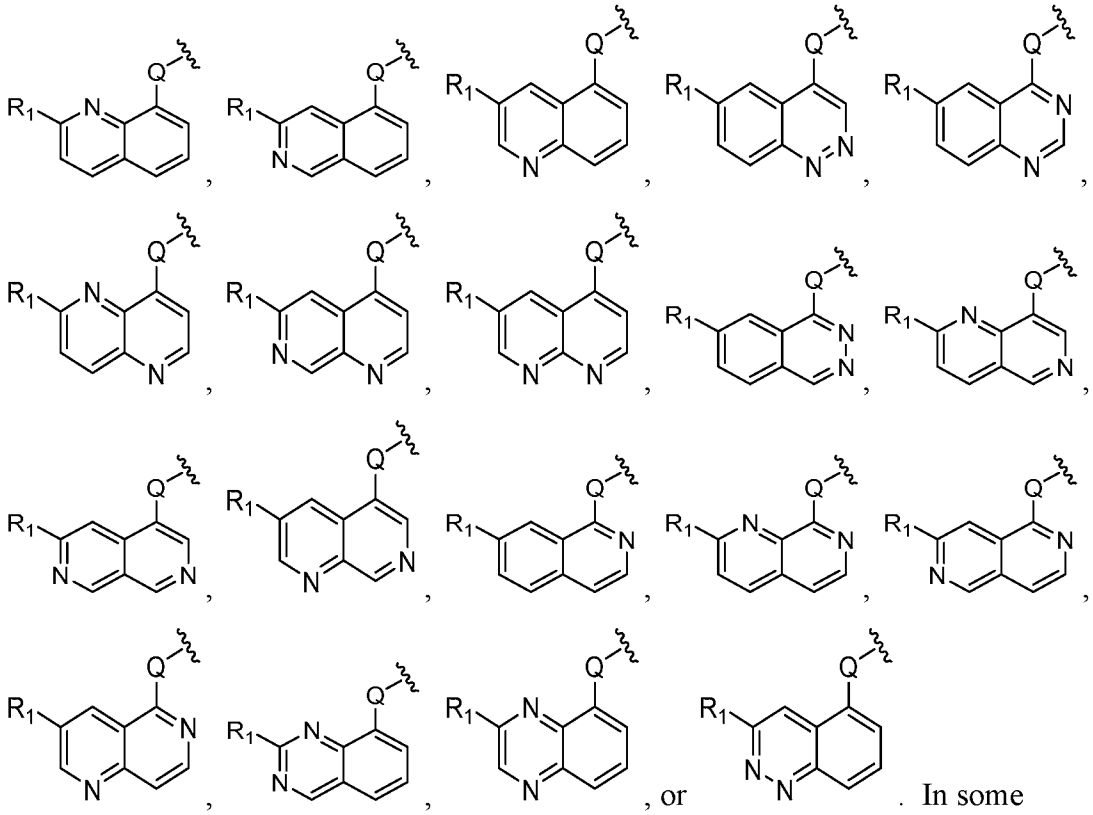
[0256] In some embodiments, the structural moiety  has the structure of



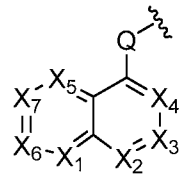


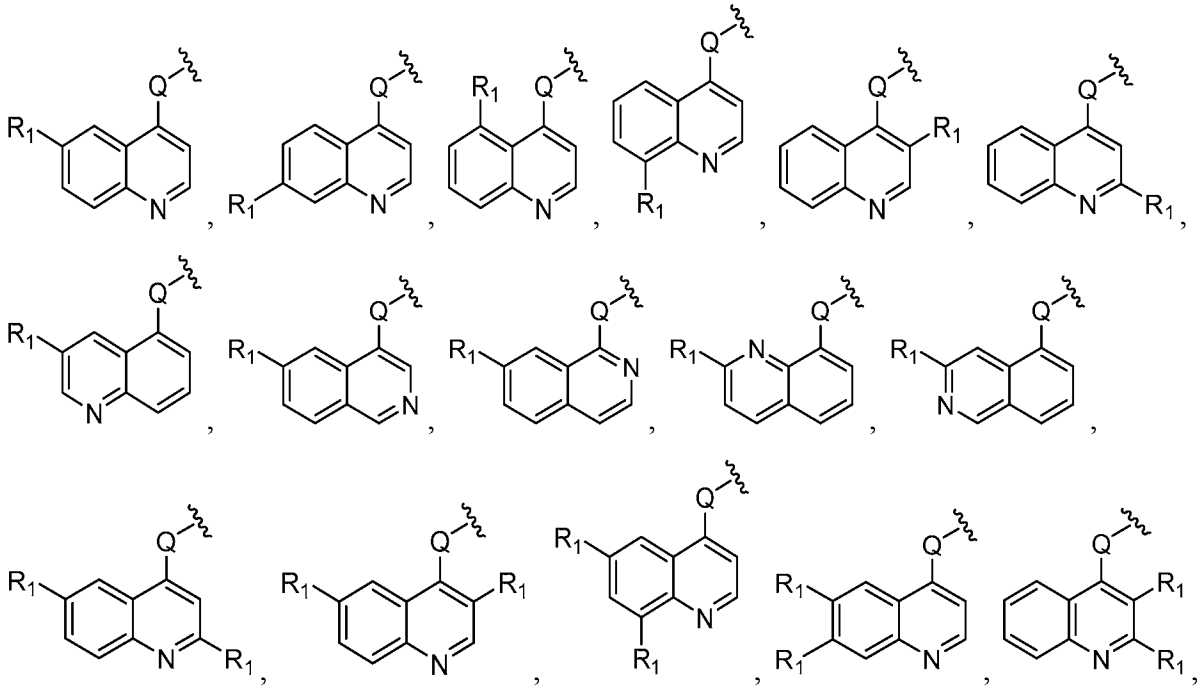
[0257] In some embodiments, the structural moiety  has the structure of

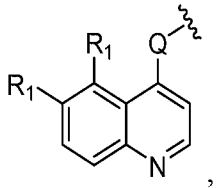
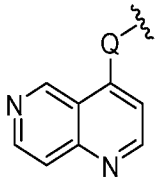
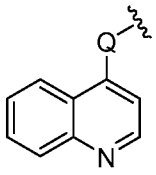
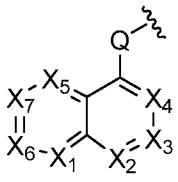
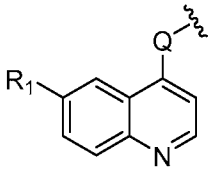
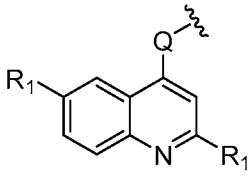


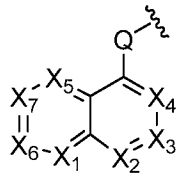
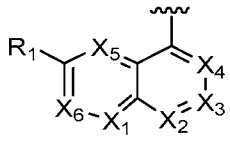


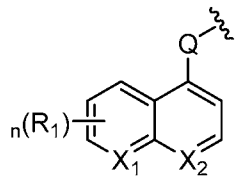
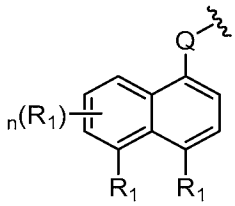
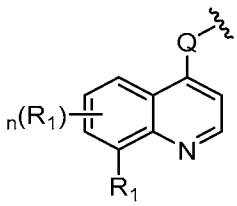
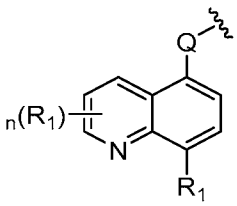
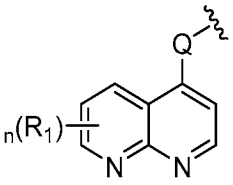
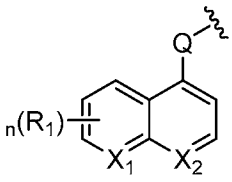
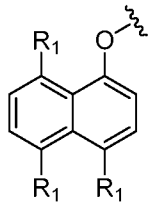
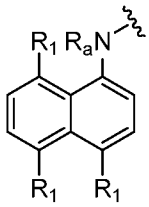
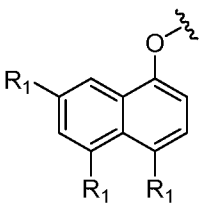
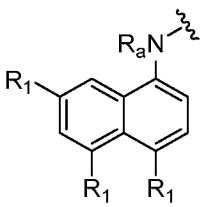
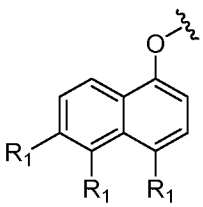
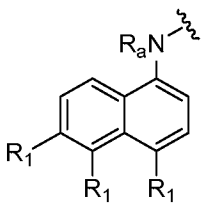
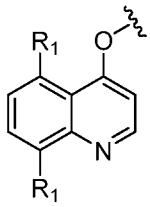
embodiments, Q is O. In some embodiments, Q is NR_a, $N(C=O)R_a$, or NSO_2R_a. In some embodiments, Q is NH. In some embodiments, Q is NCH_3 or NCH_2CH_3.

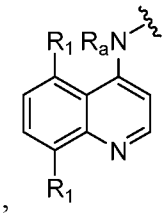
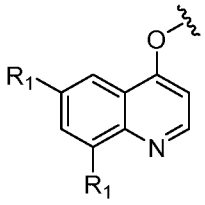
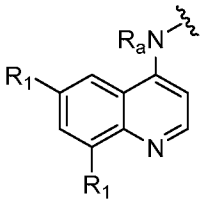
[0258] In some embodiments, the structural moiety  has the structure of

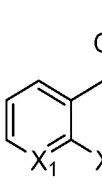
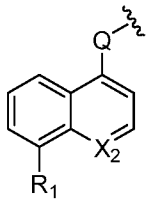
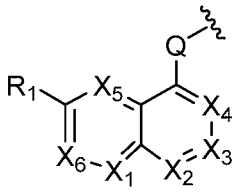
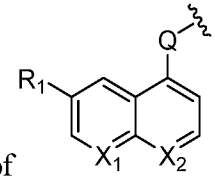


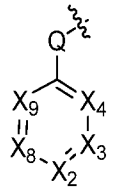
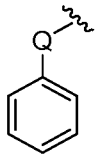
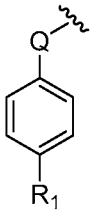
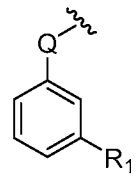
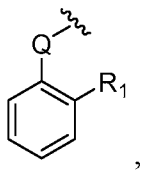
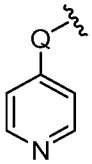
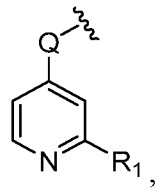
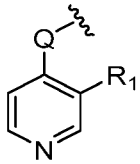
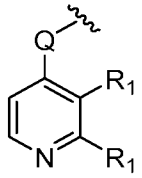
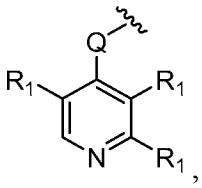
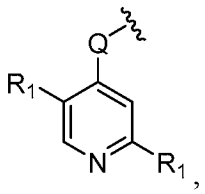
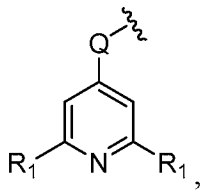
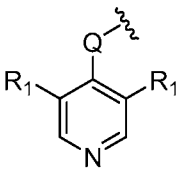
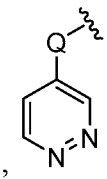
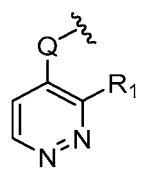
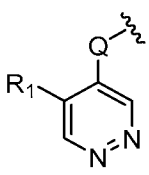
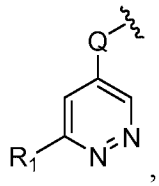
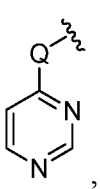
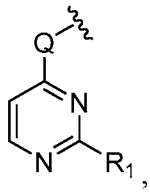
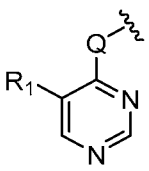
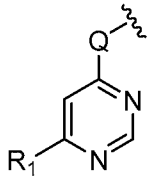
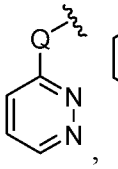
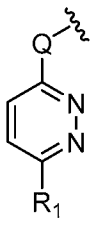
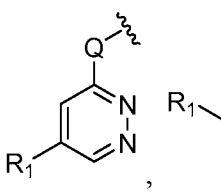
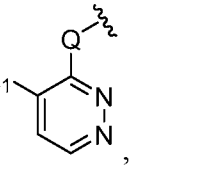
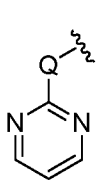
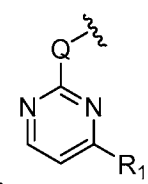
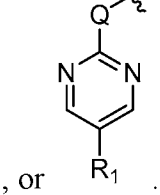
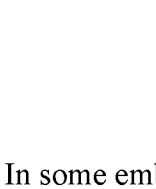
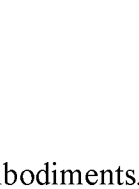



, or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, Q is O. In some embodiments, Q is NR_a, $N(C=O)R_a$, or NSO_2R_a. In some embodiments, Q is NH. In some embodiments, Q is NCH_3 or NCH_2CH_3.

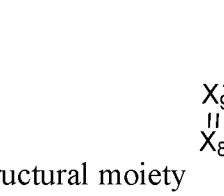
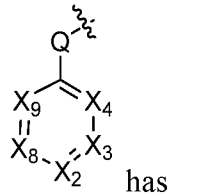
[0259] In some embodiments, the structural moiety  has the structure of .

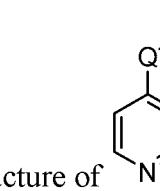
[0260] In some embodiments, the structural moiety  has the structure of , , , or . In some embodiments, the structural moiety  has the structure of , , , , , , ,

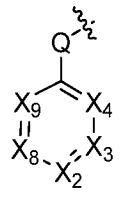
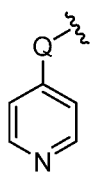
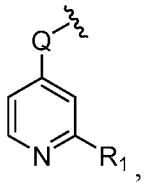
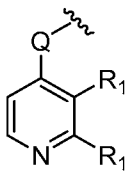
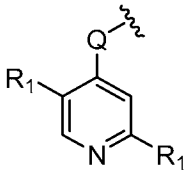

, or 
. In some embodiments, the structural moiety 
has the structure of 
.

[0261] In some embodiments, the structural moiety 
has the structure of 
, 




























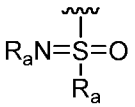
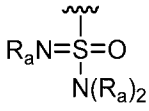
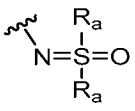
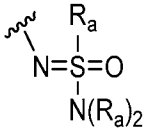
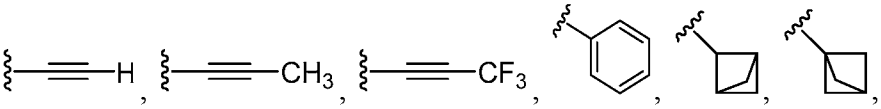



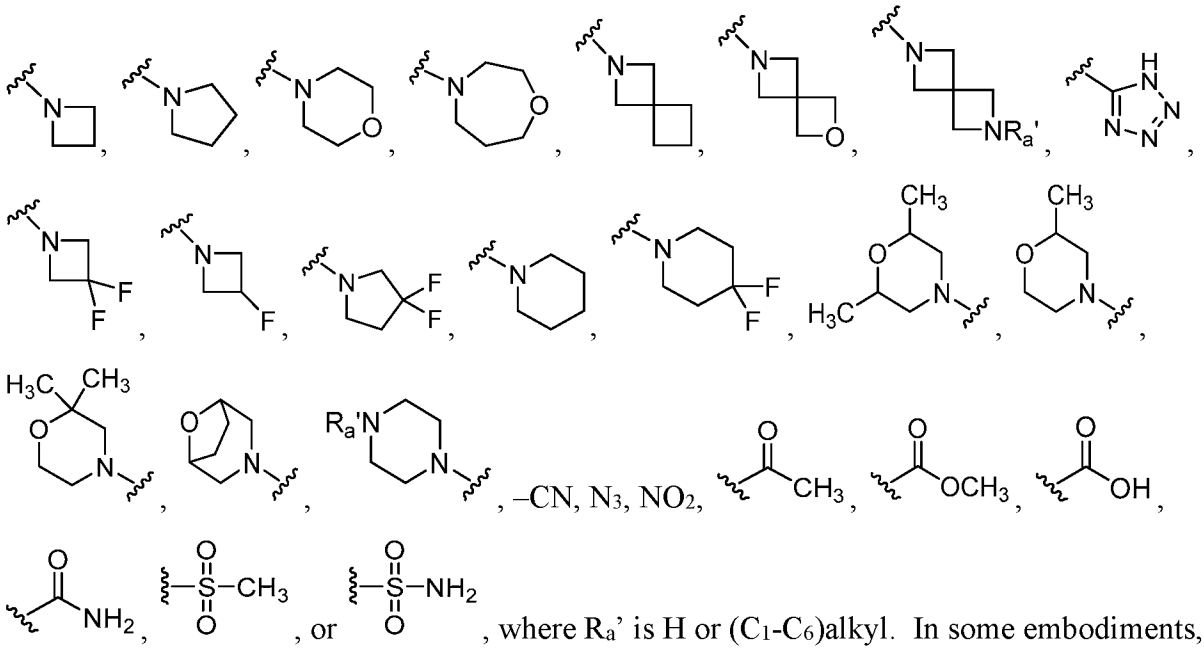


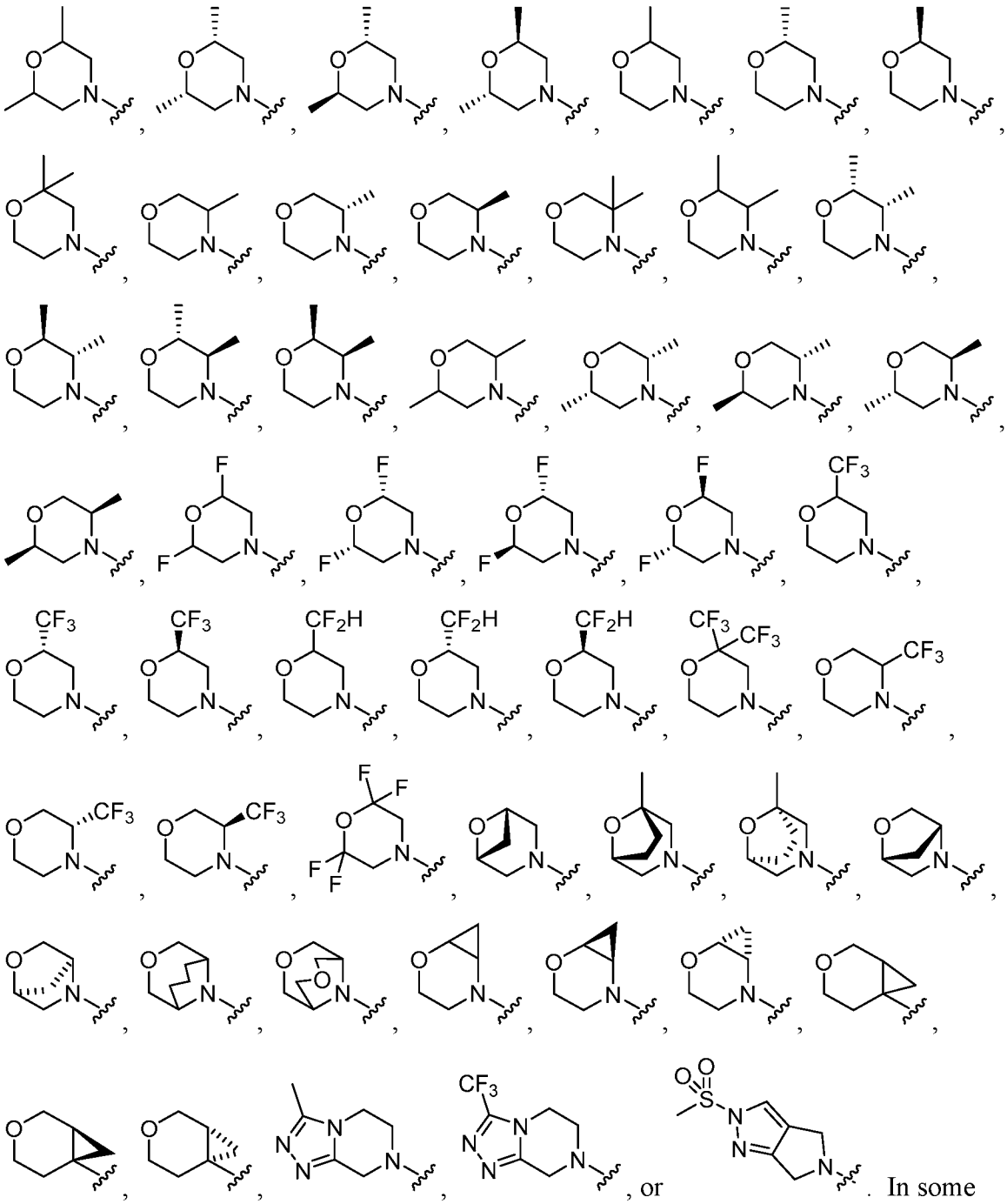
, or
. In some embodiments, the structural moiety
has the structure of
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,
, or
. In some

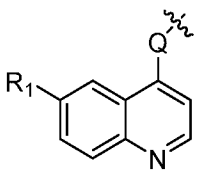
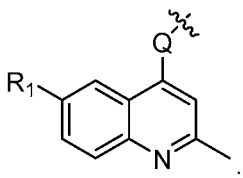
embodiments, the structural moiety  has the structure of , , , or . In some embodiments, Q is O. In some embodiments, Q is NR_a, $N(C=O)R_a$, or NSO_2R_a. In some embodiments, Q is NH. In some embodiments, Q is NCH_3 or NCH_2CH_3.

[0262] 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, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, $(C_4\text{-}C_{14})$heterotricycloalkenyl, 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, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, $(C_4\text{-}C_{14})$heterotricycloalkenyl, 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 $(C_1\text{-}C_6)$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, and $(C_4\text{-}C_{10})$heterobicycloalkyl; wherein the $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, and $(C_4\text{-}C_{10})$heterobicycloalkyl 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 $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, aryl, and heteroaryl; wherein the $(C_4\text{-}C_{10})$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 optionally substituted $(C_3\text{-}C_7)$cycloalkenyl or optionally substituted

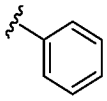
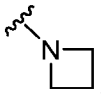
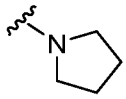
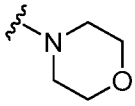
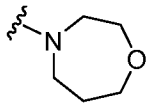
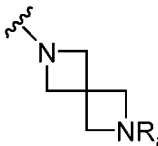
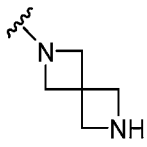
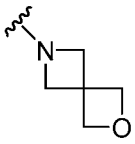
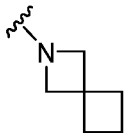
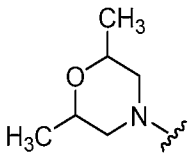
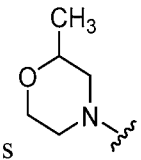
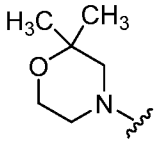
(C_3-C_7)heterocycloalkenyl. In some embodiments, each occurrence of R_1 is independently optionally substituted (C_4-C_{10})bicycloalkenyl or optionally substituted (C_4-C_{10})heterobicycloalkenyl. In some embodiments, each occurrence of R_1 is independently optionally substituted (C_4-C_{14})tricycloalkenyl or optionally substituted (C_4-C_{14})heterotricycloalkenyl. In some embodiments, each occurrence of R_1 is independently optionally substituted (C_4-C_{14})tricycloalkyl or optionally substituted (C_4-C_{14})heterotricycloalkyl. 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, $-CN$,, 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, (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, 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, 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, $NHCH_3$, $N(CH_3)_2$, .

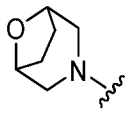
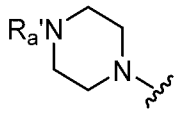
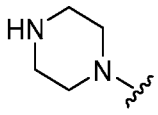
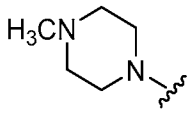
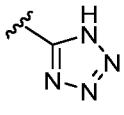
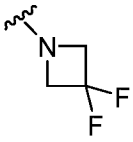
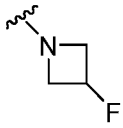
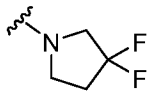
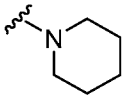
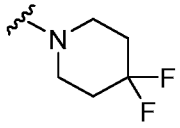
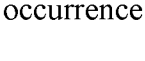
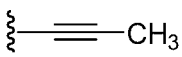
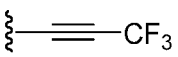
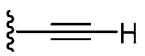
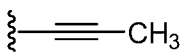
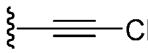
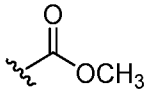
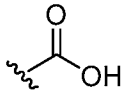
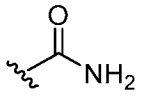

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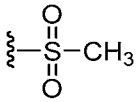
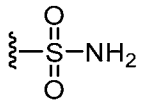


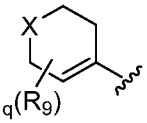
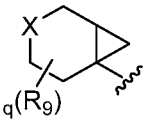
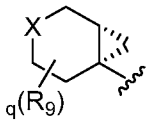
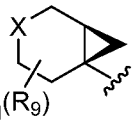
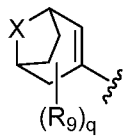
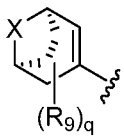
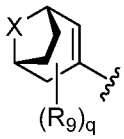
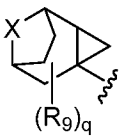
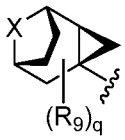
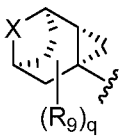
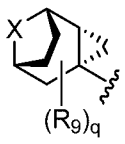
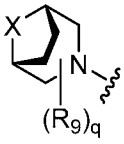
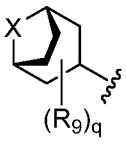
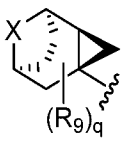
embodiments, (A) is  or .

[0265] 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 . 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 , 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 . 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 , , 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 . 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 .

[0266] In some embodiments, at least one occurrence of R_1 is , , , , , , , , , , , , , or ; wherein X is CR_{15}, O, NR_{14}, or S; each occurrence of R_9 is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; each occurrence of R_{14} is independently H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, aryl, or heteroaryl; each occurrence of R_{15} is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; and q is 0, 1, 2, or 3.

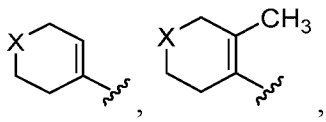
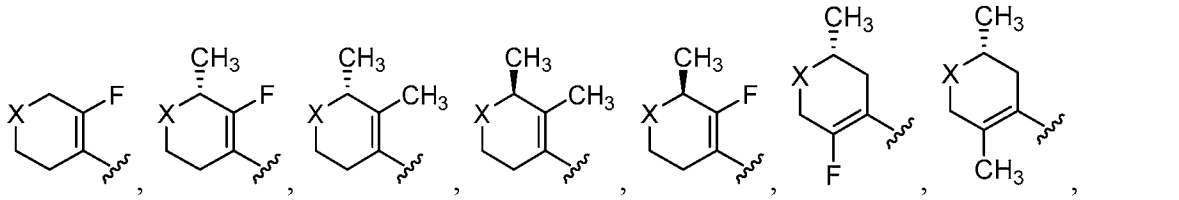
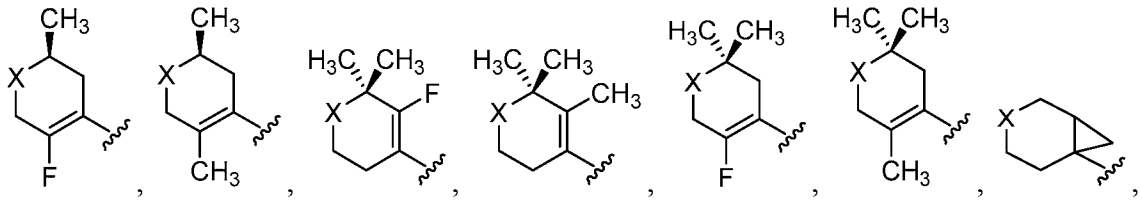
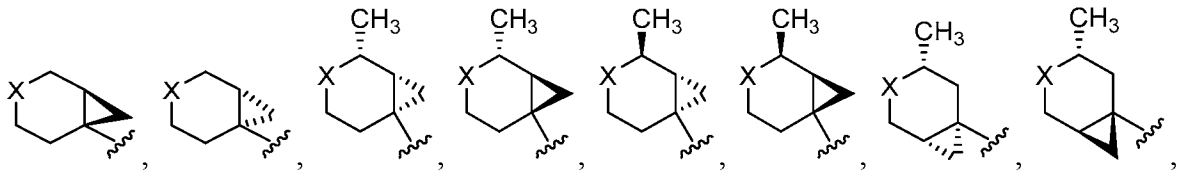
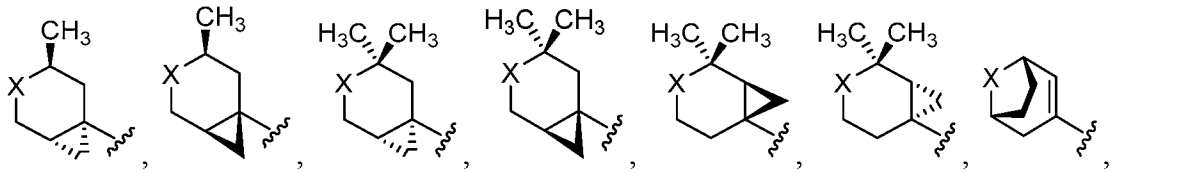
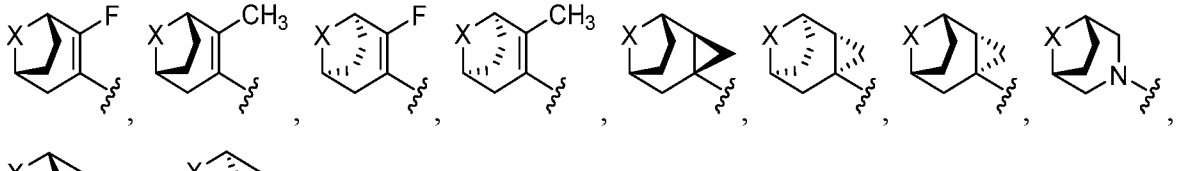
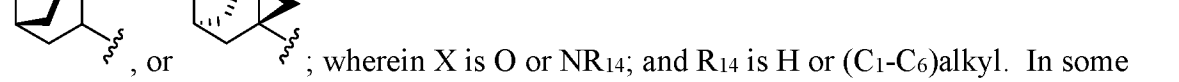
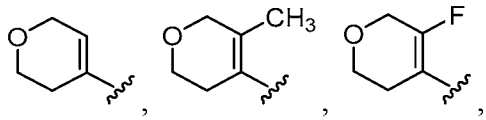
[0267] In some embodiments, X is O. In some embodiments, X is S. In some embodiments, X is CR_{15}. In some embodiments, X is NR_{14}.

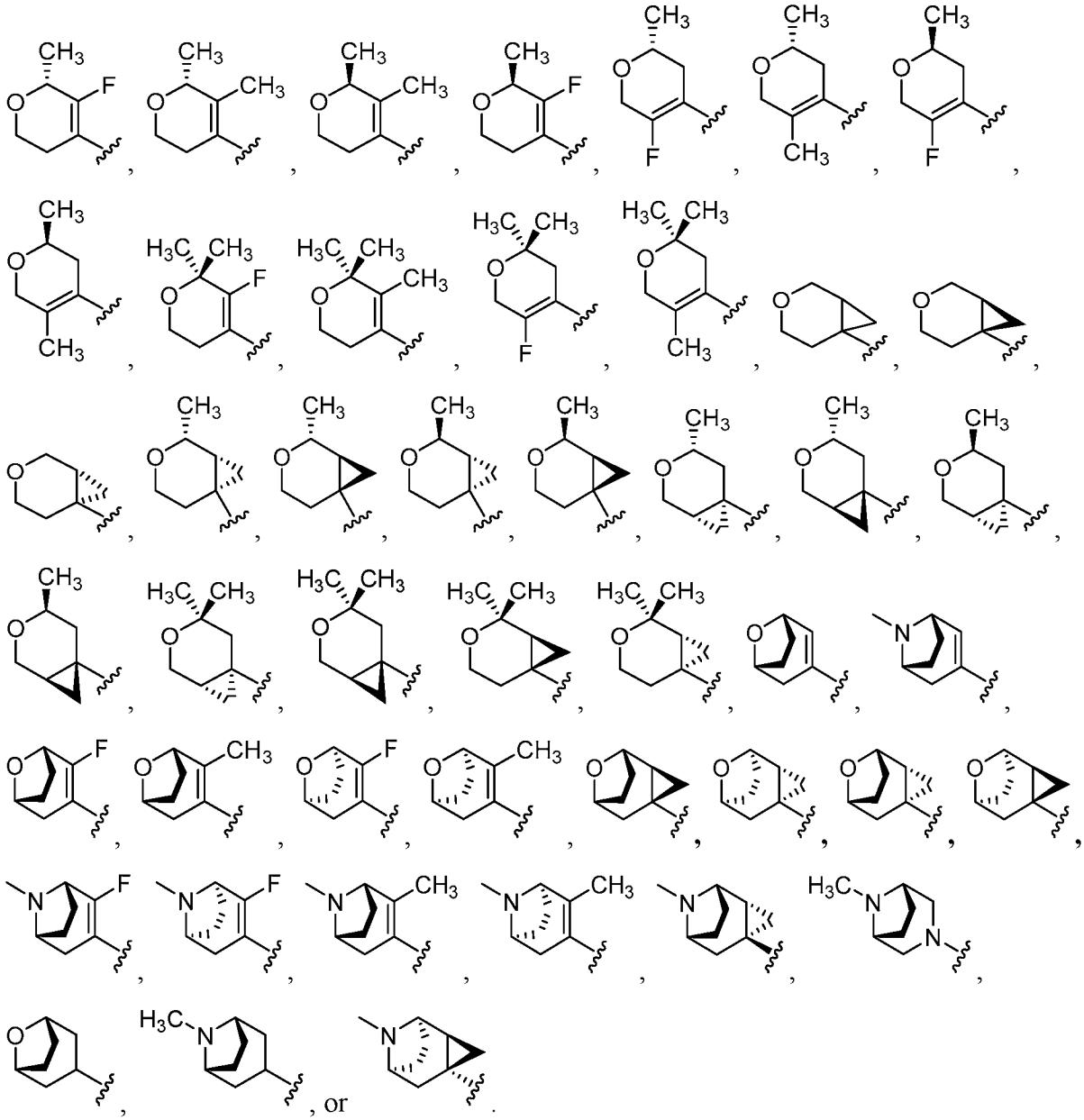
[0268] In some embodiments, each occurrence of R_9 is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$. In some embodiments, each occurrence of R_9 is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, or halogen. In some embodiments, each occurrence of R_9 is independently H, F, Cl, Br, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$. In some embodiments, each occurrence of R_9 is independently H, F, Cl, Br or CH_3.

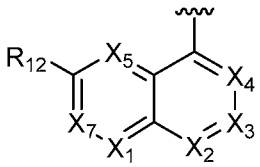
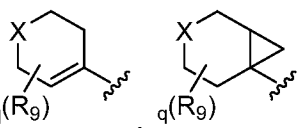
[0269] In some embodiments, each occurrence of R_{15} is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$. In some embodiments, each occurrence of R_{15} is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, or halogen. In some embodiments, each occurrence of R_{15} is independently H, F, Cl, Br, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$. In some embodiments, each occurrence of R_{15} is independently H, F, Cl, Br or CH_3.

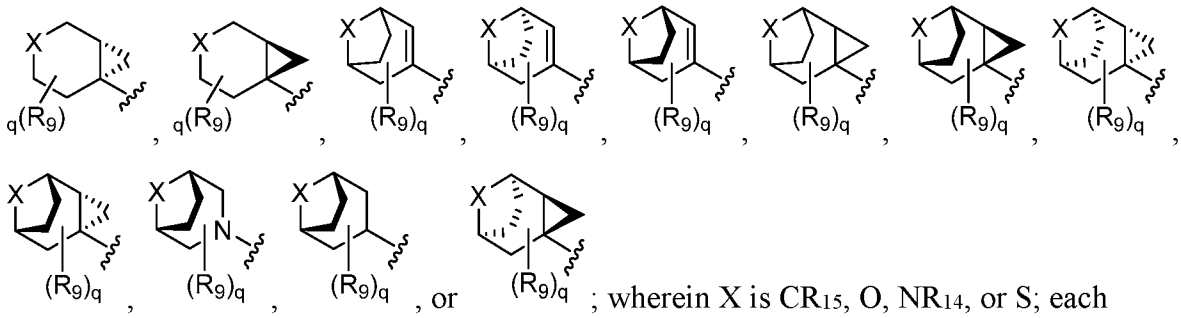
[0270] In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3.

[0271] In some embodiments, R_{14} is H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, aryl, or heteroaryl. In some embodiments, R_{14} is H, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl. In some embodiments, R_{14} is H or (C_1-C_6)alkyl. In some embodiment, R_{14} is H or CH_3.

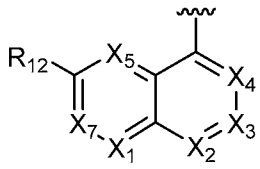
[0272] In some embodiments, at least one occurrence of R_1 is 





, wherein X is O or NR_{14}; and R_{14} is H or (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_1 is 



[0273] In some embodiments, (A) is  wherein R_{12} is (C_3-C_7)cycloalkenyl, (C_3-C_7)heterocycloalkenyl, (C_4-C_{10})bicycloalkenyl, (C_4-C_{10})heterobicycloalkenyl, (C_4-C_{14})tricycloalkenyl, or (C_4-C_{14})heterotricycloalkenyl, each of which is optionally substituted by one or more (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, $-OR_a$, $-CN$, or $-N(R_a)_2$. In some embodiments, R_{12} is ,



; wherein X is CR_{15}, O, NR_{14}, or S; each occurrence of R_9 is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; R_{14} is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, aryl, or heteroaryl; each occurrence of R_{14} is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; and q is 0, 1, 2, or 3. In some embodiments, X_2 is N. In some embodiments, X_3 is CH or CCH_3. In some embodiments (A) is



, where X_2 is N; X_3 is CH or CCH_3; and R_{12} is $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, or $(C_4\text{-}C_{14})$heterotricycloalkenyl, each of which is optionally substituted by one or more $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$.

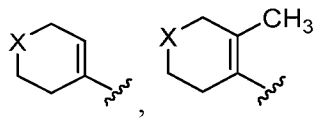
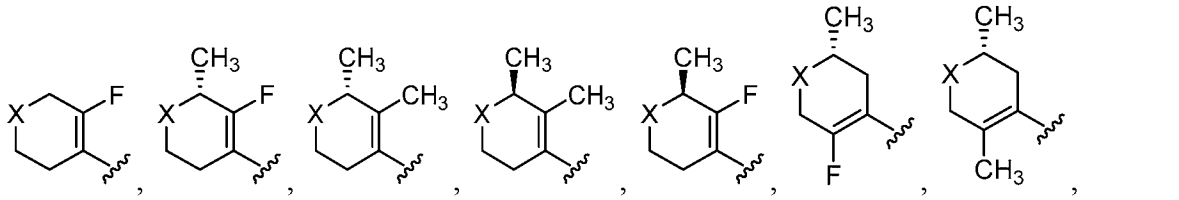
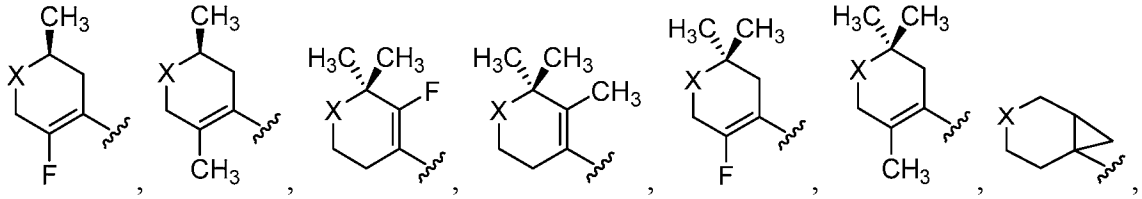
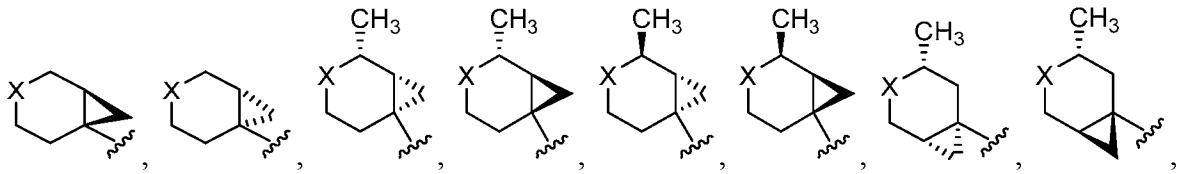
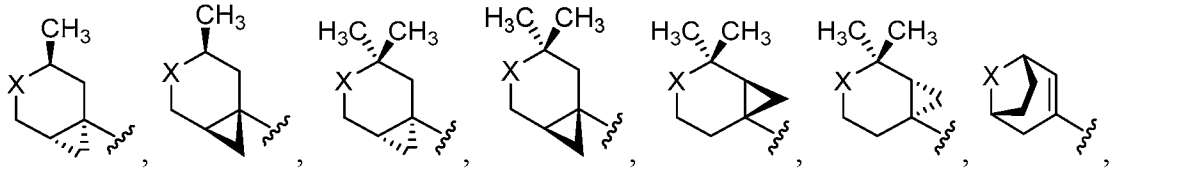
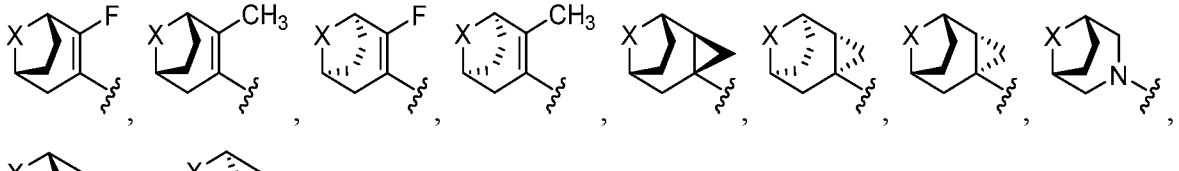
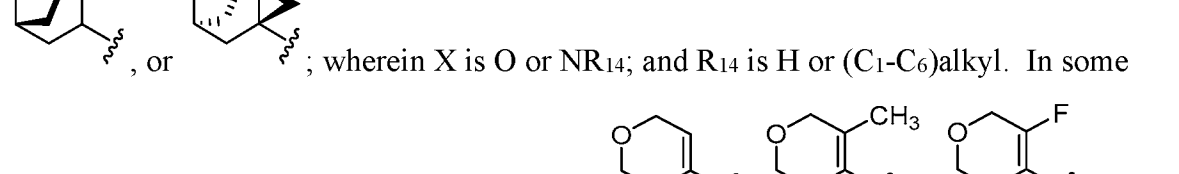
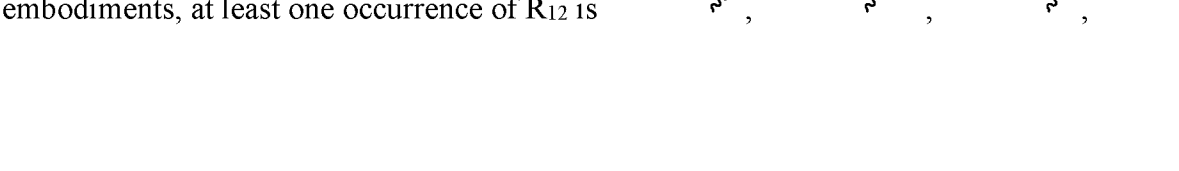
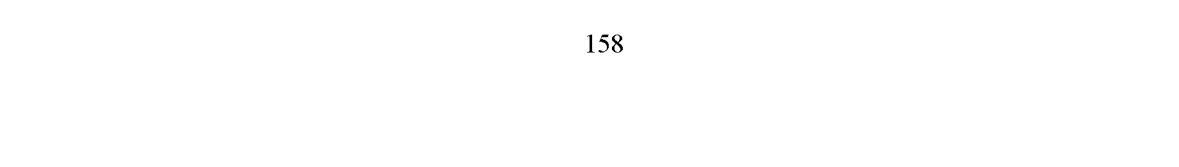
[0274] In some embodiments, X is O. In some embodiments, X is S. In some embodiments, X is CR_{15}. In some embodiments, X is NR_{14}.

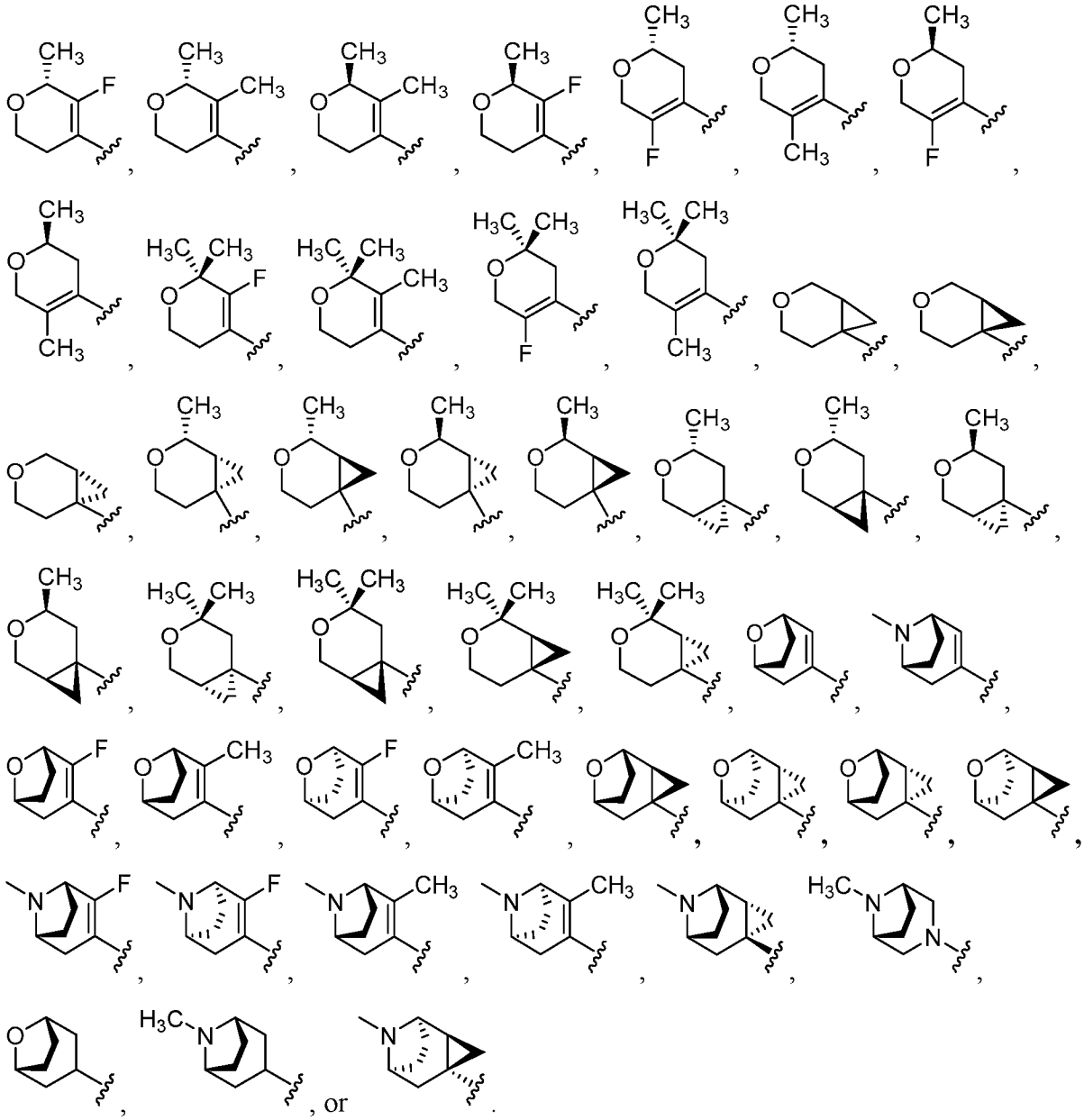
[0275] In some embodiments, each occurrence of R_9 is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$. In some embodiments, each occurrence of R_9 is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, or halogen. In some embodiments, each occurrence of R_9 is independently H, F, Cl, Br, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$. In some embodiments, each occurrence of R_9 is independently H, F, Cl, Br or CH_3.

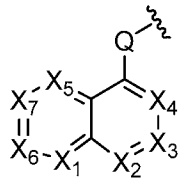
[0276] In some embodiments, each occurrence of R_{15} is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$. In some embodiments, each occurrence of R_{15} is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, or halogen. In some embodiments, each occurrence of R_{15} is independently H, F, Cl, Br, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$. In some embodiments, each occurrence of R_{15} is independently H, F, Cl, Br or CH_3.

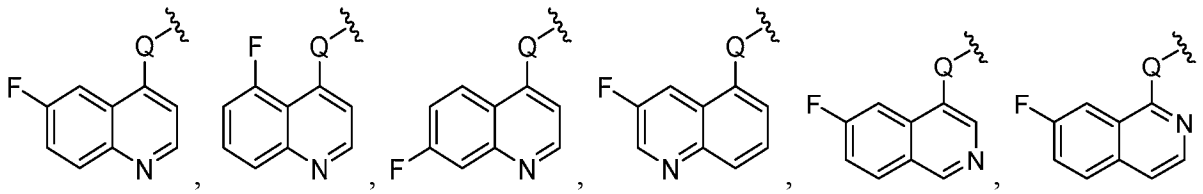
[0277] In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3.

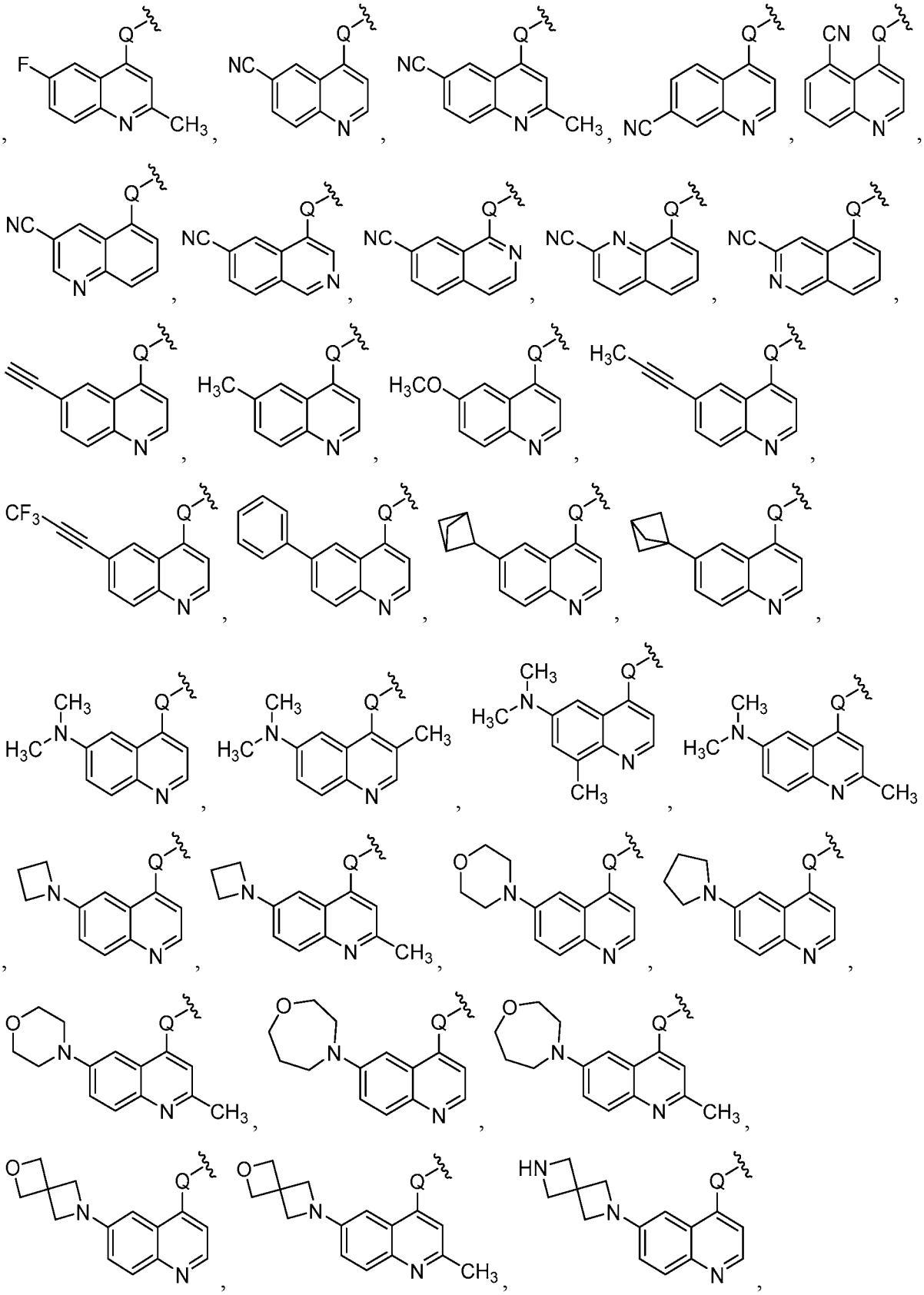
[0278] In some embodiments, R_{14} is H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl, aryl, or heteroaryl. In some embodiments, R_{14} is H, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl. In some embodiments, R_{14} is H or (C_1-C_6)alkyl. In some embodiment, R_{14} is H or CH_3.

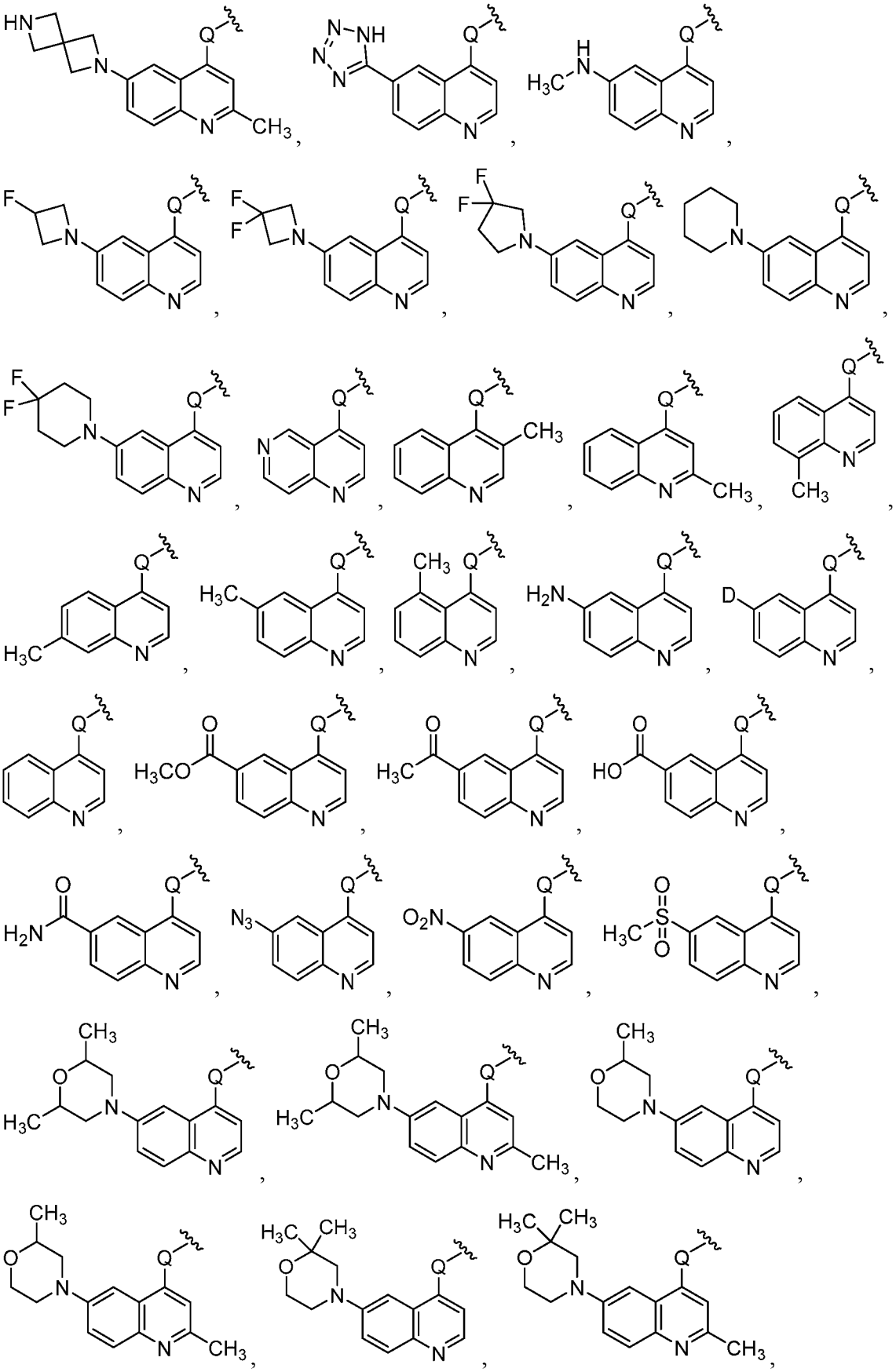
[0279] In some embodiments, at least one occurrence of R_{12} is , , , , , , , , , , or ; wherein X is O or NR_{14}; and R_{14} is H or (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_{12} is .

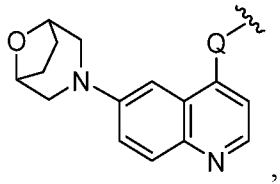
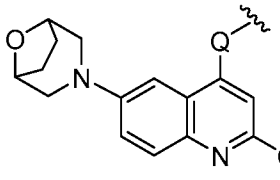
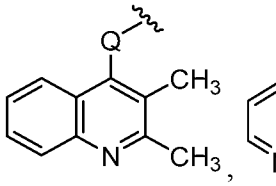
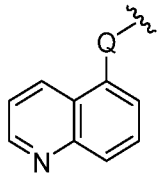
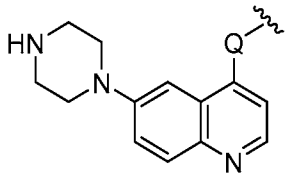
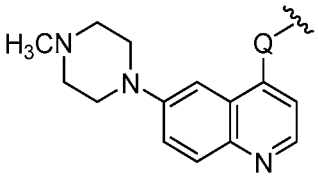
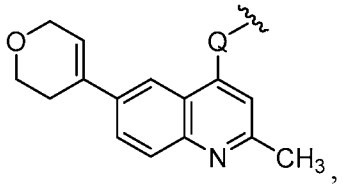
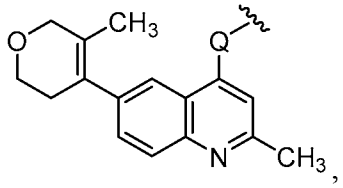
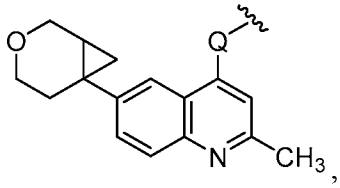
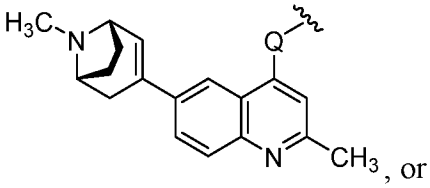
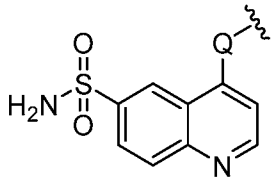
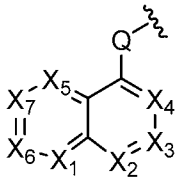
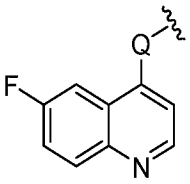
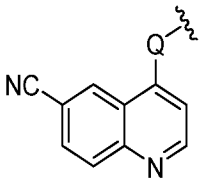
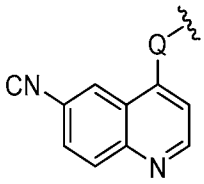
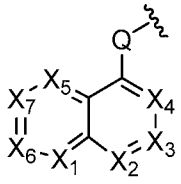
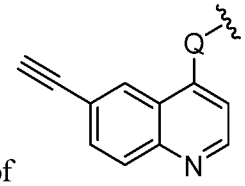
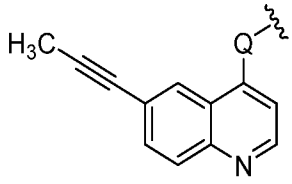
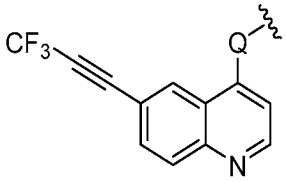
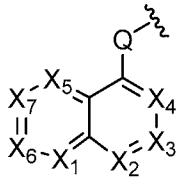
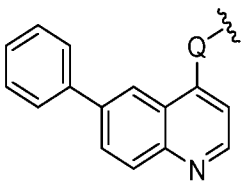
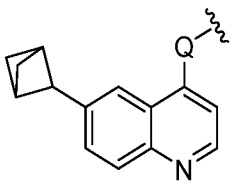
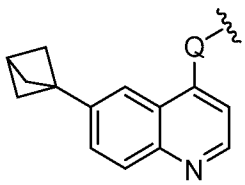
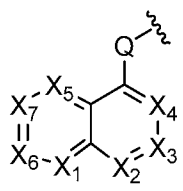
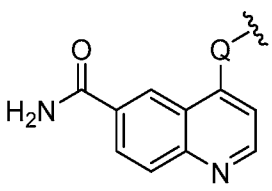


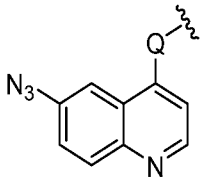
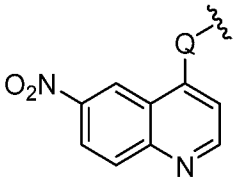
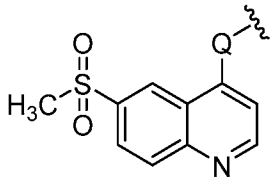
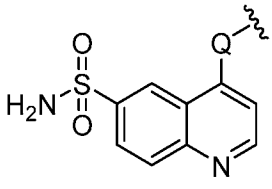
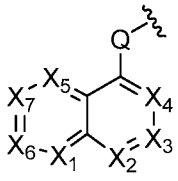
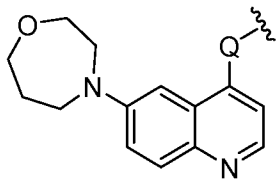
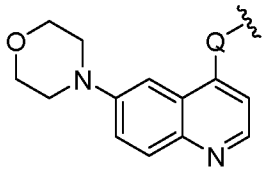
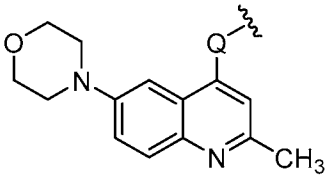
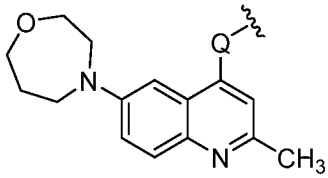
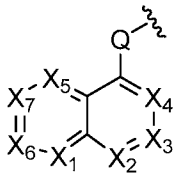
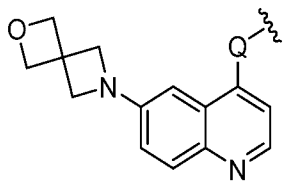
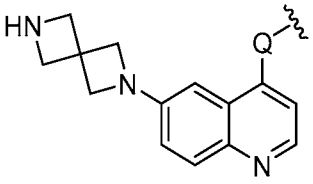
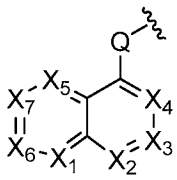
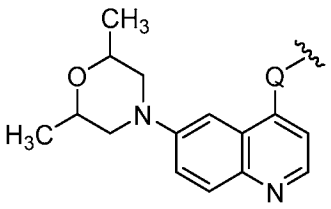
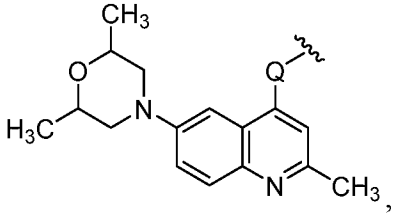
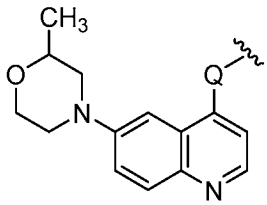
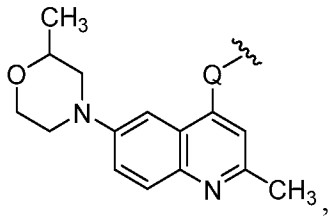
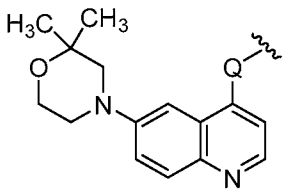
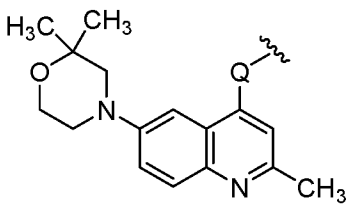
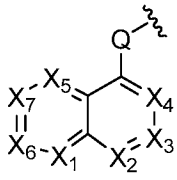
[0280] In some embodiments, the structural moiety  has the structure of

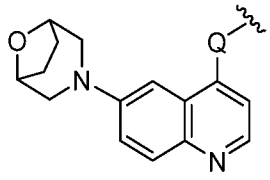
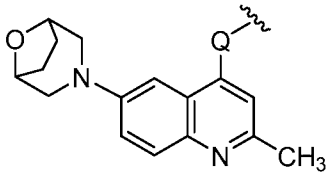
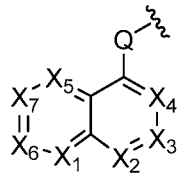
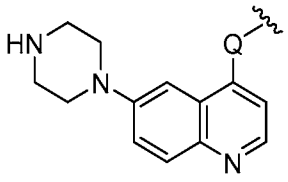
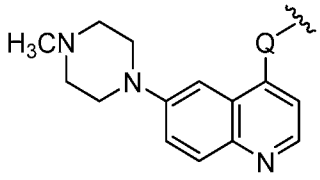
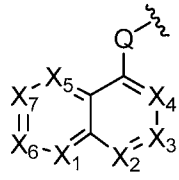
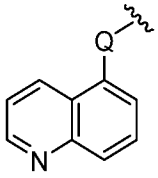
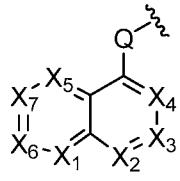
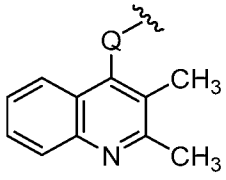
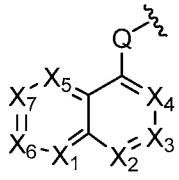
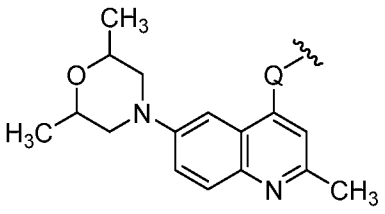


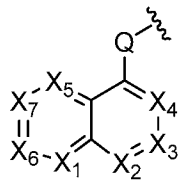
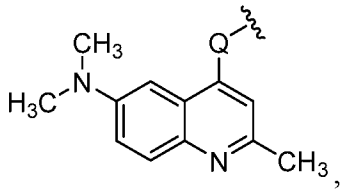
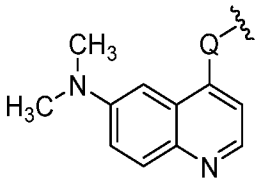
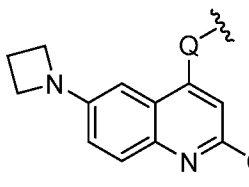
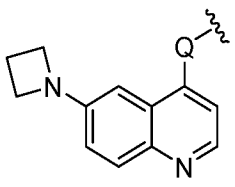


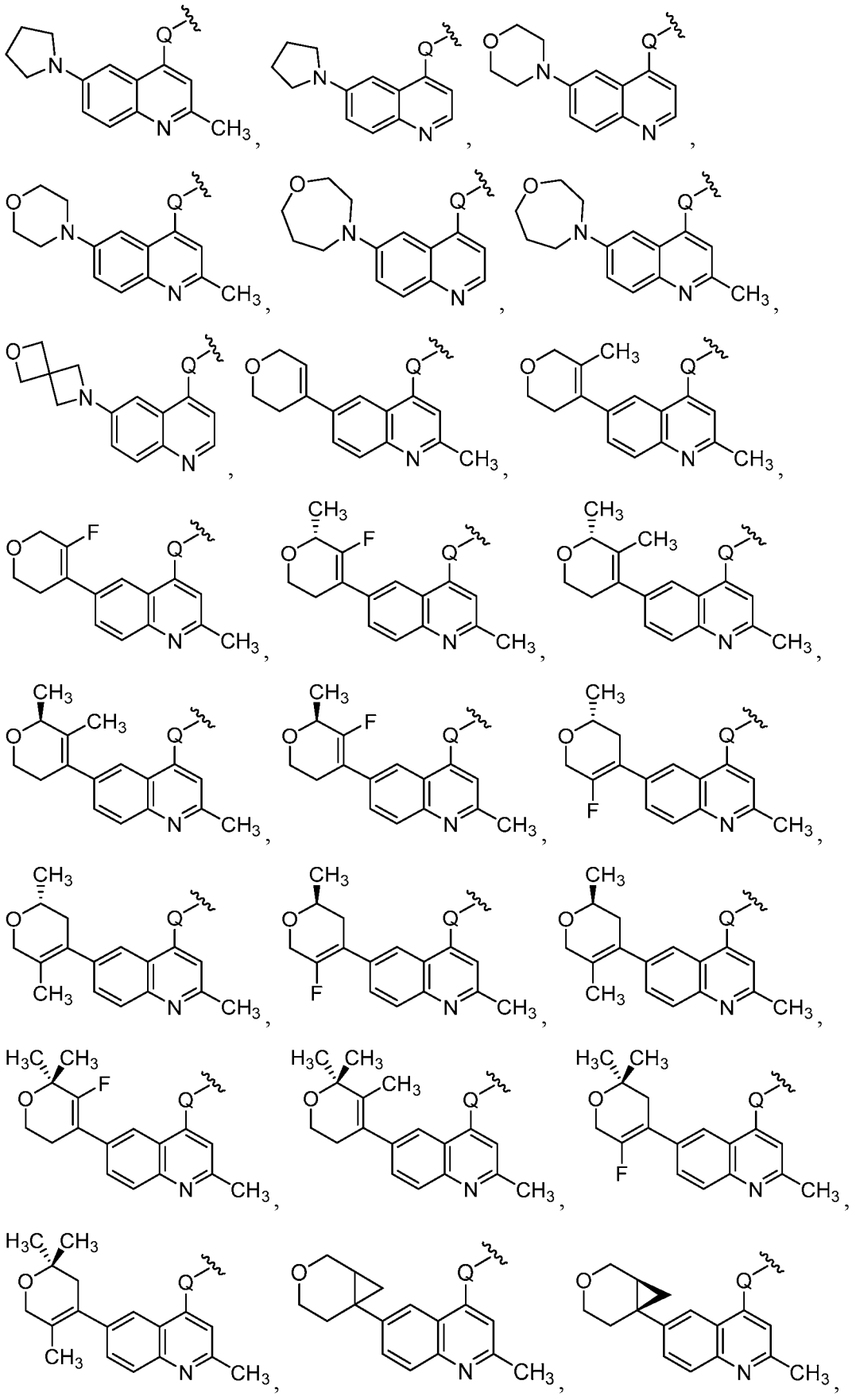


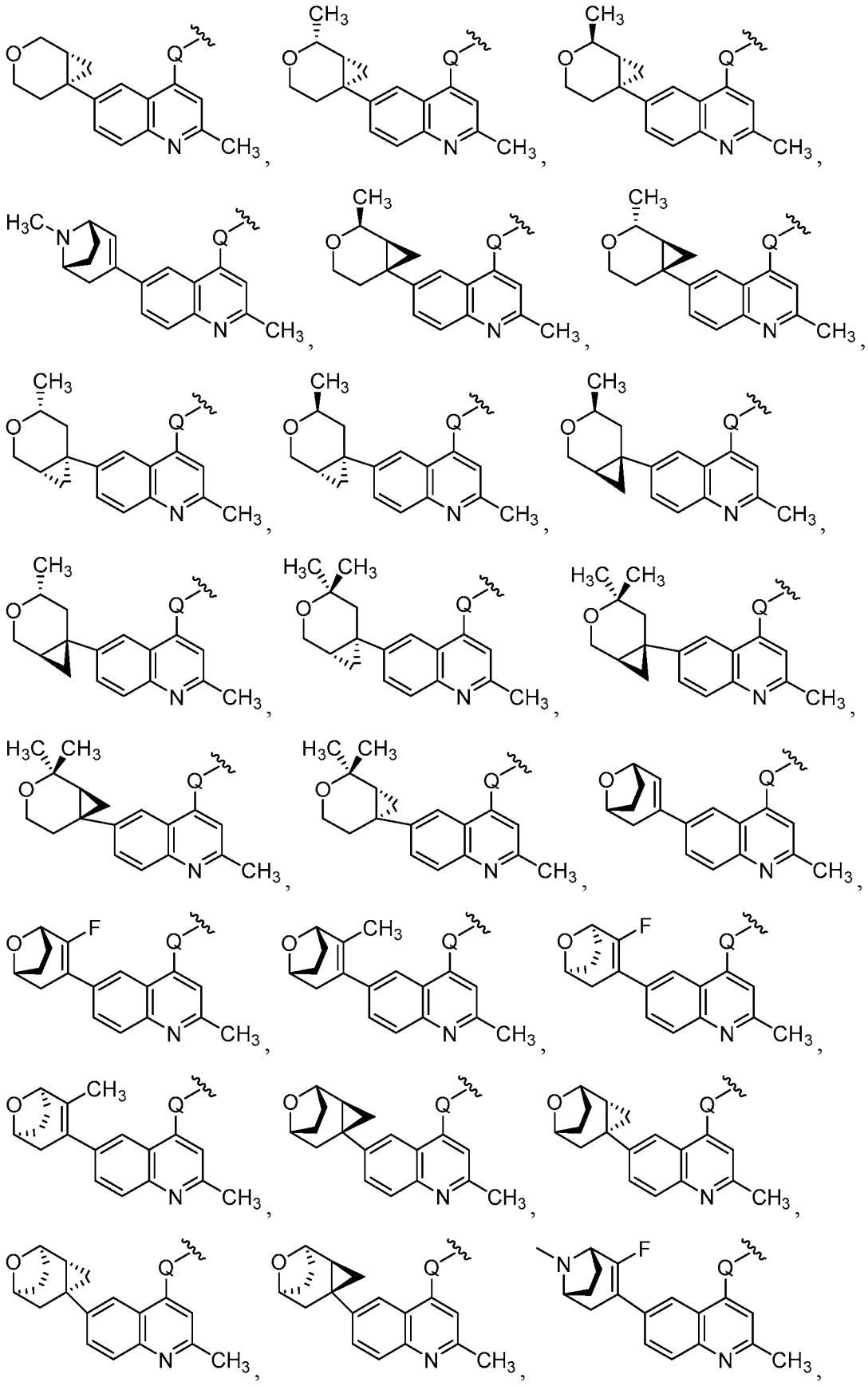









, or
. In some embodiments, the structural moiety  has the structure of , , or . In some embodiments, the structural moiety  has the structure of , , , or . In some embodiments, the structural moiety has the structure of , , or . In some embodiments, the structural moiety  has the structure of ,

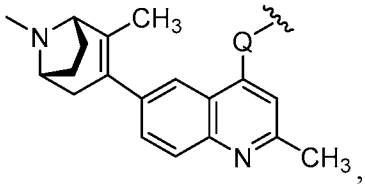
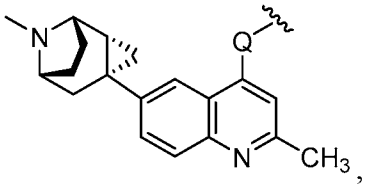
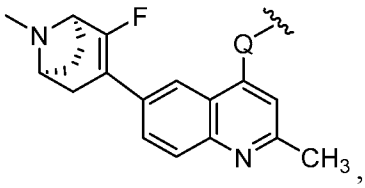
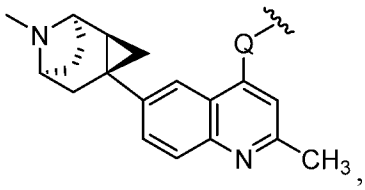
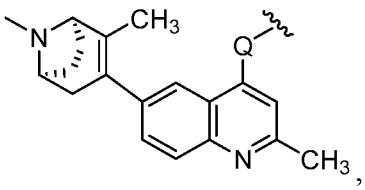
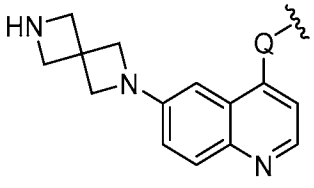



, or . In some embodiments, the structural moiety  has the structure of , , , or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, the structural moiety  has the structure of , , , , , or . In some embodiments, the structural moiety  has

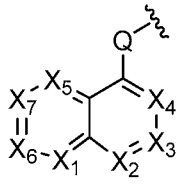
the structure of  or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, the structural moiety  has the structure of . In some embodiments, the structural moiety  has the structure of . In some embodiments, the structural moiety  has the structure of .

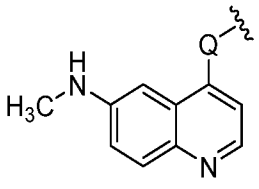
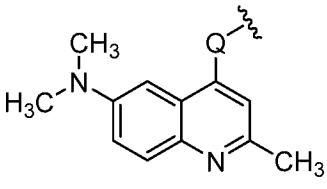
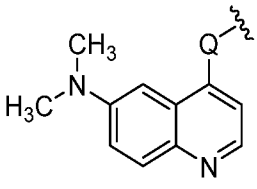
[0281] In some embodiments, the structural moiety  has the structure of , , , ,

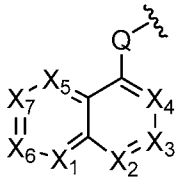


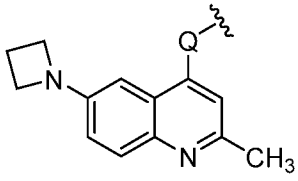
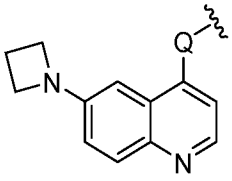


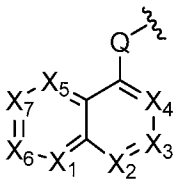
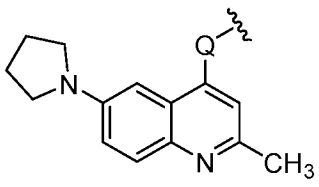







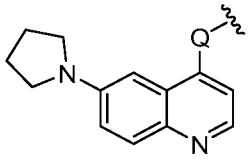
Q is O or NH. In some embodiments, the structural moiety  has the structure of

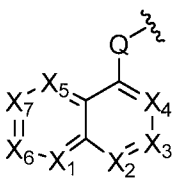
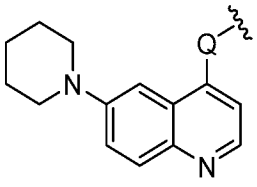




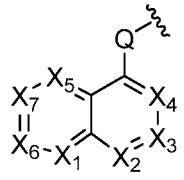
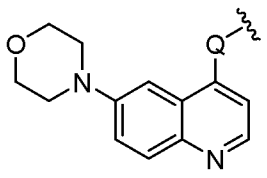
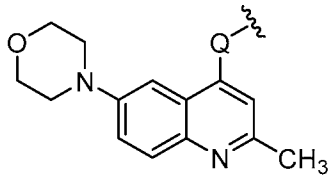
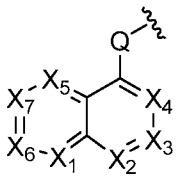
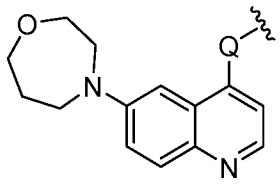
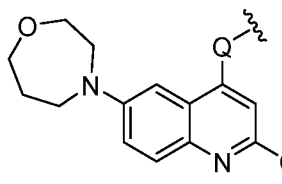
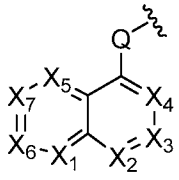
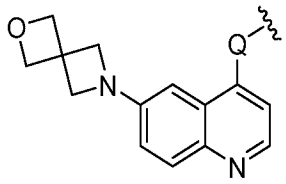
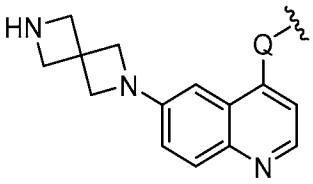
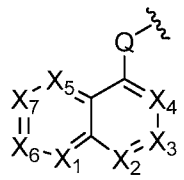
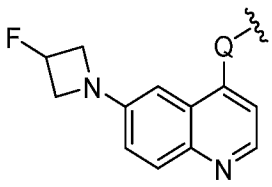
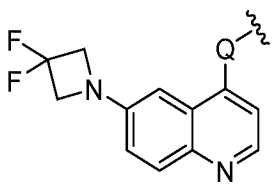
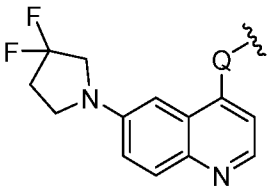
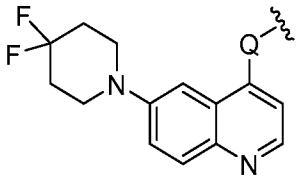
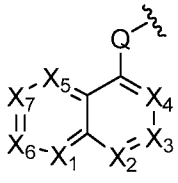
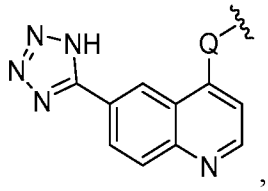
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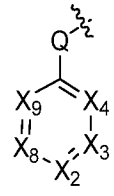
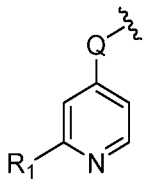
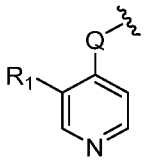
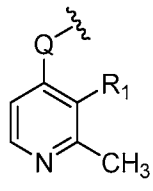
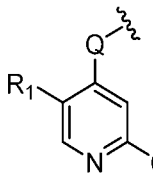
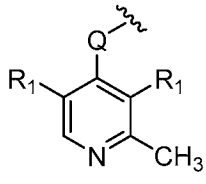
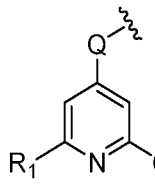
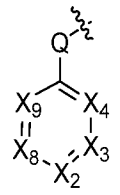
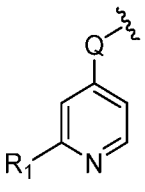
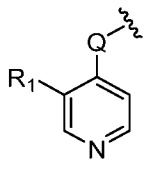
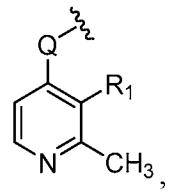
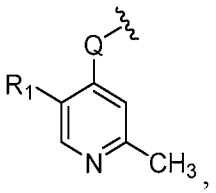
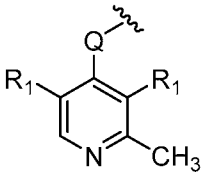
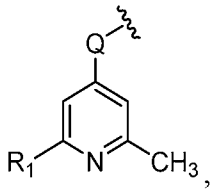



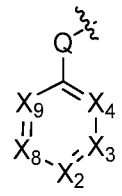
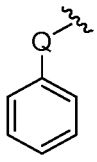
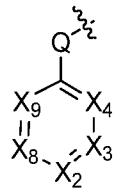
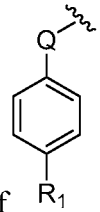
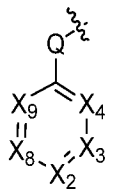
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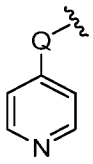
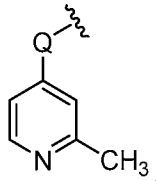
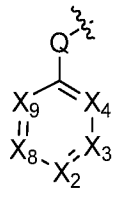
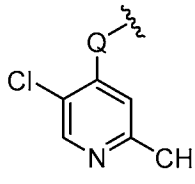
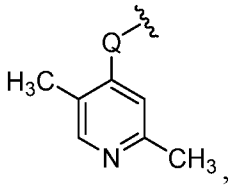
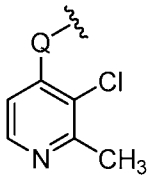
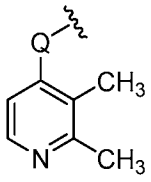
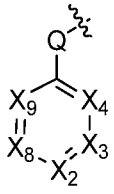
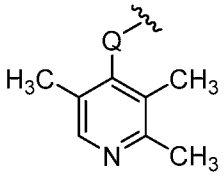


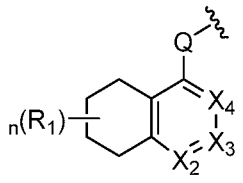
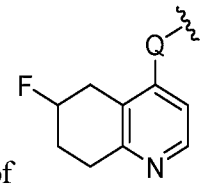
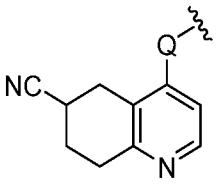
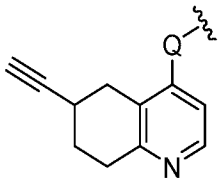
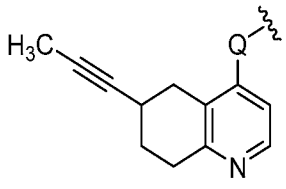
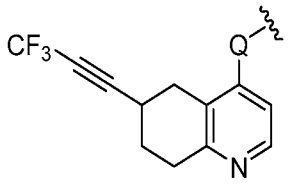
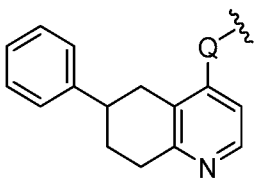
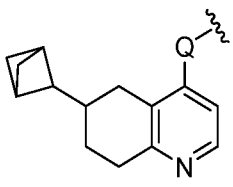
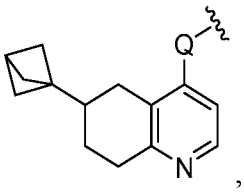
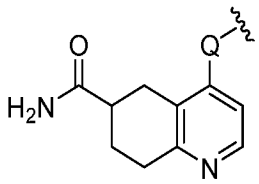
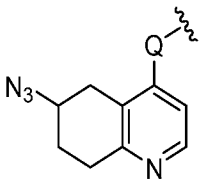
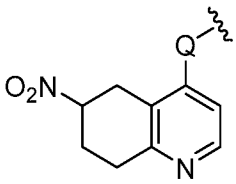
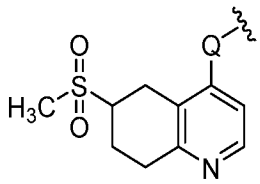
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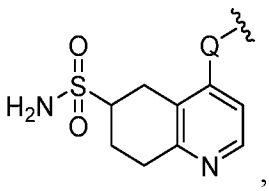
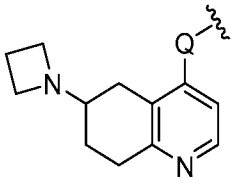
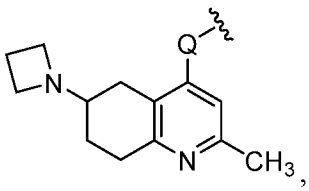
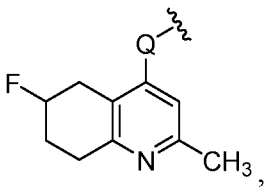
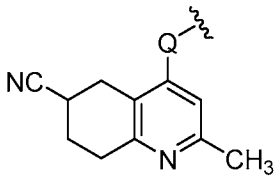
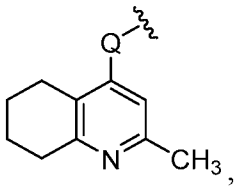
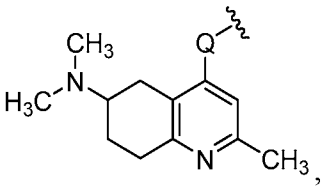
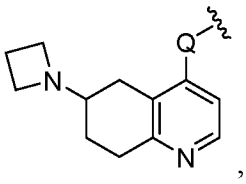
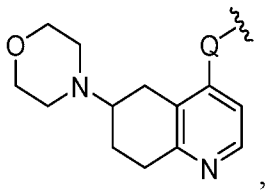
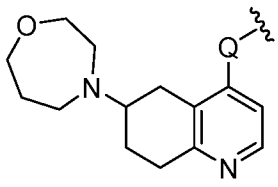
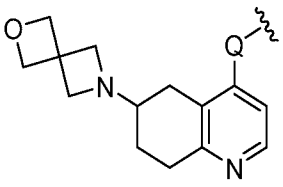
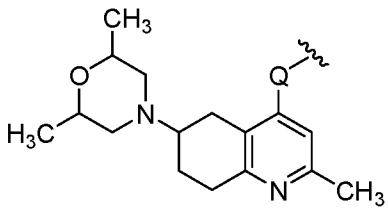
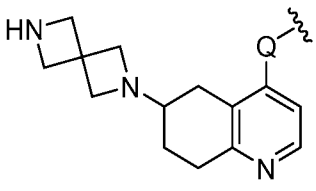
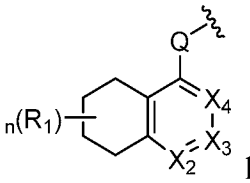
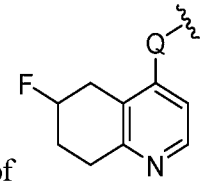
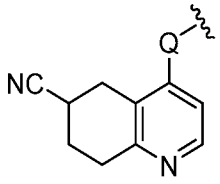
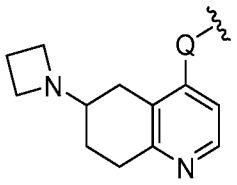
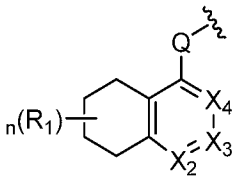
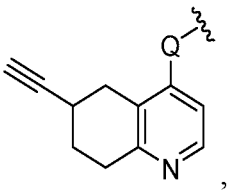
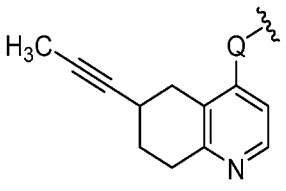
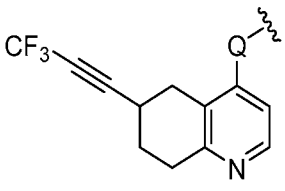
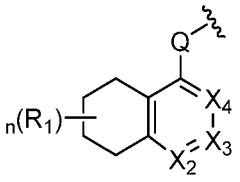
embodiments, the structural moiety  has the structure of  or , where Q is O or NH. In some embodiments, the structural moiety  has the structure of  or , where Q is O or NH. In some embodiments, the structural moiety  has the structure of  or , where Q is O or NH. In some embodiments, the structural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

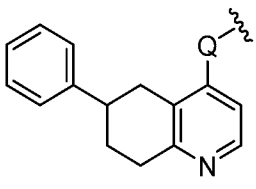
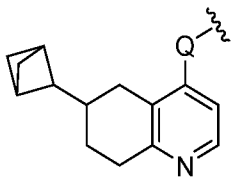
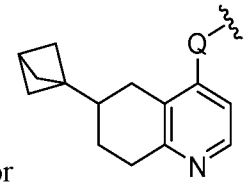
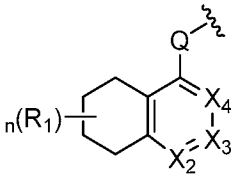
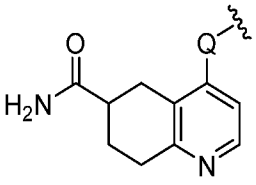
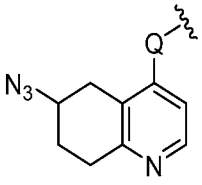
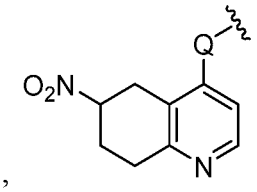
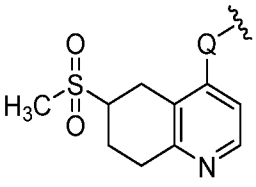
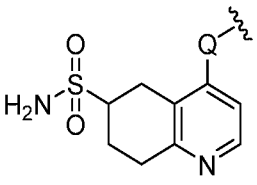
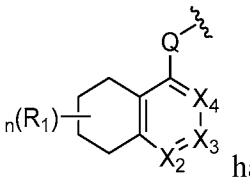
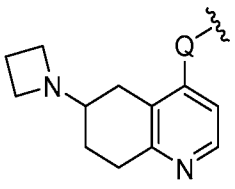
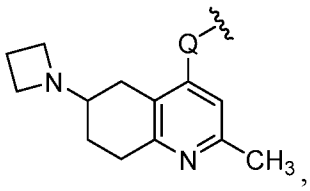
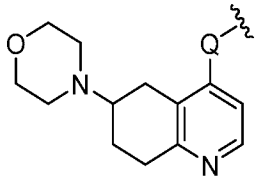
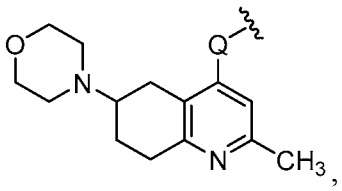
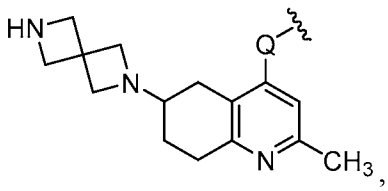
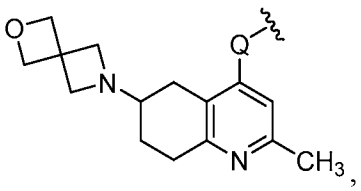
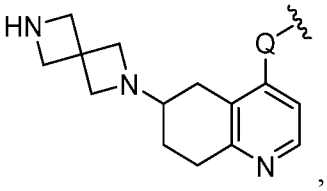
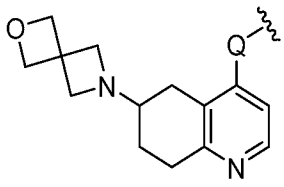
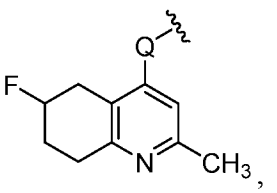
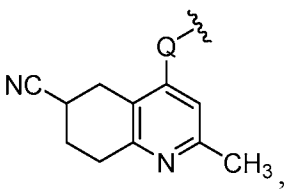
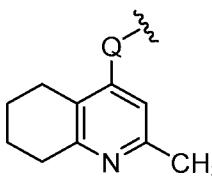
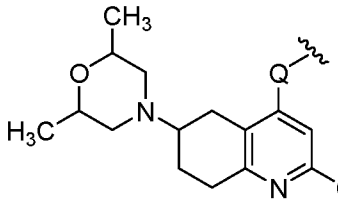
[0282] In some embodiments, the structural moiety  has the structure of , , , , , or , where Q is O or NH and R_1 is H, D, (C_1-C_6)alkyl, (C_3-C_7)heterocycloalkyl, halogenated (C_3-C_7)heterocycloalkyl, or halogen. In some embodiments, the structural moiety  has the structure of , , , , , or , where 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.

[0283] 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 , 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.

[0284] In some embodiments, the structural moiety  has the structure of , , , , , , , , , , , .

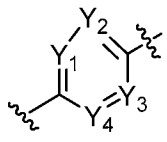
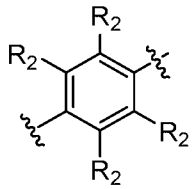
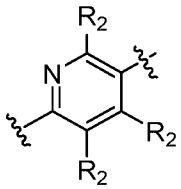
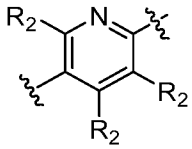
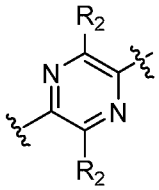
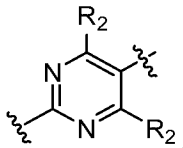
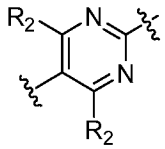
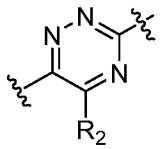
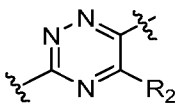
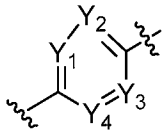
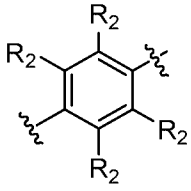
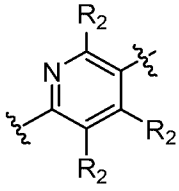
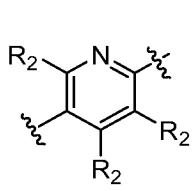
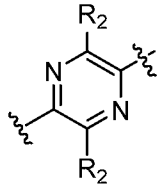
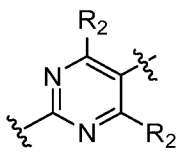
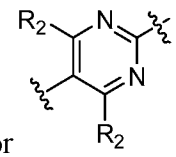

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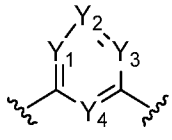
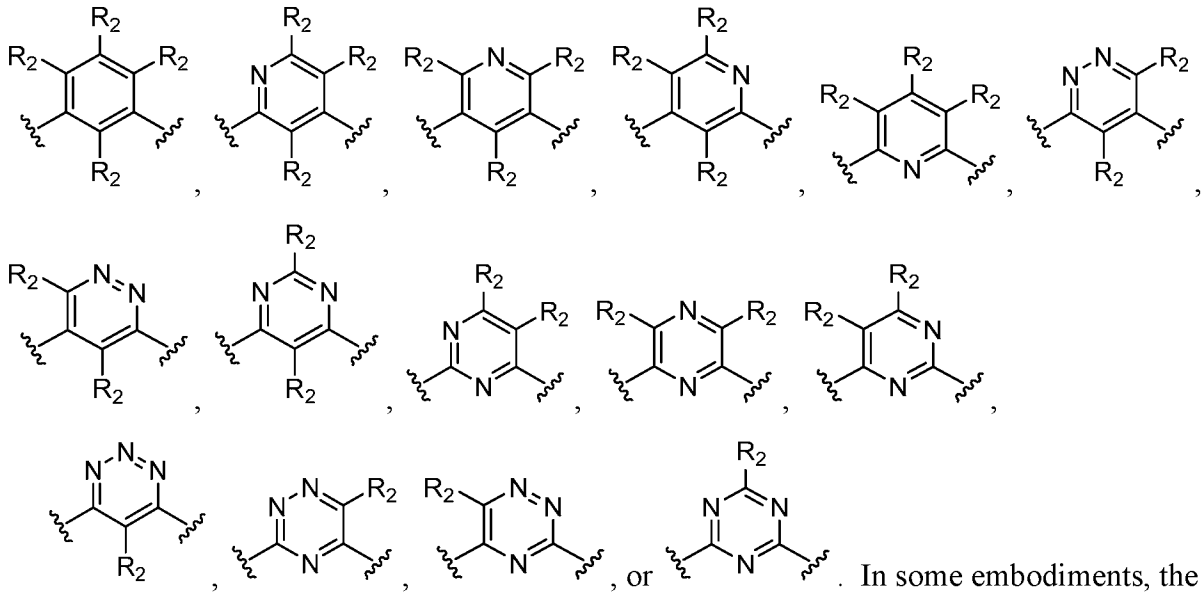
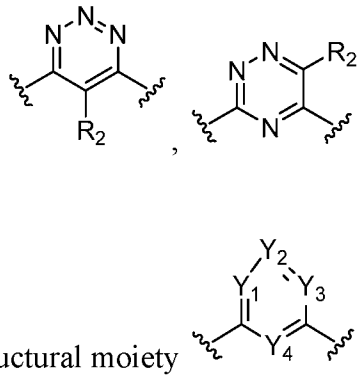
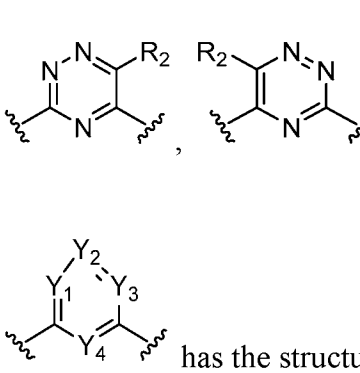
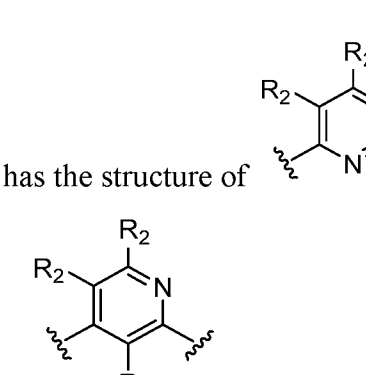
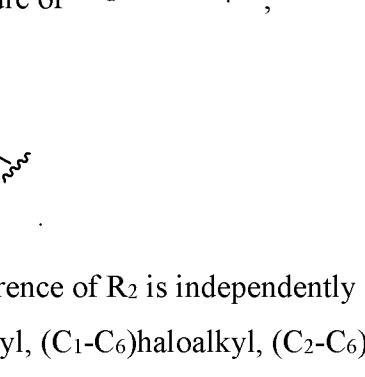
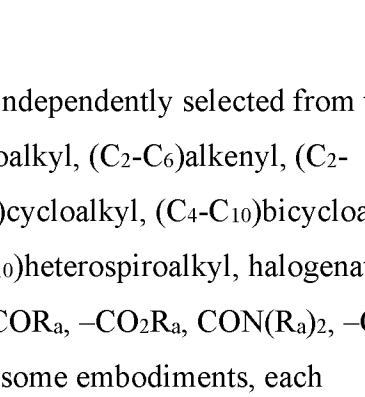
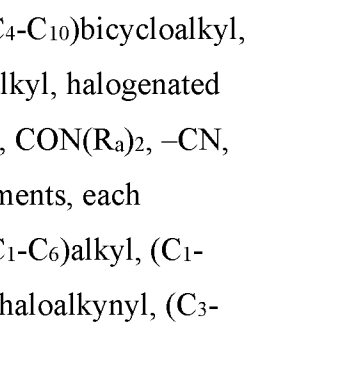
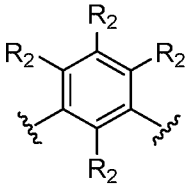
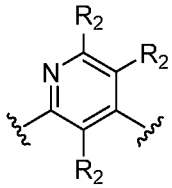



. In some embodiments, the structural moiety  has the structure of 




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










, or . In some embodiments, Q is O or NH.

[0285] In some embodiments, the compound has the structure of Formula Ia. In some embodiments, the compound has the structure of Formula IIa. In some embodiments, the

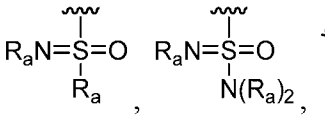
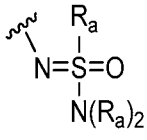
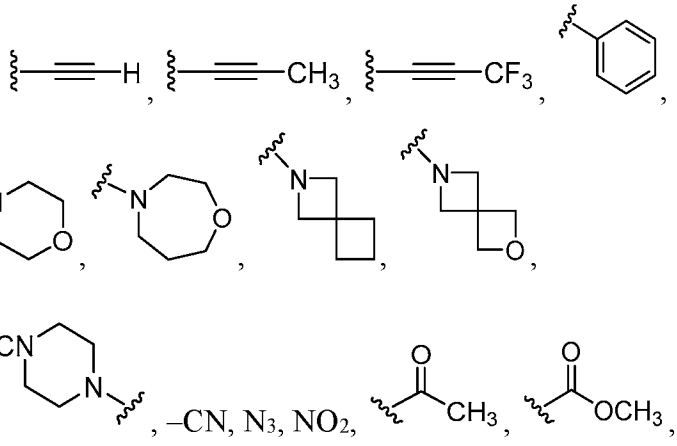
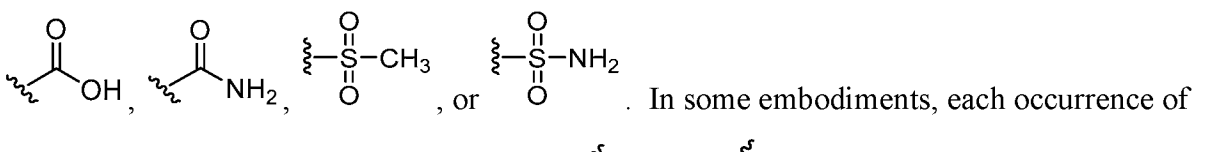
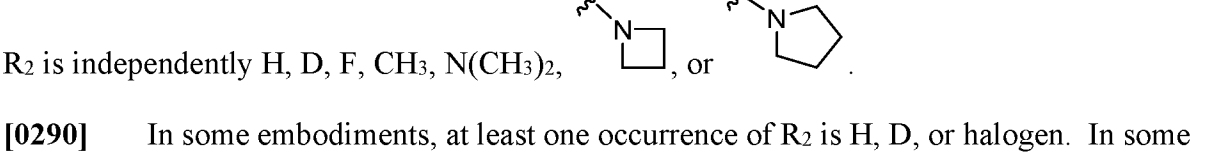
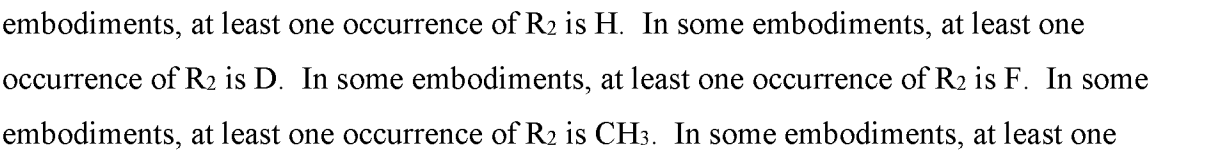
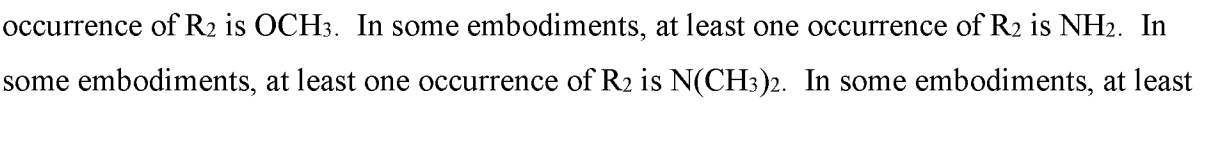
compound has the structure of Formula IIIa. In some embodiments, the compound has the structure of Formula IVa.

[0286] 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, Y_5 are N.

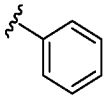
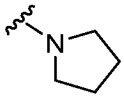
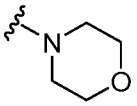
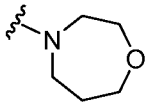
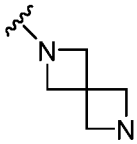
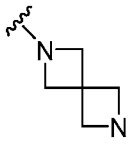
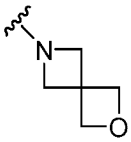
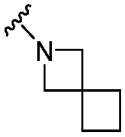
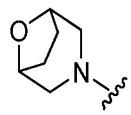
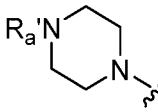
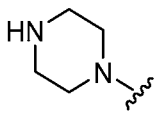
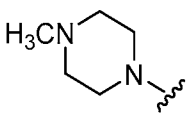
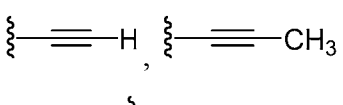
[0287] In some embodiments, the structural moiety  has the structure of , , , , , , , , or . In some embodiments, the structural moiety  has the structure of , , , ,  or .

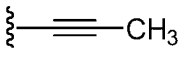
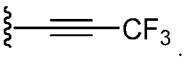
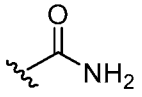
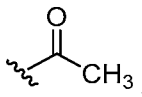
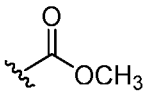
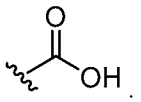
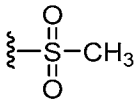
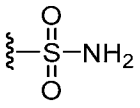
[0288] In some embodiments, the structural moiety  has the structure of , , , , , , , , , , , , , or . In some embodiments, the structural moiety has the structure of , , , , , or .

[0289] In some embodiments, each occurrence of R_2 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, $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, 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 $(C_1\text{-}C_6)$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, and $(C_4\text{-}C_{10})$heterobicycloalkyl. In some embodiments, each occurrence of R_2 is independently selected from the group consisting of $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}$

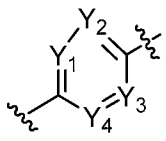
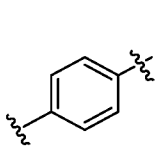
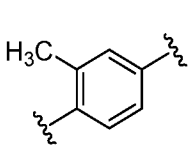
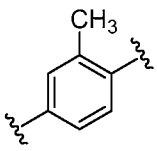
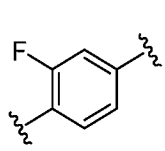
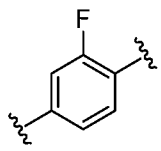
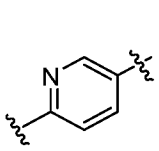
C_7)heterocycloalkyl, aryl, and heteroaryl. In some embodiments, each occurrence of R_2 is independently selected from the group consisting of $-OR_a$, $-SR_a$, $-N(R_a)_2$, $-COR_a$, $-CO_2R_a$, $CON(R_a)_2$, $-CN$, $-NC$, NO_2, N_3, $-SO_2R_a$, $-SO_2N(R_a)_2$, and $-N(R_a)SO_2R_a$. In some embodiments, 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, $-CN$, 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 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, $N(CH_3)_2$, , , , , , , , , .

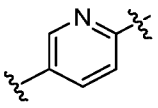
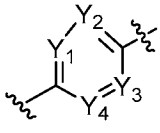
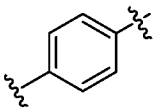
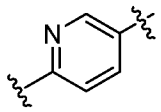
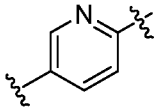
[0290] In some embodiments, at least one occurrence of R_2 is H, D, or halogen. In some embodiments, at least one occurrence of R_2 is H. In some embodiments, at least one occurrence of R_2 is D. In some embodiments, at least one occurrence of R_2 is F. In some embodiments, at least one occurrence of 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

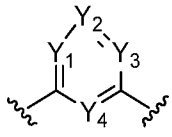
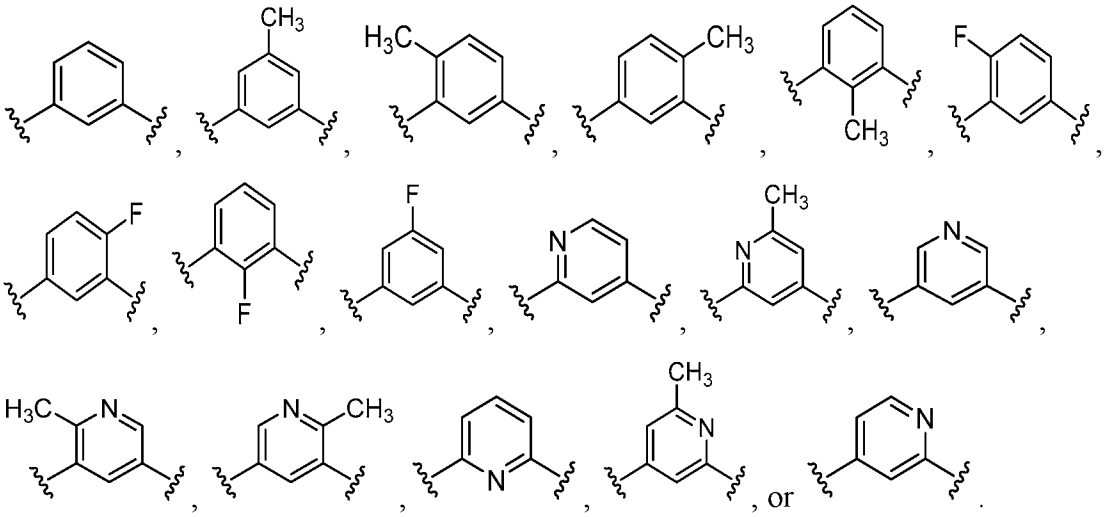
one occurrence of R_2 is . In some embodiments, at least one occurrence of R_2 is . In some embodiments, at least one occurrence of R_2 is . In some embodiments, at least one occurrence of R_2 is . In some embodiments, at least one occurrence of R_2 is . In some embodiments, at least one occurrence of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

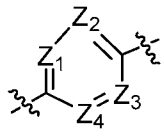
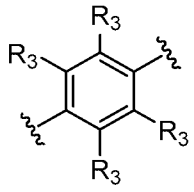
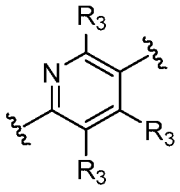
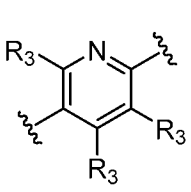
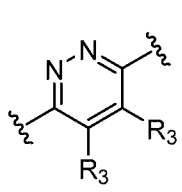
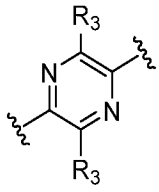
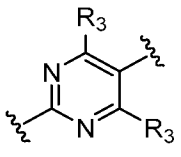
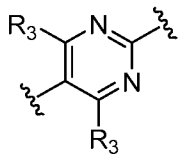
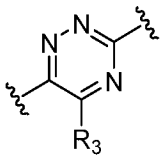
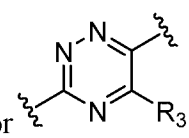
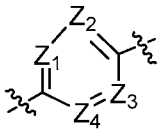
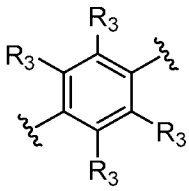
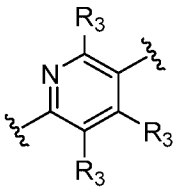
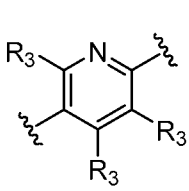
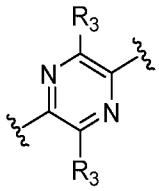
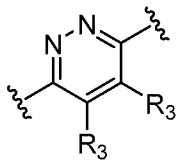
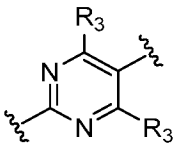
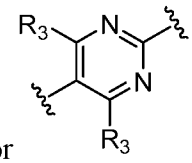
[0291] In some embodiments, each occurrence of R_2 is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $–N(R_a)_2$, NO_2, and $–OR_a$. In some embodiments, each occurrence of R_2 is independently H, halogen, CH_3, CF_3, OH, NH_2, $–NHCH_3$, 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.

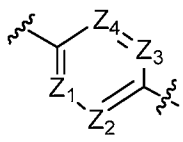
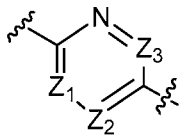
[0292] In some embodiments, the structural moiety  has the structure of , , , , , , or

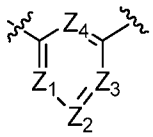
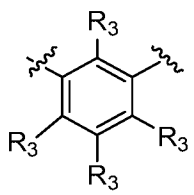
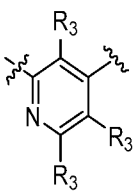
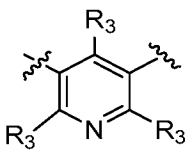
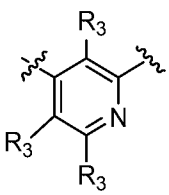
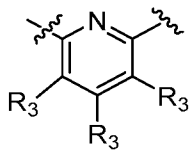
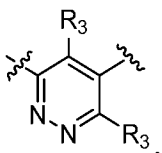

. In some embodiments, the structural moiety  has the structure of , , or .

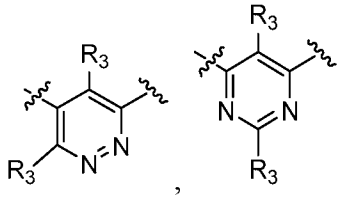
[0293] In some embodiments, the structural moiety  has the structure of .

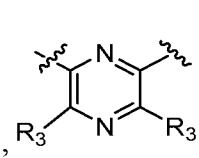
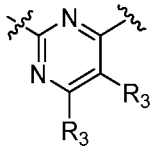
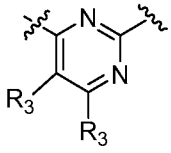
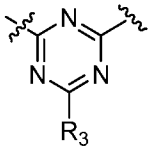
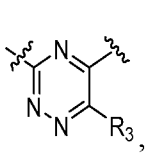
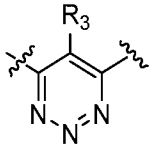
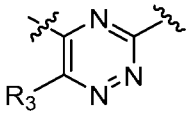
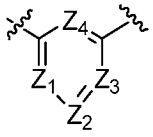
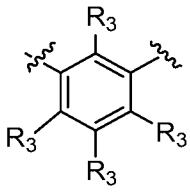
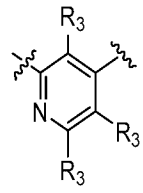
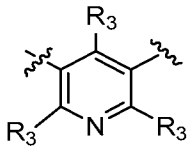
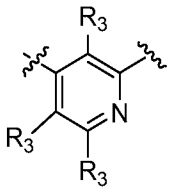
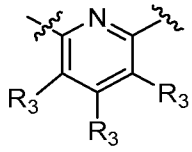
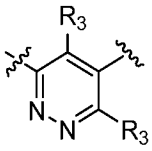
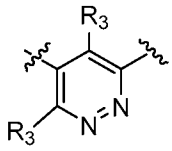
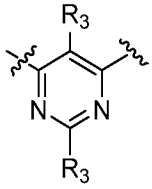
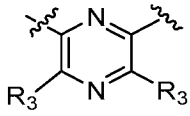
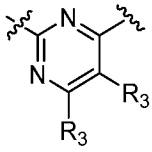
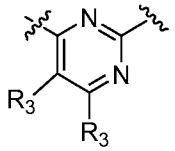
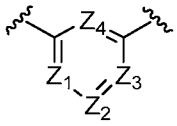
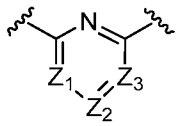
[0294] In some embodiments, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CR_3 or N. In some embodiments, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CR_3. In some embodiments, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CH. In some embodiments, Z_1, Z_2, Z_3, Z_4, and Z_5 are each 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.

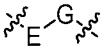
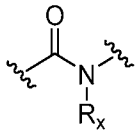
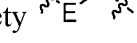
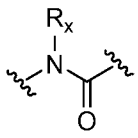
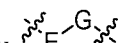
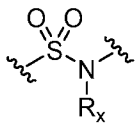
[0295] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  , or  .

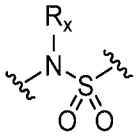
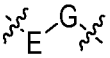
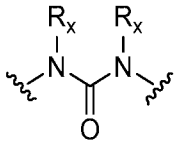
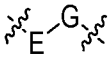
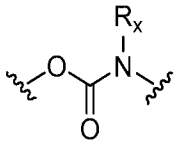
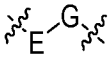
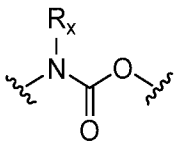
[0296] In some embodiments, the structural moiety  has the structure of  .

[0297] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  ,  ,

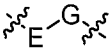
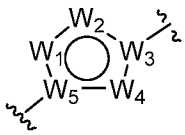









. In some embodiments, the structural moiety  has the structure of 









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

[0298] 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 .

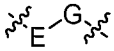
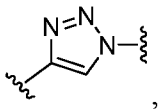
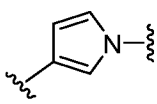
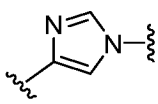
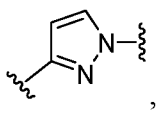
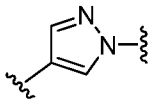
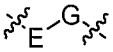
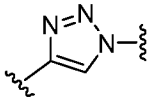
[0299] In some embodiments, each occurrence of R_x is independently H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, or heteroaryl; or where R_x and Y_2, R_x and Y_3, R_x and Z_1, or R_x and Z_4 taken together form an optionally substituted 5-6-membered heterocycle. In some embodiments, each occurrence 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_2 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.

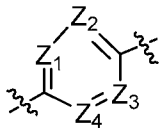
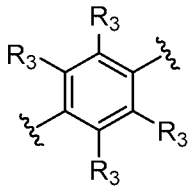
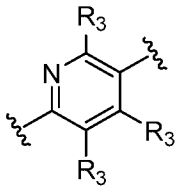
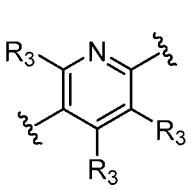
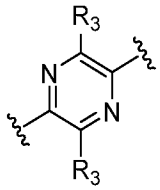
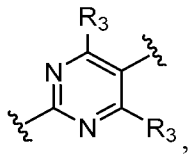
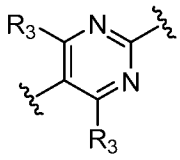
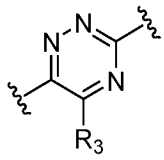
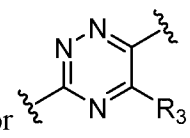
[0300] In some embodiments, the structural moiety  has the structure of .

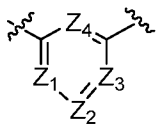
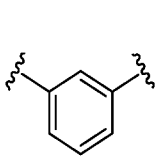
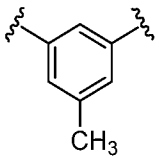
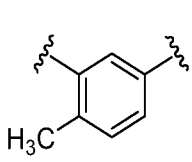
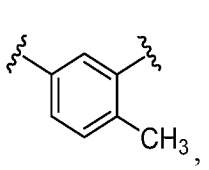
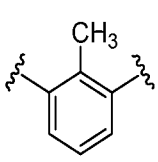
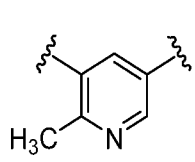
[0301] In some embodiments, W_1, W_2, W_3, W_4, and W_5 are each independently CR_6, N, or NR_6 where valence permits. In some embodiments, one of W_1, W_2, W_3, W_4, and W_5 are N or NR_6 and the rest are C or CR_6 where valence permits. In some embodiments, two of W_1, W_2, W_3, W_4, and W_5 are N 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

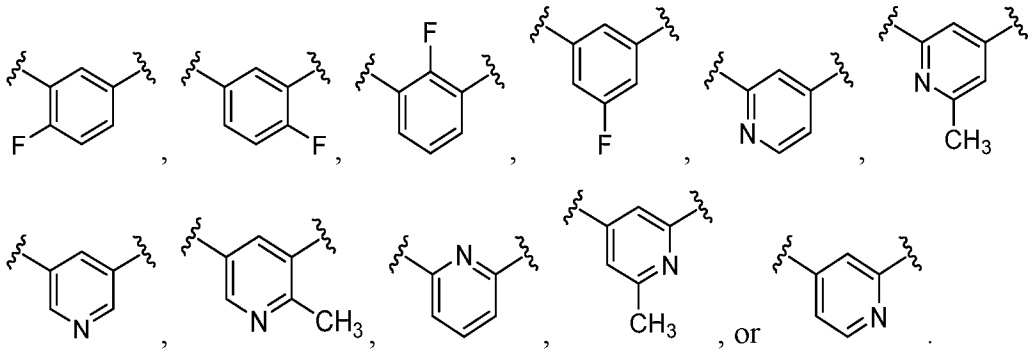
are C or CR_6 where valence permits. In some embodiments, two of W_1, W_2, W_3, W_4, and W_5 are N and the rest are C or CR_6 where valence permits. In some embodiments, three of W_1, W_2, W_3, W_4, and W_5 are N and two are C or CR_6 where valence permits.

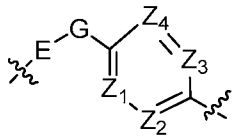
[0302] In some embodiments, each occurrence of R_6 is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$haloalkyl. In some embodiments, each occurrence of R_6 is independently selected from the group consisting of H, F, CH_3, and CH_2CH_3.

[0303] In some embodiments, the structural moiety  has the structure of , , , , or . In some embodiments, the structural moiety  has the structure of .

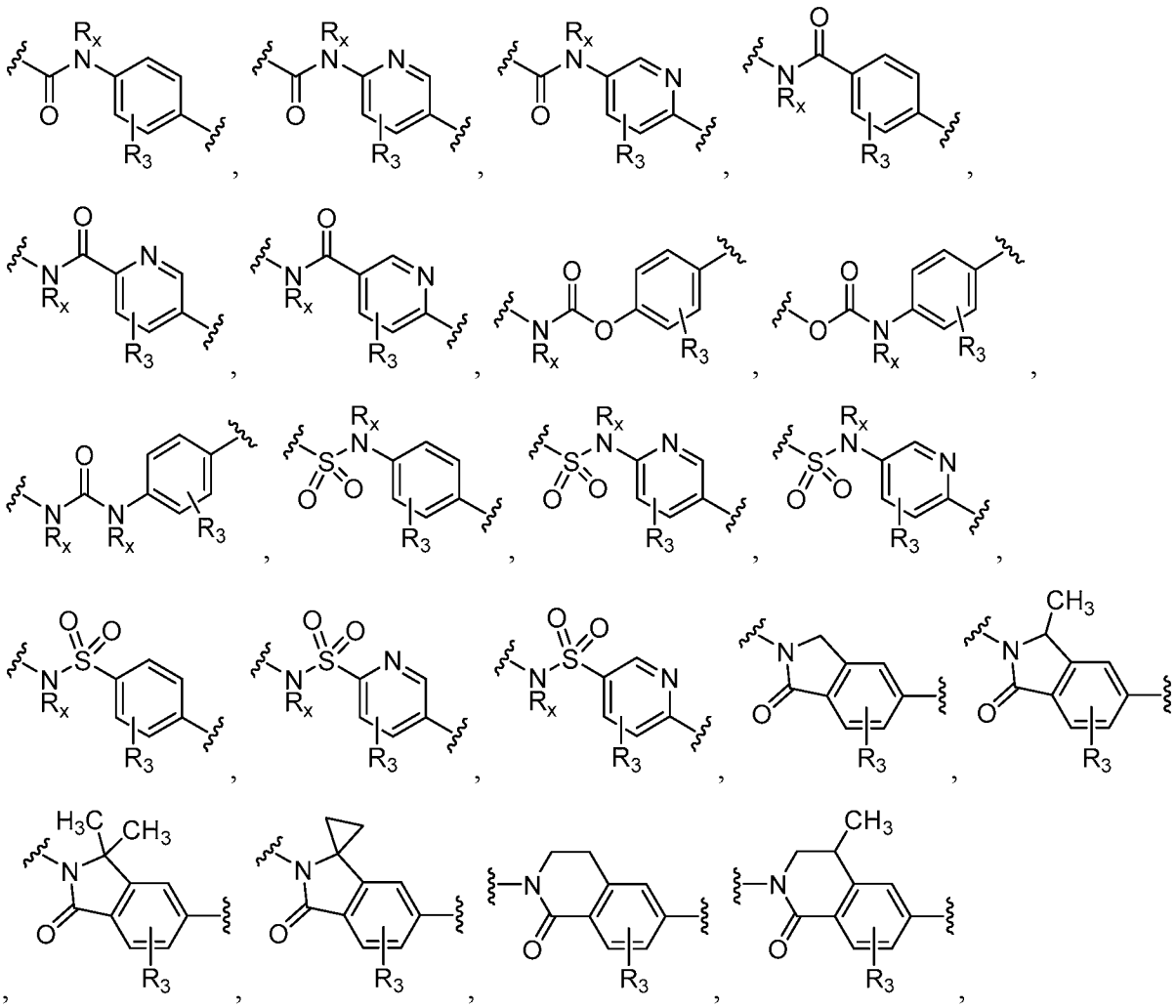
[0304] In these embodiments, the structural moiety  has the structure of , , , , , , , , or .

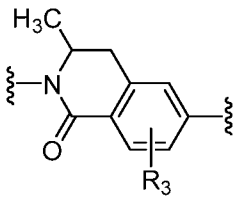
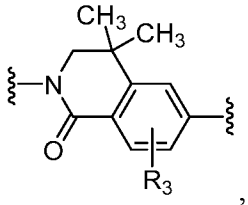
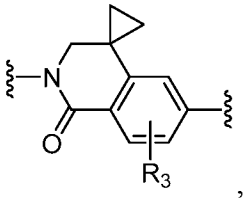
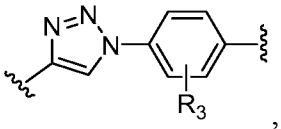
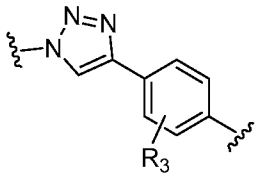
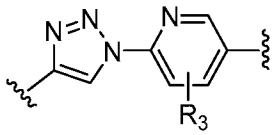
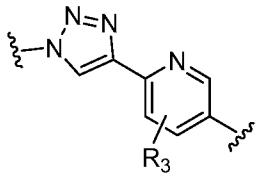
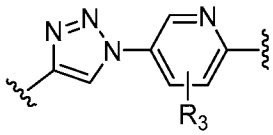
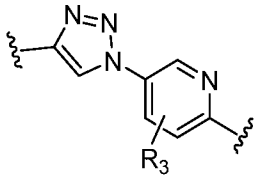
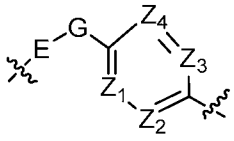
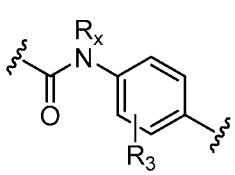
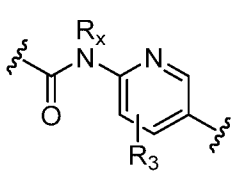
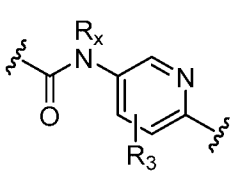
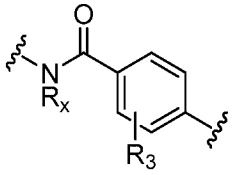
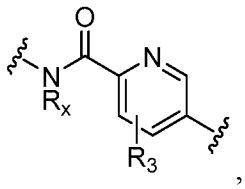
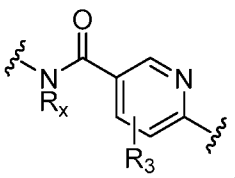
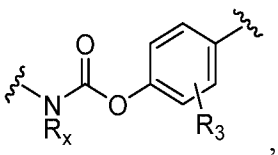
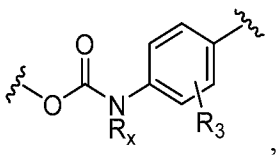
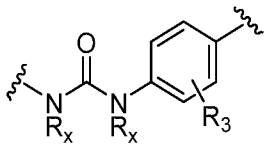
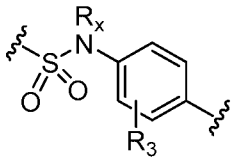
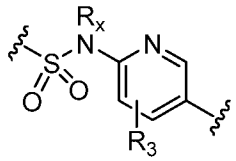
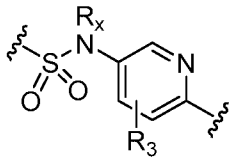
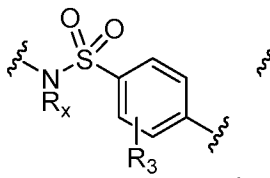
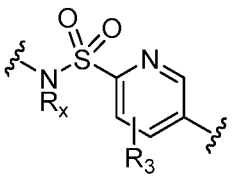
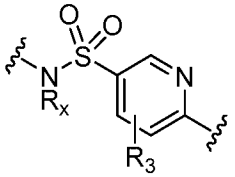
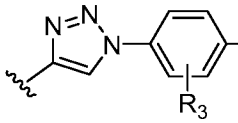
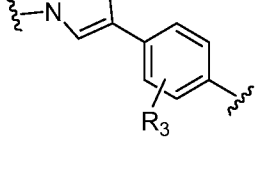
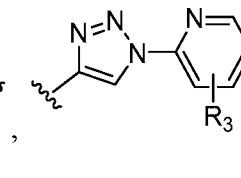
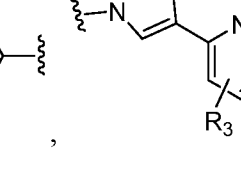
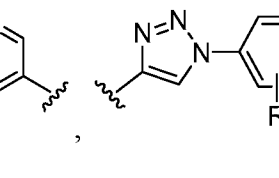
[0305] In some embodiments, the structural moiety  has the structure of , , , , , ,





[0306] In some embodiments, the structural moiety has the structure of



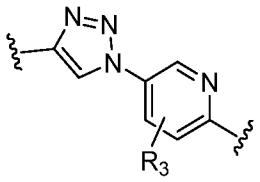

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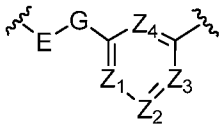
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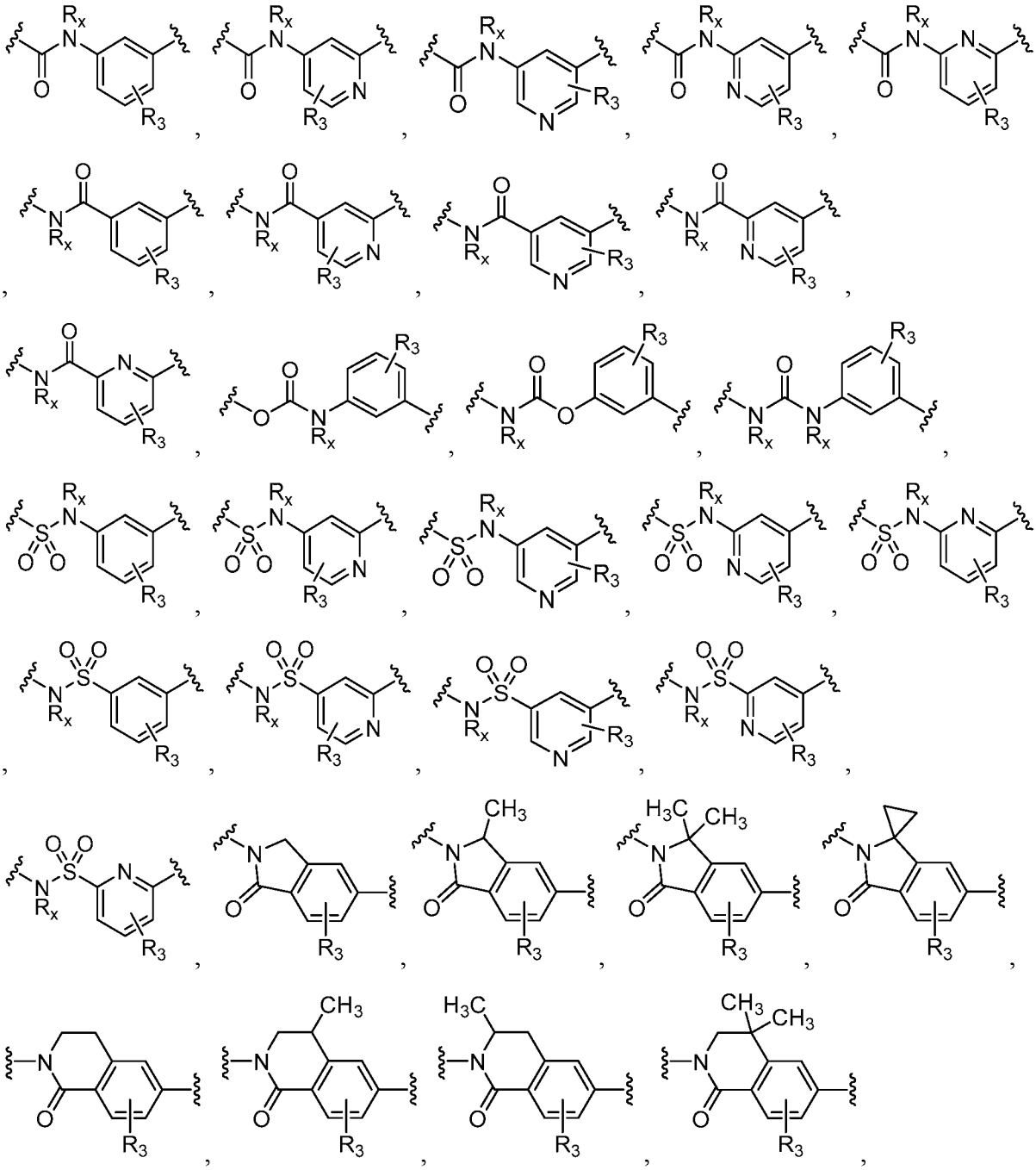
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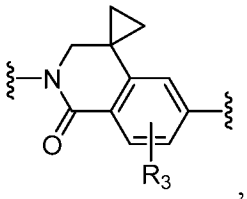
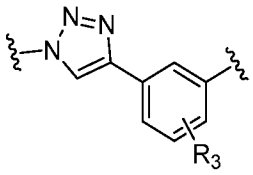
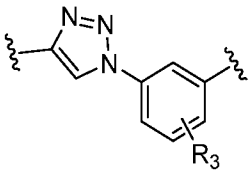
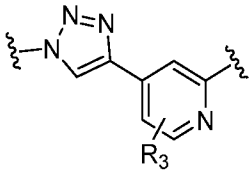
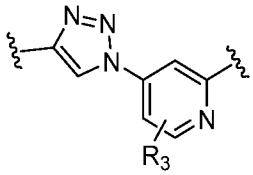
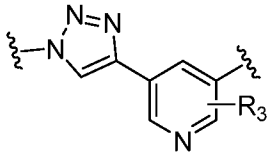
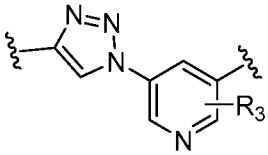
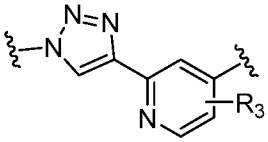
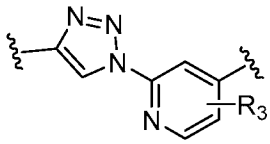
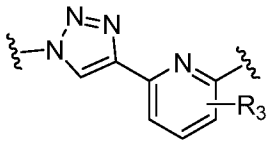
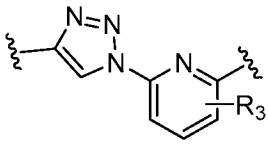
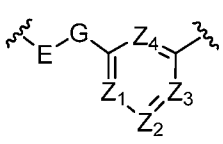
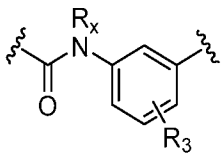
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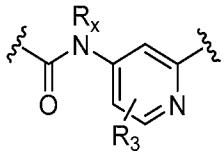
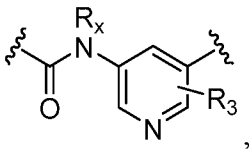
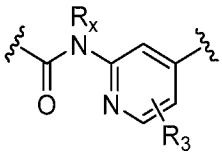
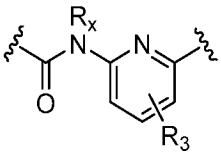
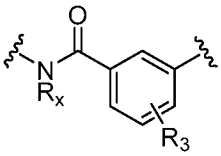
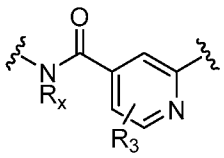
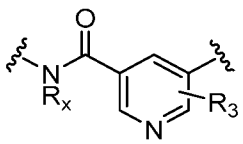
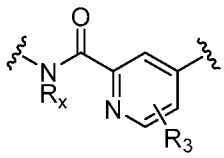
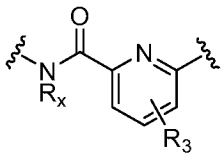
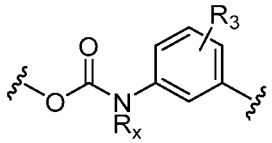
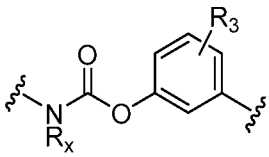
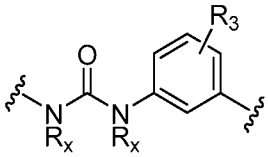
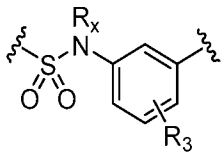
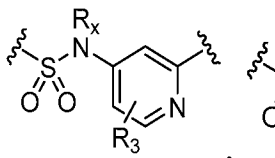
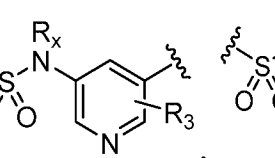
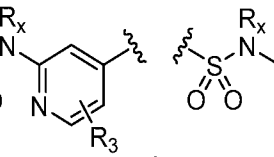
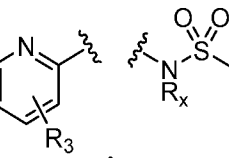
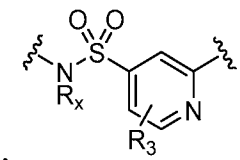
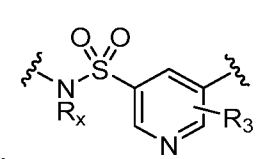
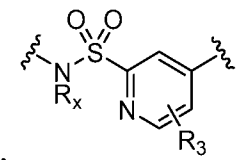
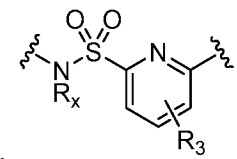


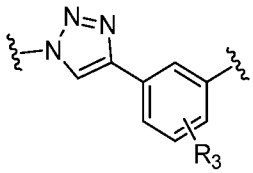
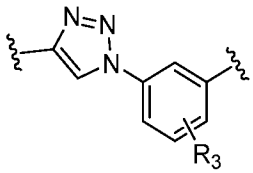
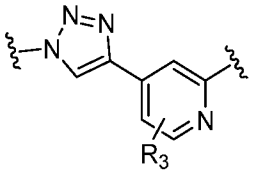
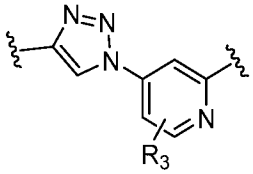
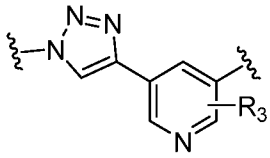
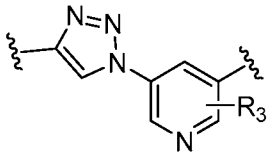
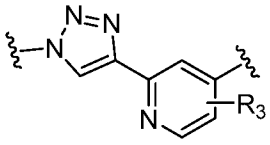
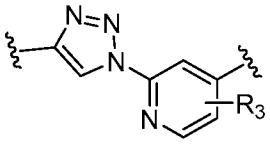
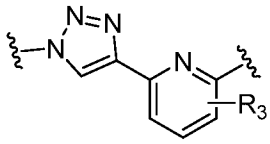
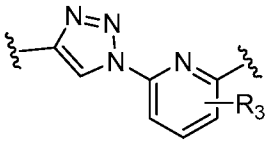
. In some embodiments, R_3 is H, CH_3, OH, halogen, or NH_2. In some embodiments, R_x is H, CH_3, or CH_2CH_3.

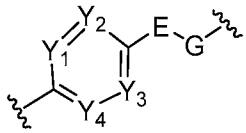
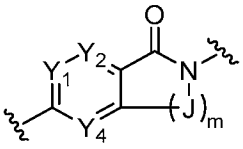
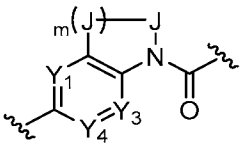
[0307] In some embodiments, the structural moiety  has the structure of

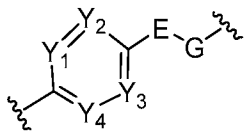
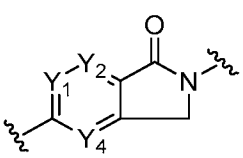
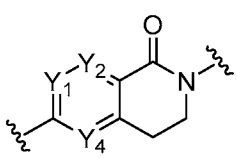
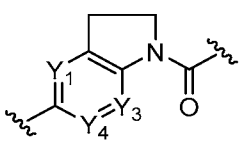
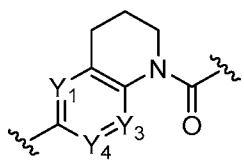
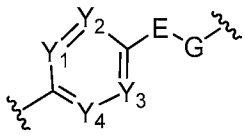


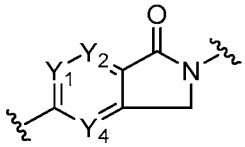
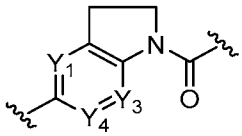
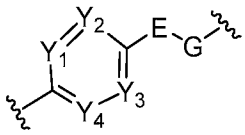
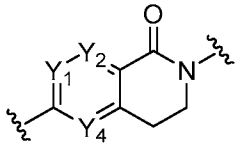
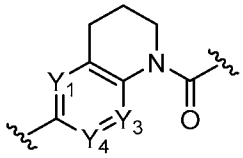










, or . In some embodiments, the structural moiety  has the structure of ,

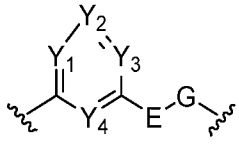
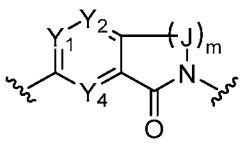
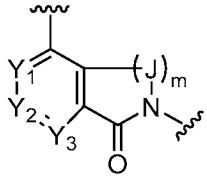
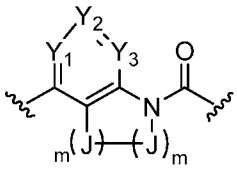
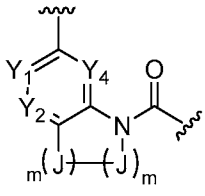
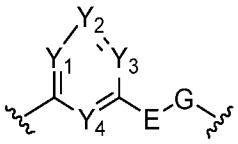
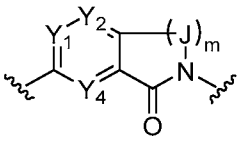
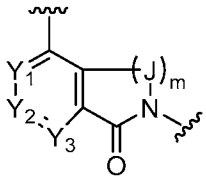
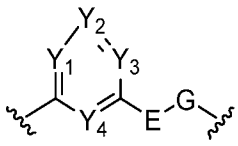
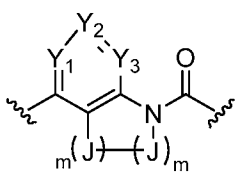






















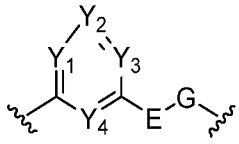
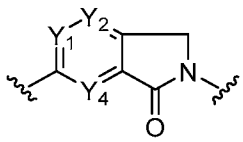
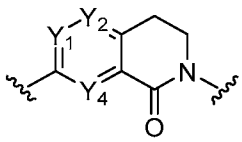
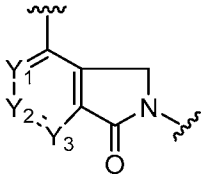
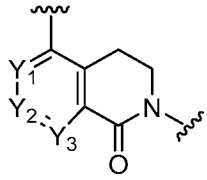
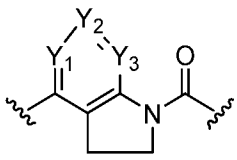
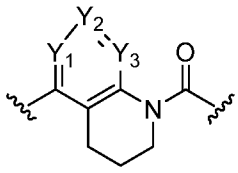
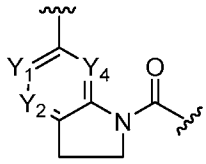
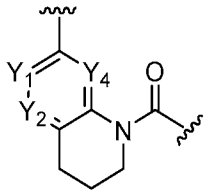
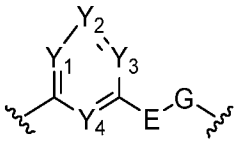
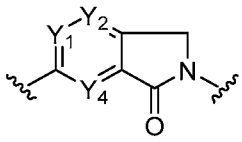
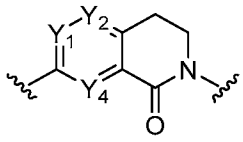
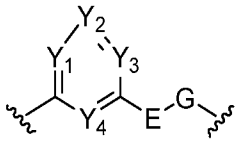
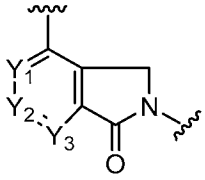
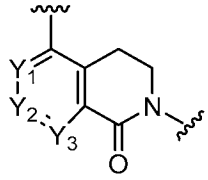
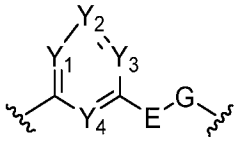
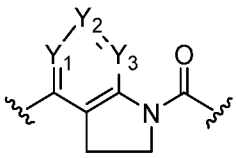
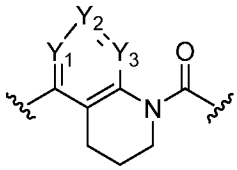
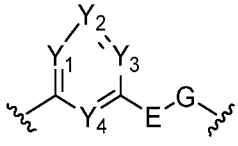
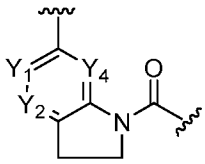
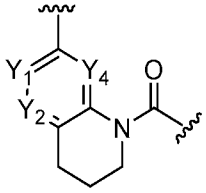










, or . In some embodiments, R_3 is H, CH_3, OH, halogen, or NH_2. In some embodiments, R_x is H, CH_3, or CH_2CH_3.

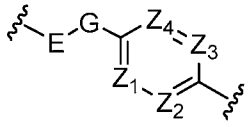
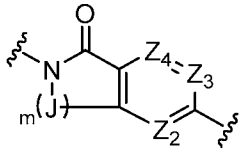
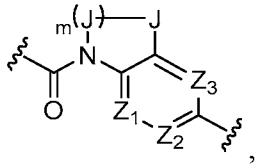
[0308] In some embodiments, the structural moiety  has the structure of  or , where each occurrence of m is independently 1 or 2, J is $C(R_y)_2$, and each occurrence of R_y is independently H, $(C_1$-$C_6)$alkyl, OH, $O(C_1$-$C_6)$alkyl, or halogen. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments each occurrence of R_y is independently H or $(C_1$-$C_6)$alkyl. In some embodiments each occurrence of R_y is independently OH, $O(C_1$-$C_6)$alkyl, or halogen. In some embodiments each occurrence of R_y is H.

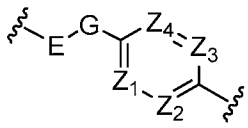
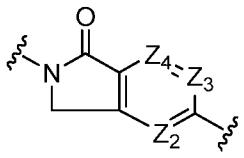
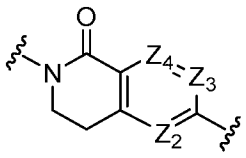
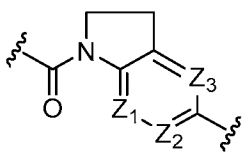
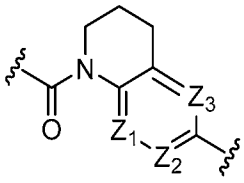
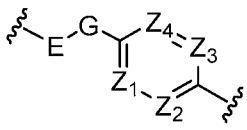
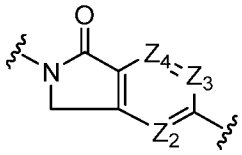
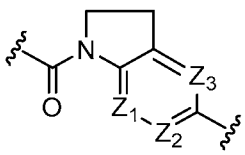
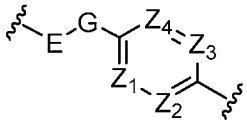
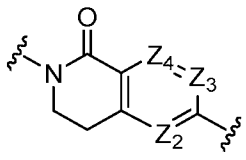
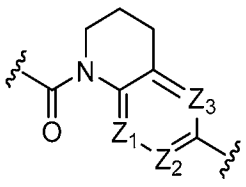
[0309] In some embodiments, the structural moiety  has the structure of , , , or . In some embodiments, the structural moiety  has the structure of

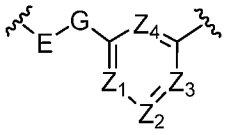
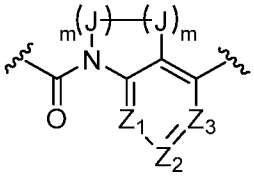
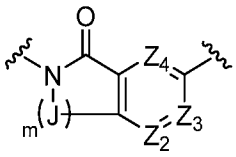
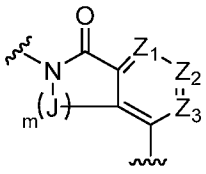
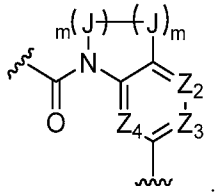
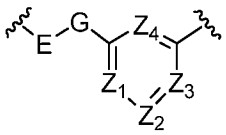
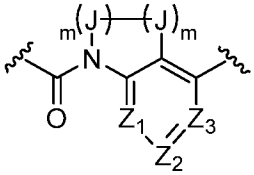
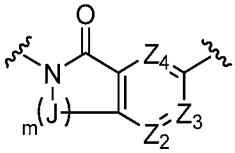
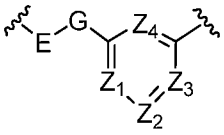
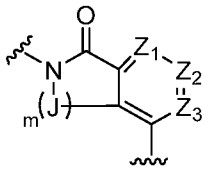
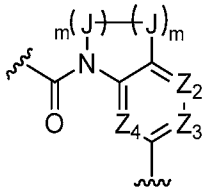
 or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, Y_1, Y_2, Y_3, and Y_4 are each independently N, CH, CCH_3, or CF. In some embodiments, Y_1, Y_2, Y_3, and Y_4 are each independently N or CH.

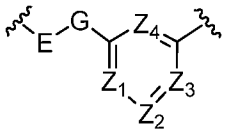
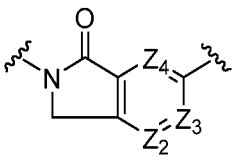
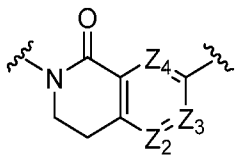
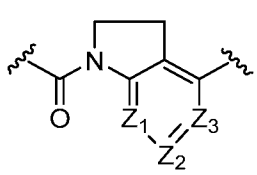
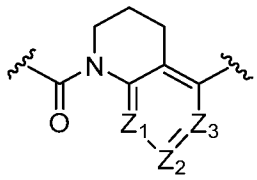
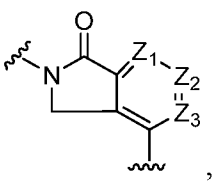
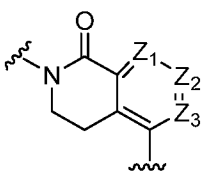
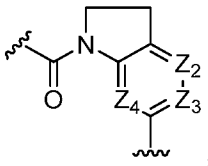
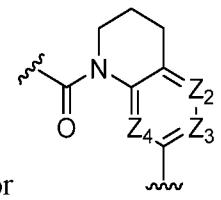
[0310] In some embodiments, the structural moiety  has the structure of , , , or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, each occurrence of m is independently 1 or 2, J is $C(R_y)_2$, and each occurrence of R_y is independently H, (C_1-C_6)alkyl, OH, O(C_1-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-C_6)alkyl. In some embodiments each occurrence of R_y is independently OH, O(C_1-C_6)alkyl, or halogen. In some embodiments each occurrence of R_y is H.

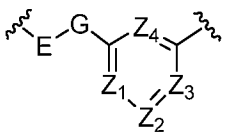
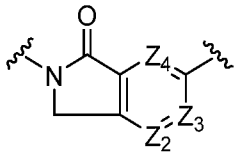
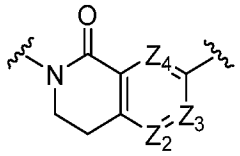
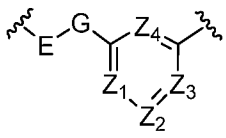
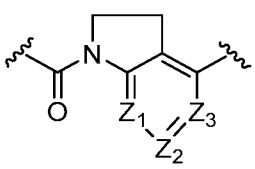
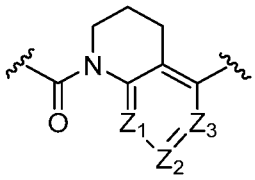
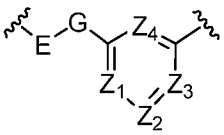
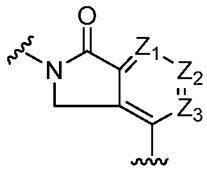
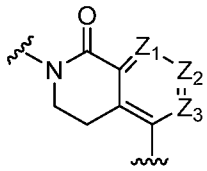
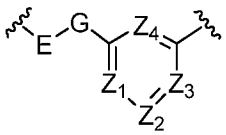
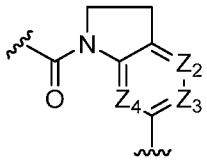
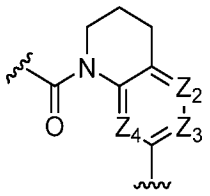
[0311] In some embodiments, the structural moiety  has the structure of , , , , , , , or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, the structural moiety  has the structure of  or . 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.

[0312] In some embodiments, 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. 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.

[0313] 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.

[0314] 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 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.

[0315] In some embodiments, the structural moiety  has the structure of , , , , , , , or . In some

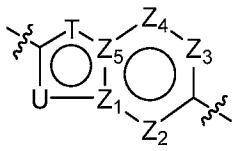
embodiments, the structural moiety  has the structure of  or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, the structural moiety  has the structure of  or . In some embodiments, Z_1, 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.

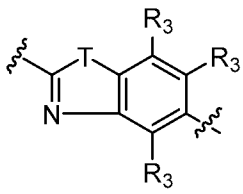
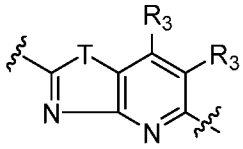
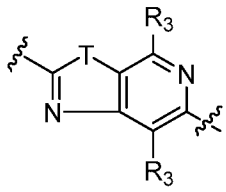
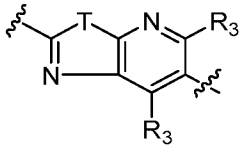
[0316] In some embodiments, the compound has the structure of Formula Ib. In some embodiments, the compound has the structure of Formula IIb. In some embodiments, the compound has the structure of Formula IIIb. In some embodiments, the compound has the structure of Formula IVb.

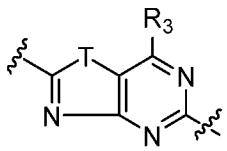
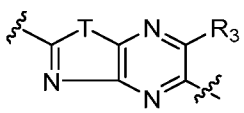
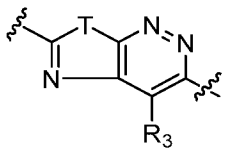
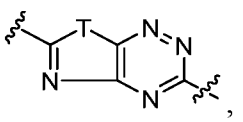
[0317] In some embodiments, T is $N(C=O)R_a$ or NSO_2R_a. In some embodiments, T is N(C=O)Me or N(C=O)Et. In some embodiments, T is NSO_2Me or NSO_2Et. In some embodiments, T is O or NR_a. In some embodiments, T is O. In some embodiments, T is NR_a. In some embodiments, T is NH. In some embodiments, T is NCH_3 or NCH_2CH_3. In some embodiments, T is $NC(R_b)_2OP(=O)(OR_b)_2$. In some embodiments, T is N or O, where valence permits.

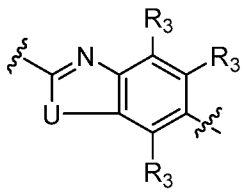
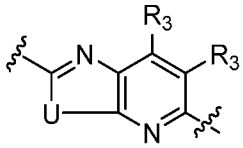
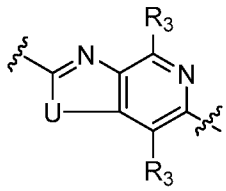
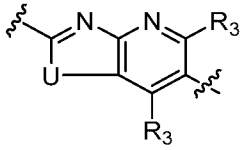
[0318] In some embodiments, U is $N(C=O)R_a$ or NSO_2R_a. In some embodiments, U is N(C=O)Me or N(C=O)Et. In some embodiments, U is NSO_2Me or NSO_2Et. In some embodiments, U is O or NR_a. In some embodiments, U is O. In some embodiments, U is NR_a. In some embodiments, U is NH. In some embodiments, U is NCH_3 or NCH_2CH_3. In some embodiments, T is $NC(R_b)_2OP(=O)(OR_b)_2$. In some embodiments, U is N or O, where valence permits.

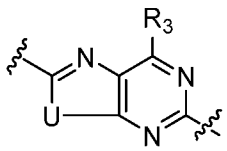
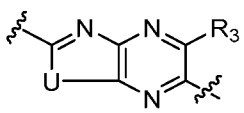
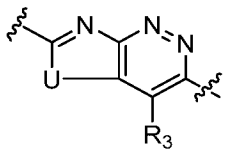
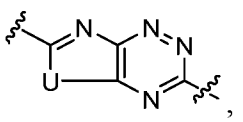
[0319] In some embodiments, each occurrence of R_b is independently H or $(C_1\text{-}C_6)$alkyl. In some embodiments, each occurrence of R_b is independently H, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, or *tert*-butyl. In some embodiments, each occurrence of R_b is independently H or CH_3. In some embodiments, each occurrence of R_b is H.

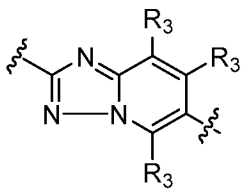
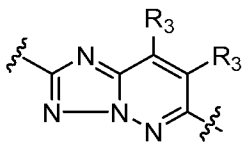
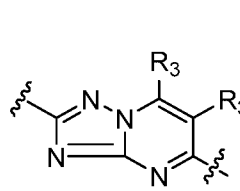
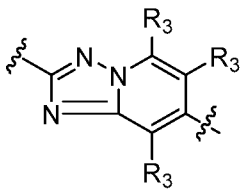
[0320] In some embodiments, the structural moiety  has the structure of

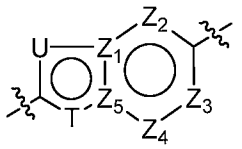
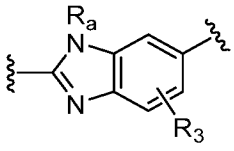
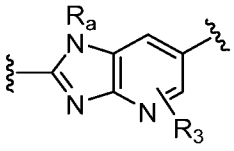
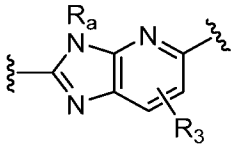
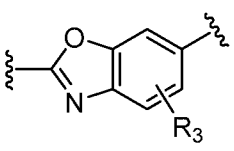
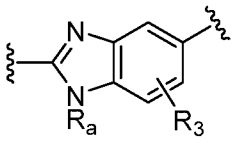
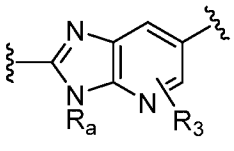
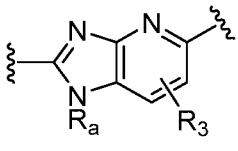
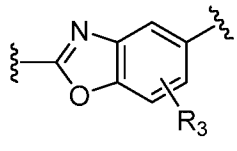
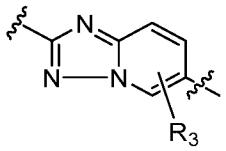
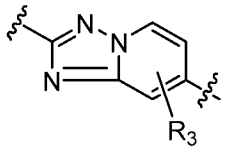
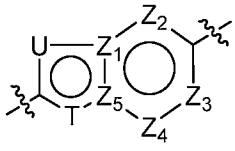
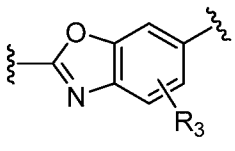
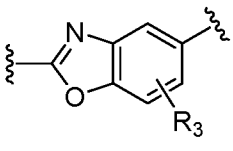
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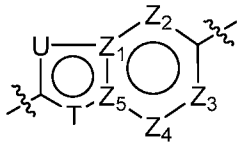
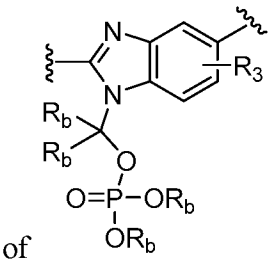
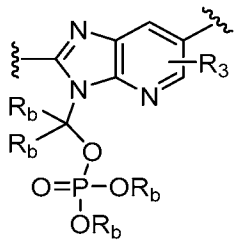
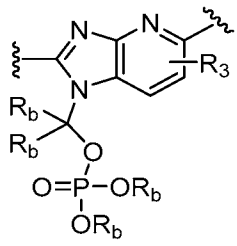
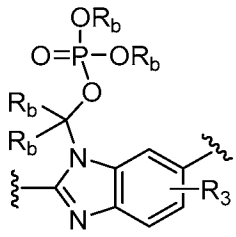
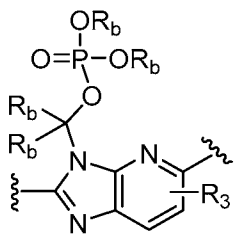
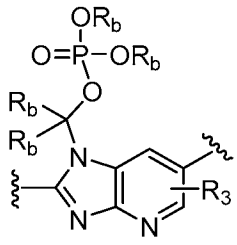
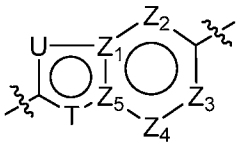
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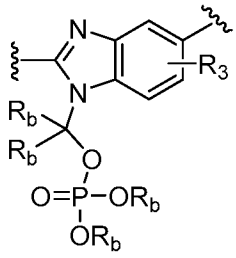
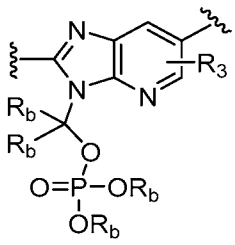
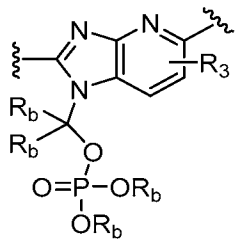
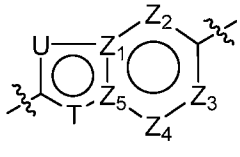
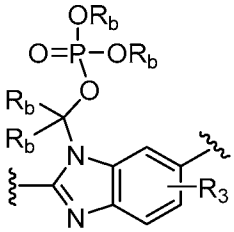
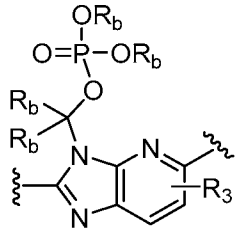
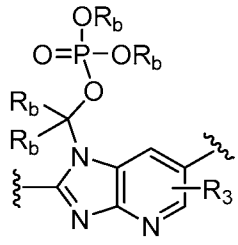
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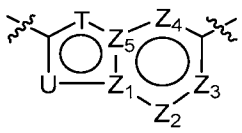
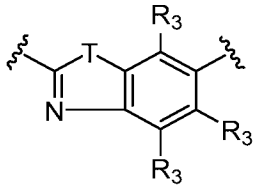
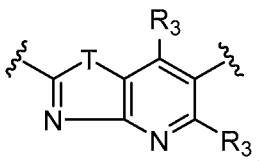
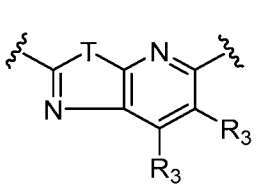
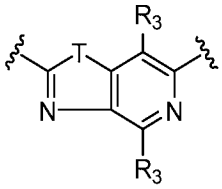
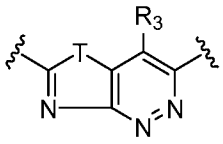
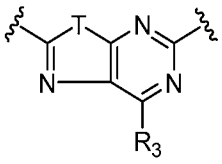
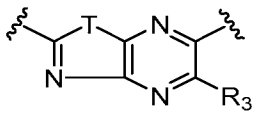
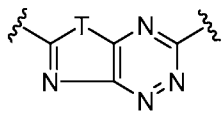
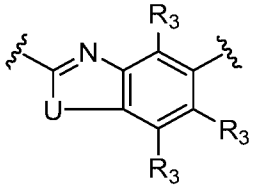
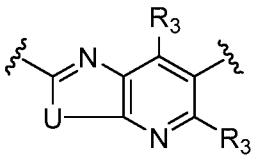
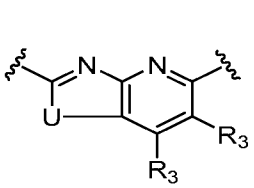
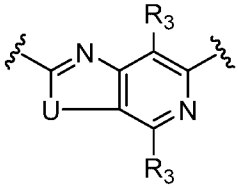
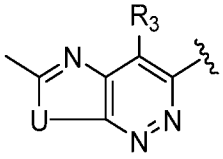
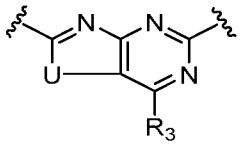
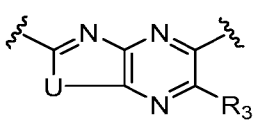
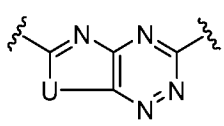
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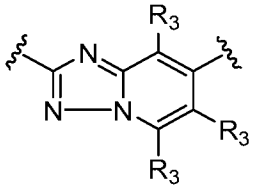
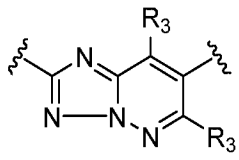
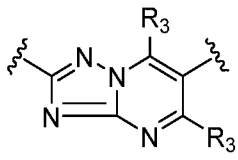
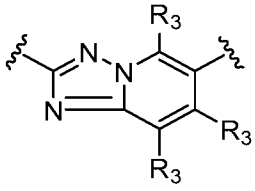
, , , or , where each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

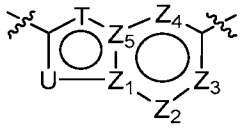
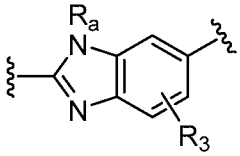
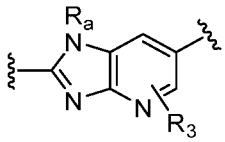
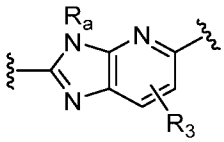
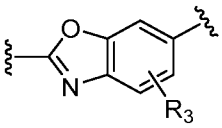
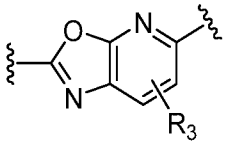
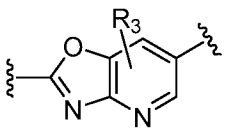
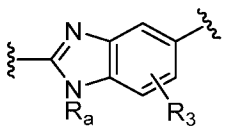
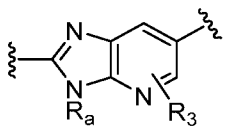
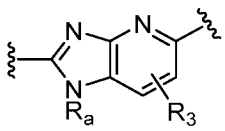
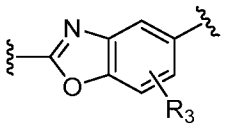
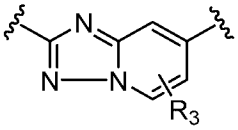
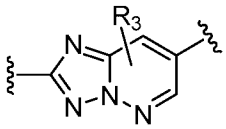
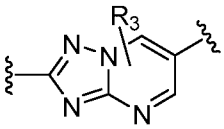
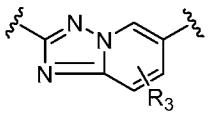
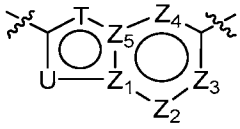
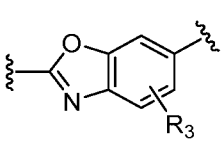
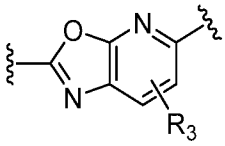
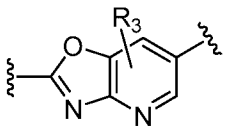
[0321] In some embodiments, the structural moiety  has the structure of , , , , , , , , , , or . In some embodiments, the structural moiety has the structure of  or .

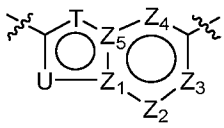
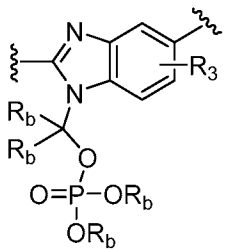
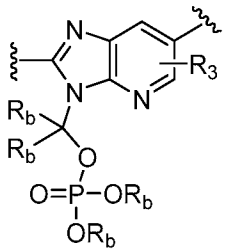
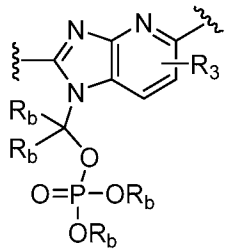
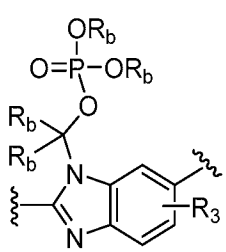
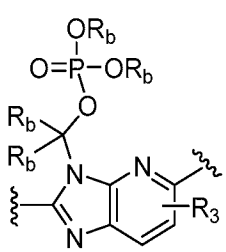
[0322] In some embodiments, the structural moiety  has the structure of , , , , , or , where each occurrence of R_b is independently H or CH_3. In some embodiments, the structural moiety  has the structure of

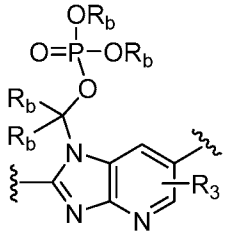
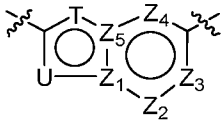
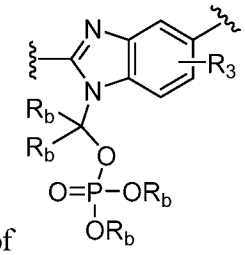
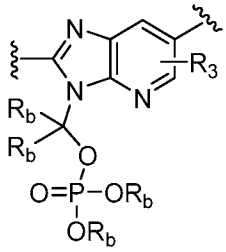
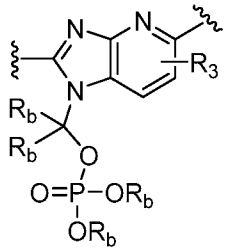
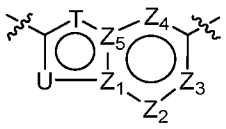
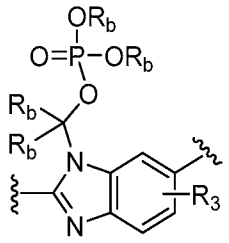
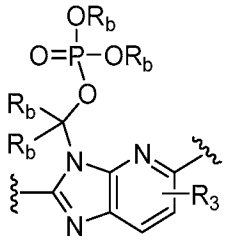
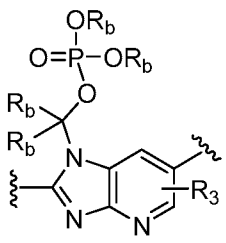


, or , where each occurrence of R_b is independently H or CH_3. In some embodiments, the structural moiety  has the structure of , , or , where each occurrence of R_b is independently H or CH_3.

[0323] In some embodiments, the structural moiety  has the structure of , , , , , , , , , , , , , , , .

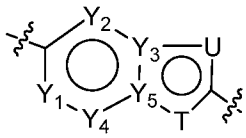
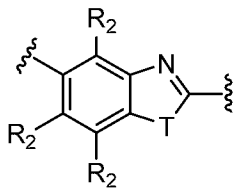
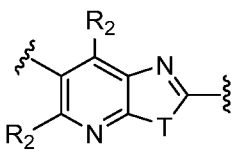
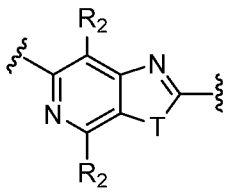
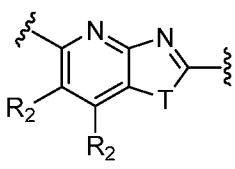




, wherein each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

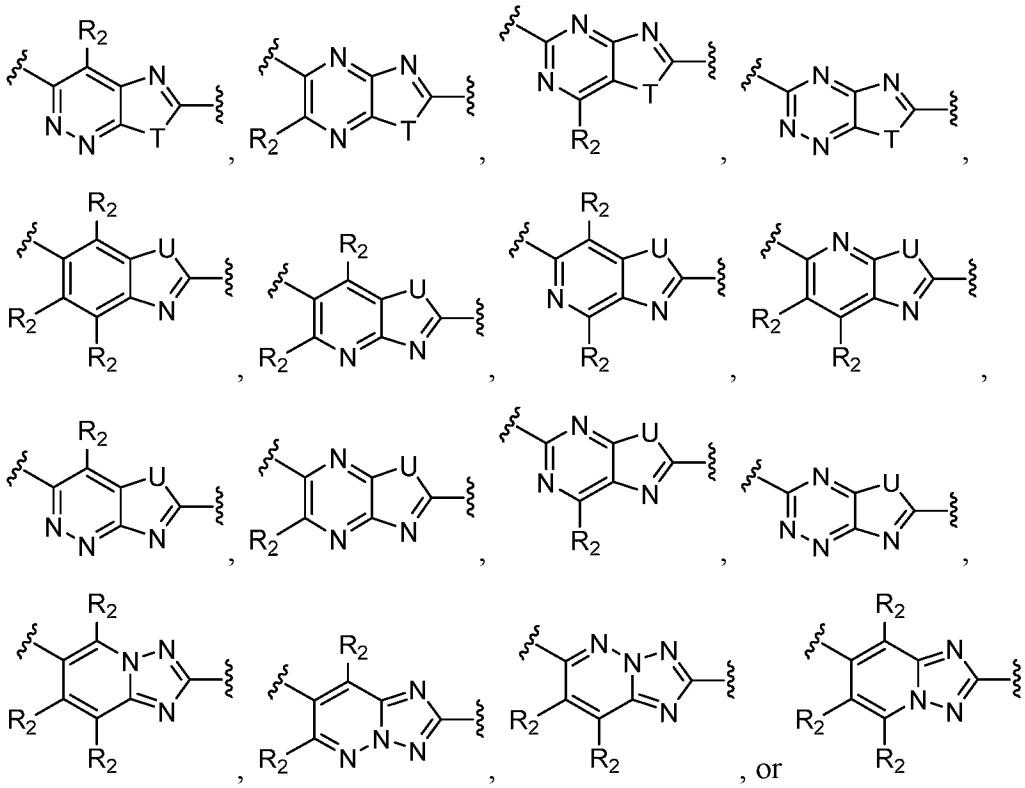
[0324] In some embodiments, the structural moiety  has the structure of 












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

, or . In some embodiments, R_3 is H, CH_3, OH, halogen, or NH_2; and R_a is H, CH_3, or CH_2CH_3.

[0325] In some embodiments, the structural moiety  has the structure of 





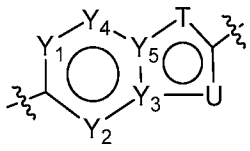

or . In some embodiments, the structural moiety has the structure of , , or . In some embodiments, the structural moiety  has the structure of , , or . In some embodiments, each occurrence of R_b is independently H or CH_3.

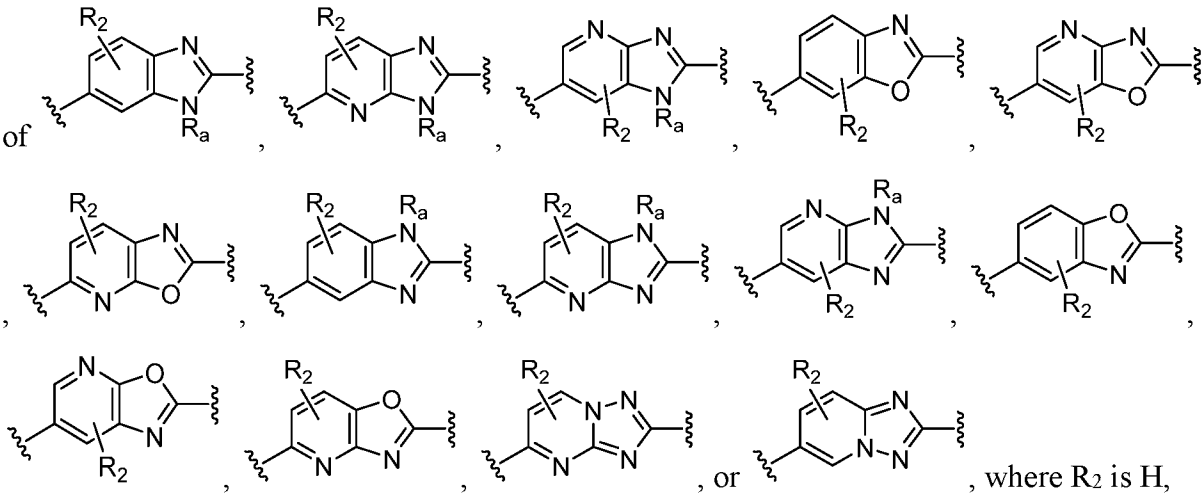
[0326] In some embodiments, the compound has the structure of Formula Ic. In some embodiments, the compound has the structure of Formula IIc. In some embodiments, the compound has the structure of Formula IIIc. In some embodiments, the compound has the structure of Formula IVc.

[0327] In some embodiments, the structural moiety  has the structure of , , , ,

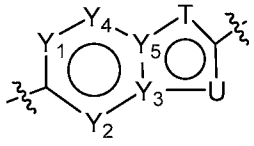
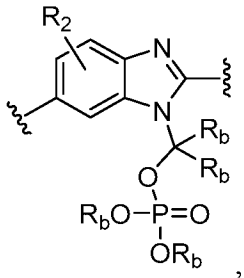
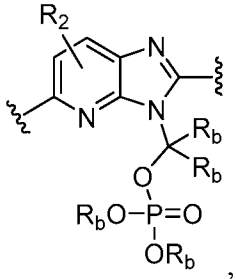
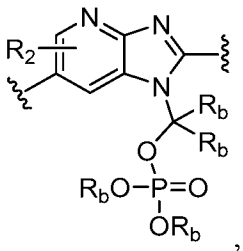
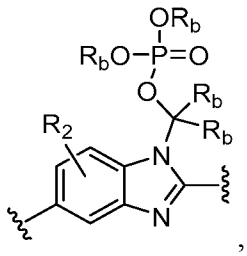
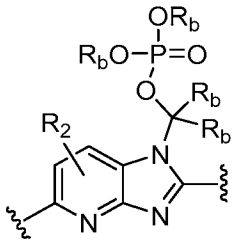
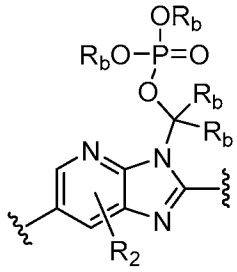
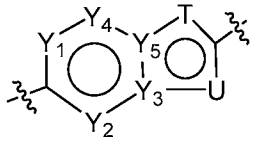
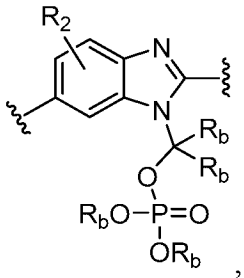
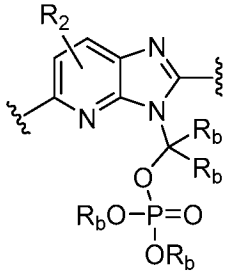
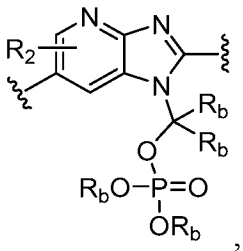
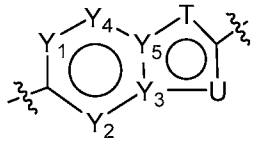
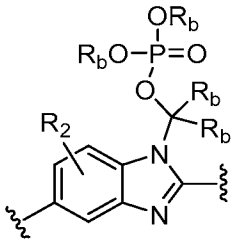
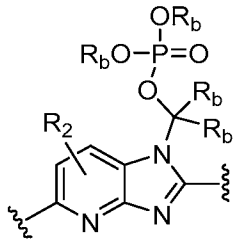
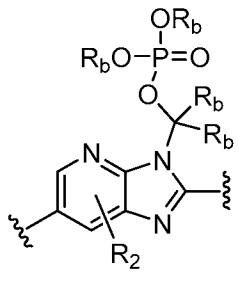


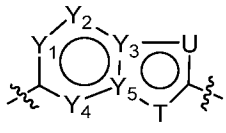
, where each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, or NSO_2R_a where valance permits.

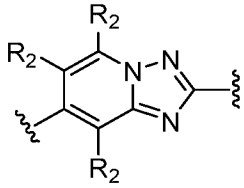
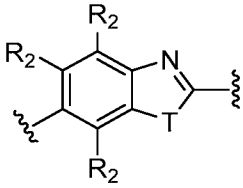
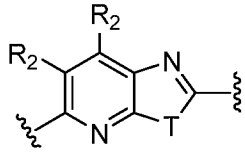
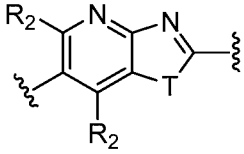
[0328] In some embodiments, the structural moiety  has the structure of

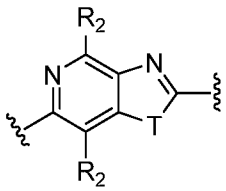
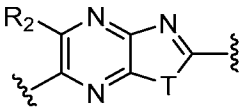
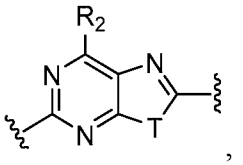
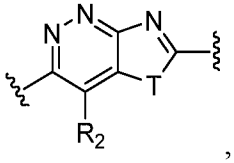


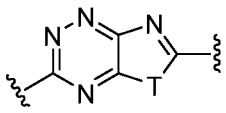
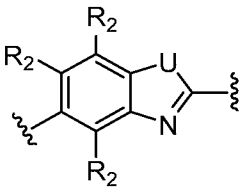
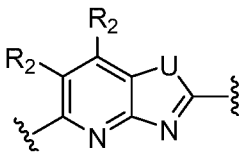
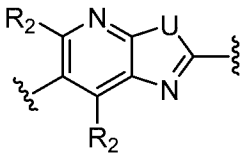
, where R_2 is H, CH_3, OH, halogen, or NH_2; and where R_a is H, CH_3, or CH_2CH_3. In some embodiments, R_2 is H, CH_3, OH, halogen, or NH_2. In some embodiments, R_a is H, CH_3, or CH_2CH_3.

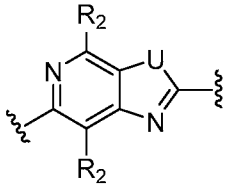
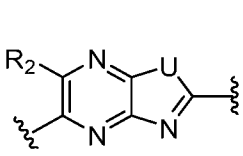
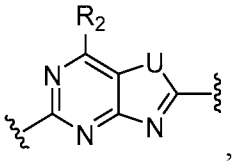
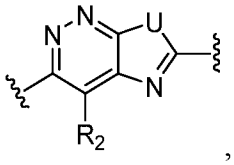
[0329] In some embodiments, the structural moiety  has the structure of  ,  ,  ,  ,  , or  , where each occurrence of R_b is independently H or CH_3. In some embodiments, the structural moiety  has the structure of  ,  , or  , where each occurrence of R_b is independently H or CH_3. In some embodiments, the structural moiety  has the structure of  ,  , or  , where each occurrence of R_b is independently H or CH_3.

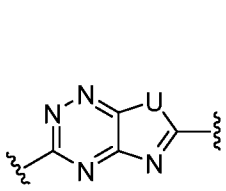
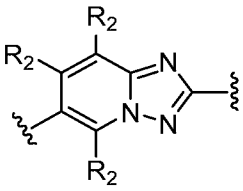
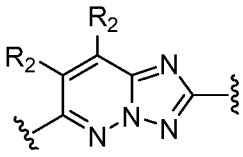
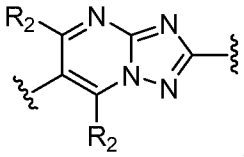
[0330] In some embodiments, the structural moiety  has the structure of

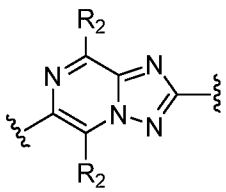
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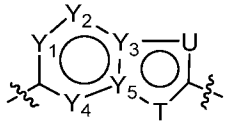
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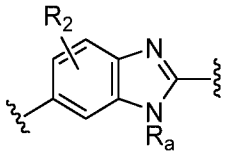
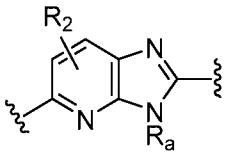
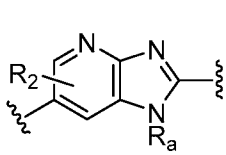
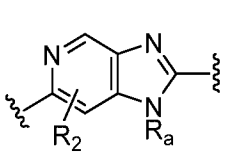
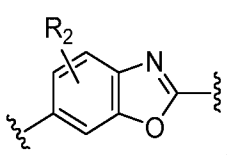
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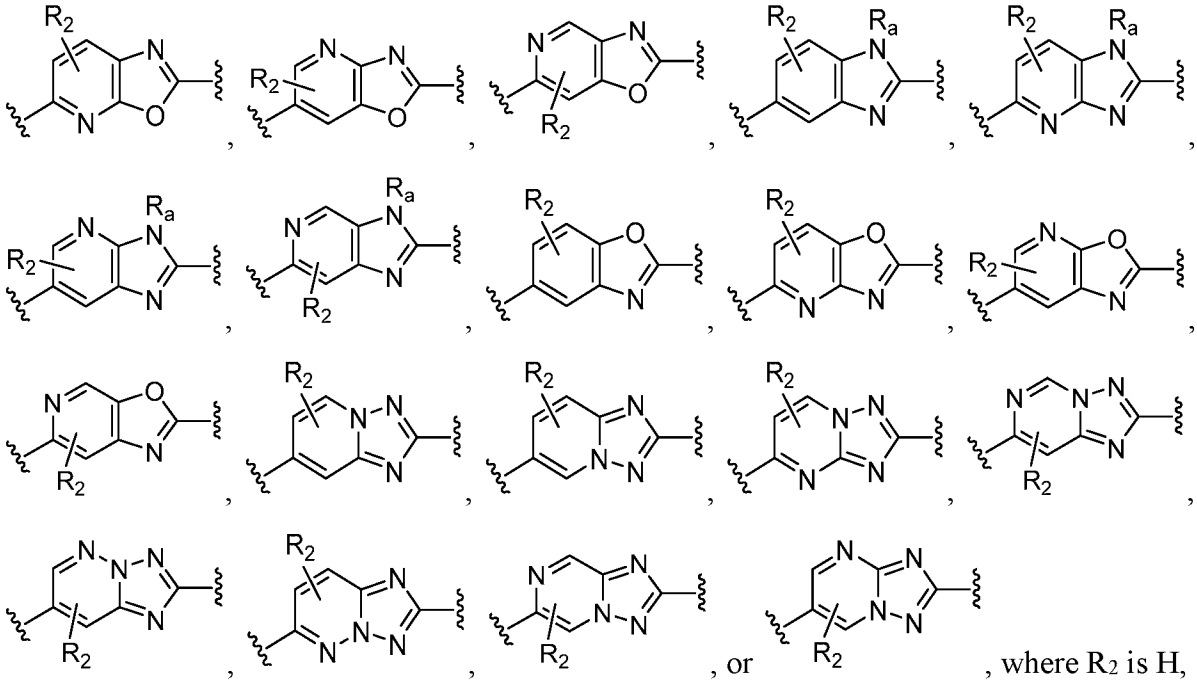
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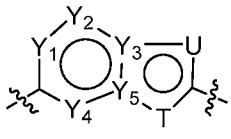
, wherein each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

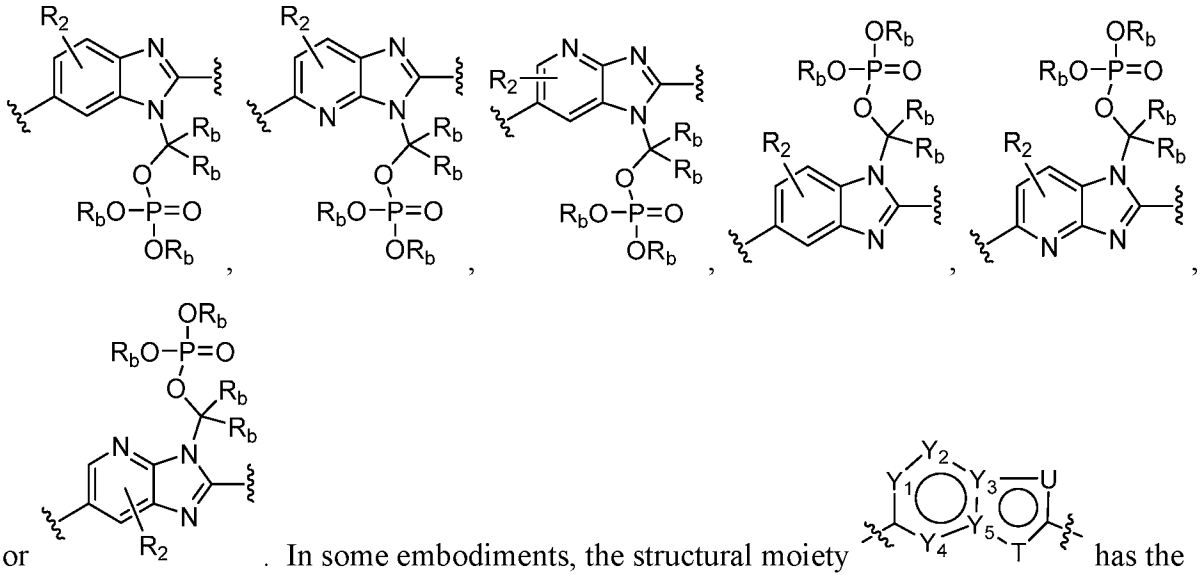
[0331] In some embodiments, the structural moiety  has the structure of

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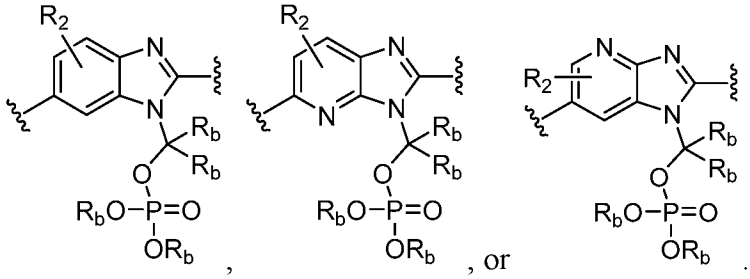


, where R_2 is H, CH_3, OH, halogen, or NH_2; and where R_a is H, CH_3, or CH_2CH_3. In some embodiments, R_2 is H, CH_3, OH, halogen, or NH_2. In some embodiments, R_a is H, CH_3, or CH_2CH_3.

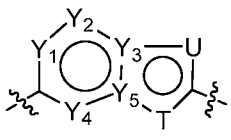
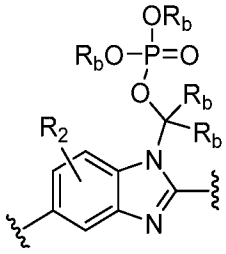
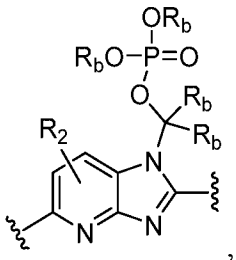
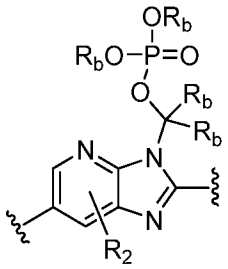
[0332] In some embodiments, the structural moiety  has the structure of

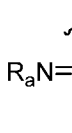
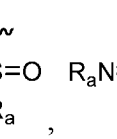
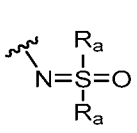
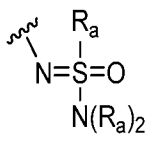


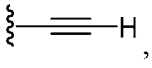
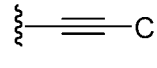
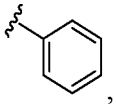
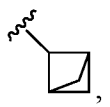
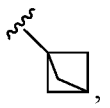
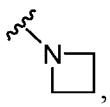
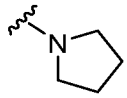
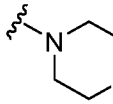
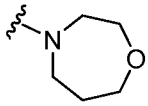
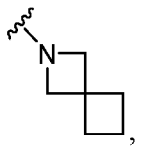
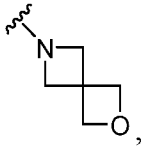
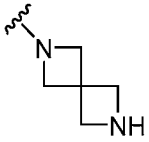
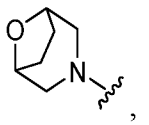
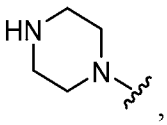
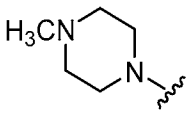
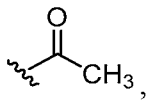
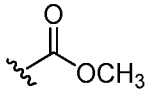
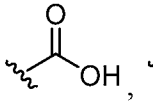
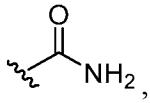
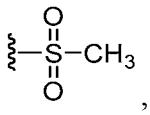
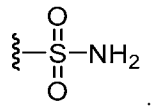
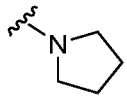
. In some embodiments, the structural moiety has the structure of

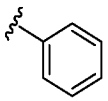
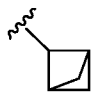
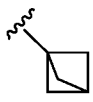
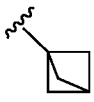
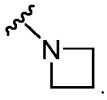
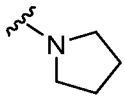
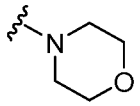
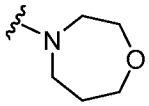


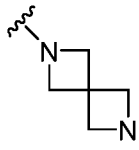
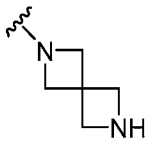
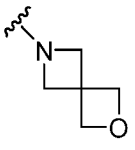
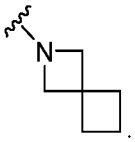
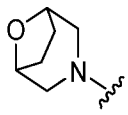
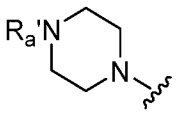
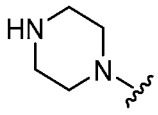
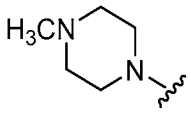
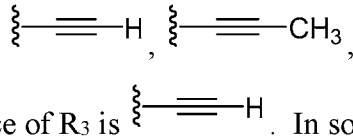
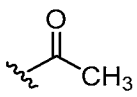
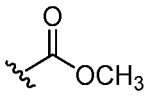
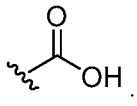
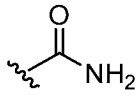
. In some

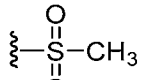
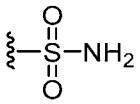
embodiments, the structural moiety  has the structure of , , or . In some embodiments, each occurrence of R_b is independently H or CH_3.

[0333] 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, $(C_4$-$C_{10})$heterospiroalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, 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 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 $(C_4$-$C_{10})$heterospiroalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, 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, $-CN$, 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, $(C_1$-$C_6)$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, 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, D, F, Cl, Br, CH_3, OCH_3, NH_2, $N(CH_3)_2$, , , , , , , , , , , , , , , , , –CN, N_3, NO_2, , , , , , or . In some embodiments, each occurrence of R_3 is independently H, D, F, CH_3, $N(CH_3)_2$, , or .

[0334] 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

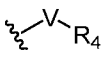
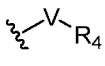
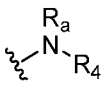
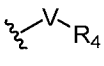
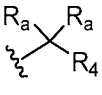
embodiments, at least one occurrence of R_3 is , where R_a' is H or (C_1-C_6)alkyl. In some embodiments, at least one occurrence of R_3 is . In some embodiments, at least one occurrence of R_3 is . In some embodiments, at least one occurrence of R_3 is . In some embodiments, at least one occurrence of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

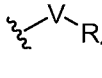
occurrence of R_3 is . In some embodiments, at least one occurrence of R_3 is .

[0335] 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.

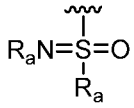
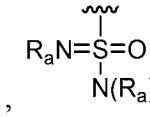
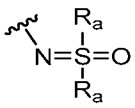
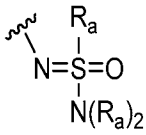
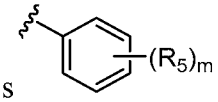
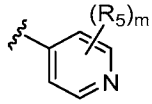
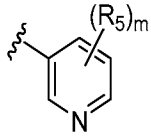
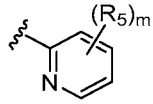
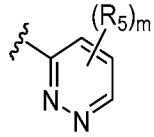
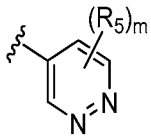
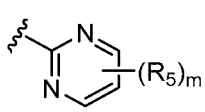
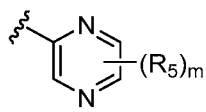
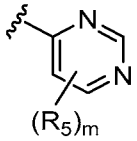
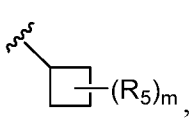
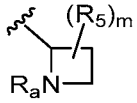
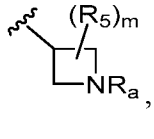
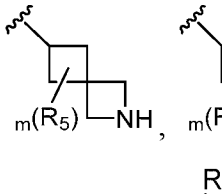
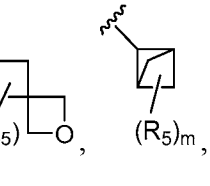
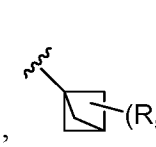
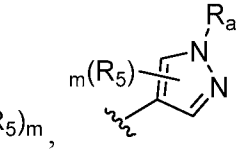
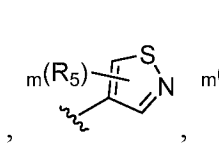
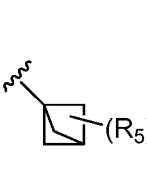
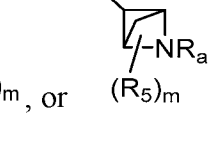
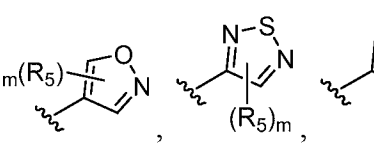
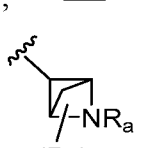
[0336] In some embodiments, V is absent, O, or NR_a. In some embodiments, V is absent. In some embodiments, V is O. In some embodiments, V is NR_a. In some embodiments, V is NH. In some embodiments, V is NCH_3 or NCH_2CH_3.

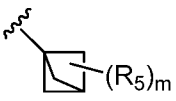
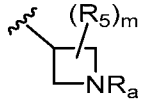
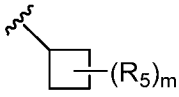
[0337] In some embodiments, V is $N(C{=}O)R_a$ or NSO_2R_a. In some embodiments, V is $N(C{=}O)H$. In some embodiments, V is $N(C{=}O)CH_3$ or $N(C{=}O)CH_2CH_3$. In some embodiments, V is NSO_2H. In some embodiments, V is NSO_2CH_3 or $NSO_2CH_2CH_3$.

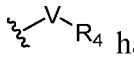
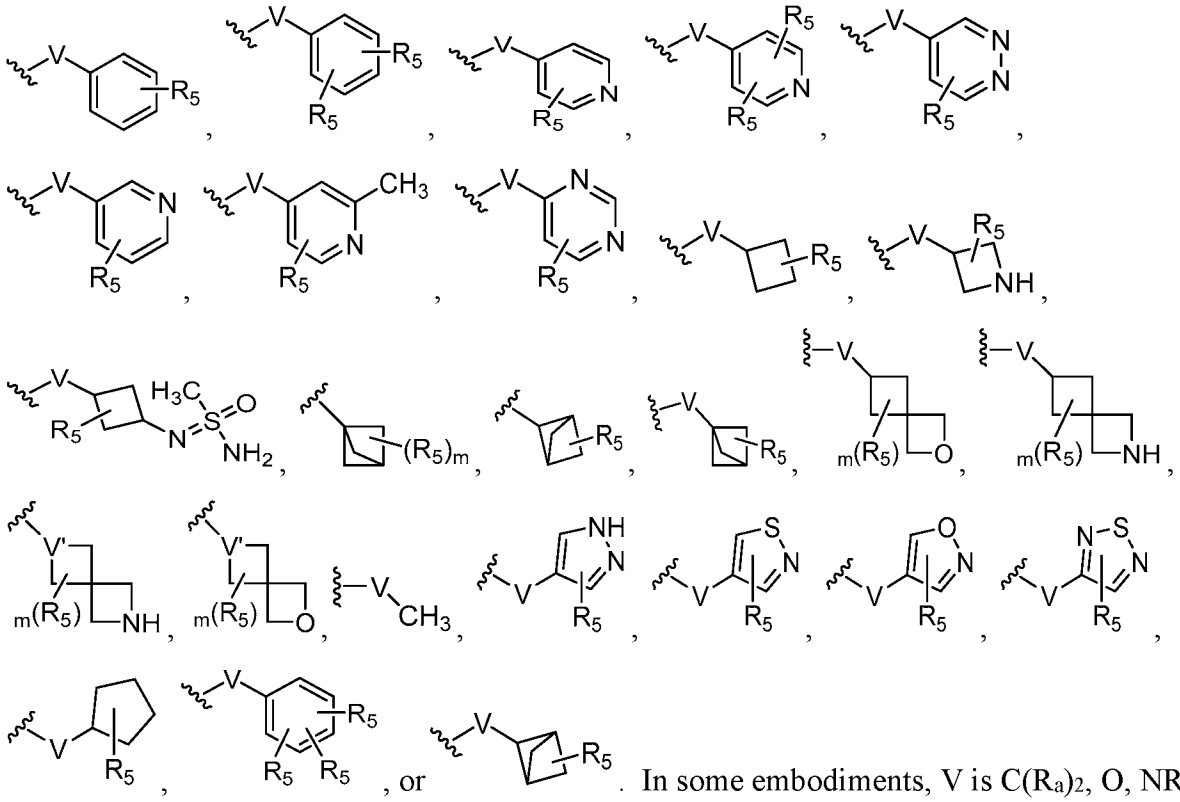
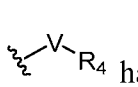
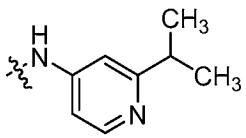
[0338] In some embodiments, the structural moiety  has the structure of . In some embodiments, the structural moiety  has the structure of . In some embodiments, the structural moiety  has the structure of .

[0339] In some embodiments, the V and R_4 of the structural moiety  taken together form a $(C_4\text{-}C_{10})$heterospiroalkyl.

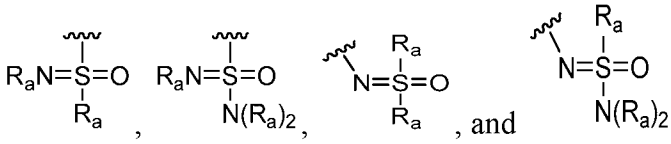
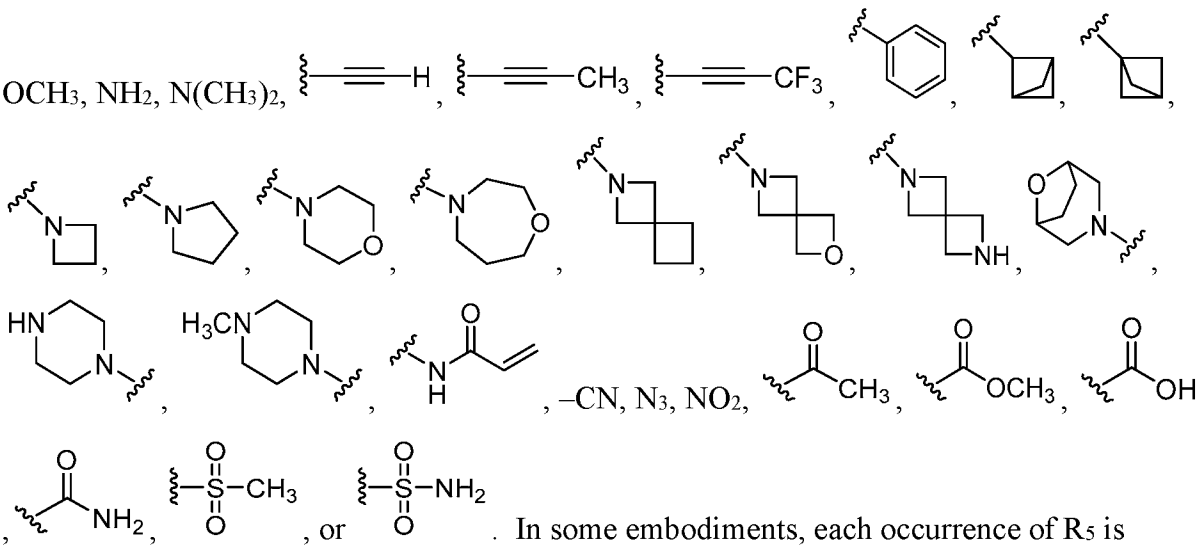
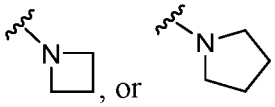
[0340] In some embodiments, R_4 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, aryl, and heteroaryl, each optionally substituted with one or 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, (C_4-C_{10})heterospiroalkyl, halogenated (C_3-C_7)heterocycloalkyl, 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, R_4 is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , where in , , , , , , , or , R_5 may be attached to any position of the bicycloalkyl or heterobicycloalkyl including the bridge head carbon, and where in and , R_5 may be attached to any available position in either ring. 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, R_4 is . In some

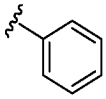
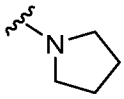
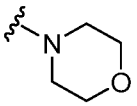
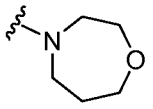
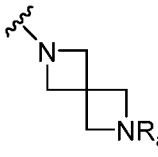
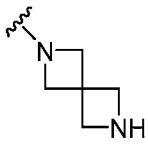
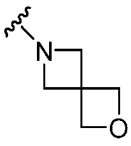
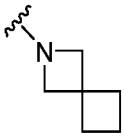
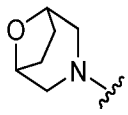
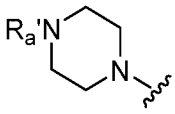
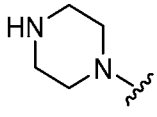
embodiments, R_4 is . In some embodiments, R_4 is . In some embodiments, R_4 is . In some embodiments, m is an integer from 0-3. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

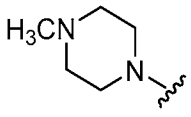
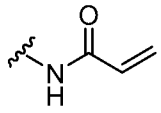
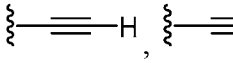
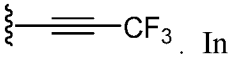
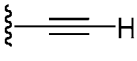
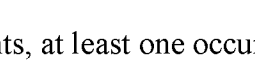
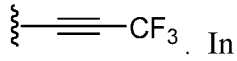
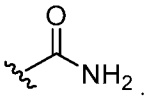
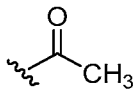
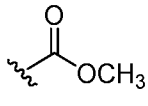
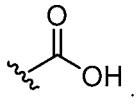
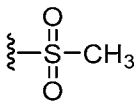
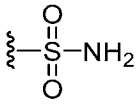
[0341] In some embodiments, the structural moiety  has the structure of . In some embodiments, V is $C(R_a)_2$, O, NR_a, $N(C=O)R_a$, or NSO_2R_a. In some embodiments, V' is CR_a or N. In some embodiments, the structural moiety  has the structure of .

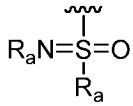
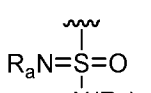
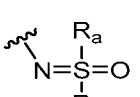
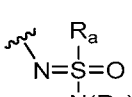
[0342] In some embodiments, each occurrence of R_5 is independently selected from the group consisting of H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$haloalkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_{10})$bicycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, $(C_4$-$C_{10})$heterobicycloalkyl, $(C_4$-$C_{10})$heterospiroalkyl, halogenated $(C_3$-$C_7)$heterocycloalkyl, 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

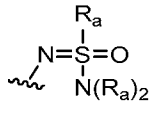
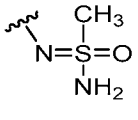
embodiments, each occurrence of R_5 is independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, and (C_4-C_{10})heterobicycloalkyl. 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, $-CN$, 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, isopropyl, OCH_3, NH_2, $N(CH_3)_2$, , $-CN$, N_3, NO_2, . In some embodiments, each occurrence of R_5 is independently H, D, F, CH_3, $N(CH_3)_2$, .

[0343] 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

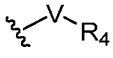
occurrence of R_5 is D. In some embodiments, at least one occurrence of R_5 is F. In some embodiments, at least one occurrence of R_5 is CH_3. In some embodiments, at least one occurrence of R_5 is OCH_3. In some embodiments, at least one occurrence of R_5 is NH_2. In some embodiments, at least one occurrence 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,

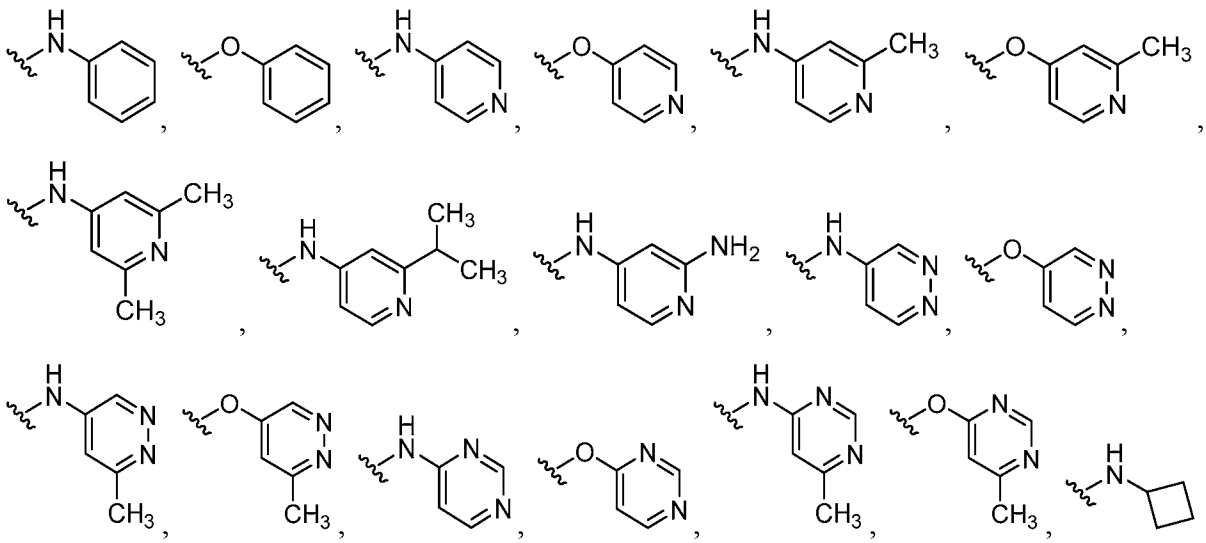
at least one occurrence of R_5 is . In some embodiments, at least one occurrence of R_5 is . In some embodiments, at least one occurrence of R_5 is , or . In some embodiments, at least one occurrence of R_5 is . In some embodiments, at least one occurrence of R_5 is . In some embodiments, at least one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

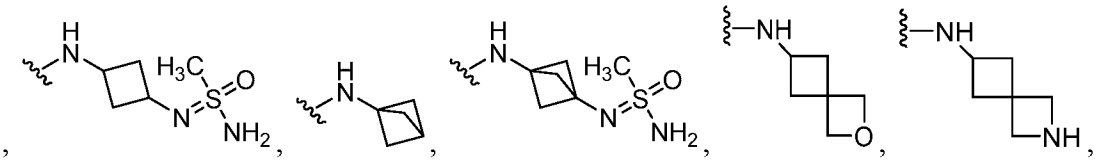
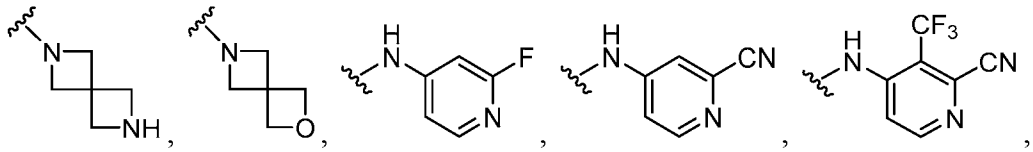
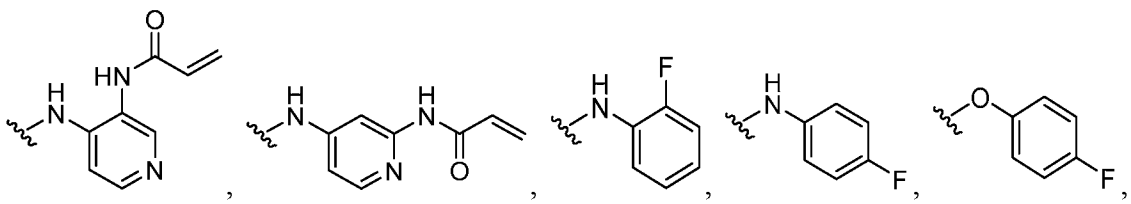
[0344] In some embodiments, each occurrence of R_5 is independently selected from the group consisting of halogen, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, OR_a, $–N(R_a)_2$, $–COR_a$, $–CO_2R_a$, $CON(R_a)_2$, $N(R_a)COR_a$, –CN, NO_2, $–SO_2R_a$, $–SO_2N(R_a)_2$, $–N(R_a)SO_2R_a$, , , , and . In some embodiments, at least one occurrence of

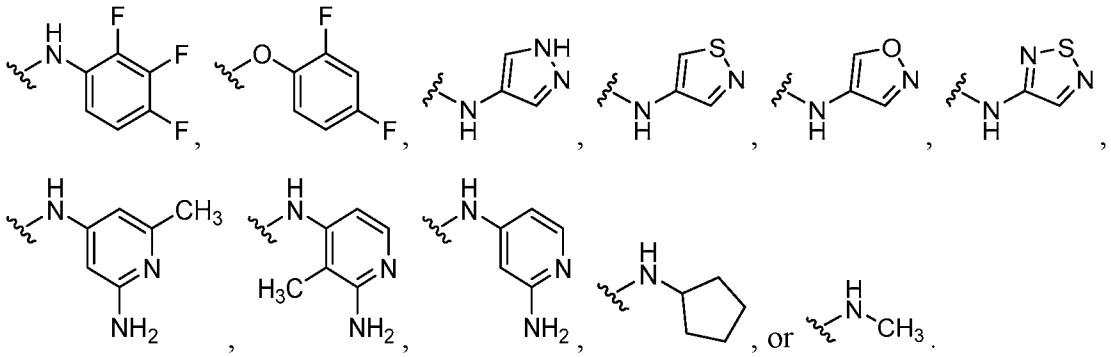
R_5 is (C_1-C_6)alkyl, halogen, OH, NH_2, or . In some embodiments, at least one occurrence of R_5 is CH_3, halogen, OH, or NH_2. In some embodiments, at least one occurrence of R_5 is OH. In some embodiments, at least one occurrence of R_5 is CH_3. In some embodiments, at least one occurrence of R_5 is .

[0345] 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.

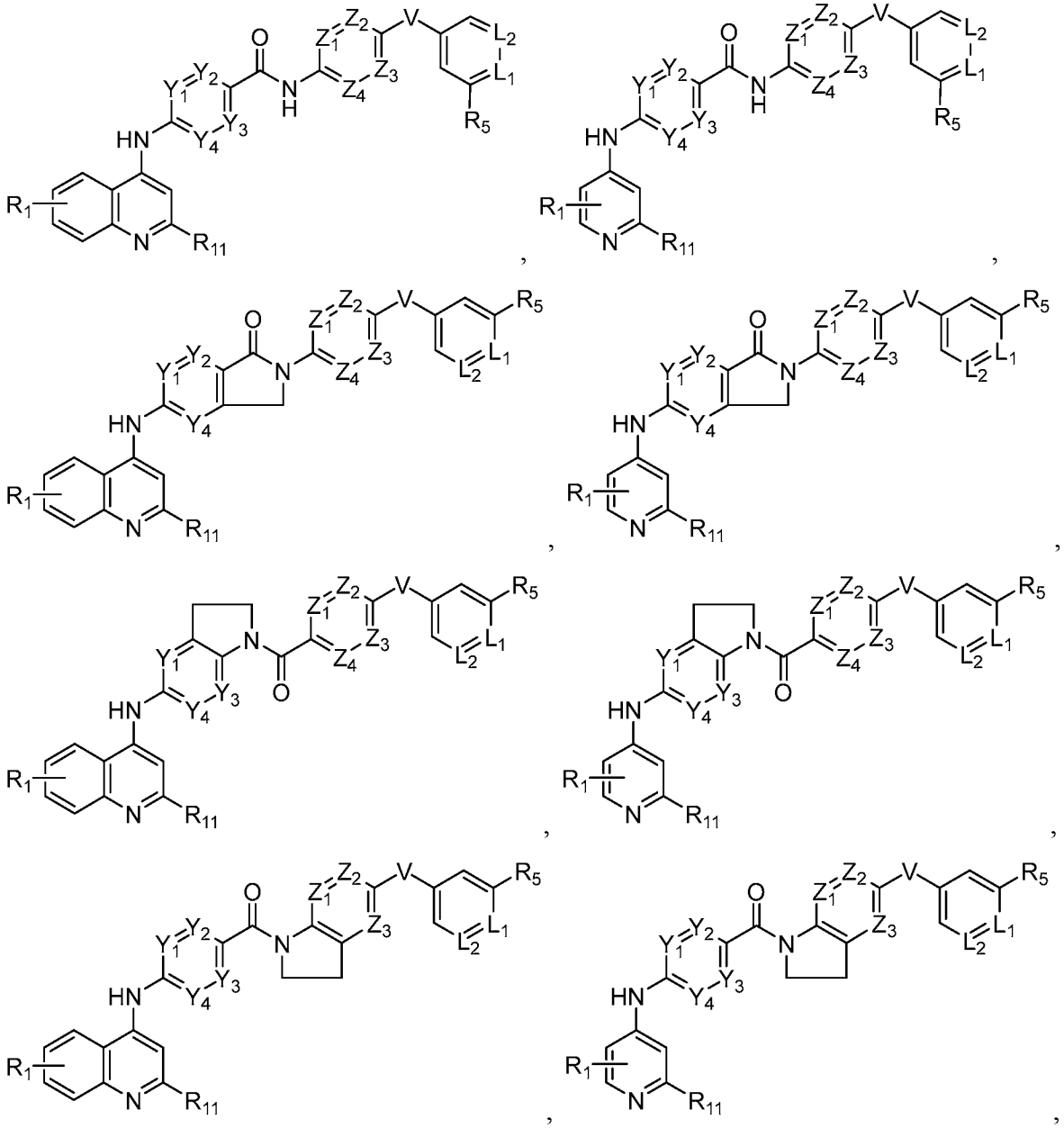
[0346] In some embodiments, the structural moiety  has the structure of

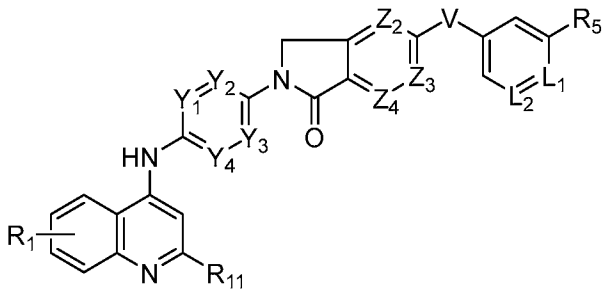
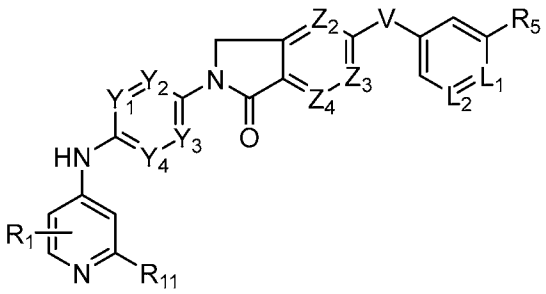
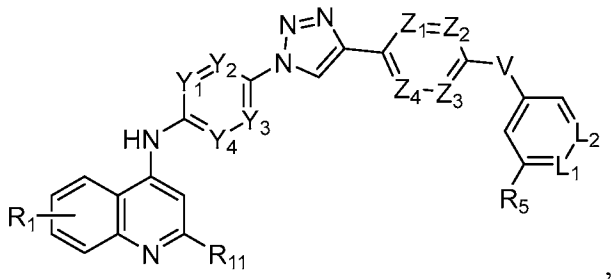
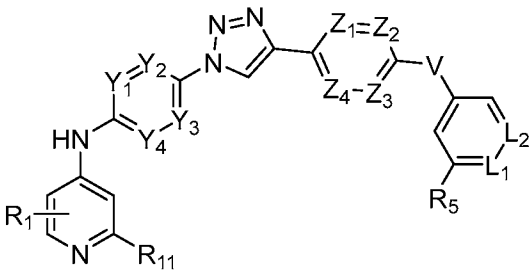
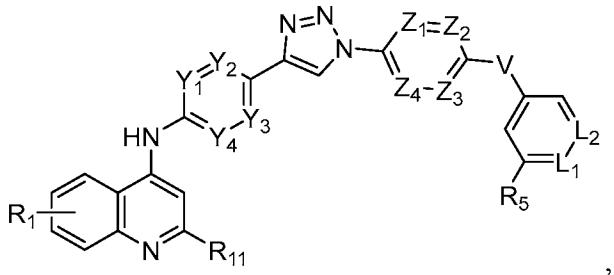
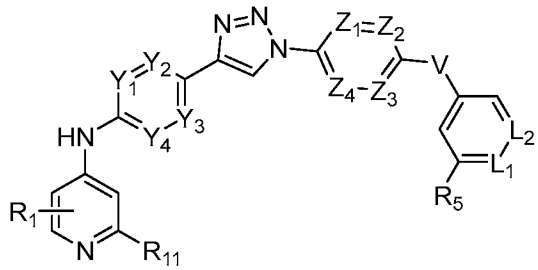


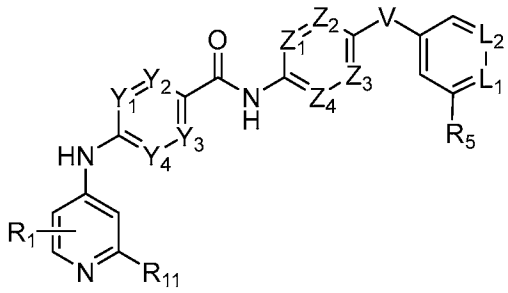


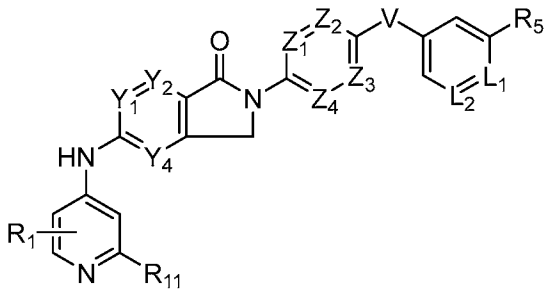
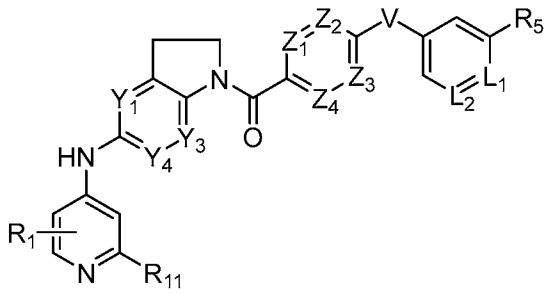
[0347] In some embodiments, the compound of Formula Ia has the structure of

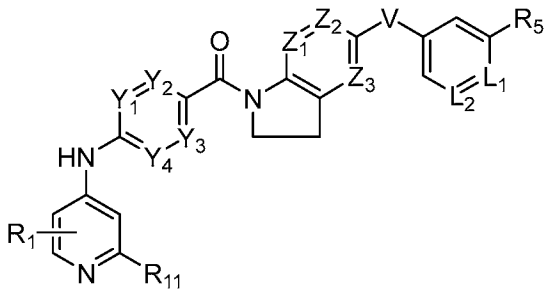
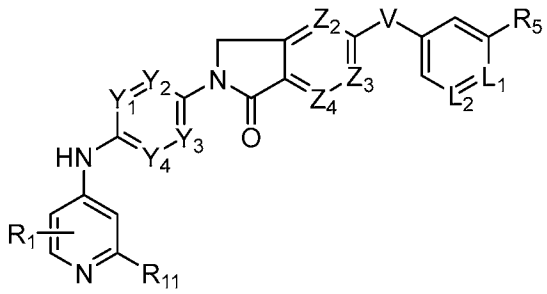
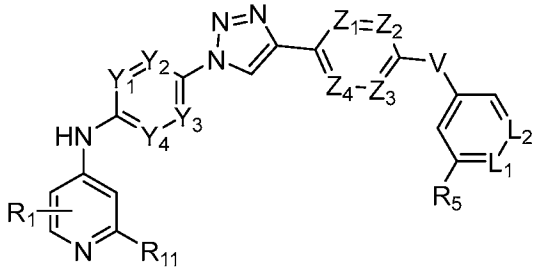
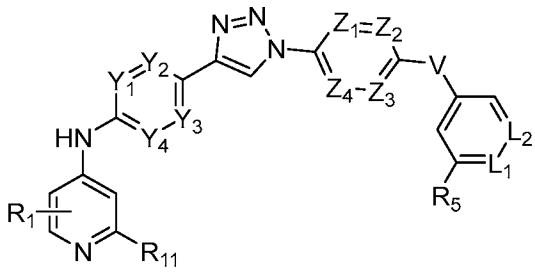



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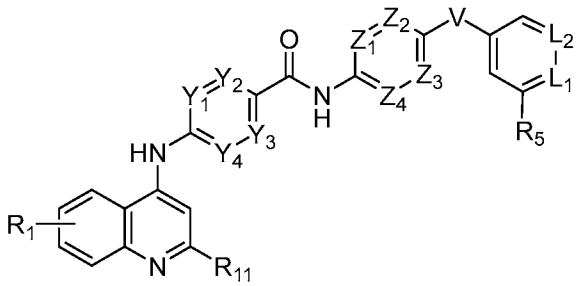
where R_1 is H, (C_1-C_6)alkyl, N(R_a)$_2$, (C_3-C_7)heterocycloalkyl, or halogen; R_5 and R_{11} are each independently H, halogen, or CH_3; Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, Z_3, Z_4, L_1, and L_2 are each independently CH or N; and V is NH or O. In some embodiments, the compound of Formula Ia has the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

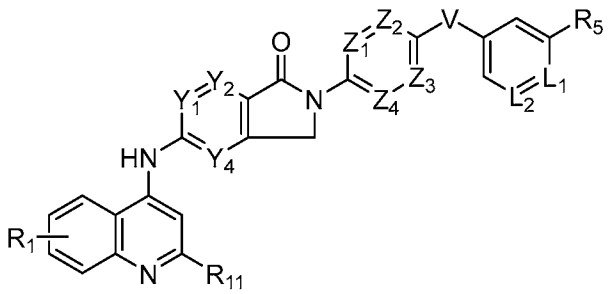

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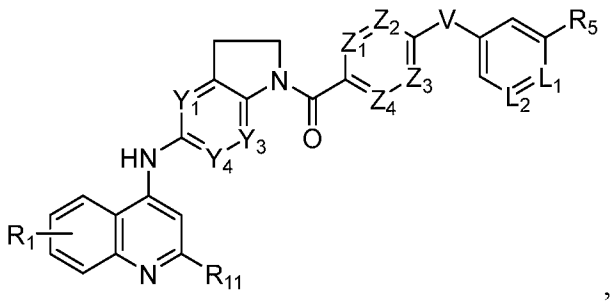

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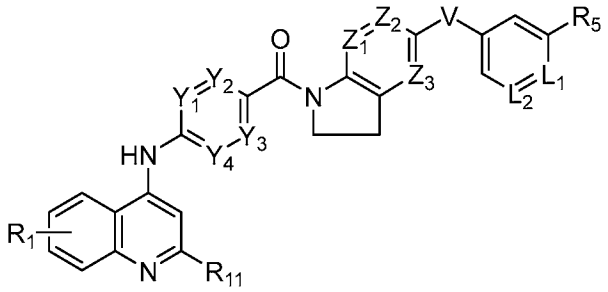

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where R_1 is H, (C_1-C_6)alkyl, $N(R_a)_2$, (C_3-C_7)heterocycloalkyl, or halogen; R_5 and R_{11} are each independently H, halogen, or CH_3; Y_1, Y_2, Y_3, Y_4, Z_1, Z_2, Z_3, Z_4, L_1, and L_2 are each independently CH or N; and V is NH or O. In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

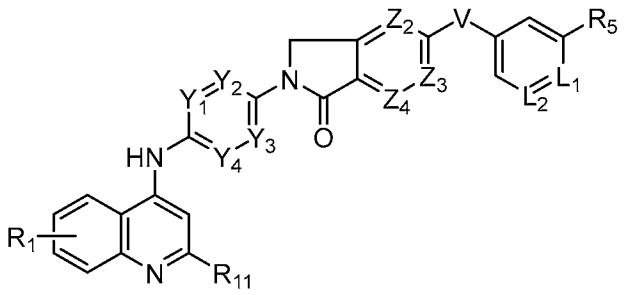

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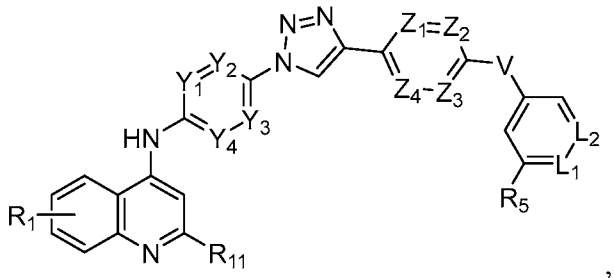

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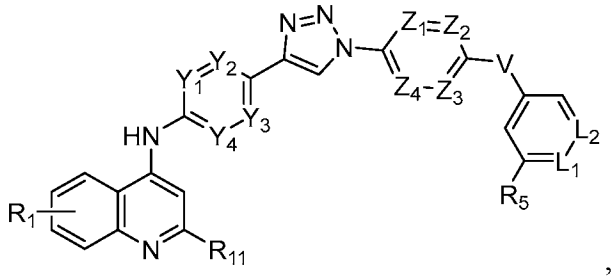
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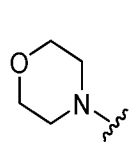
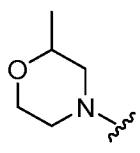


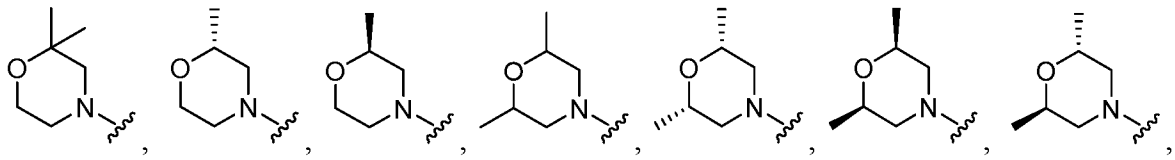
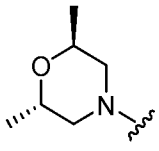
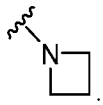
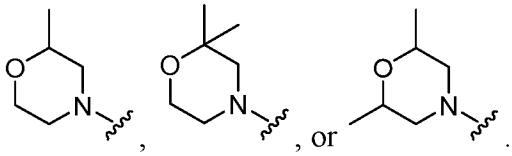
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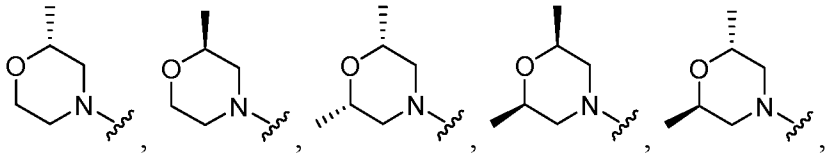


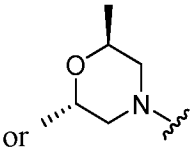
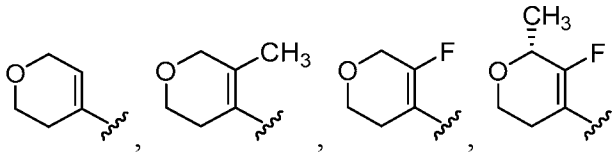
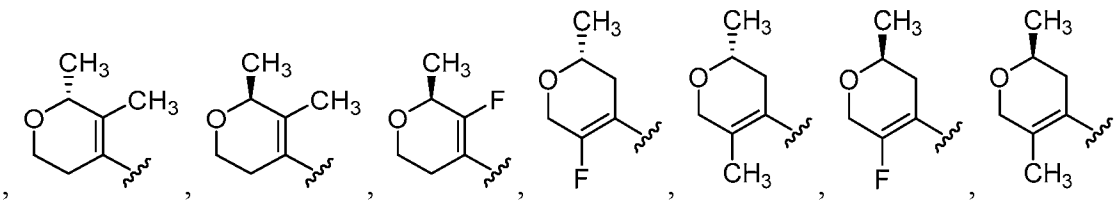
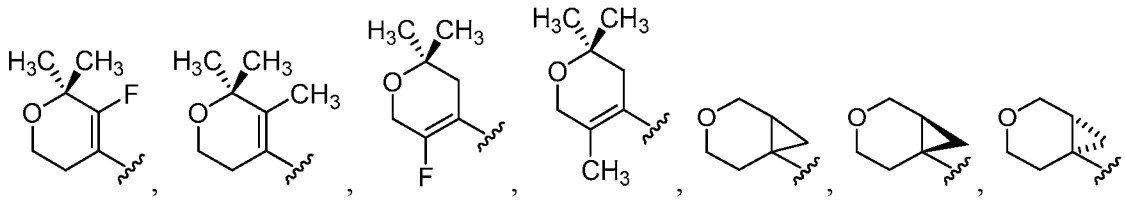
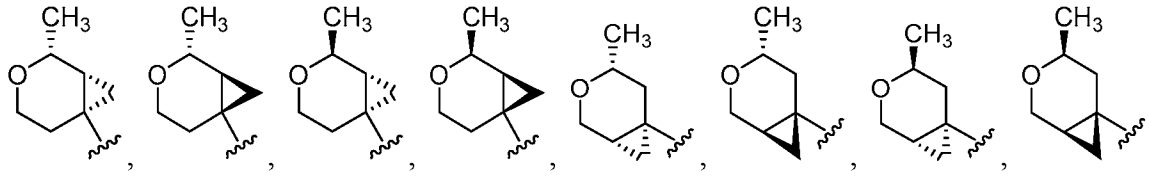
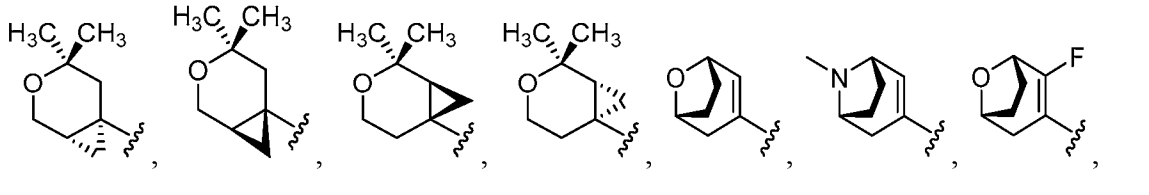
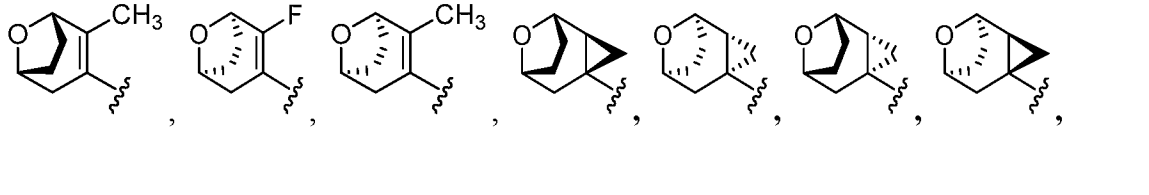
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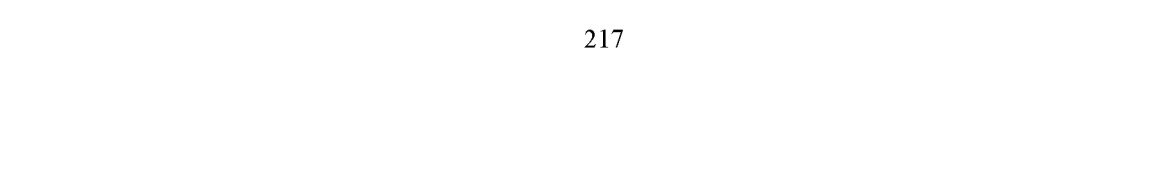


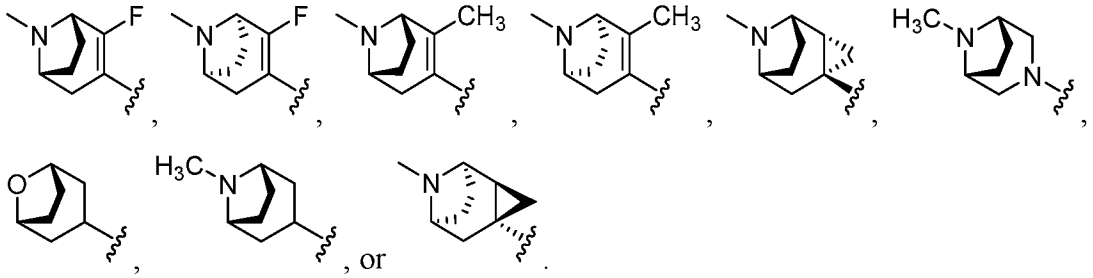
, where R_1 is H, $(C_1\text{-}C_6)$alkyl, $N(R_a)_2$, $(C_3\text{-}C_7)$heterocycloalkyl, halogen, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, or $(C_4\text{-}C_{14})$heterotricycloalkenyl; R_5 and R_{11} are each independently H, halogen, 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 $CH(CH_3)_2$, , ,




. In some embodiments, R_1 is

.

In some embodiments, R_1 is

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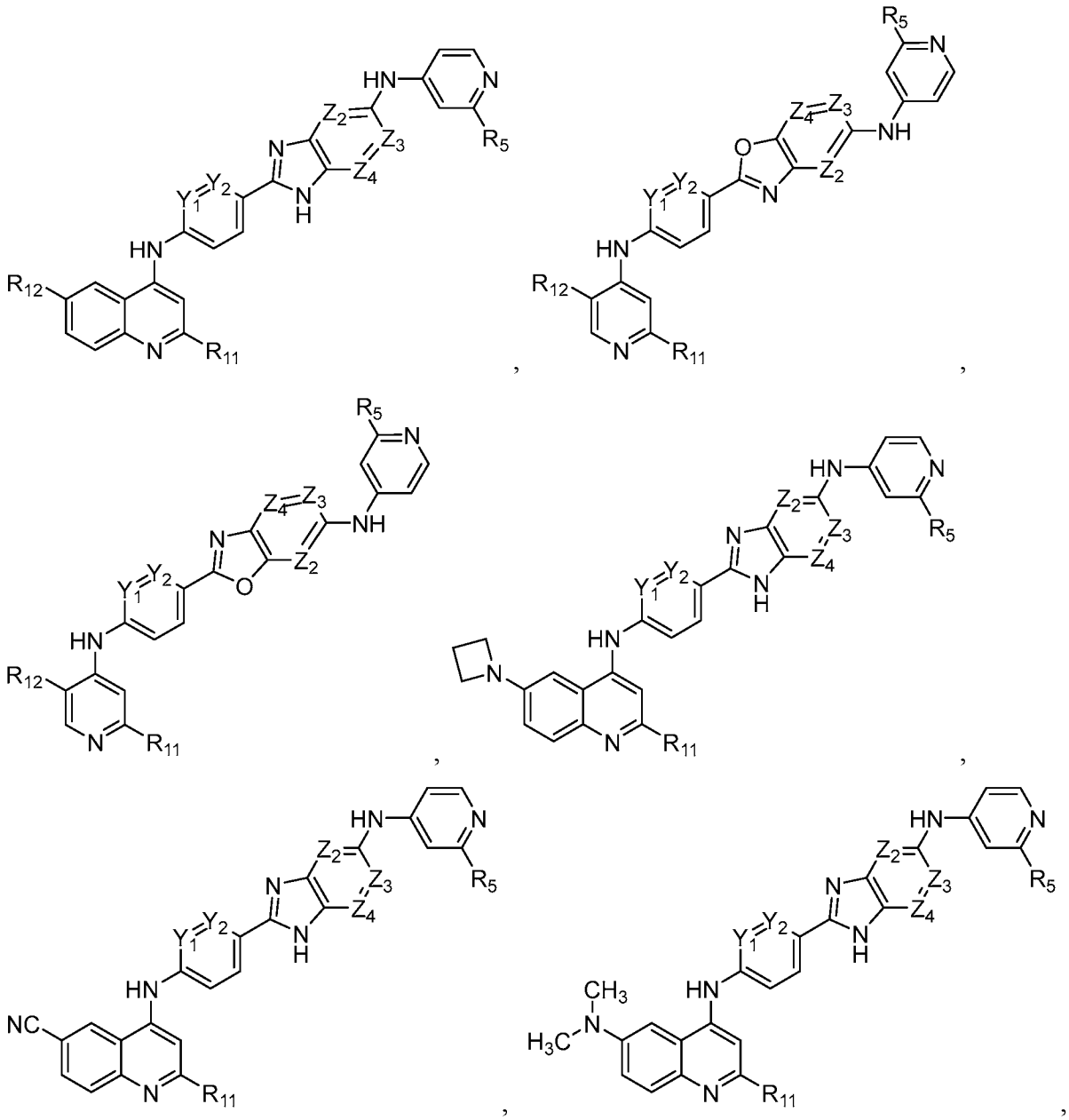

. In some embodiments, R_1 is







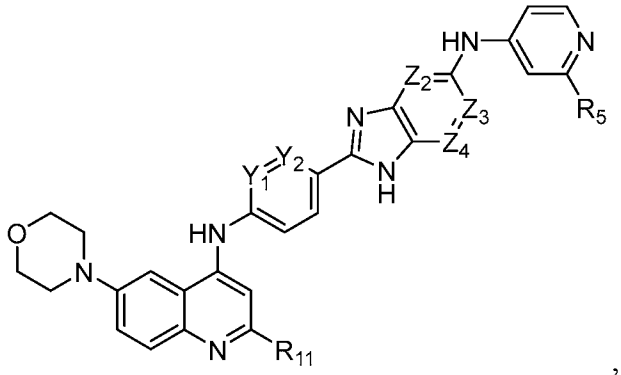




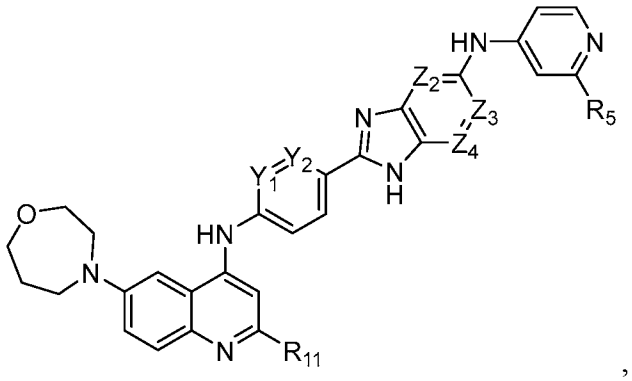
, or .

[0348] In some embodiments, the compound of Formula Ib has the structure of

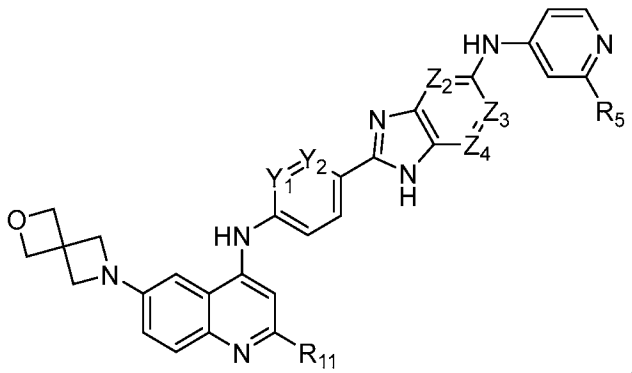




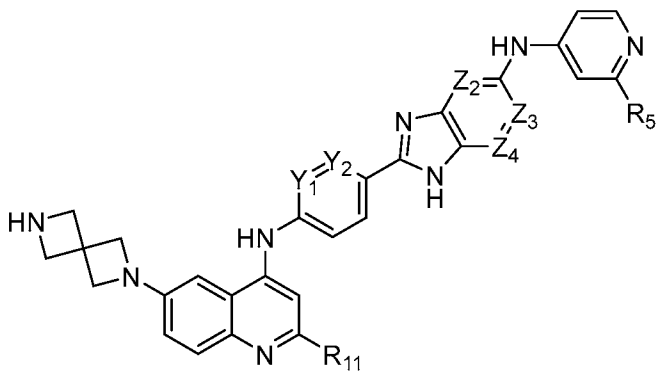
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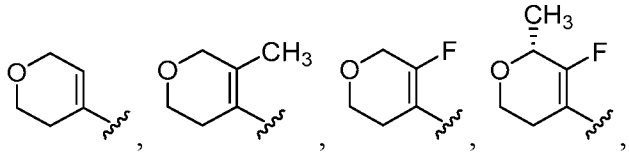


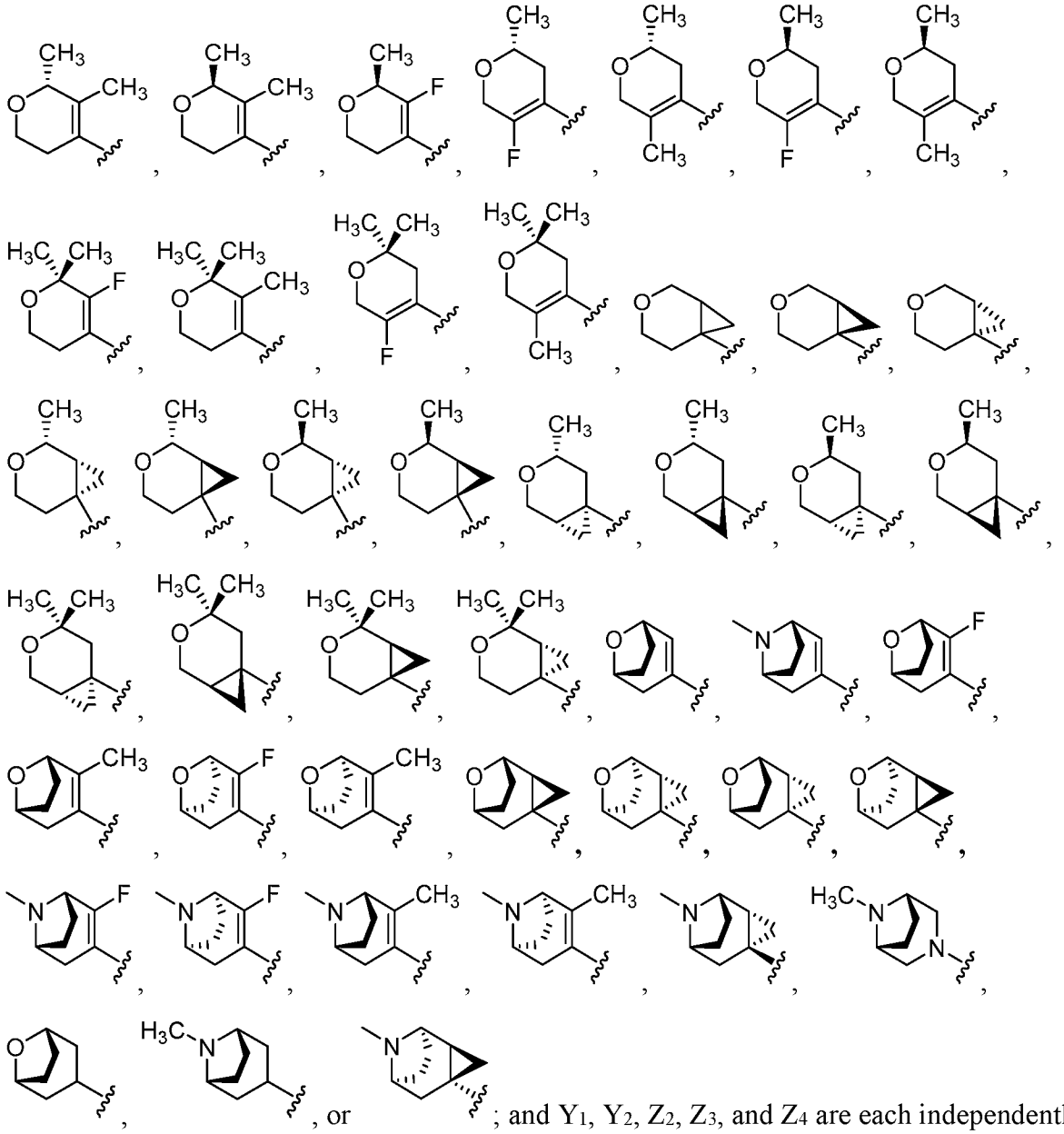
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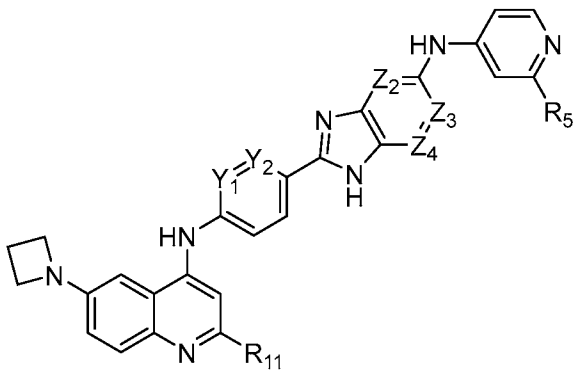
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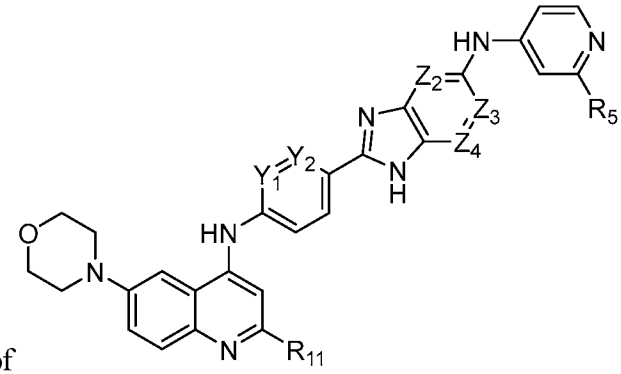
, where R_{11} and R_5 are each independently H, halogen, or CH_3; R_{12} is H, halogen, CH_3, ,

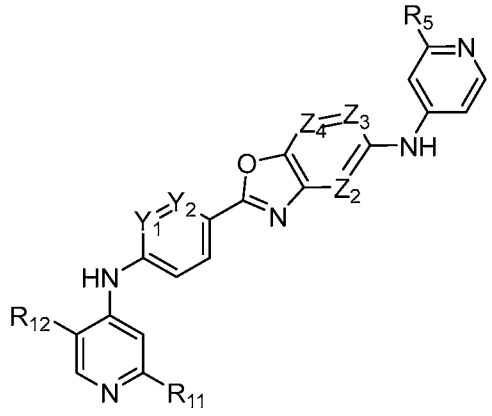
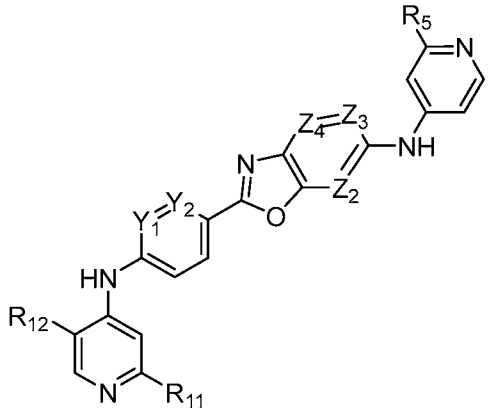


; and Y_1, Y_2, Z_2, Z_3, and Z_4 are each independently CH or N. In some embodiments, the compound of Formula Ib has the structure of

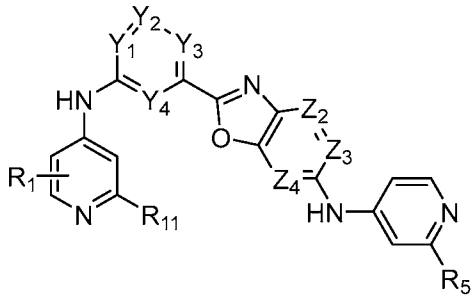
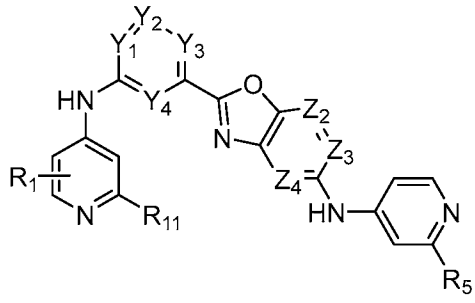


, where R_{11} and R_5 are each independently H or CH_3; and Y_1, Y_2, Z_2, Z_3, and Z_4 are each independently CH or N. In some embodiments, the

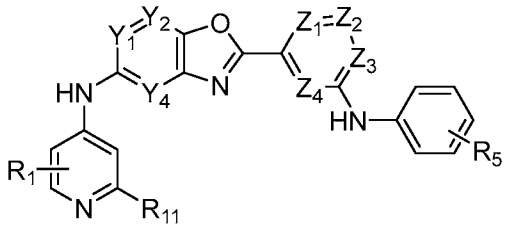
compound of Formula Ib has the structure of ,

where R_{11} and R_5 are each independently H or CH_3; and Y_1, Y_2, 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  or ,

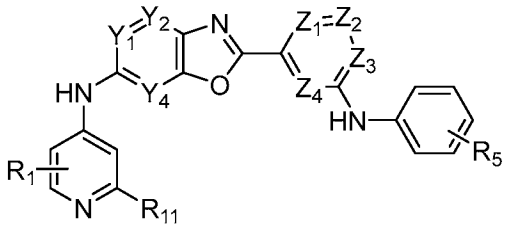
wherein R_{11} and R_5 are each independently H, halogen, or CH_3; R_{12} is H, halogen, CH_3; and Y_1, Y_2, Z_2, Z_3, and Z_4 are each independently CH or N.

[0349] In some embodiments, the compound of Formula IIb has the structure of  or , wherein R_1, R_5, and R_{11} are each independently H, halogen, 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.

[0350] In some embodiments, the compound of Formula IIc has the structure of

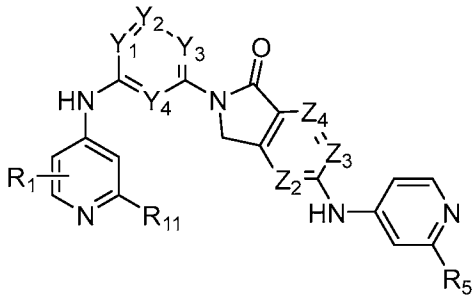


or



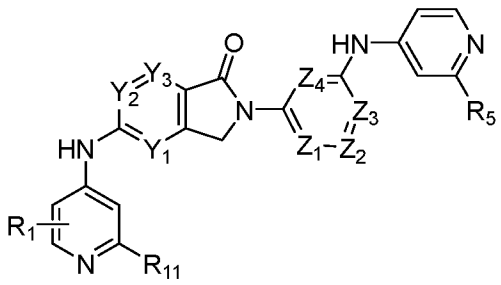
, wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_4, Z_1, Z_2, Z_3, and Z_4 are each independently CH or N.

[0351] In some embodiments, the compound of Formula IIIa has the structure of



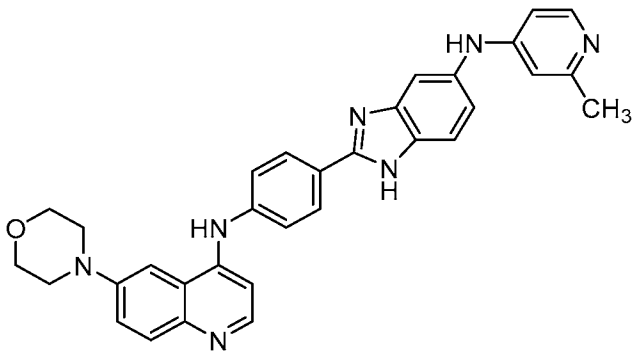
, wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_3, Y_4, Z_2, Z_3, and Z_4 are each independently CH or N.

[0352] In some embodiments, the compound of Formula IVa has the structure of

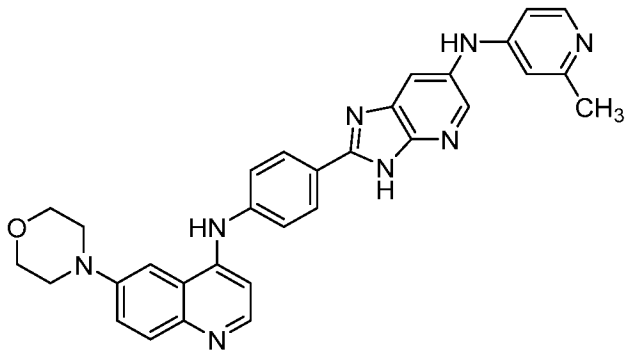


, wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_3, Z_1, Z_2, Z_3, and Z_4 are each independently CH or N.

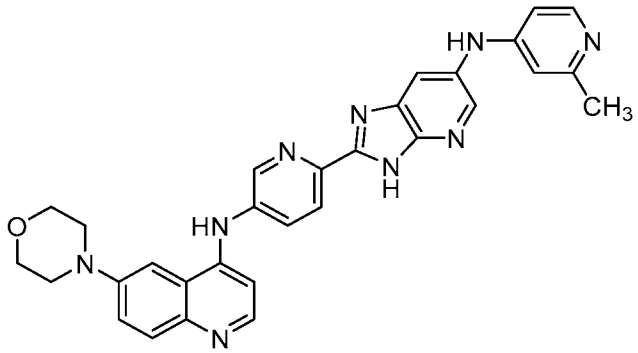
[0353] In some embodiments, the compound of Formula Ia, Ib, or Ic activates Akt3 and is selected from the group consisting of



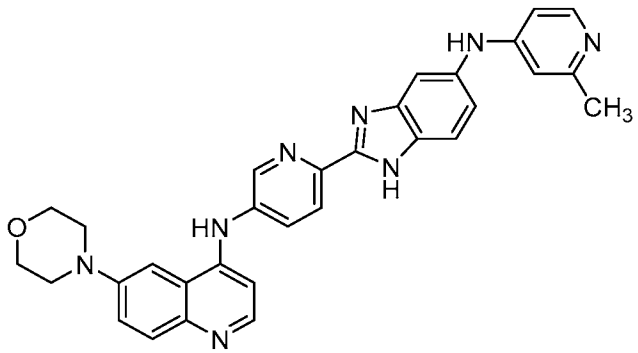
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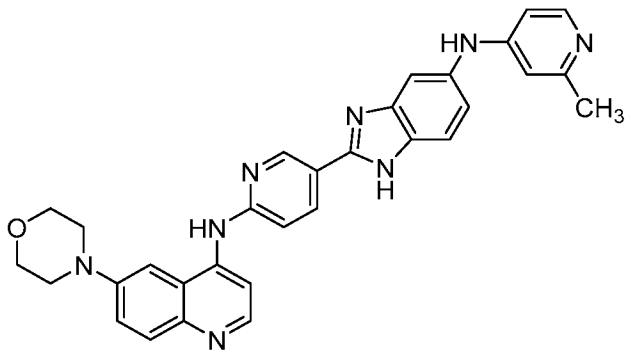
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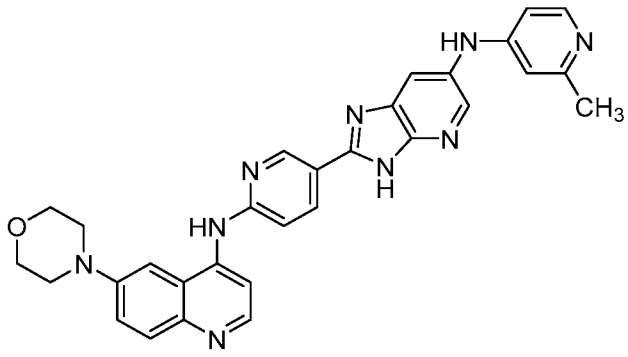
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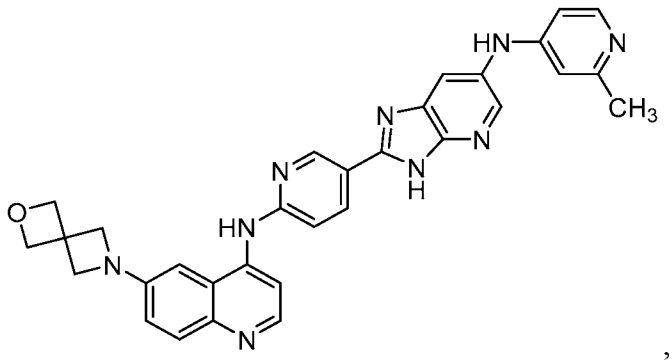
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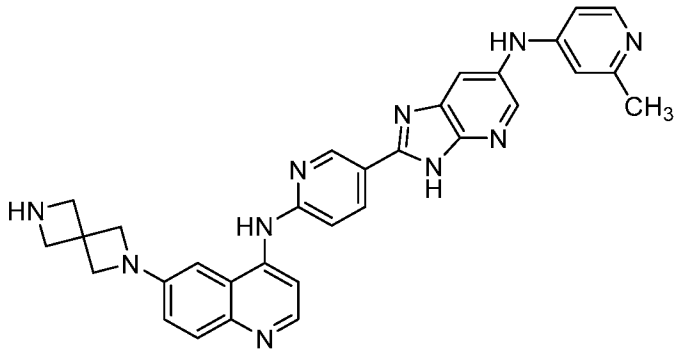
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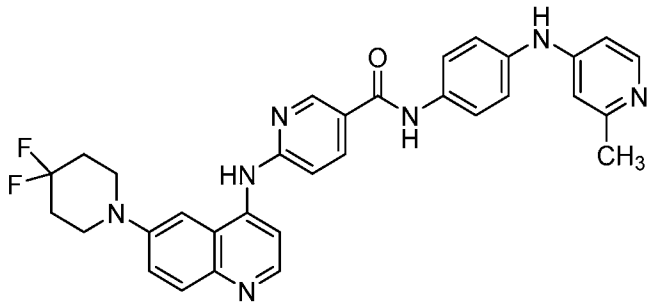
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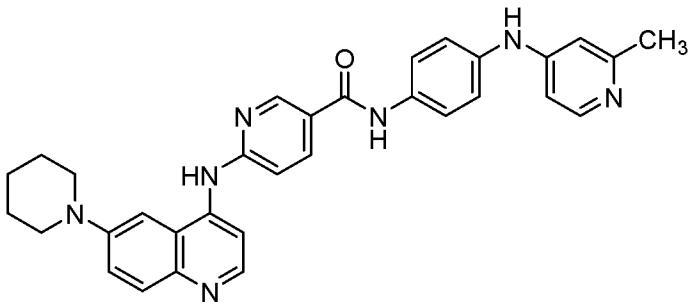
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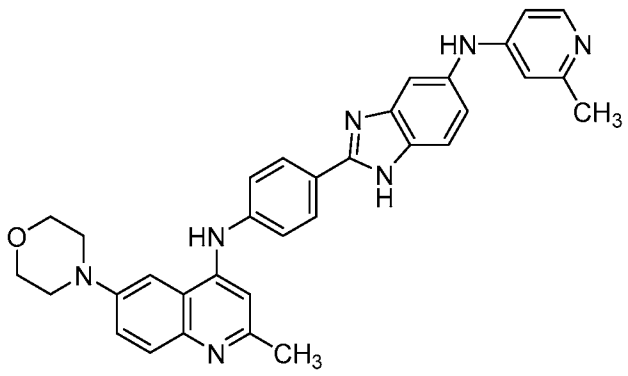
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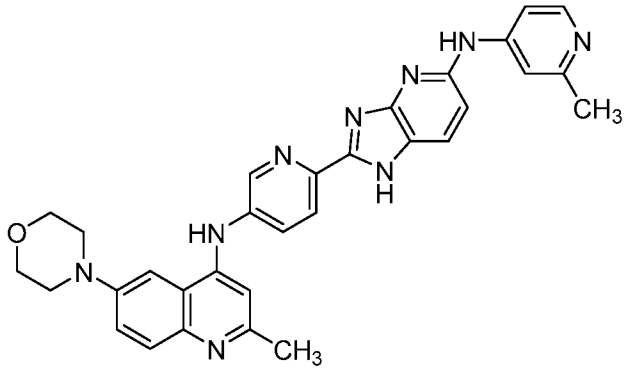
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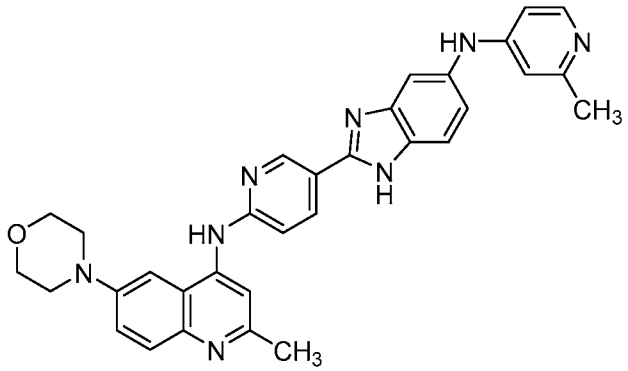
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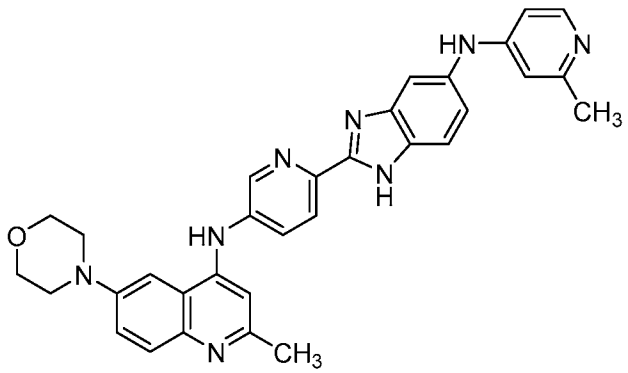
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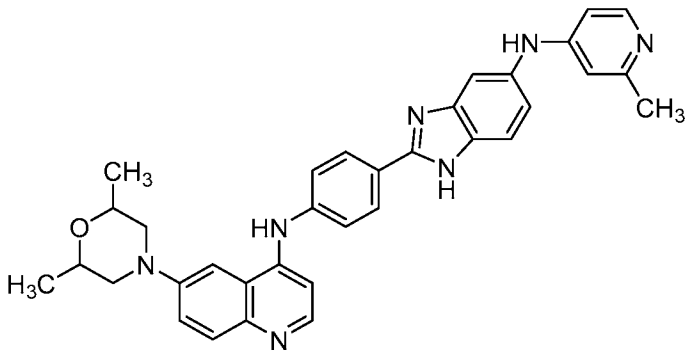
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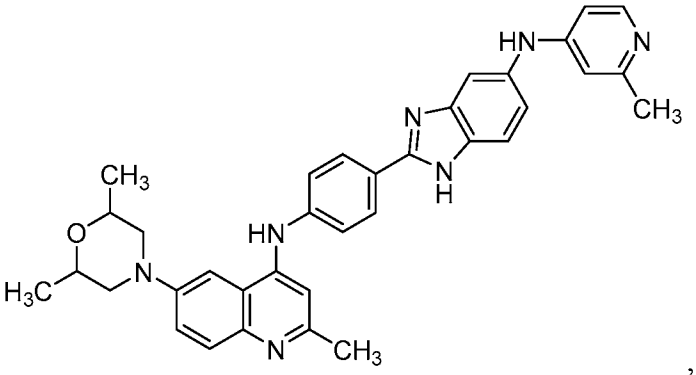
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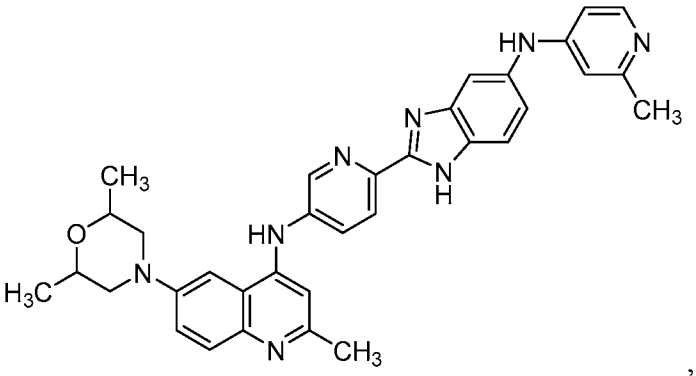
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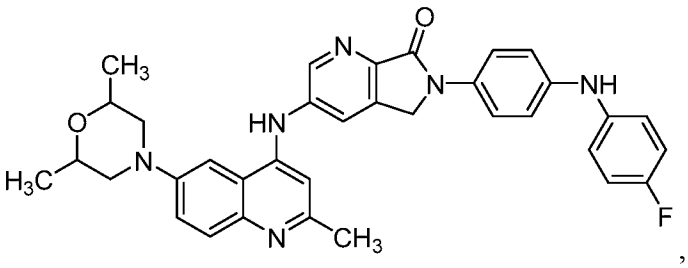
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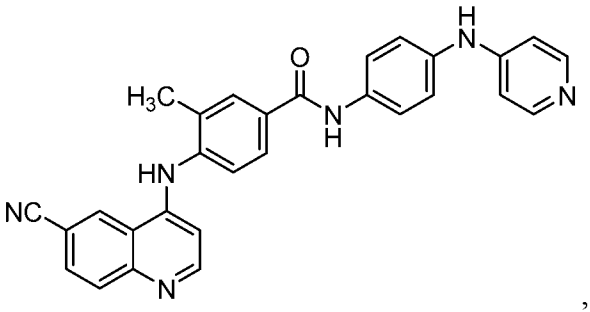
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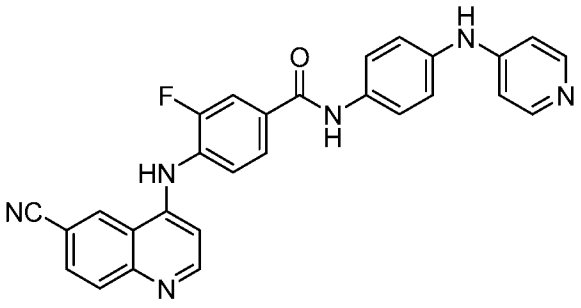
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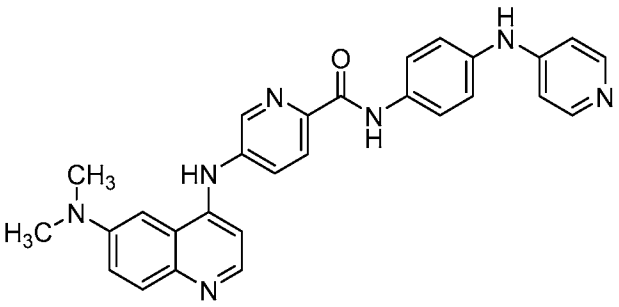
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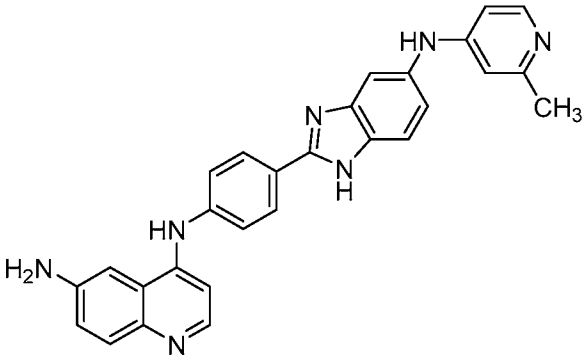
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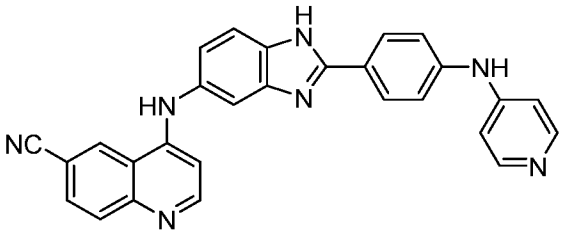
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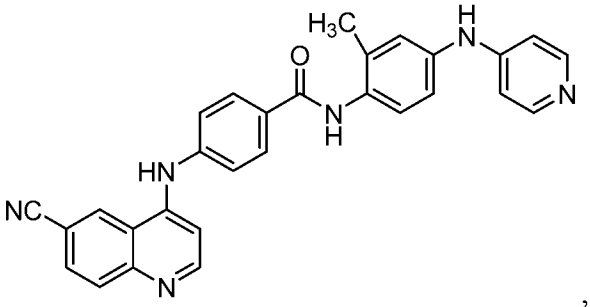
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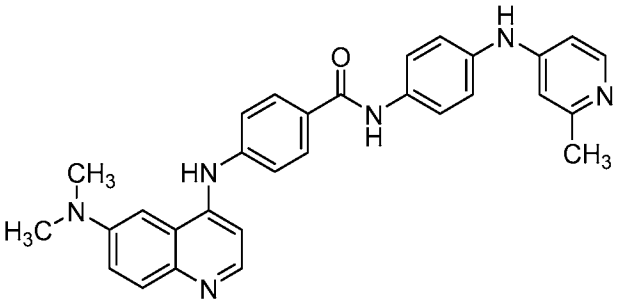
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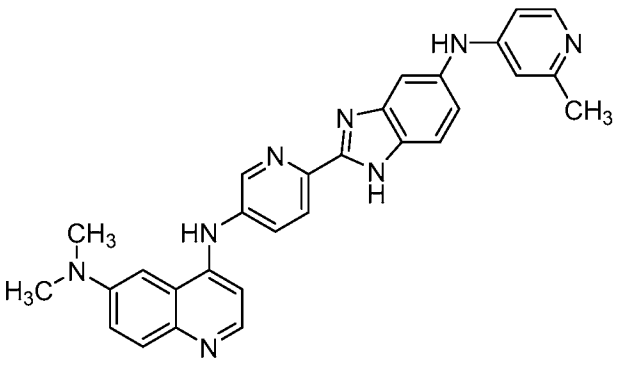
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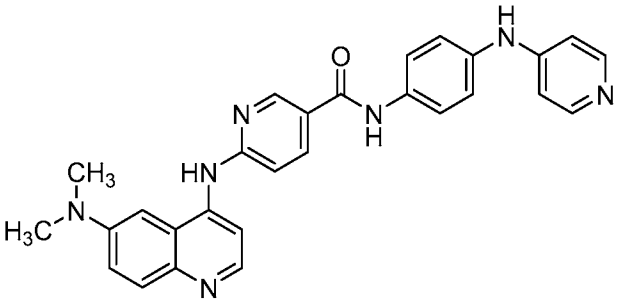
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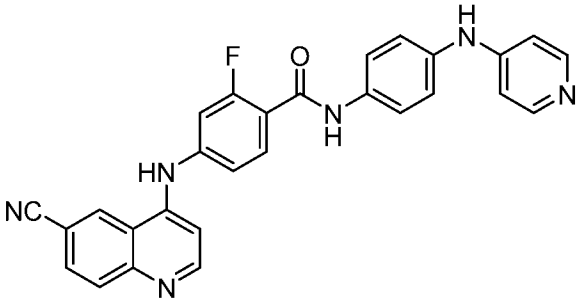
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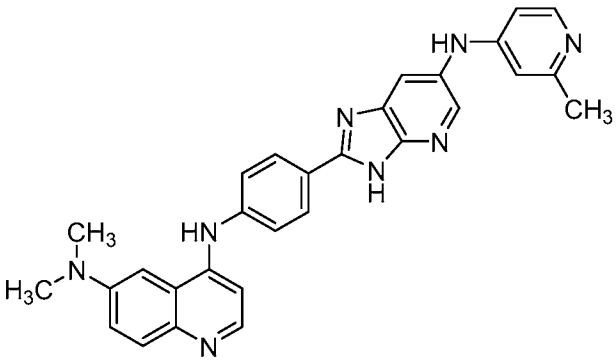
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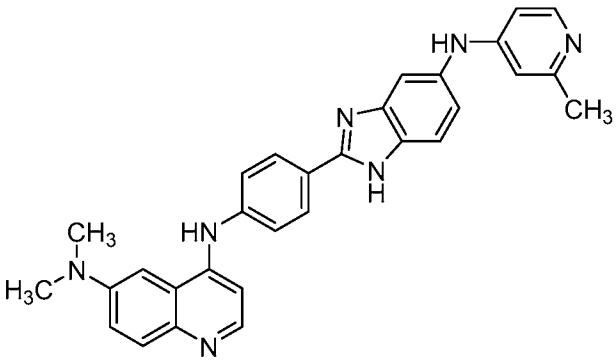
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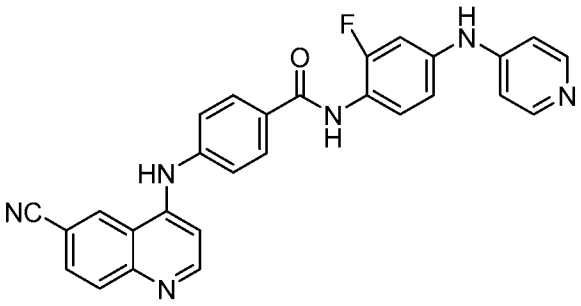
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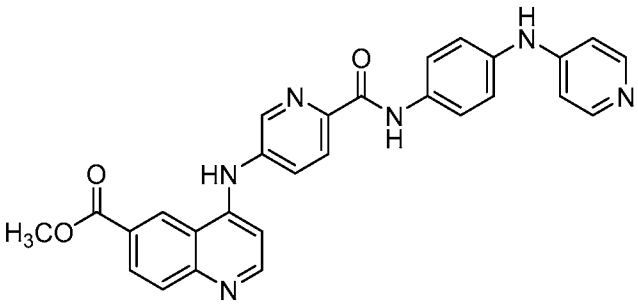
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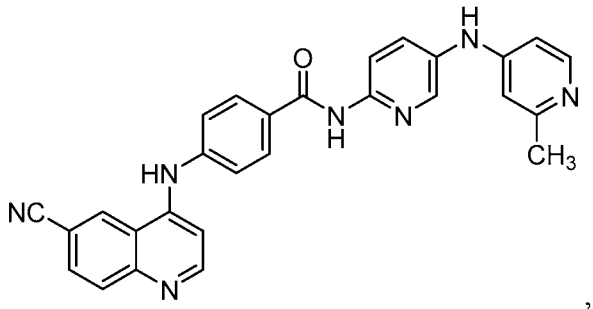
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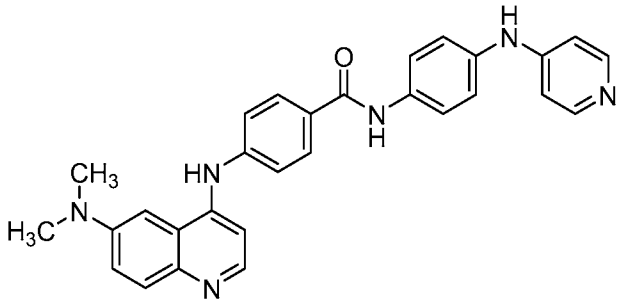
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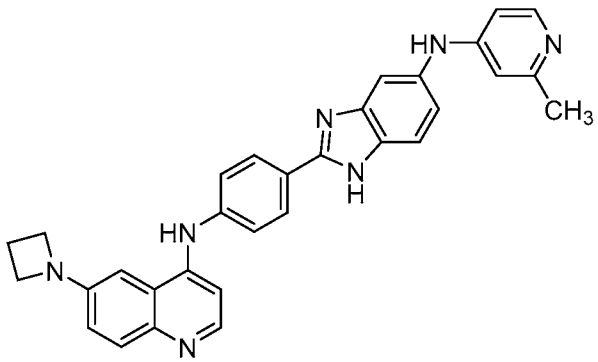
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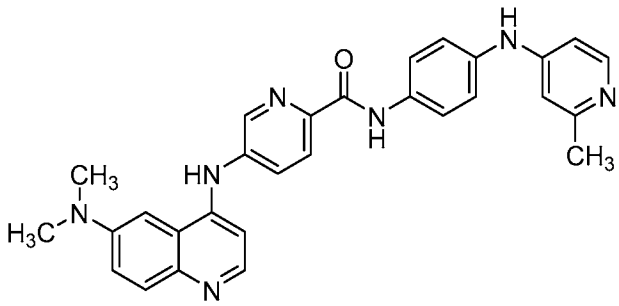
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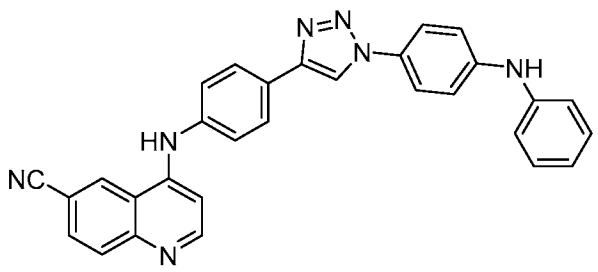
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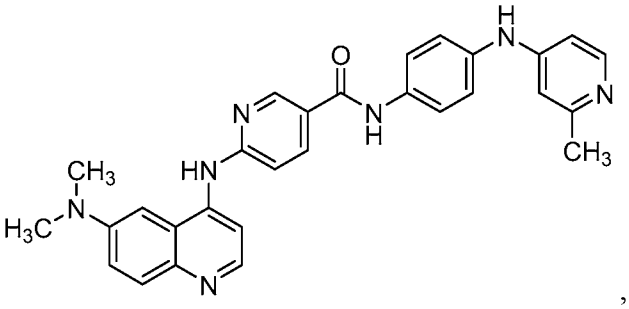
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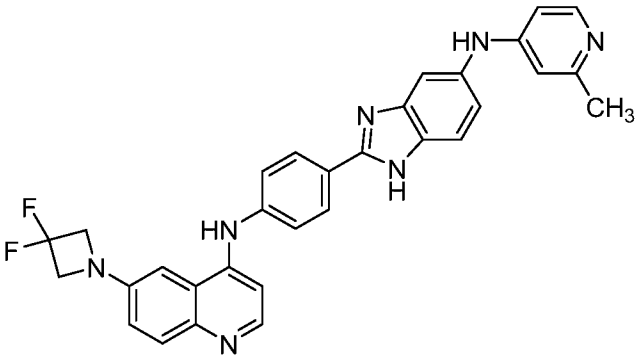
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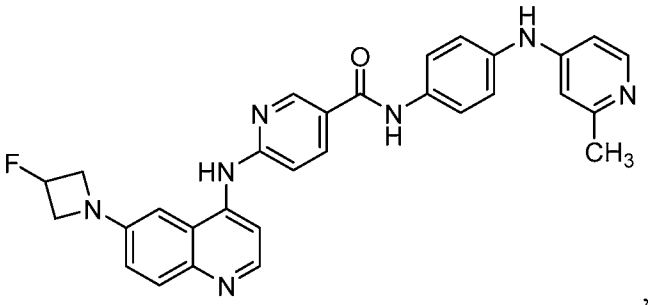
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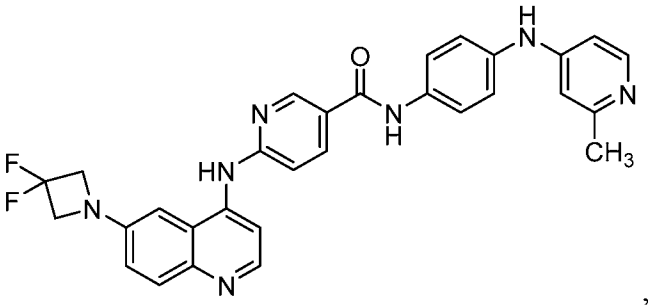
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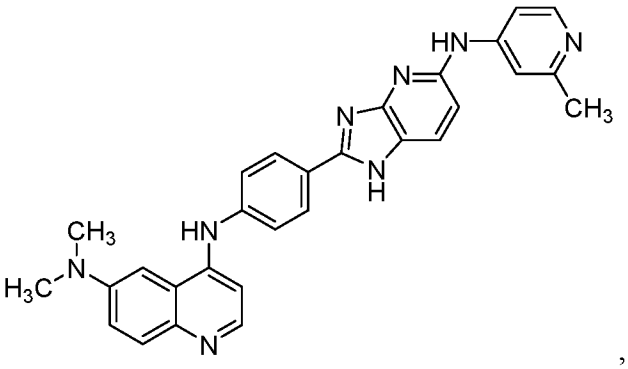
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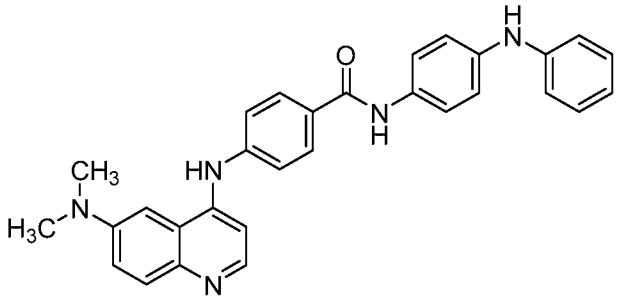
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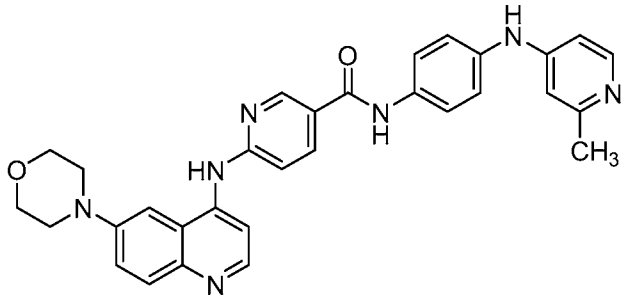
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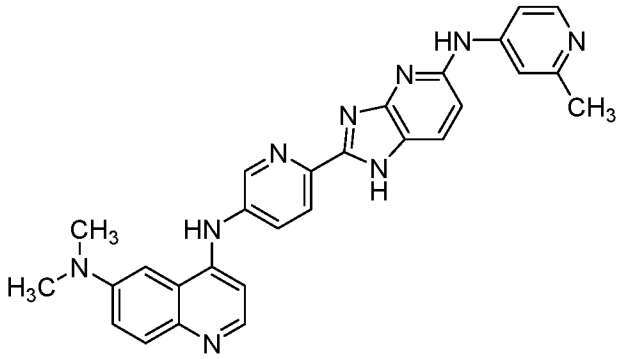
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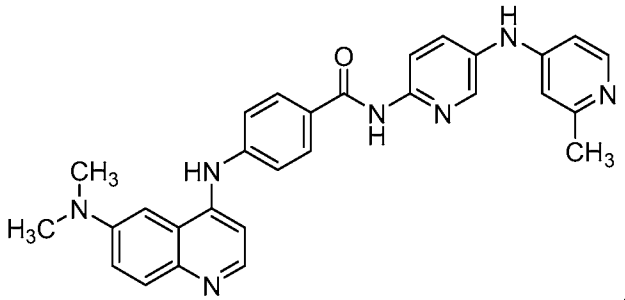
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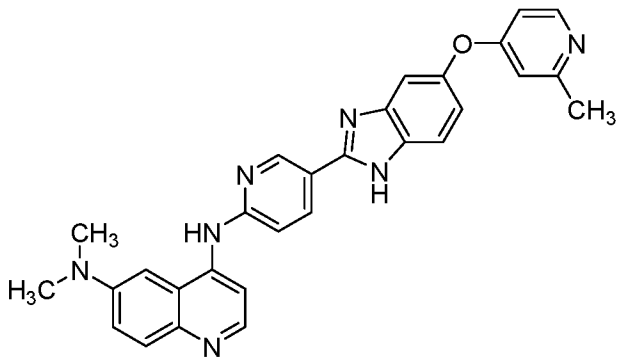
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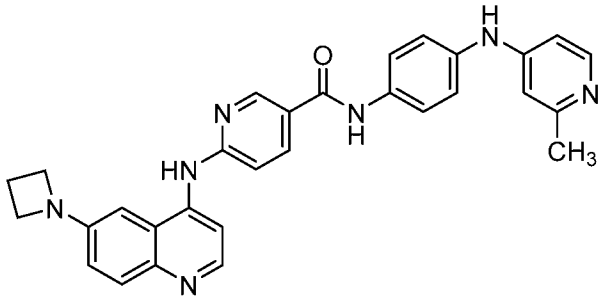
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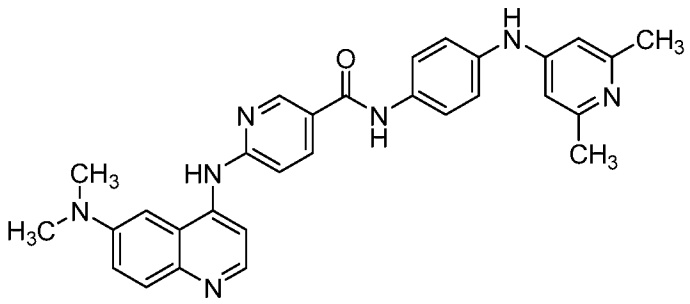
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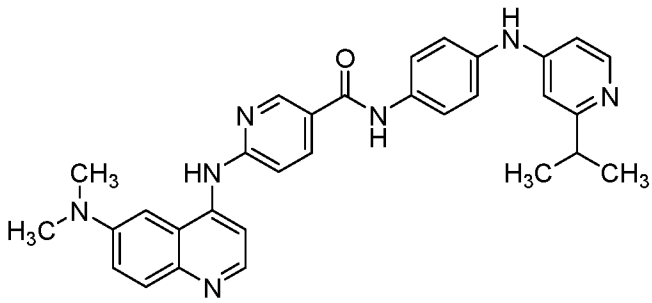
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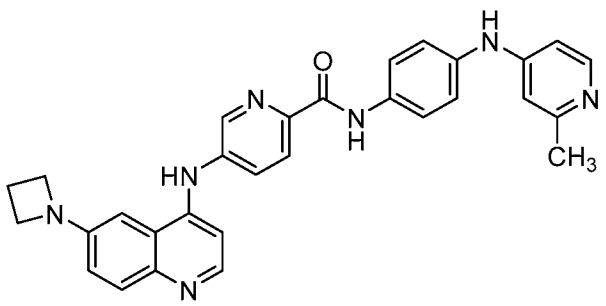
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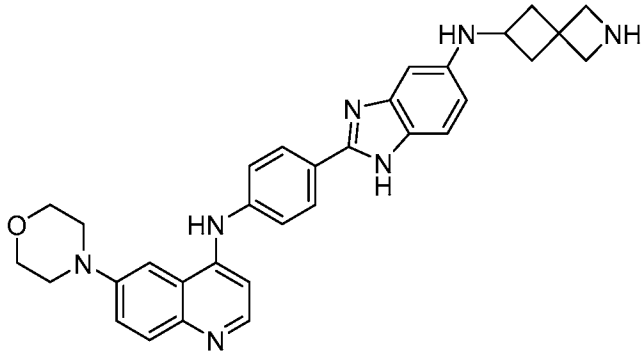
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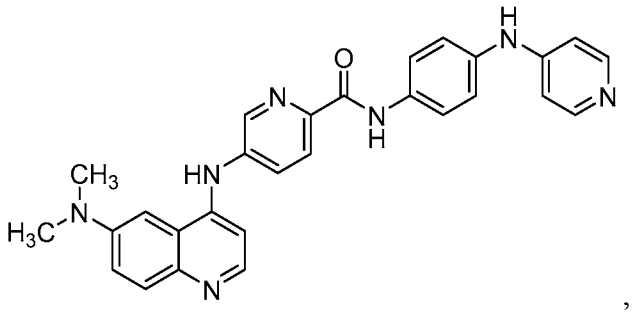
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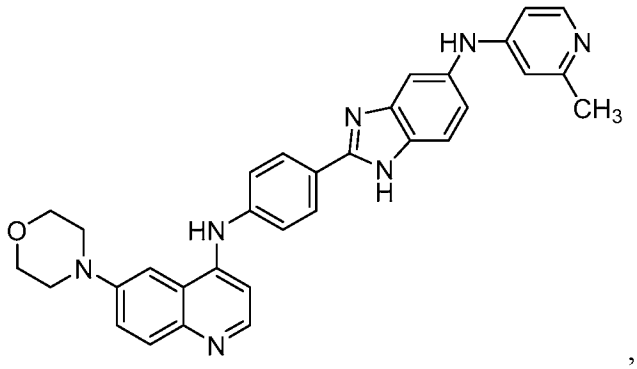
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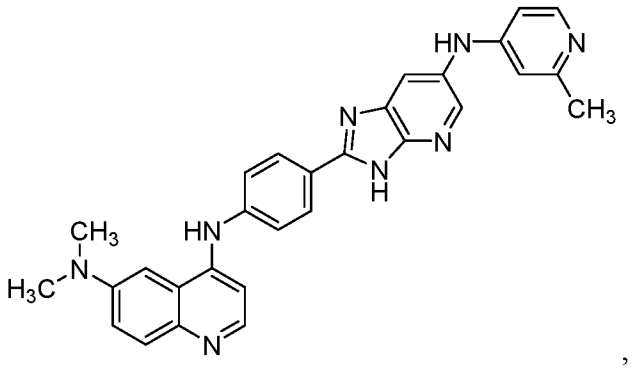
. In some embodiments, the compound of Formula Ia, Ib, or Ic activates Akt3 and is selected from the group consisting of



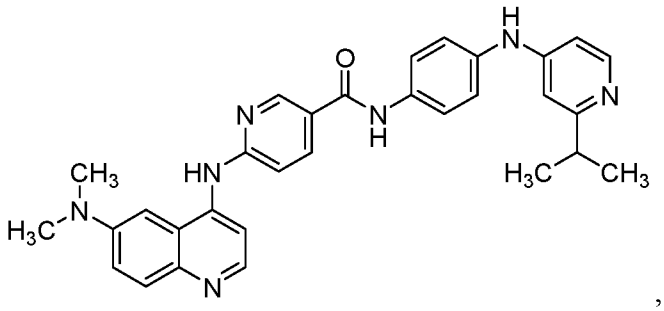
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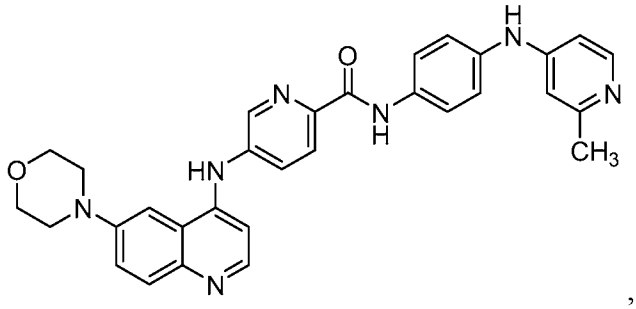
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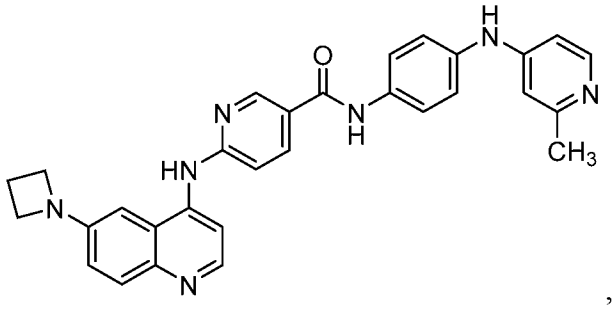
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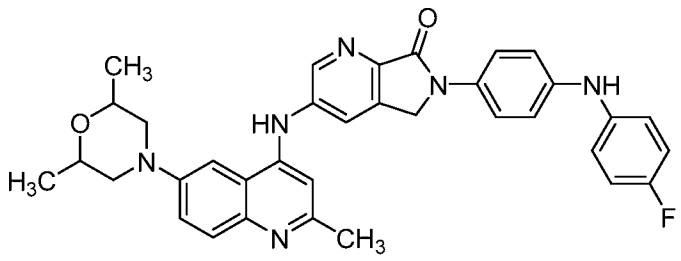
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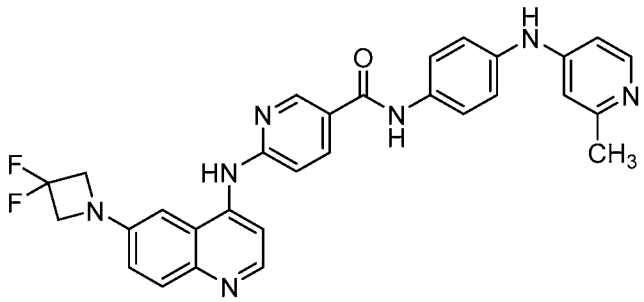
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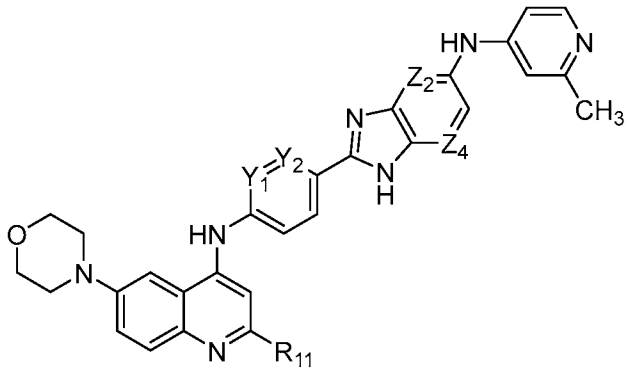
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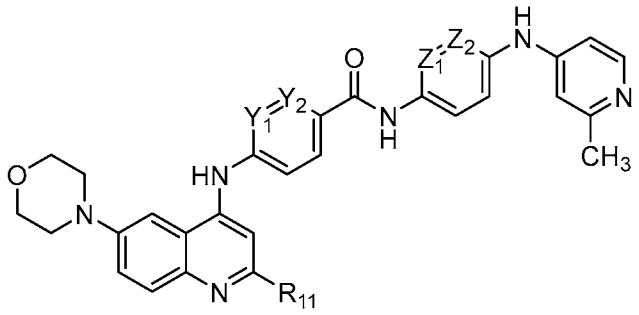
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. In some embodiments, the compound of Formula Ia, Ib, or Ic activates Akt3 and is selected from the group consisting of



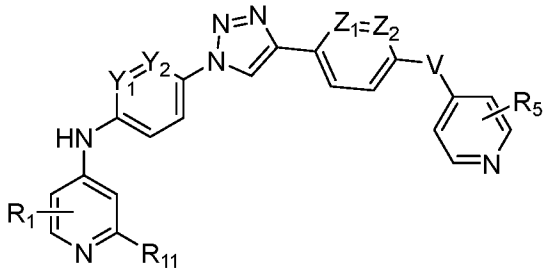
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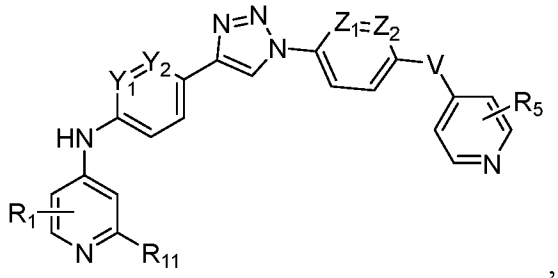


, where R_{11} is (C_1-C_6)alkyl and Y_1, Y_2, Z_1, Z_2, and Z_4 are each independently CH or N. In some embodiments, R_{11} is methyl. In some embodiments, the compound of Formula Ia, Ib, or Ic activates Akt3 and is selected from the

group consisting of Compounds 2, 4-7, 10-11, 15, 18-19, 24, 53, 55, 57, 62, 68-70, 77-79, 83-84, 87-88, 90-92, 96-97, 102, 110-111, 120-123, 125-129, 135, and 138 as shown in Table 2.

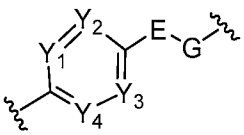
[0354] In some embodiments, the compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc inhibits Akt3 and is selected from the group consisting of

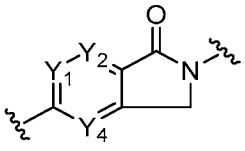


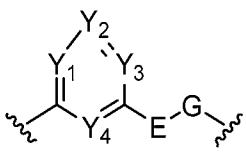
or


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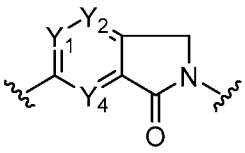
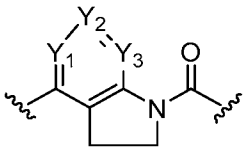
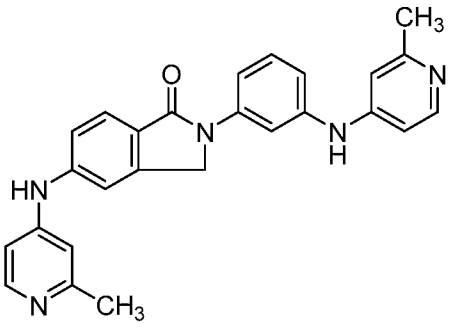
where R_1 is H, (C_1-C_6)alkyl, or halogen; R_5 and R_{11} are independently H or (C_1-C_6)alkyl; Y_1, Y_2, Z_1, and Z_2 are each independently CH or N; and V is NH or O. In some embodiments, R_1 is H, methyl, F, or Cl. In some embodiments, R_5 and R_{11} are independently H or methyl. In some embodiments, the compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc inhibits Akt3 and is Compound 3 or 137 as shown in Table 1.

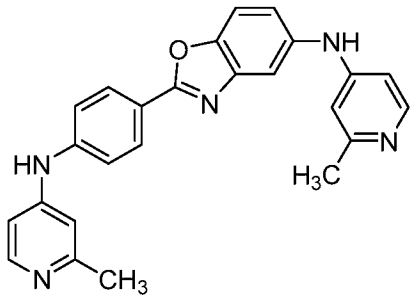
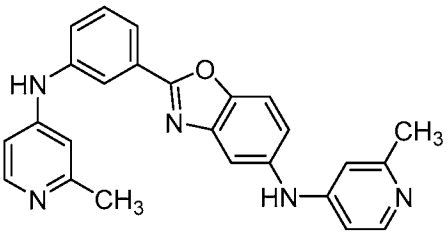
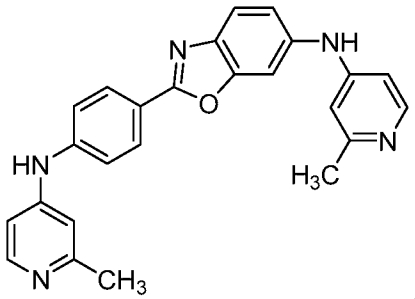
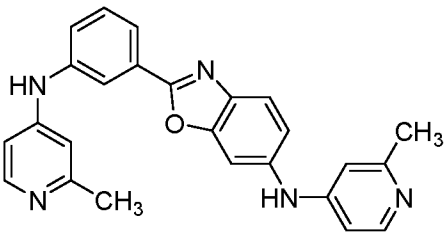
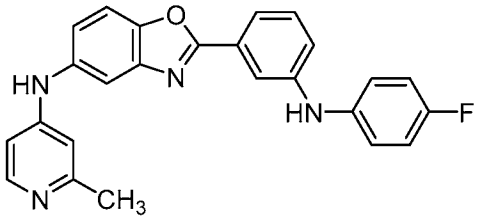
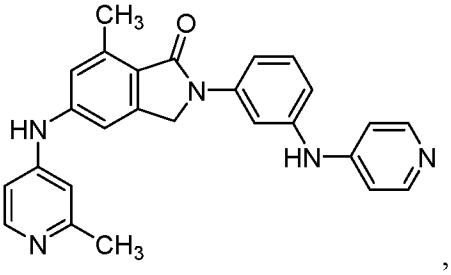
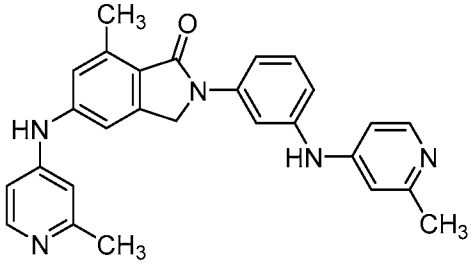
[0355] In some embodiments, the compound of invention modulates Akt3 having the structure of Formula Ia or IVa wherein -E-G- is –(C=O)NR_x– and R_x and Y_3 form a 5-membered heterocycle. In some embodiments, the compound of invention modulates Akt3 having the structure of Formula IIa or IIIa wherein -E-G- is –(C=O)NR_x– and R_x and Y_3 or R_x and Y_4 form a 5-membered heterocycle. In some embodiments, the compound of invention modulates Akt3 having the structure of Formula Ia or IVa wherein the structural moiety 

has a structure of 

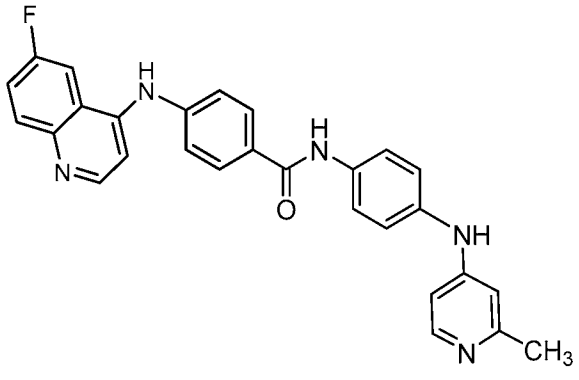
. In some embodiments, the compound of invention modulates Akt3 having the structure of Formula IIa or IIIa wherein the structural moiety the structural moiety 

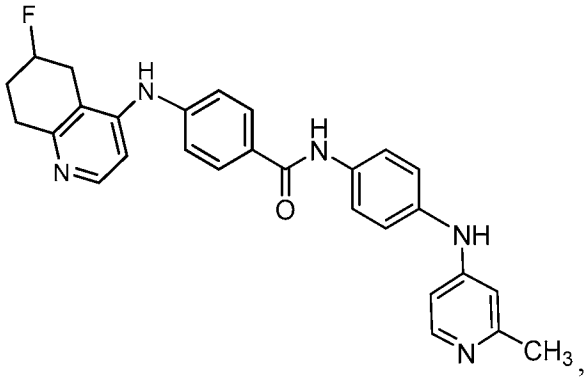
has the structure of

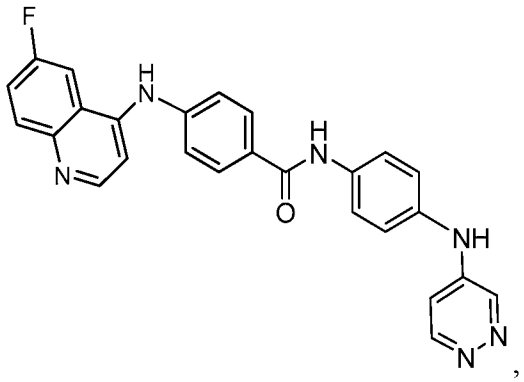

or

. In some embodiments, the compound of invention modulates Akt3 having the structure of

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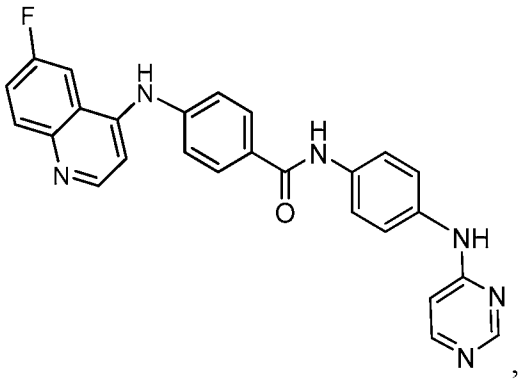
[0356] In some embodiments, the compound of Formula Ia, Ib, IIa, IIb, IIc, IIIa, or IVa, inhibits Akt3 and is selected from the group consisting of

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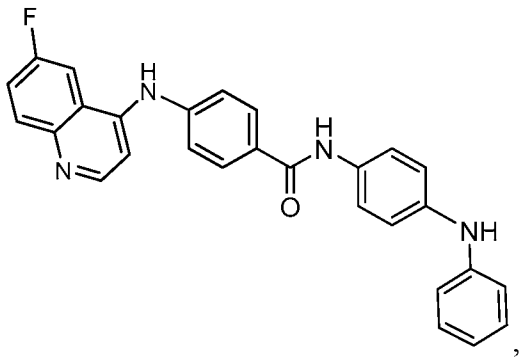
[0357] In some embodiments, the compound of Formula Ia is

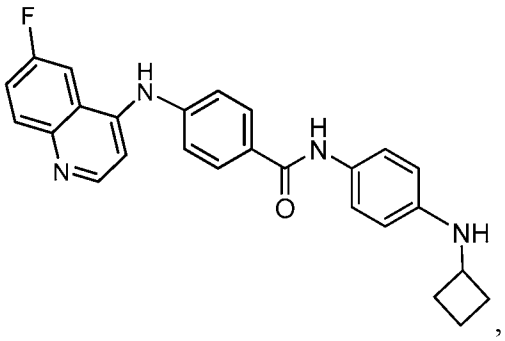


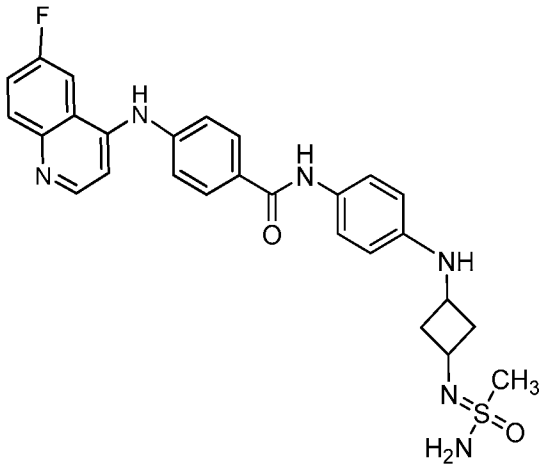


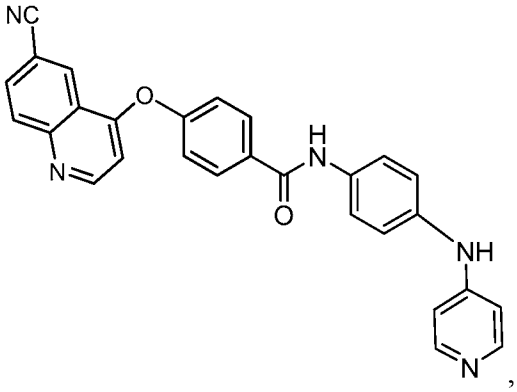


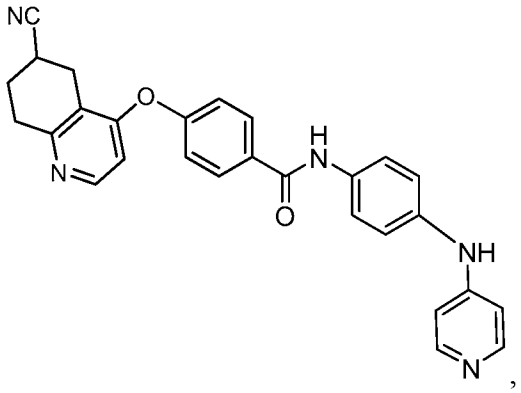


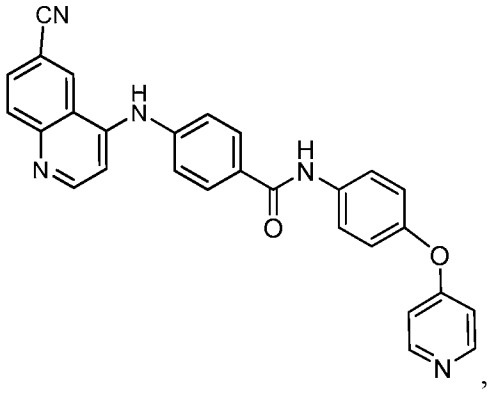


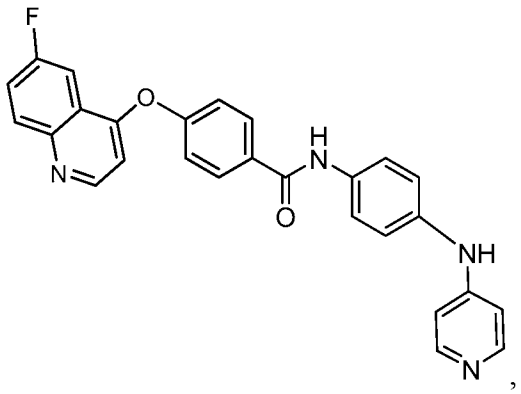


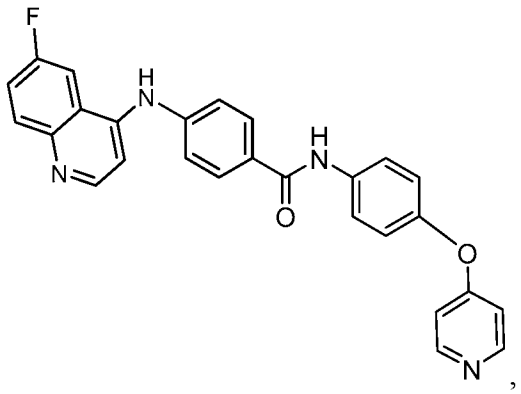


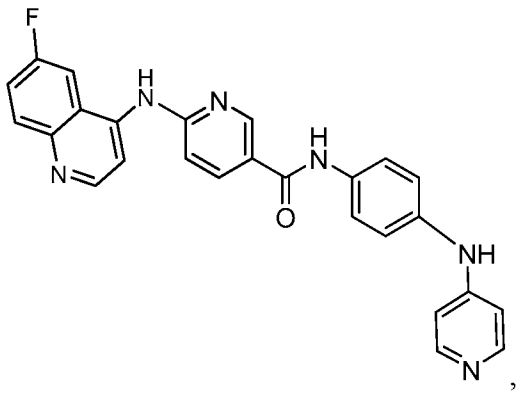


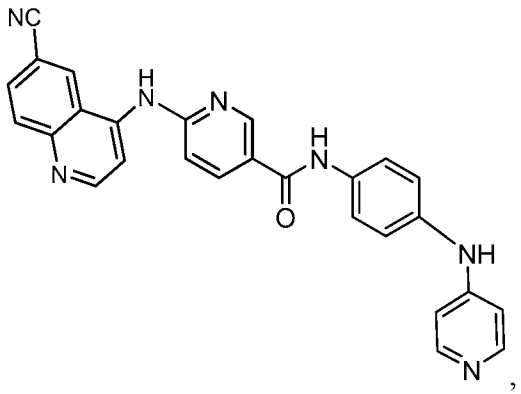


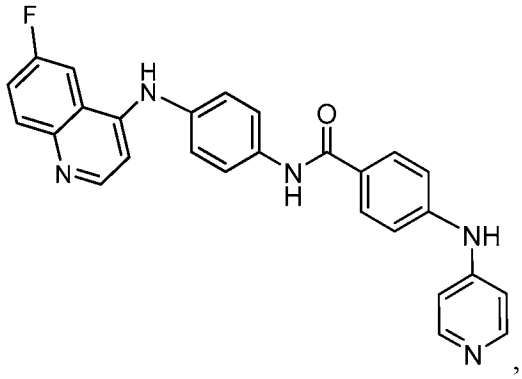


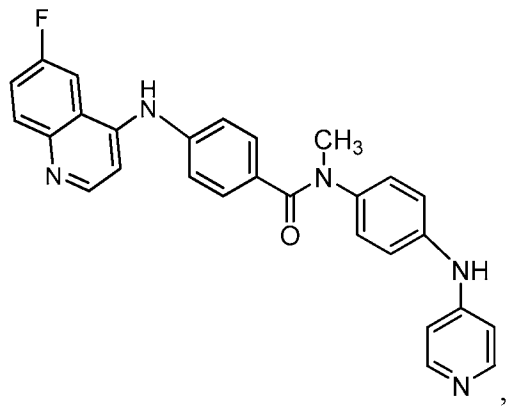


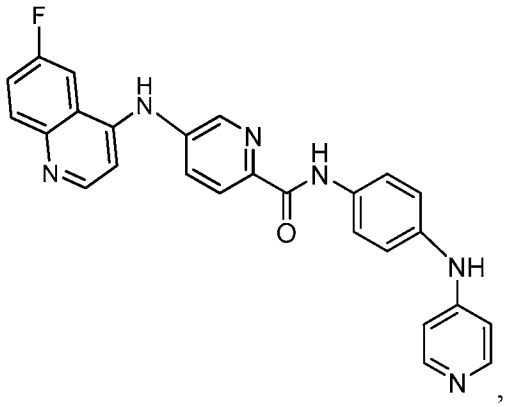
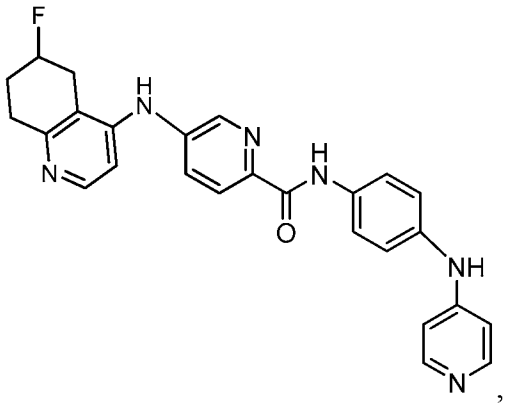
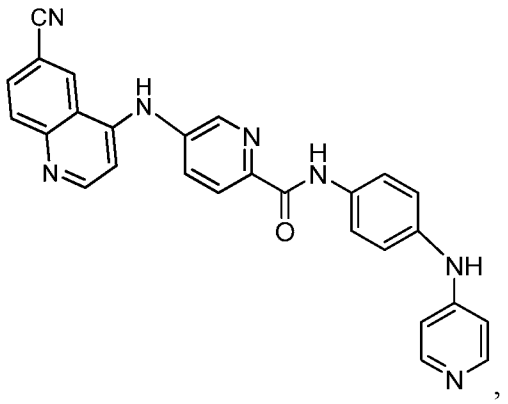
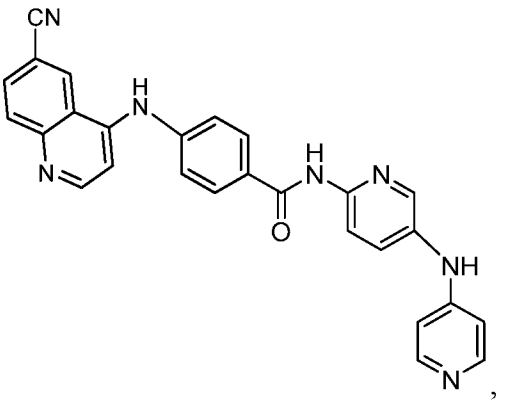
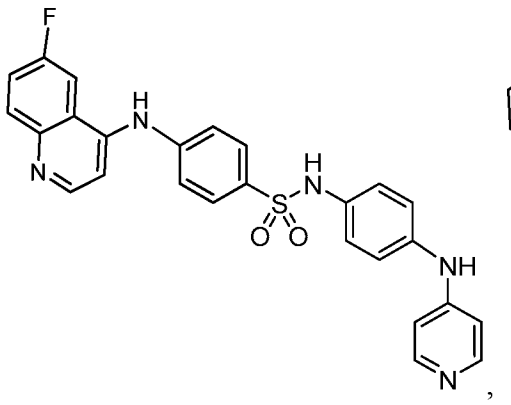
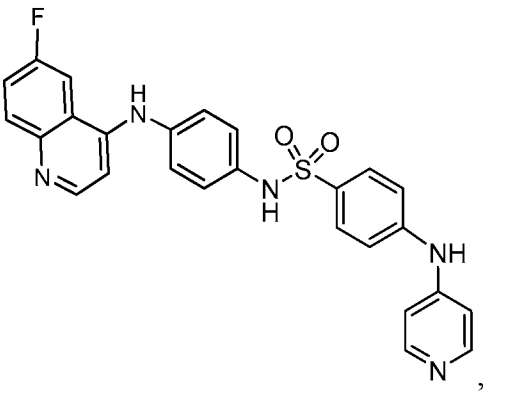
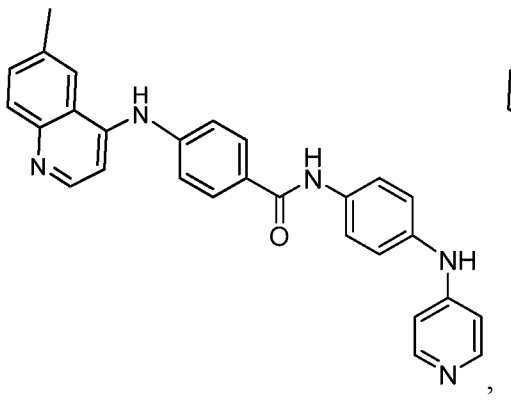
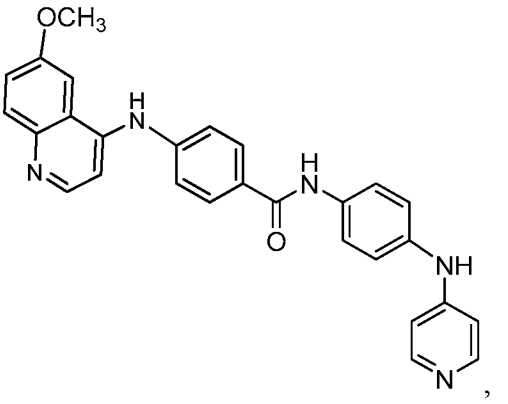


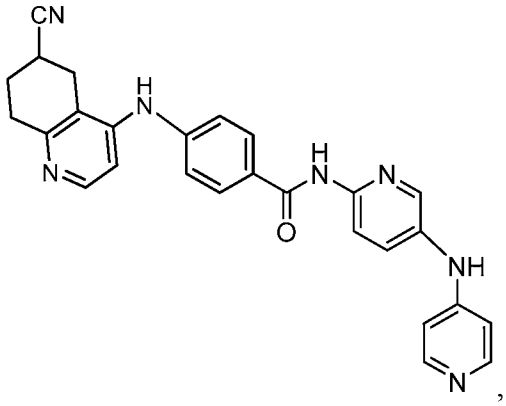
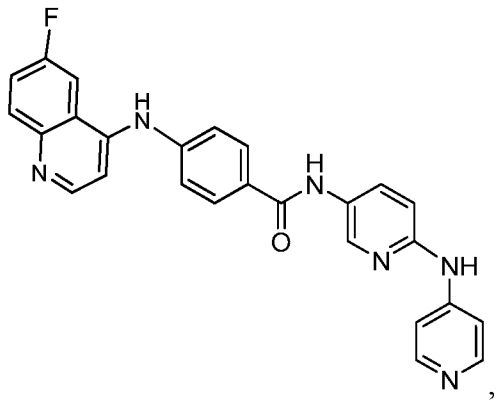
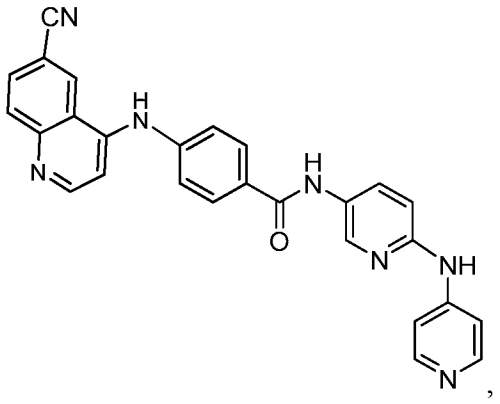
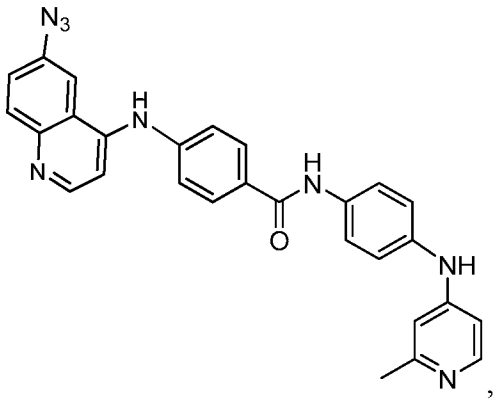
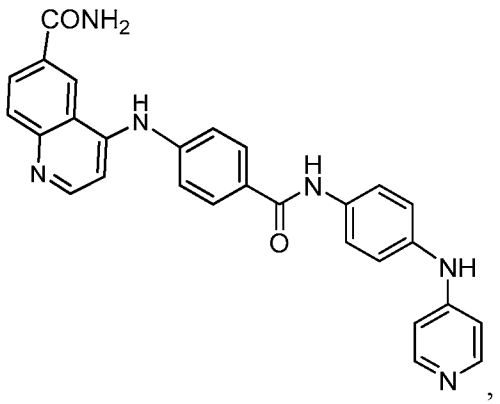
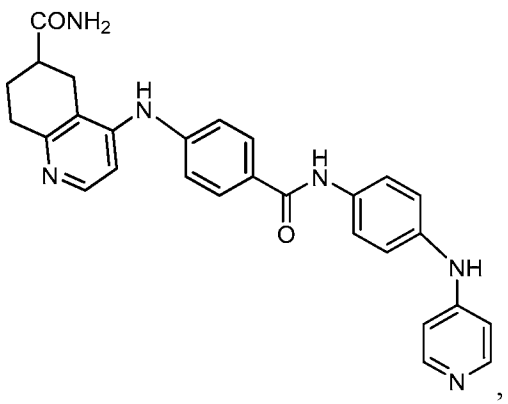
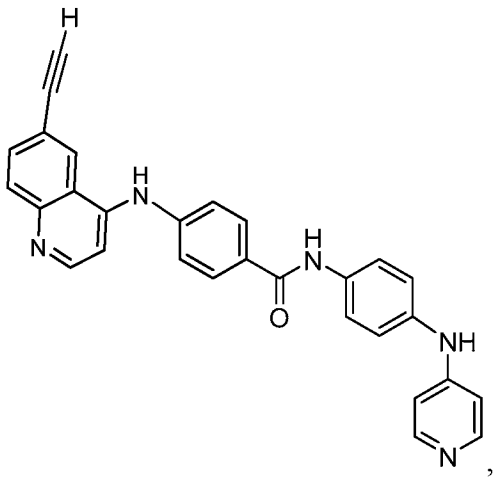
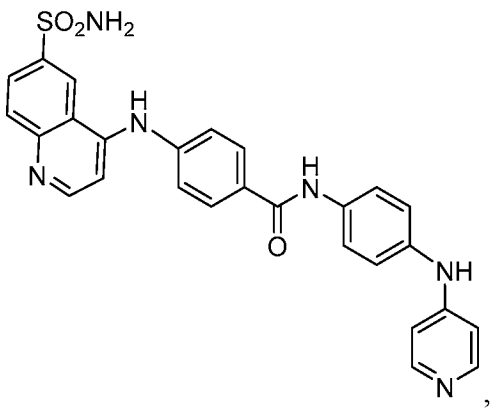


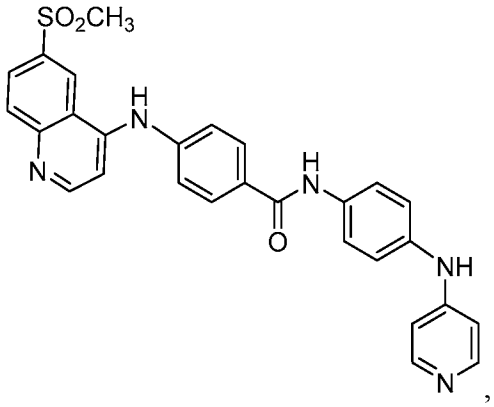
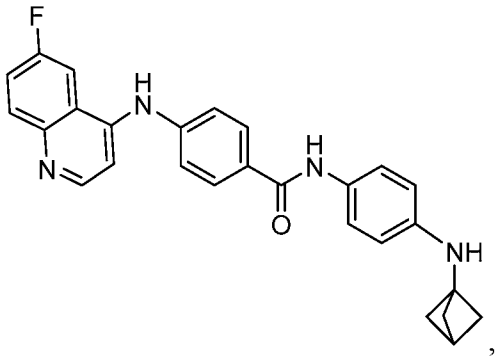
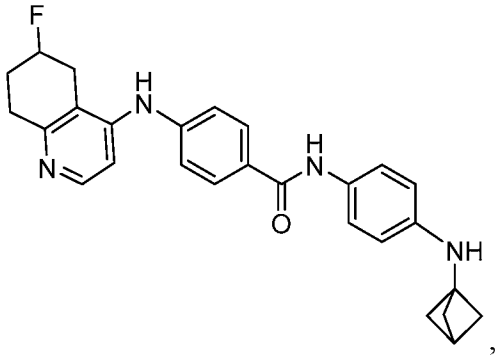
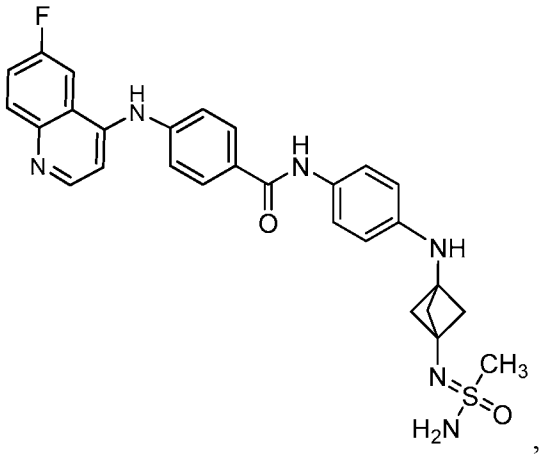
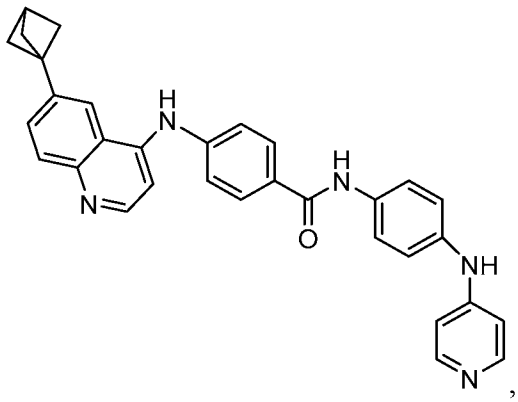
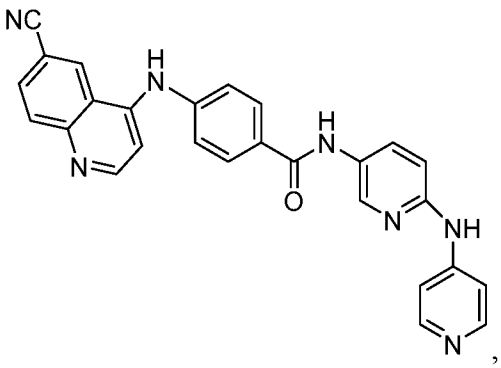
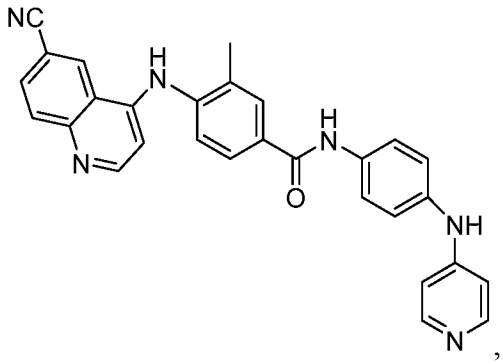
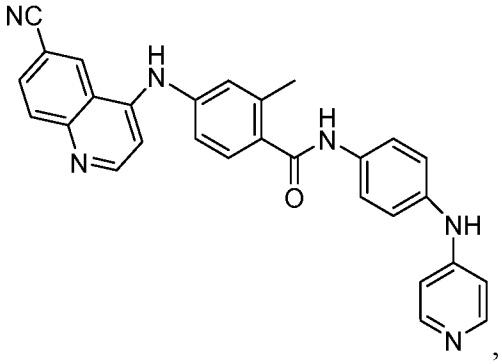


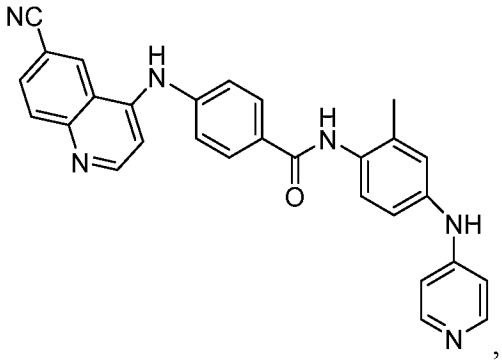
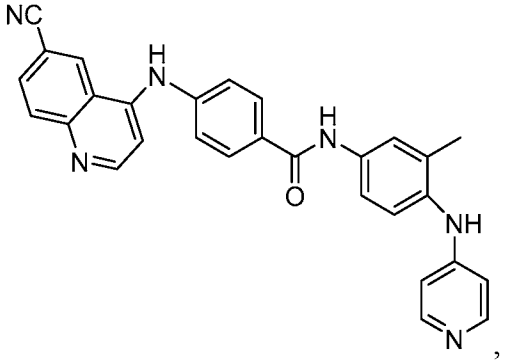
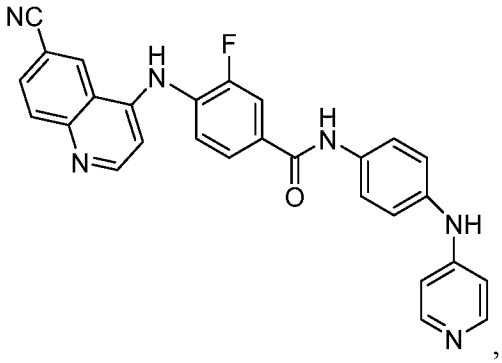
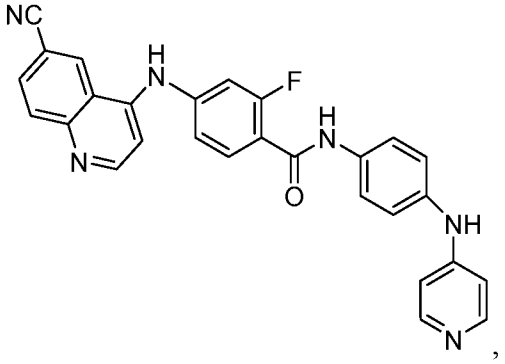
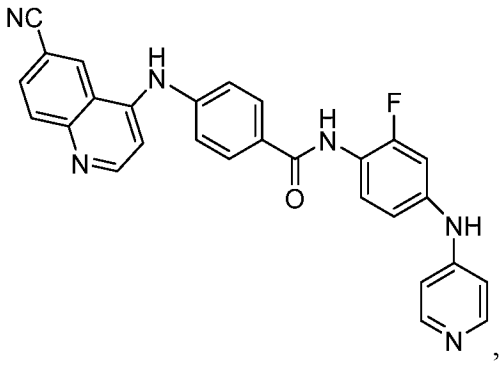
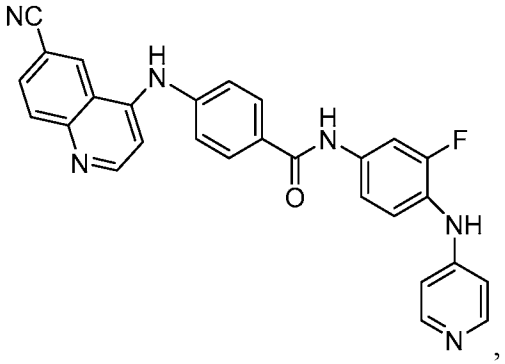
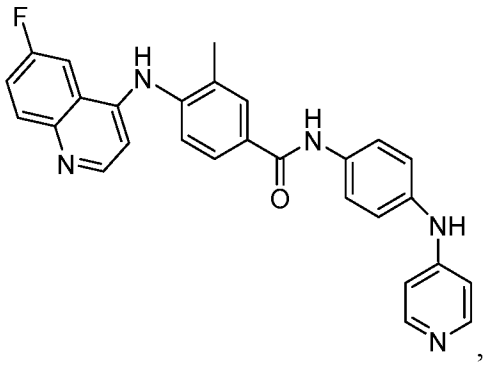
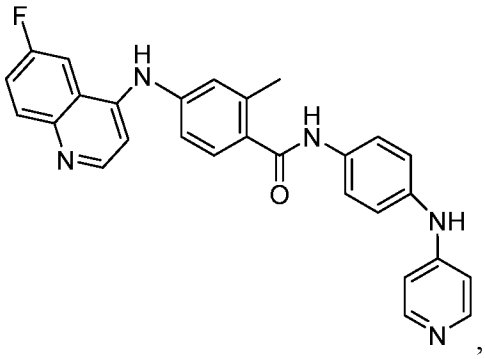


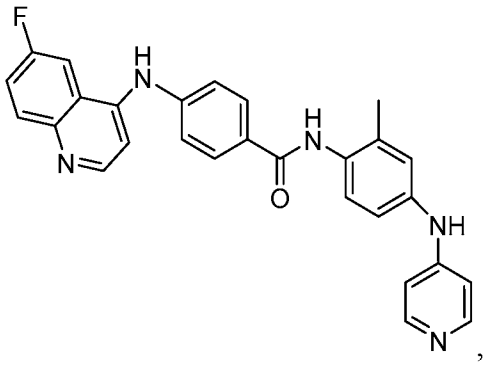
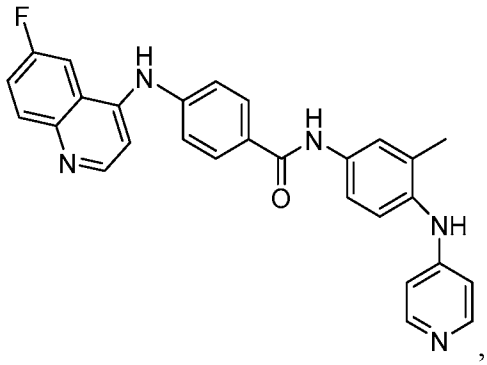
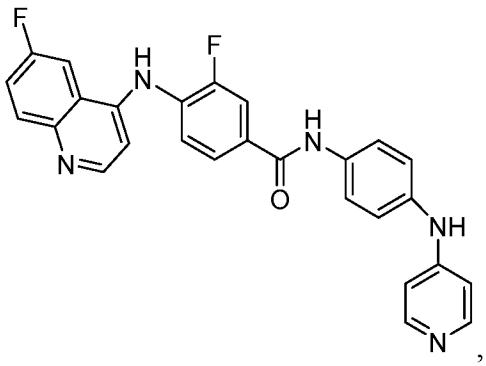
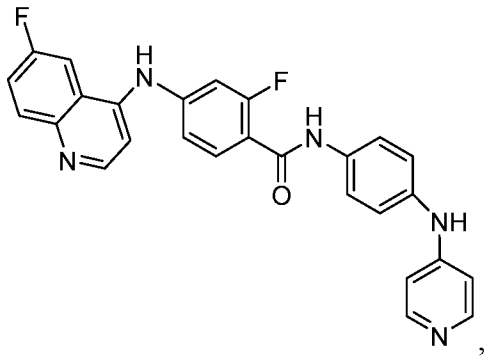
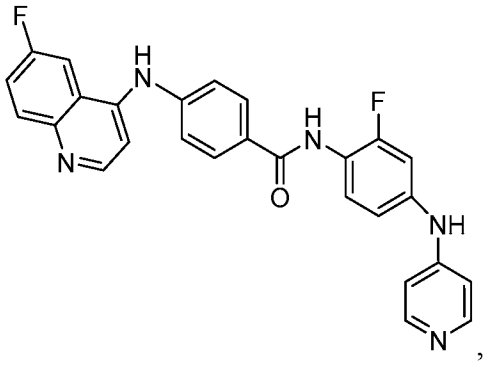
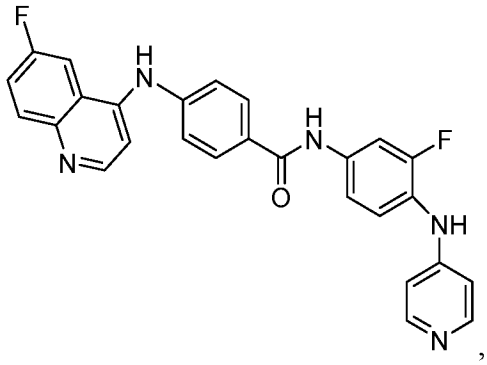
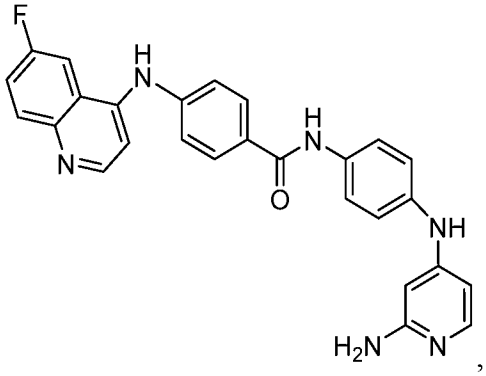
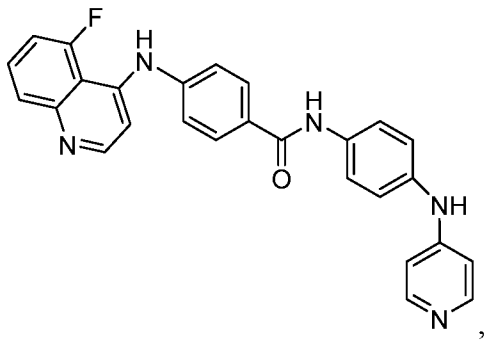


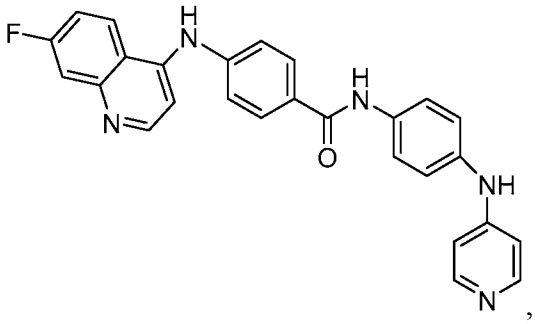

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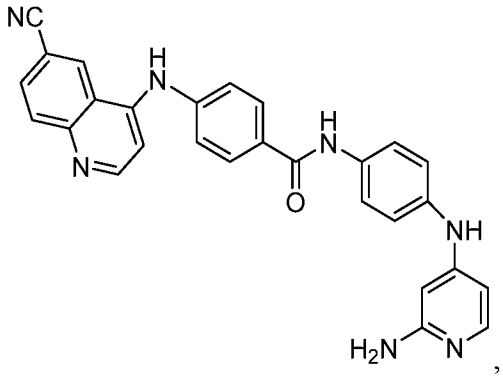

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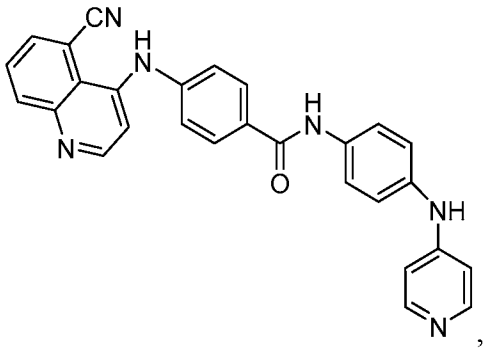









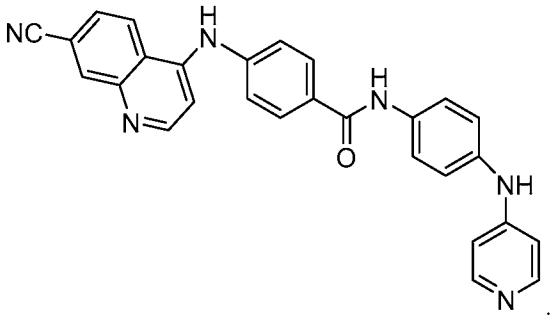

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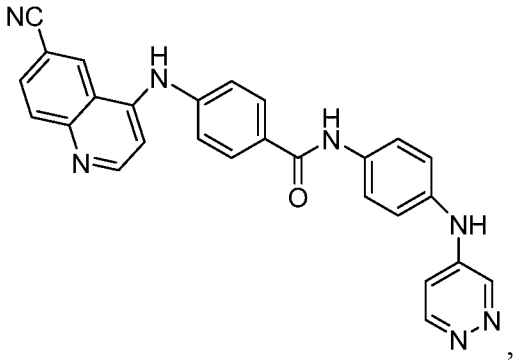

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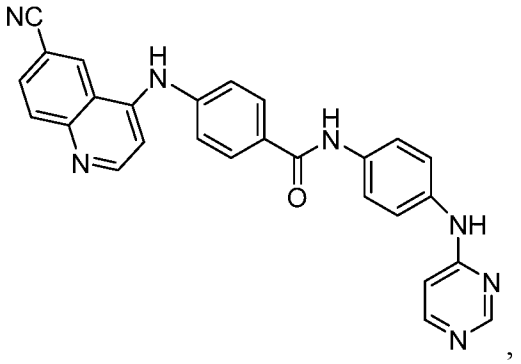


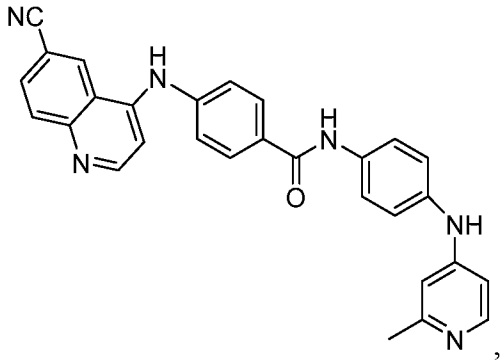


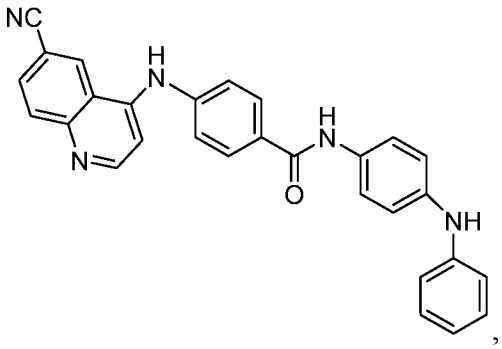


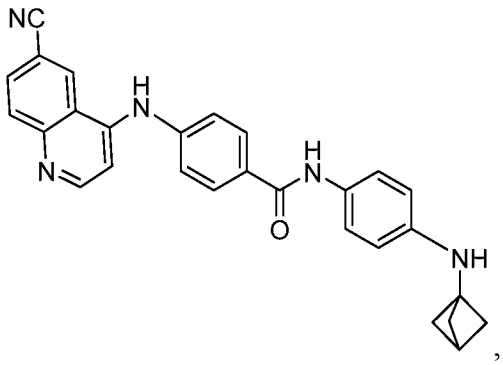


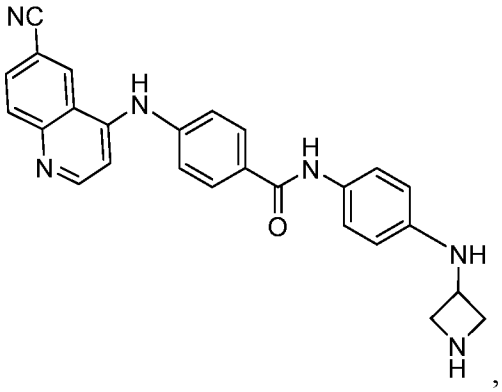


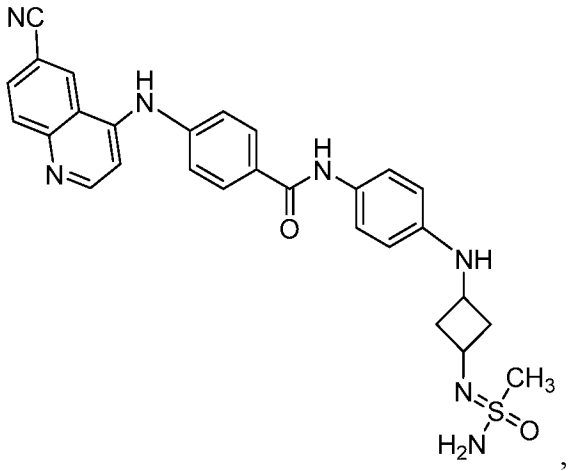


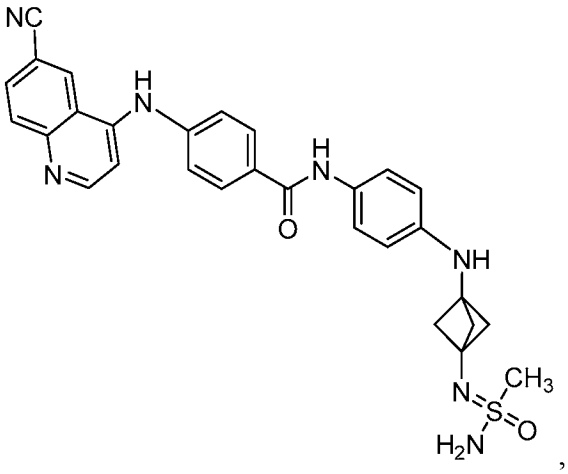


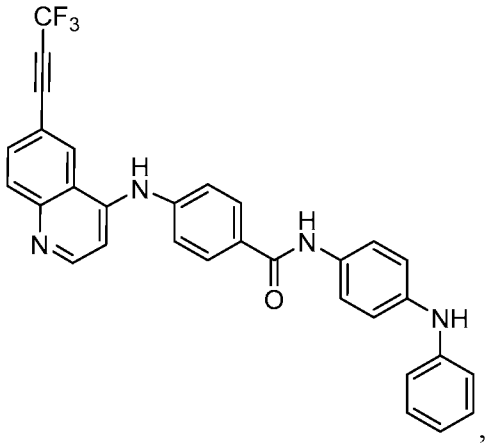


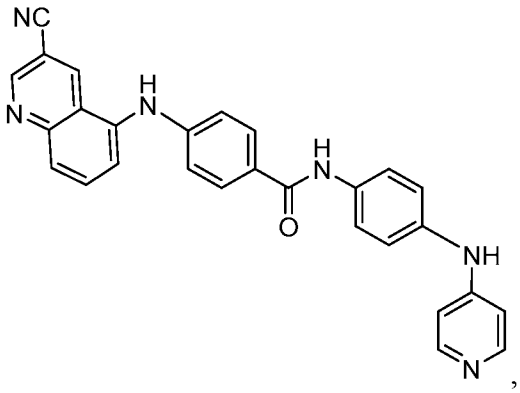


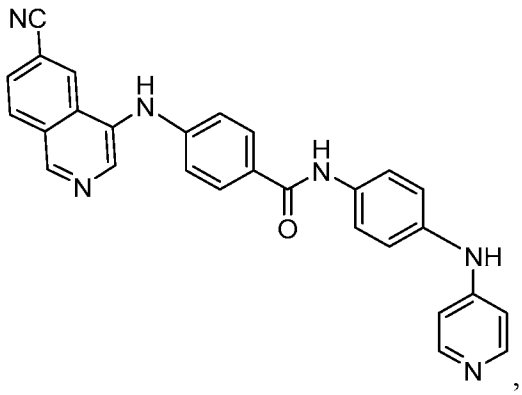


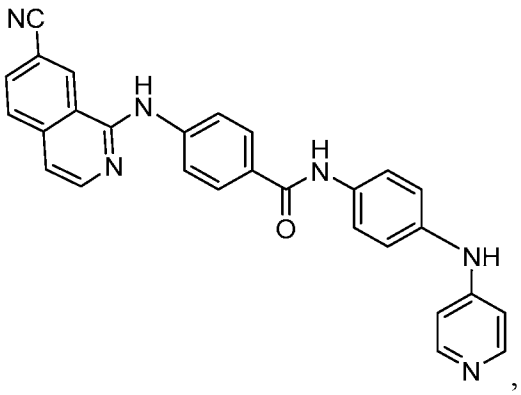


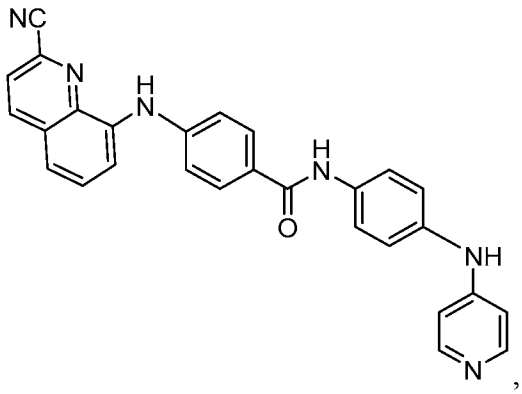


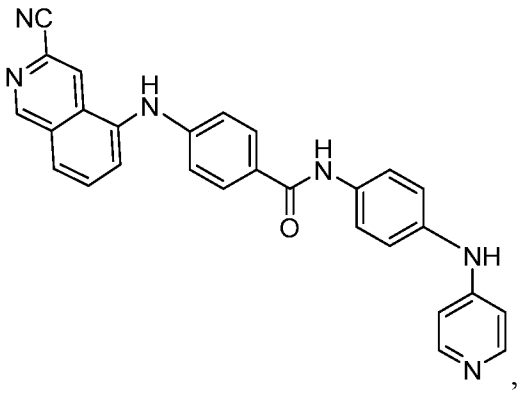


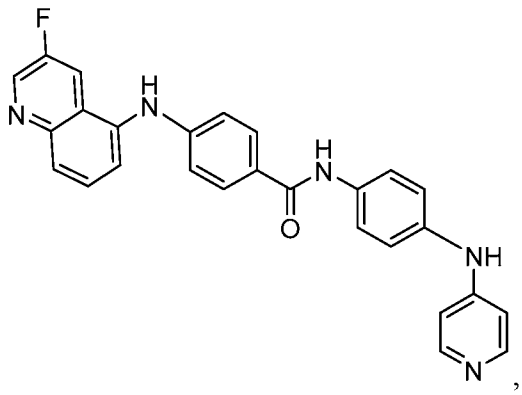


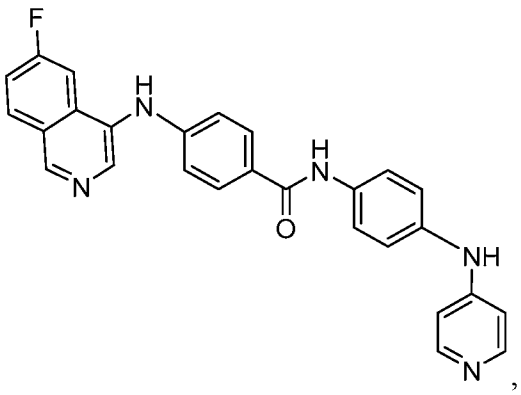


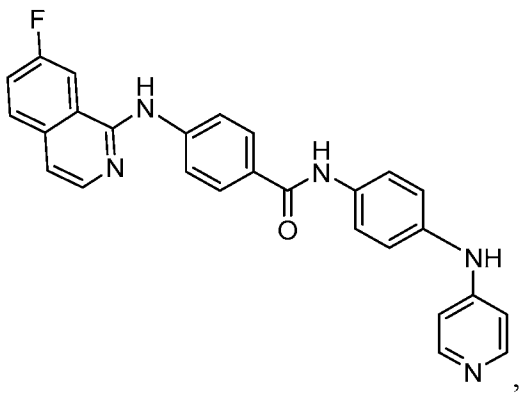


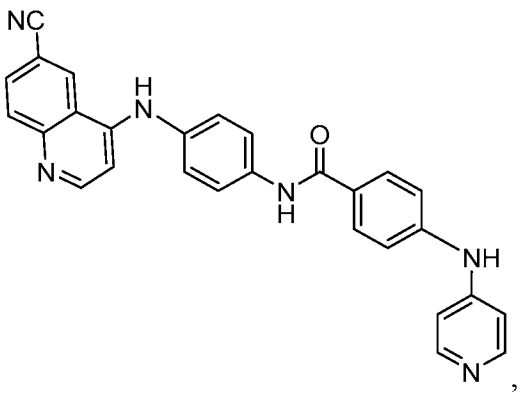


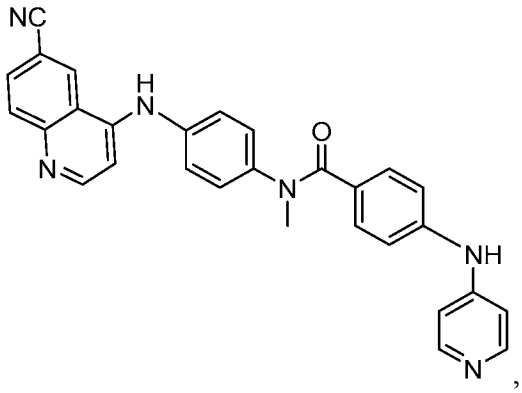


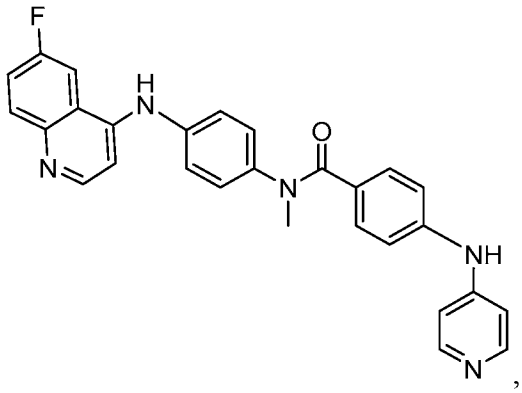


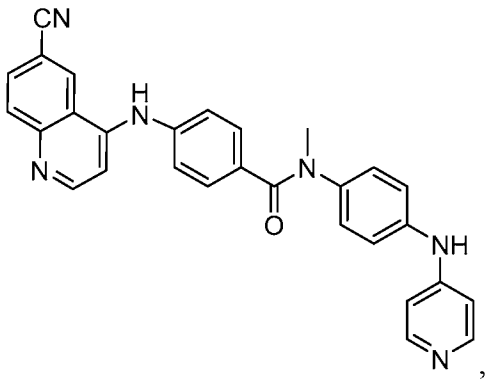


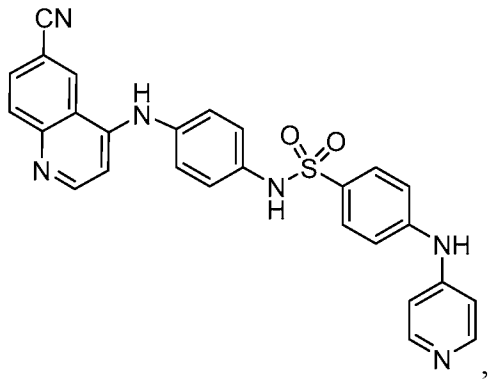


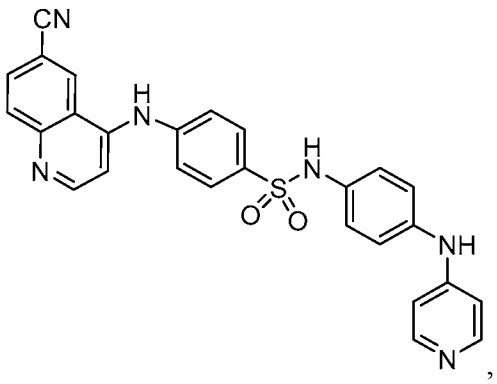


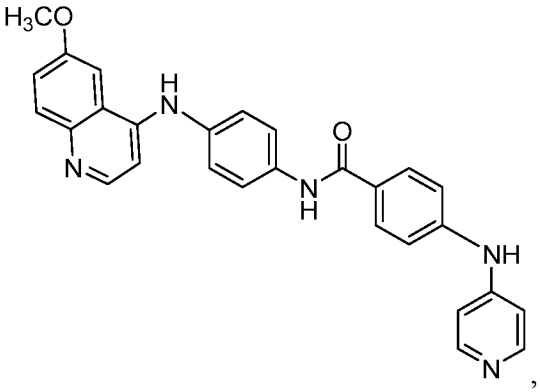


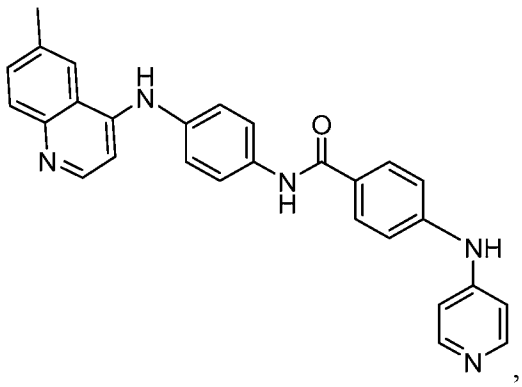


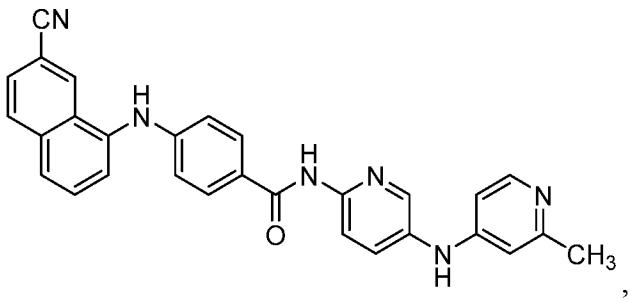


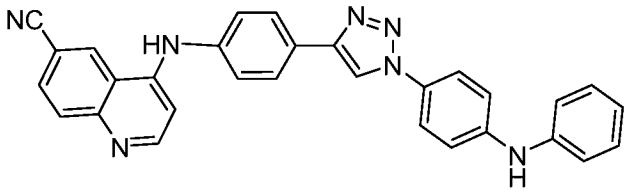


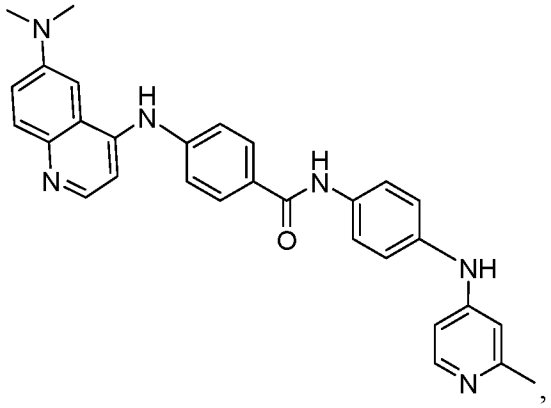


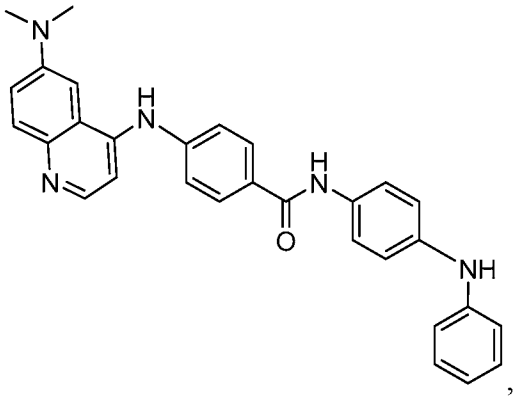


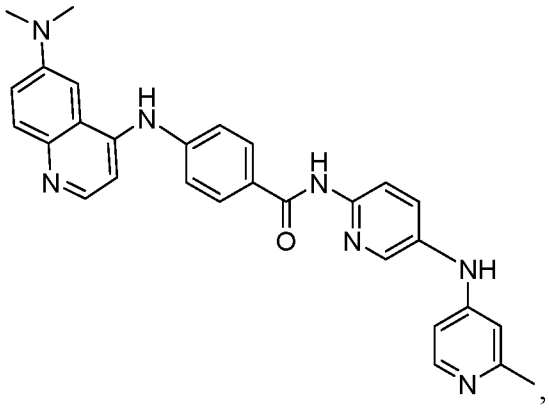


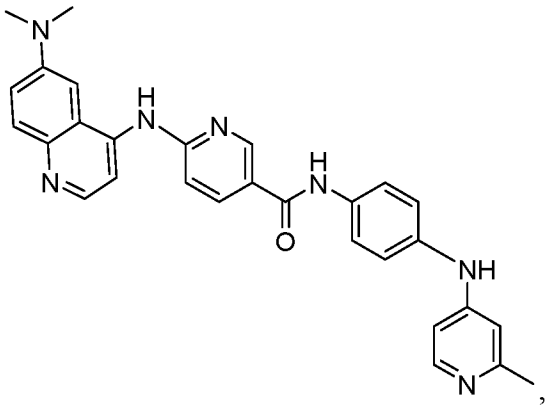


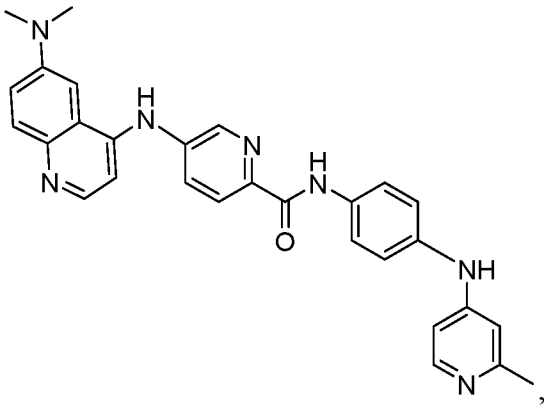


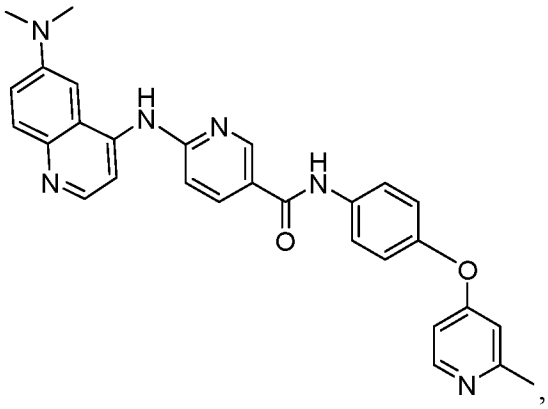


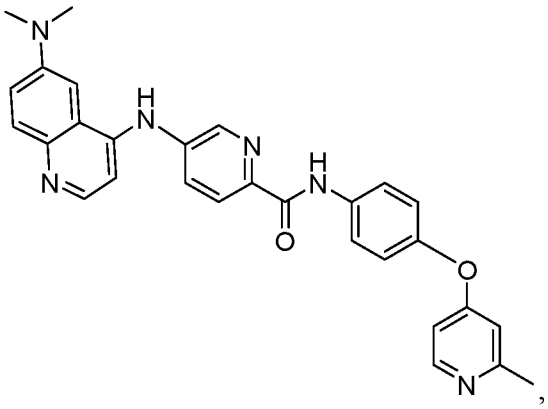


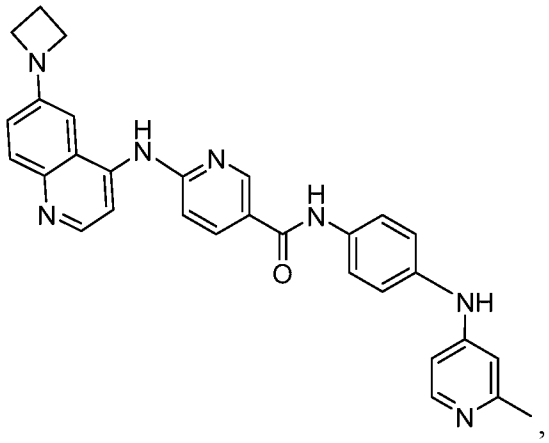


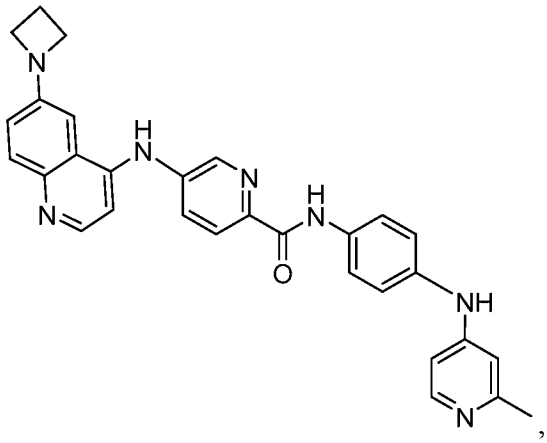


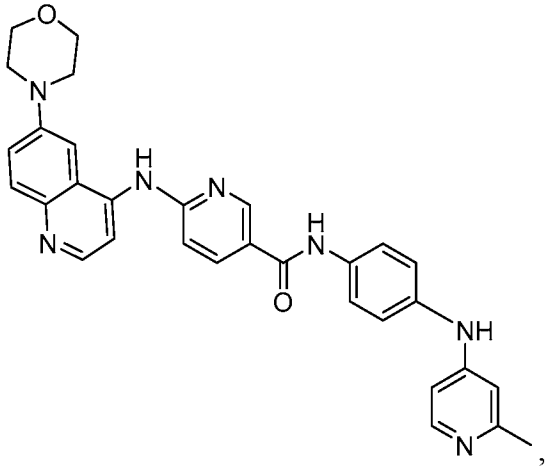


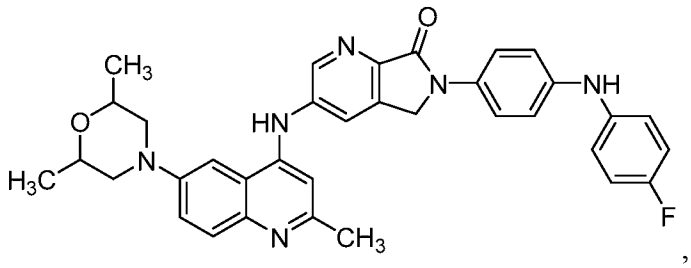


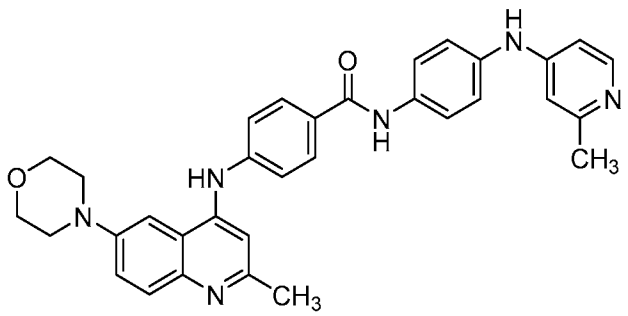


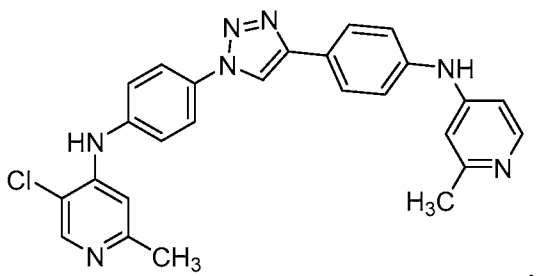


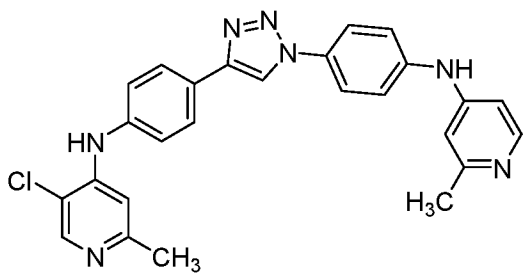


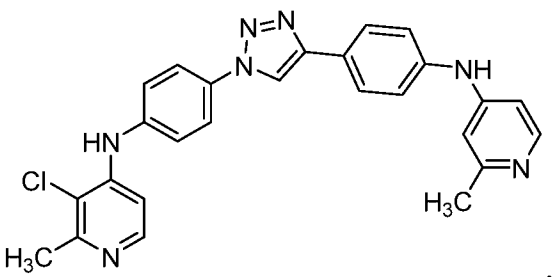


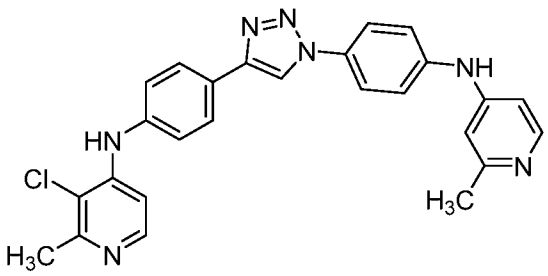


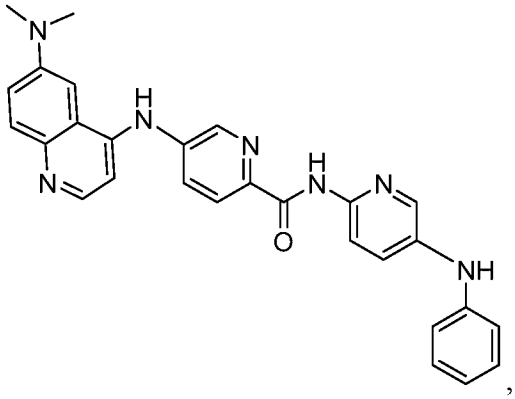


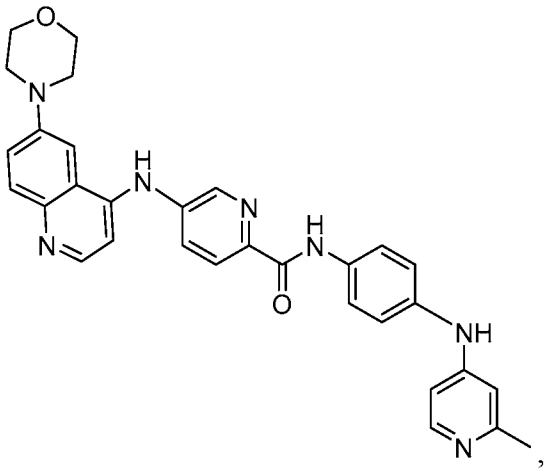


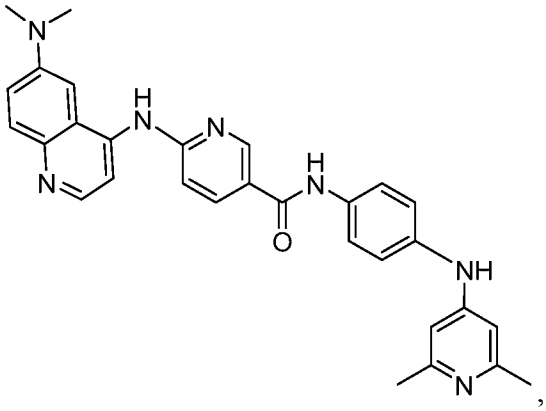


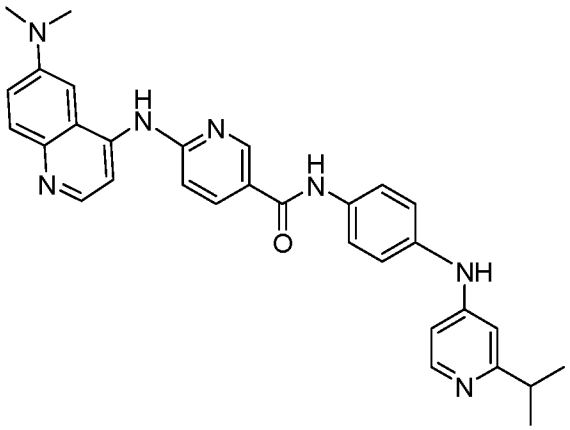


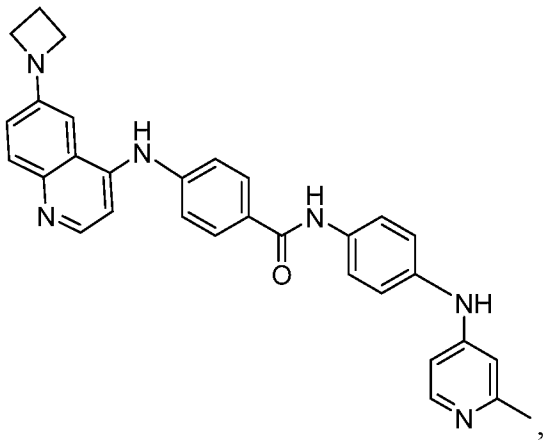


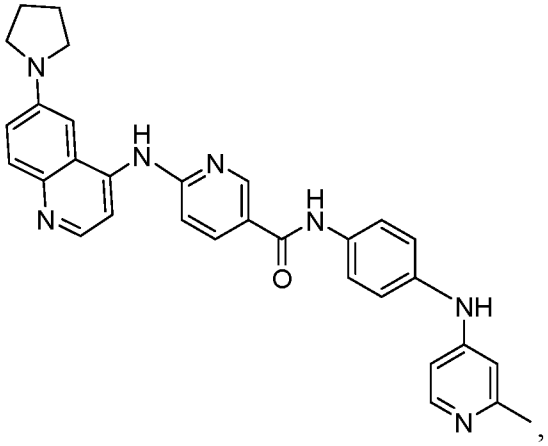


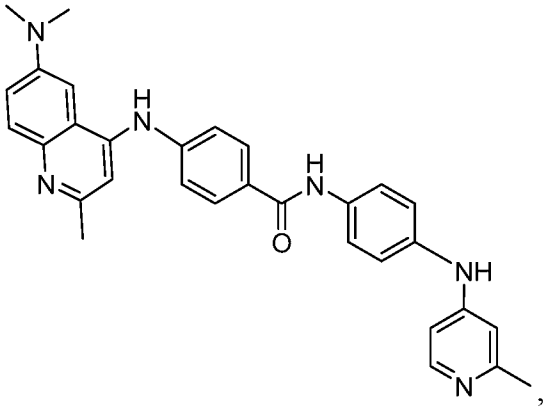


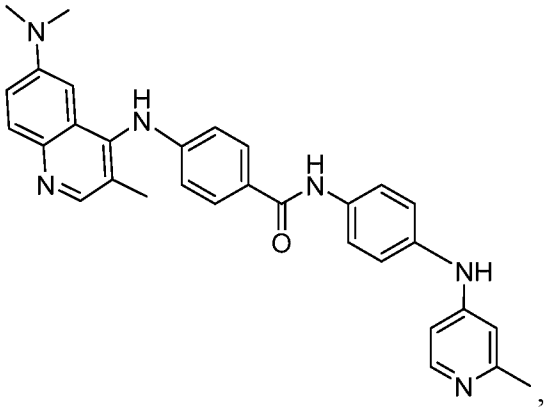


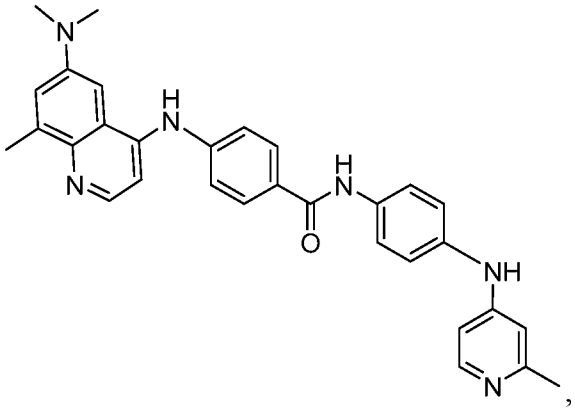


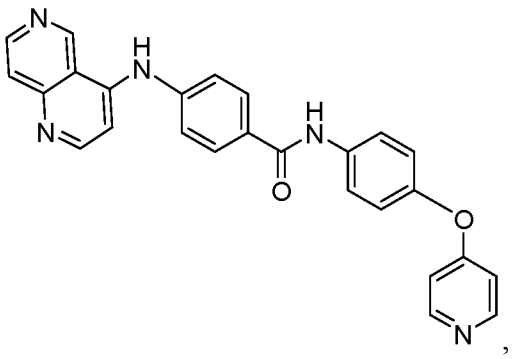


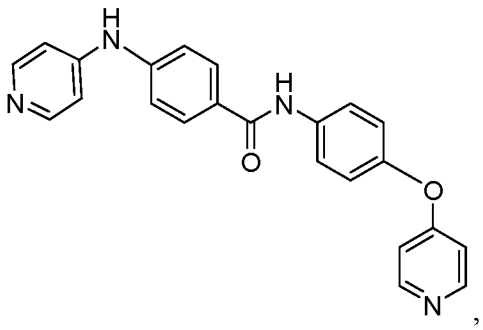


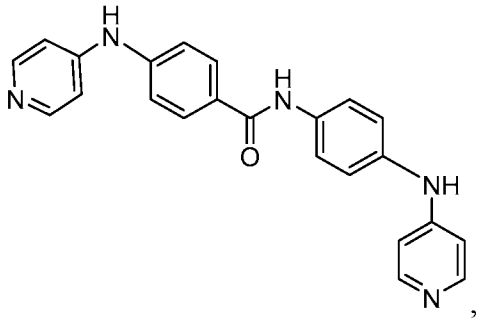


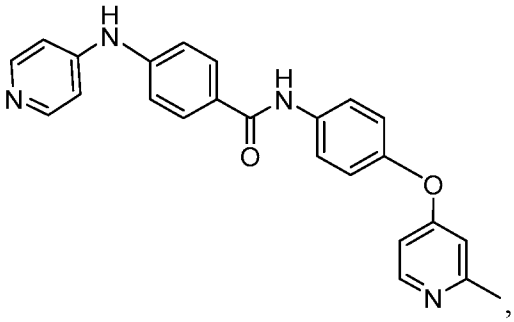


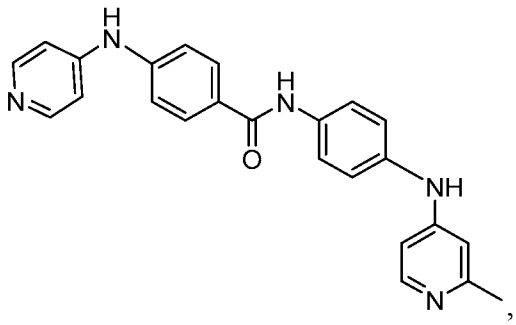


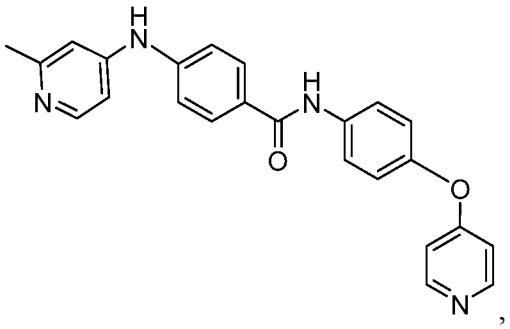


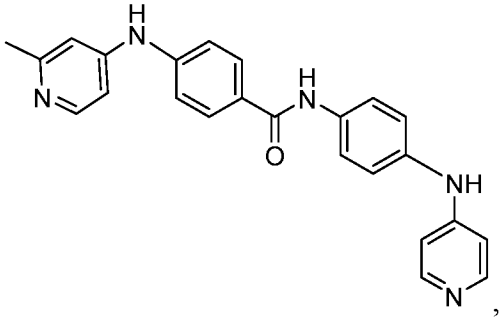


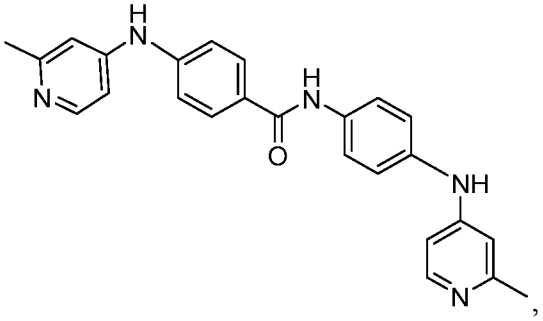


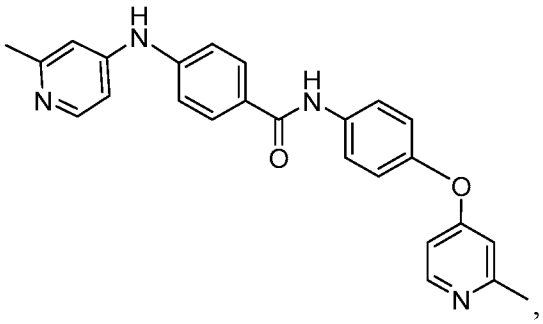


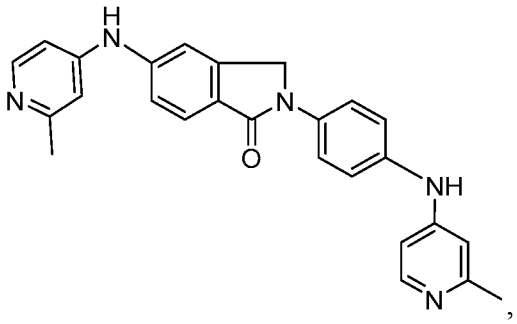


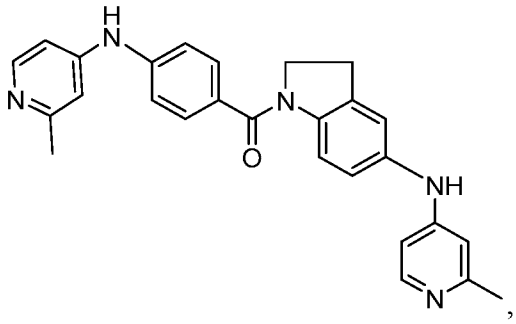


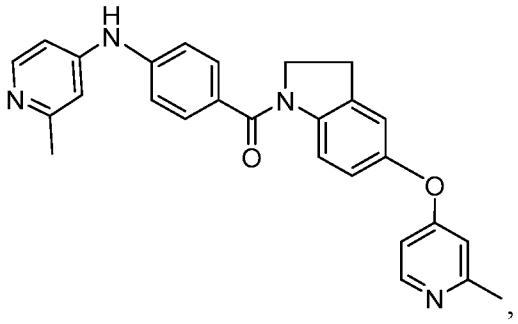


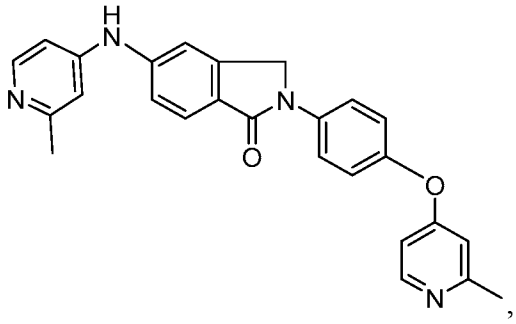


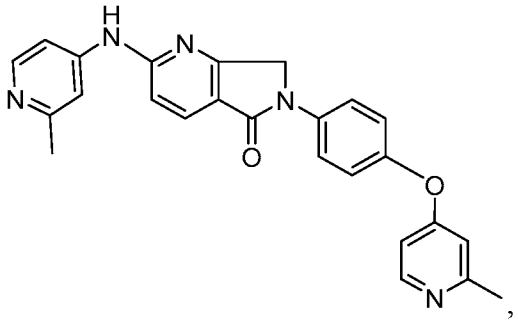


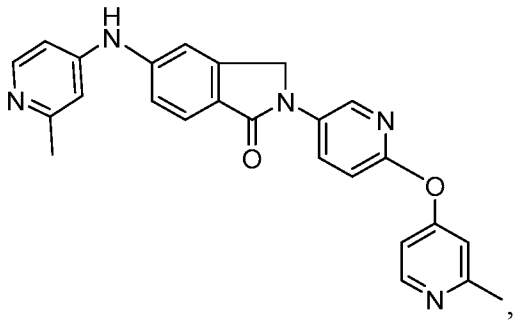


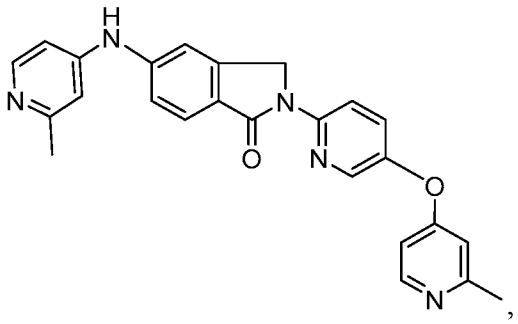


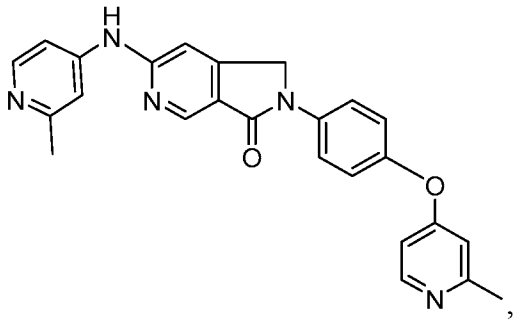


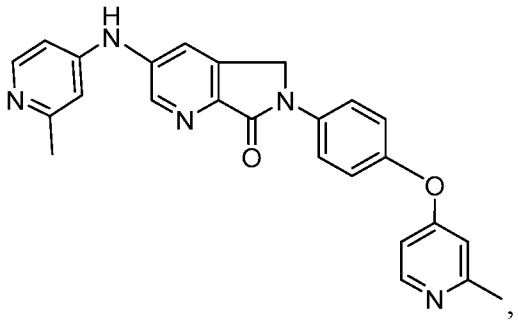


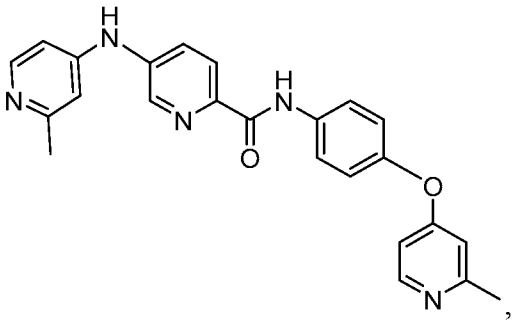
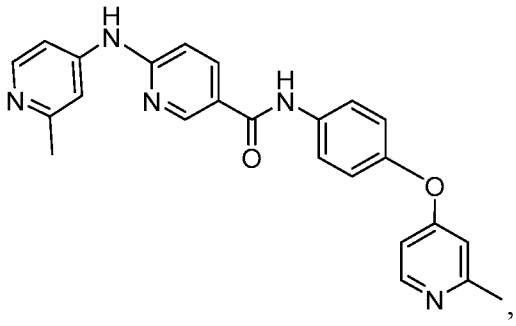
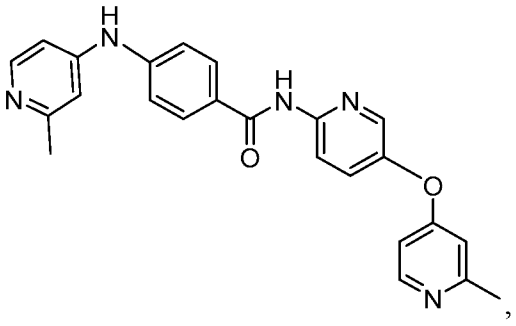
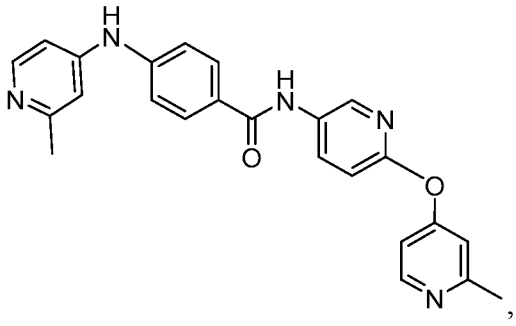
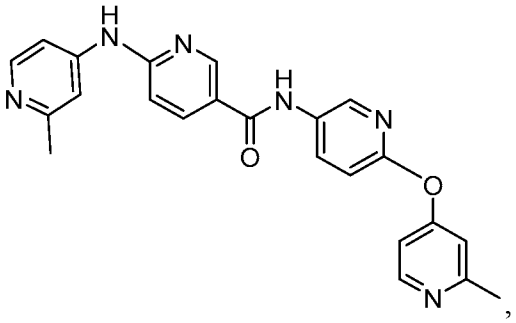
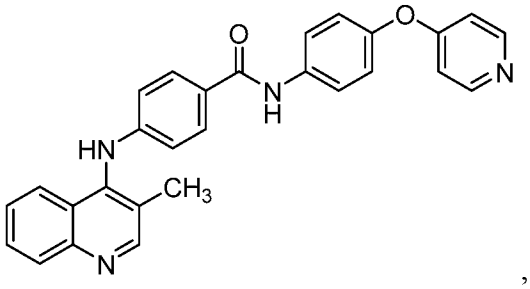
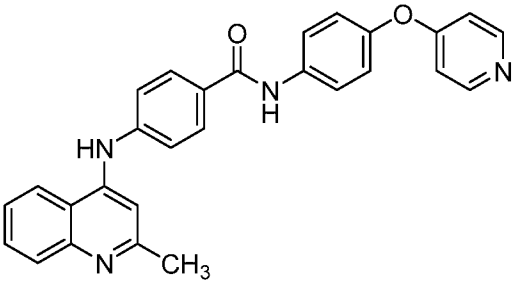
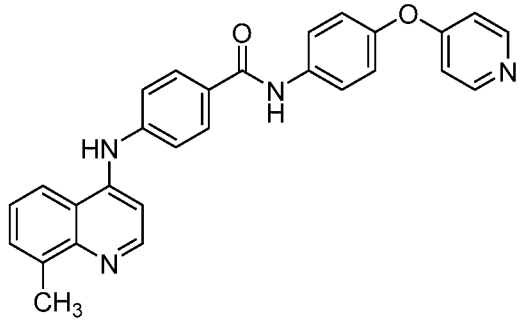
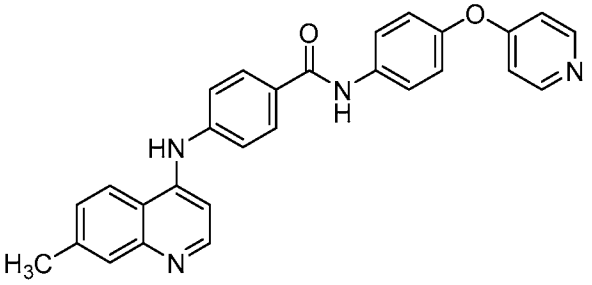
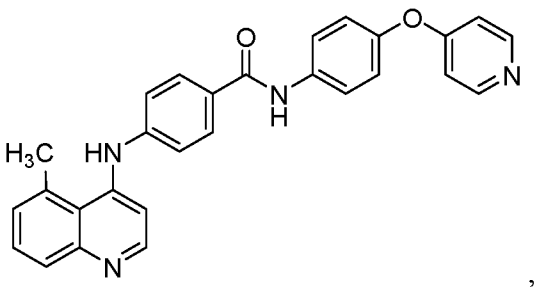


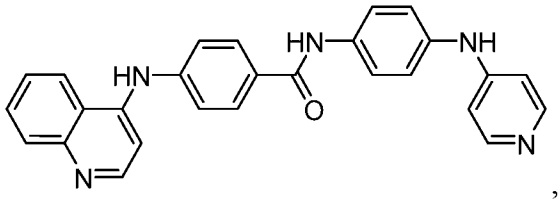
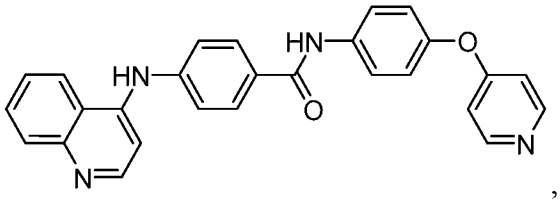
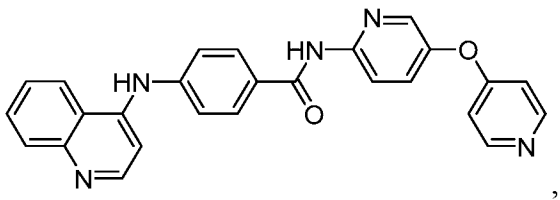
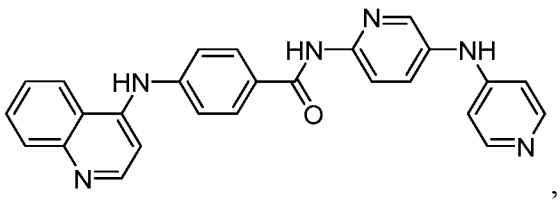
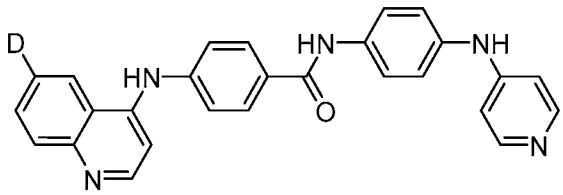
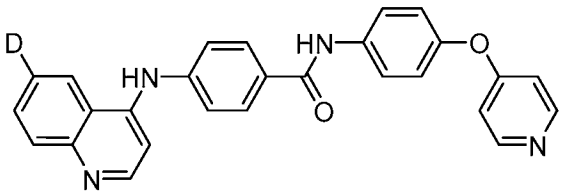
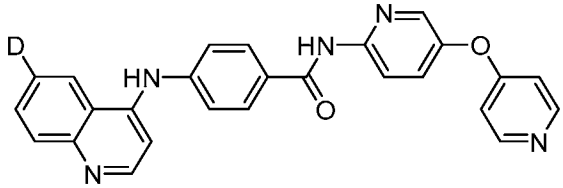
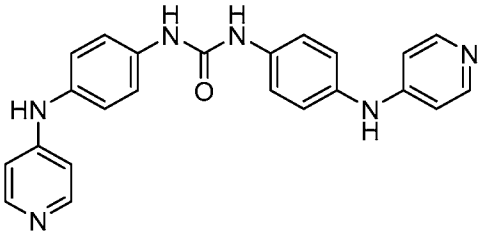
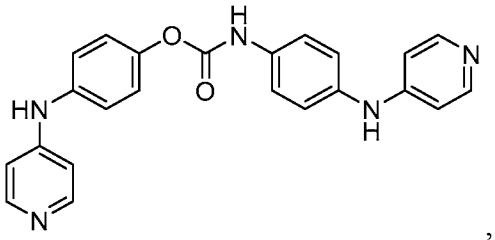
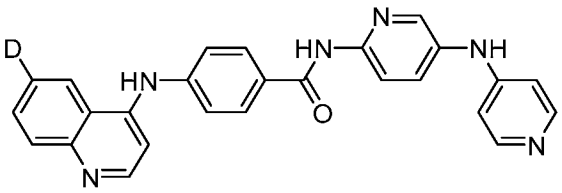




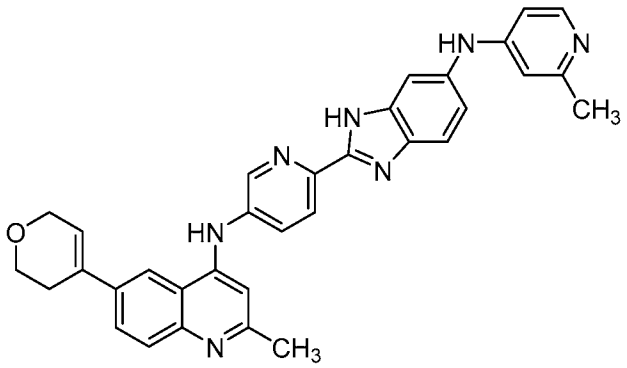


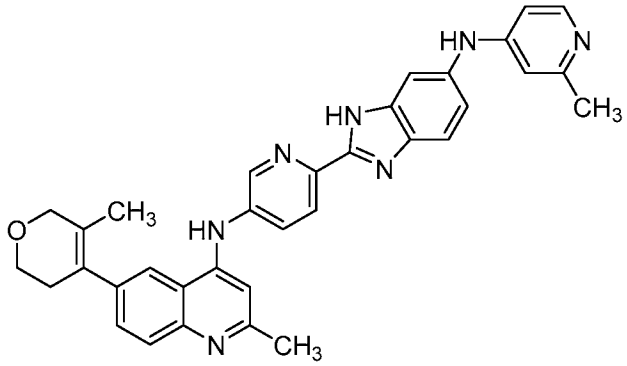



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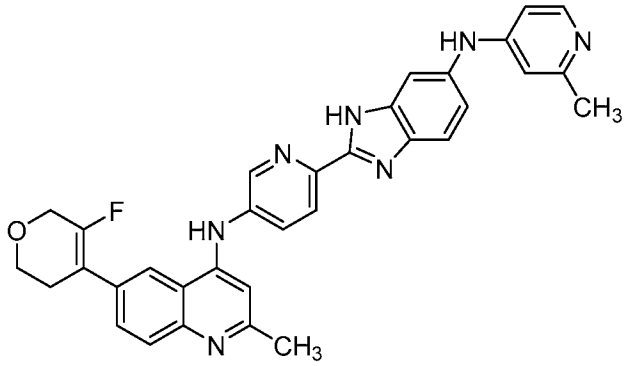

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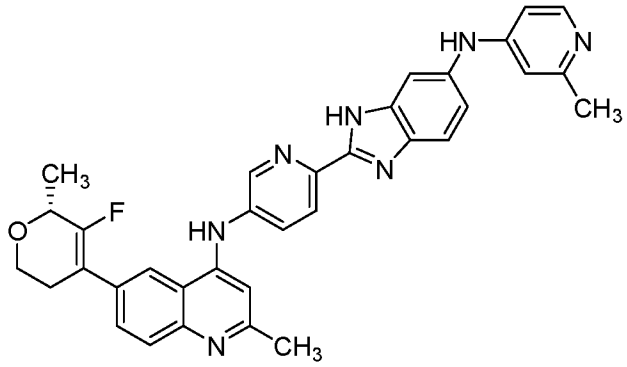

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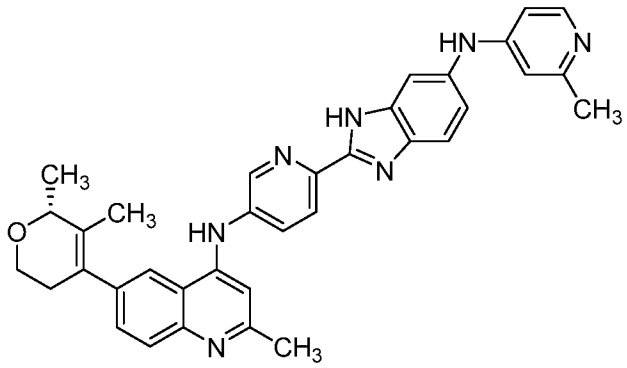
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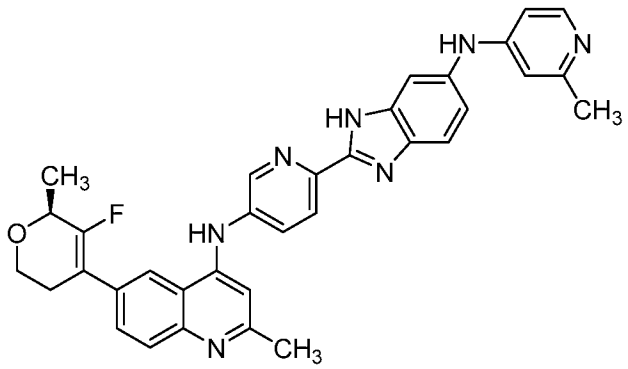
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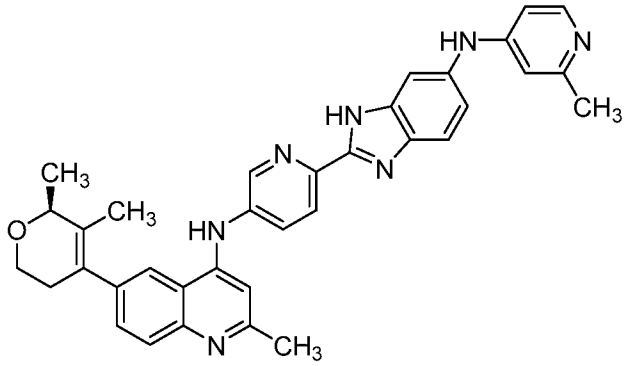
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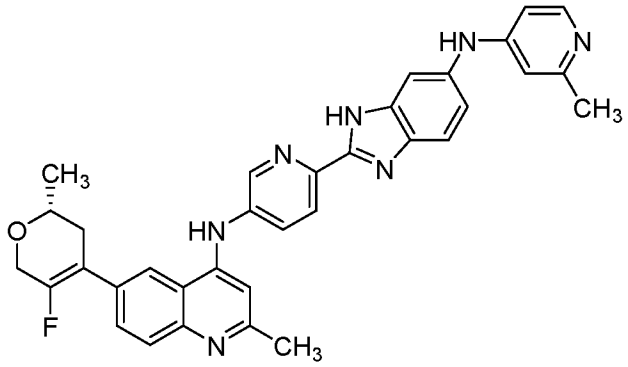
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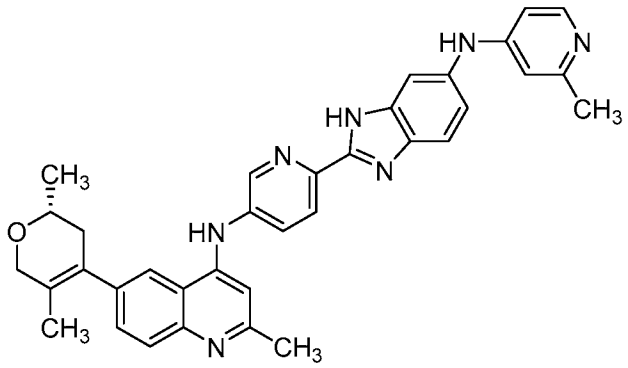
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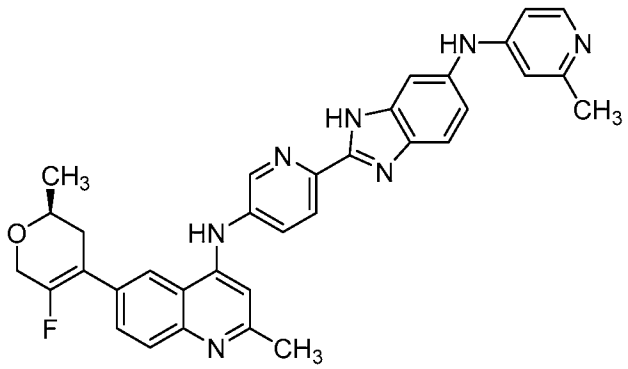
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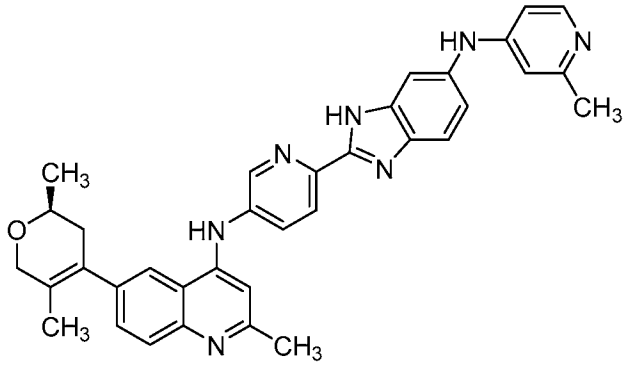
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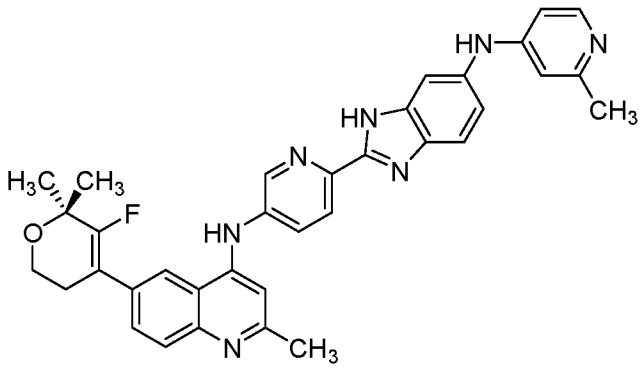
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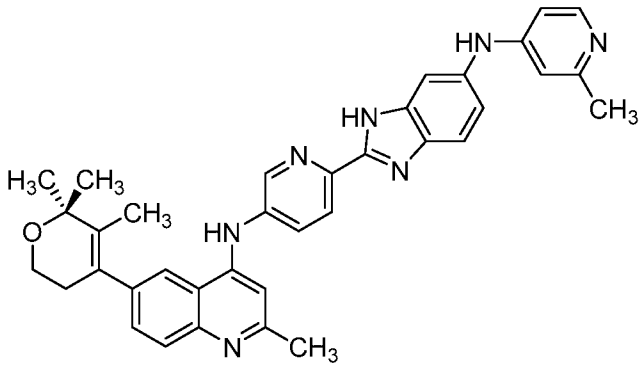
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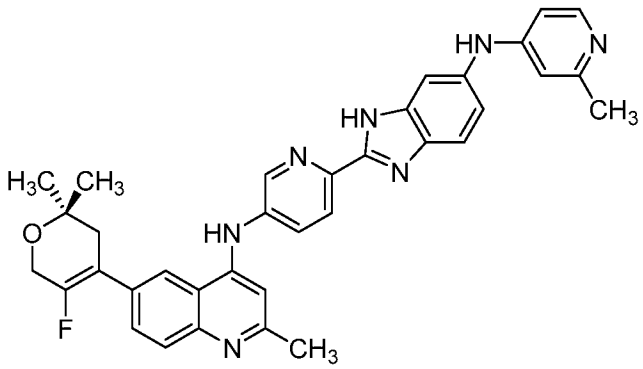
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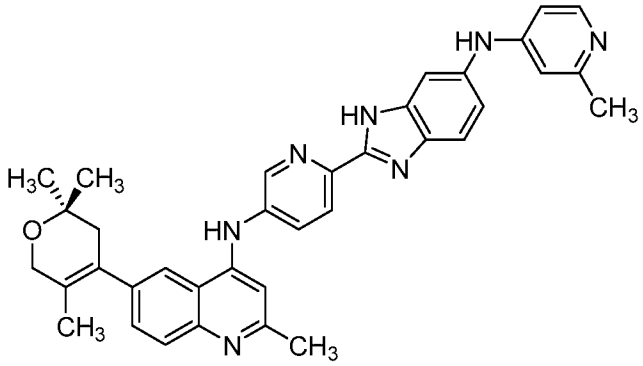
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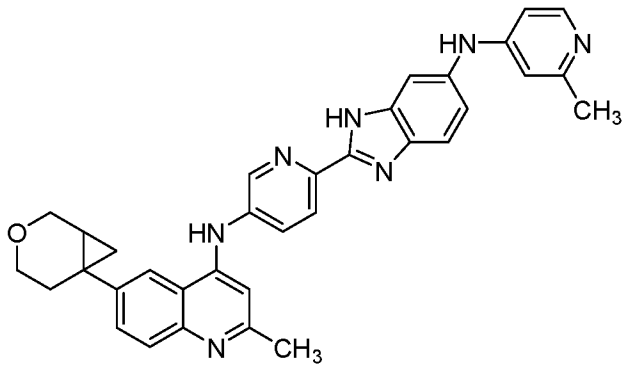
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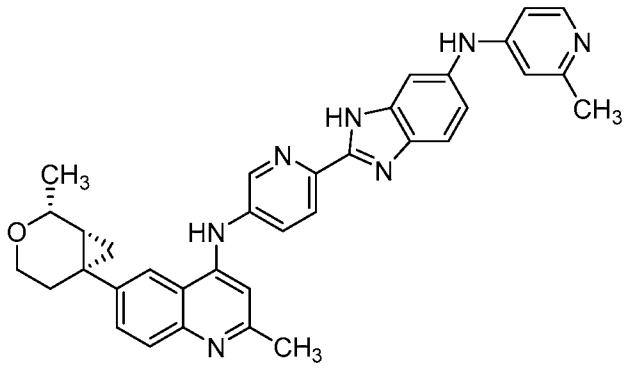
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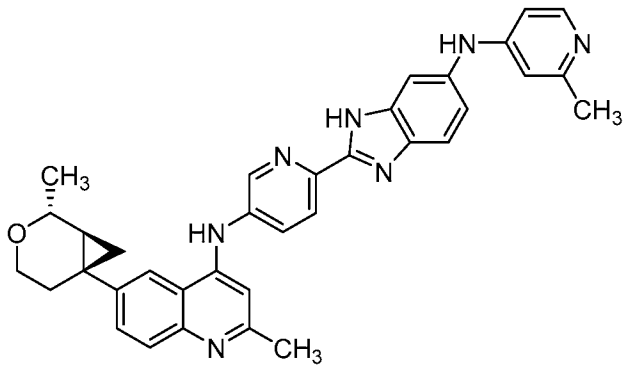
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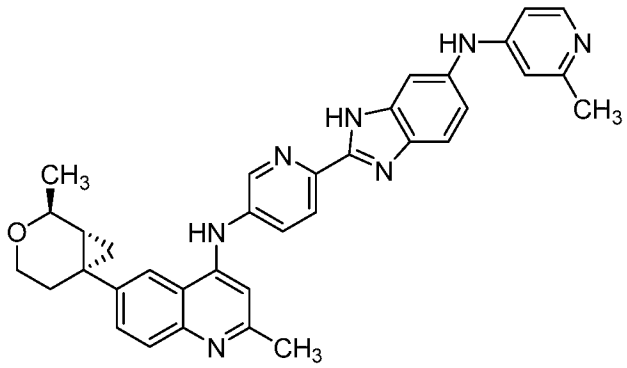
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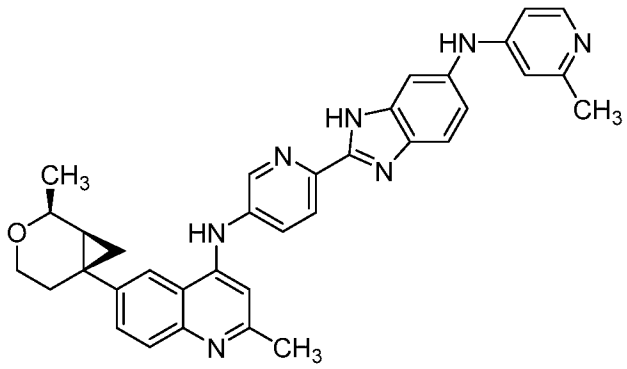
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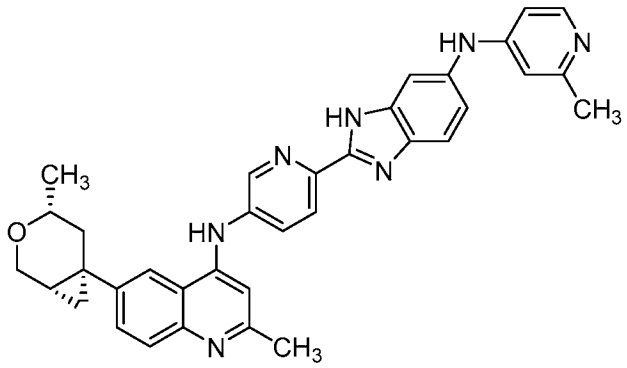
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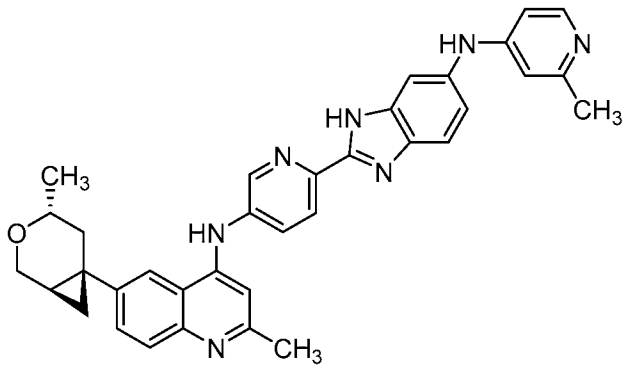
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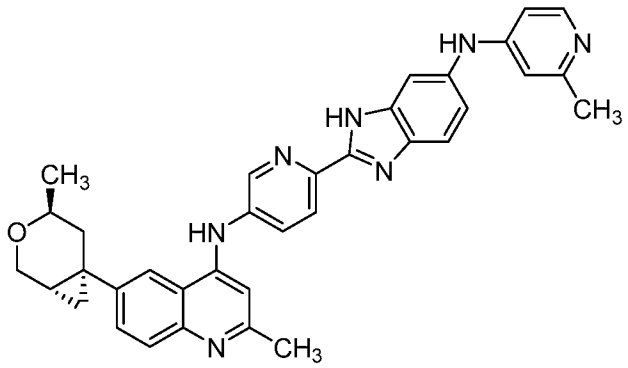
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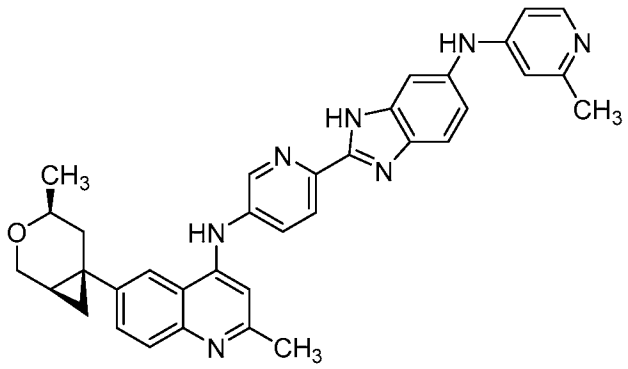
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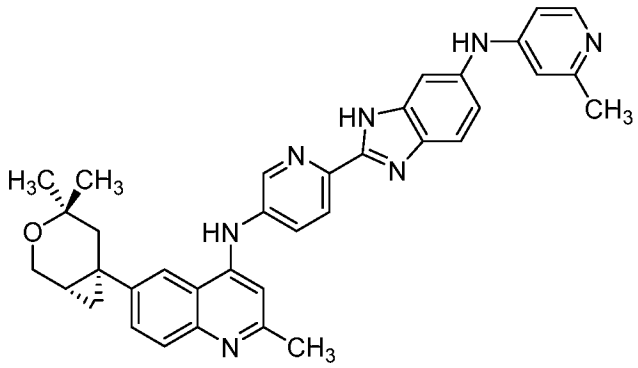
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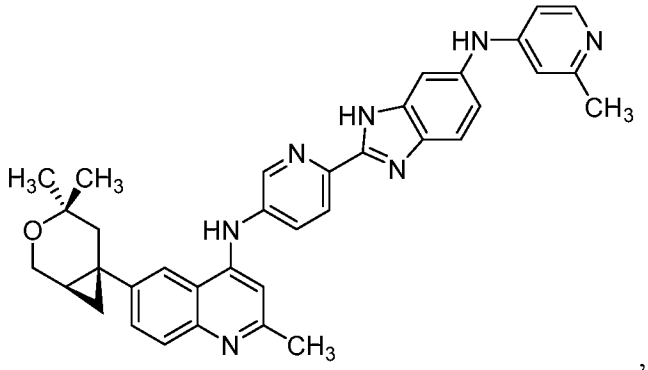
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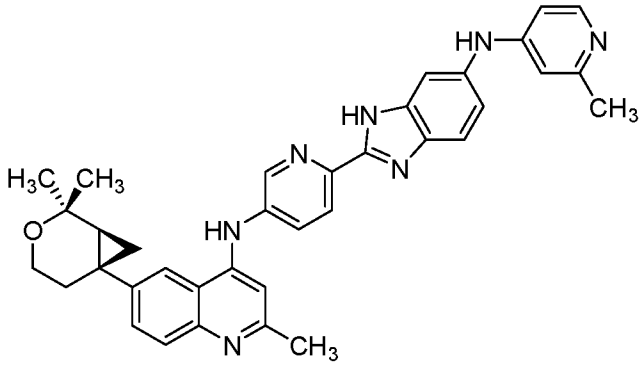
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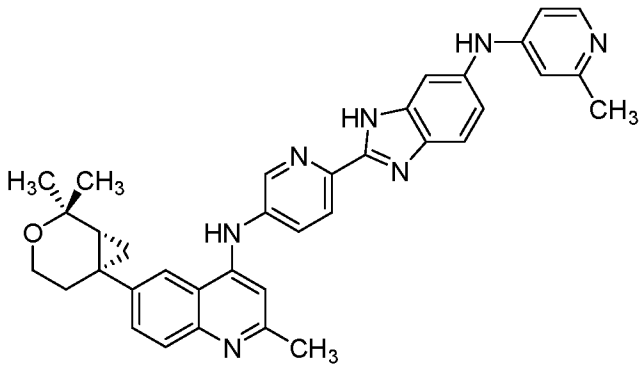
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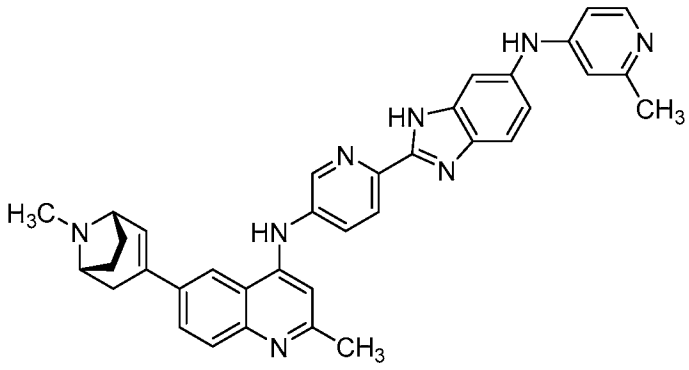
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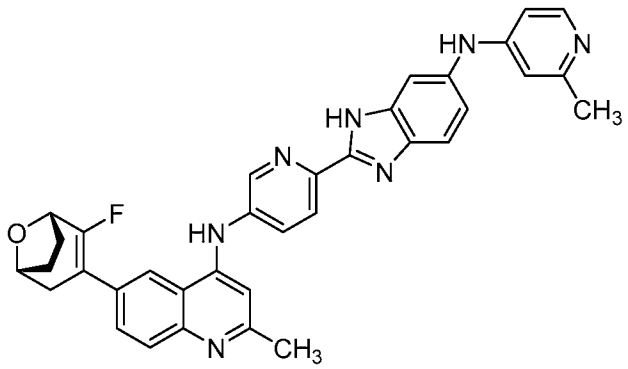
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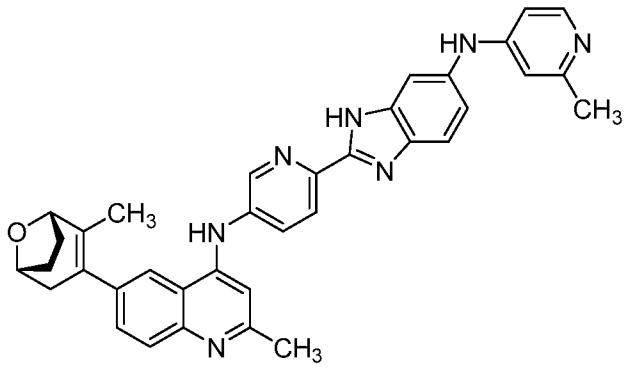
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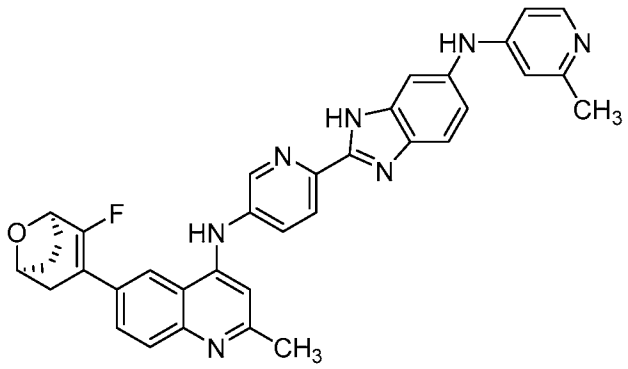
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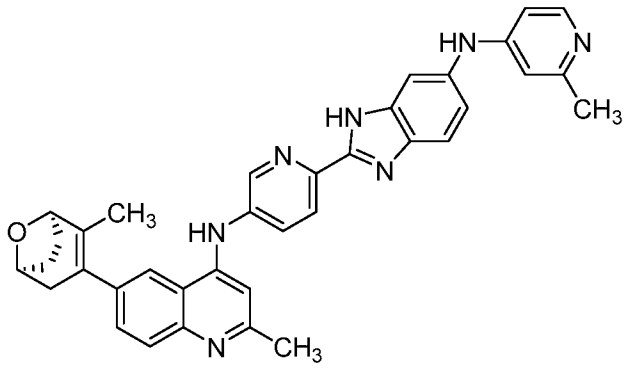
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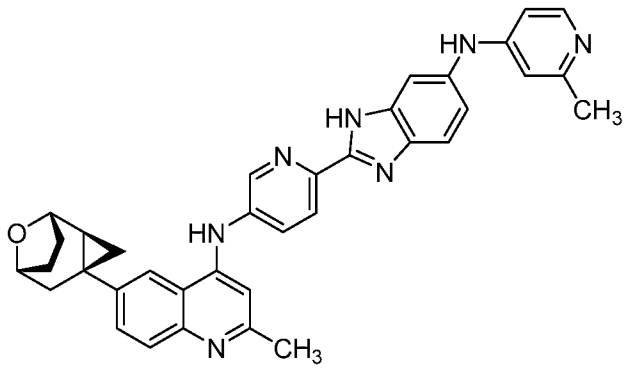
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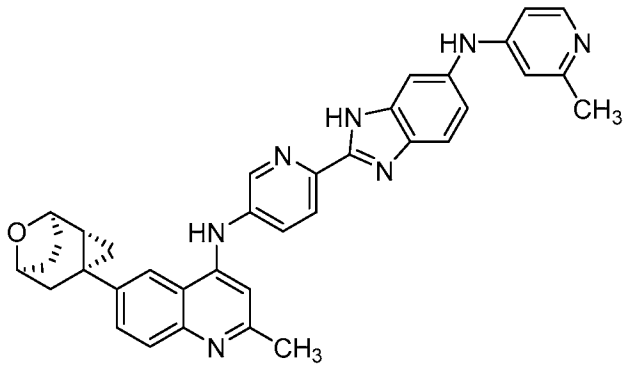


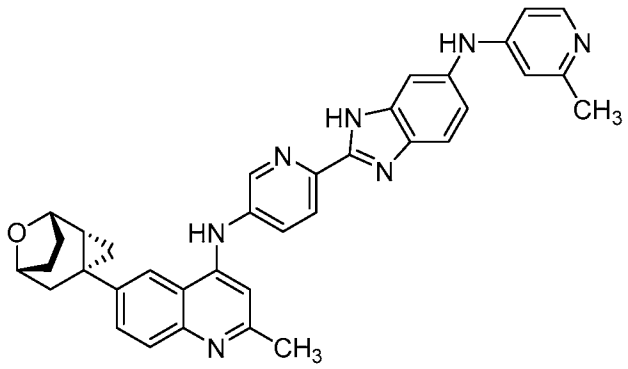
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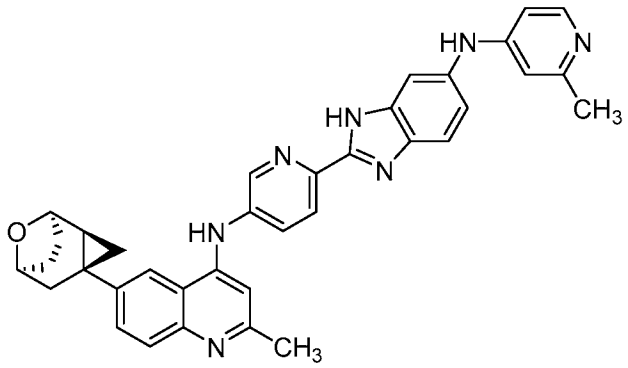


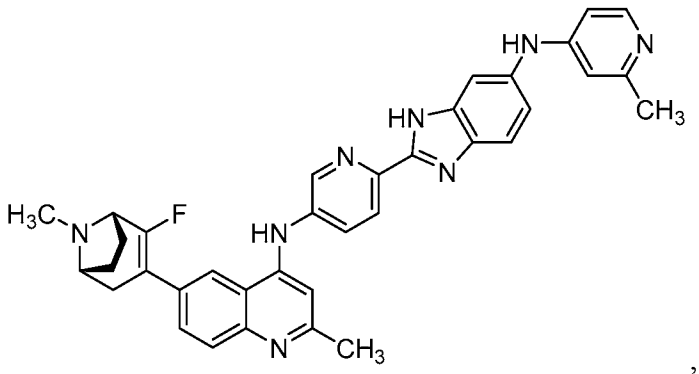
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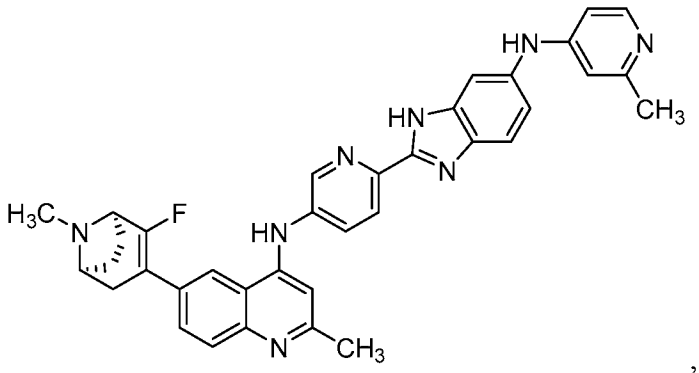

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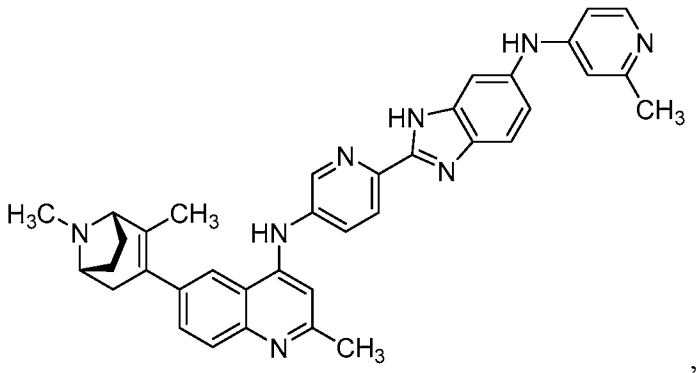

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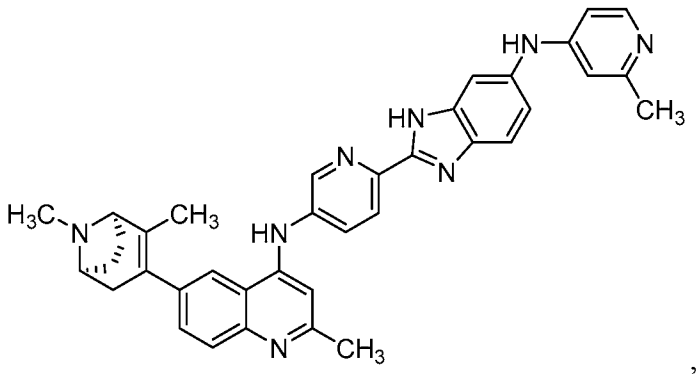
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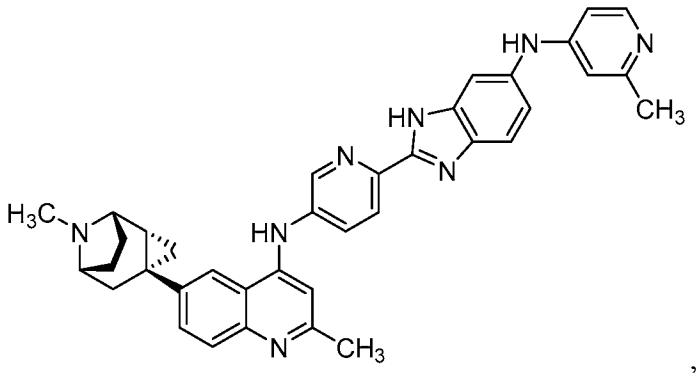
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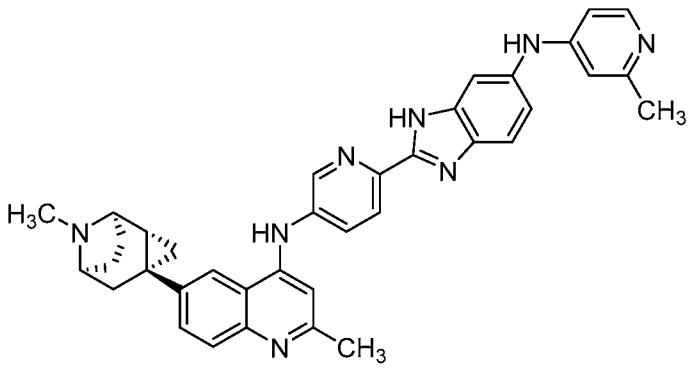
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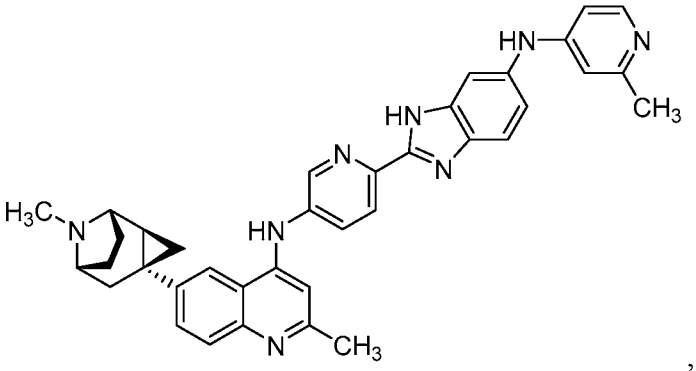
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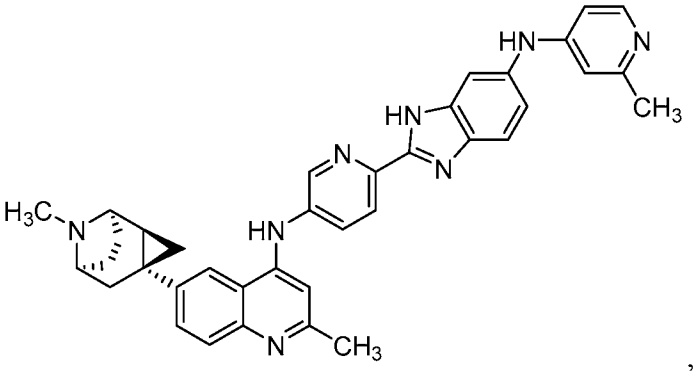
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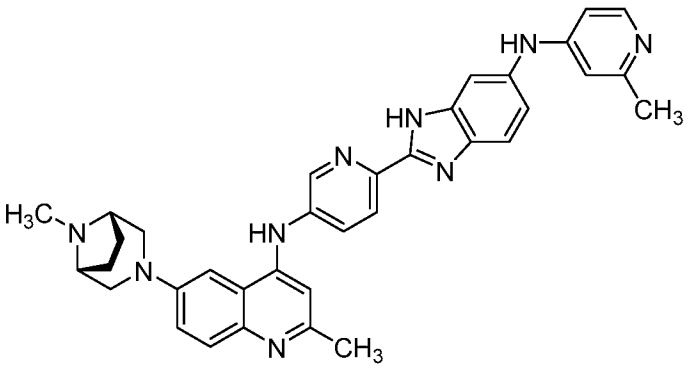
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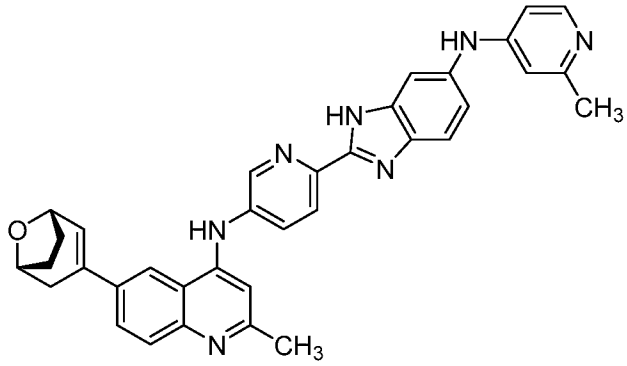
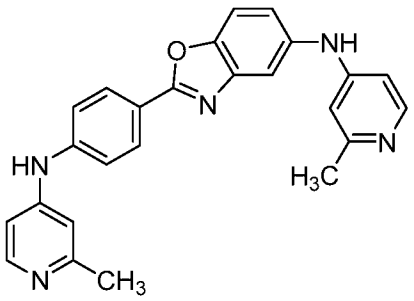
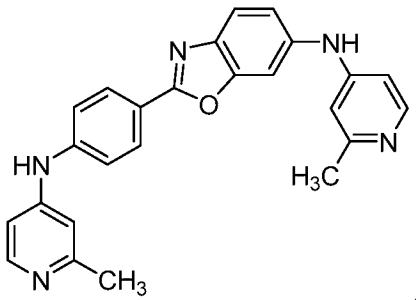
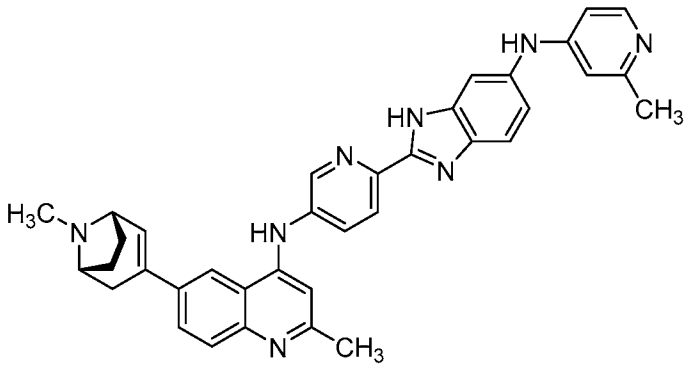
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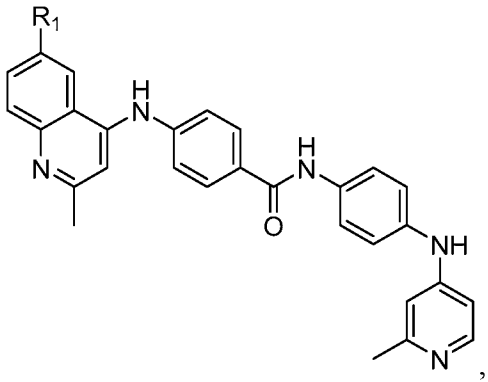
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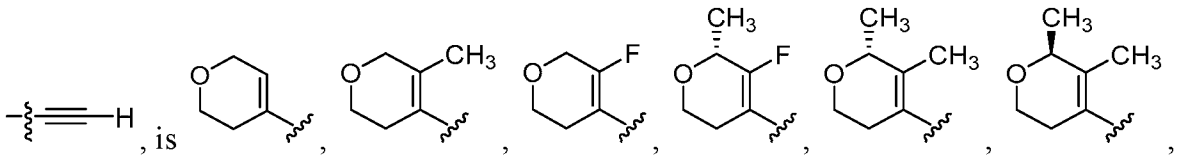
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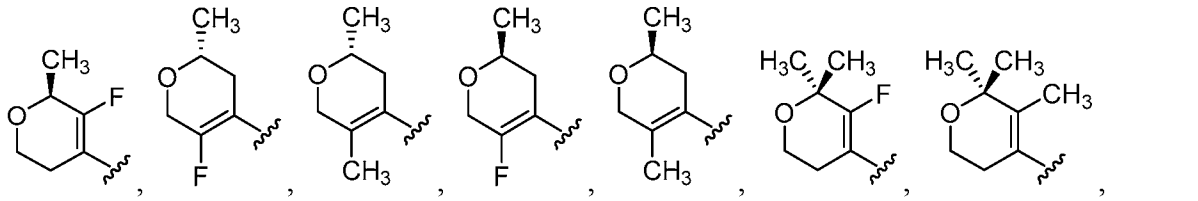
[0359] In some embodiments, the compound of Formula Ia is

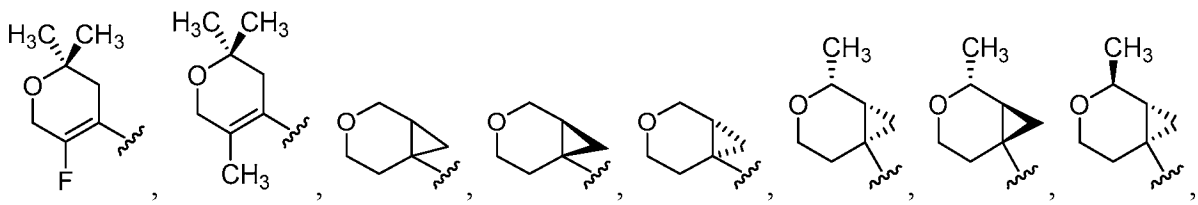


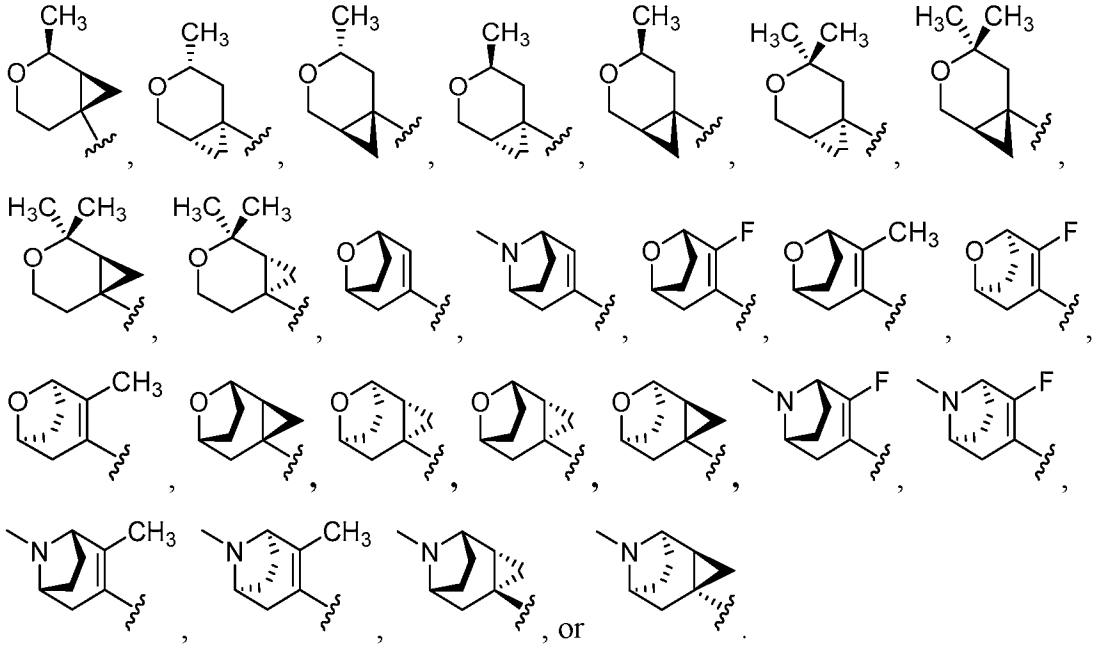
, where R_1 is $-CONH_2$, $-SO_2NH_2$, $-SO_2CH_3$,



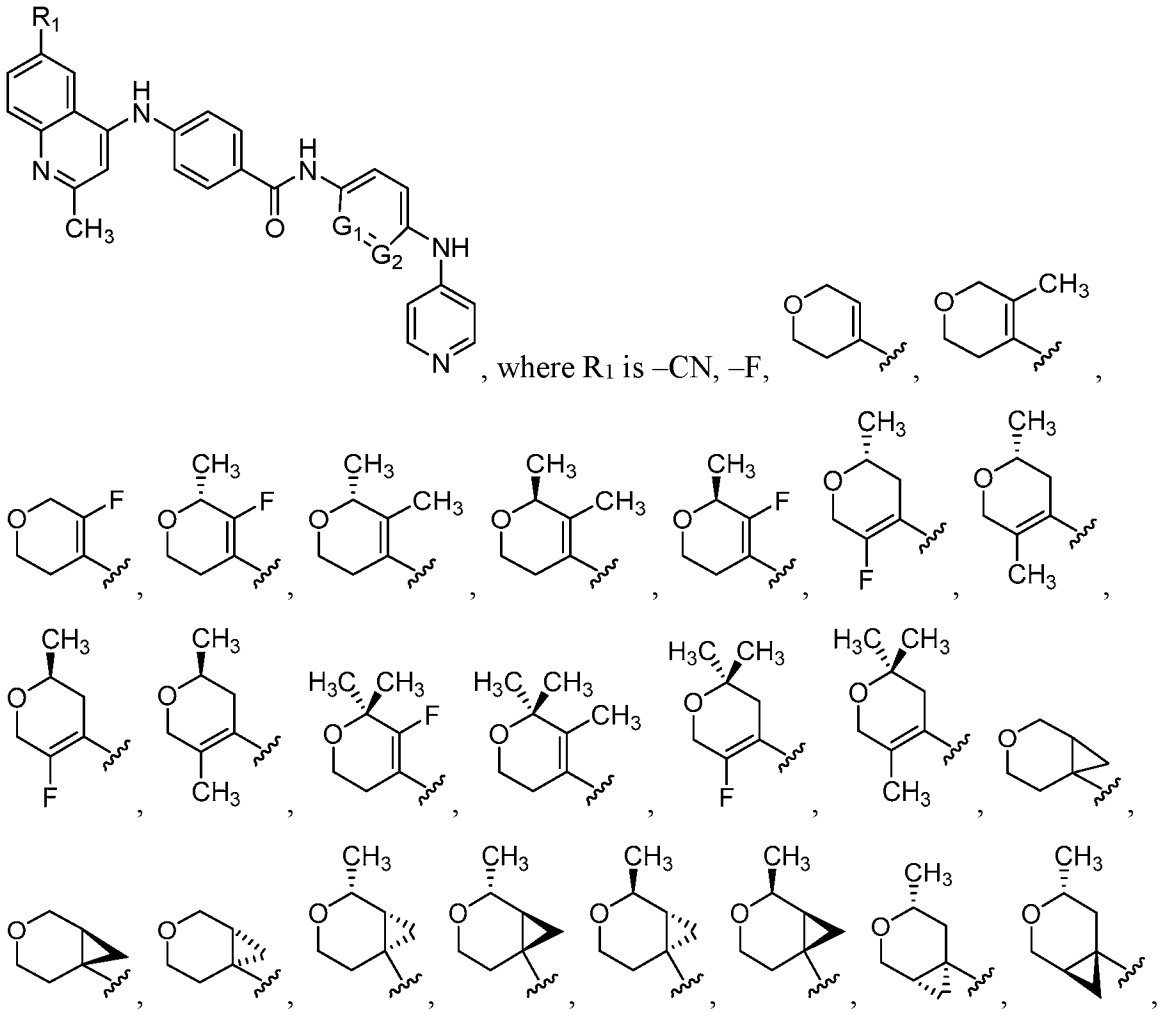
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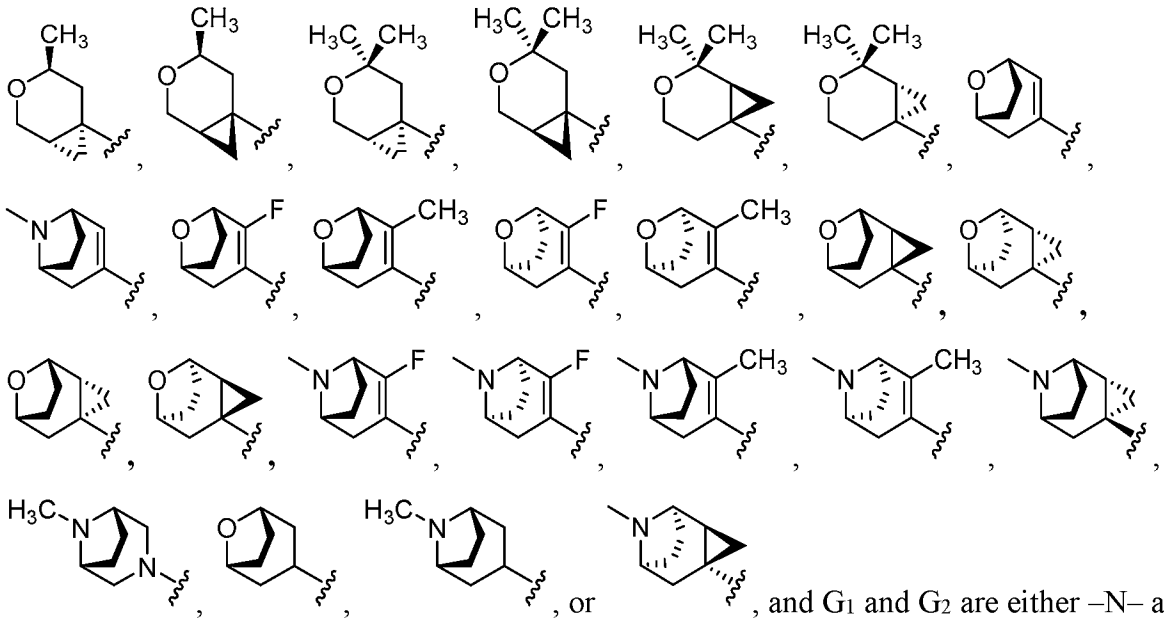




[0360] In some embodiments, the compound of Formula Ia is

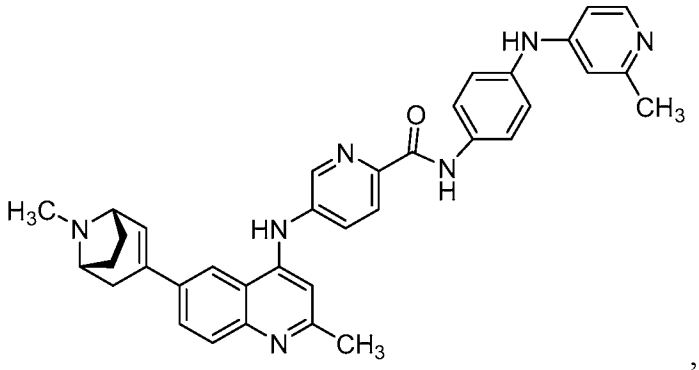


, where R_1 is –CN, –F,

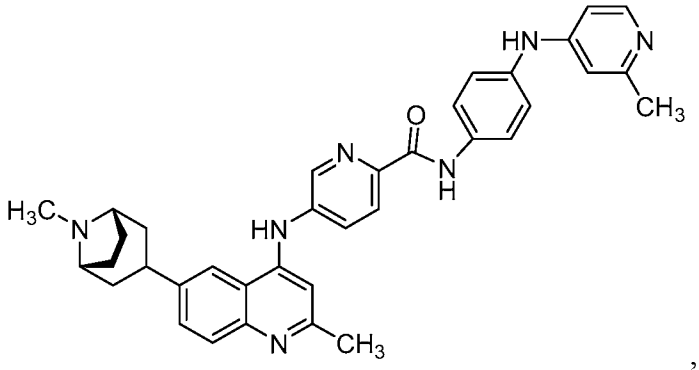


, and G_1 and G_2 are either –N– and –CH–, or –CH– and –N–.

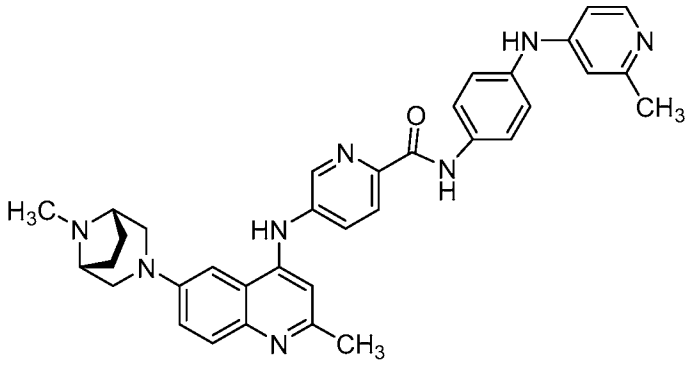
[0361] In some embodiments, the compound of Formula Ia is



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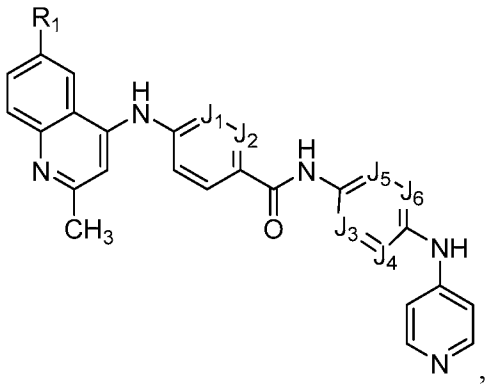


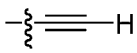
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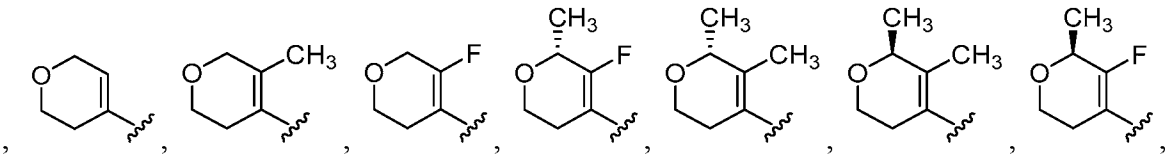


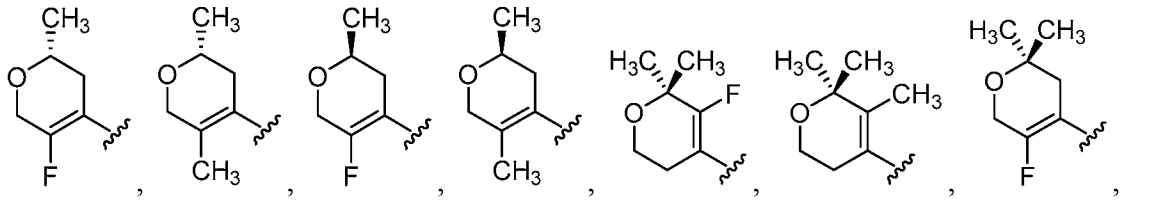
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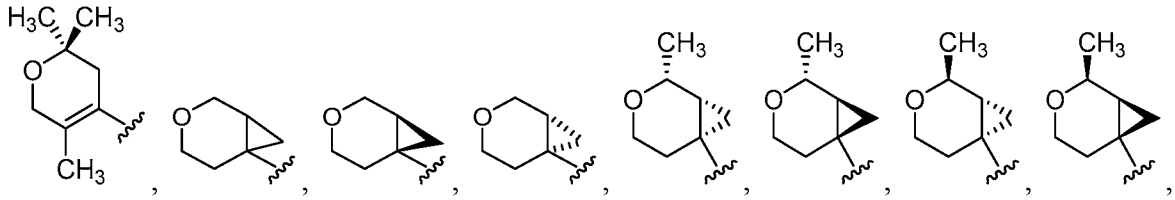
[0362] In some embodiments, the compound of Formula Ia is

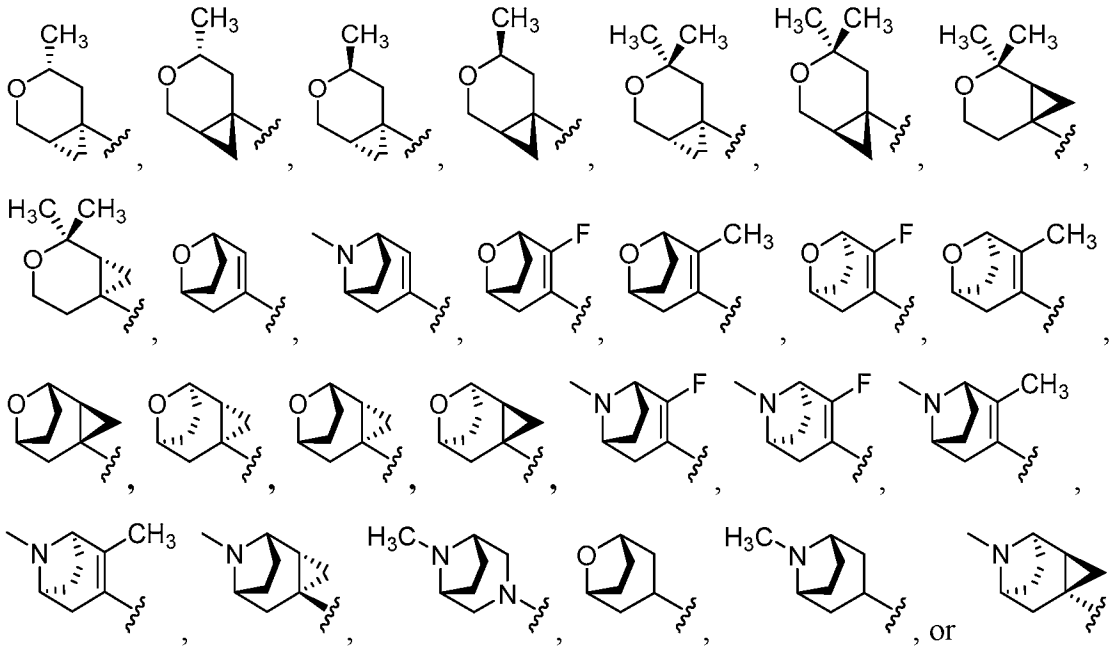


, where R_1 is $-CONH_2$, $-SO_2NH_2$, $-SO_2CH_3$, 



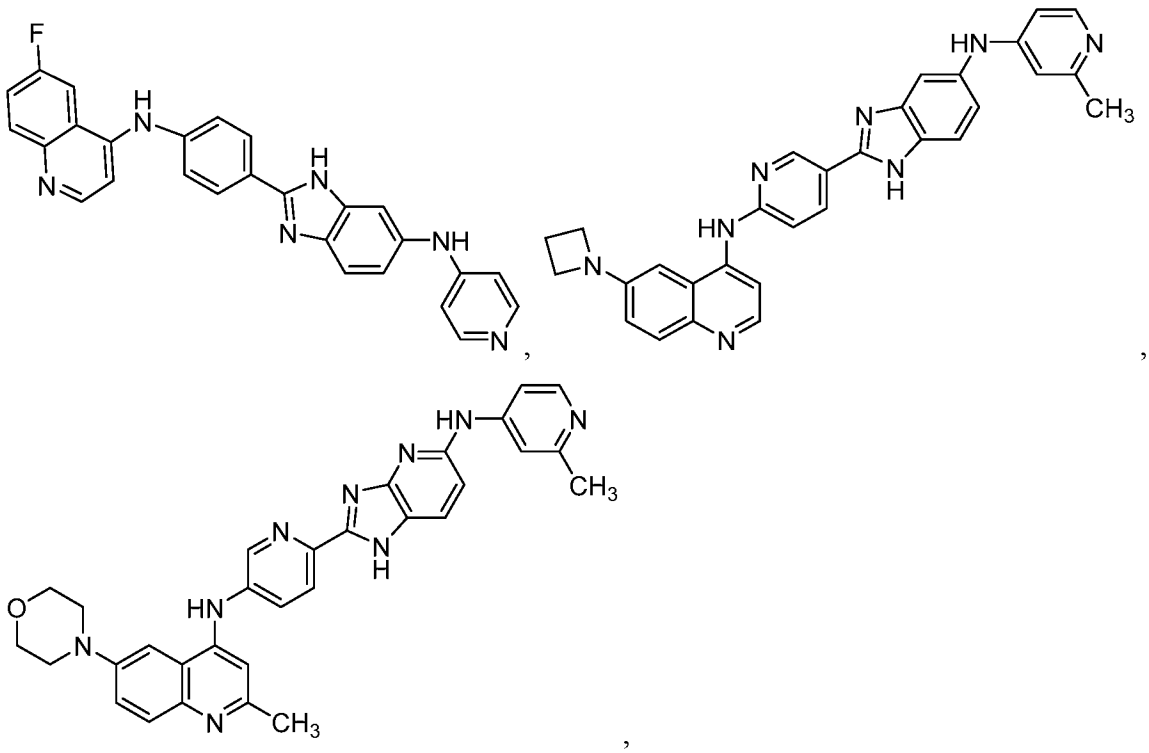


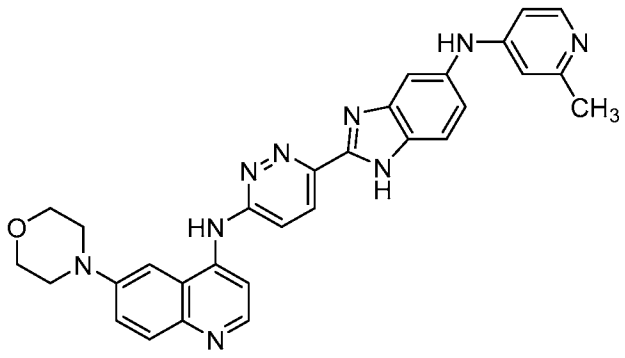




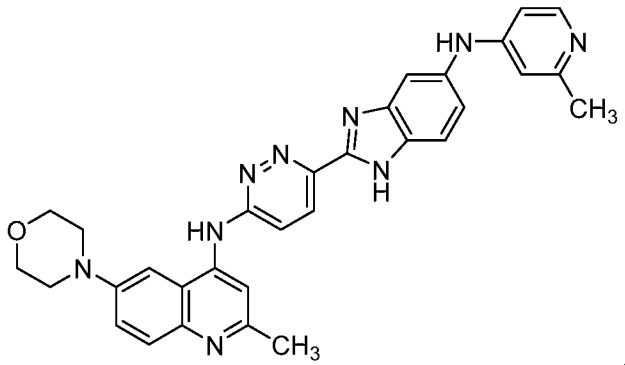
each of J_1, J_2, J_3, J_4, J_5, and J_6 is independently –N– or –CF.

[0363] In some embodiments, the compound of Formula Ib is

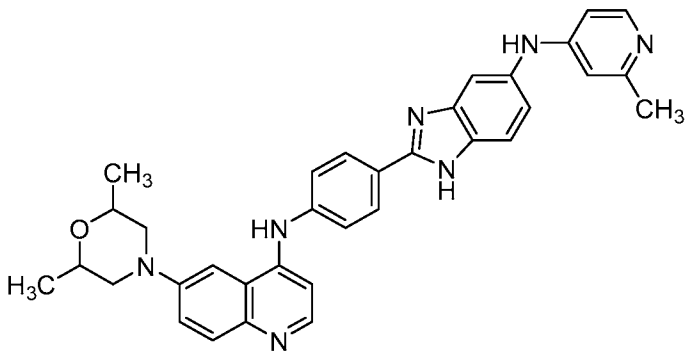




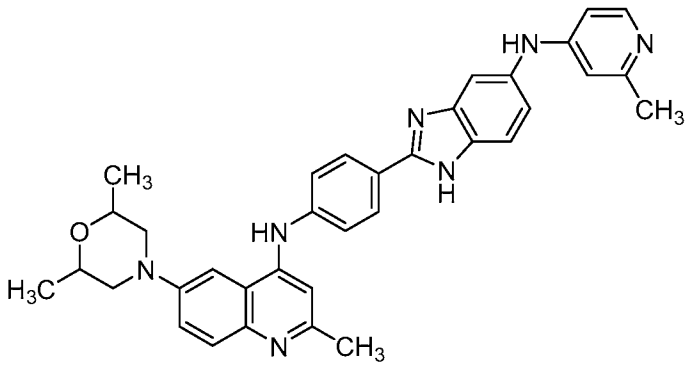
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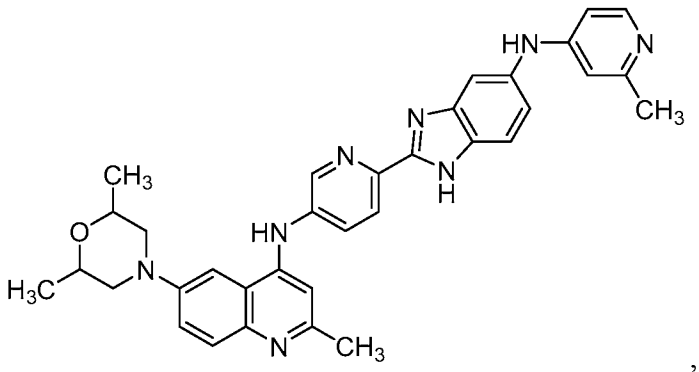
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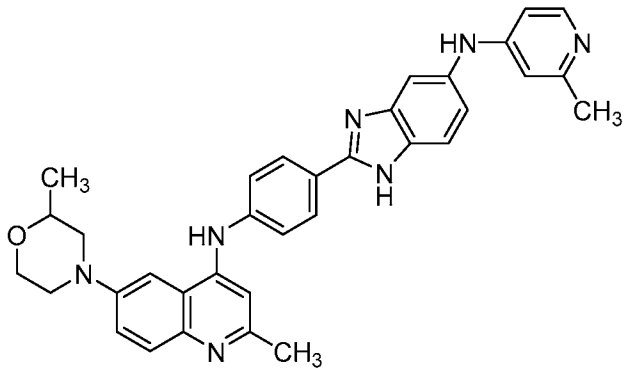
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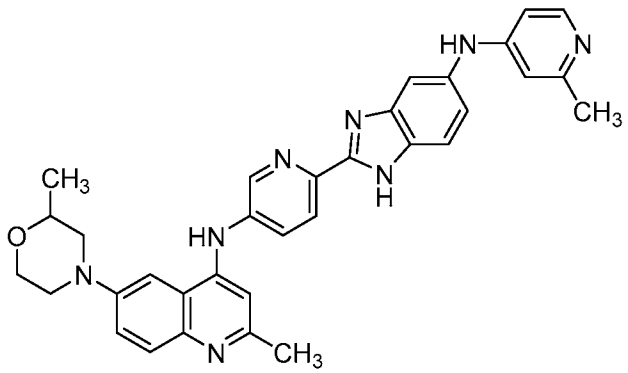
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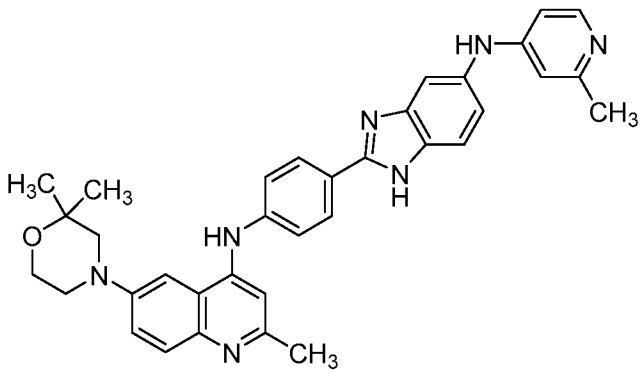
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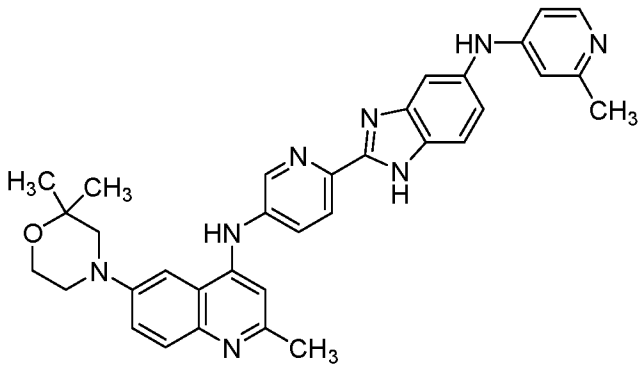
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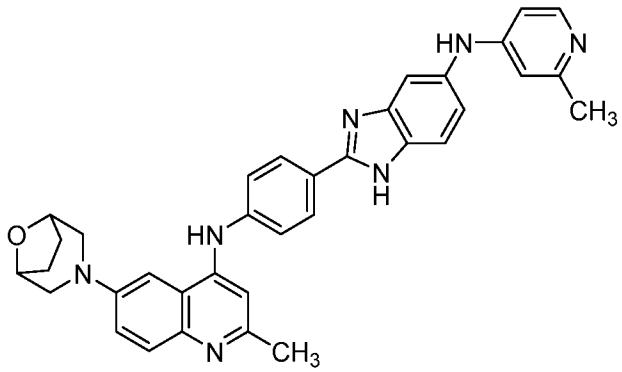
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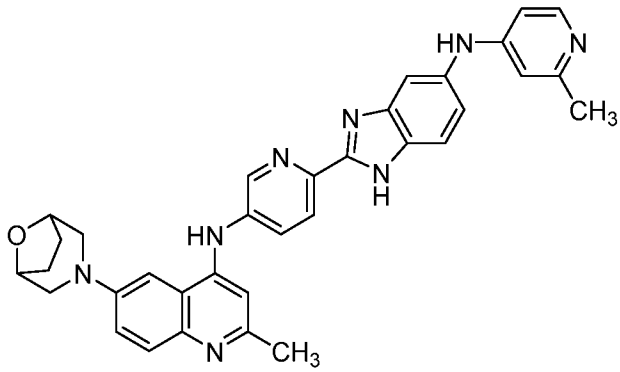
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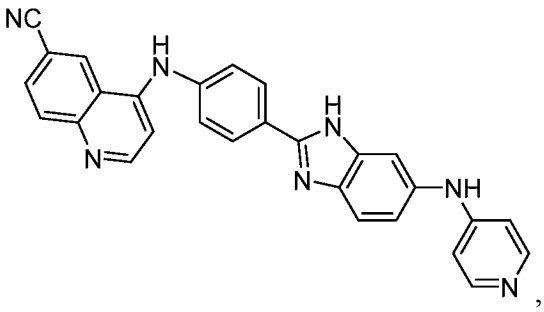
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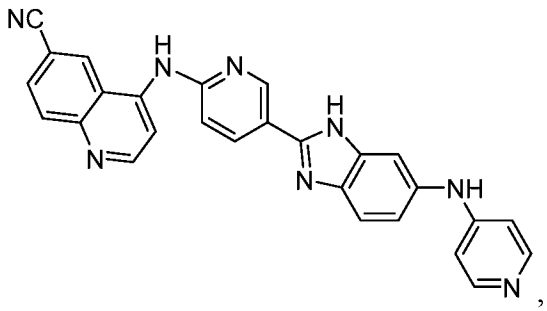
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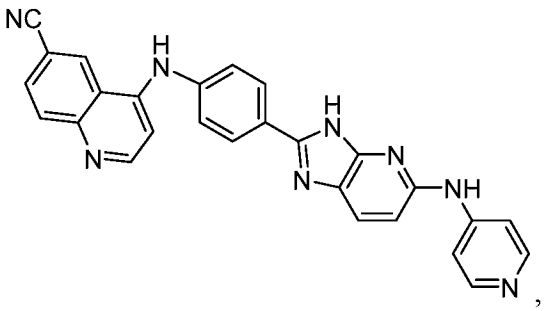
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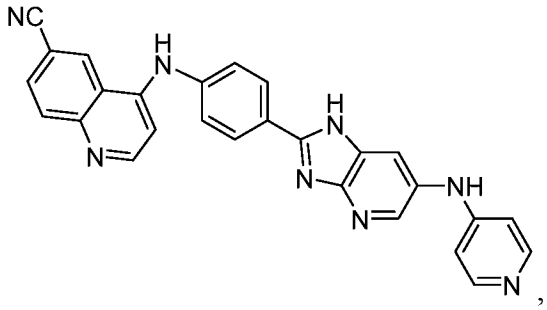
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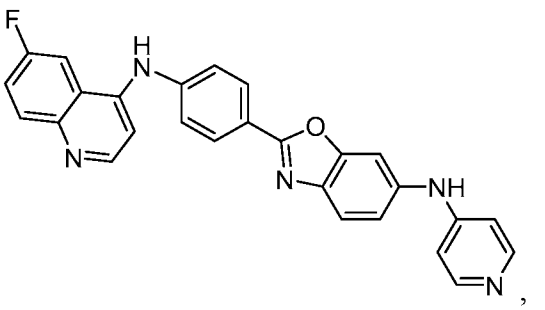
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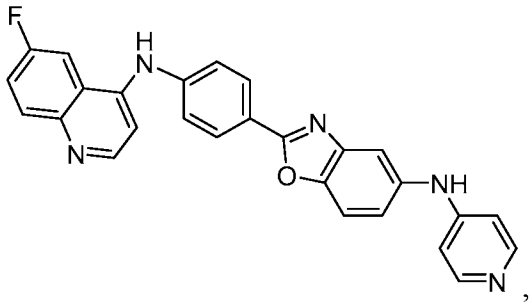
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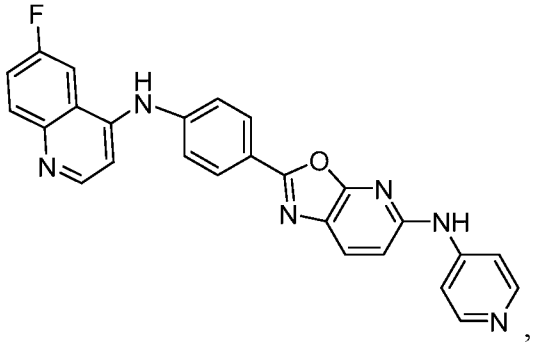


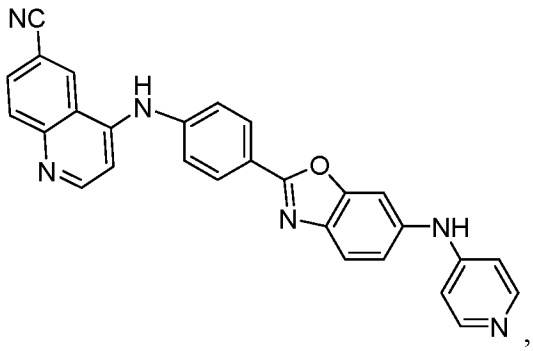
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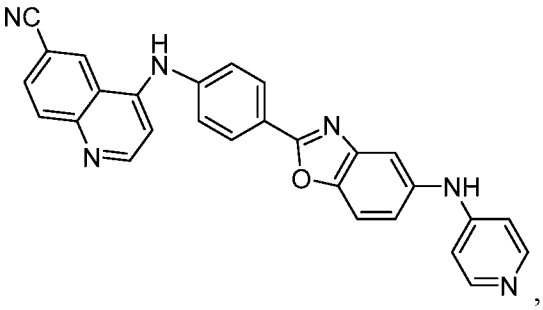


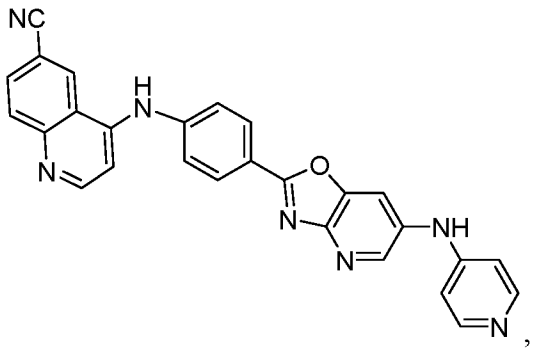
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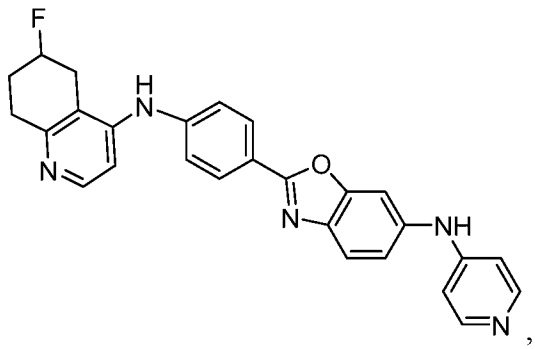


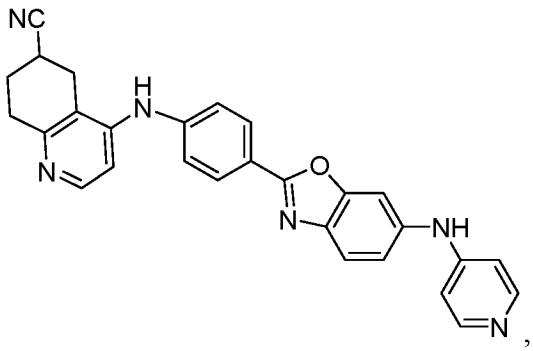


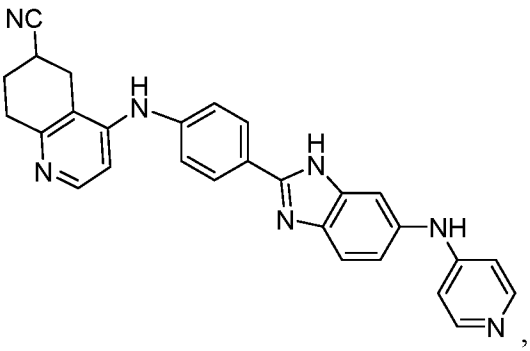


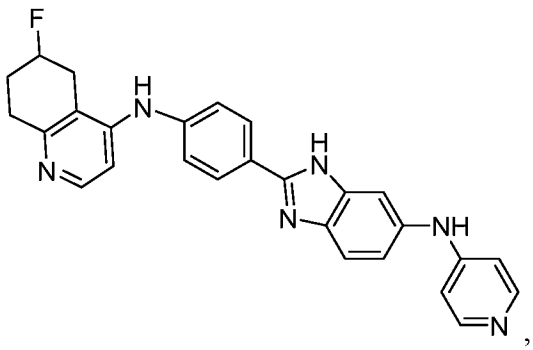


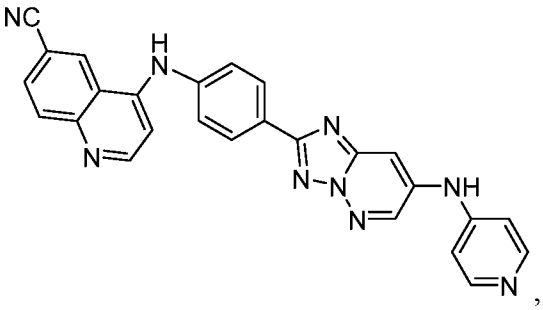


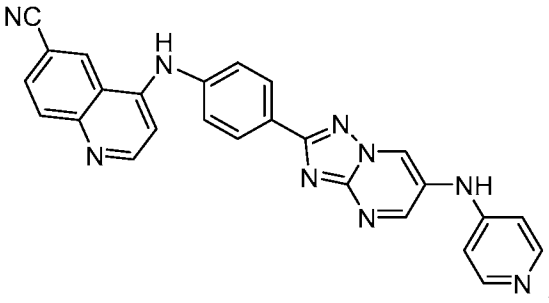
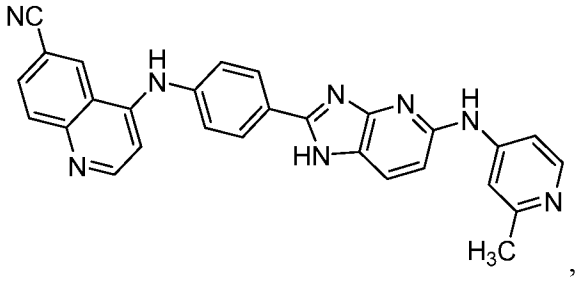
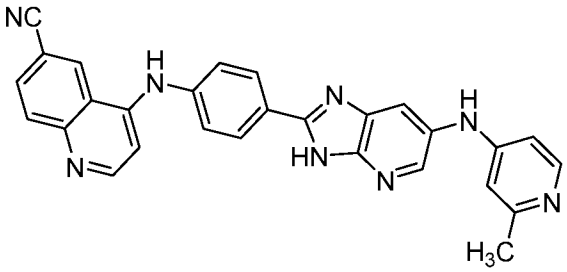
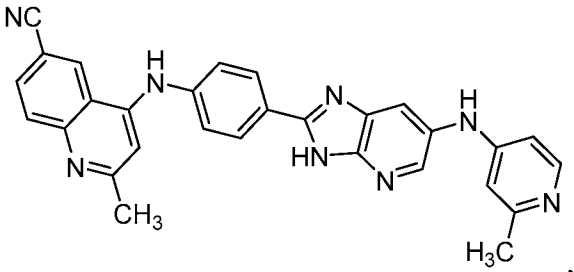
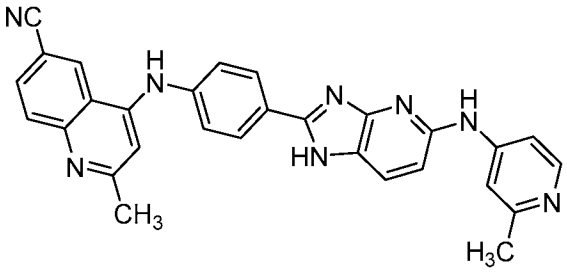
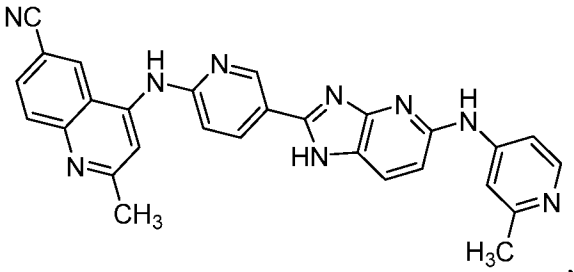
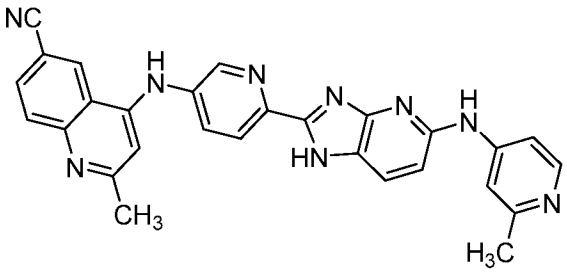
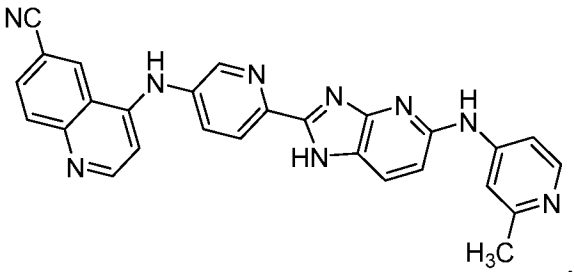
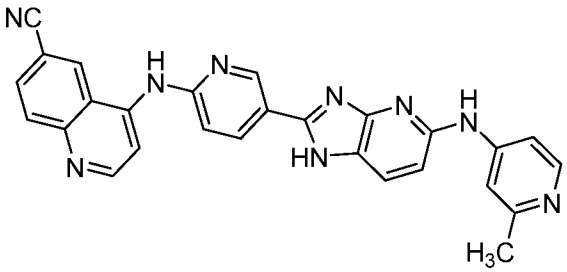
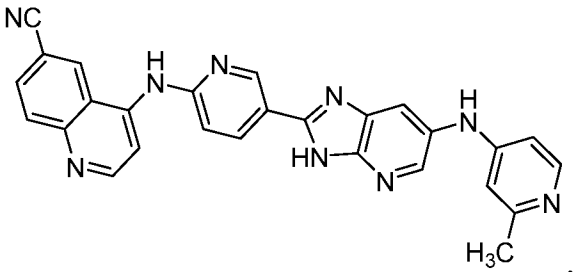
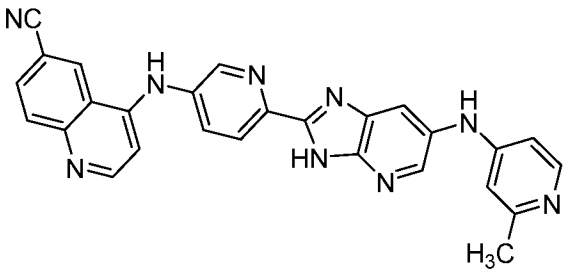
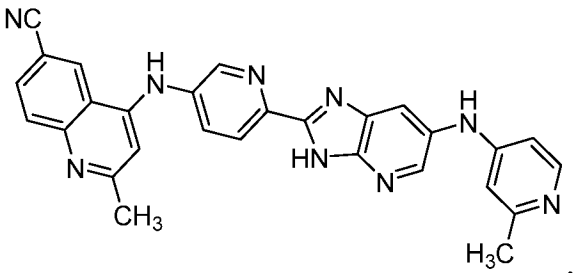


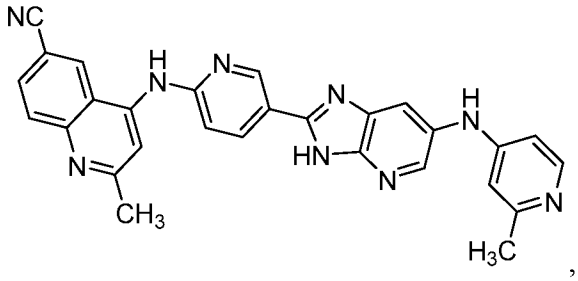
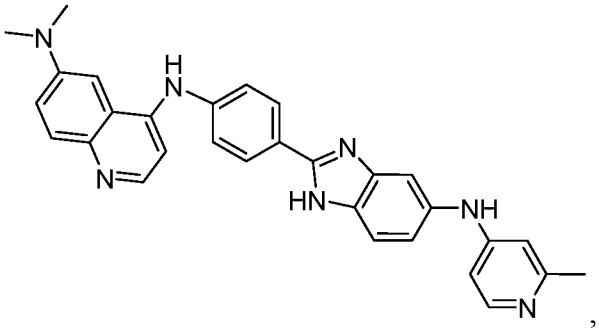
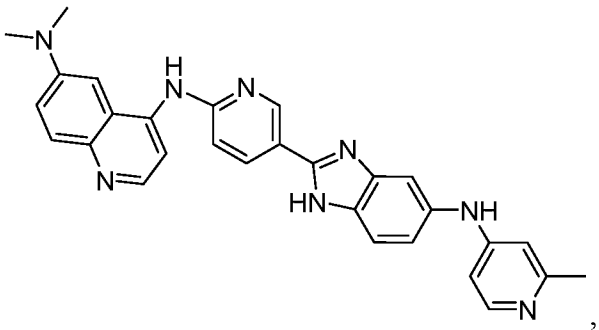
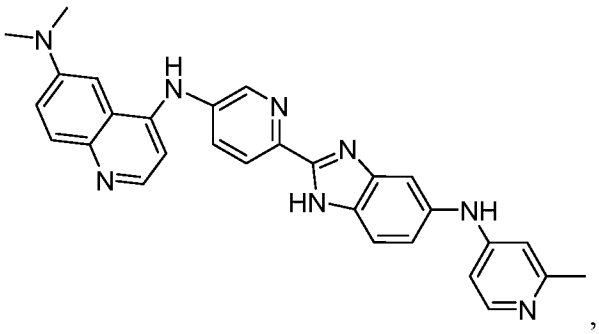
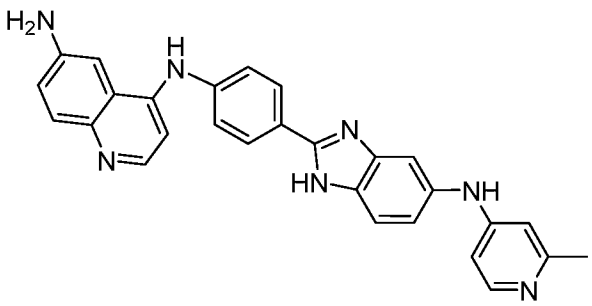
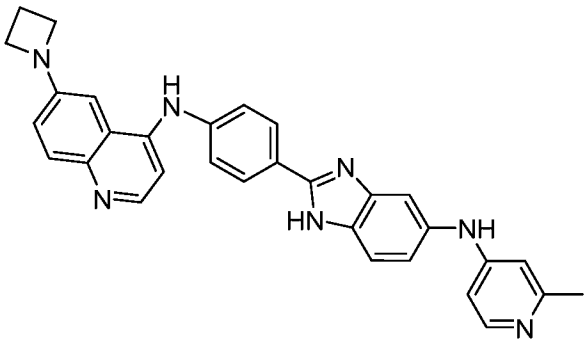
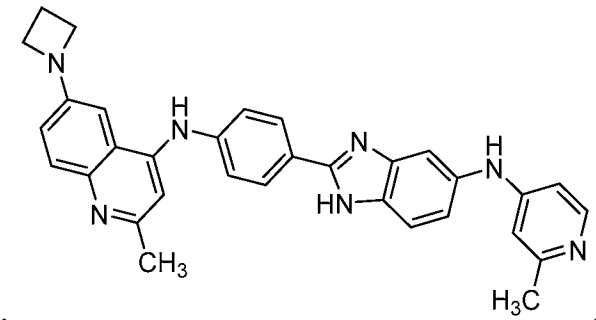
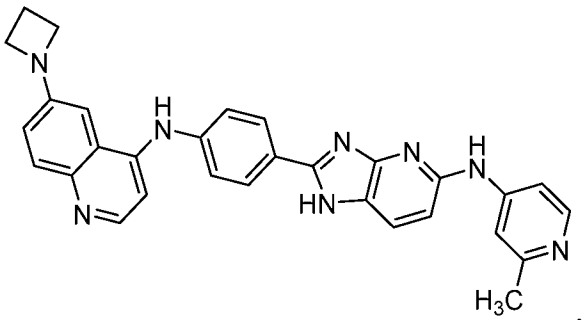
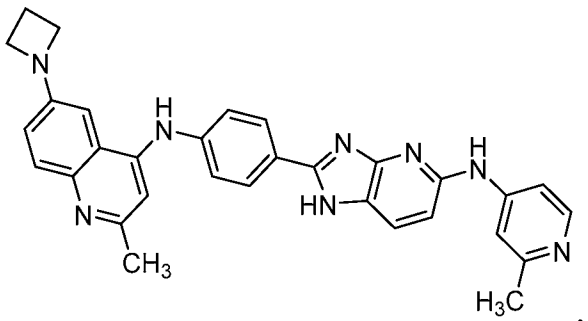
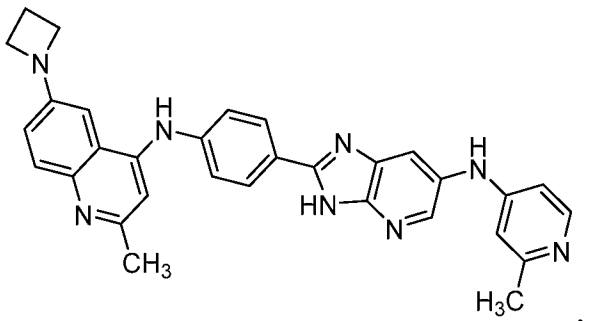


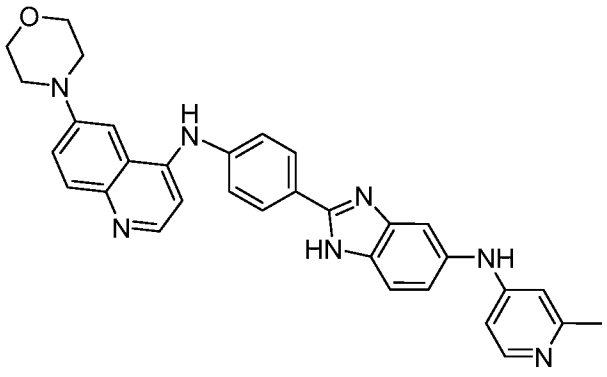




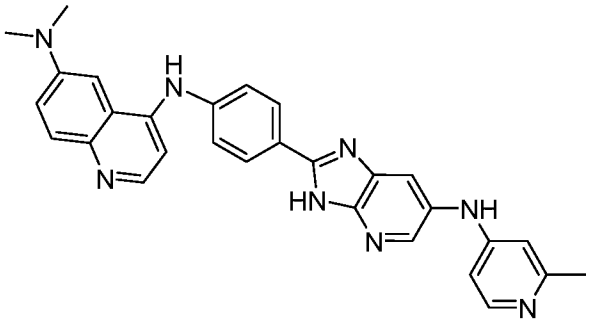



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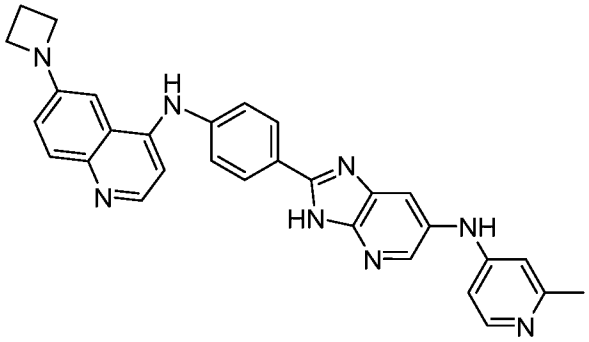

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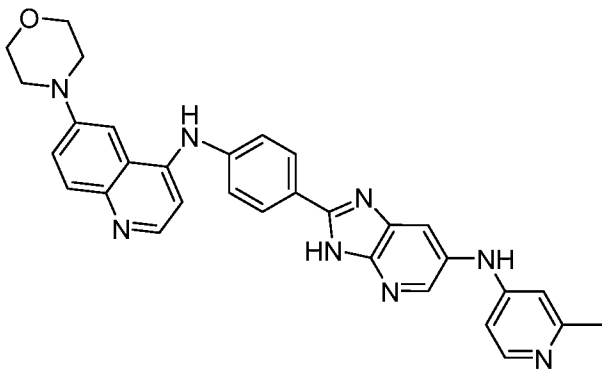
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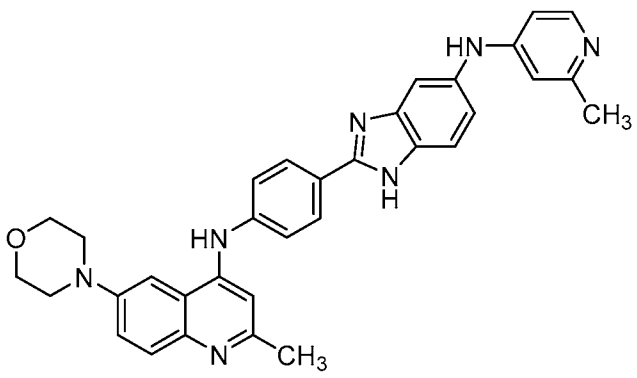
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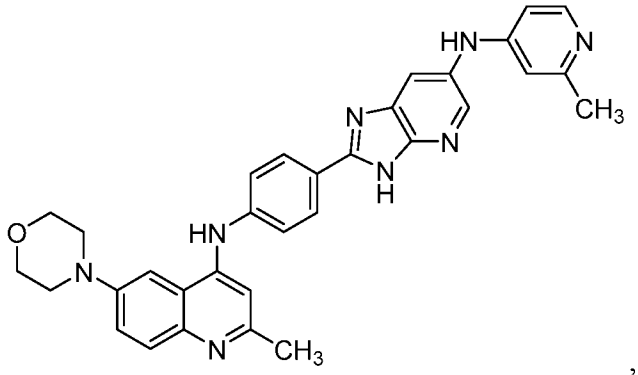
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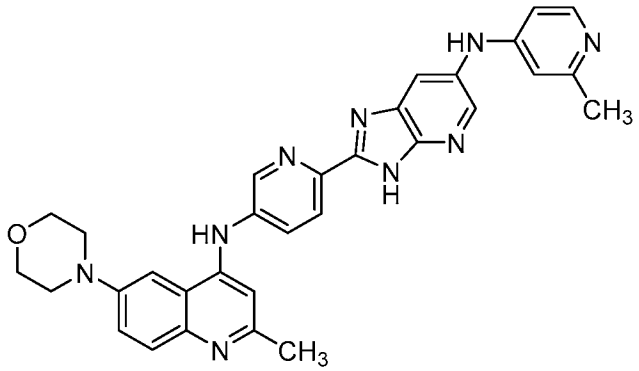
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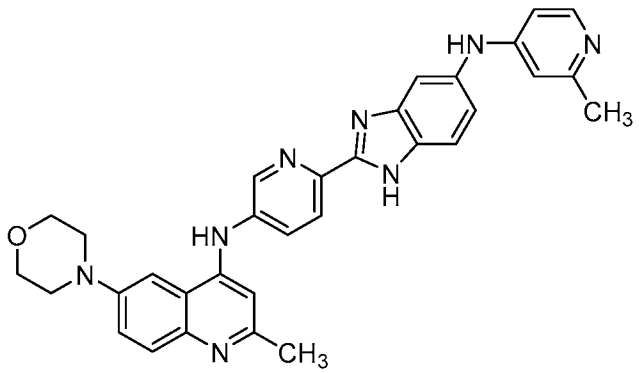
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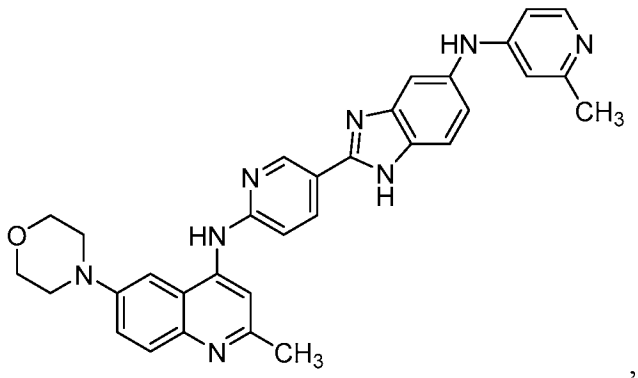
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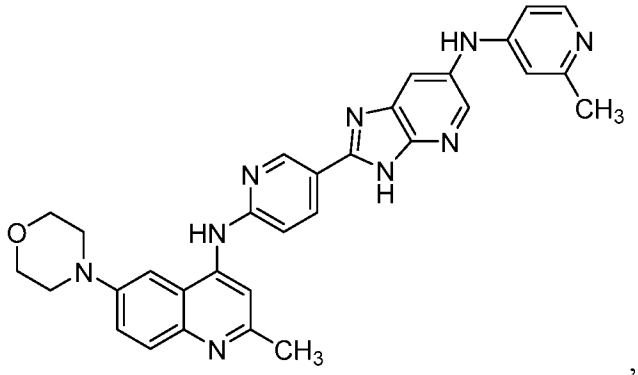
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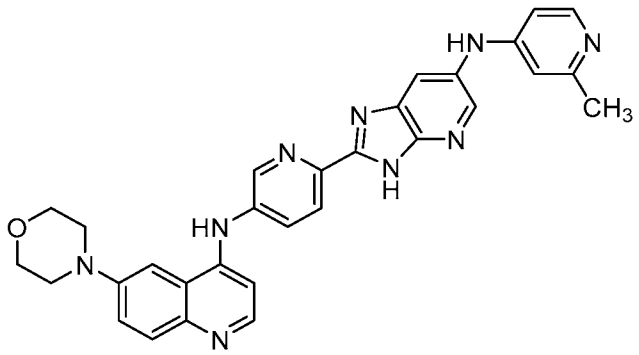
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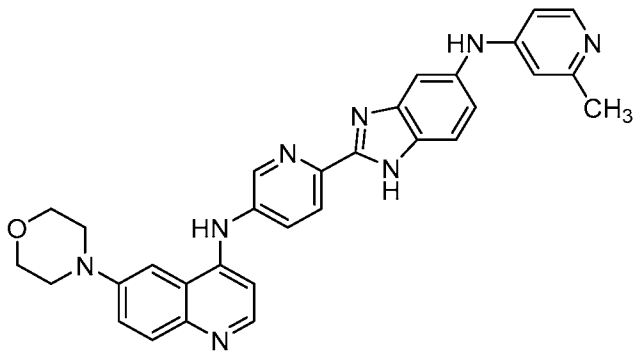
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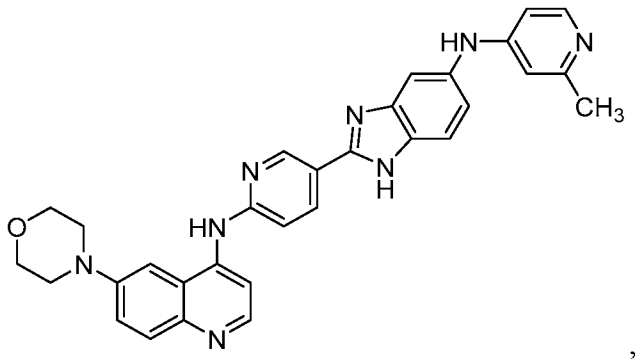
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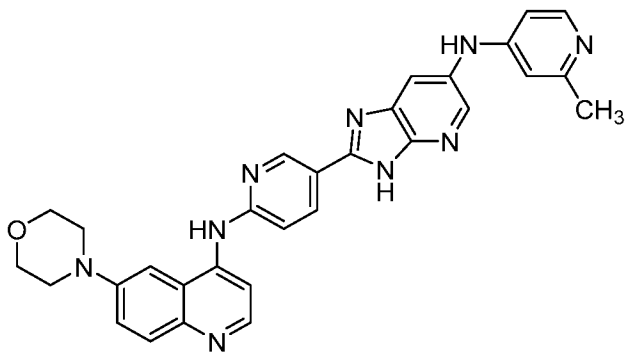
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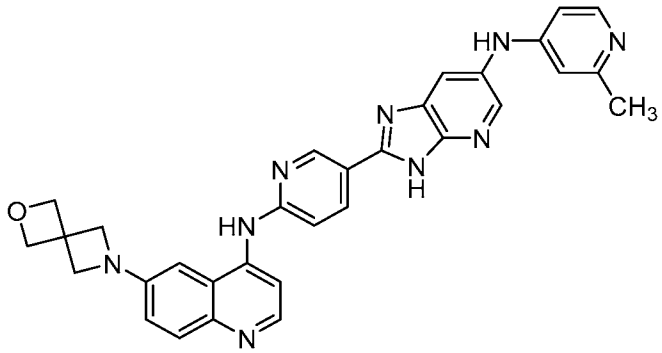
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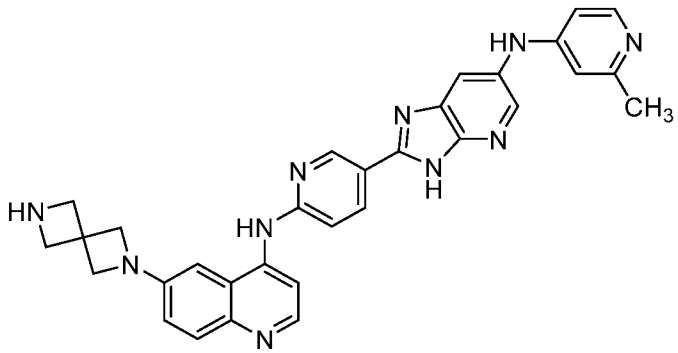
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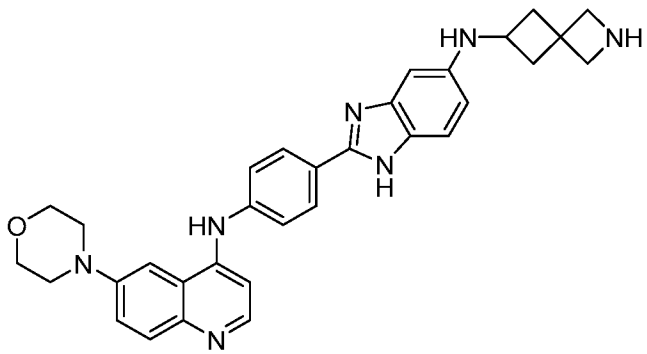
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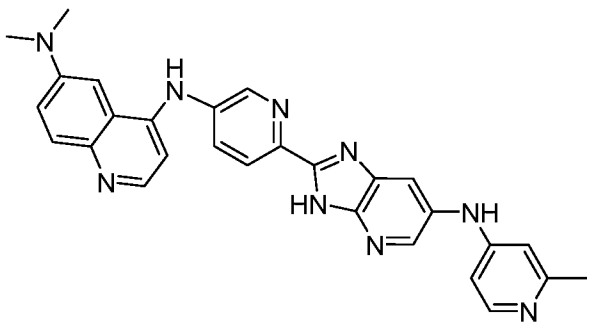
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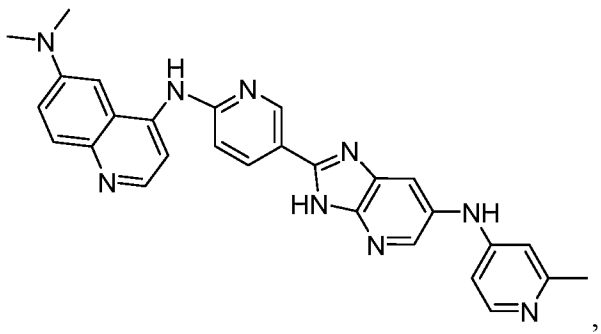
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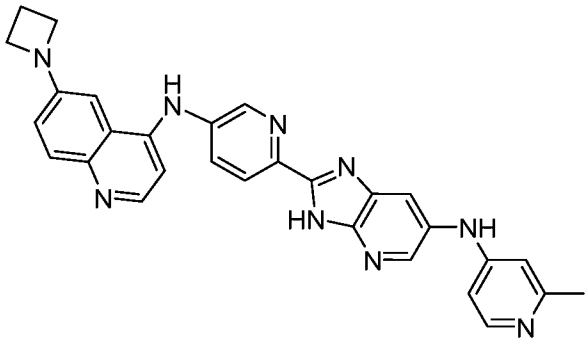
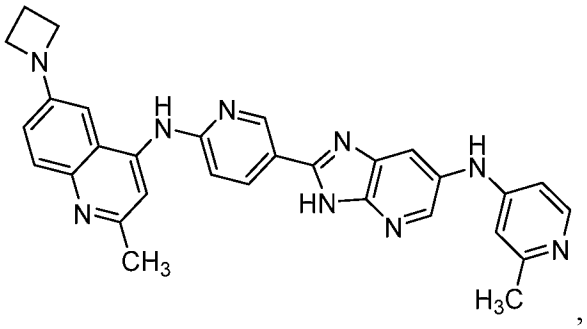
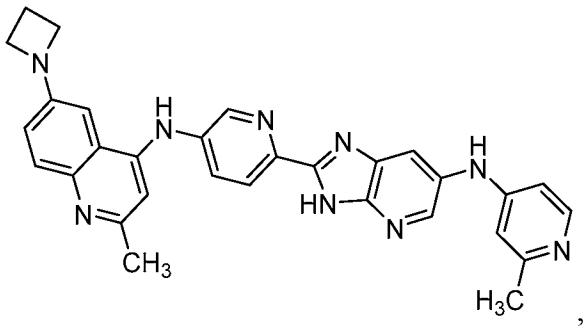
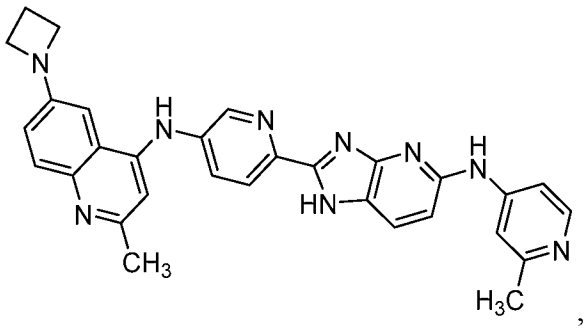
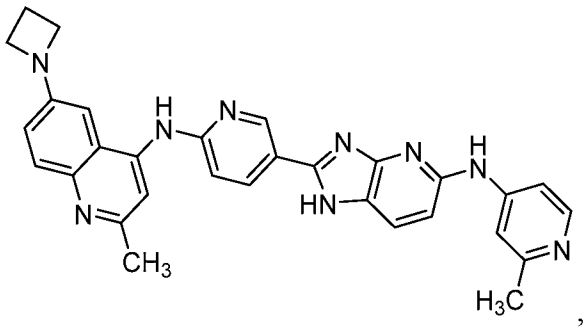
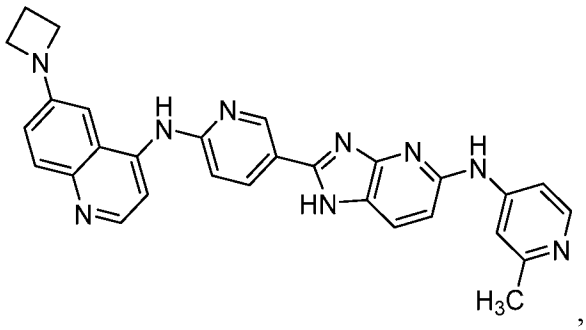
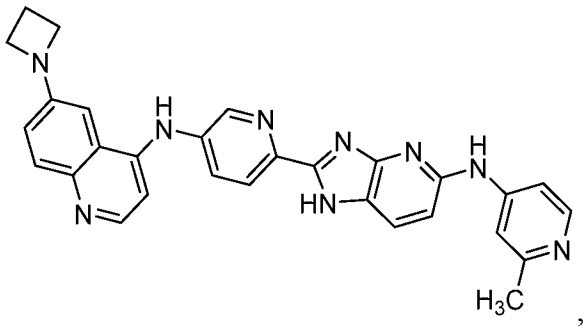
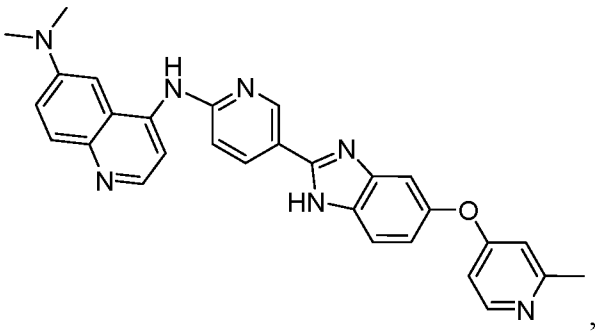
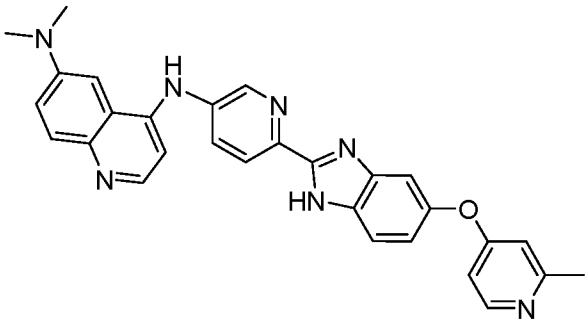
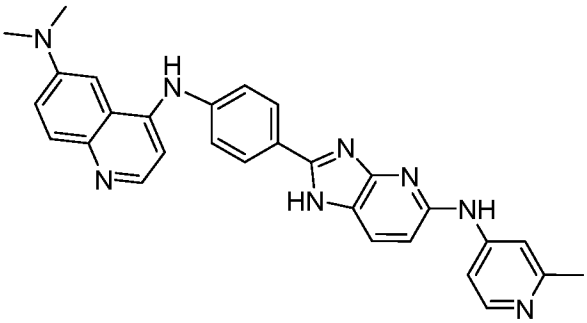
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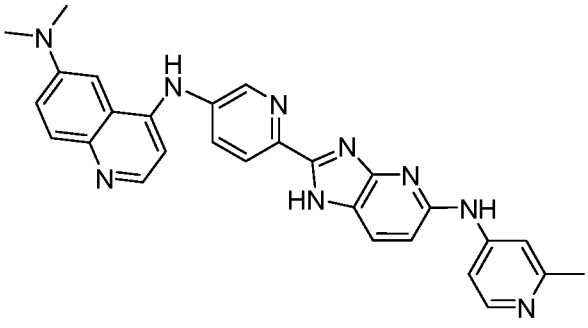


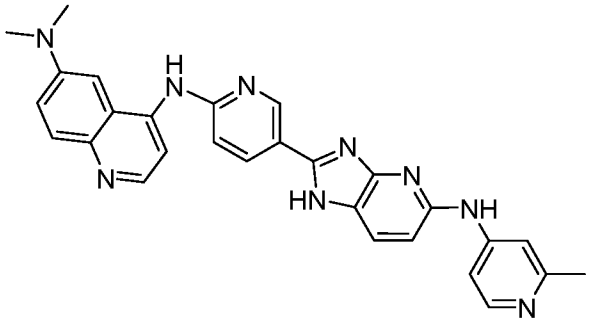
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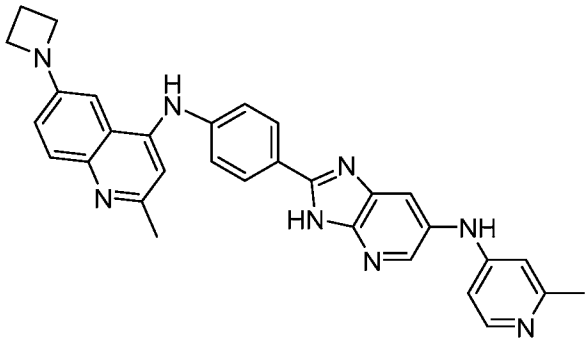


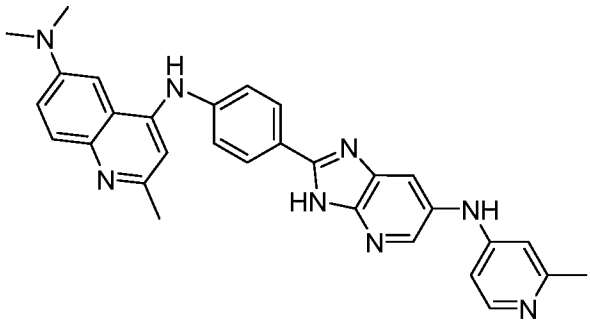
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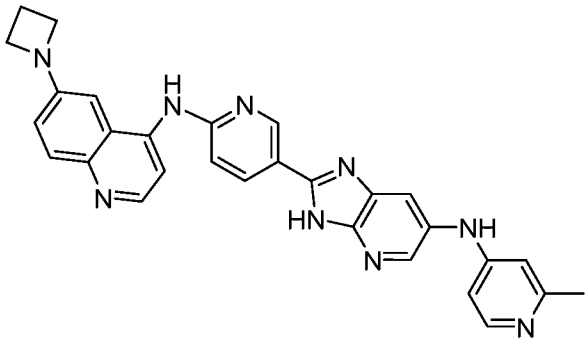

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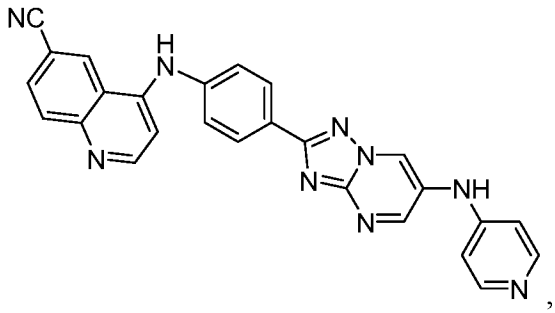

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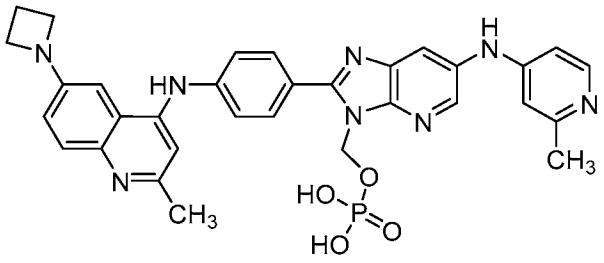

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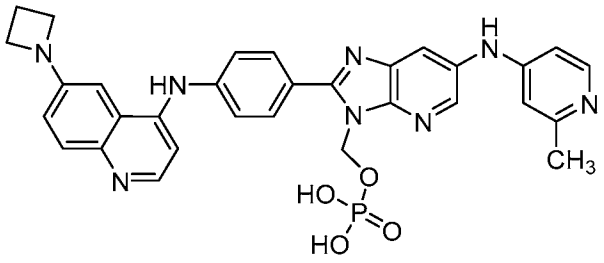

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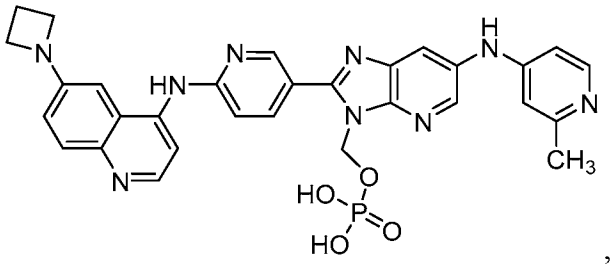

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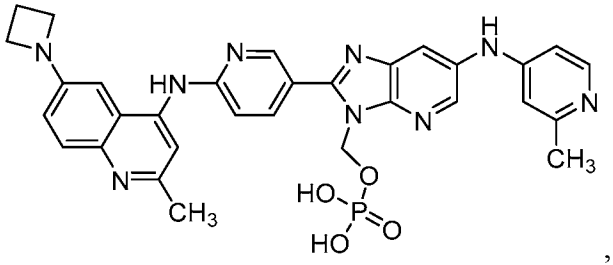

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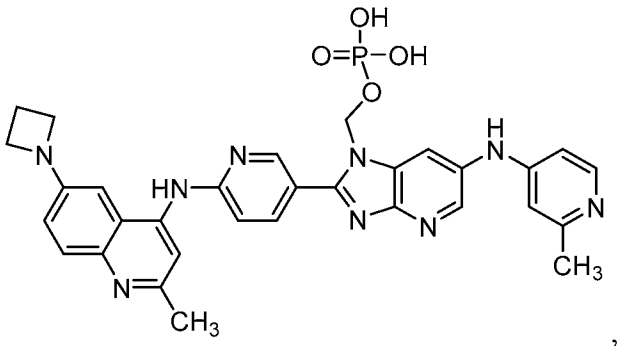

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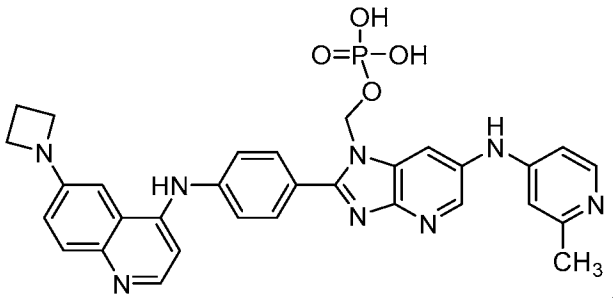
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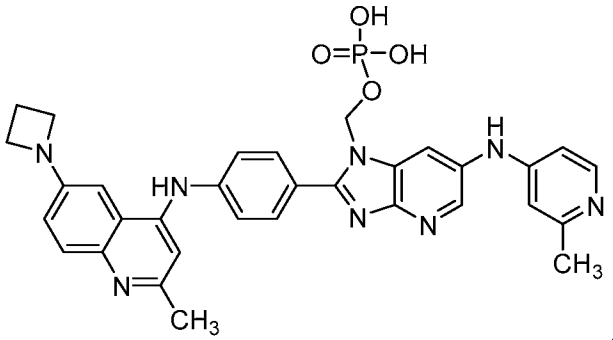
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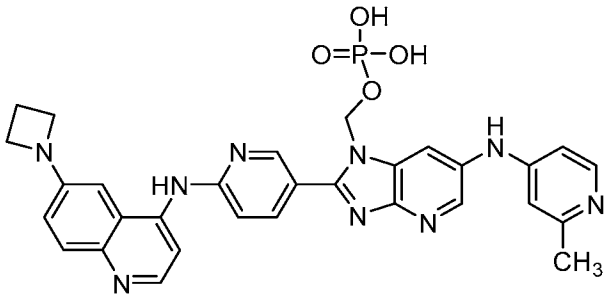
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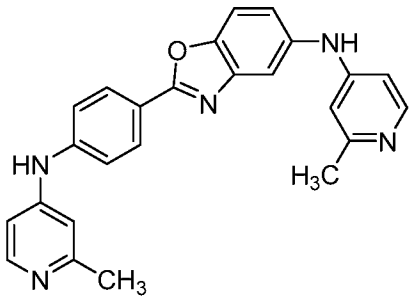
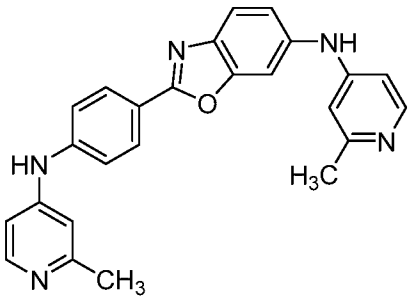


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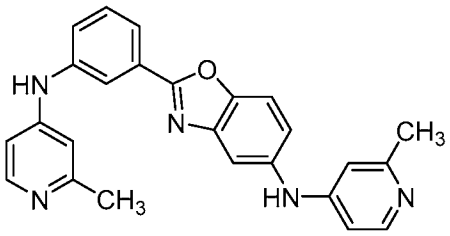
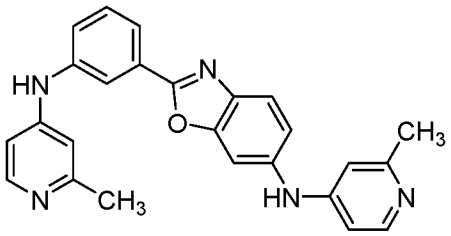


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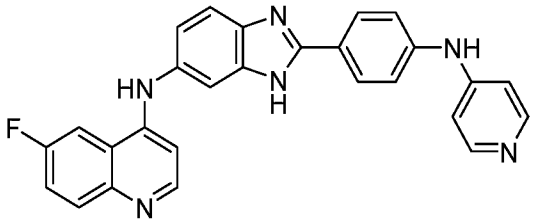
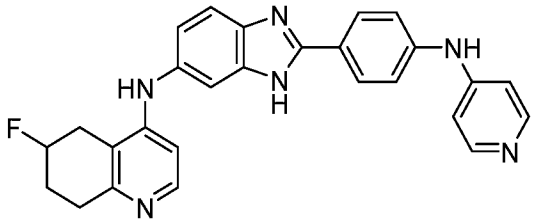


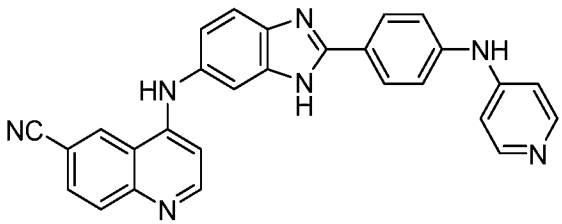
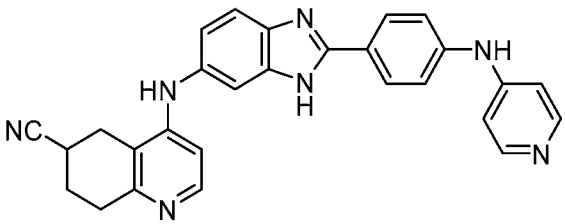
. In some embodiments, the compound of Formula Ib is  or .

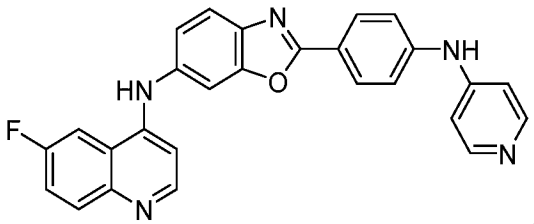
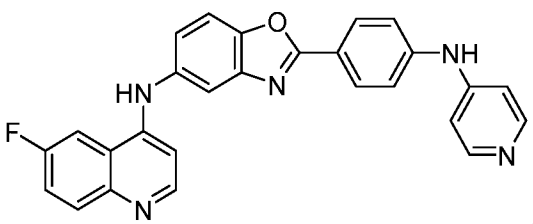
[0364] In some embodiments, the compound of Formula IIb is

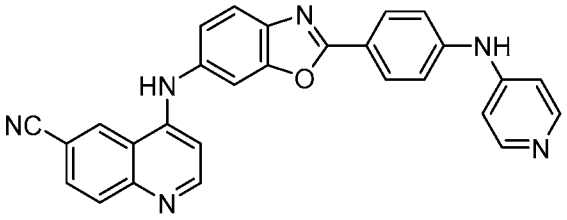
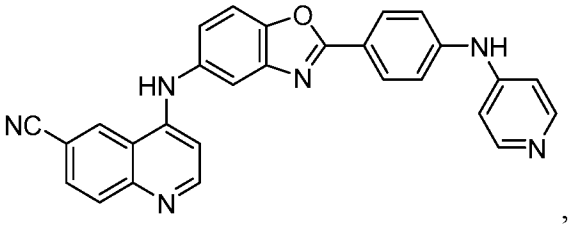
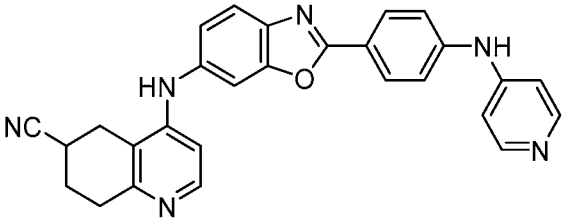
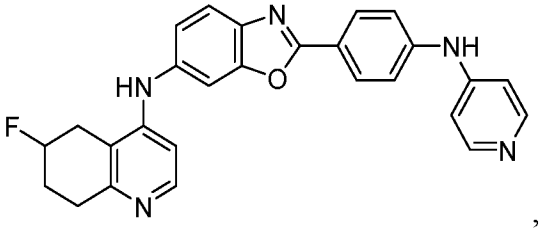
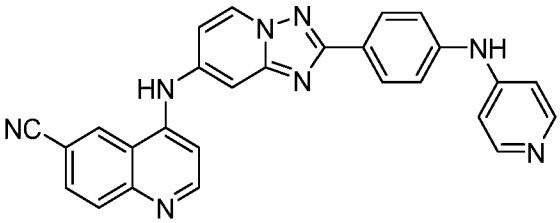
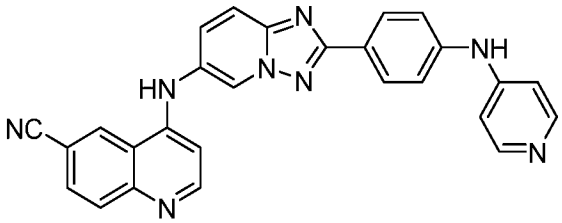
 or .

[0365] In some embodiments, the compound of Formula Ic is

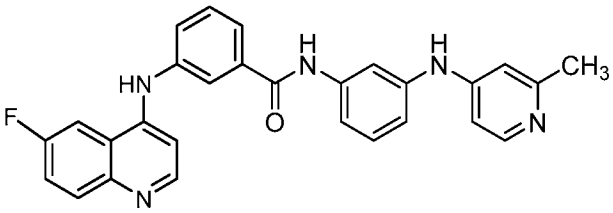
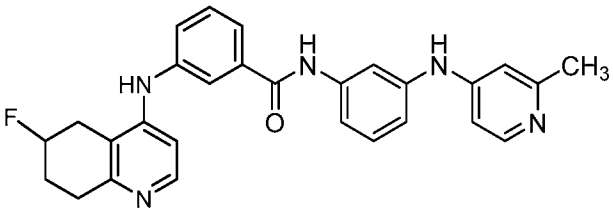
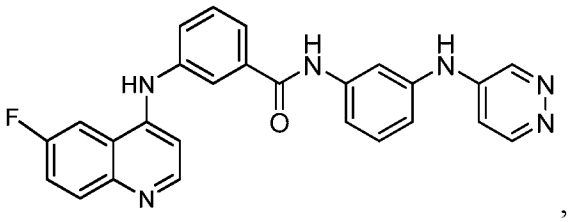
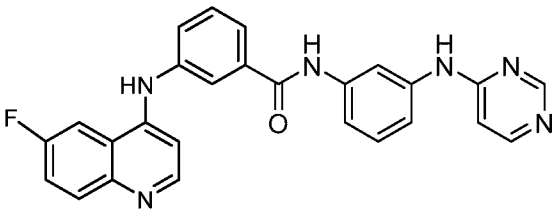
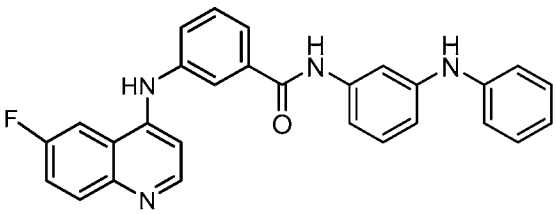
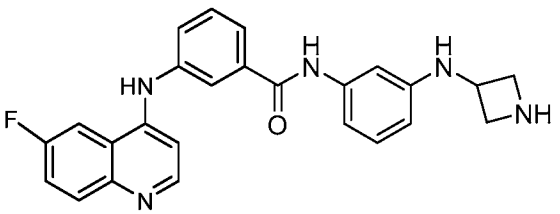
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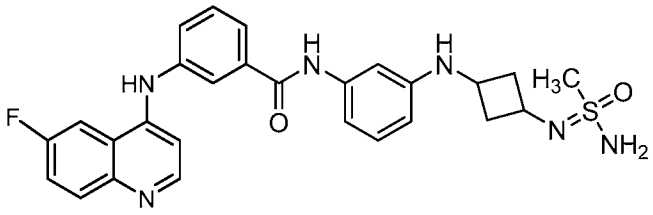
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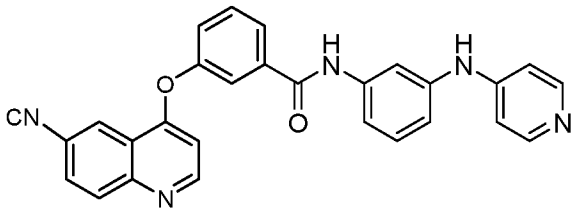

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[0366] In some embodiments, the compound of Formula IIa is

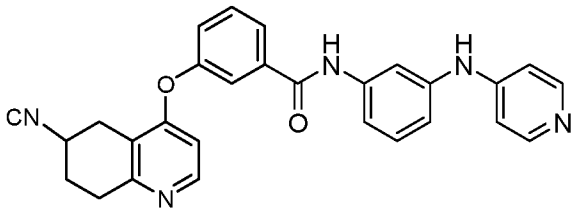

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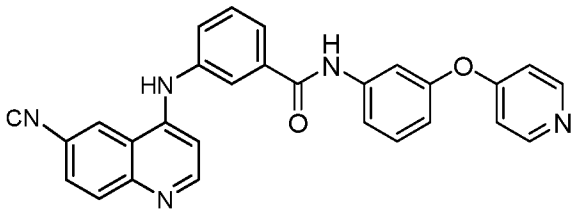
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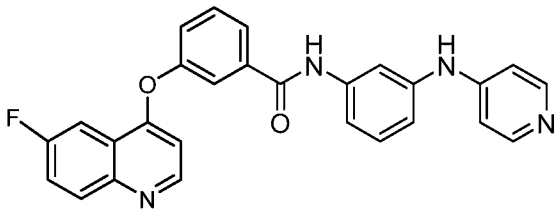
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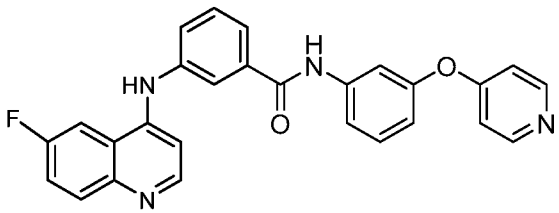
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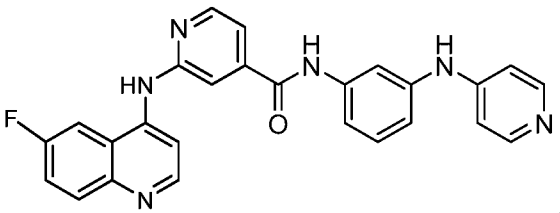
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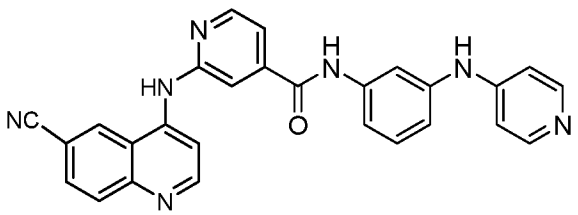
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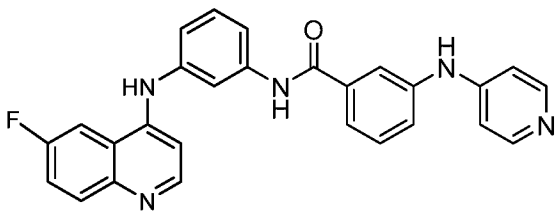
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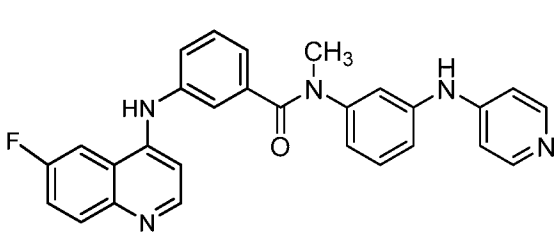
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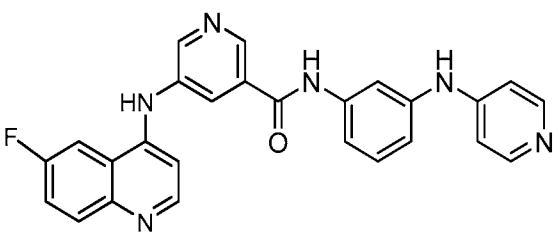
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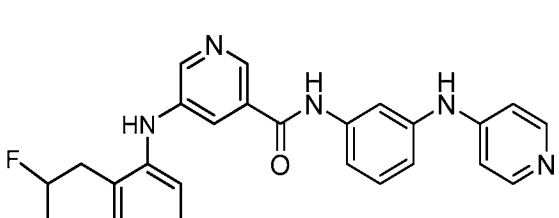
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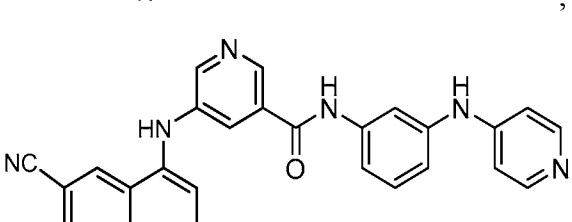
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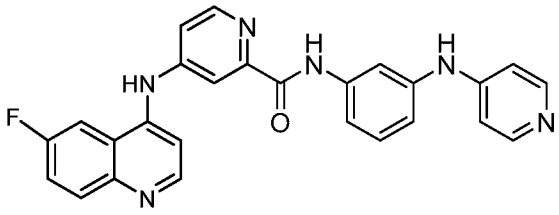
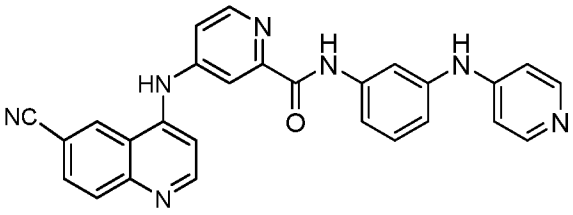
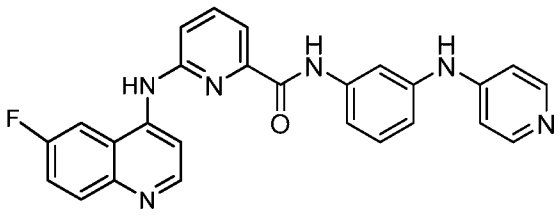
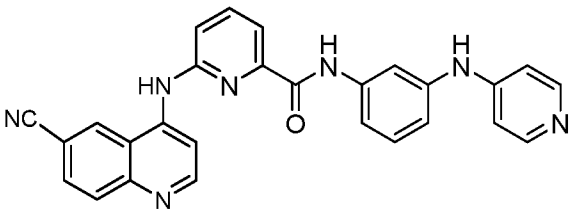
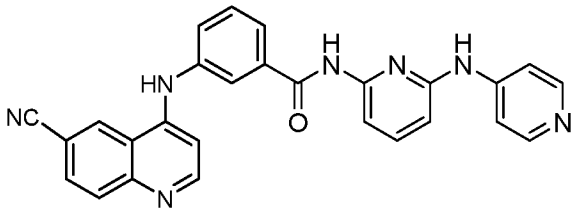
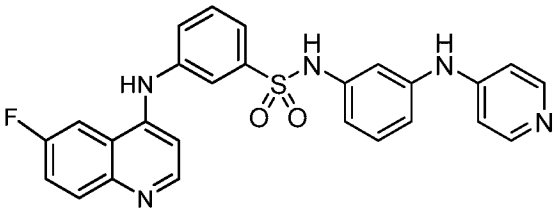
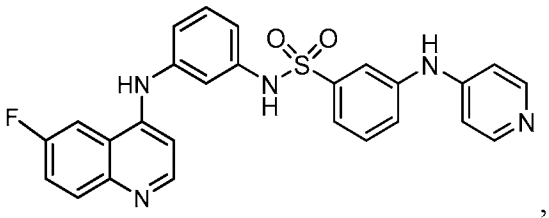
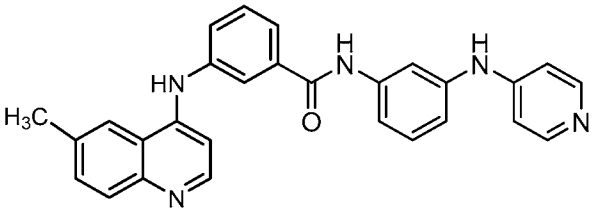
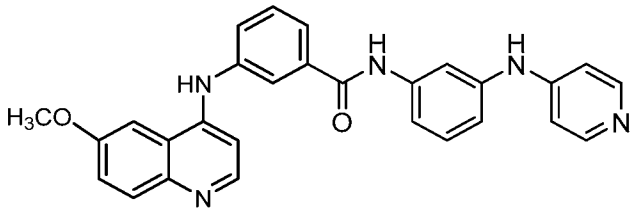
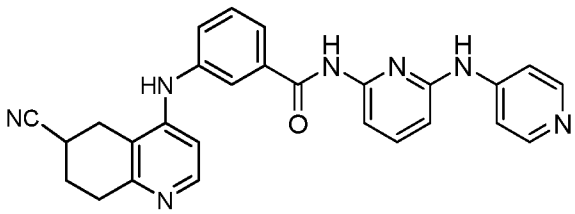
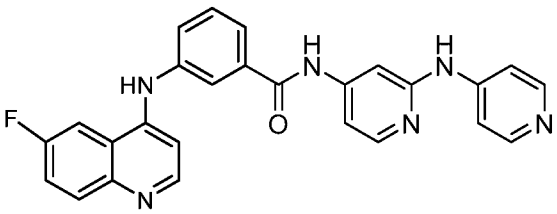
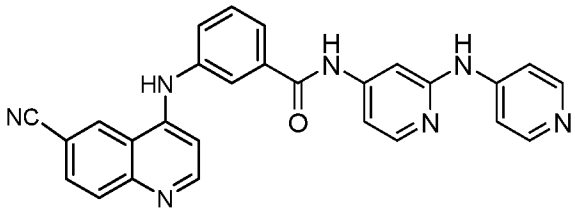
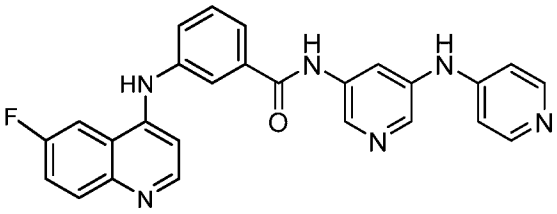
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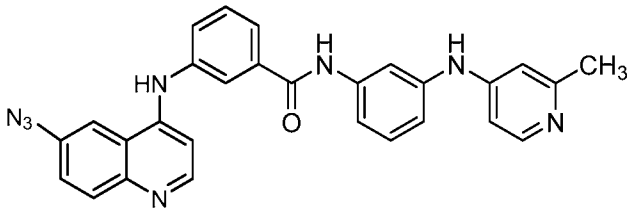


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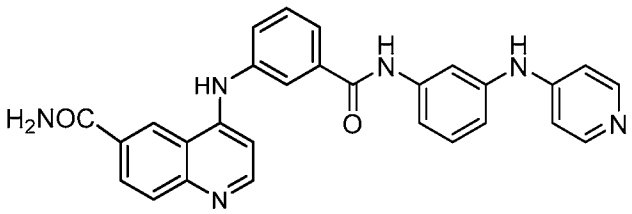


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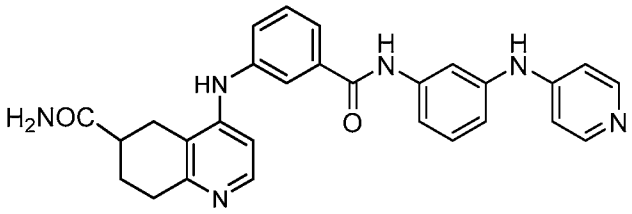

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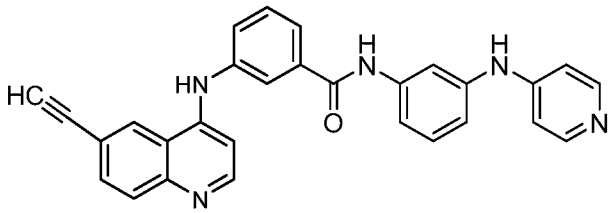
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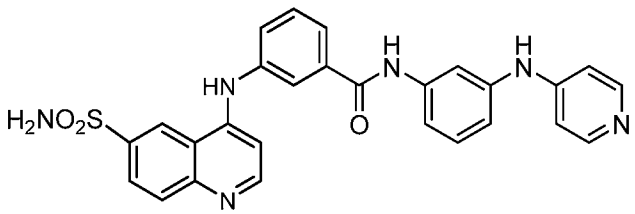
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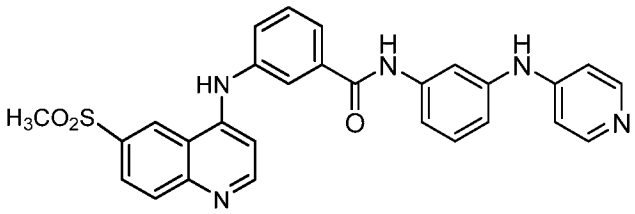
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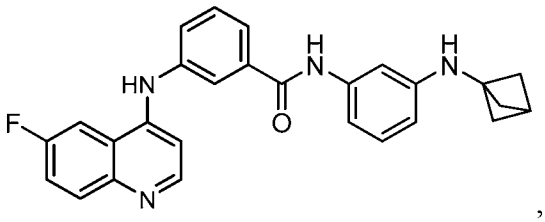
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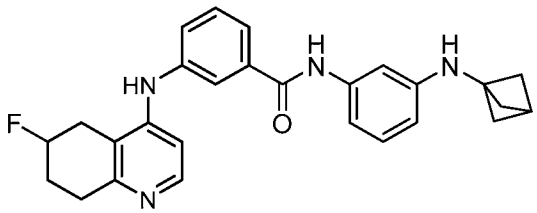
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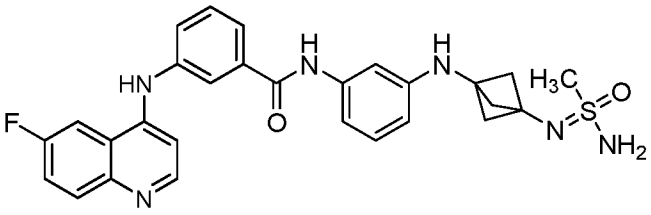
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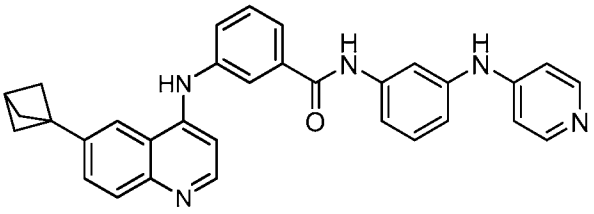
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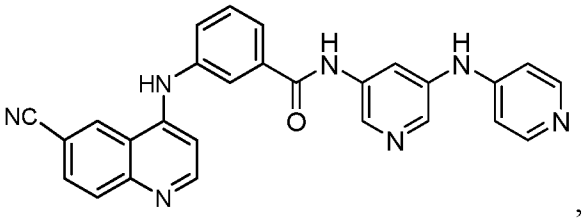
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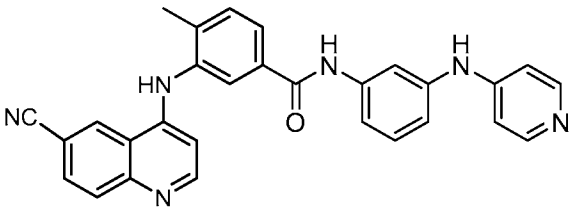
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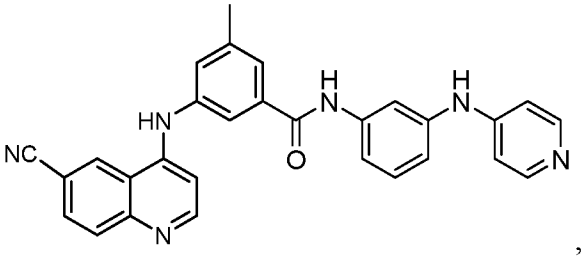
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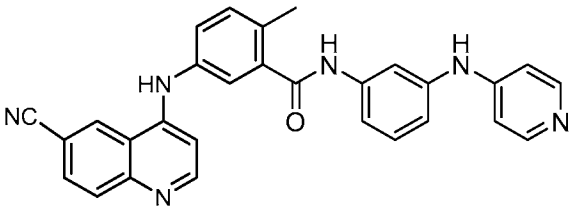
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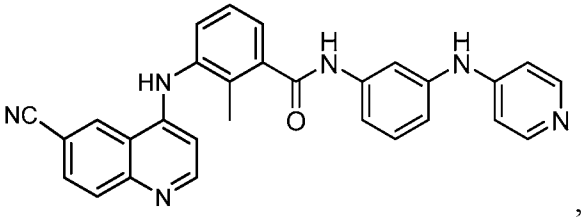
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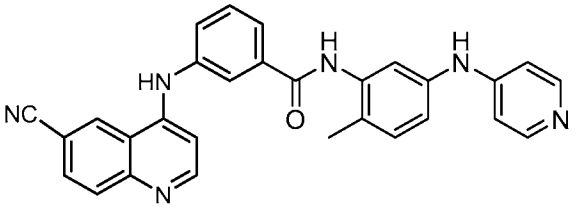
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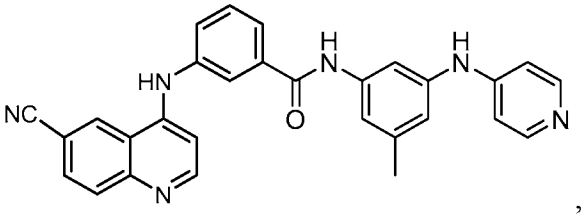
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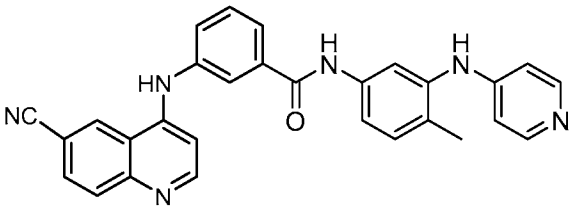
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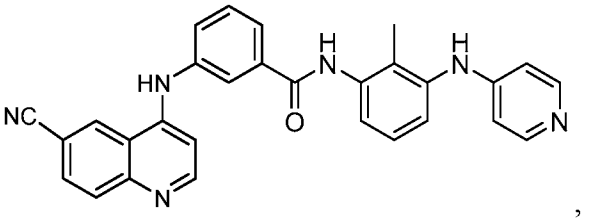
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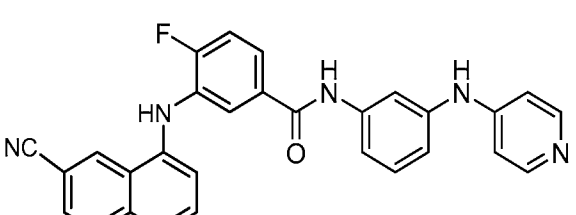
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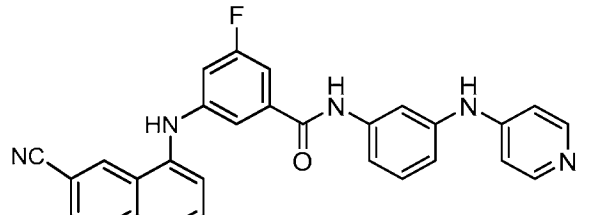
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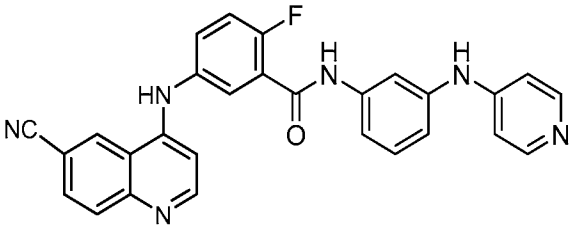
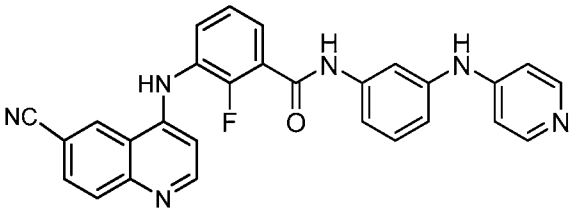
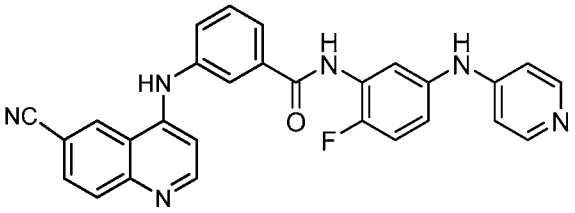
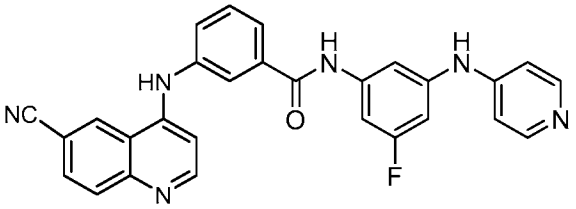
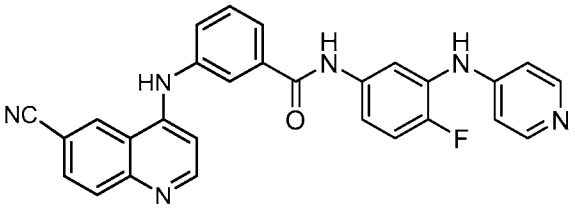
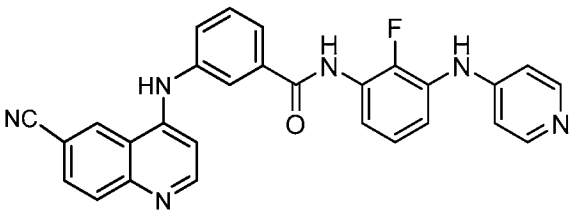
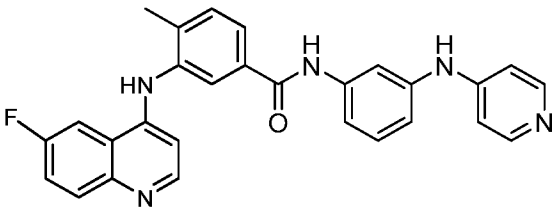
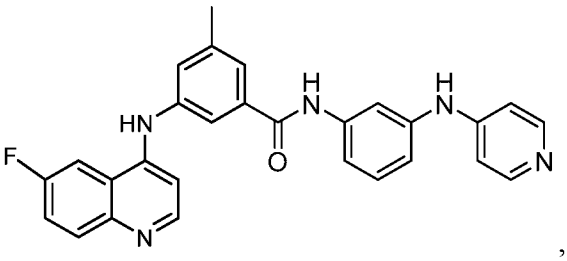
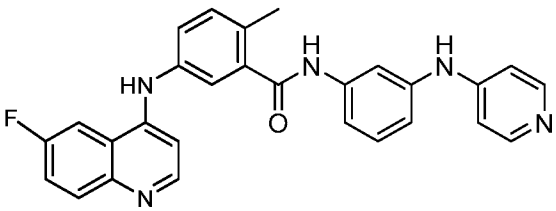
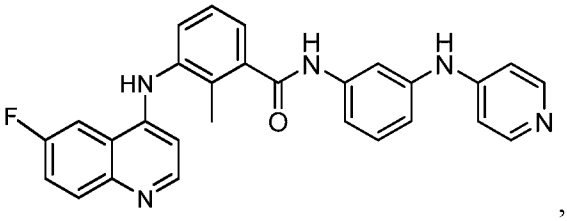
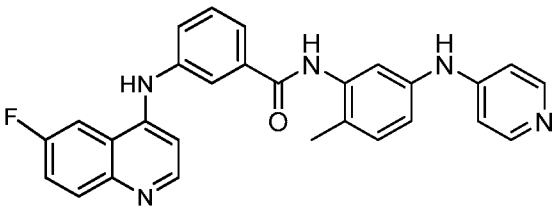
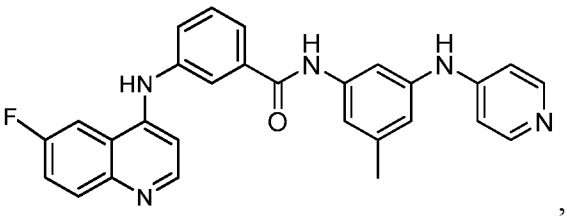
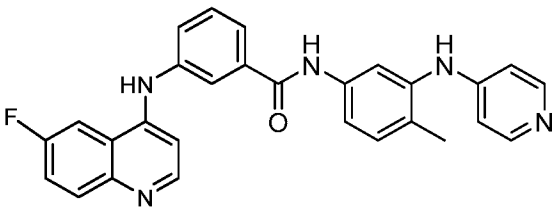
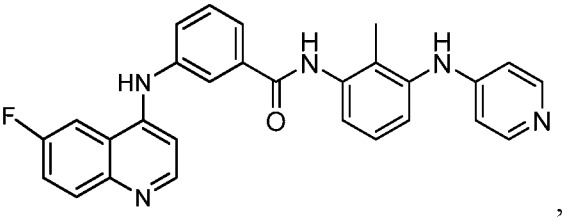
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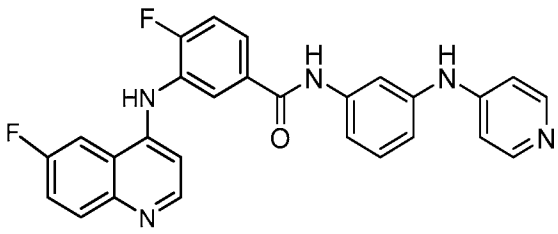
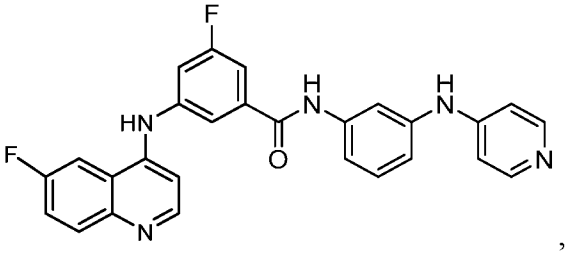
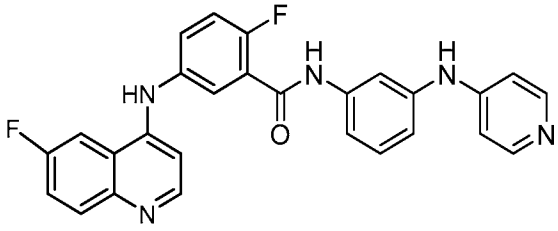
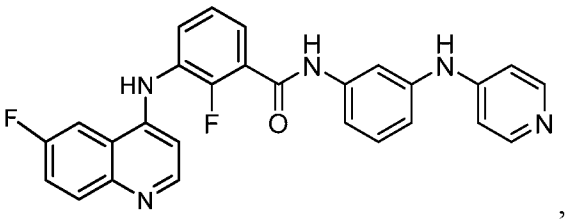
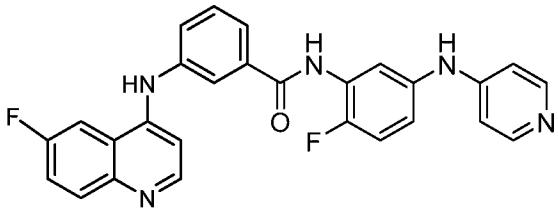
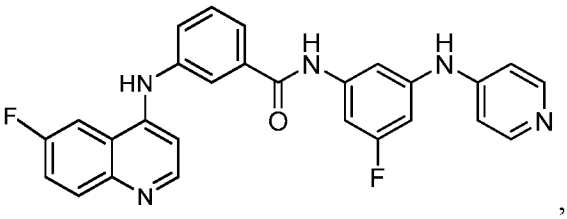
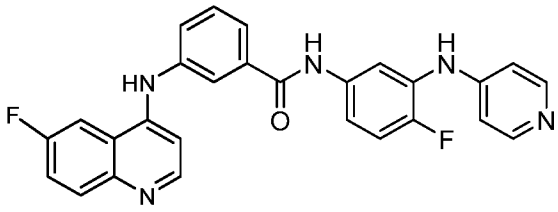
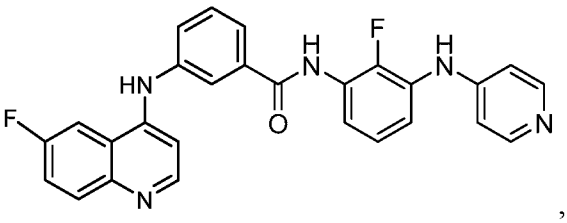
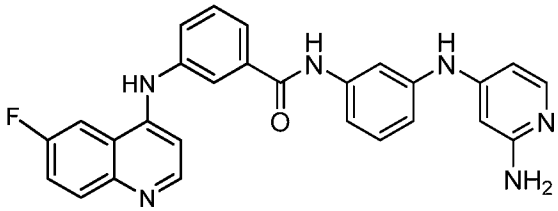
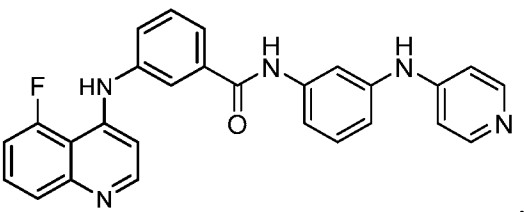
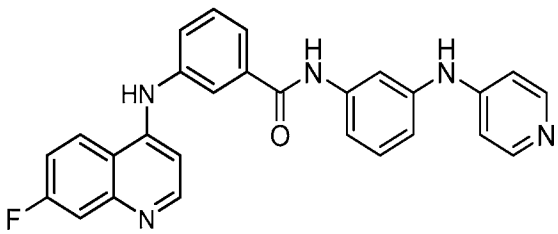
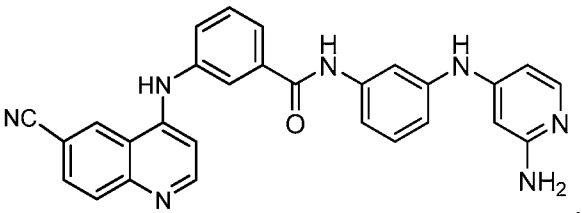
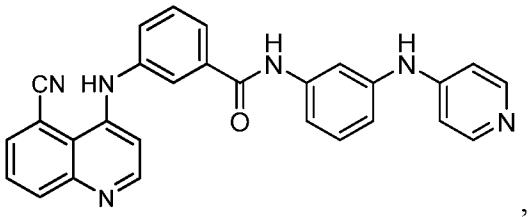
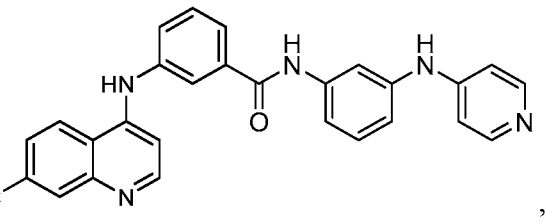


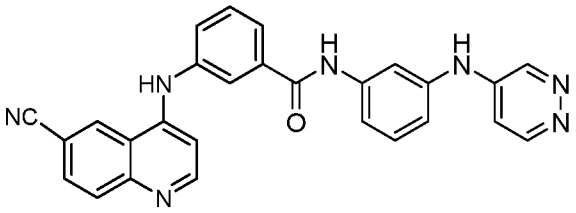
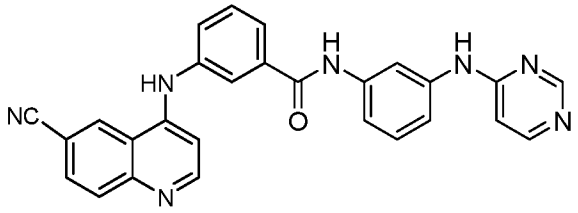
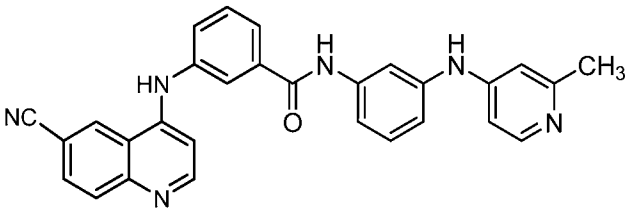
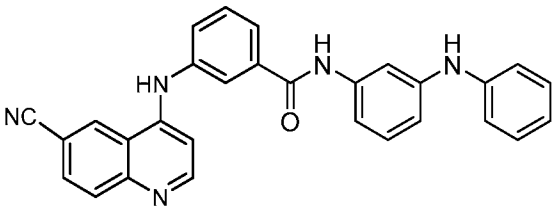
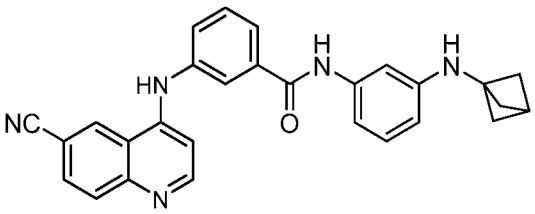
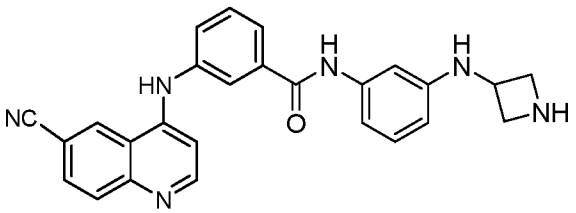
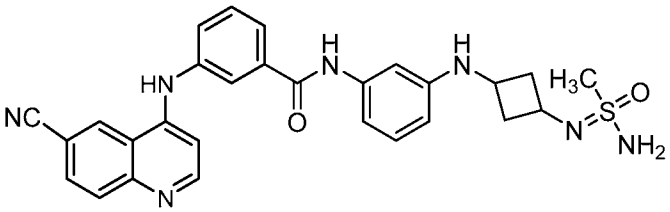
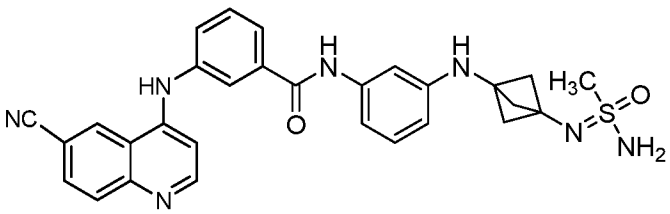
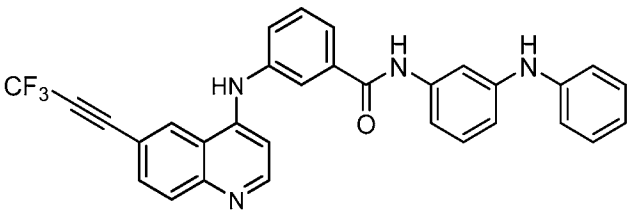
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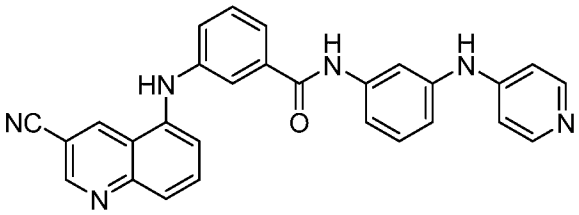
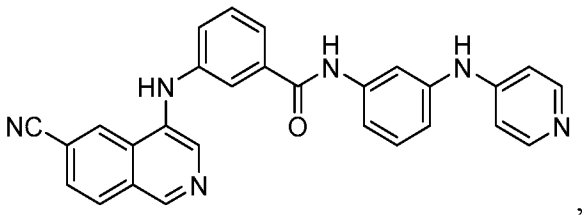
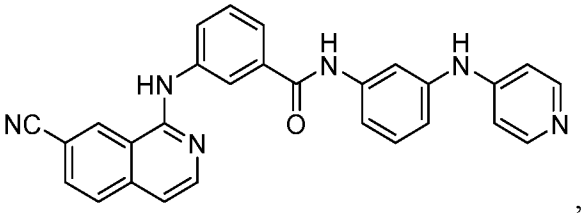
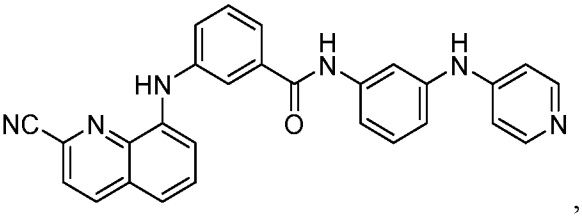
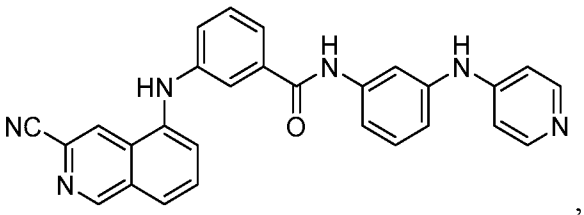
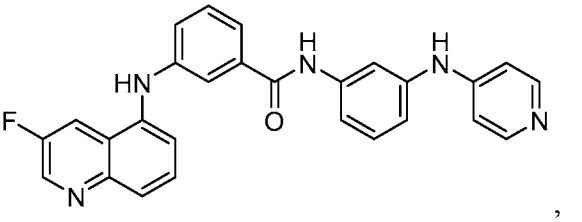
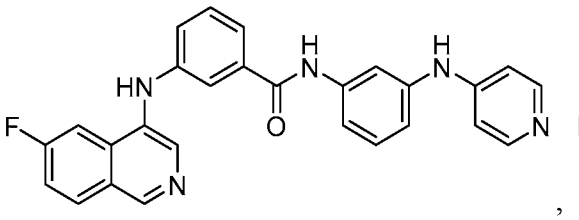
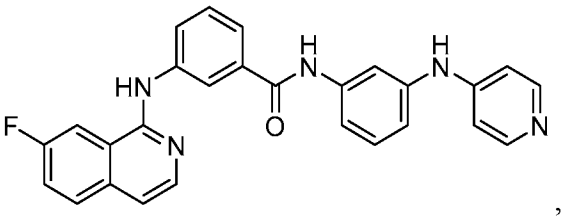
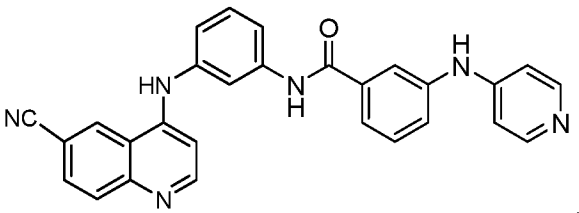
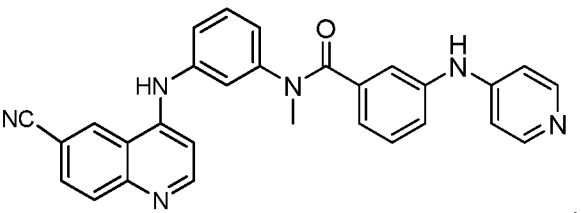
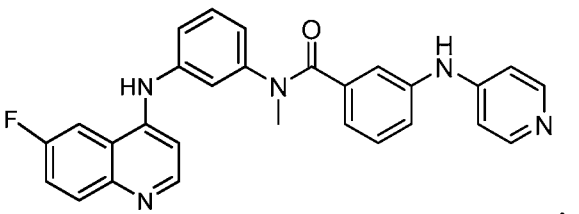
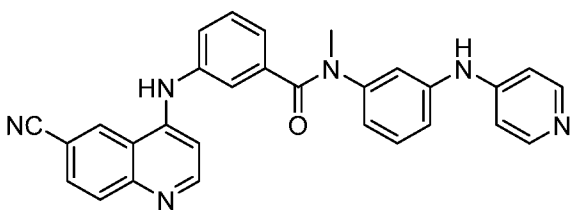
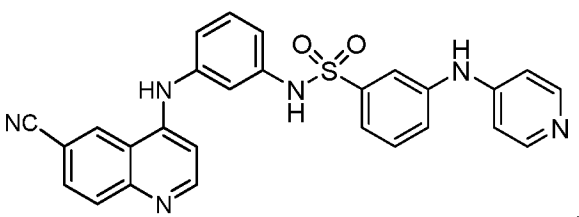
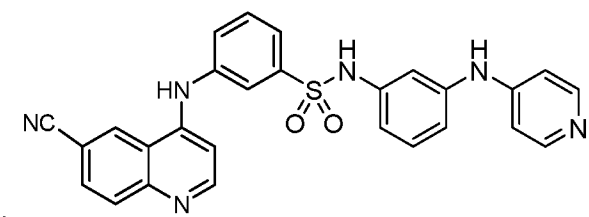
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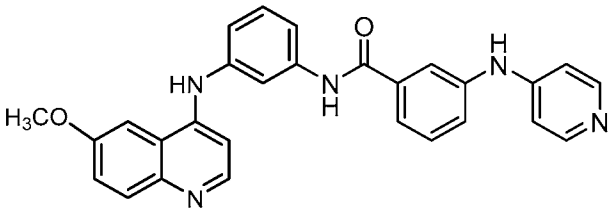

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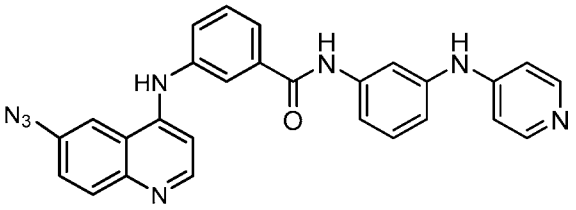

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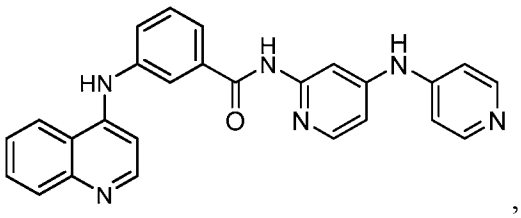
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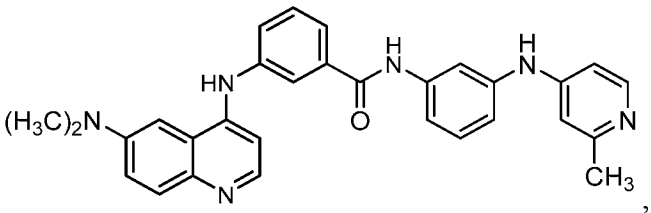
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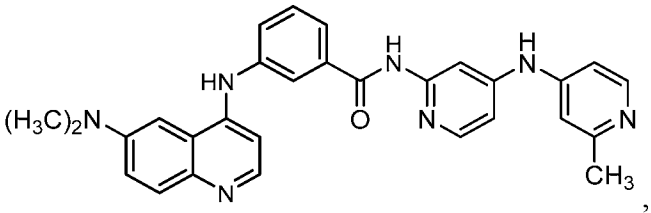
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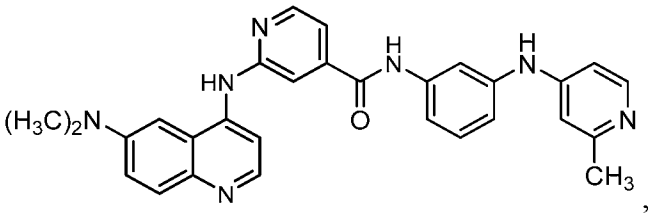
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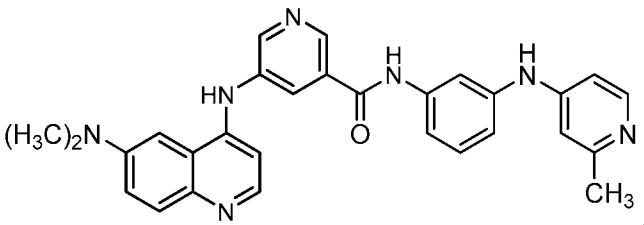
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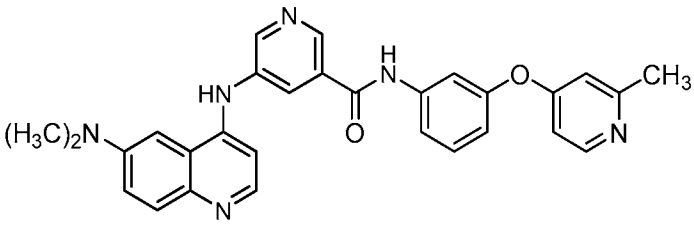
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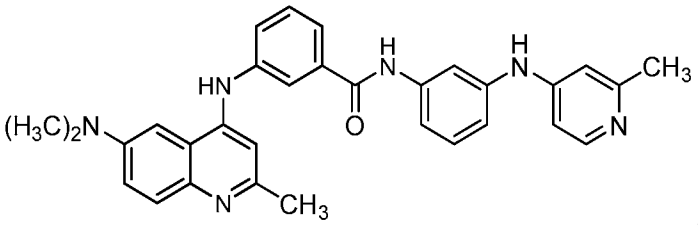
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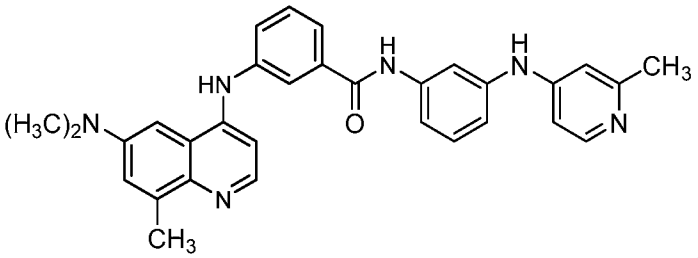
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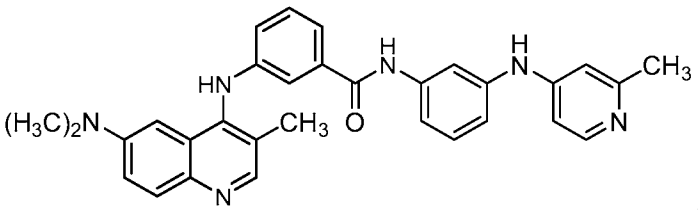
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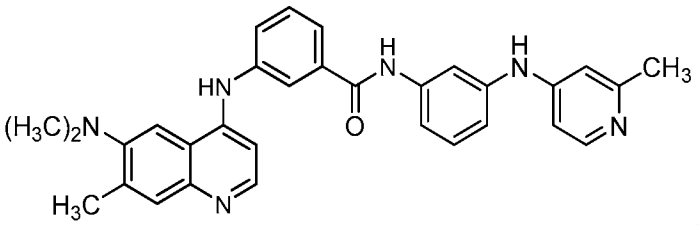
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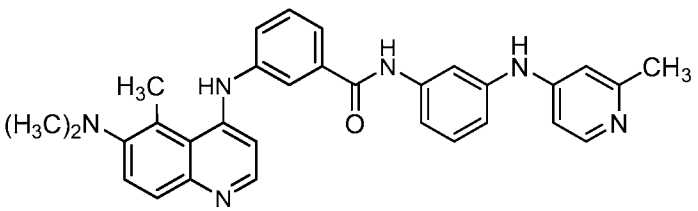
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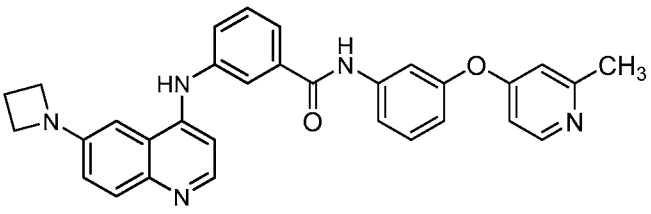
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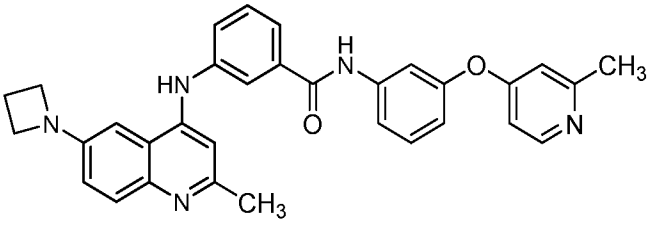
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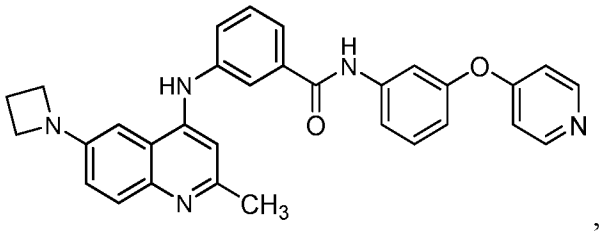
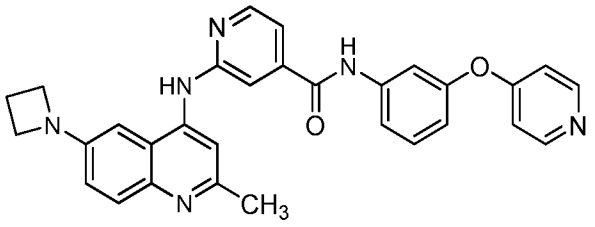
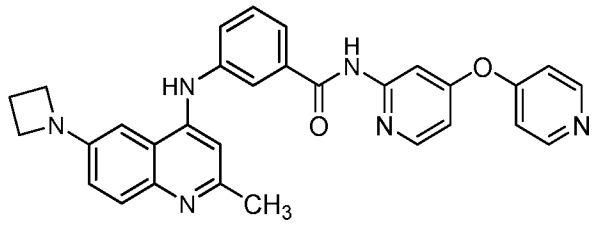
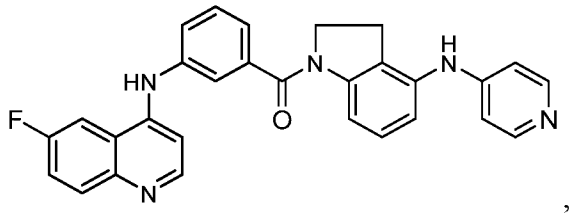
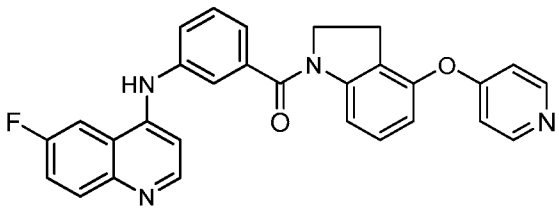
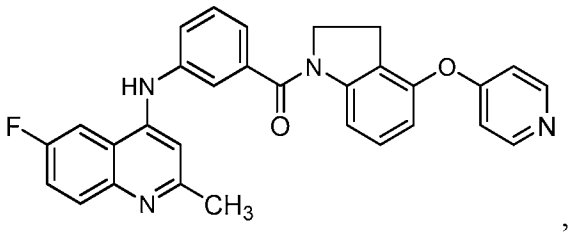
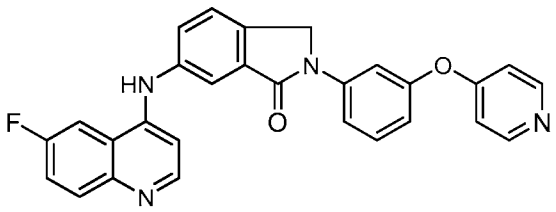
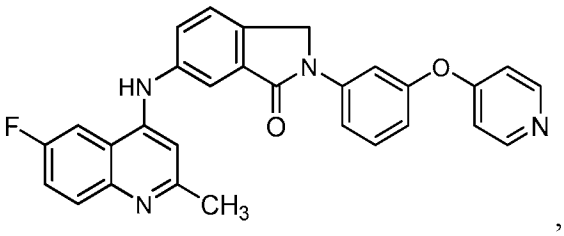
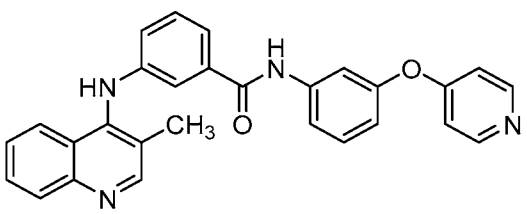
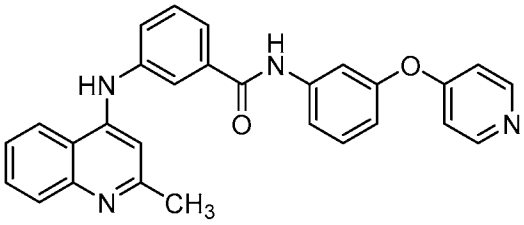
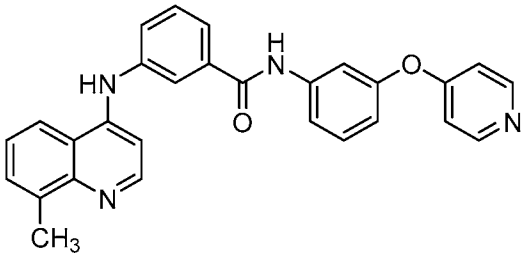
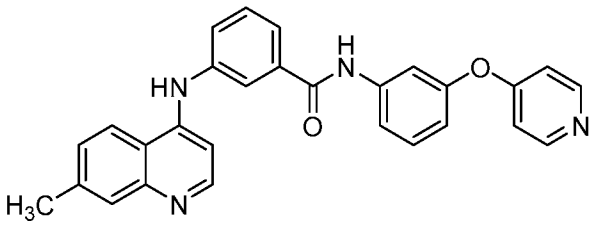
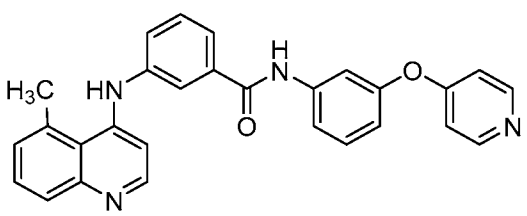
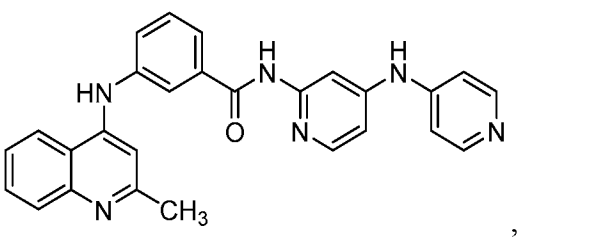
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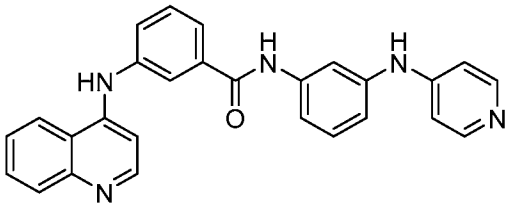
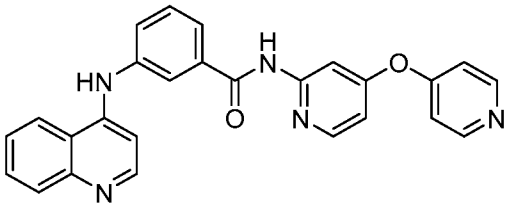
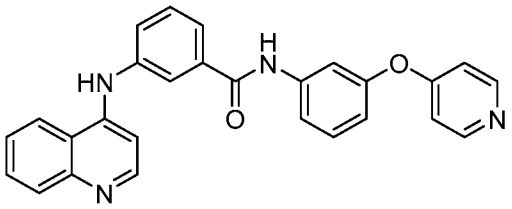
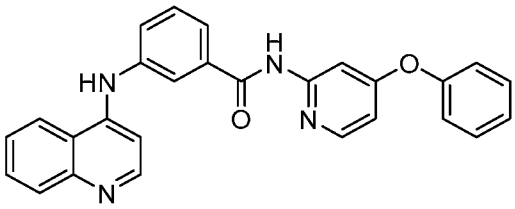
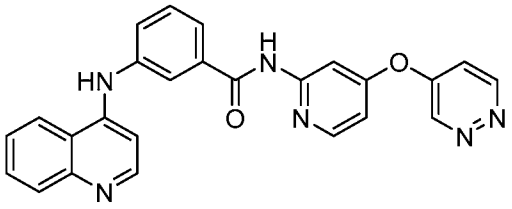
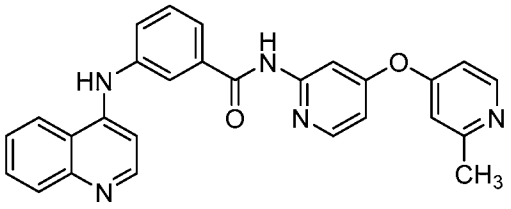
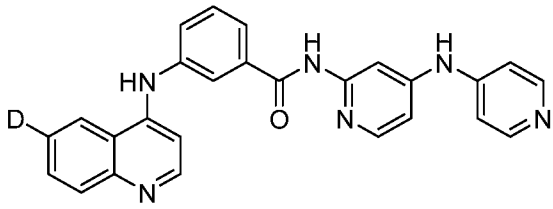
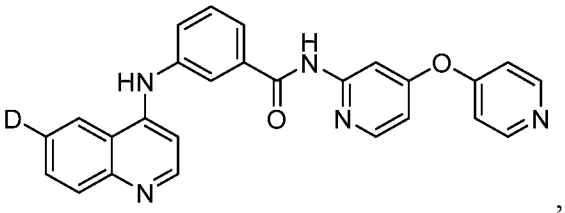
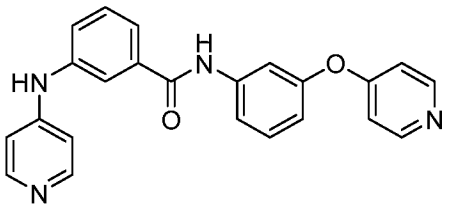
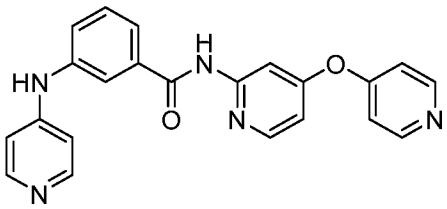
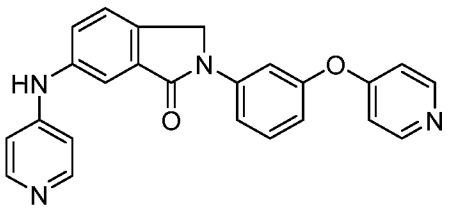
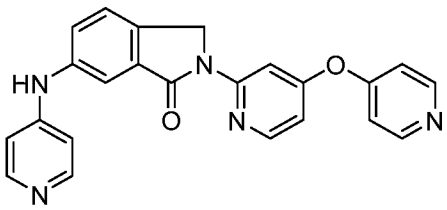
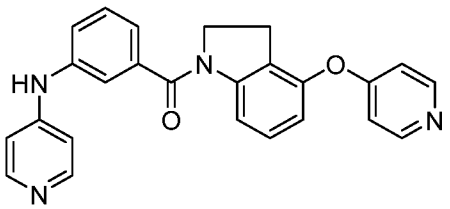
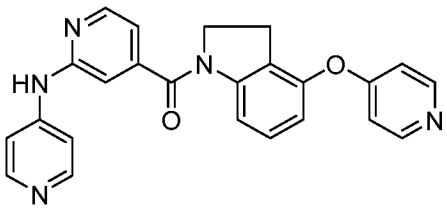
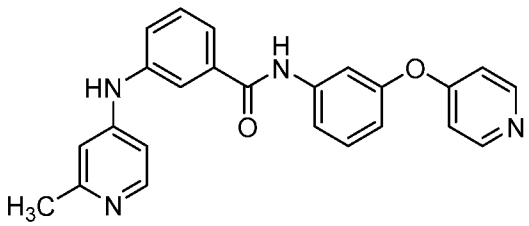
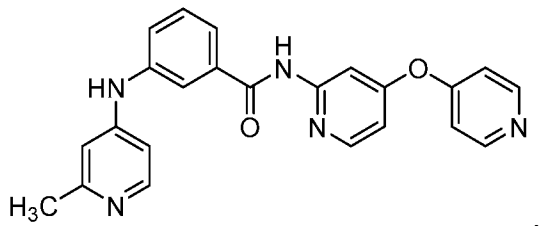


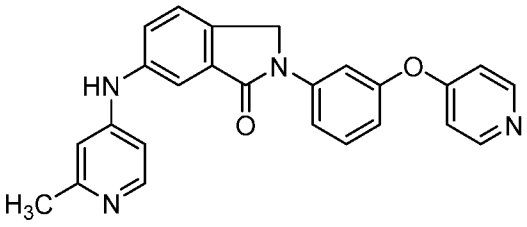
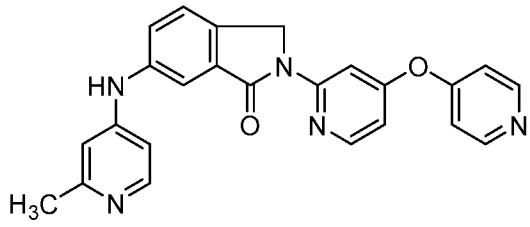
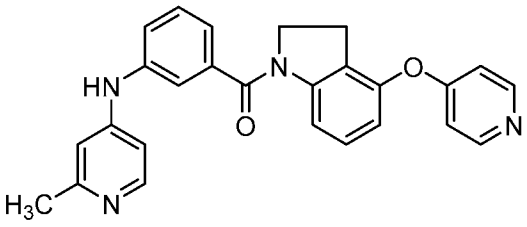
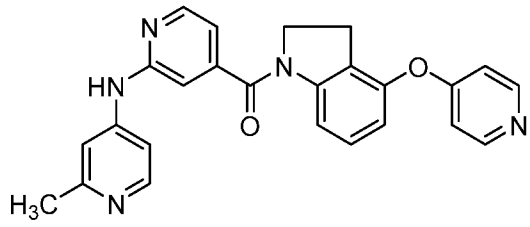
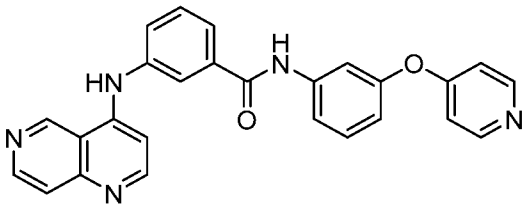
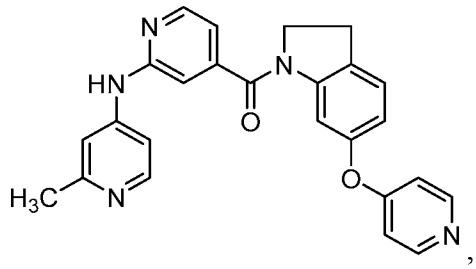
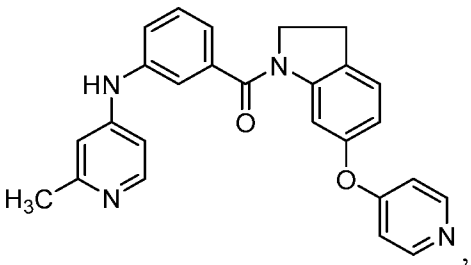
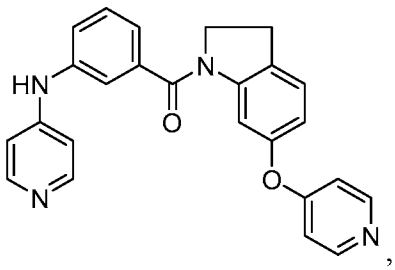
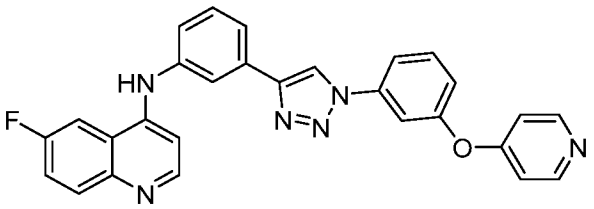
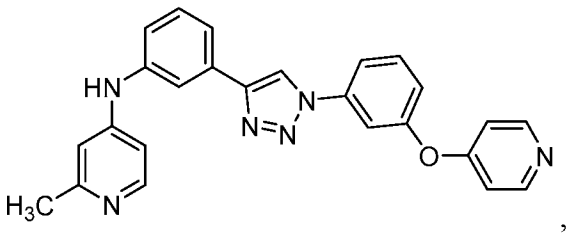
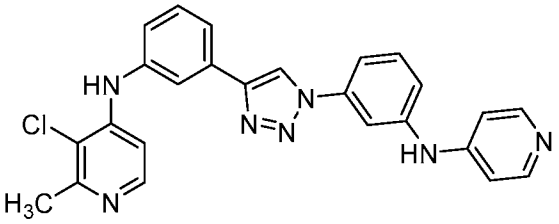
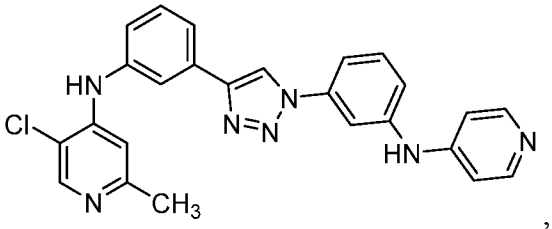
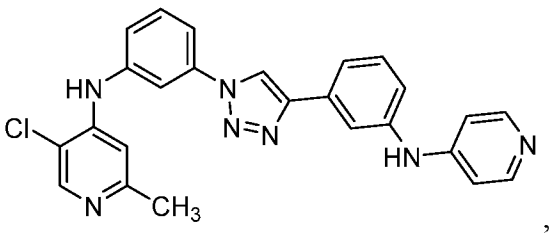
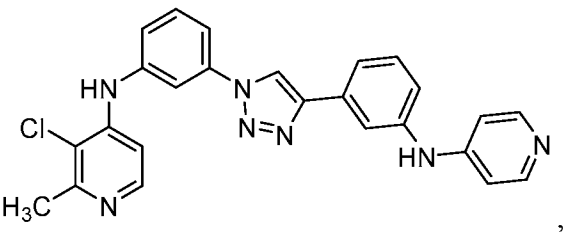
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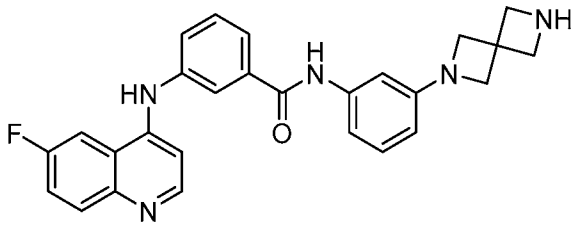
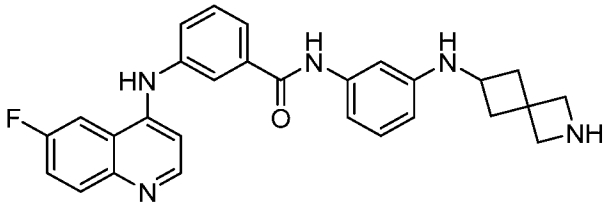
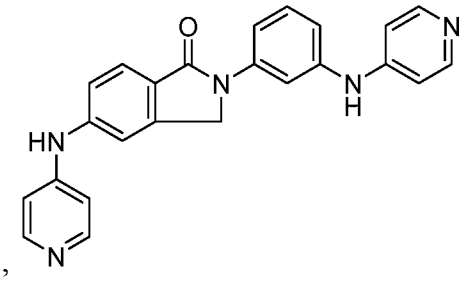
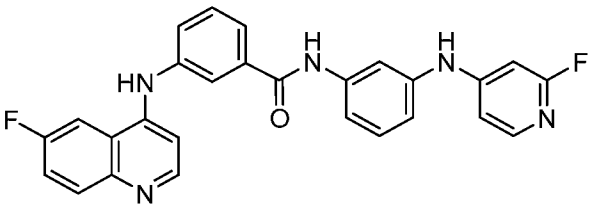
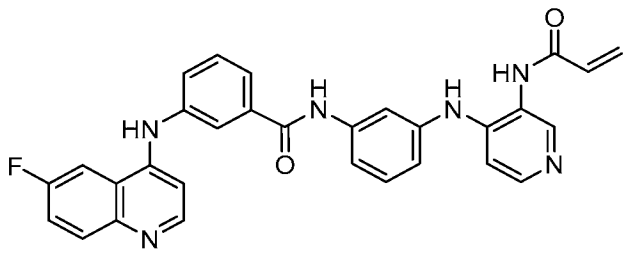
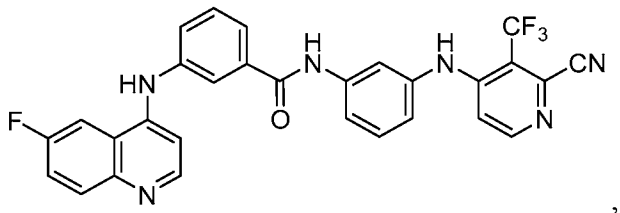
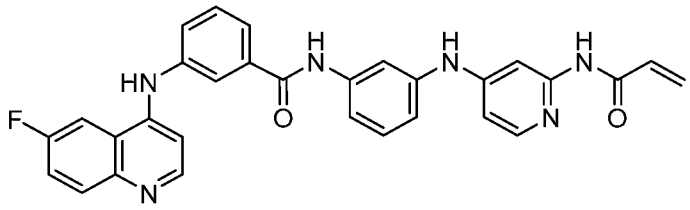
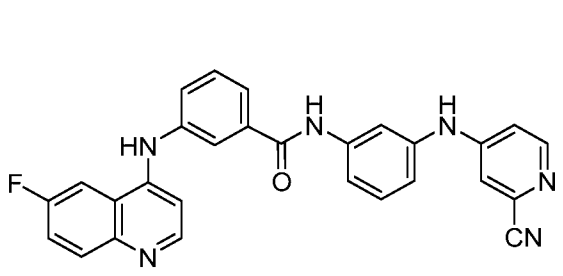
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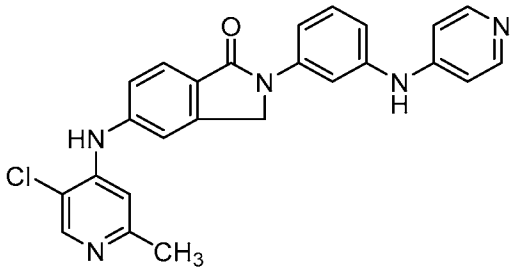
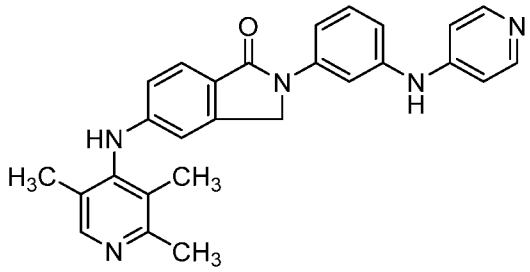
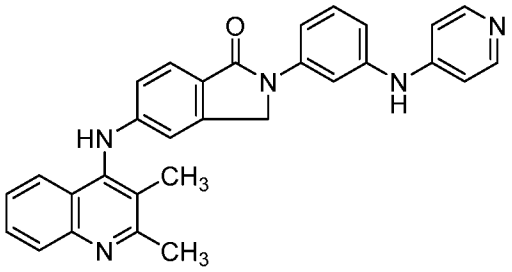
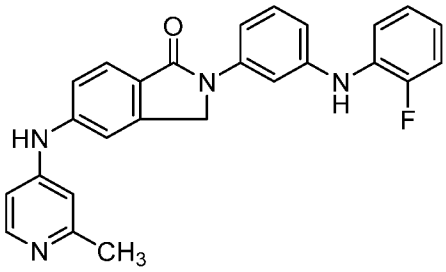
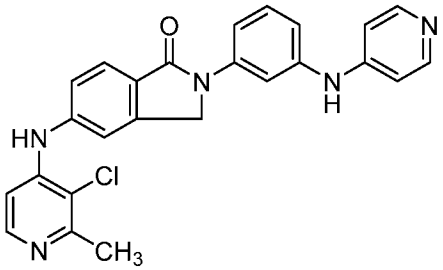
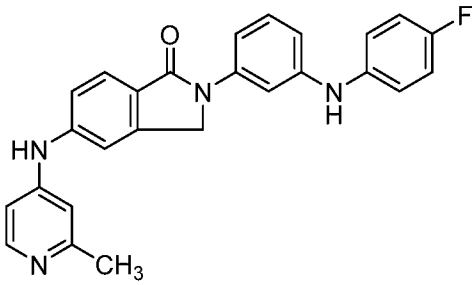
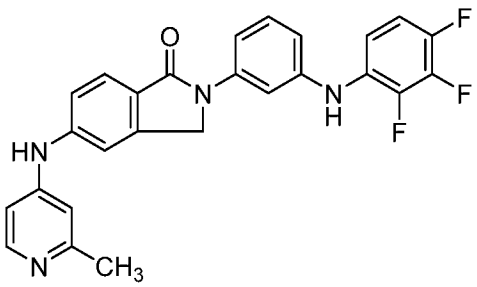
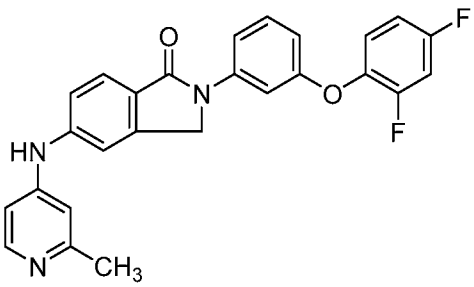
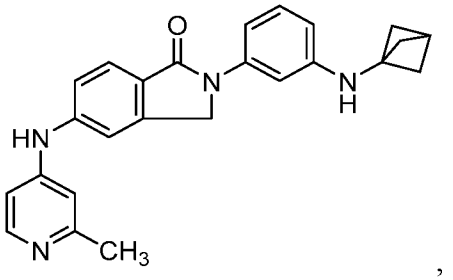
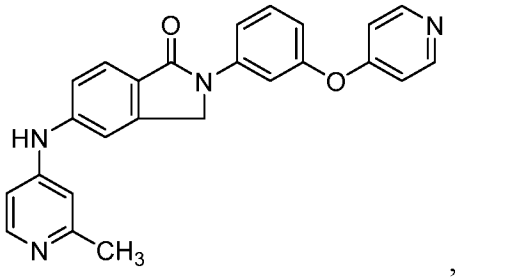
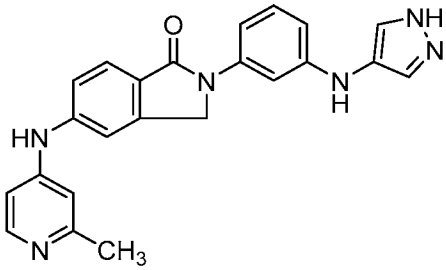
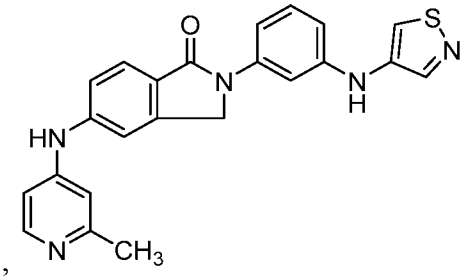
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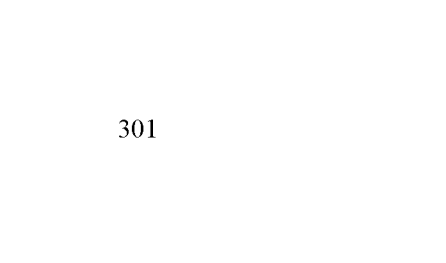

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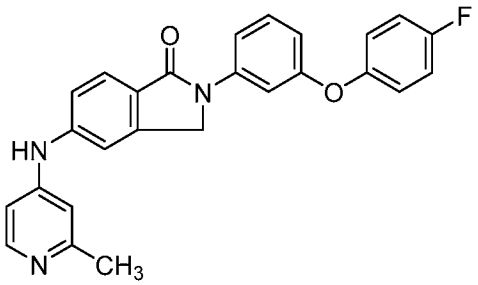
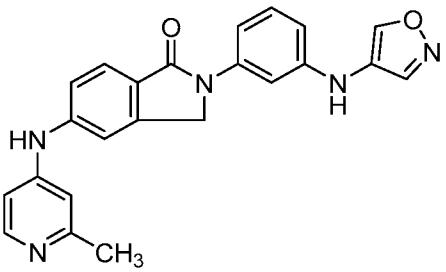
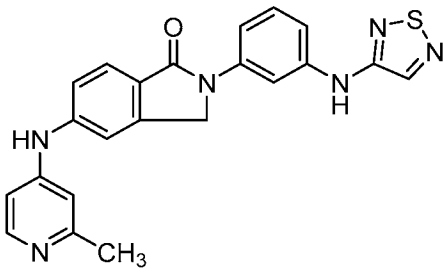
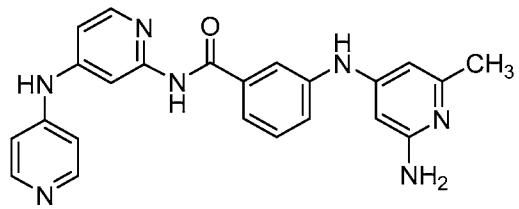
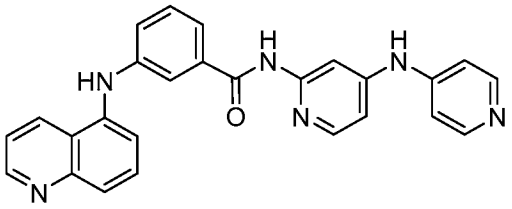
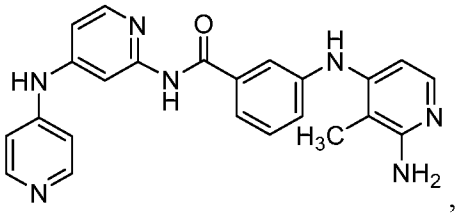
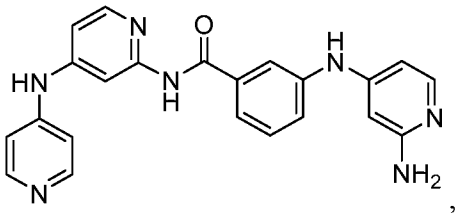
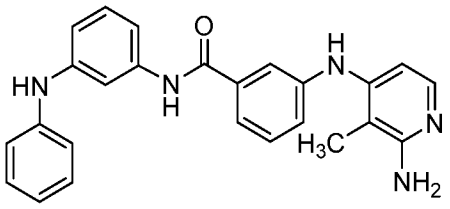
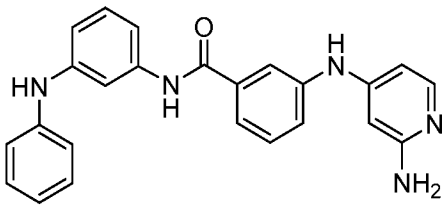
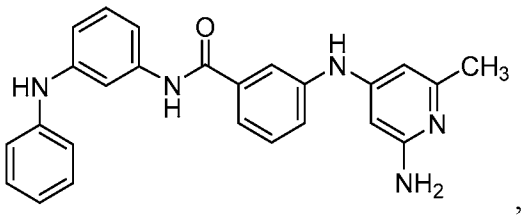
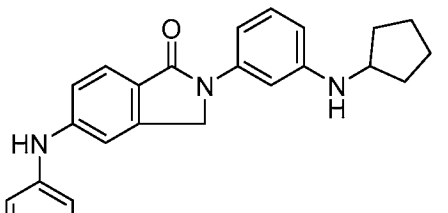
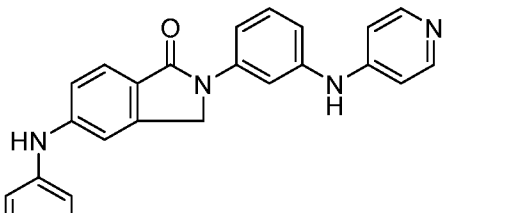
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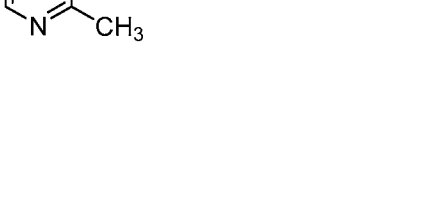
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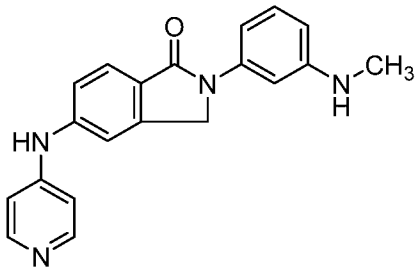
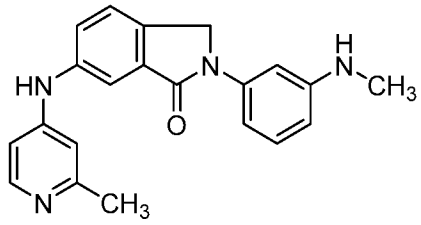
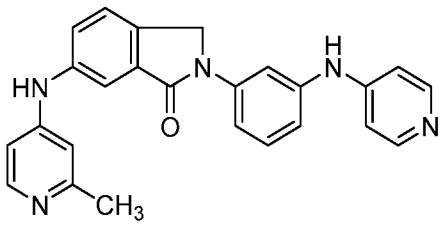
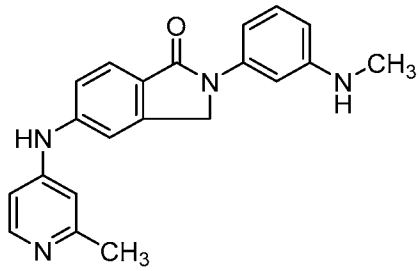
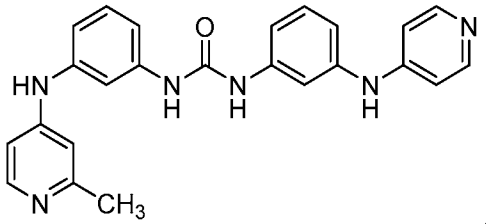
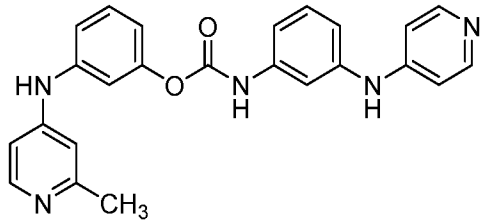
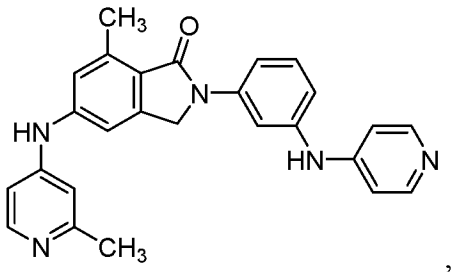
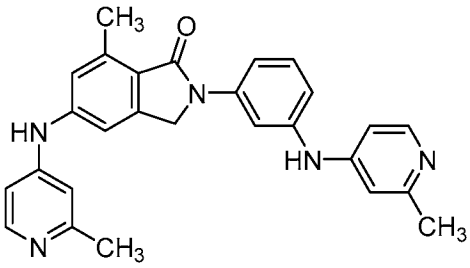
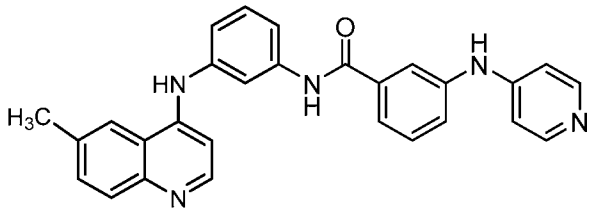
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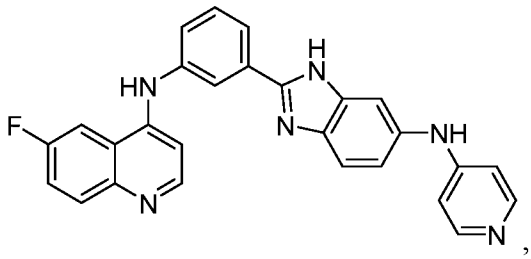
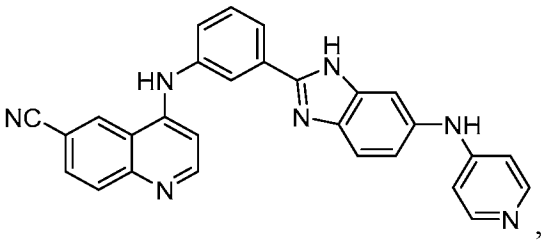
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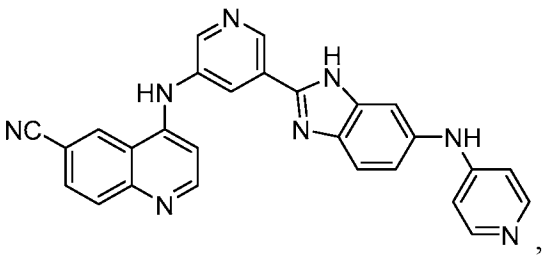

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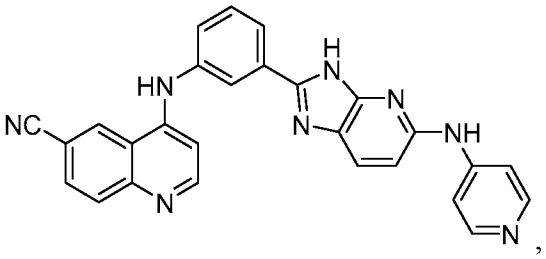
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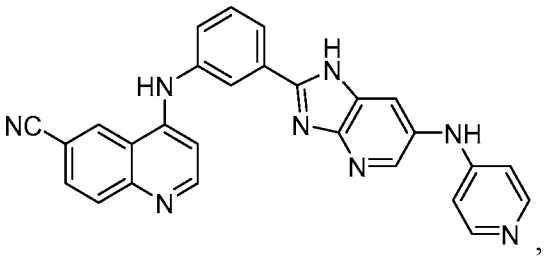

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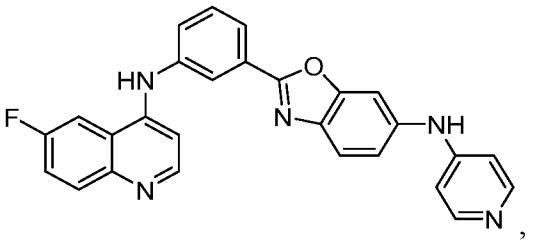
[0367] In some embodiments, the compound of Formula IIb is

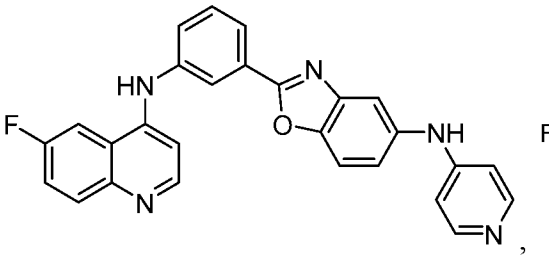

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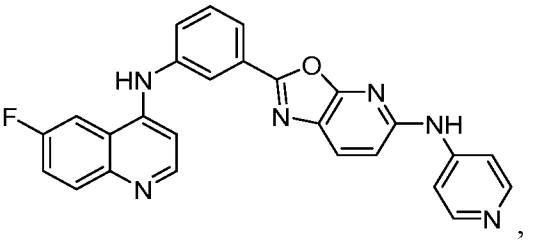


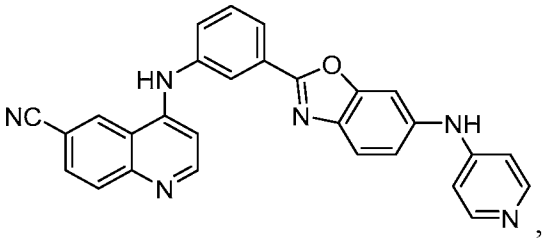


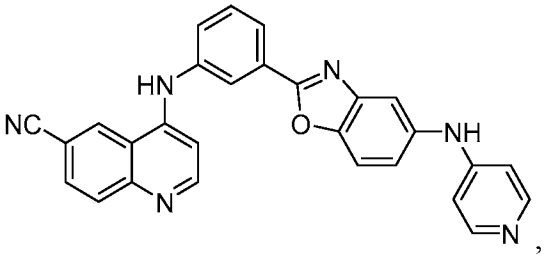


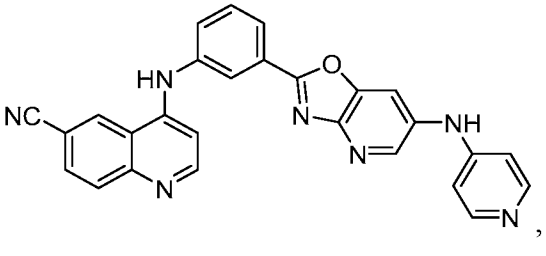


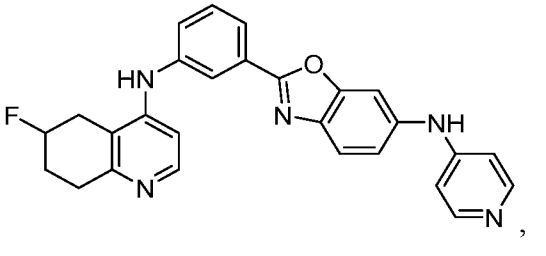


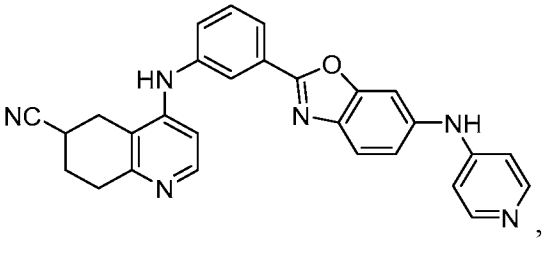


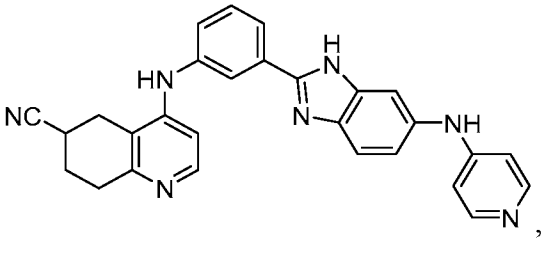


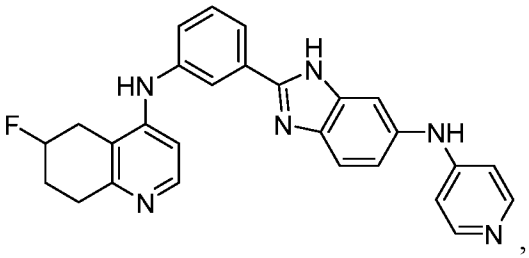


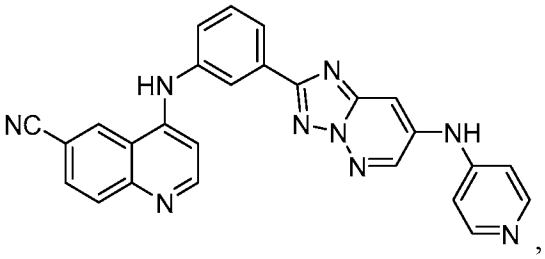


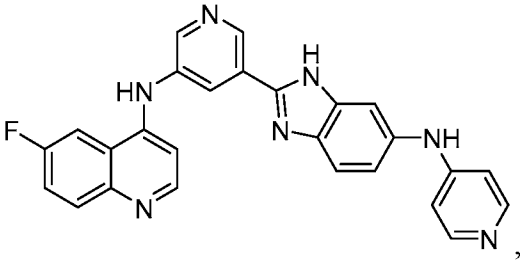


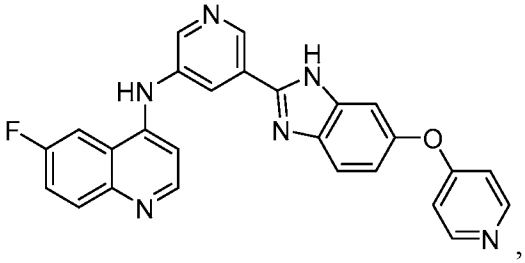


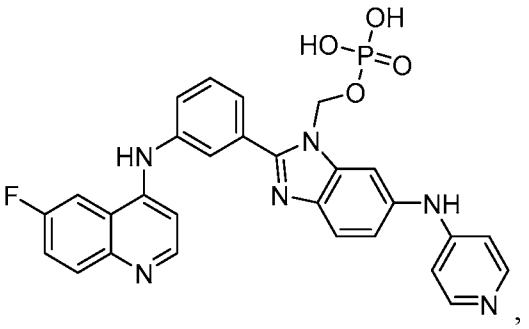


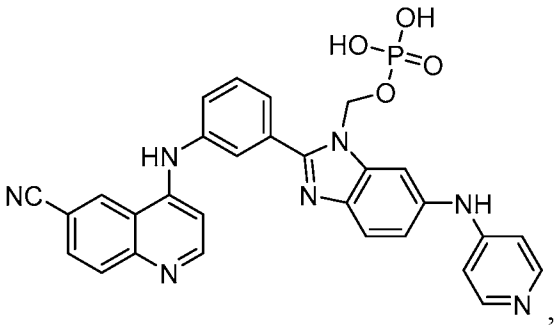


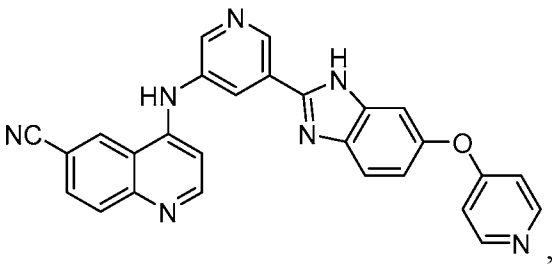


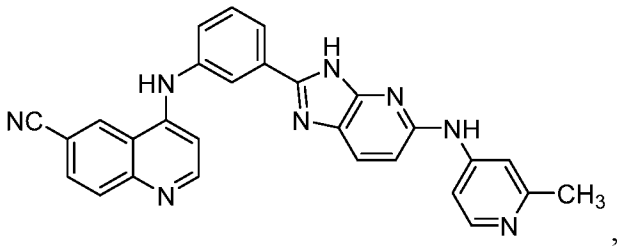


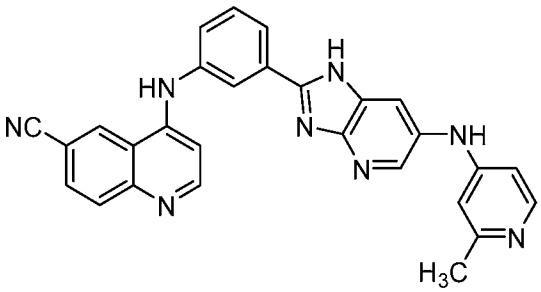


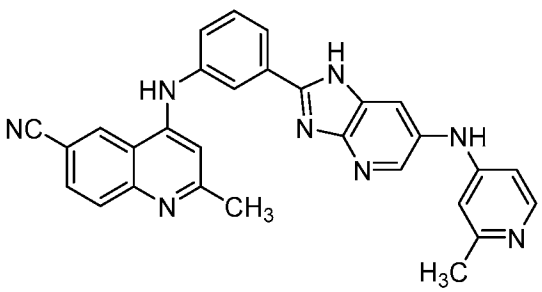


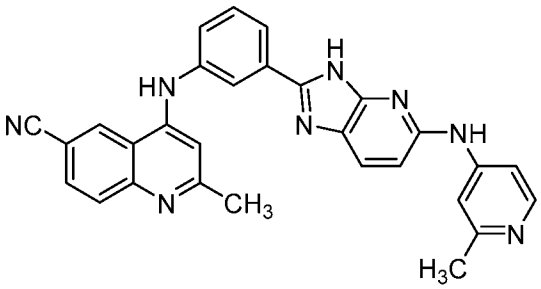


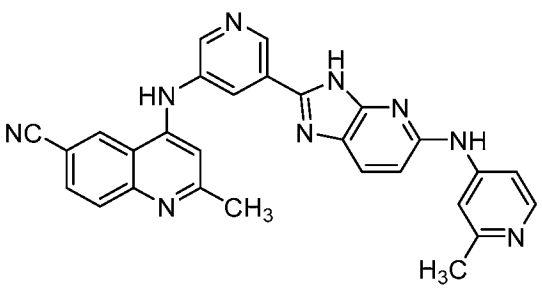


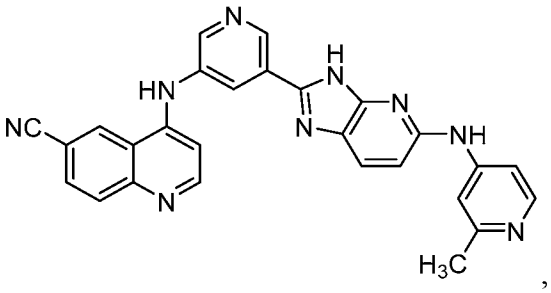




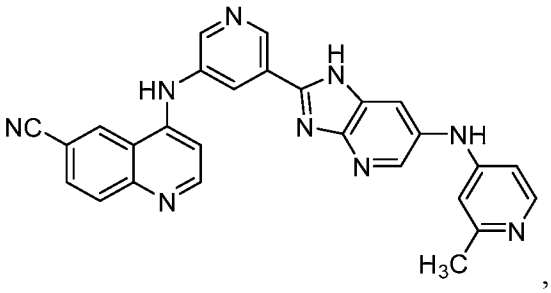




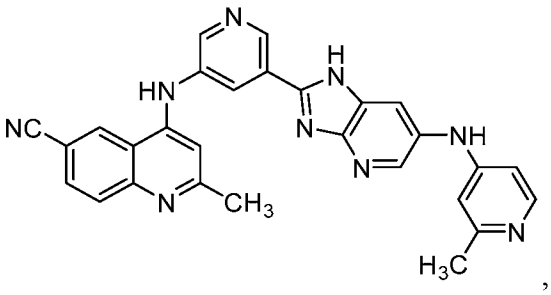




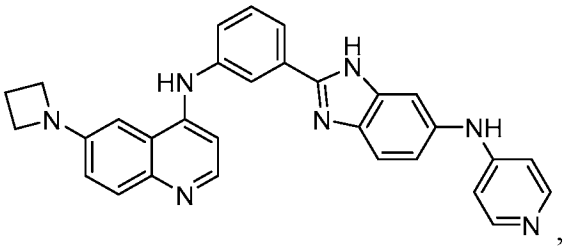
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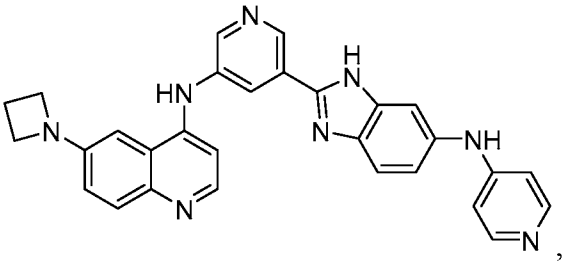
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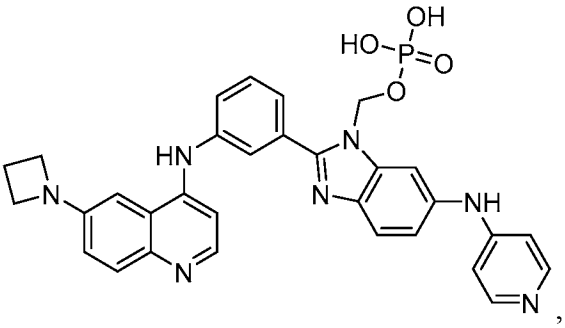
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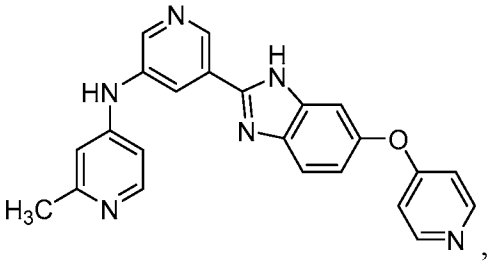
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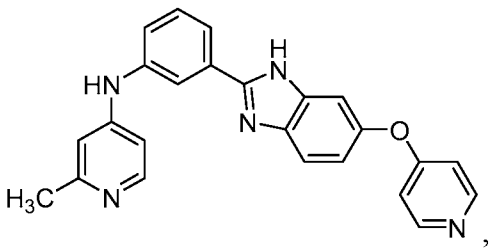
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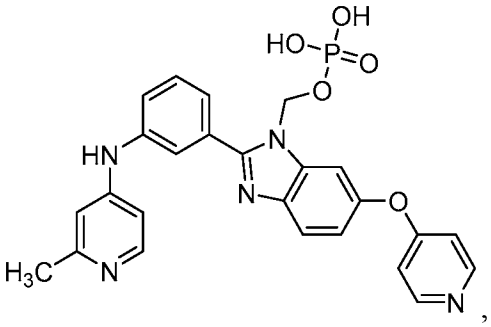
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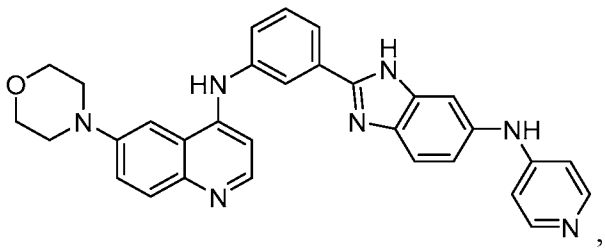
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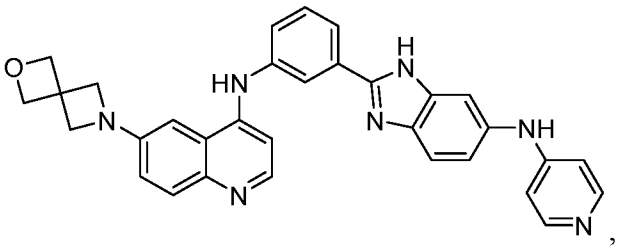
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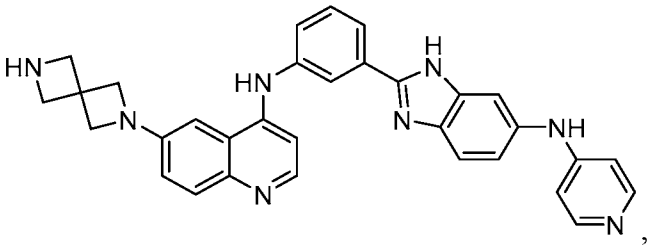
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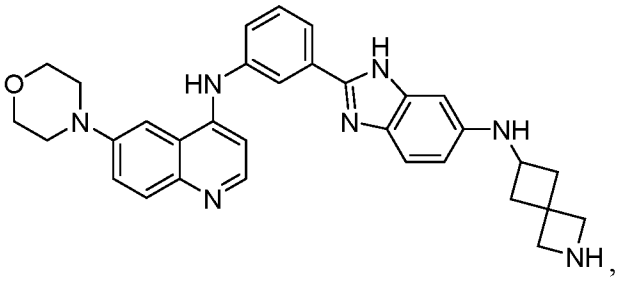


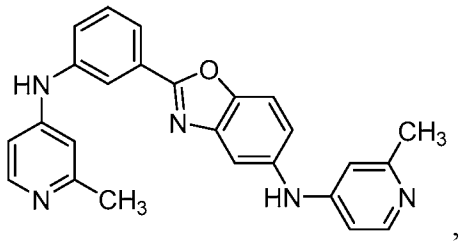
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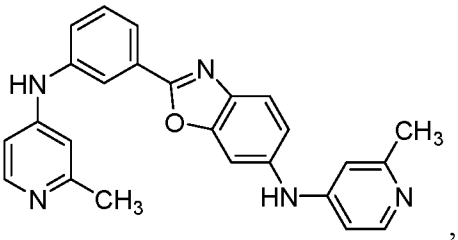


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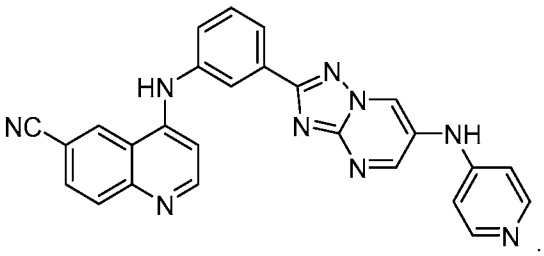






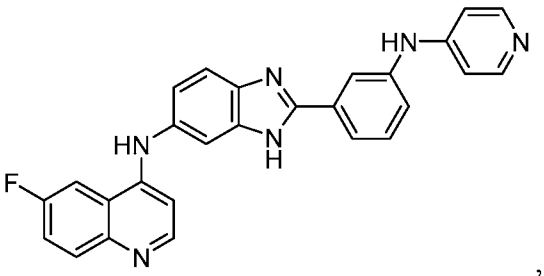


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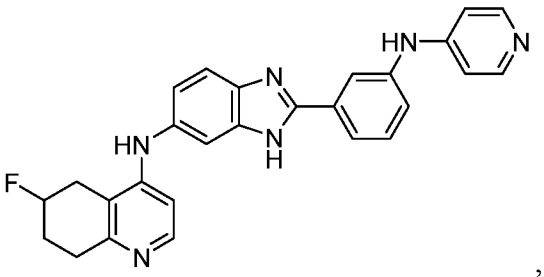


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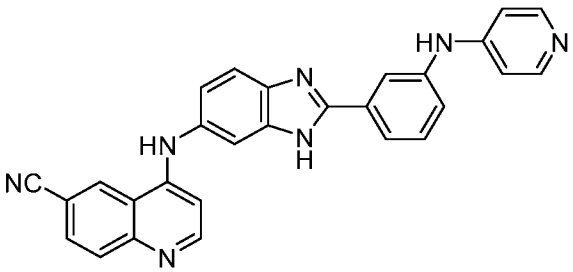
[0368] In some embodiments, the compound of Formula IIc is



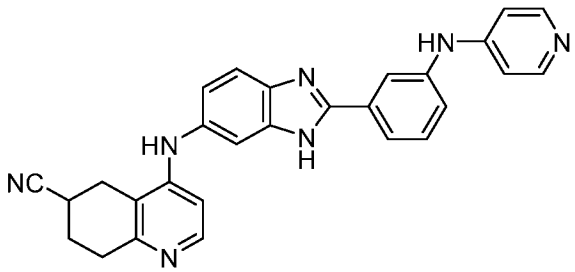
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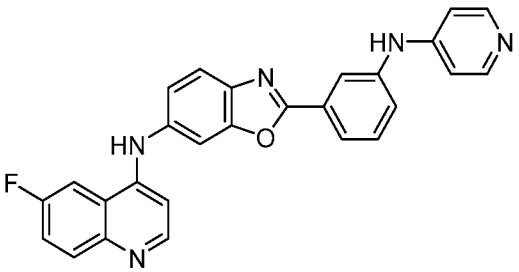
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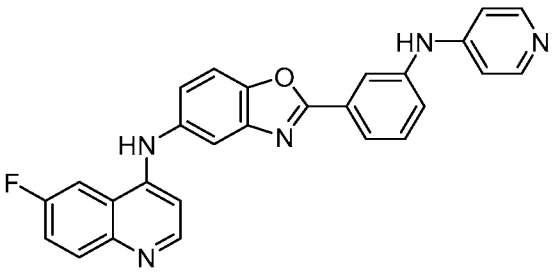
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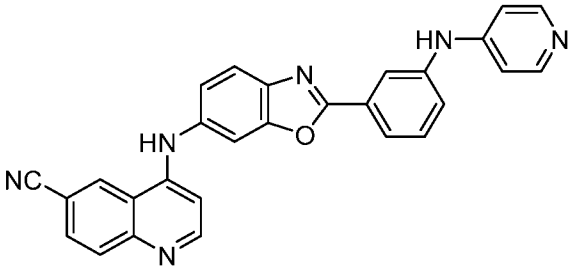
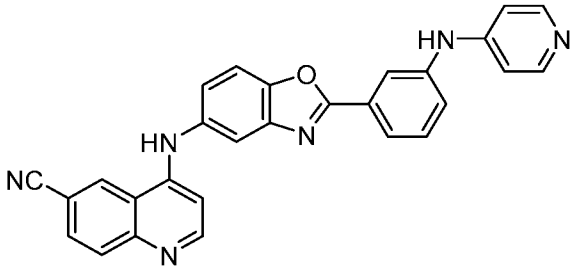
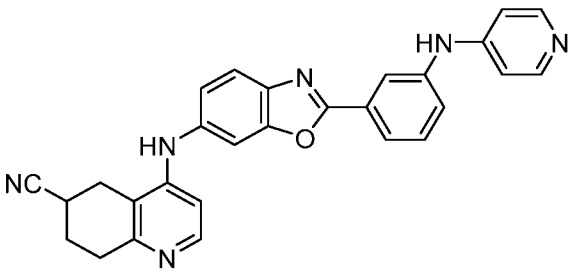
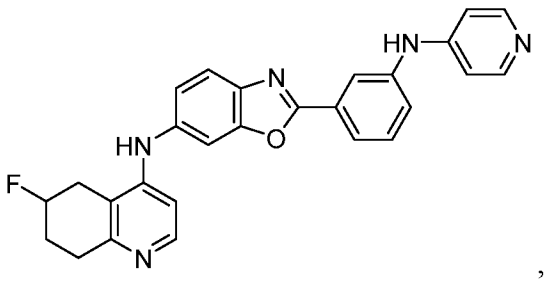
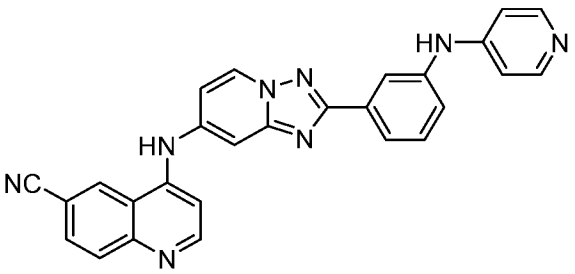
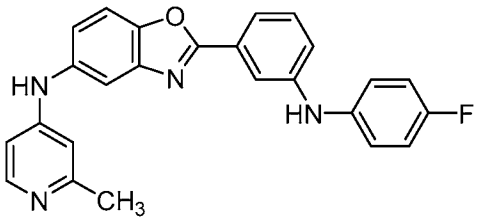
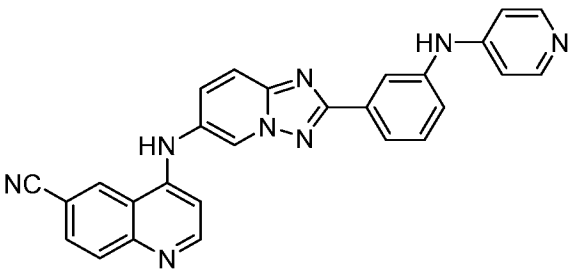
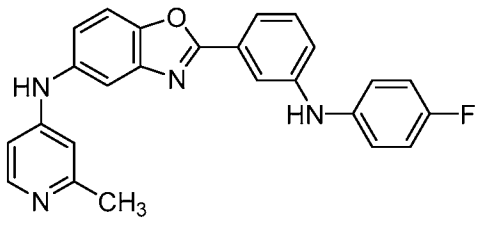
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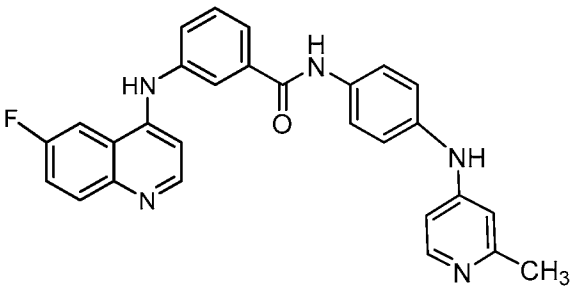
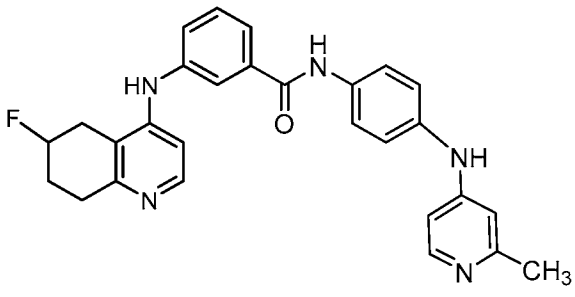
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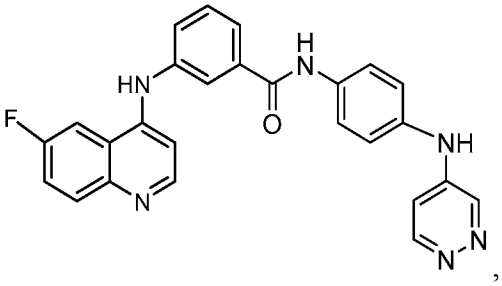
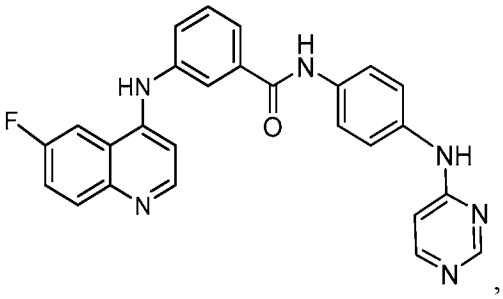
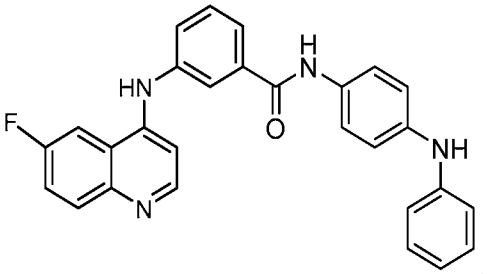
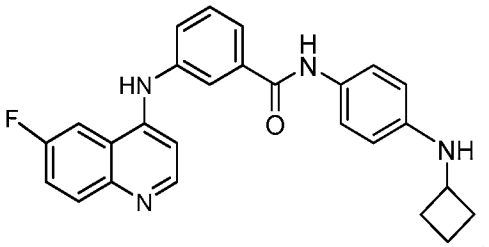
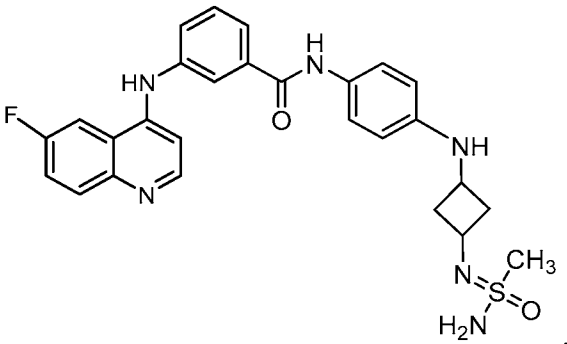
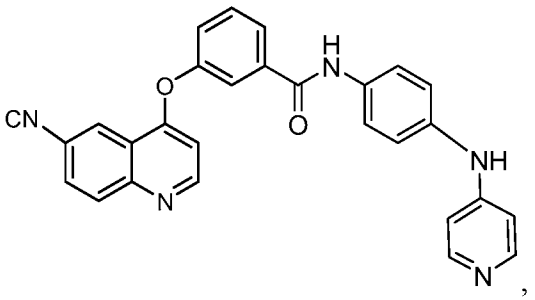
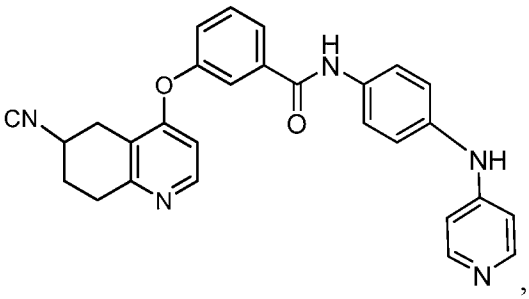
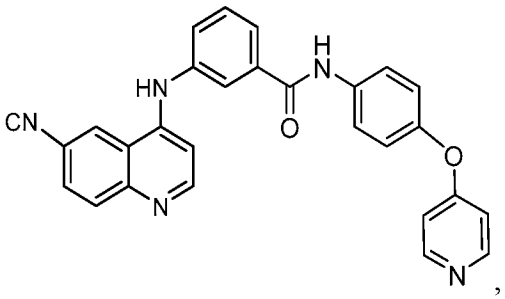
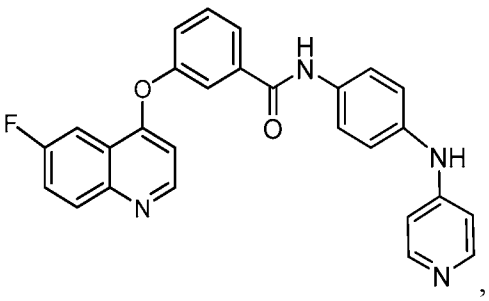


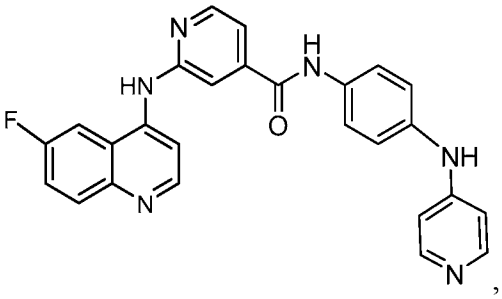
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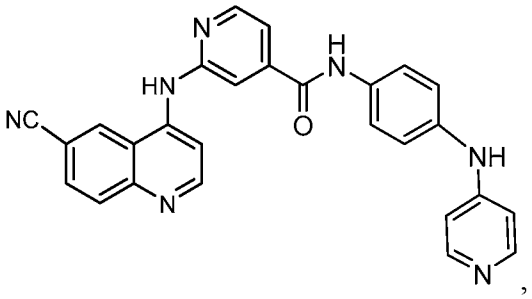

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, or

. In some embodiments, the compound of Formula IIc is

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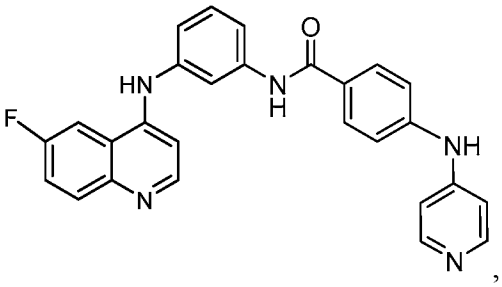
[0369] In some embodiments, the compound of Formula IIIa is

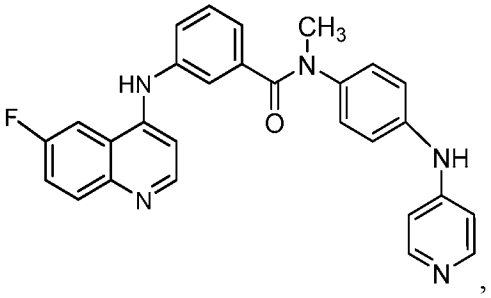

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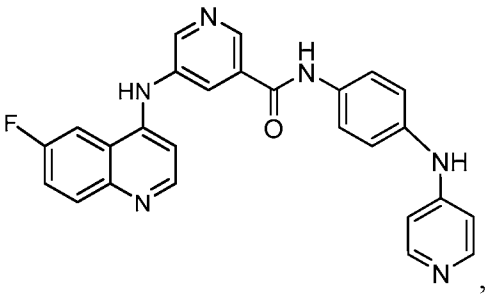

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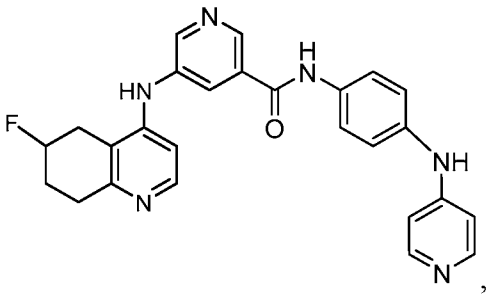


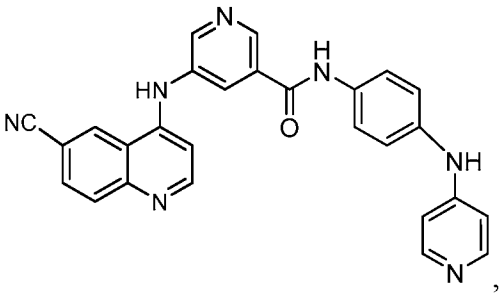


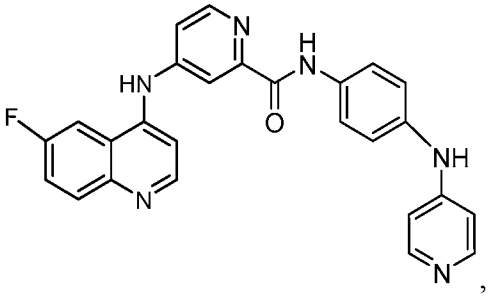


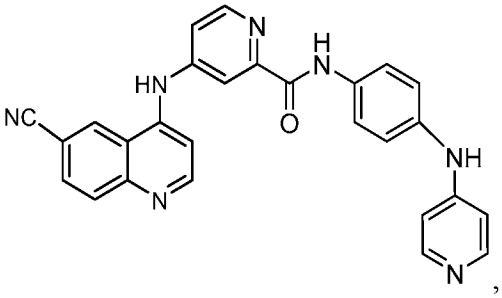


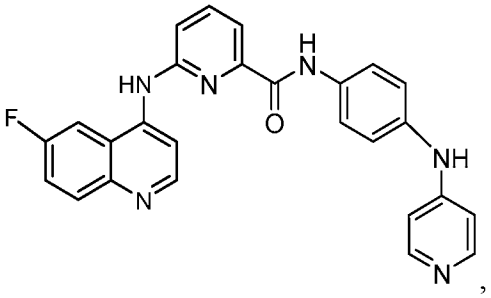


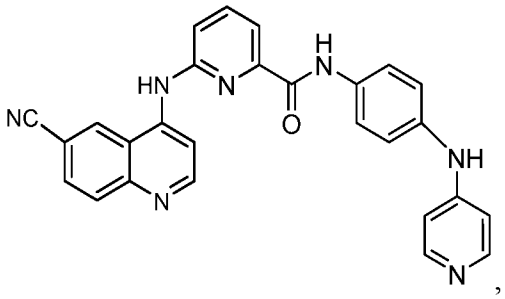
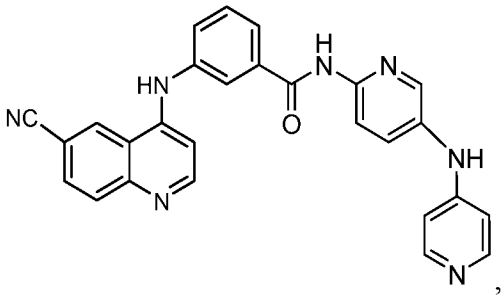
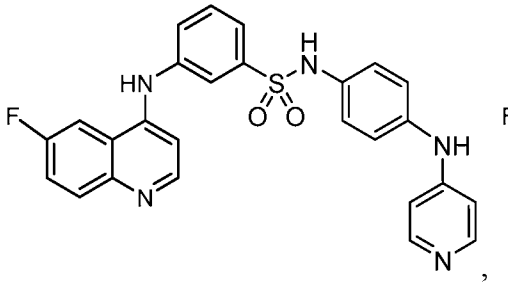
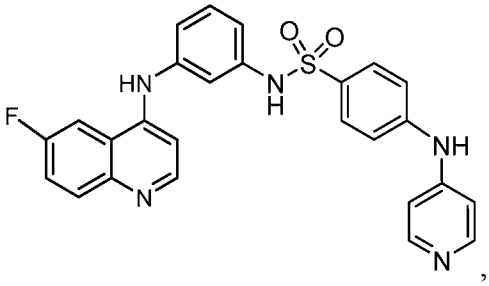
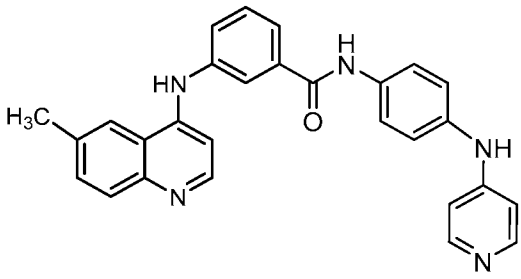
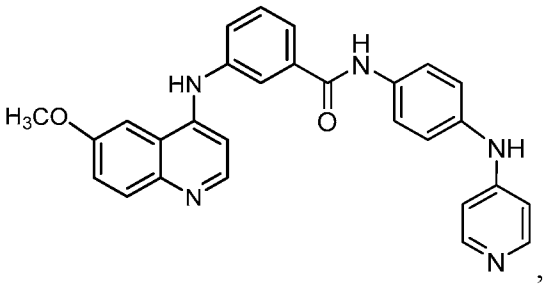
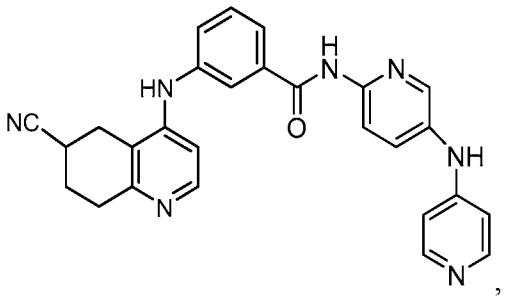
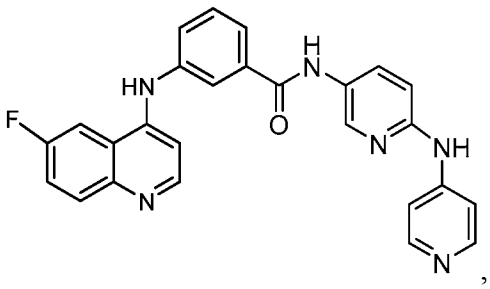
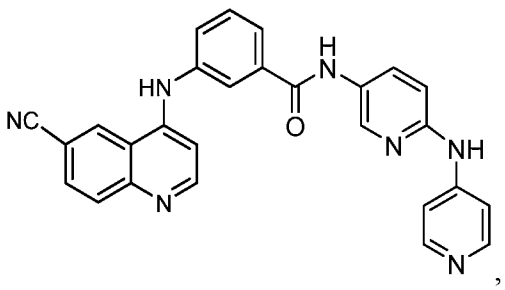
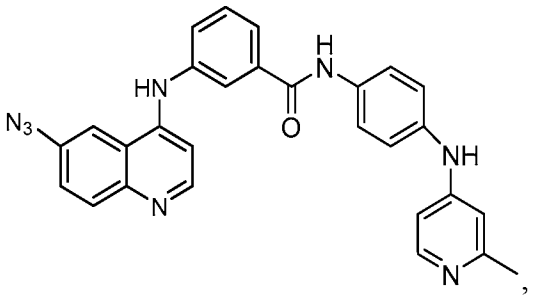
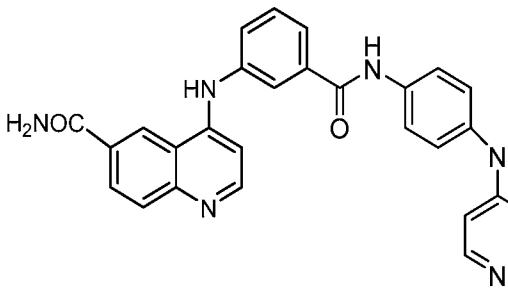
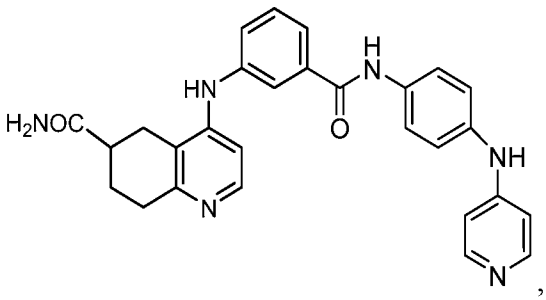






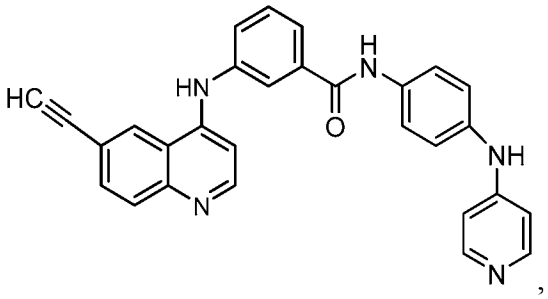


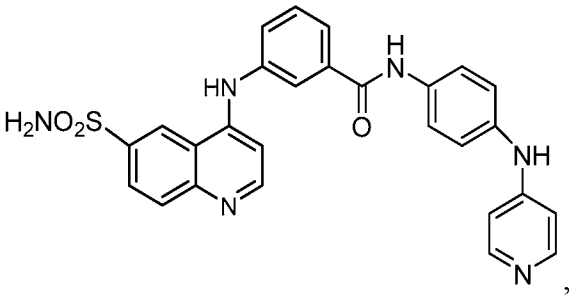


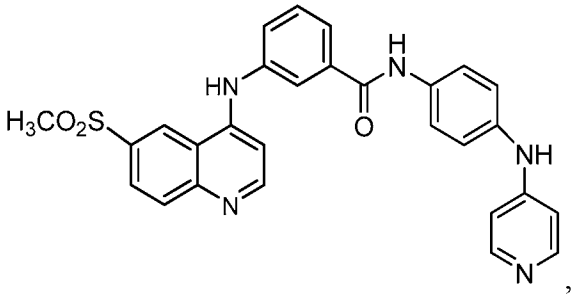

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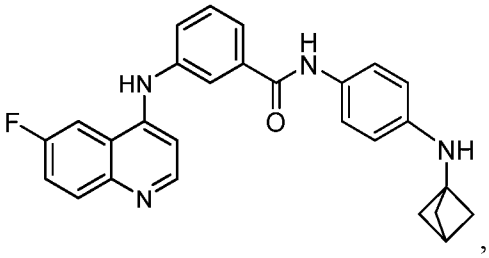
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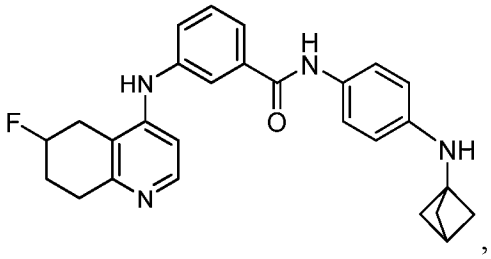
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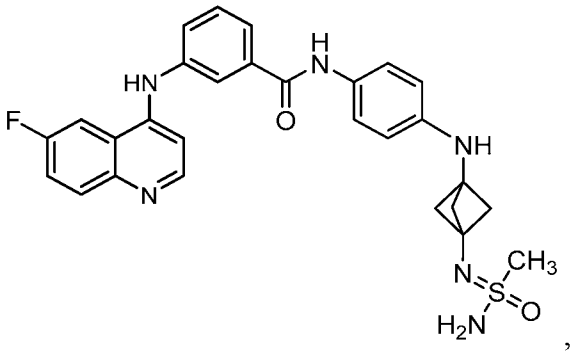


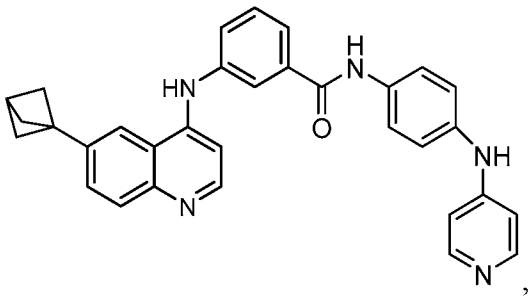


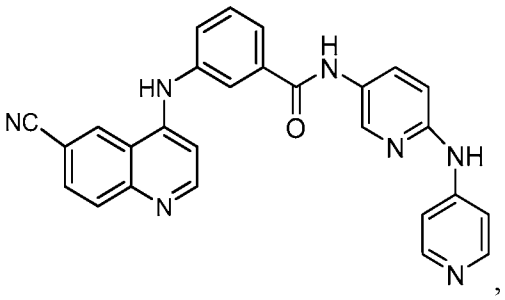


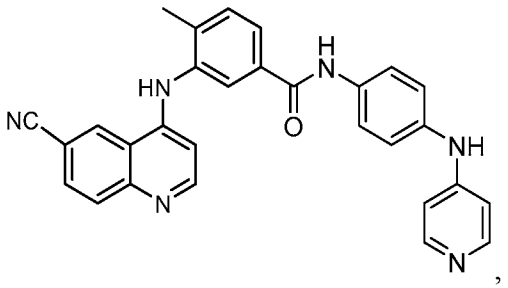


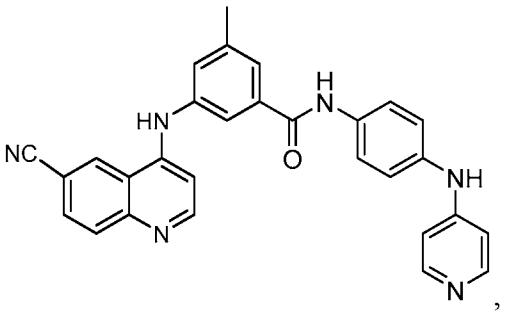


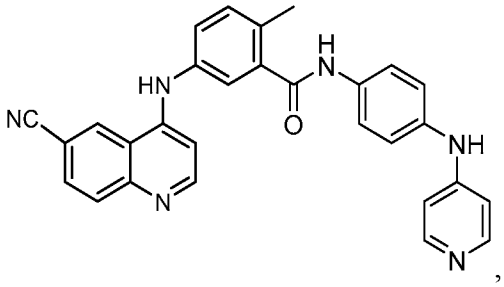
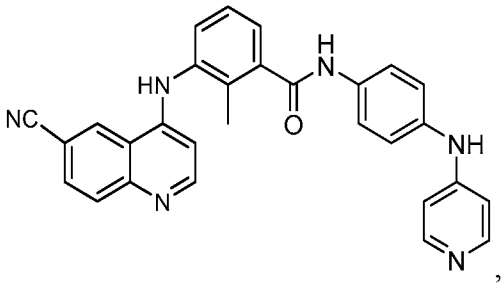
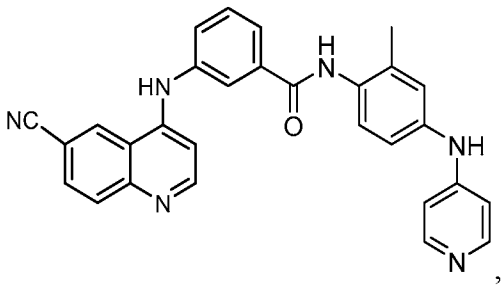
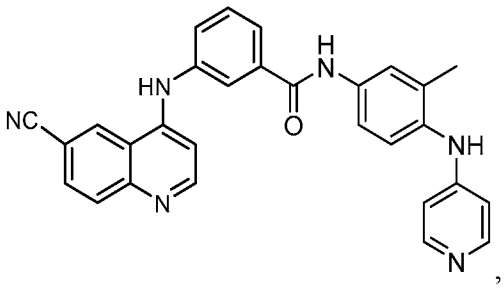
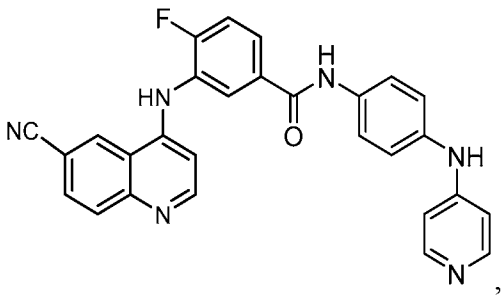
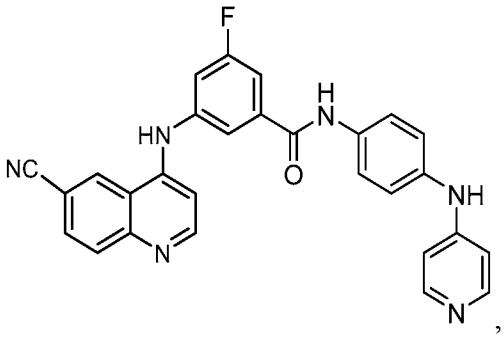
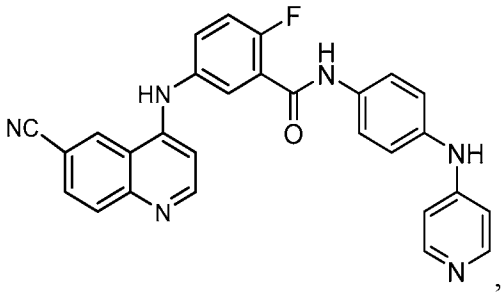
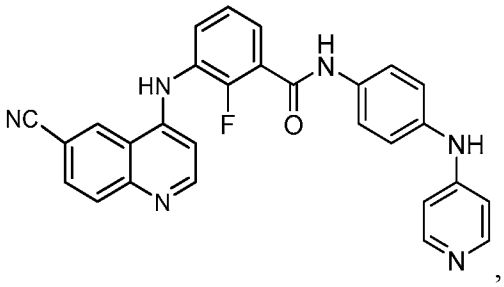
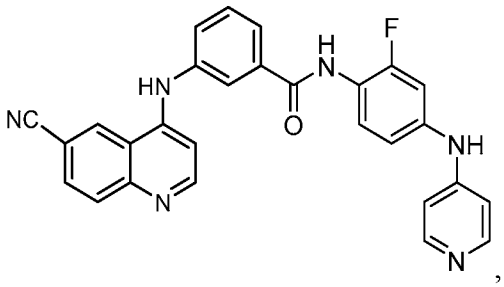
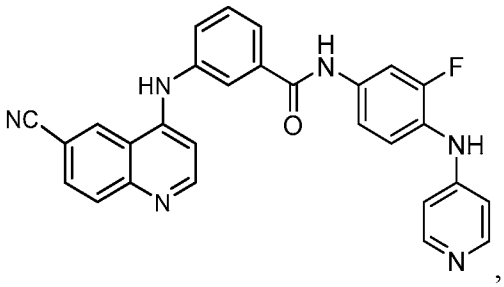


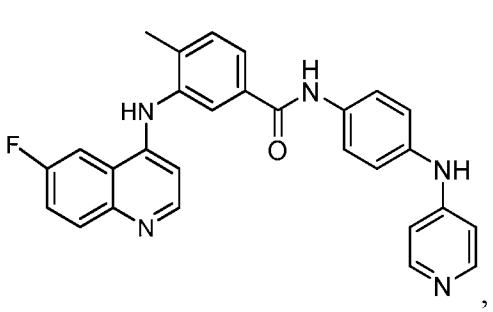
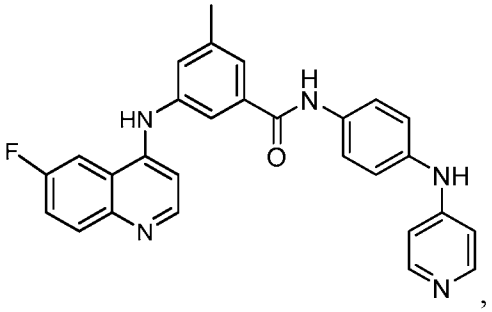
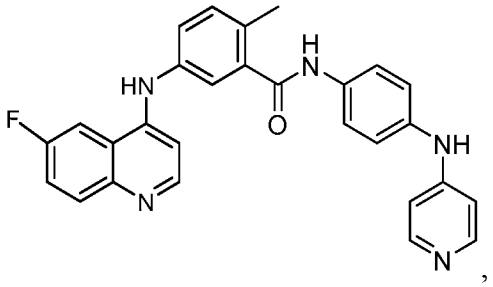
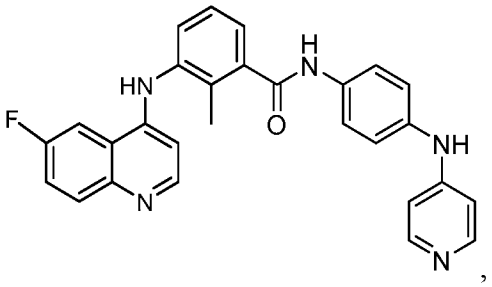
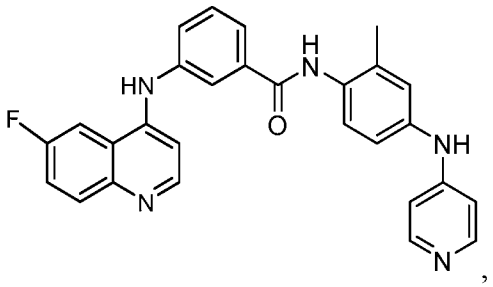
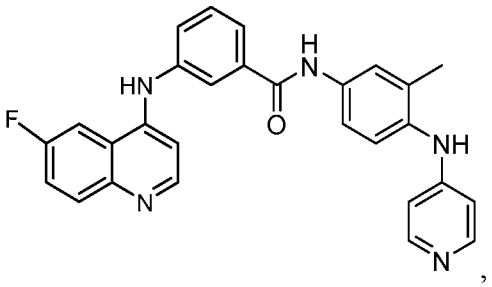
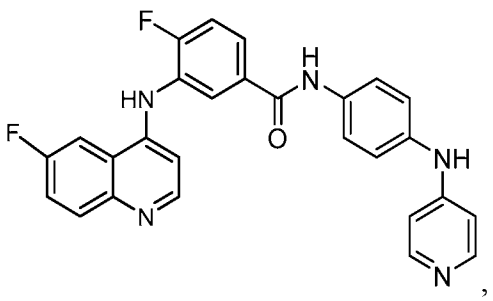
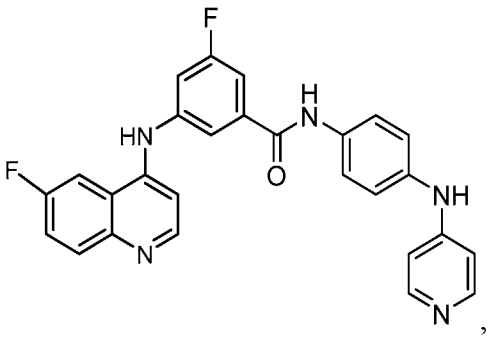
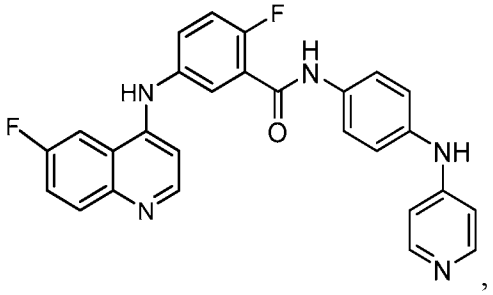
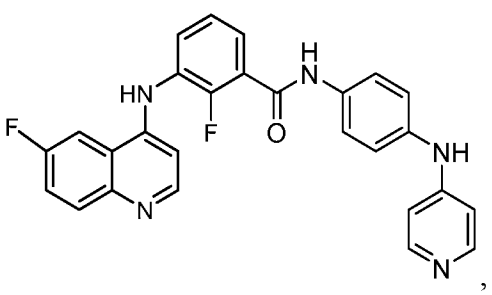


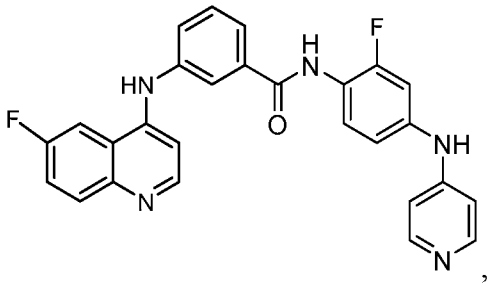
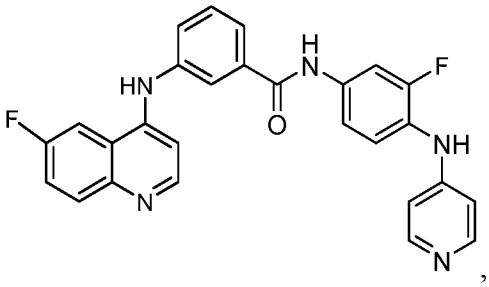
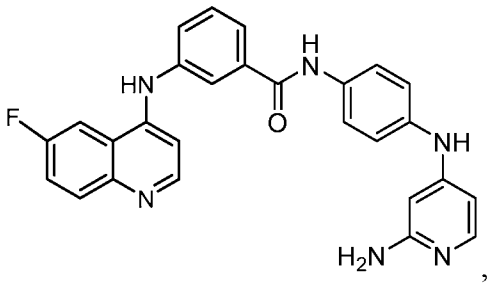
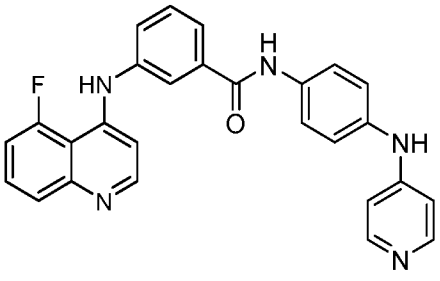
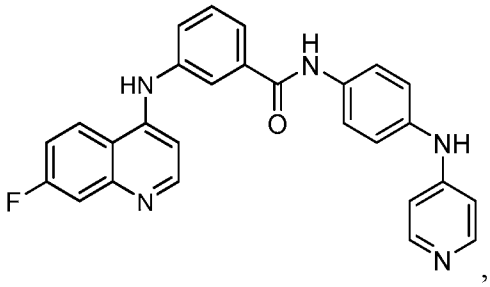
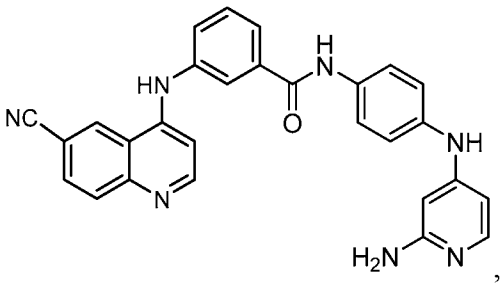
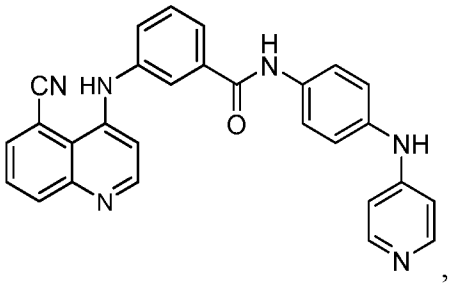
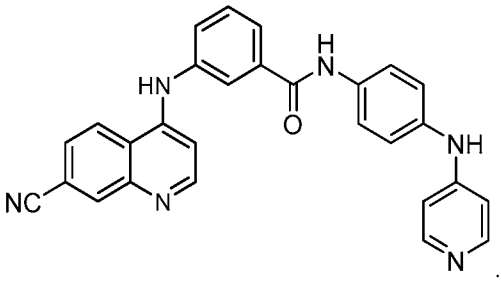
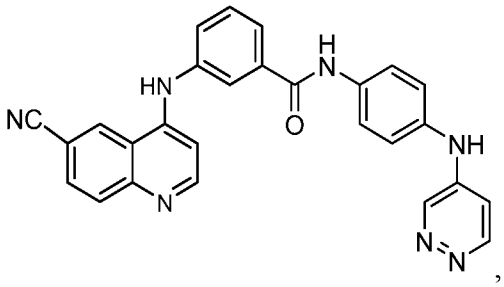
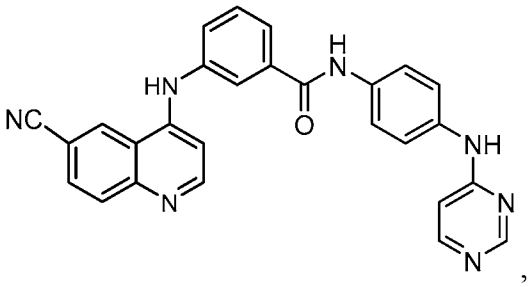


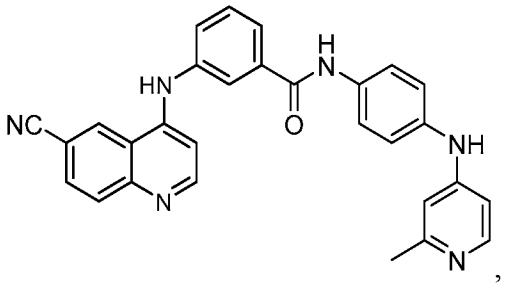
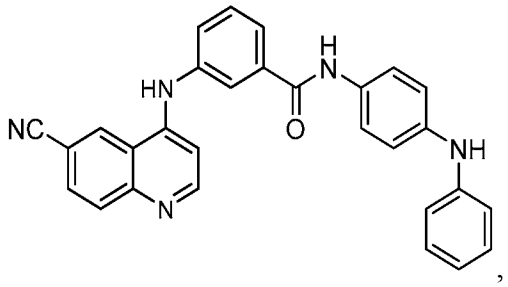
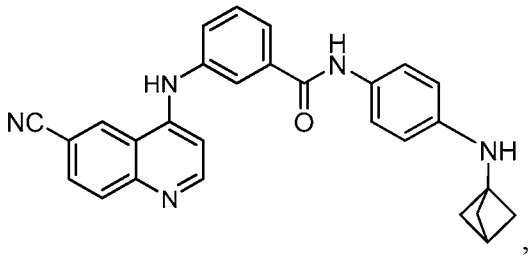
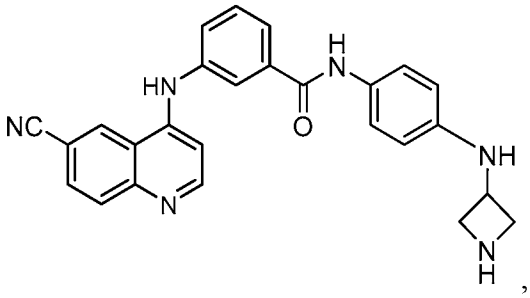
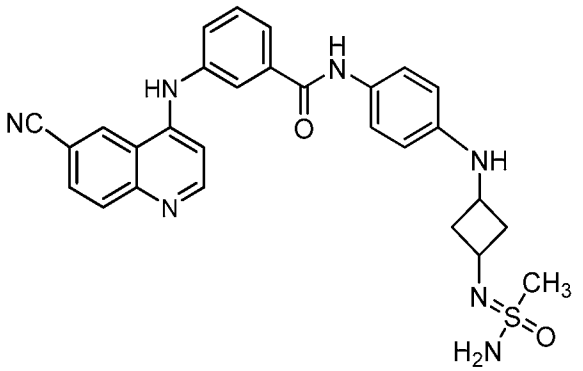
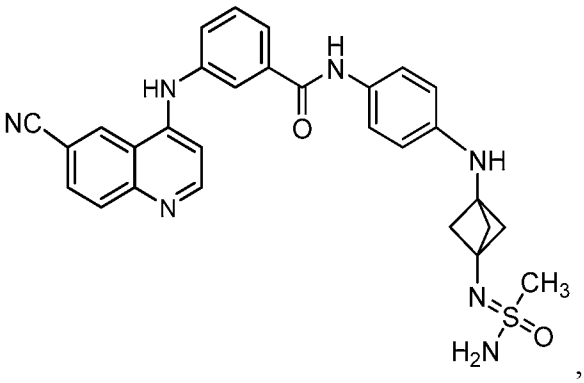
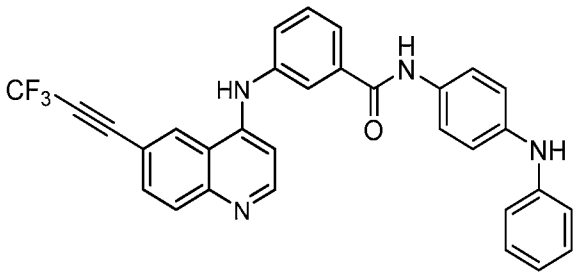
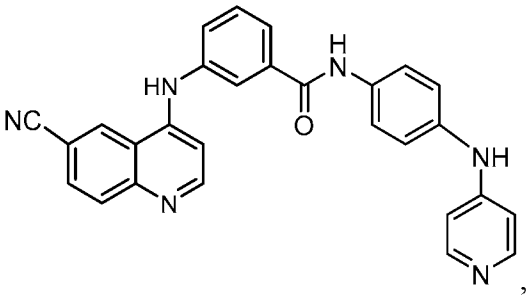
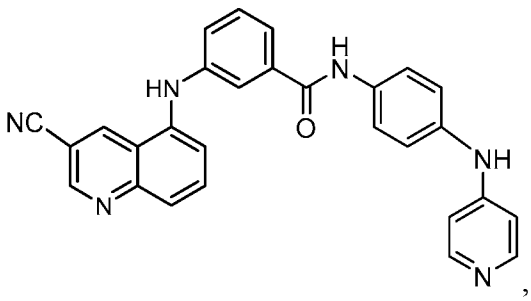
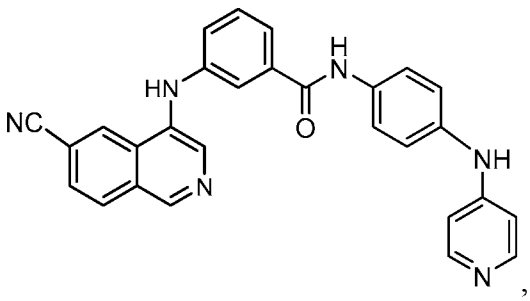


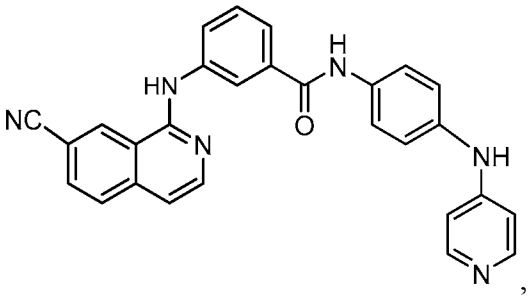
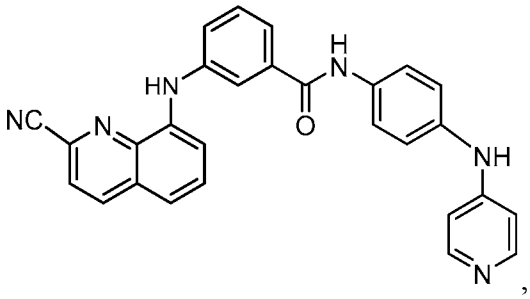
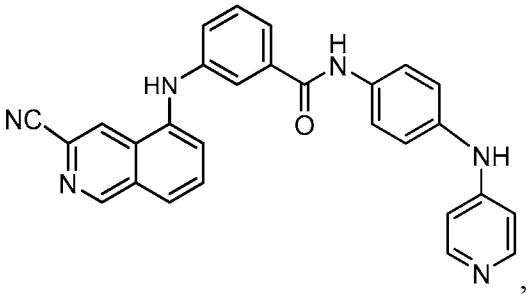
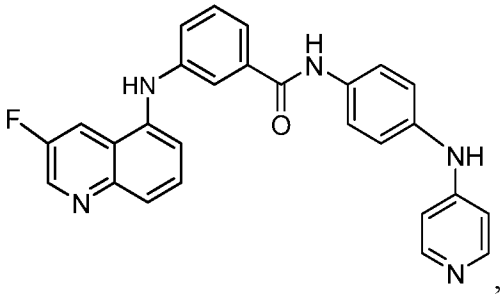
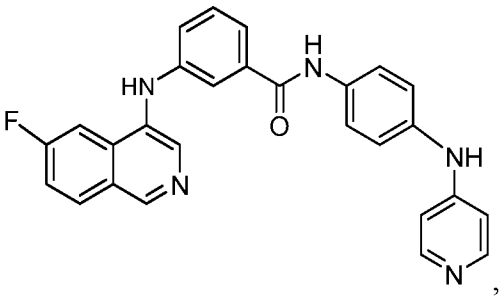
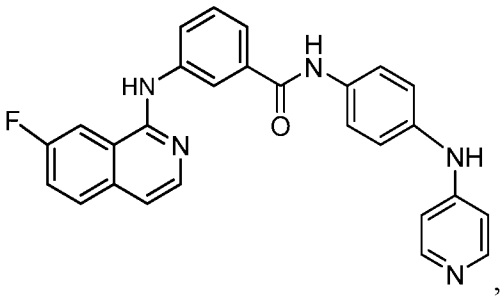
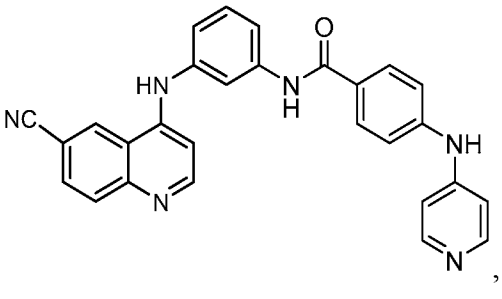
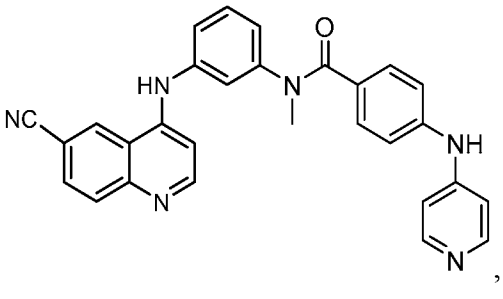
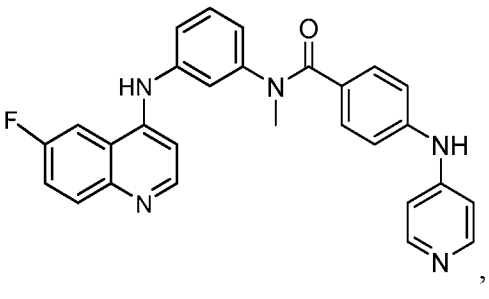
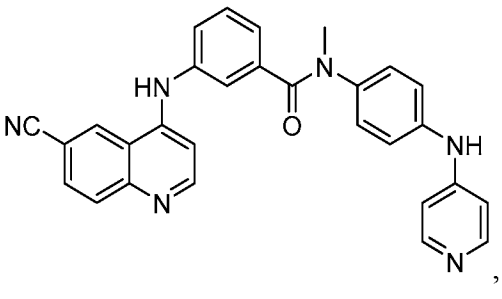
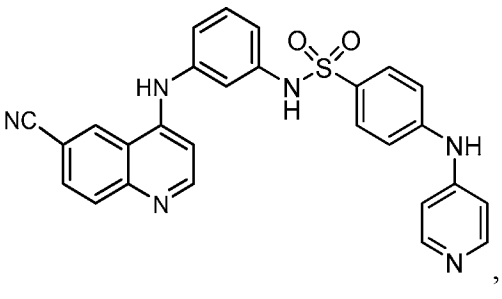
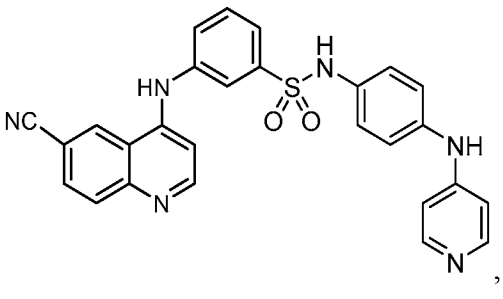


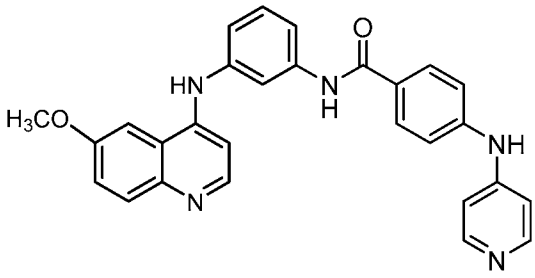
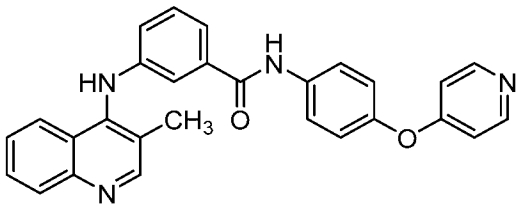
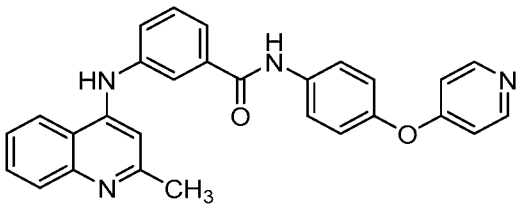
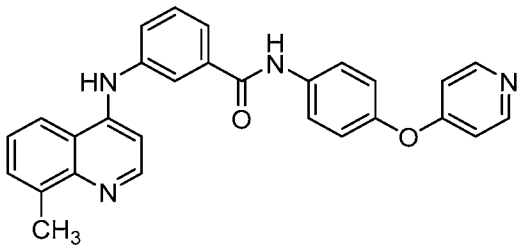
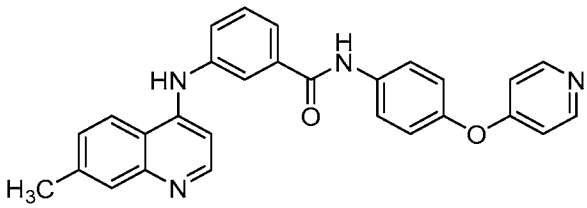
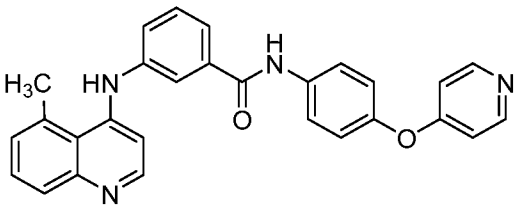
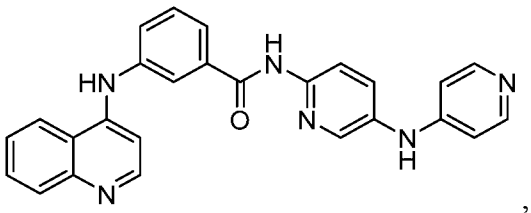
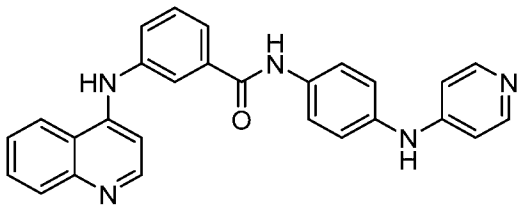
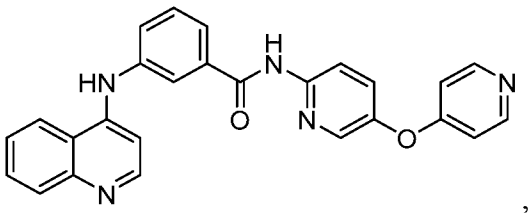
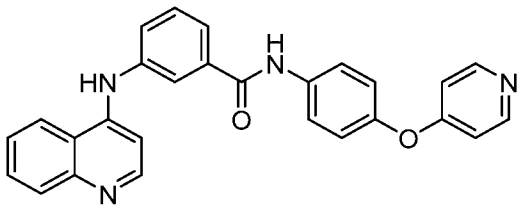
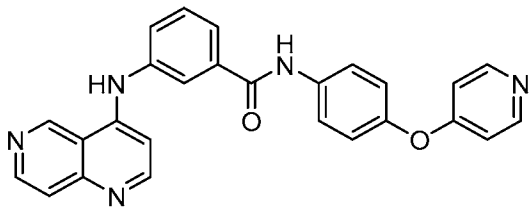
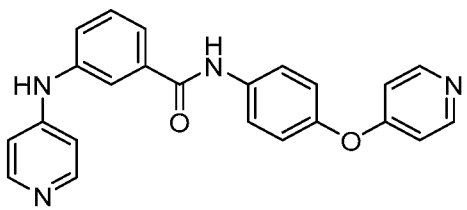
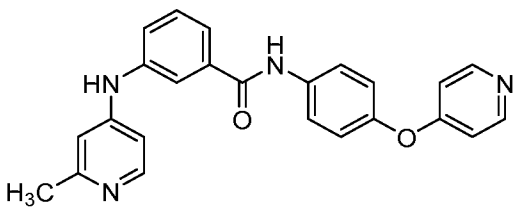
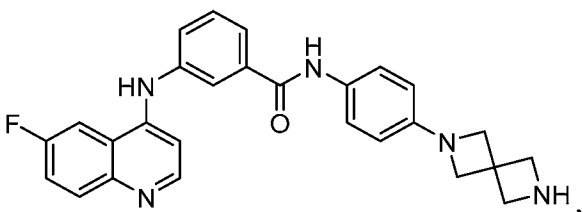

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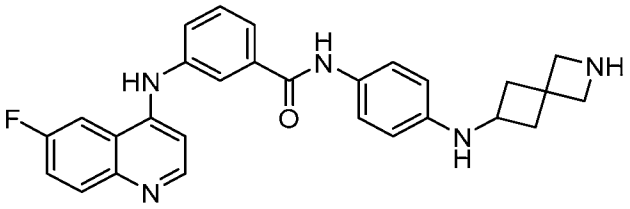

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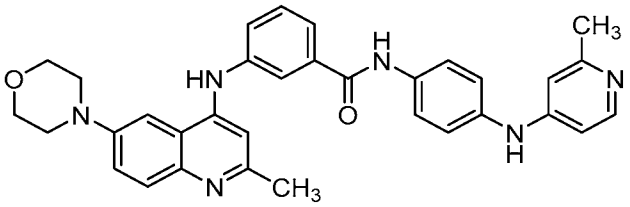

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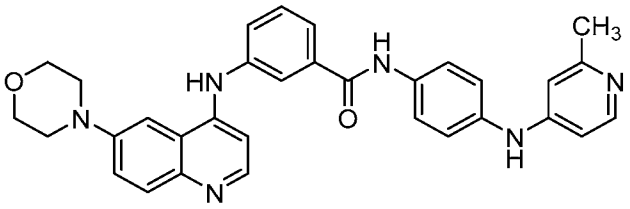

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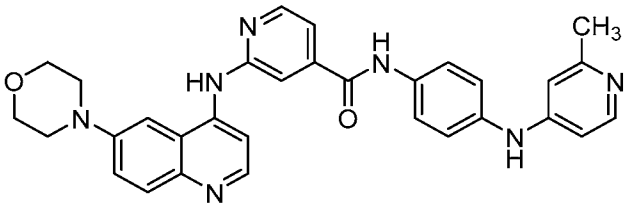

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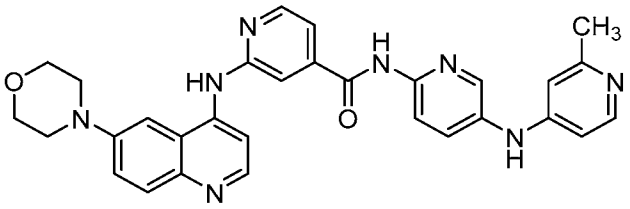

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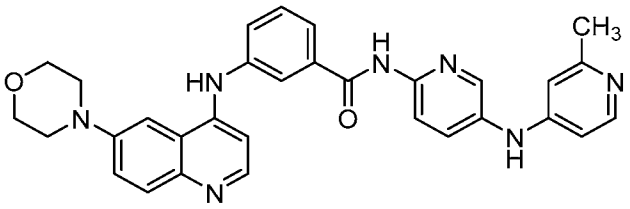

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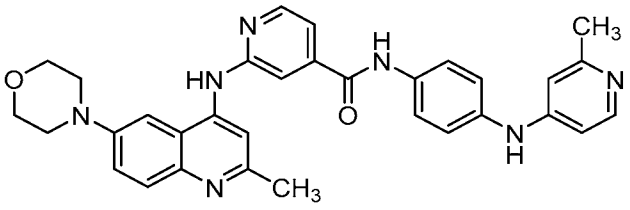

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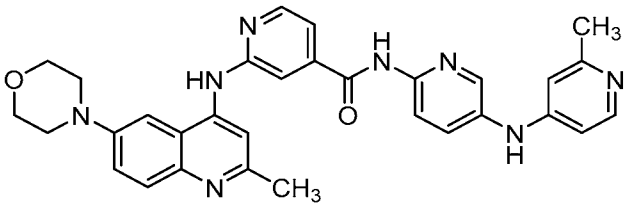

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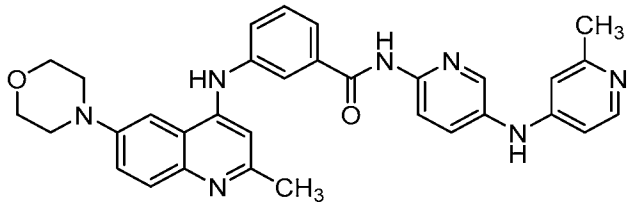

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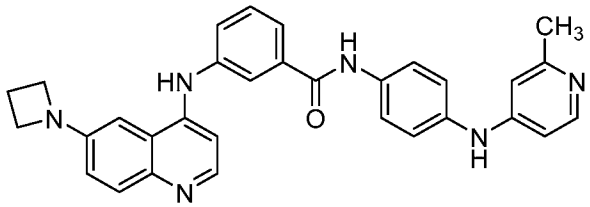

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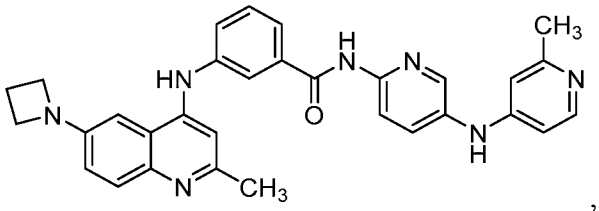

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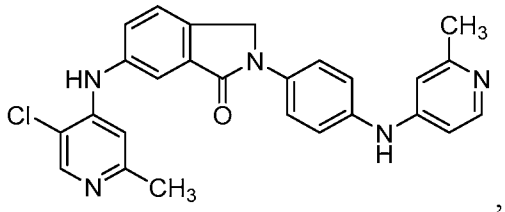
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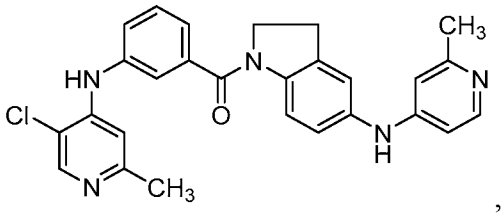
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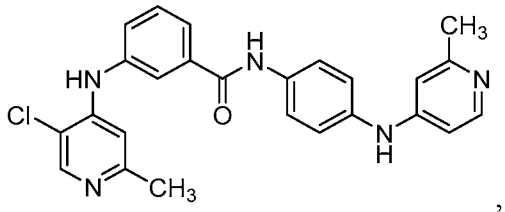
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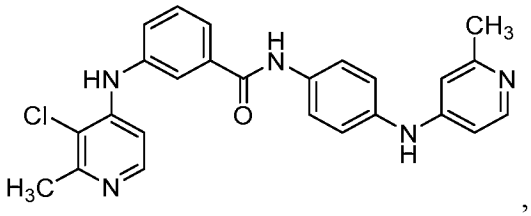
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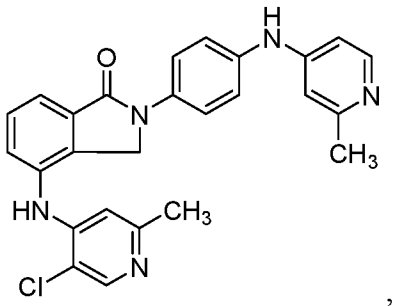
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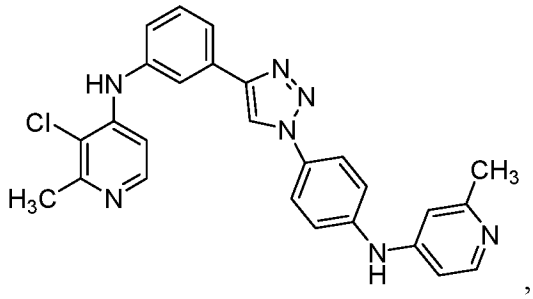
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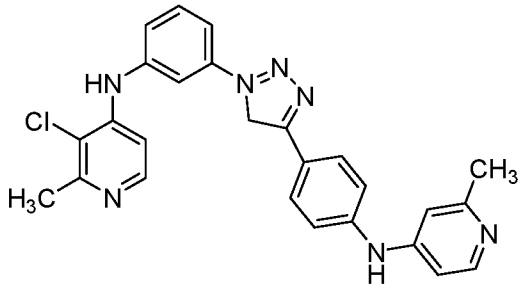
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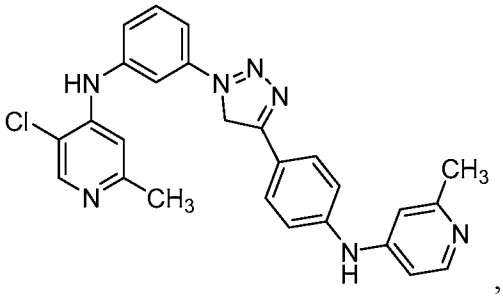
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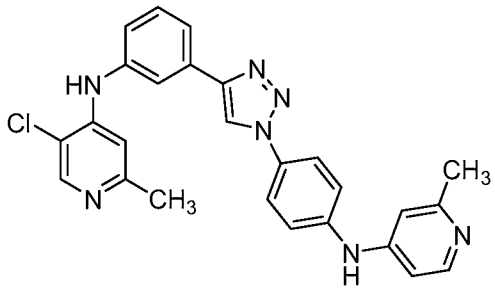
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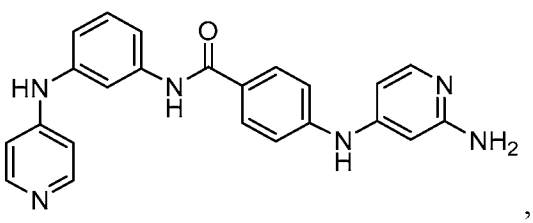
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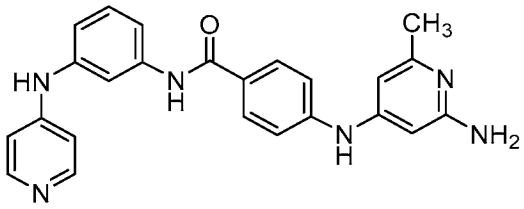
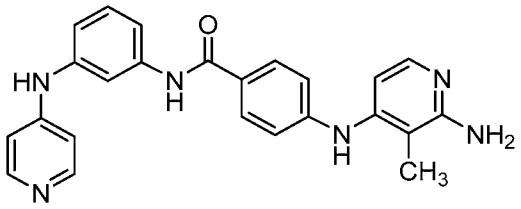
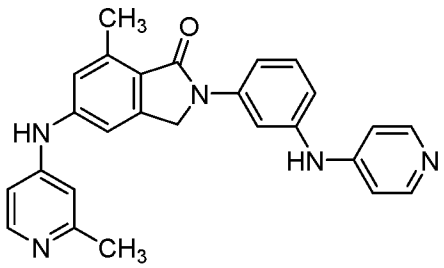
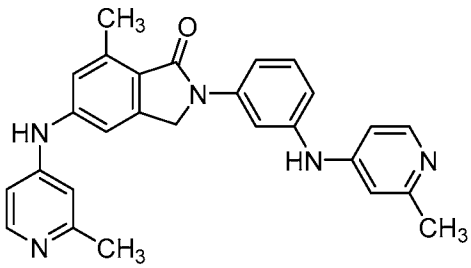
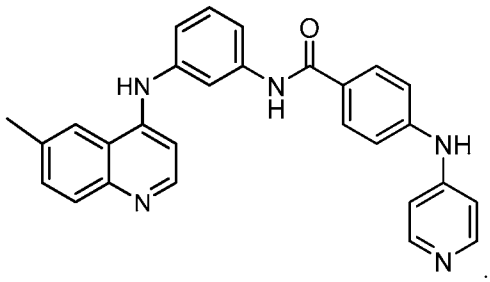
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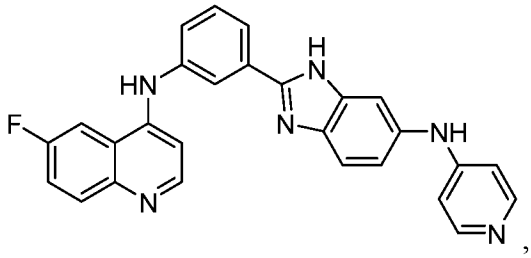
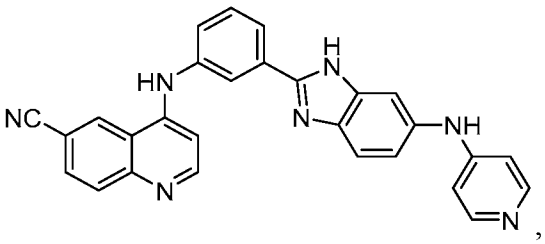
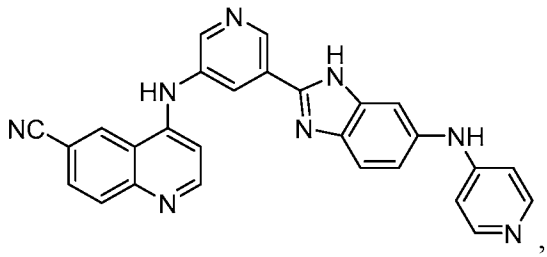
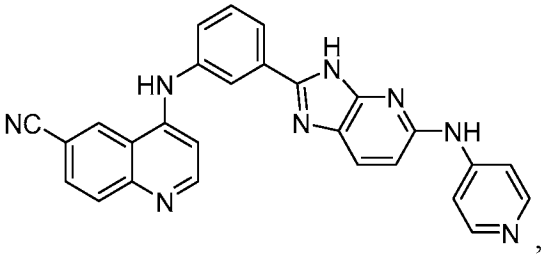
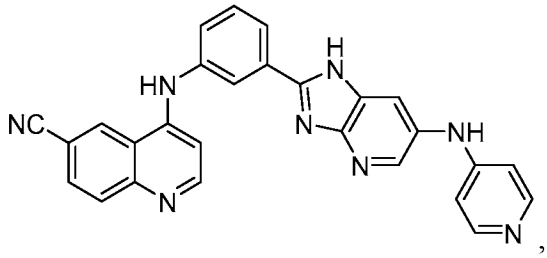
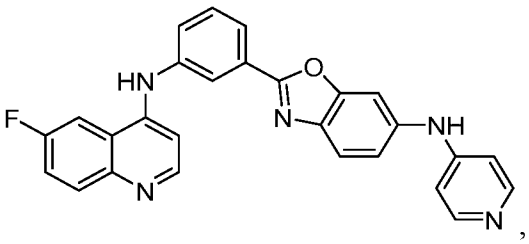
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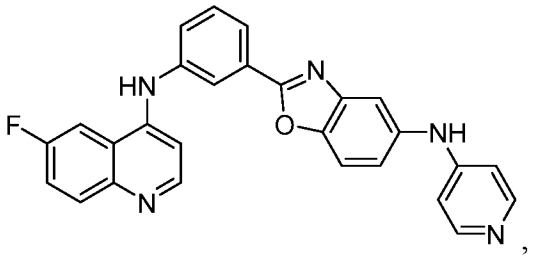
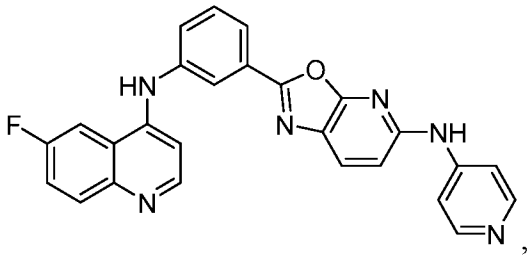
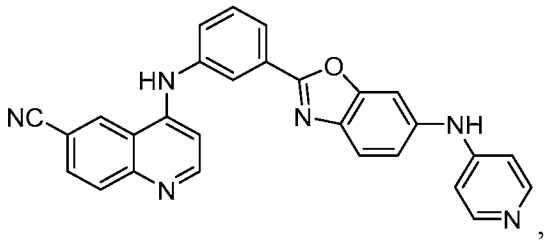
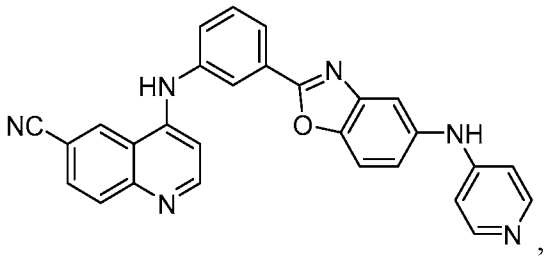
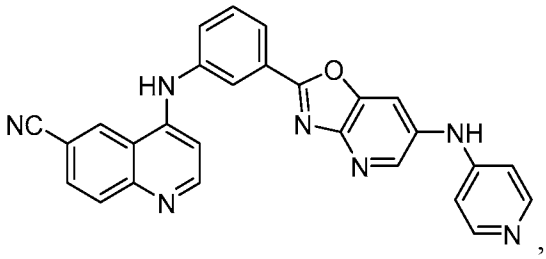
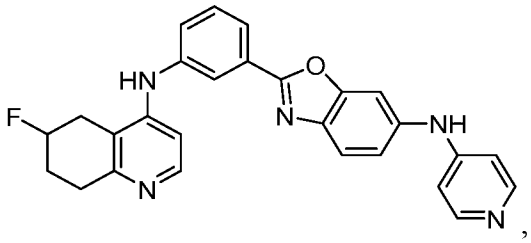
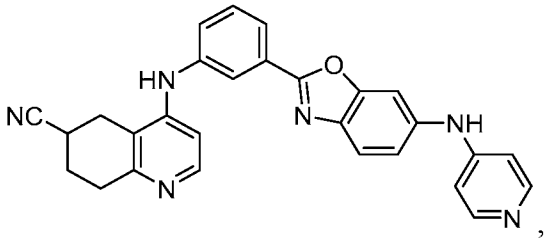
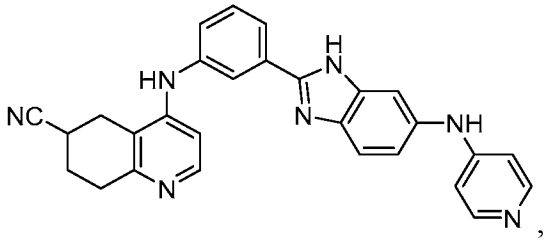
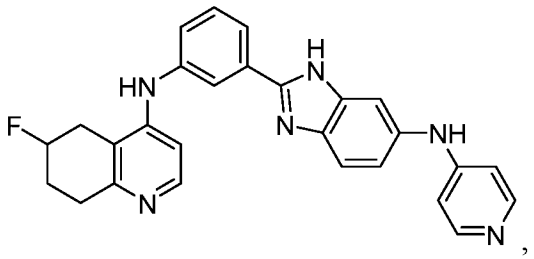
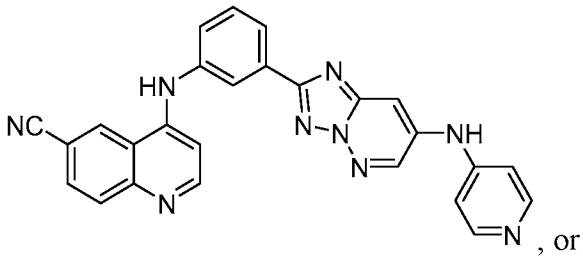
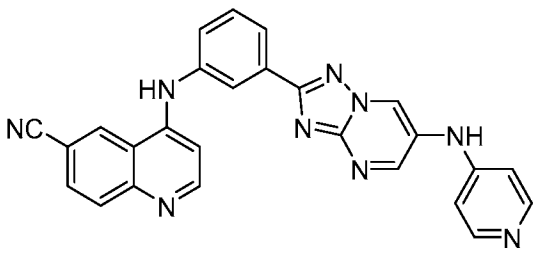


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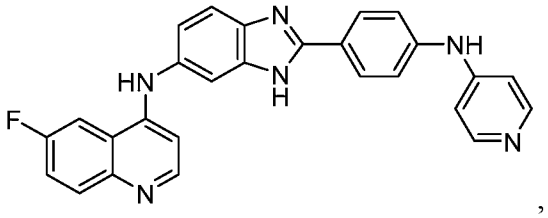
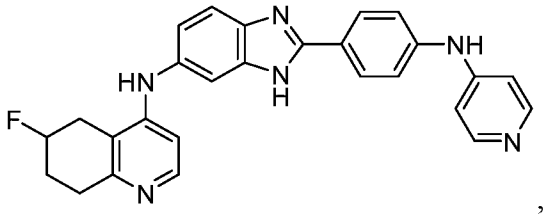
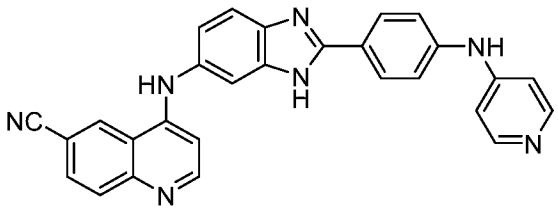
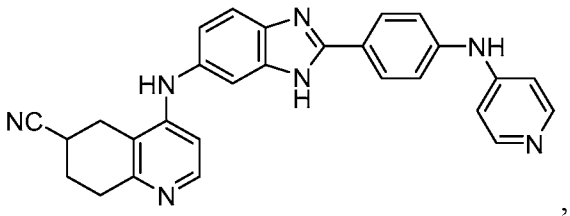
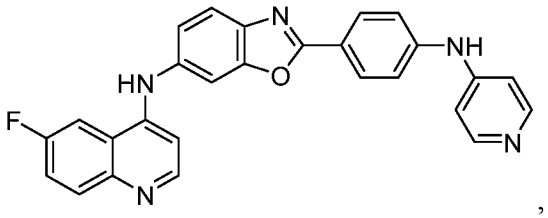
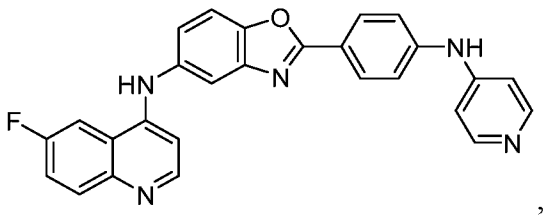
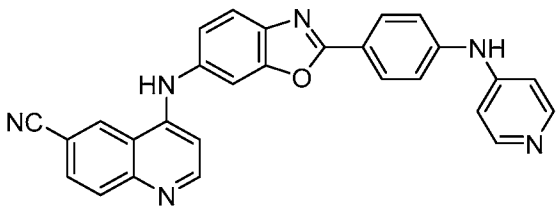
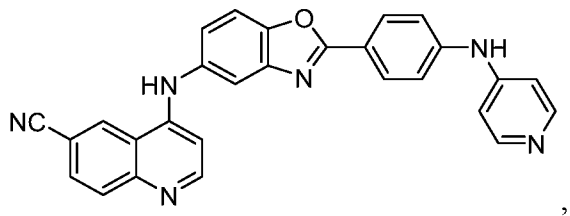
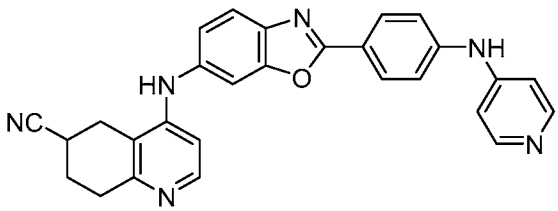
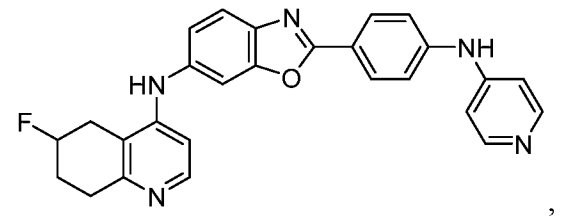
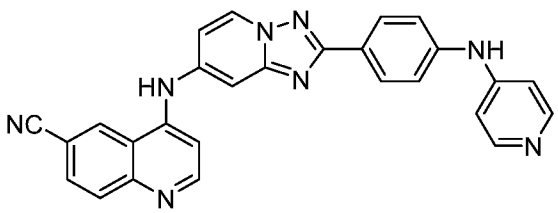
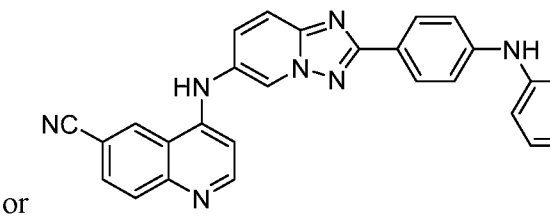

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[0370] In some embodiments, the compound of Formula IIIb is


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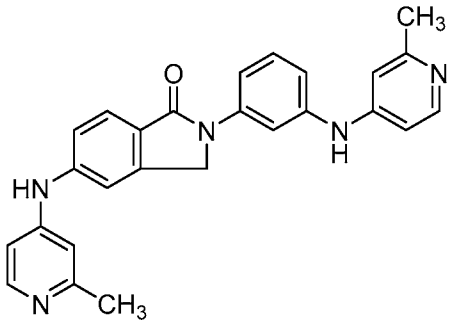
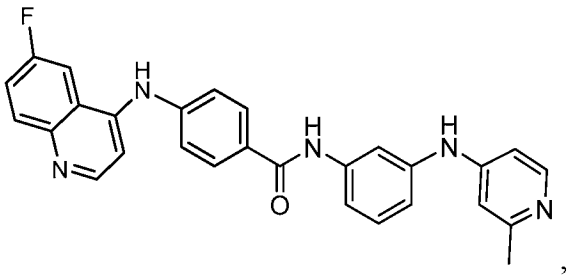
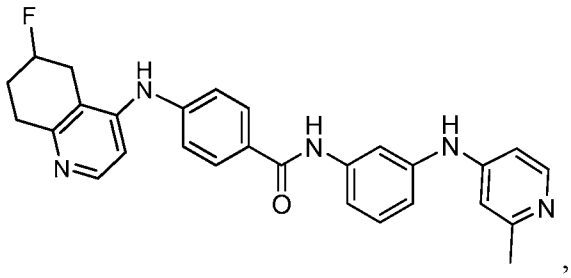
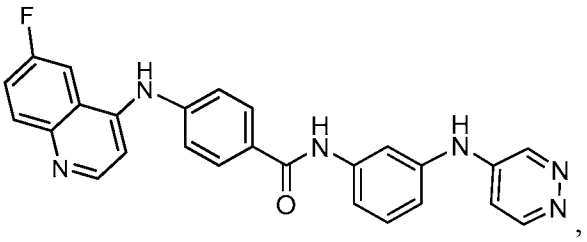
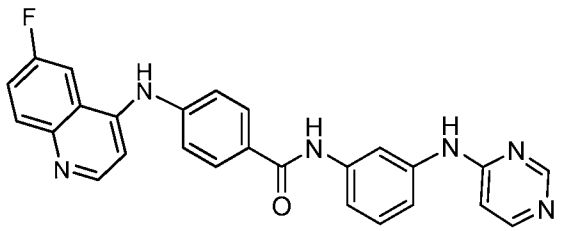
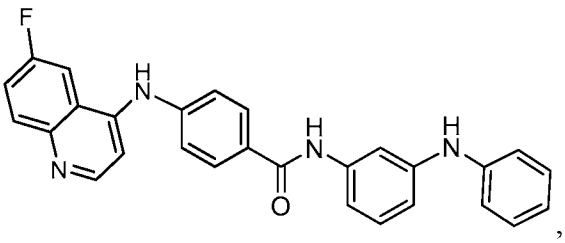
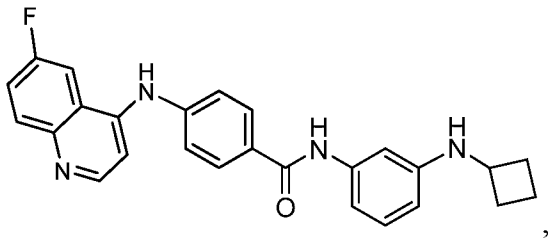
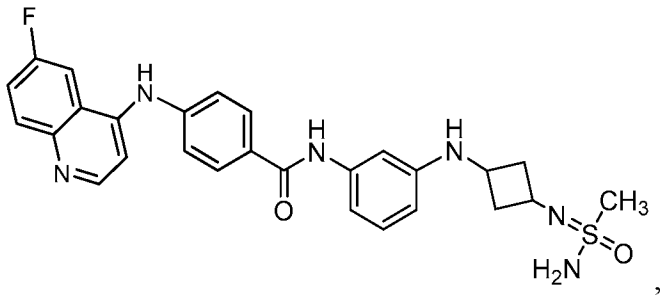
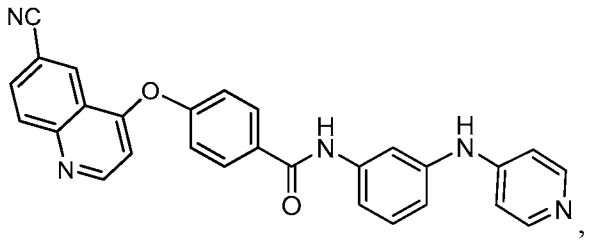
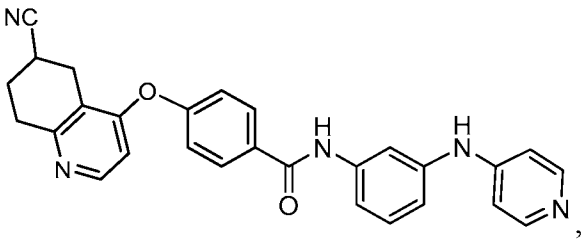
[0371] In some embodiments, the compound of Formula IIIc is

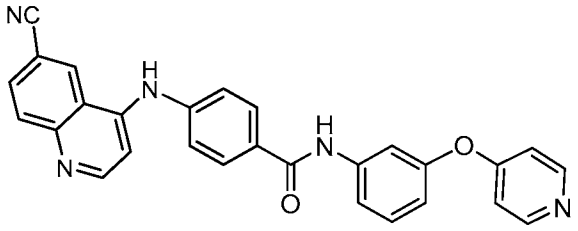

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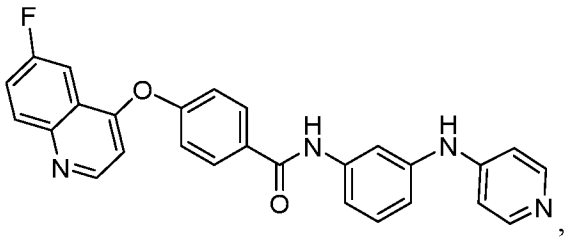
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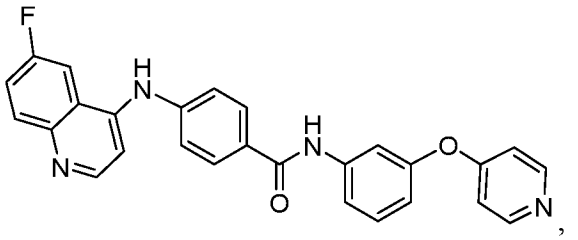
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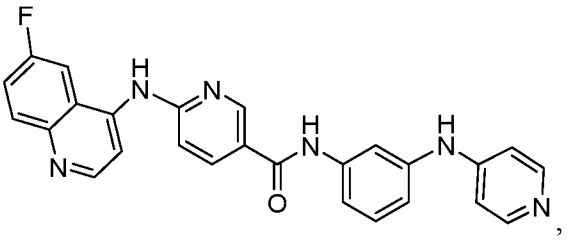
[0372] In some embodiments, the compound of Formula IVa is

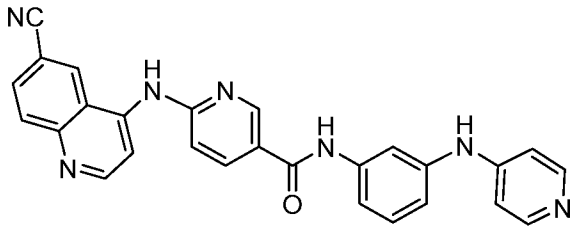

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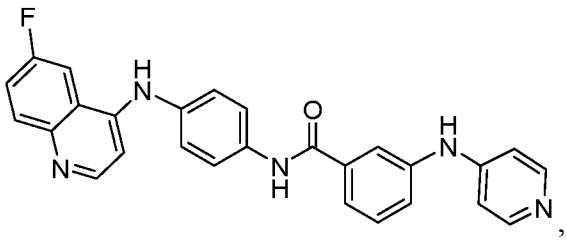


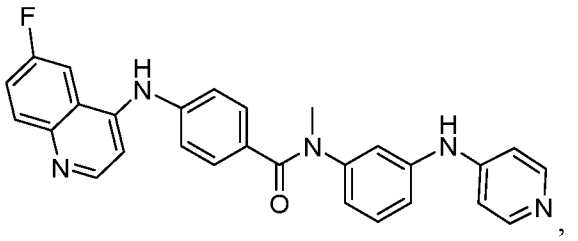


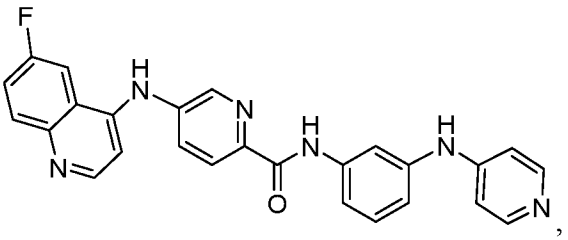


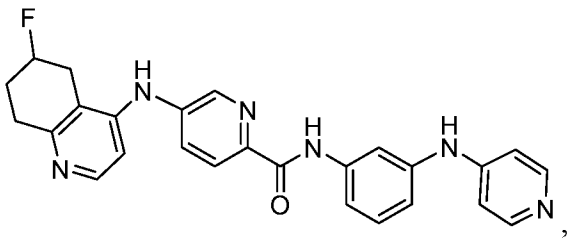


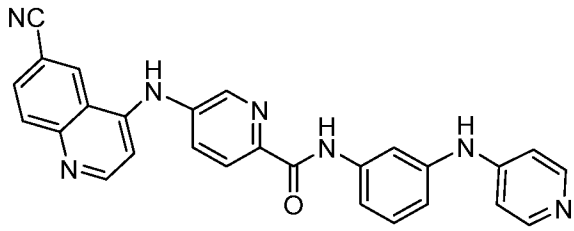


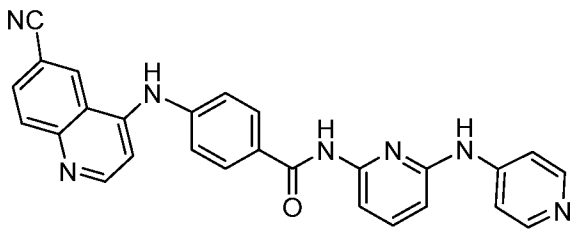


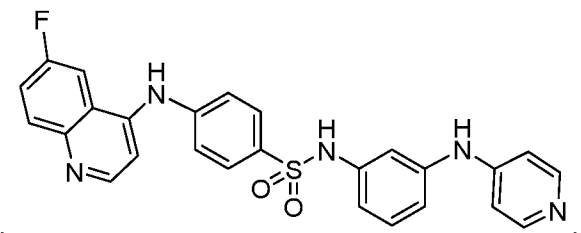


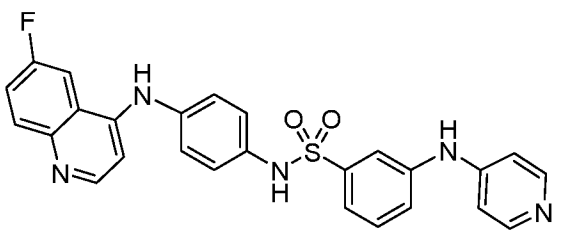


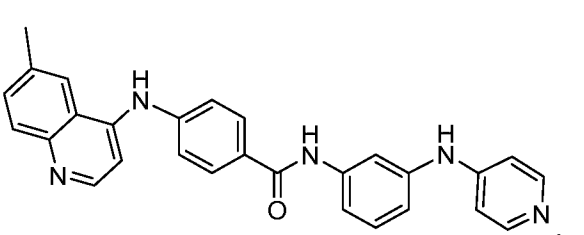




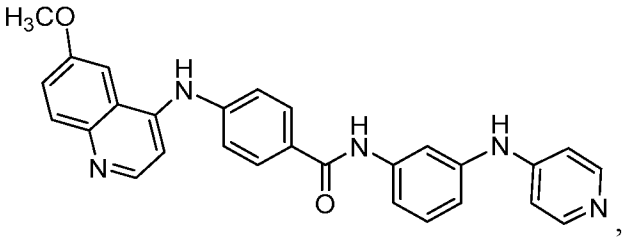


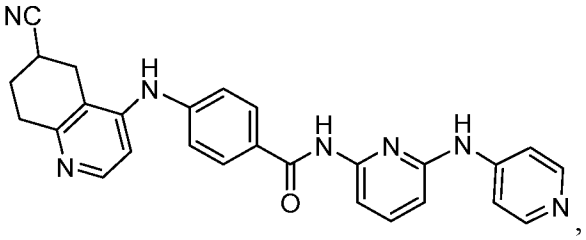


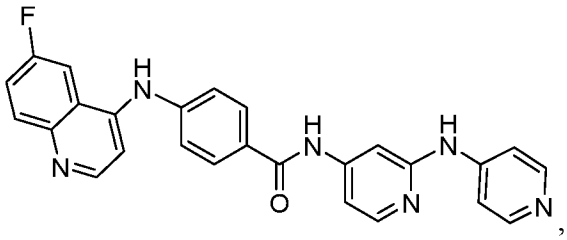


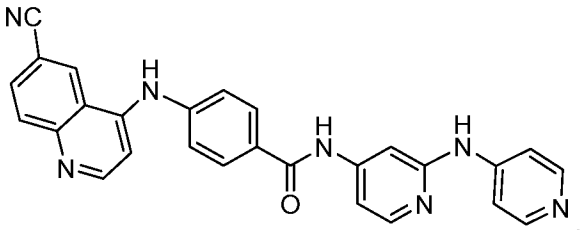


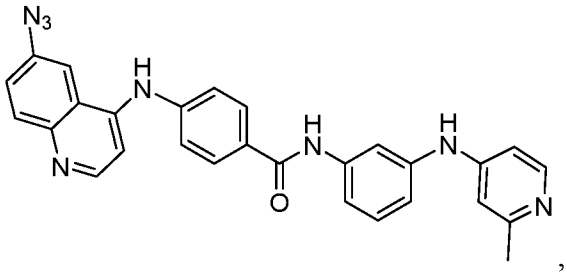


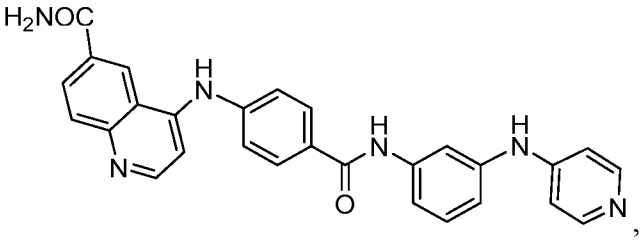


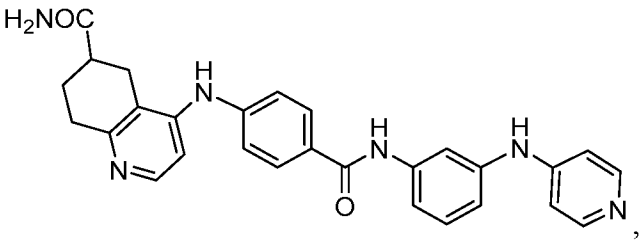


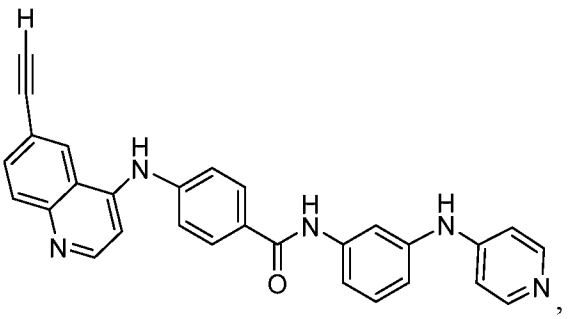


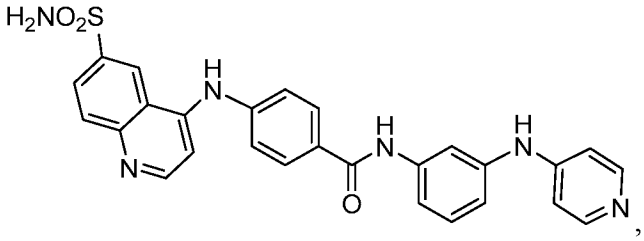


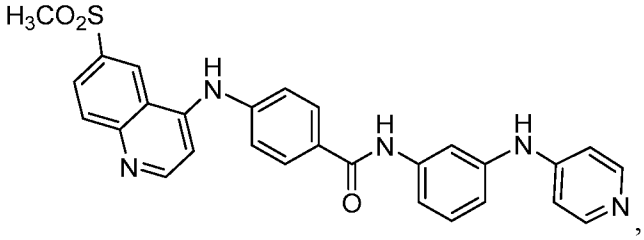


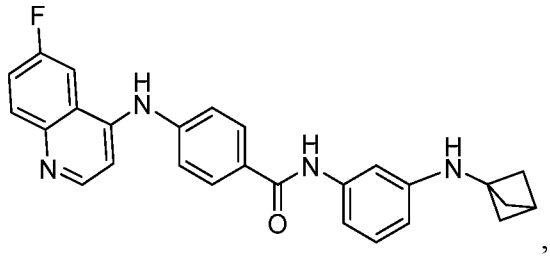


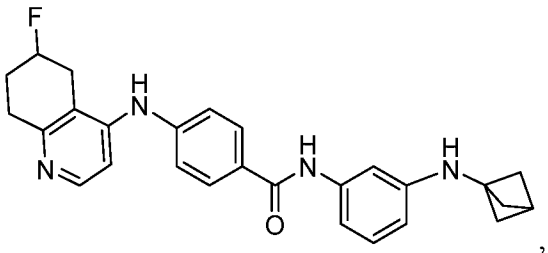


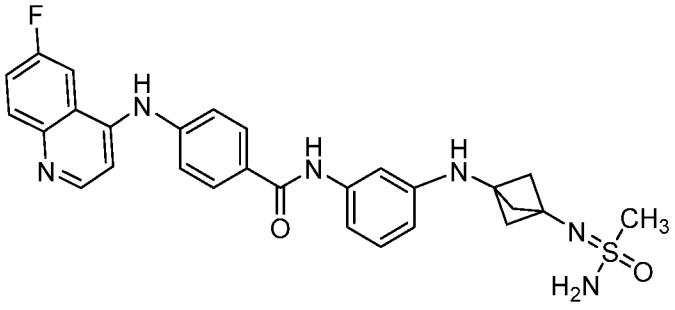


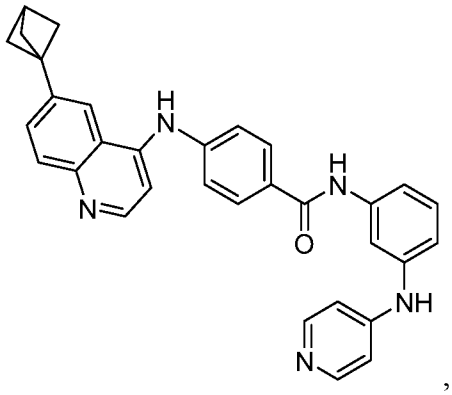


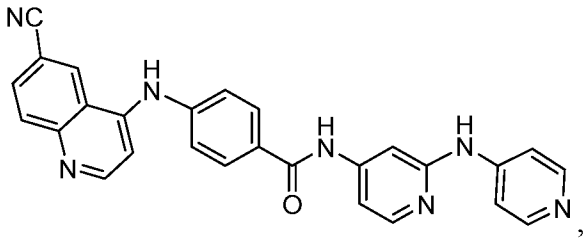


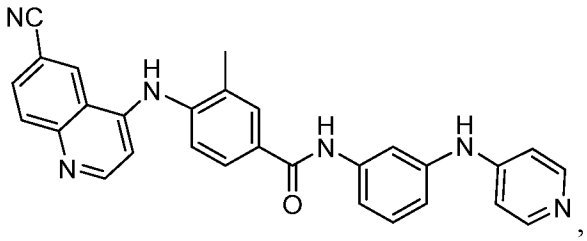


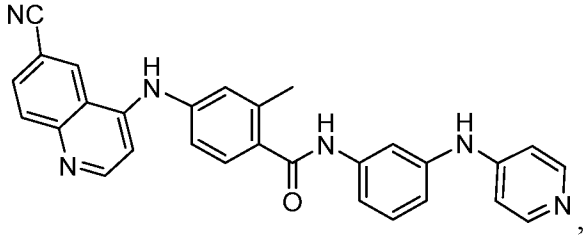


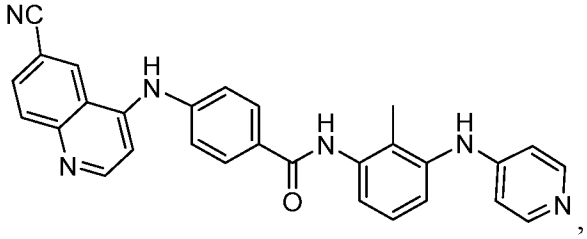


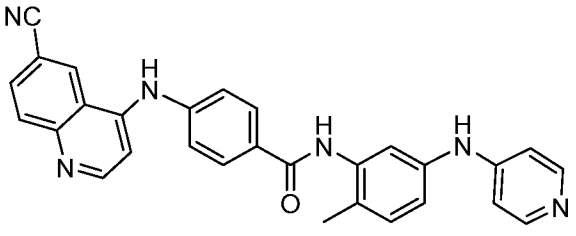
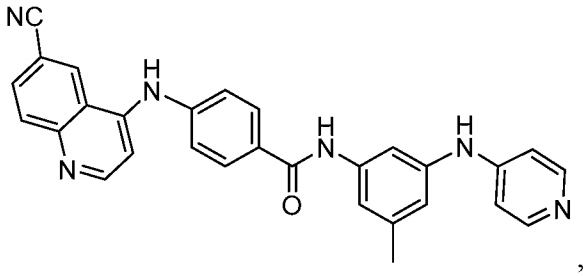
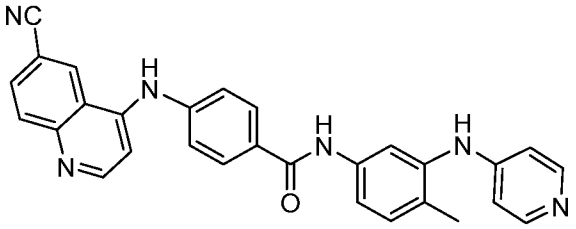
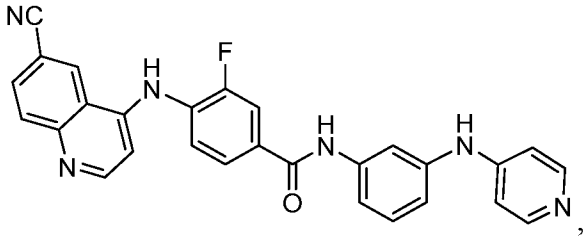
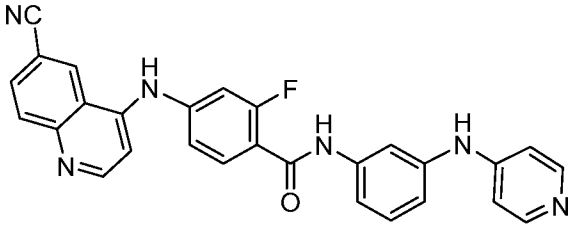
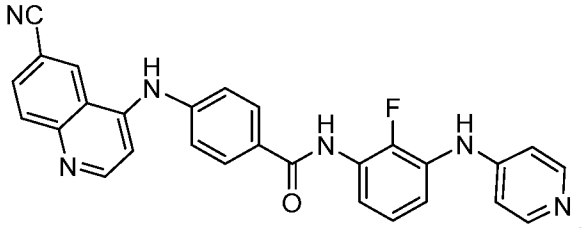
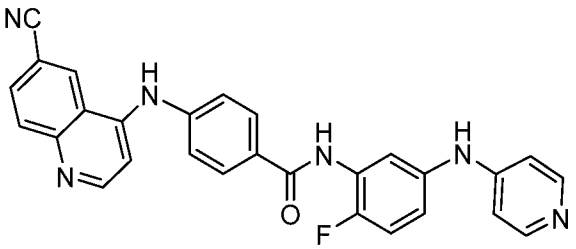
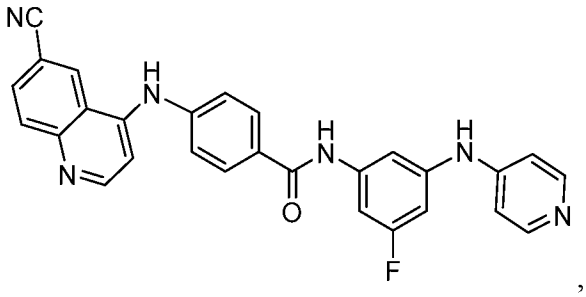
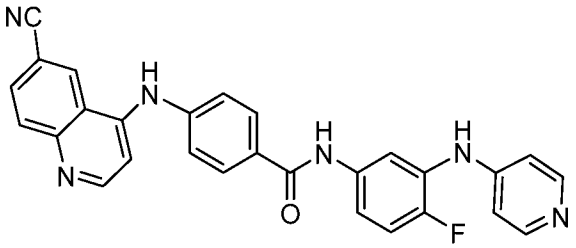
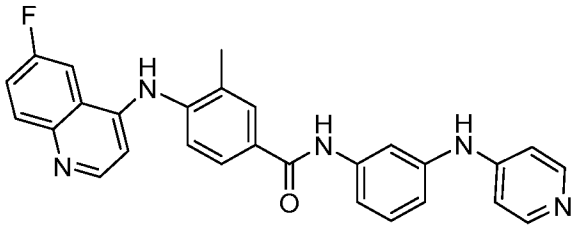
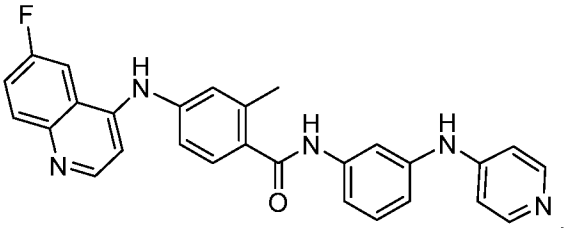
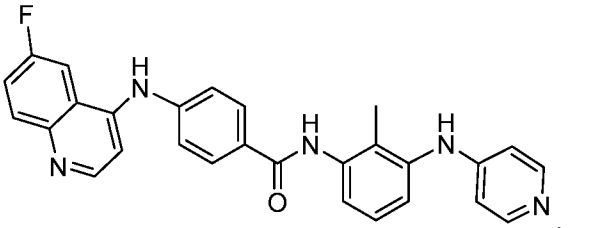






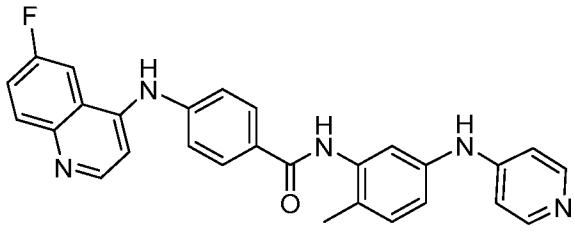
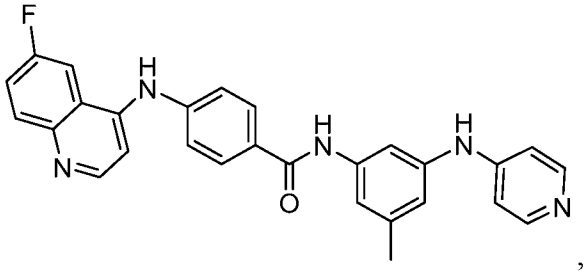
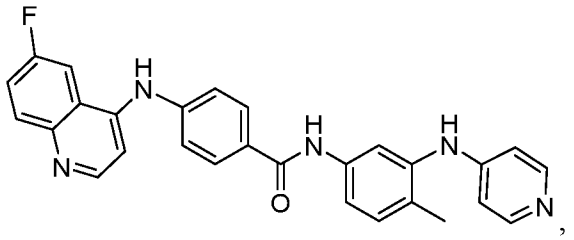
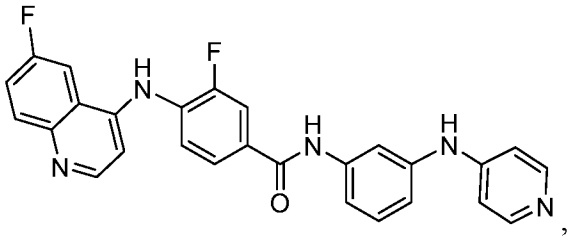
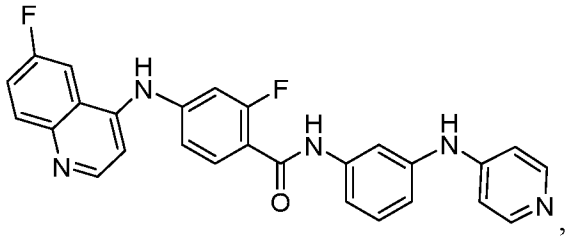
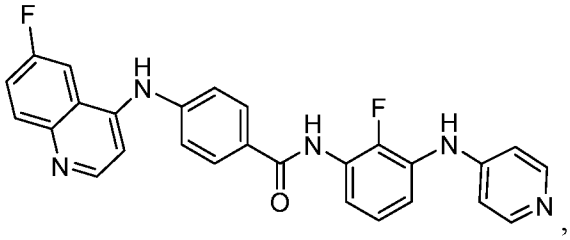
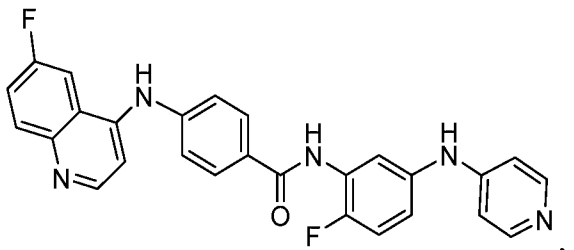
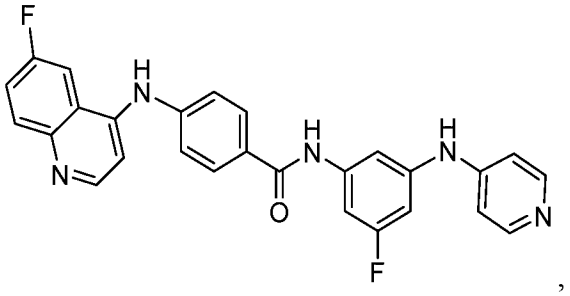
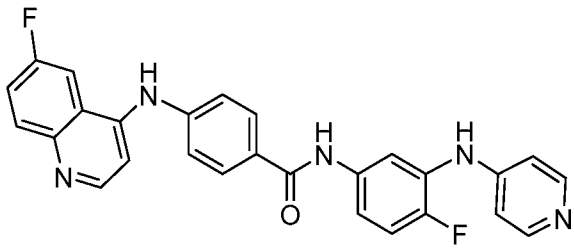
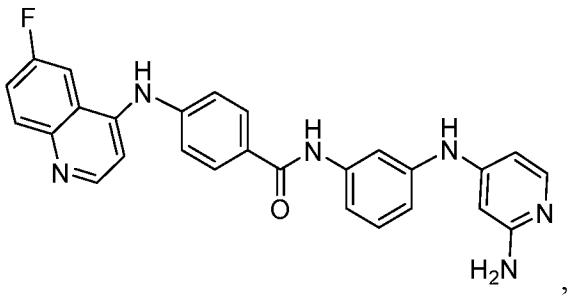
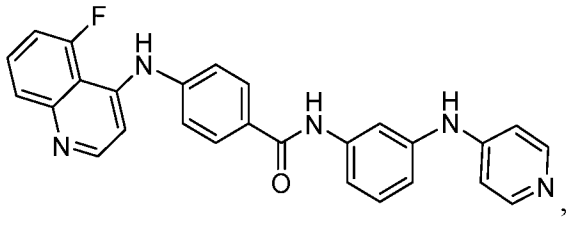
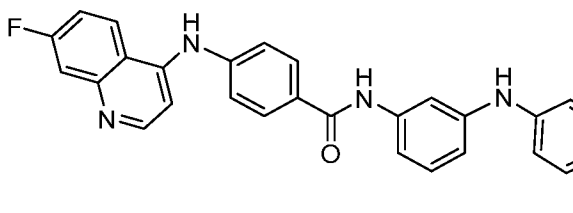


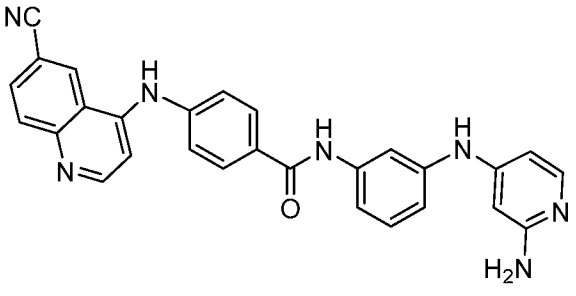
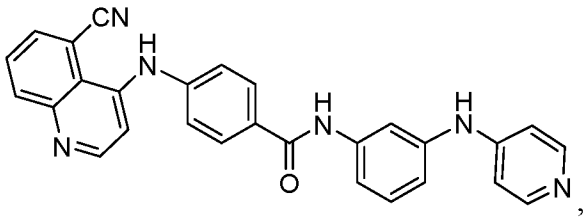
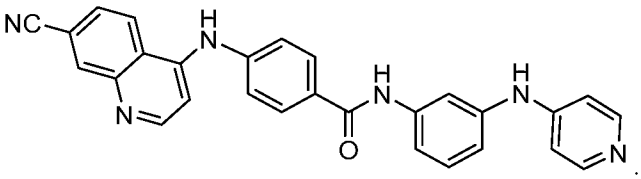
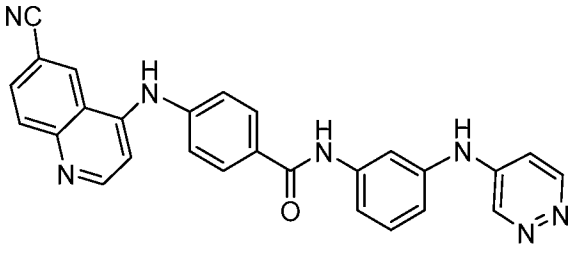
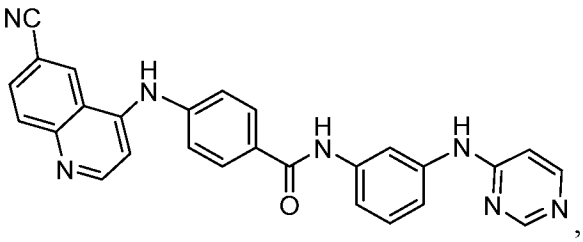
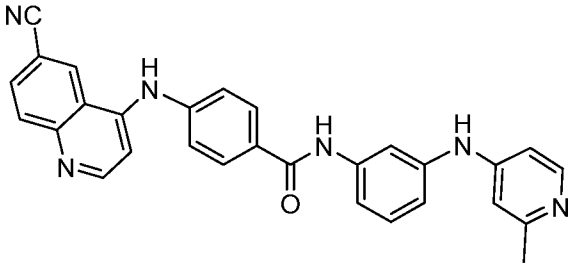
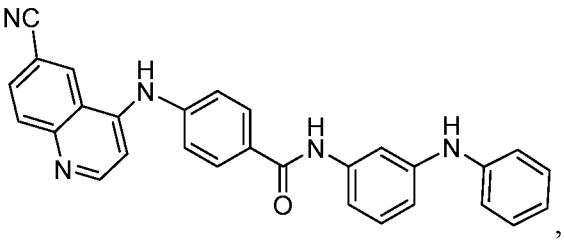
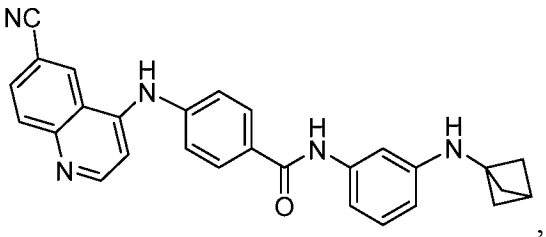
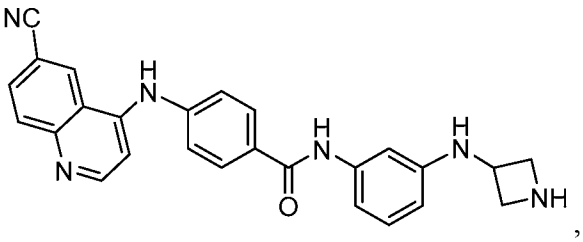
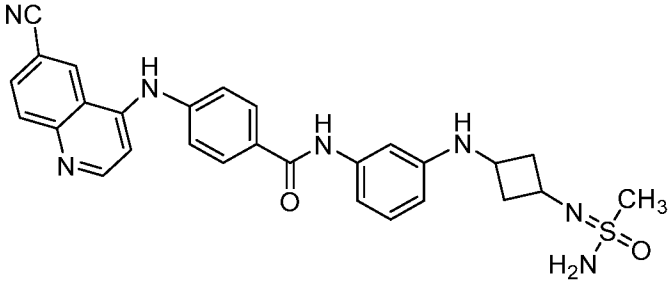


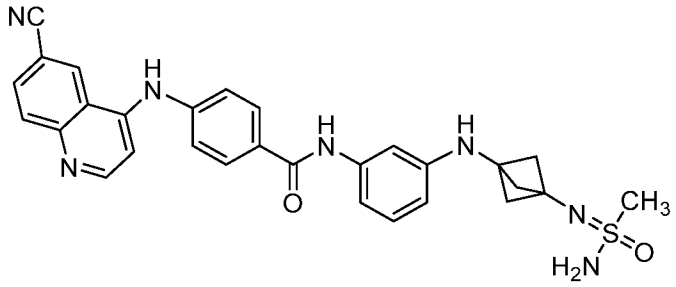
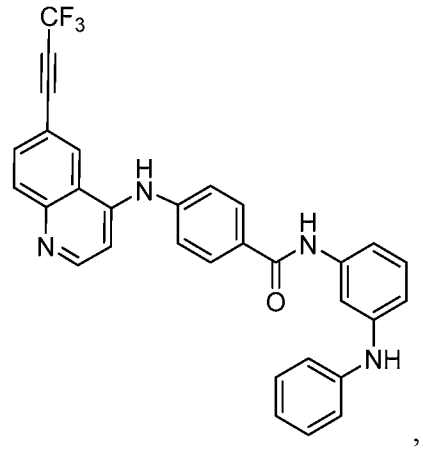
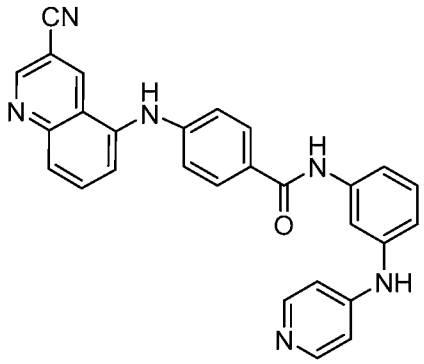
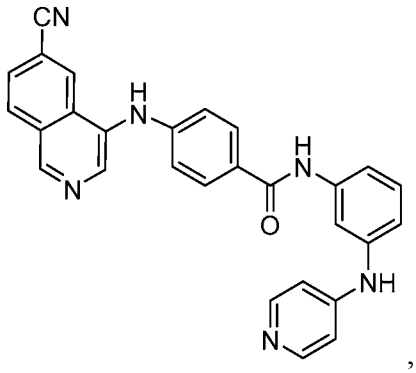
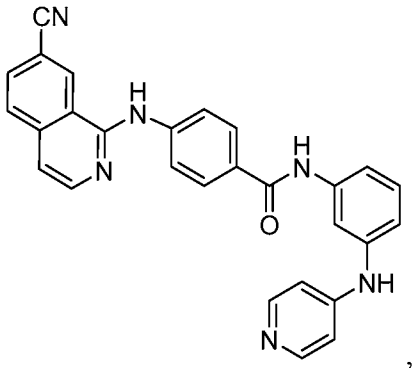
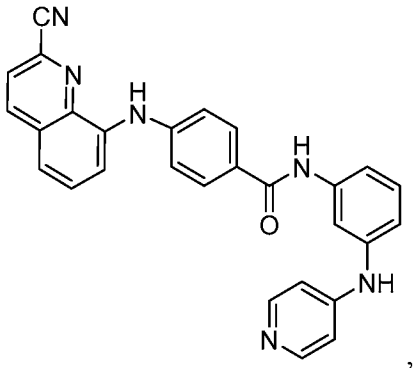
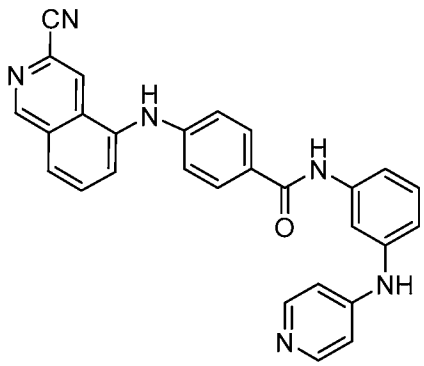
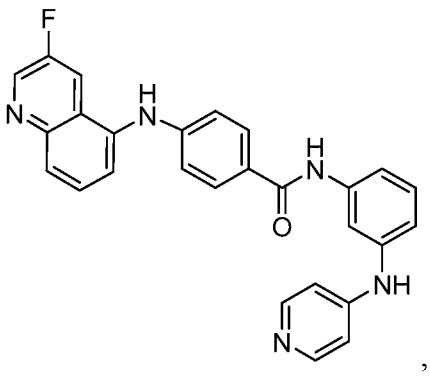

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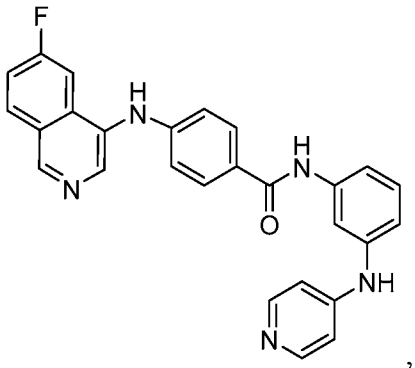
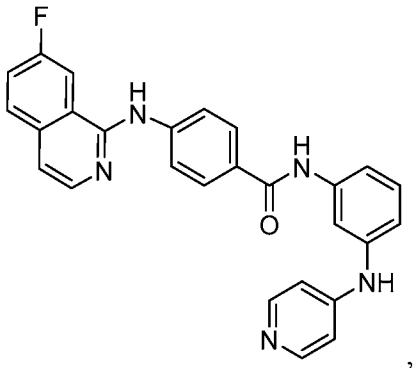
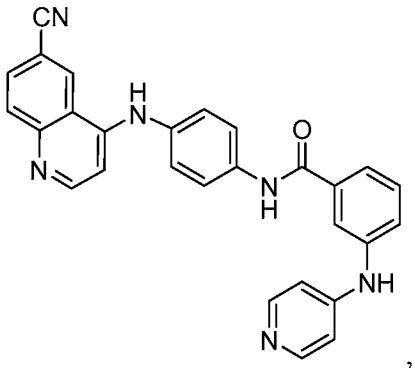
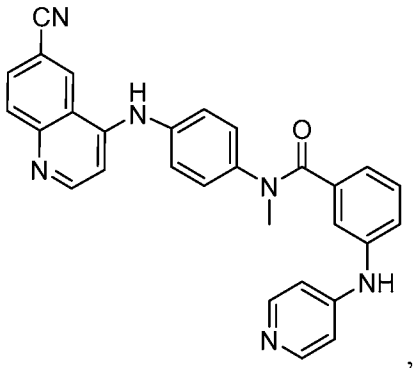
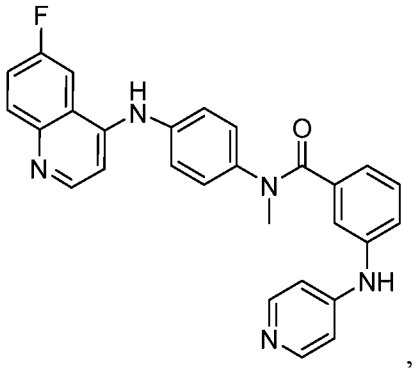
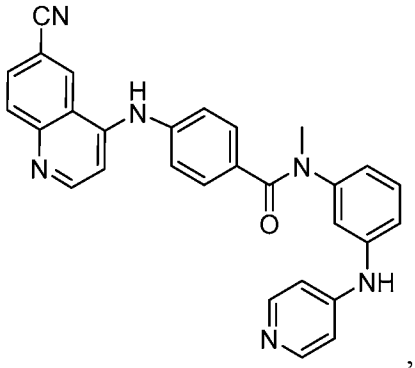
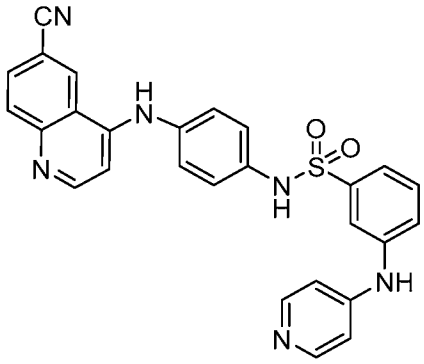
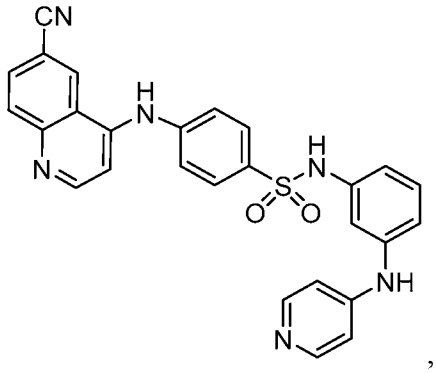
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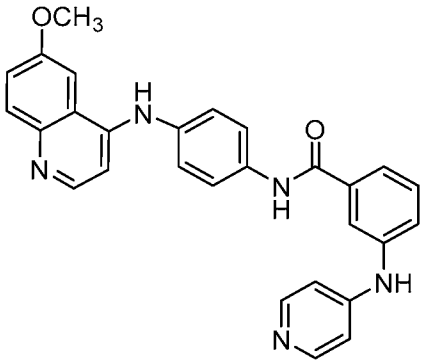
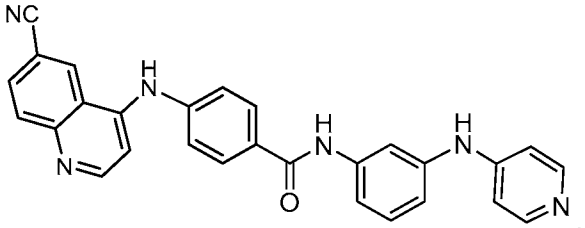
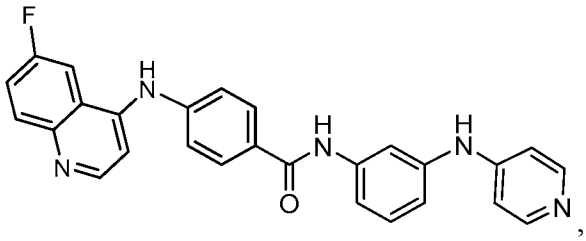
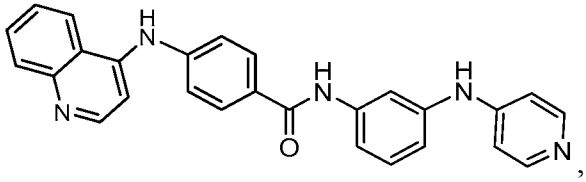
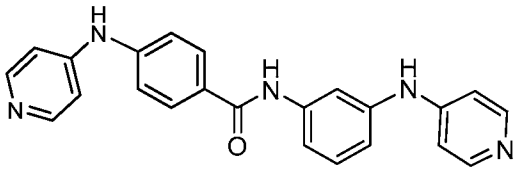
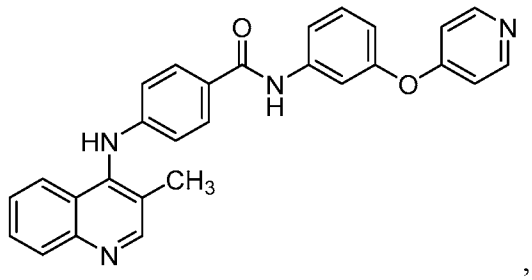
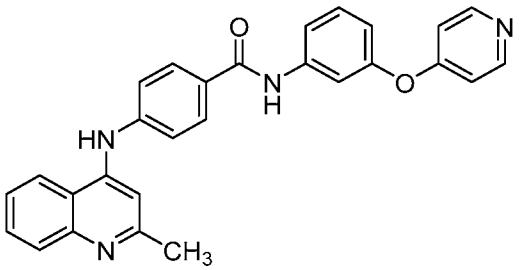
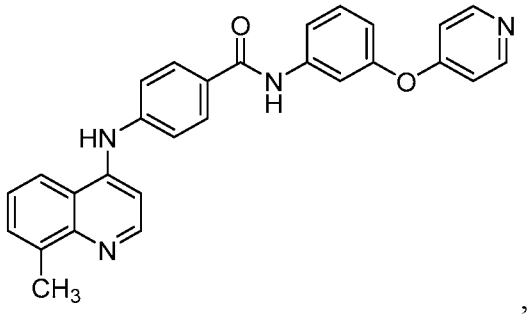
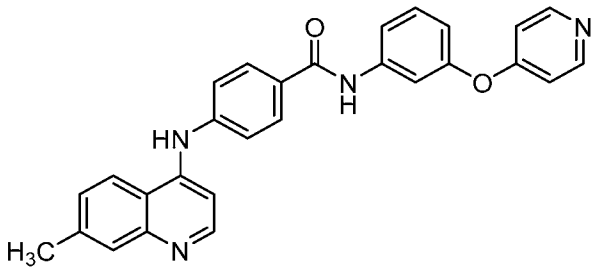
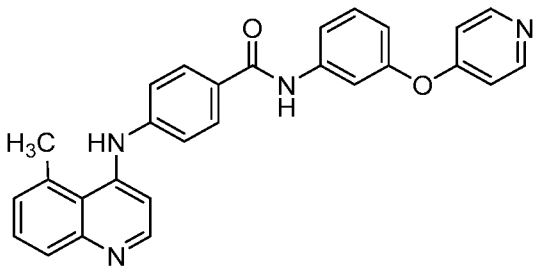
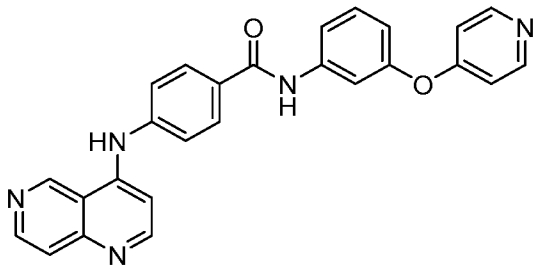
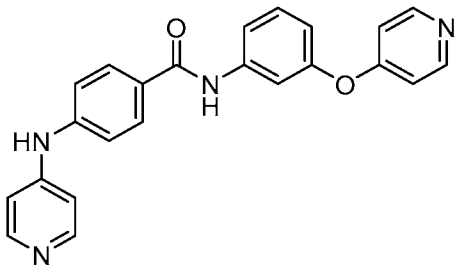
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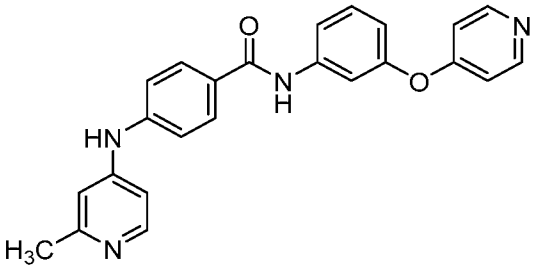
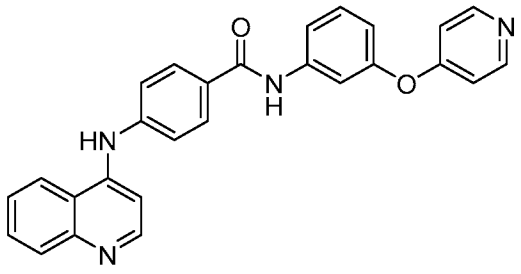
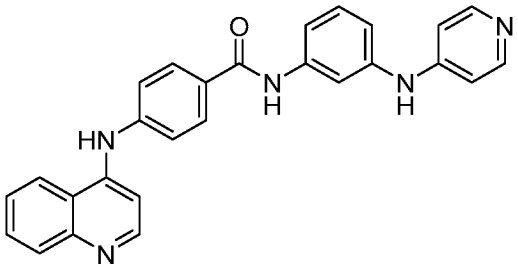
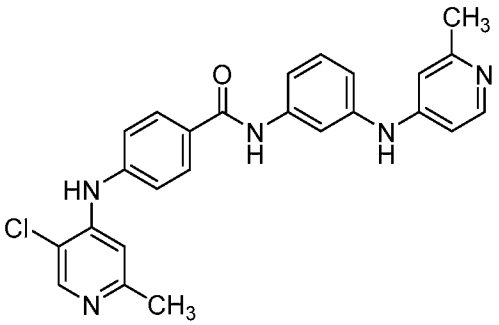
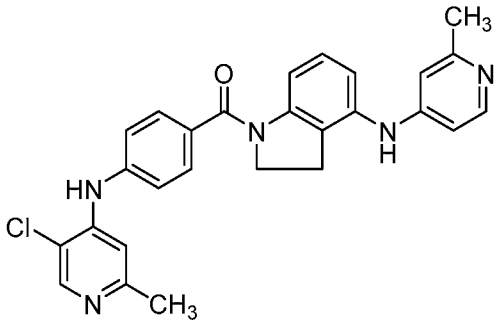
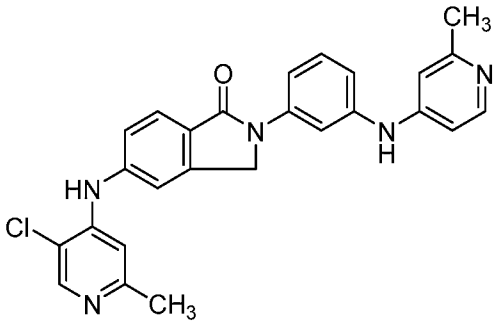
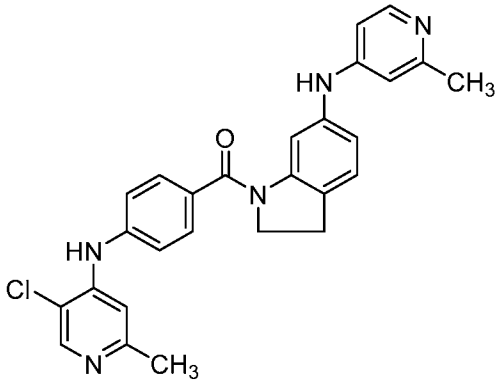
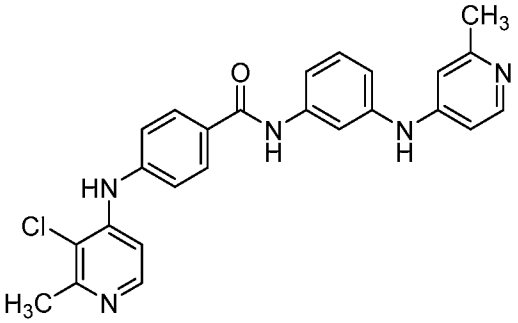
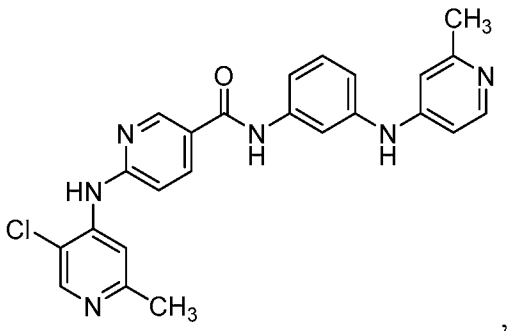
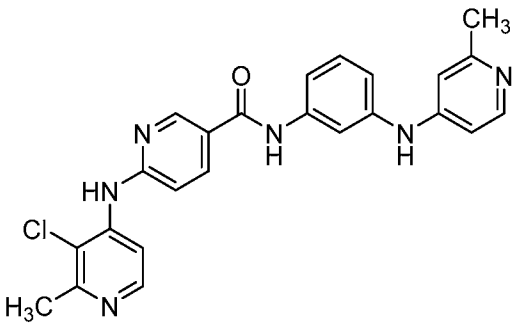
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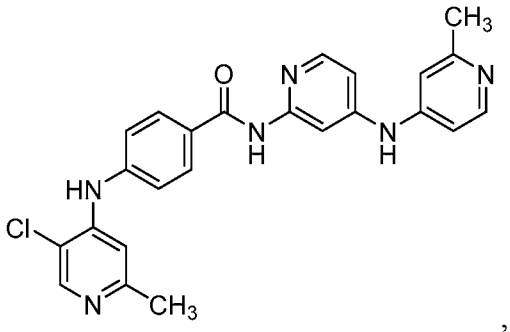
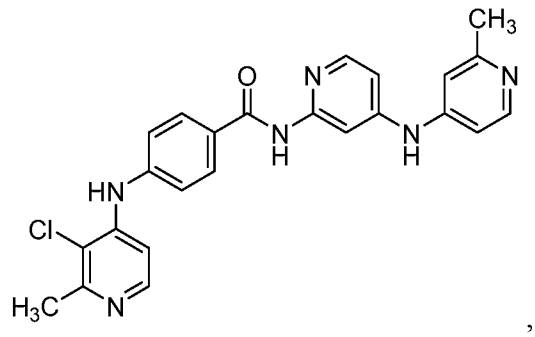
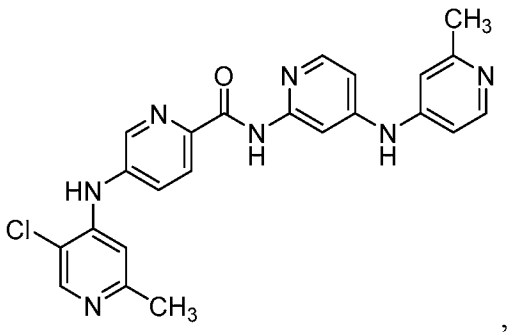
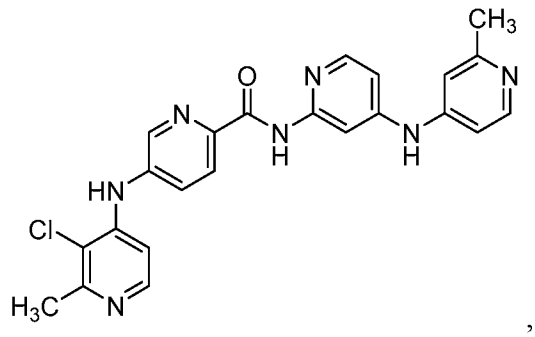
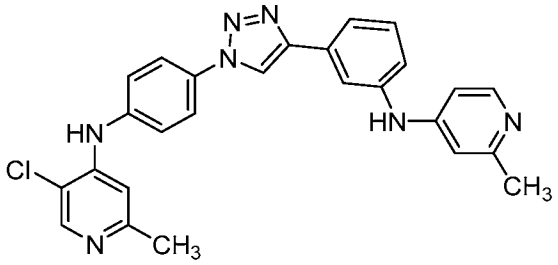
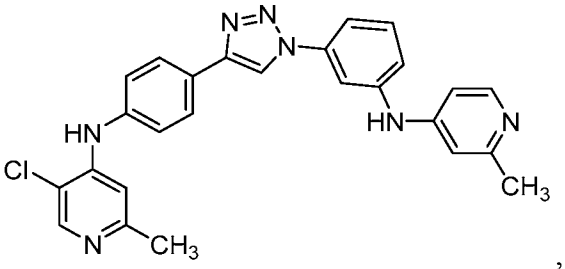
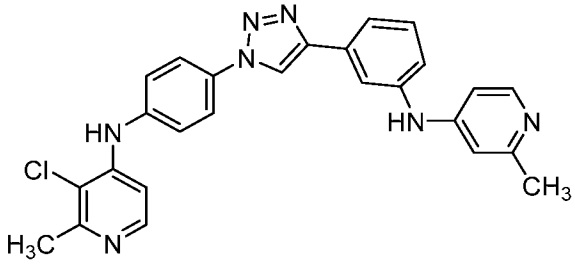
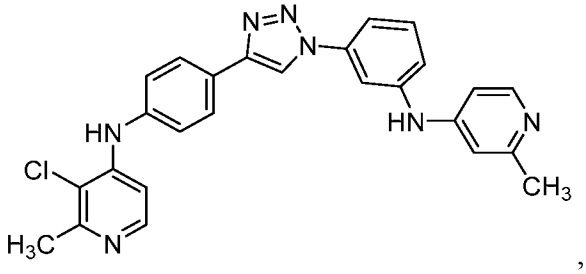
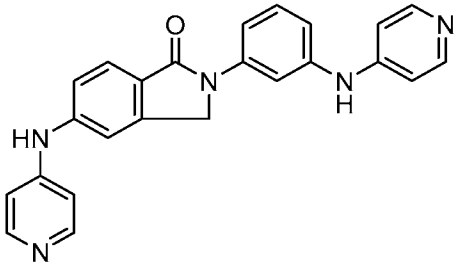
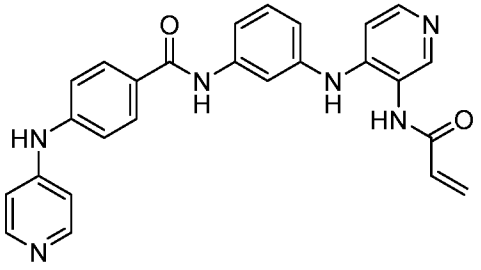

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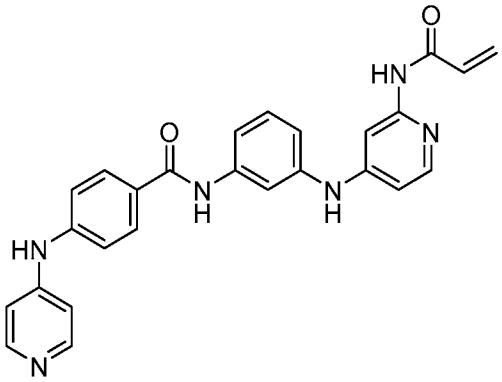
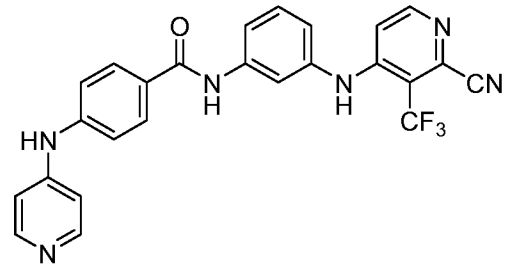
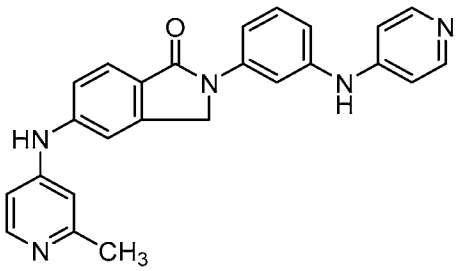
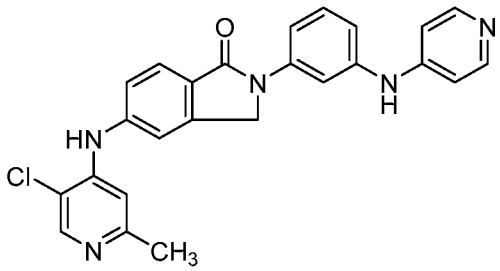
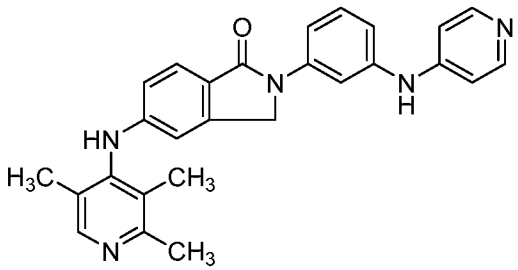
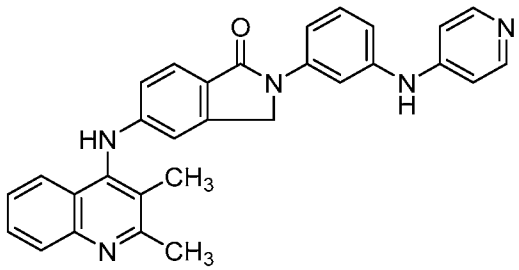
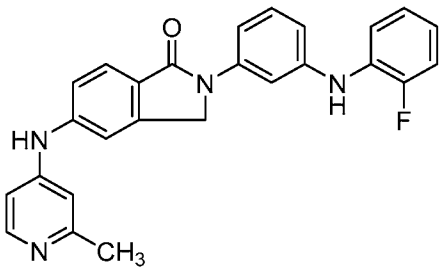
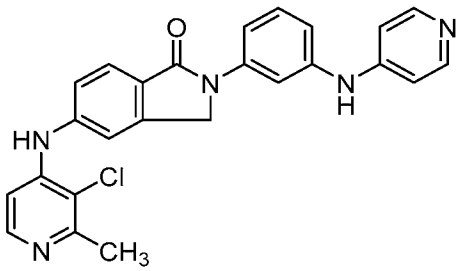
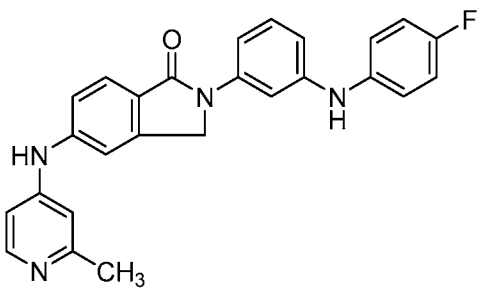
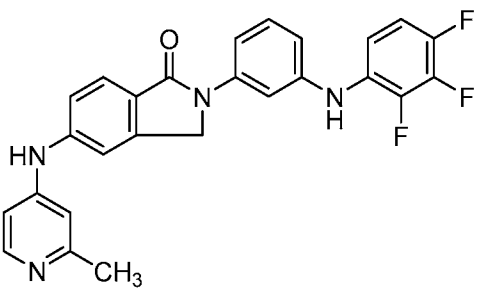

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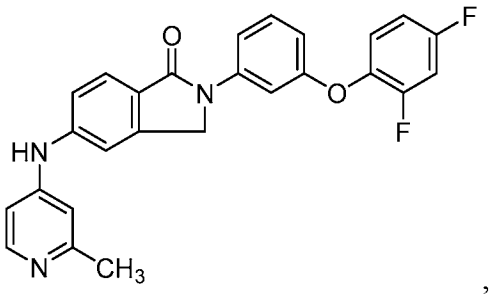
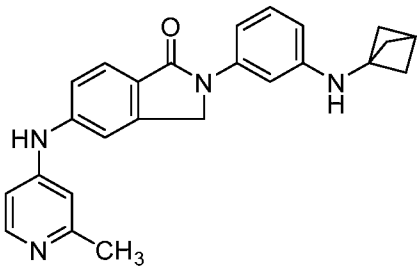
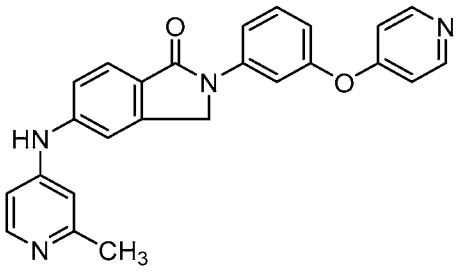
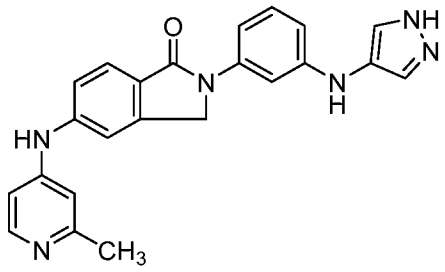
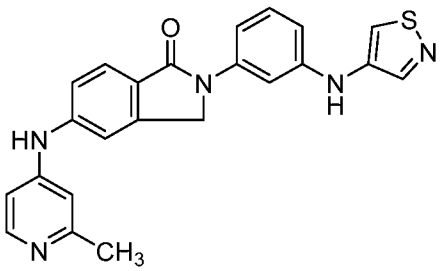
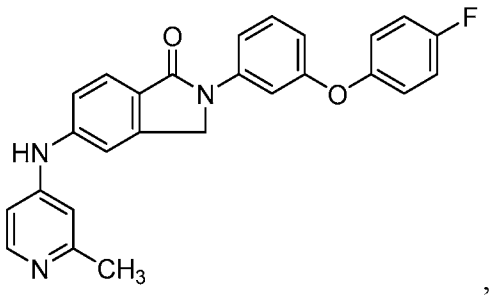
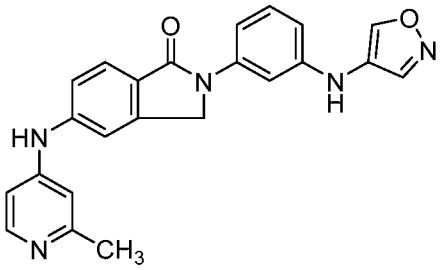
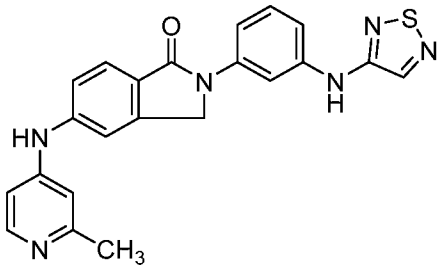
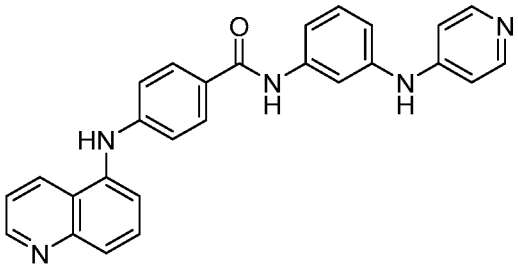
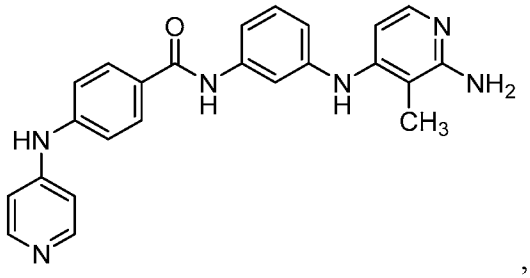
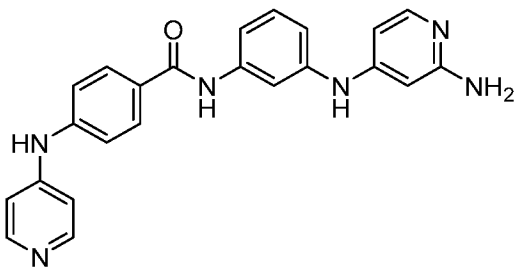
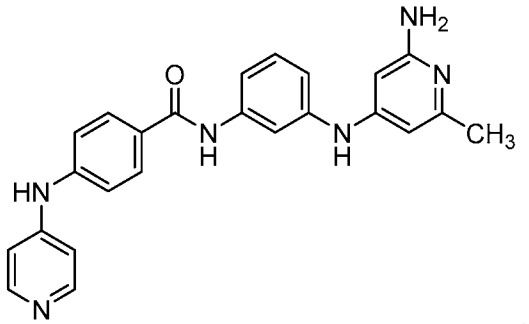

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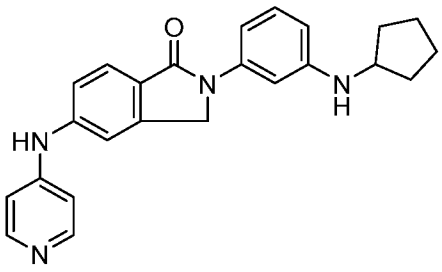
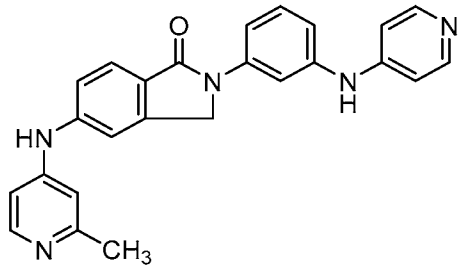
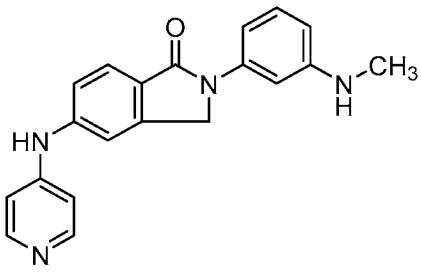
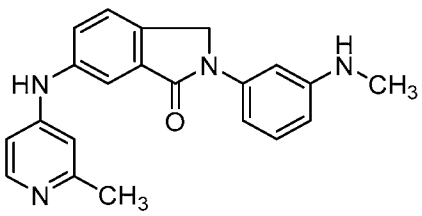
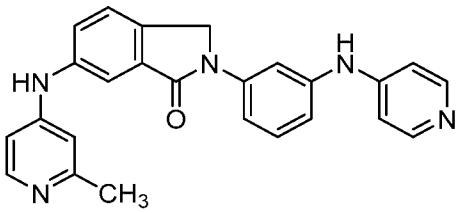
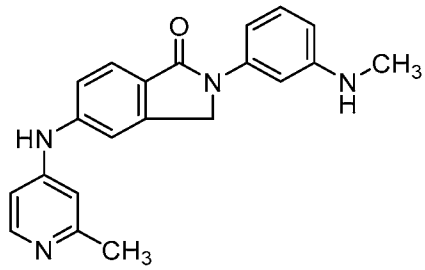
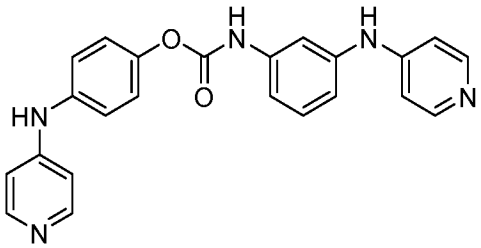
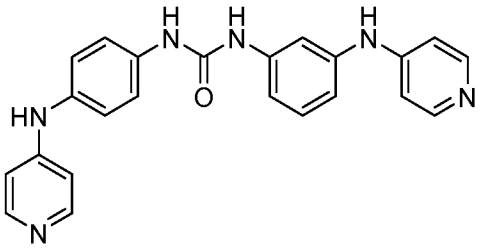
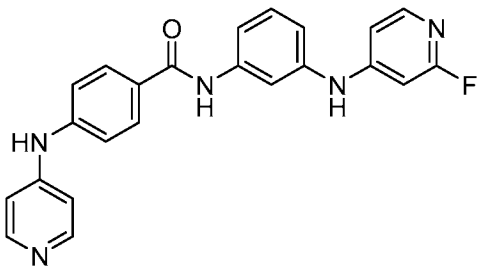
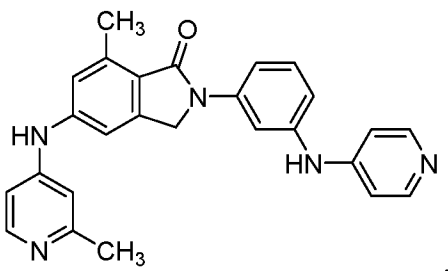
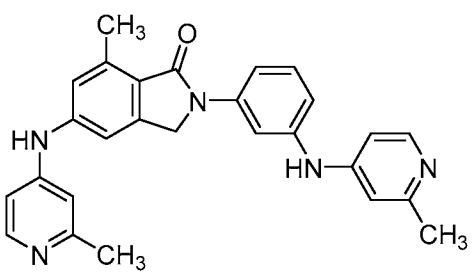
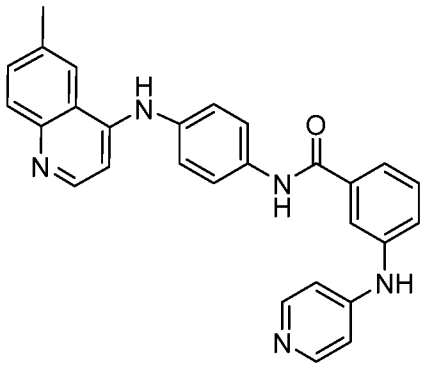

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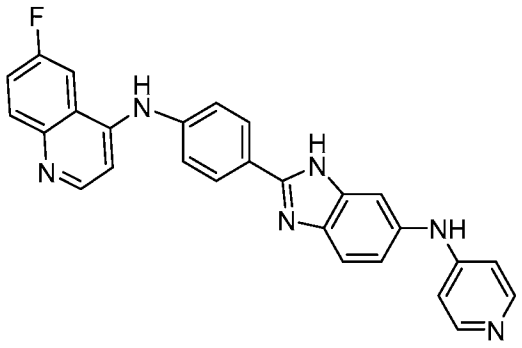
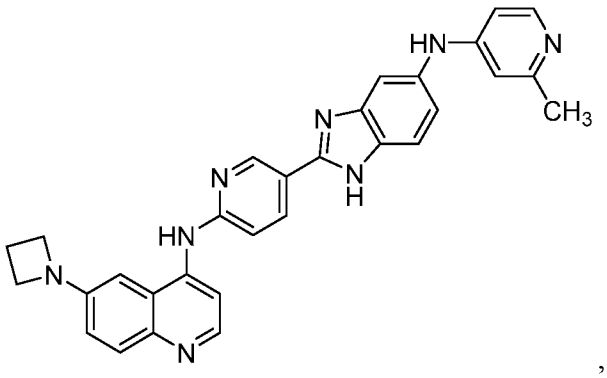
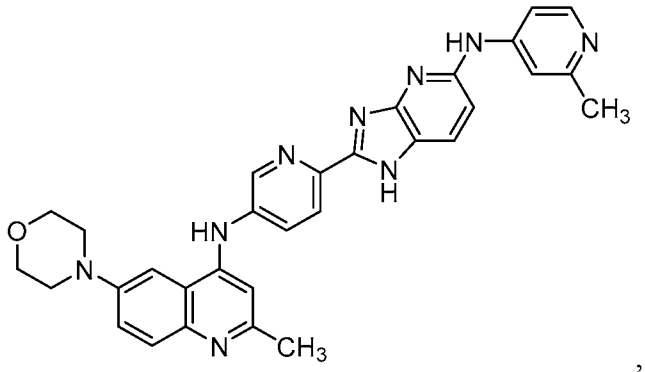
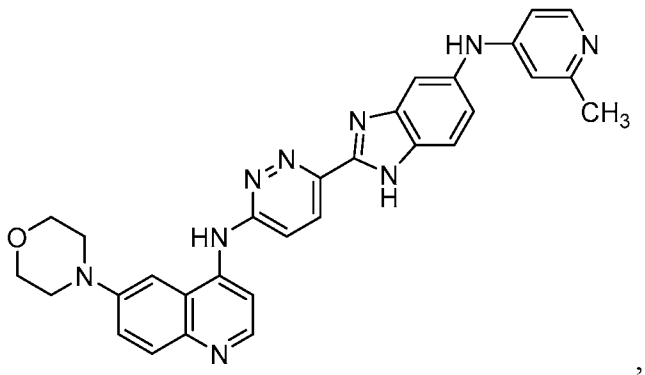
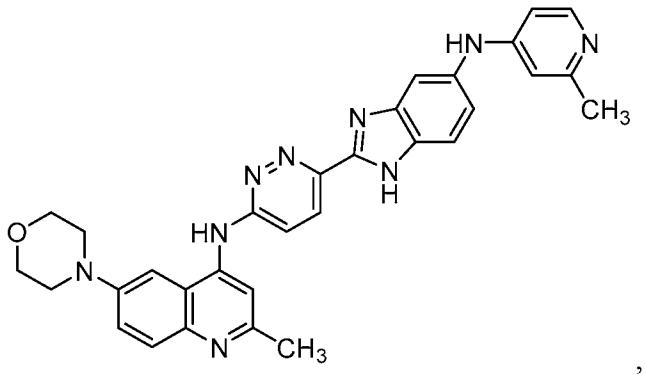

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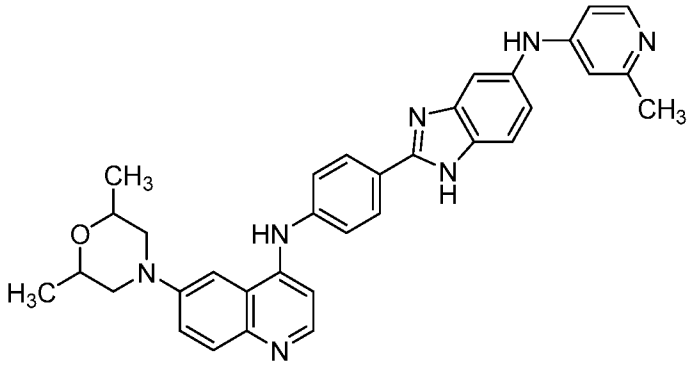

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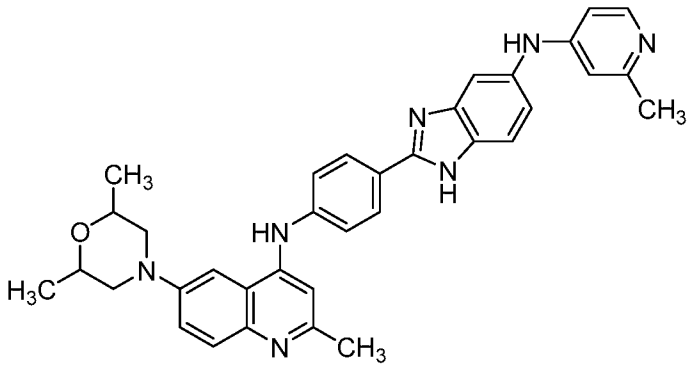

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[0373] In some embodiments, the compound of Formula IVb is

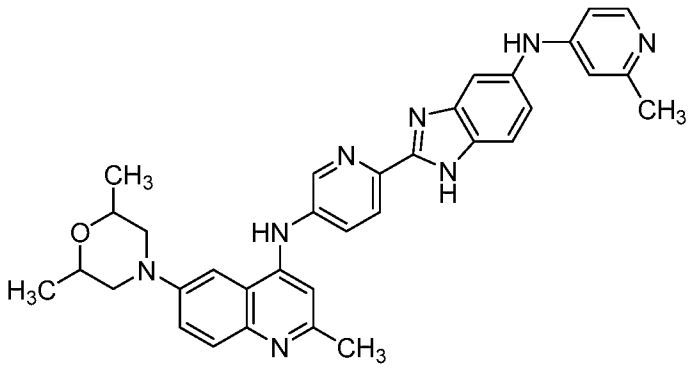

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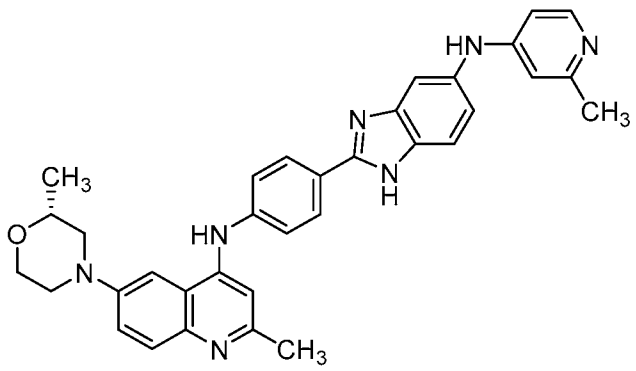
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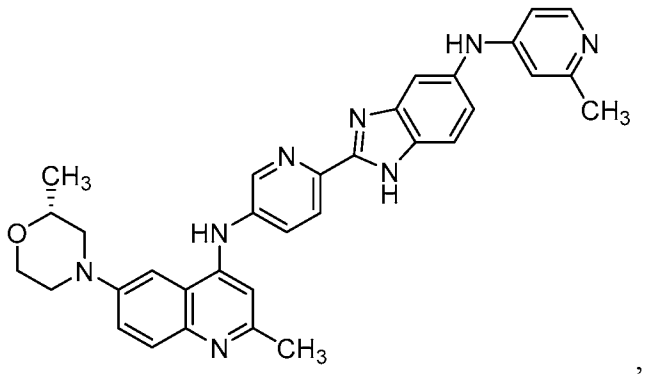
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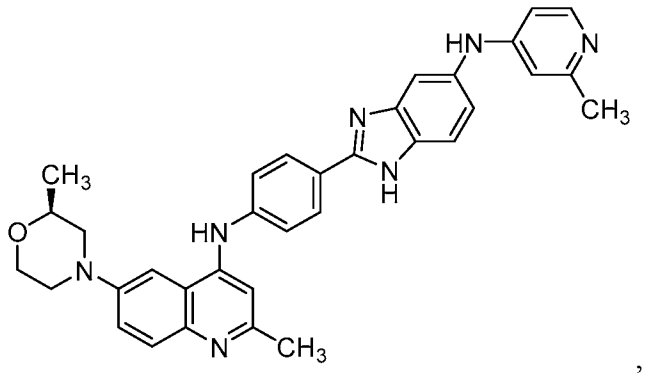


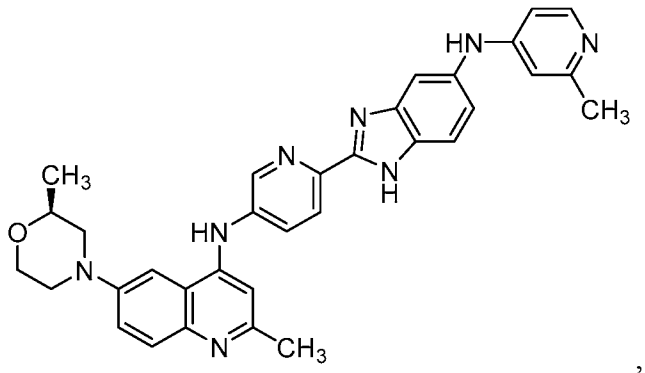
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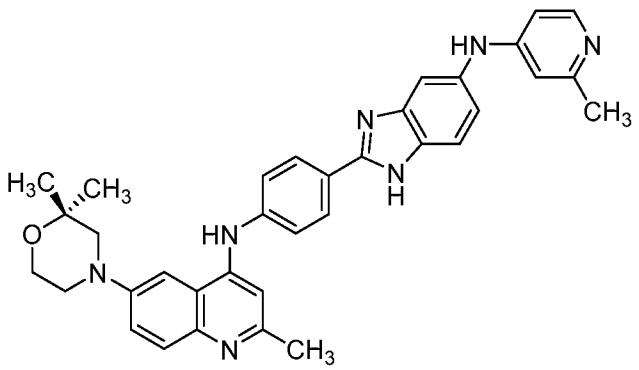


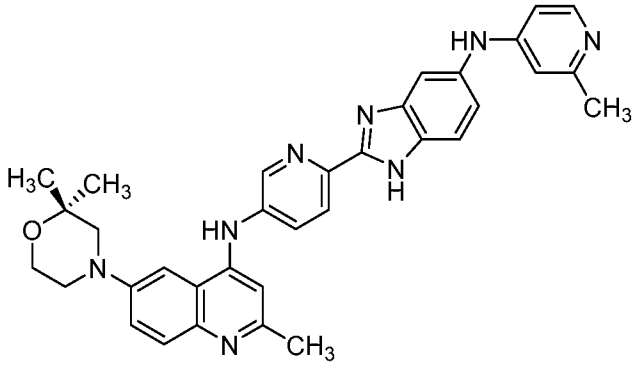
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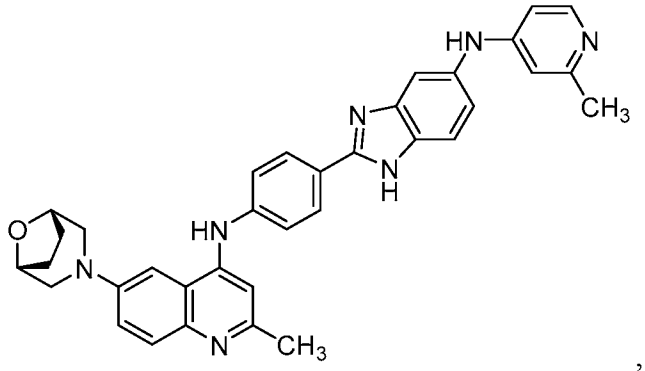

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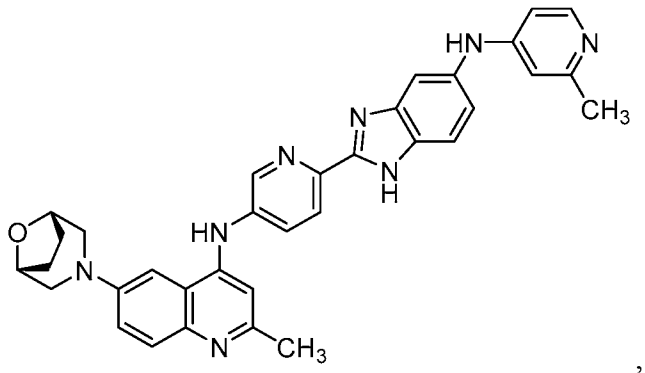

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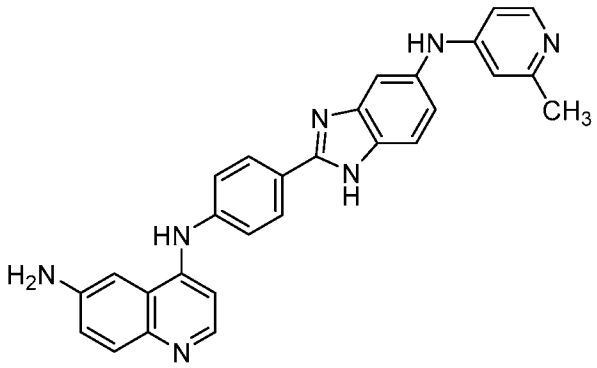

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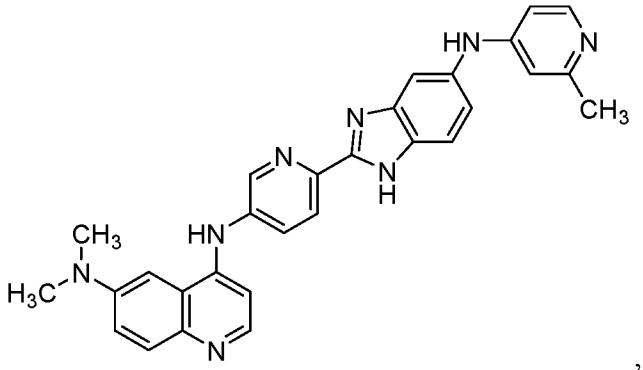

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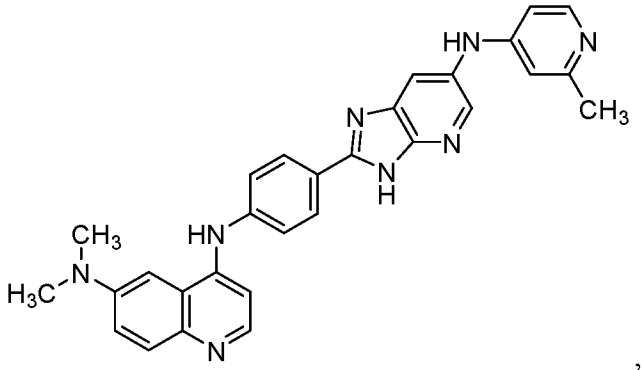

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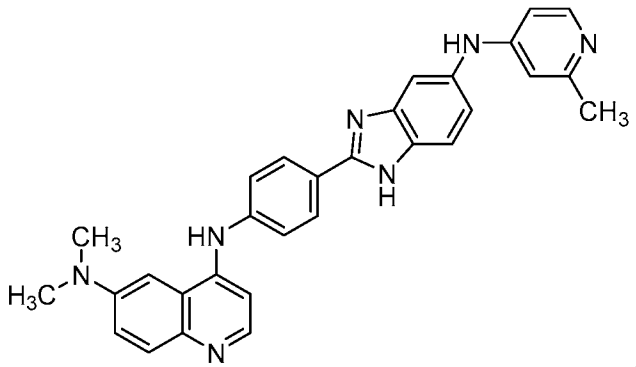

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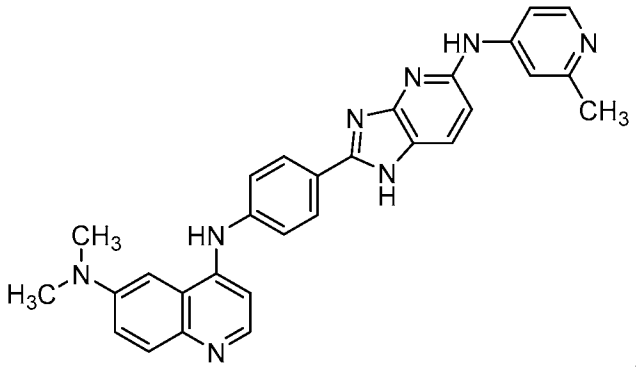
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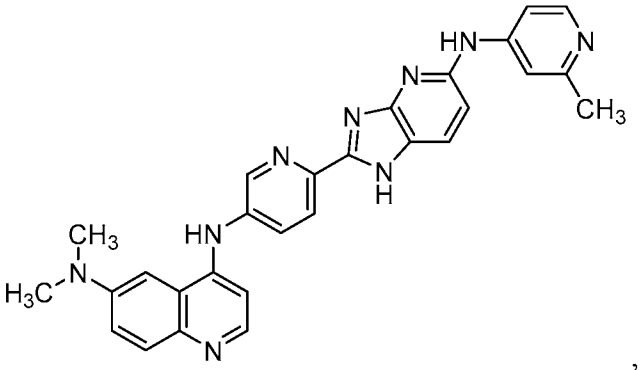
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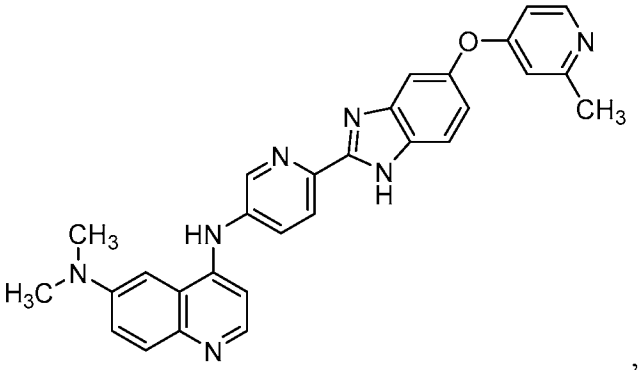
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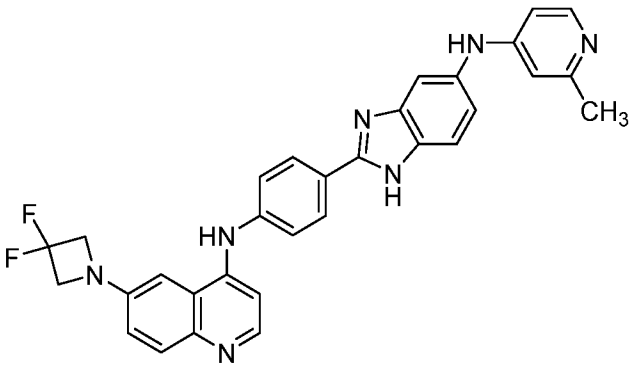
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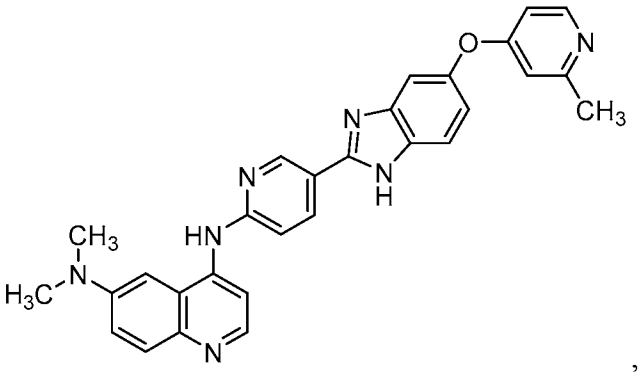
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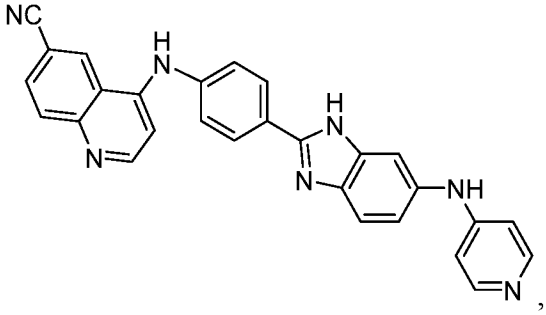
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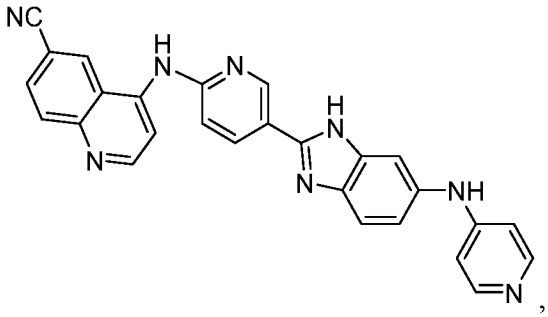
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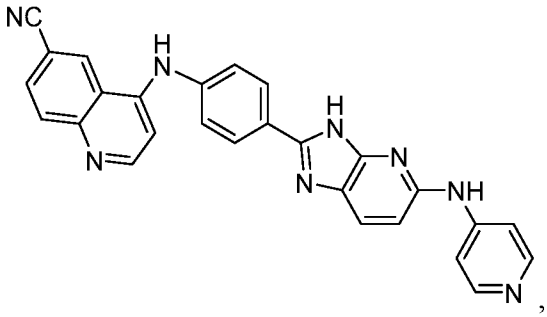


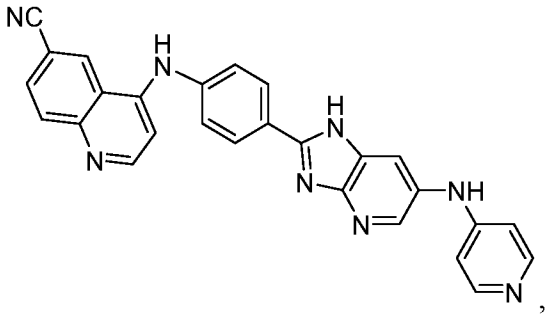
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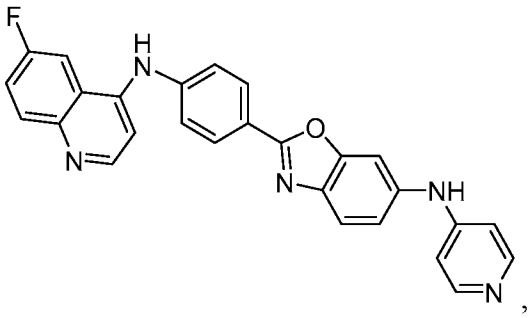


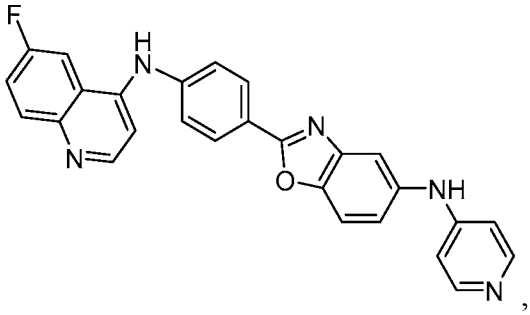
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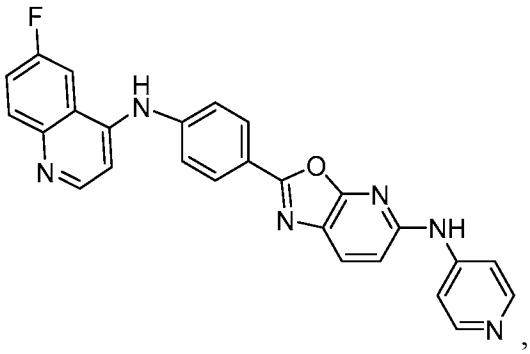


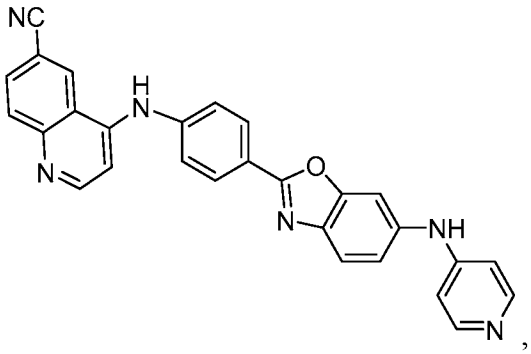


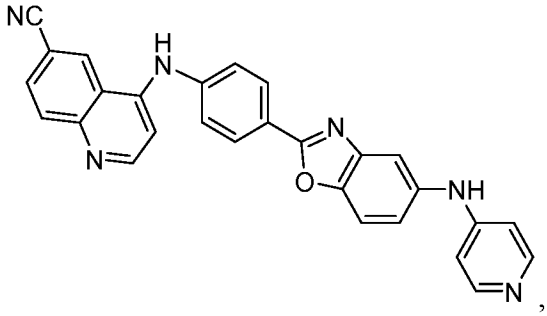


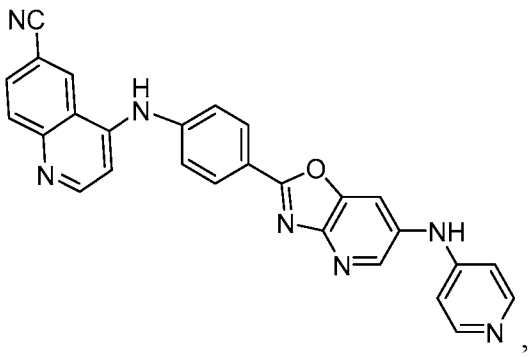


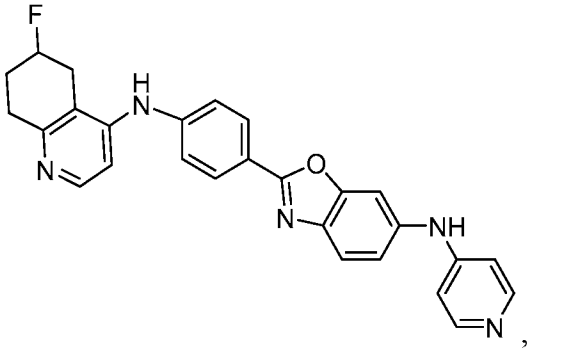


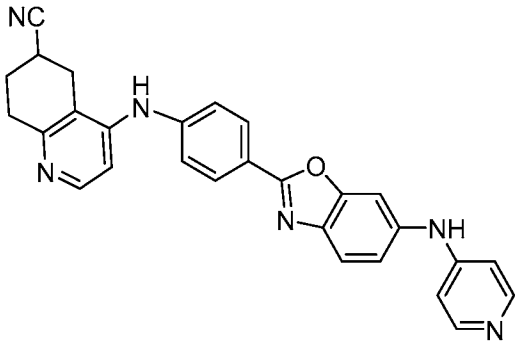




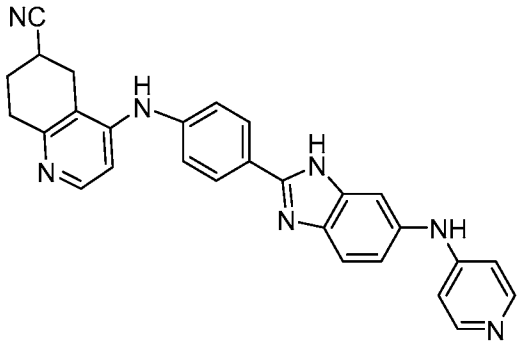




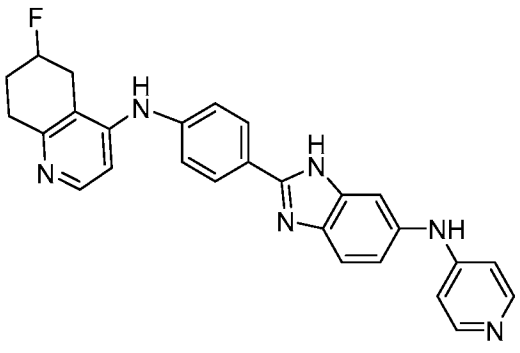




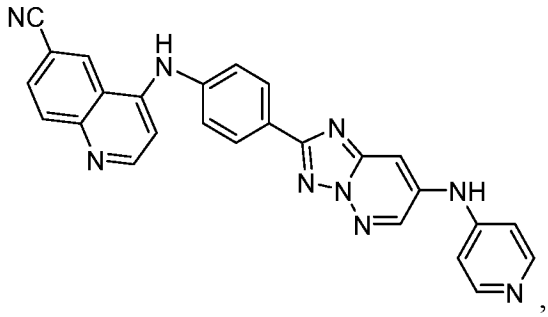
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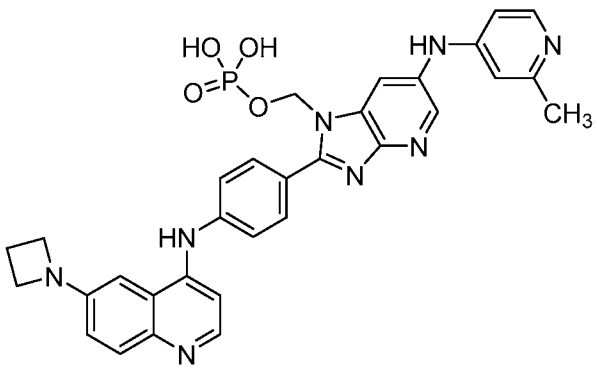
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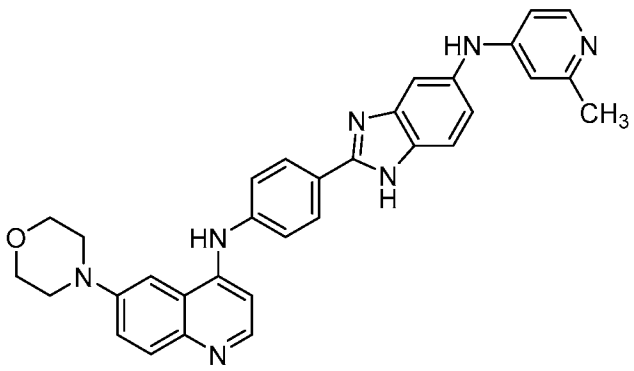
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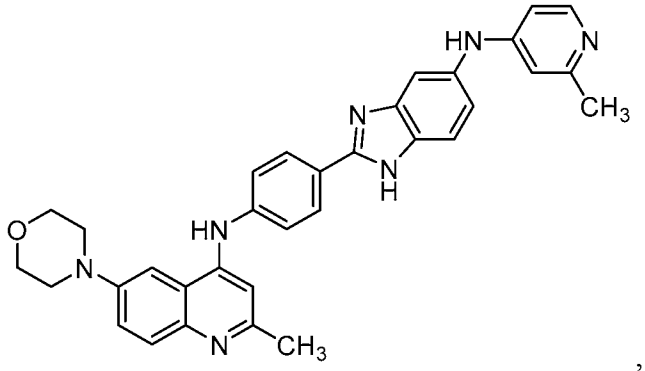
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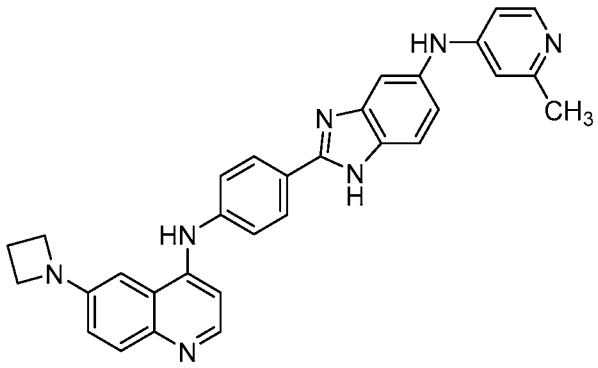
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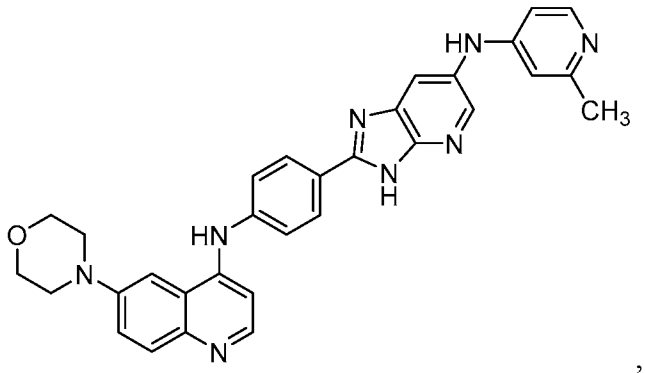
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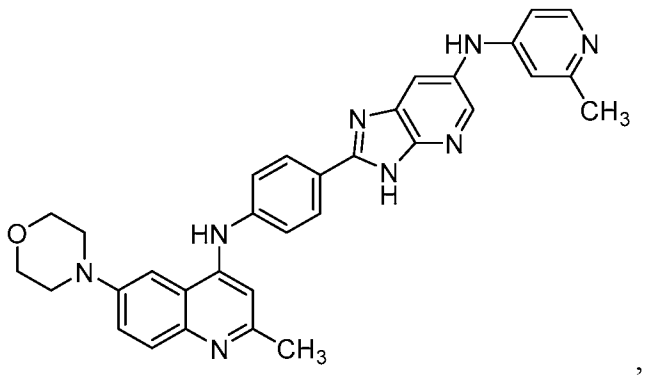
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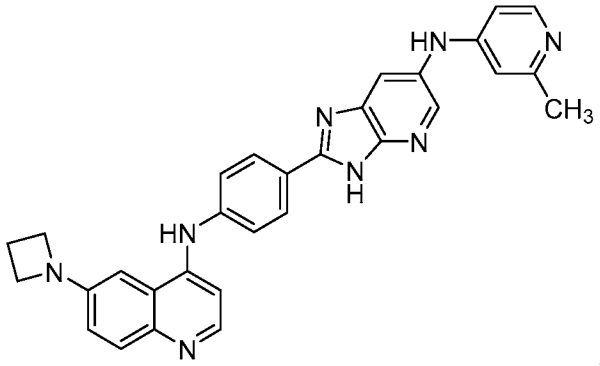
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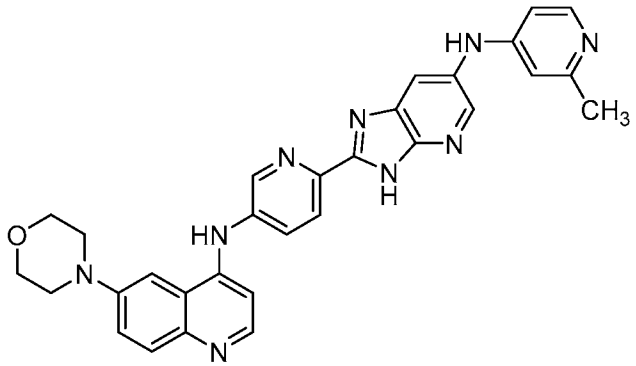
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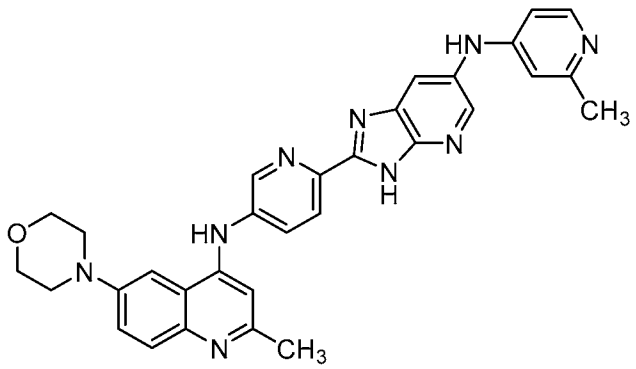
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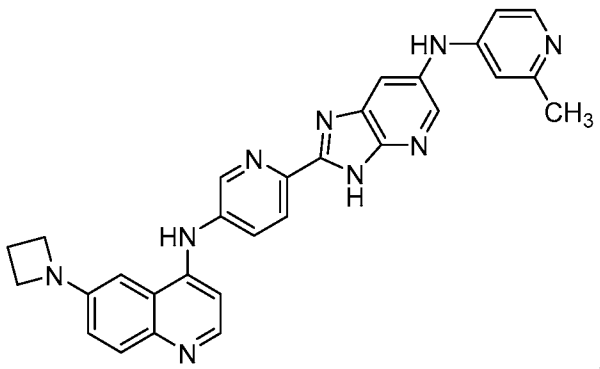
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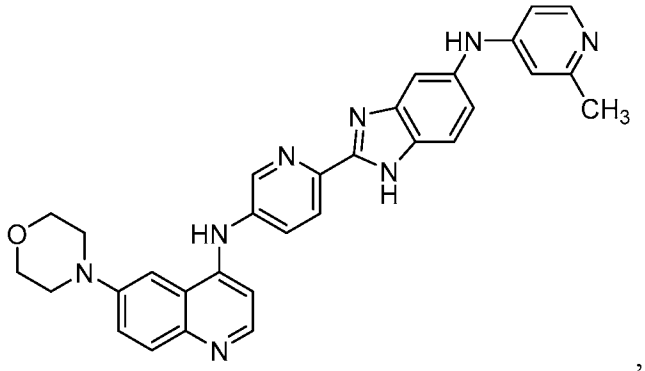
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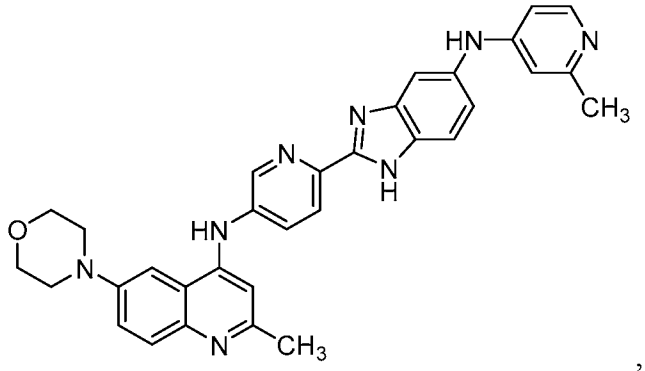
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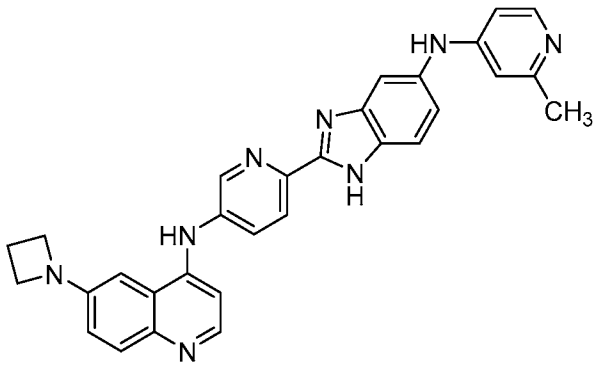
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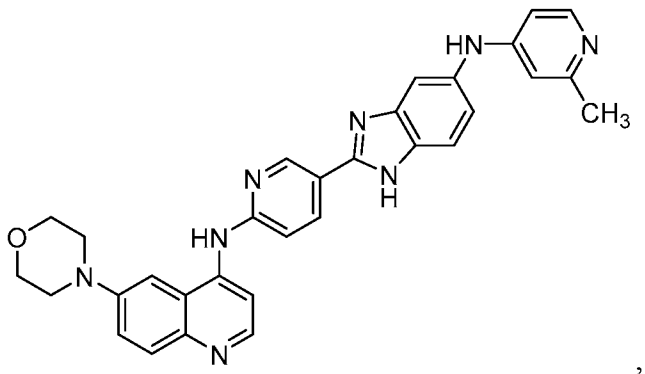
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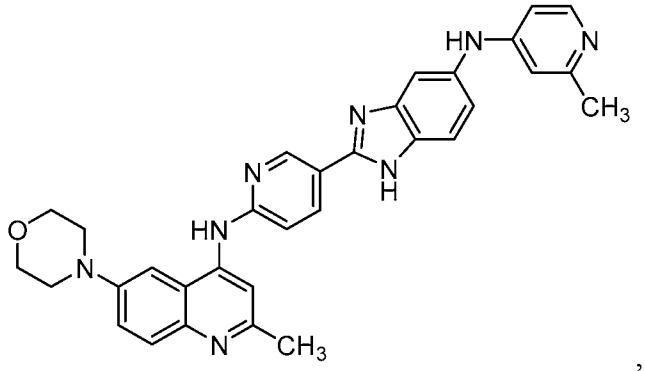
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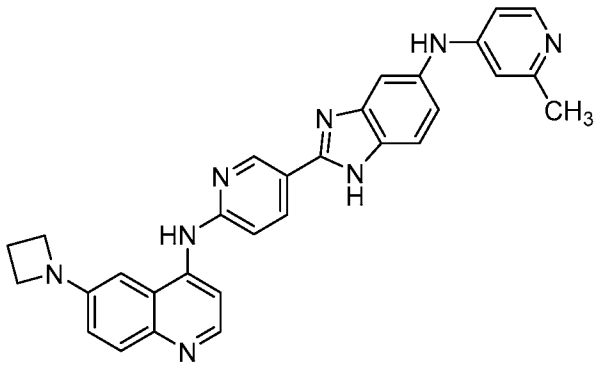
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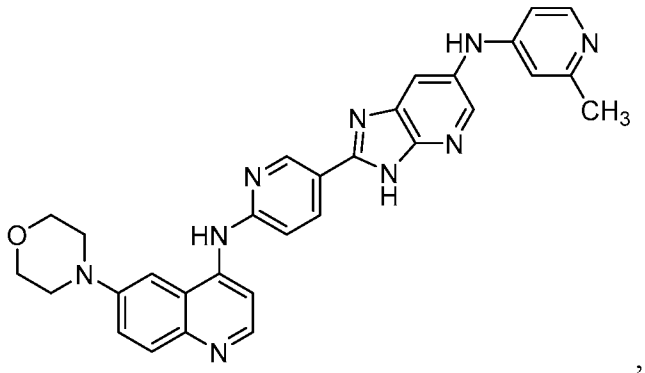
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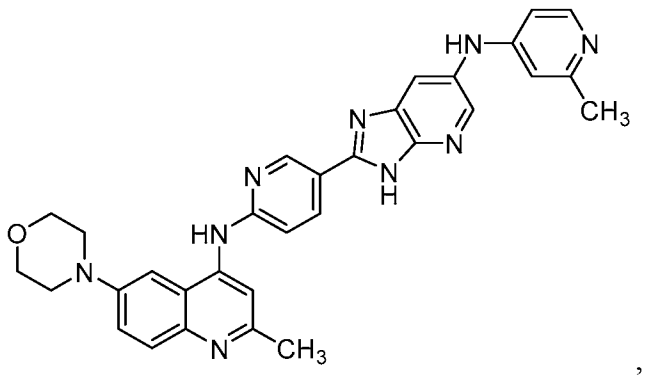
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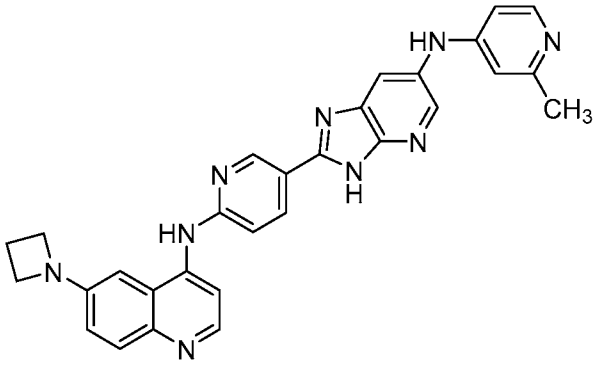
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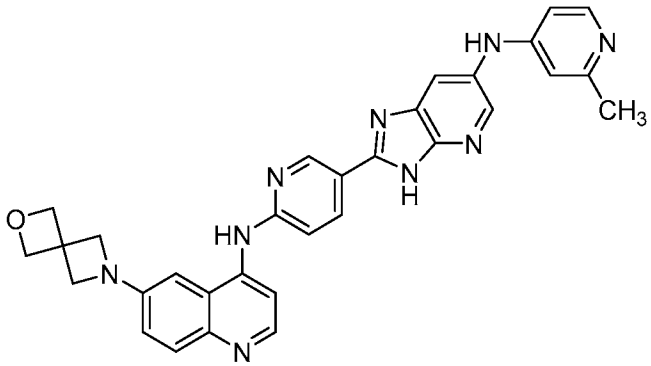
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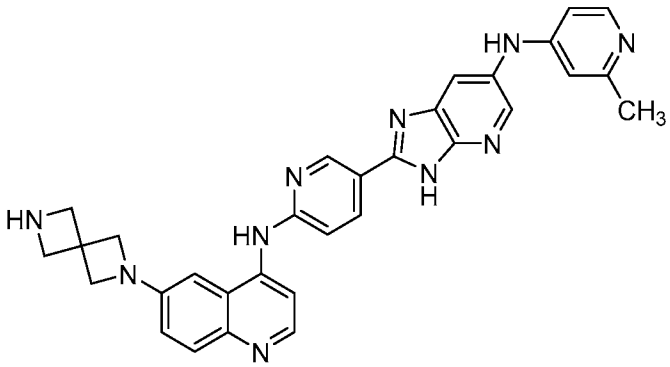
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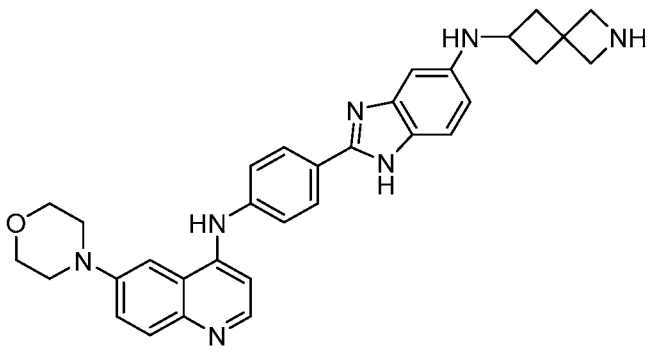
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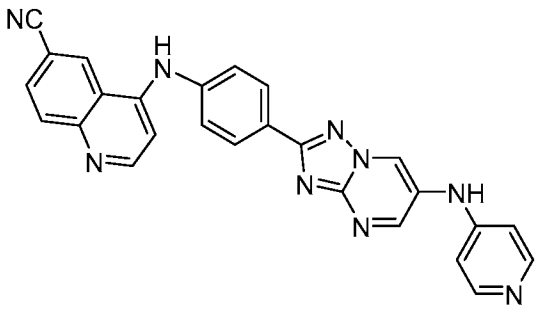
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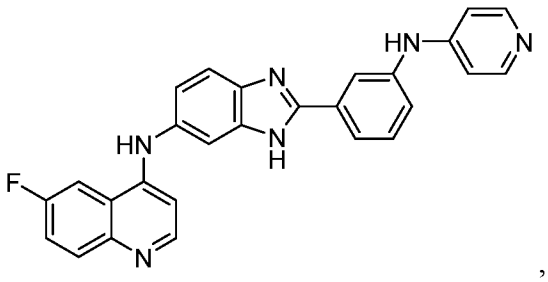
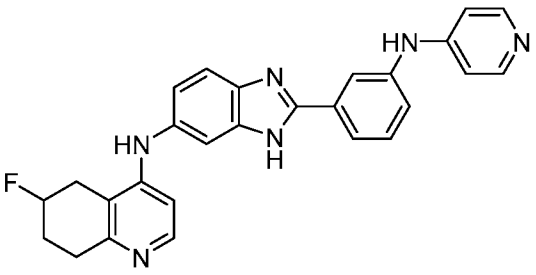
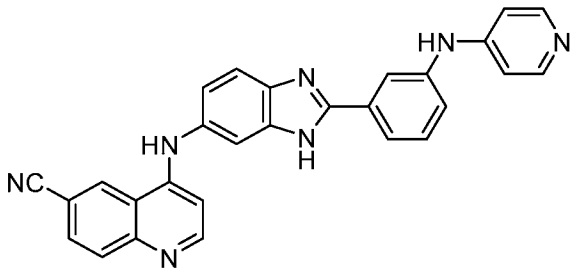
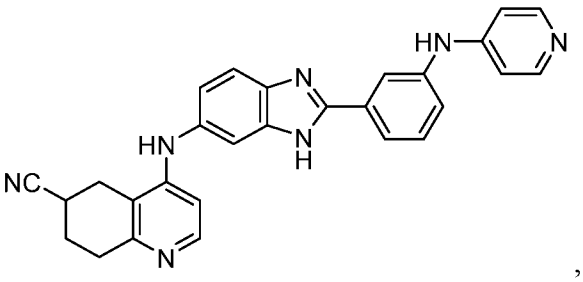
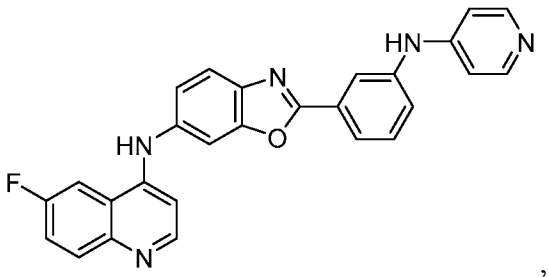
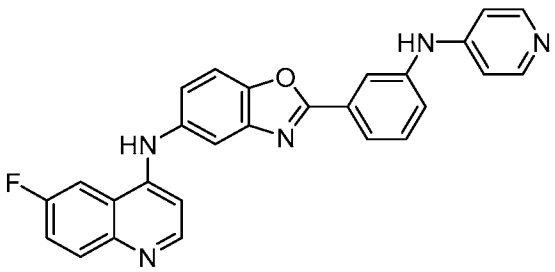
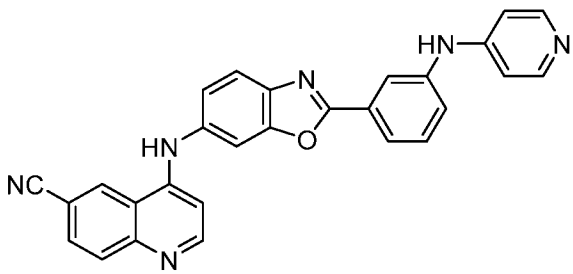
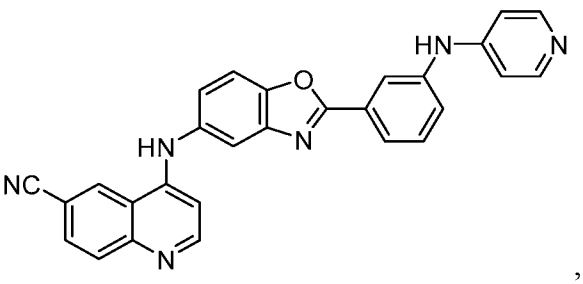
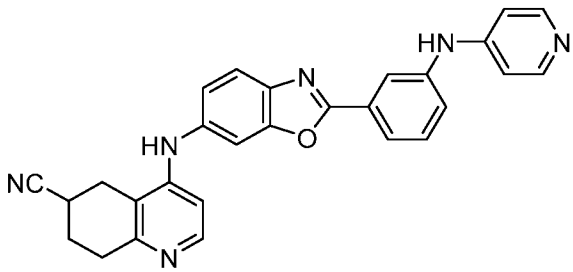
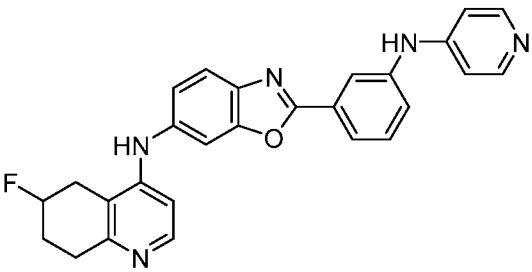
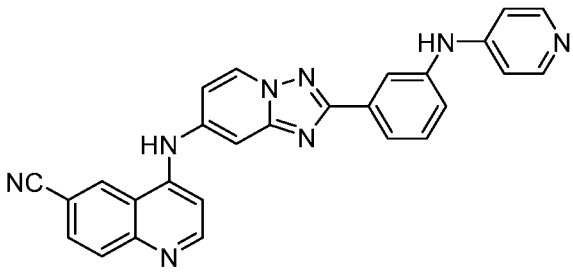
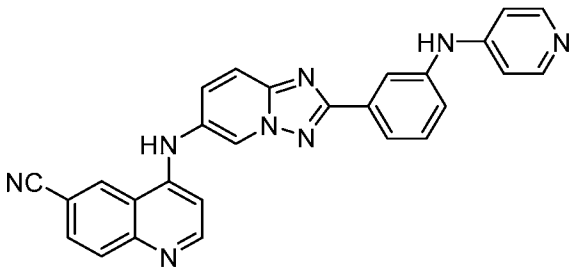


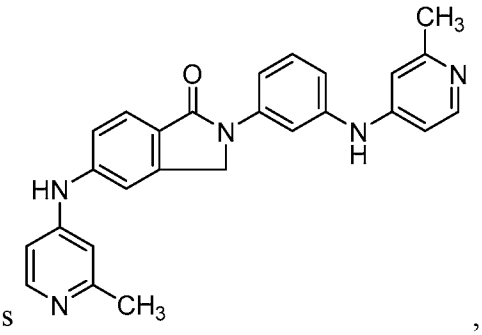
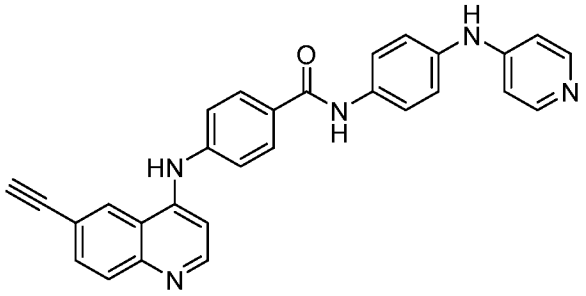
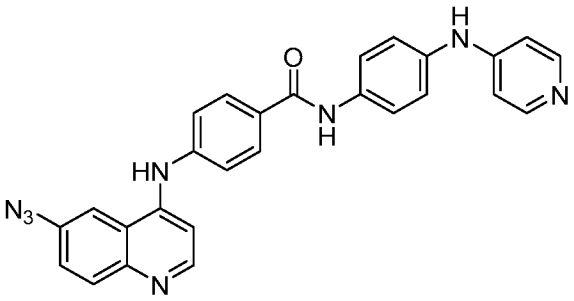
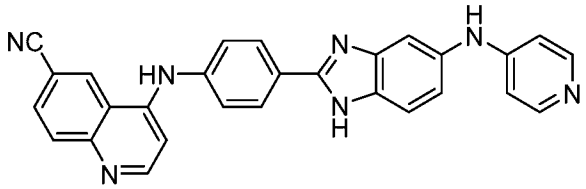
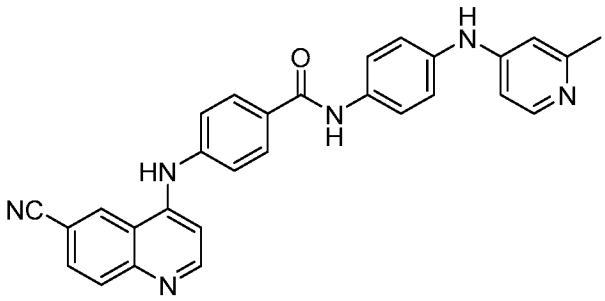
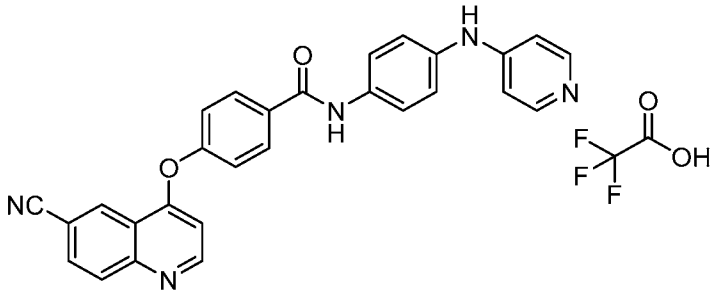
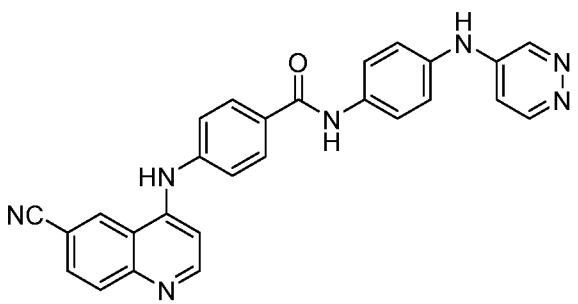
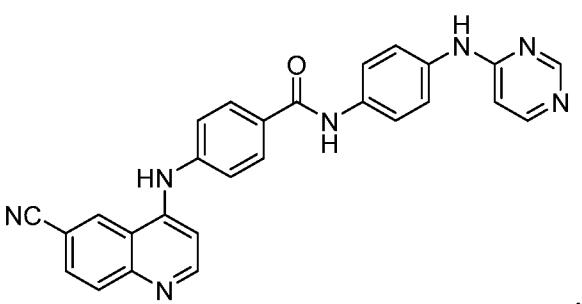
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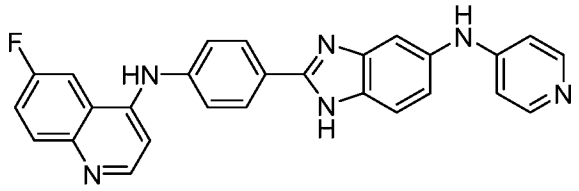


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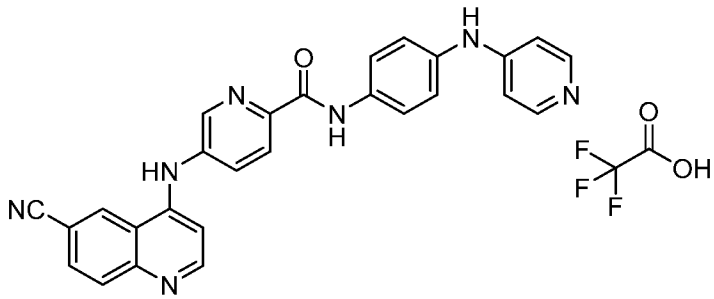
[0374] In some embodiments, the compound of Formula IVc is


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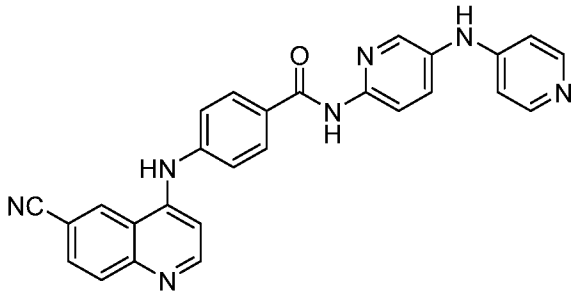
[0375] In some embodiments, the compound is , , , , , , , ,



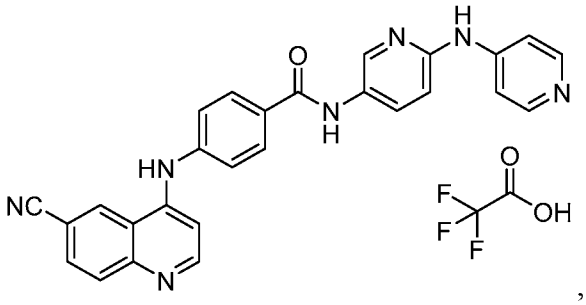
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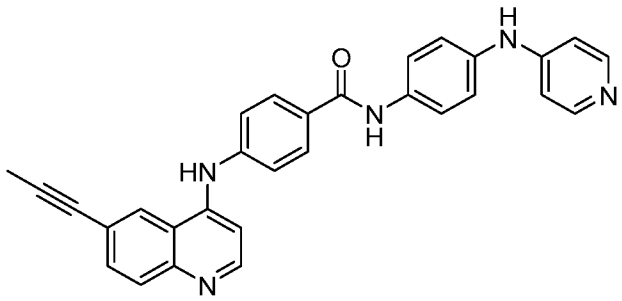
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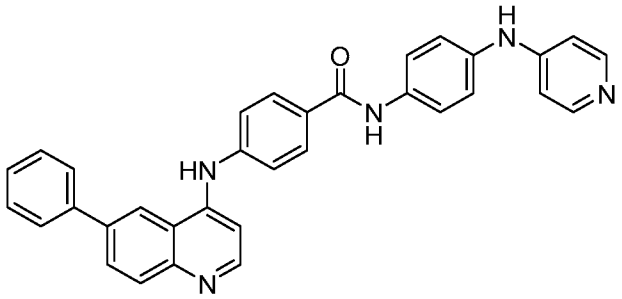
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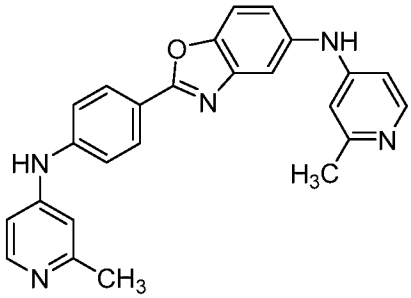
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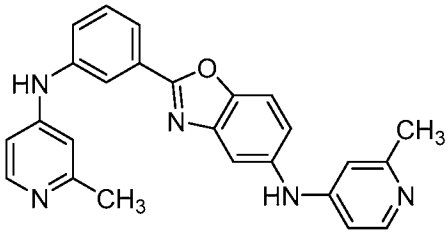
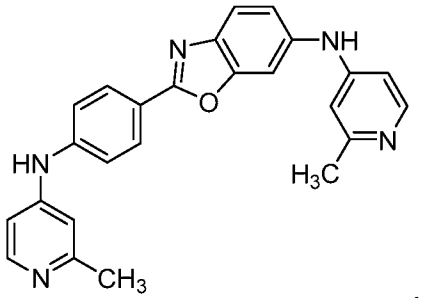


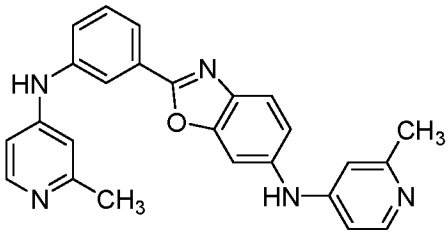
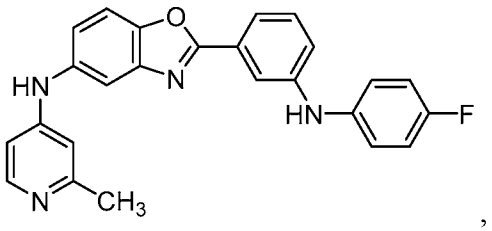
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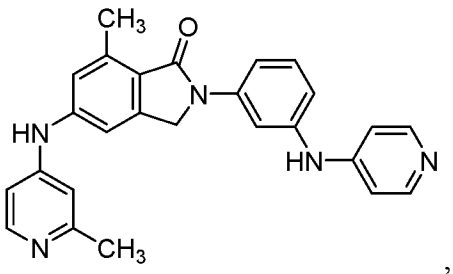
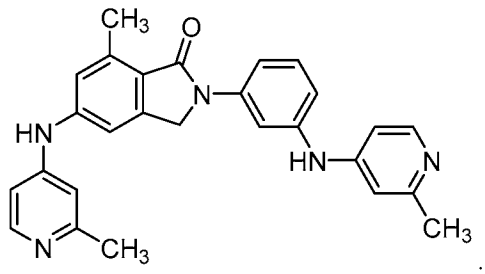


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[0376] In some embodiments, the compound is ,

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[0377] In some embodiments, the compound is selected from the group consisting of Compounds 2-9, 11-14, 30, and 32-145 in Examples 2-9, 11-14, 30, and 32-146, respectively.

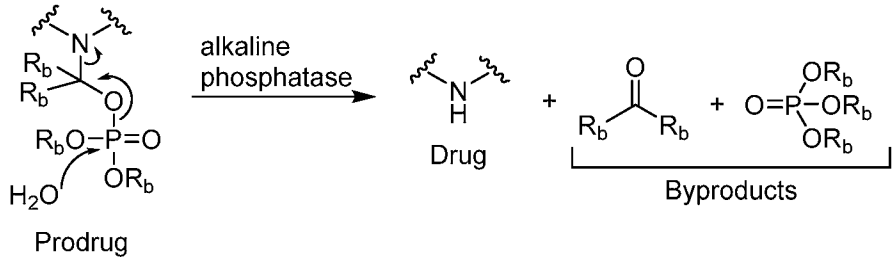
[0378] In some embodiments, the compound is selected from the group consisting of Compounds 5, 15, 18-19, 24, 42, 50-51, 53, 55-57, 62-63, 65, 67-70, 72, 77-79, 83-84, 87-89, 90-94, 96-97, 102-104, 110-111, 121, 123, 126-127, 129, 131-134, and 138-145 in Examples 5, 15, 18-19, 24, 42, 50-51, 53, 55-57, 62-63, 65, 67-70, 72, 77-79, 83-84, 87-89, 90-94, 96-97, 102-104, 110-111, 121, 123, 126-127, 129, 131-134, and 138-145, respectively. In some embodiments, the compound is selected from the group consisting of Compounds 24, 69-70, 87, 90, 97, 102, 121, 123, 126-127, 129, 131-134 and 138-145 in Examples 24, 69-70, 87, 90, 97, 102, 121, 123, 126-127, 129, 131-134 and 138-145, respectively.

[0379] In some embodiments, the Compound is selected from the group consisting of Compounds 2, 4-7, 10-11, 15, 18-19, 24, 53, 55, 57, 62, 68-70, 77-79, 83-84, 87-88, 90-92, 96-97, 102, 110-111, 120-123, 125-129, 135, and 138 as shown in Table 2.

[0380] In some embodiments, the Compound is Compound 3, 137, or 139-145 as shown in Table 1.

Prodrugs

[0381] 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

[0382] 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").

[0383] 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).

[0384] 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).

[0385] 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

[0386] 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).

[0387] 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.

[0388] In some embodiments, a compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc as described herein is an inhibitor of Akt3. In other embodiments, a compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc as described herein is an activator of Akt3.

Pharmaceutical Compositions

[0389] 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.

[0390] 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.

[0391] 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.

[0392] 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.

[0393] 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.

[0394] 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.

[0395] 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.

[0396] 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).

[0397] 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.

[0398] 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.

[0399] 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.

[0400] 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.

[0401] 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

[0402] 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc as described herein.

[0403] 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.

[0404] In some embodiments, the compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc activates Akt3 signaling. In other embodiments, the compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc inhibits Akt3 signaling. In some embodiments, the compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc modulates Akt3 in Tregs. The inventors surprisingly found that, in some embodiments, the compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc activates Akt3 signaling while, in other embodiments, the compound inhibits Akt3 signaling.

Neurodegenerative Disease

[0405] 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

[0406] 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.

[0407] 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.

[0408] 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

[0409] 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

[0410] In one embodiment, the compounds of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

[0411] In some embodiments, administration of Akt3 activators of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc as described herein to a subject having ALS slows disease progression and prolongs the subject's survival.

[0412] 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.

[0413] 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.

[0414] 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.

[0415] In some embodiments, the disclosed Akt3 activators of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

[0416] 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.

[0417] 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.

[0418] 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.

[0419] 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.

[0420] 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.

[0421] 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

[0422] 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.

[0423] One embodiment provides a method of treating SMA in a subject by administering an Akt3 modulator of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

[0424] 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.

[0425] One embodiment provides a method of treating MS in a subject by administering an Akt3 modulator of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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

[0426] 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

[0427] 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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.

[0428] 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc disclosed herein can be used to treat anorexia. In one embodiment, the disclosed Akt3 inhibitors of a compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc 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

[0429] 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.

[0430] 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

[0431] 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.

[0432] Non-limiting examples of inflammatory disease include atopic dermatitis, allergy, asthma, and a combination thereof.

Viral-Induced Inflammatory Reaction

[0433] 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

[0434] 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, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc as described herein. In some embodiments, the compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc inhibits Akt3 signaling and/or decreases Treg activity or production, resulting in an immune response-activating effect.

[0435] 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.

[0436] 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).

[0437] 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).

[0438] 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.

[0439] 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

[0440] 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

[0441] 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

[0442] 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.

[0443] 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.

[0444] 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.

[0445] 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.

[0446] 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

[0447] 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

[0448] 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.

[0449] 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

[0450] 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.

[0451] 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.

[0452] 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.

[0453] 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.

[0454] 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.

[0455] 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.

[0456] 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.

[0457] 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.

[0458] 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.

[0459] 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.

[0460] 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.

[0461] 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

[0462] 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.

[0463] 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.

[0464] 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.

[0465] 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

[0466] 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.

[0467] 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.

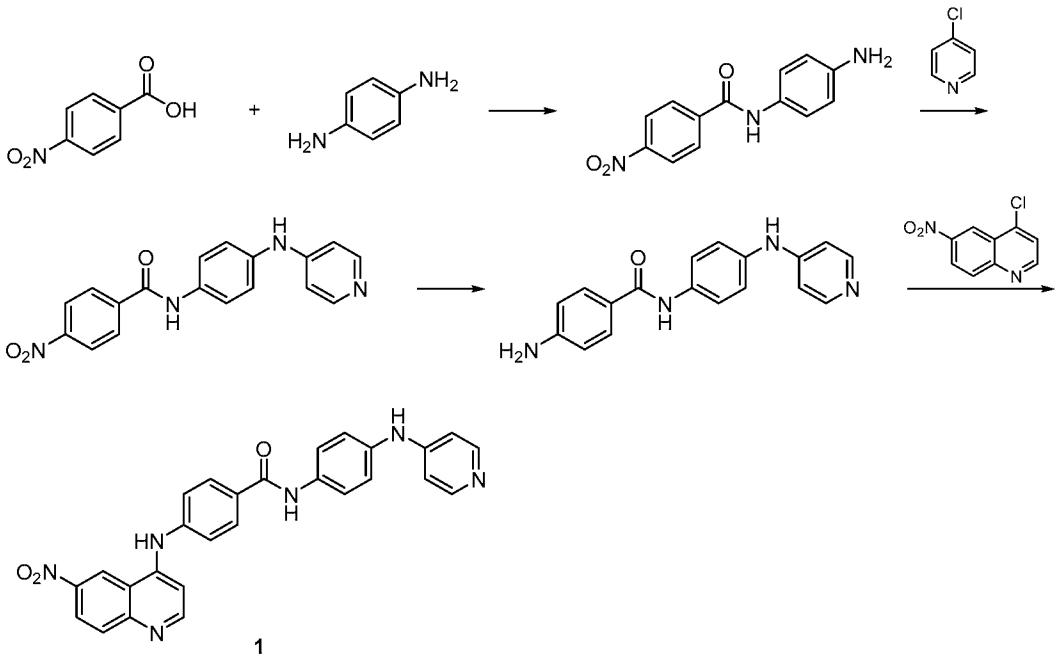
Equivalents

[0468] 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 (4-((6-nitroquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



Scheme 1

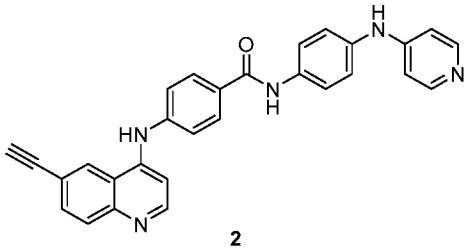
[0469] As shown in Scheme 1, *para*-nitrobenzoic acid was coupled with 1,4-phenylenediamine using EDCI in the presence of HOBt and DIPEA. The resulting intermediate was coupled with 4-chloro-pyridine followed by reduction of the nitro group into an amino group using Sn/HCl. The resulting amino-intermediate 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 *para*-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.

[0470] 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.

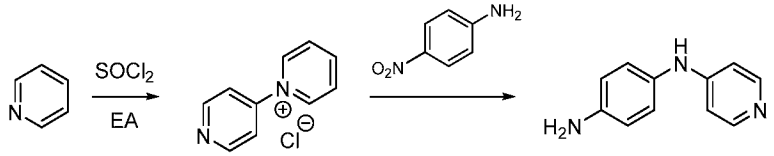
[0471] The following abbreviations as used in the following examples have the following definitions: AIBN = azobisisobutyronitrile; BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; DCE = dichloroethane; DCM = dichloromethane; DIEPA or DIPEA = N,N-diisopropylethylamine; DMAP = 4-dimethylaminopyridine; 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; LCMS = liquid chromatography mass spectrometry; MS = mass spectrometry; NBS = N-bromosuccinimide; NMR = nuclear magnetic resonance; PE = petroleum ether; RT = retention time (*e.g.*, HPLC retention time); TEA = triethylamine; TFA = trifluoroacetic acid; THF = tetrahydrofuran; TLC = thin layer chromatography; 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.

[0472] In one or more of the following examples, the following general methods were used. Substrates and reagents were commercially available and used without further purification. The reaction was monitored by LCMS or TLC using pre-coated glass plates. Column chromatography was performed using silica gel (200-300 mesh) or a Biotage machine (normal HPLC). The prep-HPLC method used a Gilson 281 (PHG012) instrument, a Welch 10 μm 150A 21.2*250 mm column, a mobile phase consisting of A: water (12 mM NH_4HCO_3), B: acetonitrile, a flow rate of 30.00 mL/minute, and detection at 214/254 nm. ^1H NMR spectra were recorded in $CDCl_3$/MeOD/DMSO-d*6* on 500 or 400 MHz Bruker NMR spectrometer and resonances are given in parts per million relative to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration. MS data were obtained on a LCMS machine equipped with an electrospray source.

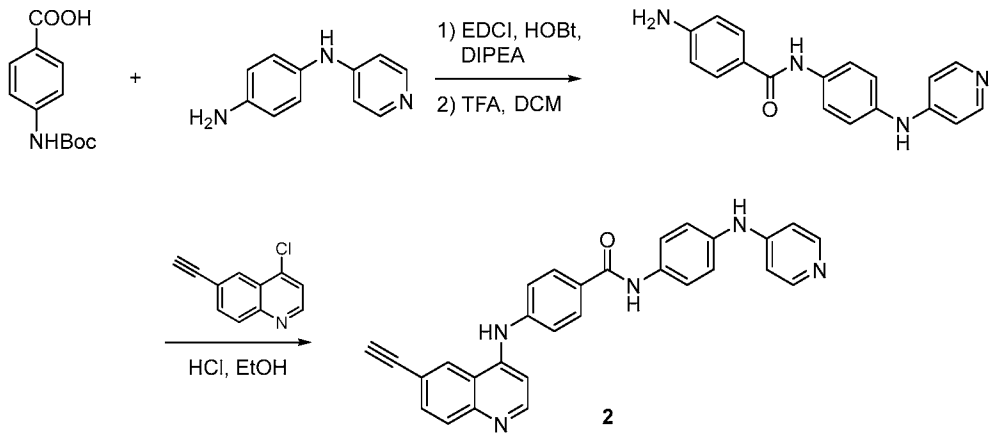
Example 2: Compound 2 (4-((6-ethynylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



2



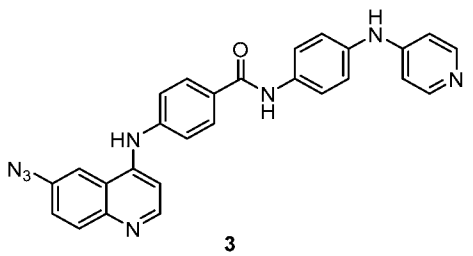
Scheme 2



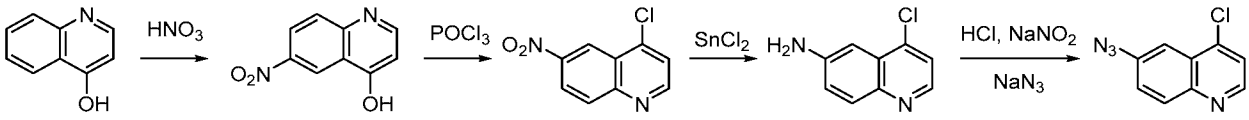
Scheme 3

[0473] **Compound 2** was prepared by the method shown in Schemes 2-3. **Compound 2** (4-((6-ethynylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Schemes 2-3: $C_{29}H_{21}N_5O$; 455.52 g/mol; 47 mg; yellow solid; ESI-LCMS m/z = 456 $[M+H]^+$; LCMS RT = 1.598 min, 100% (214 nm).

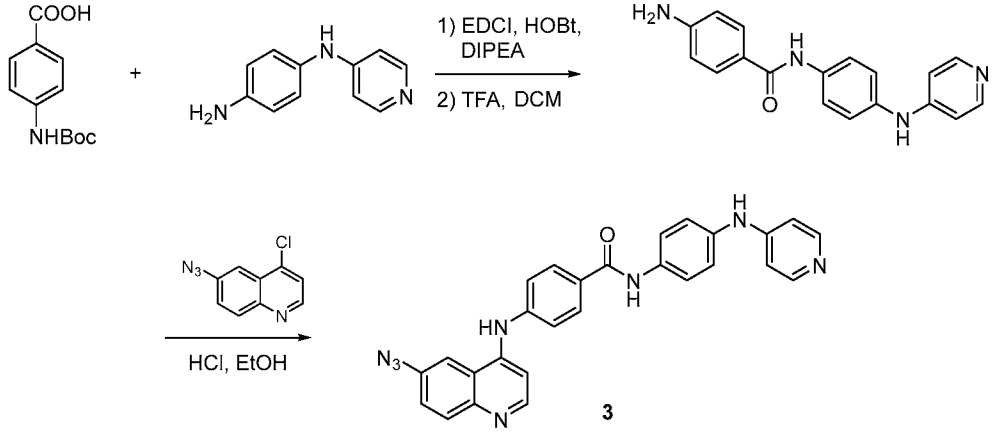
Example 3: Compound 3 (4-((6-azidoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



3



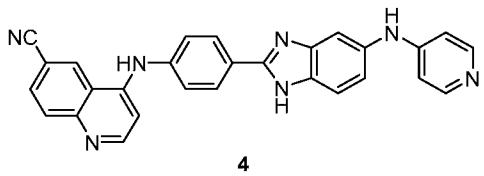
Scheme 4



Scheme 5

[0474] **Compound 3** was prepared by the method shown in Schemes 4-5. **Compound 3** (4-((6-azidoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Schemes 4-5: $C_{27}H_{20}N_8O$; 472.51 g/mol; 25 mg; yellow solid; ESI-LCMS m/z = 473 $[M+H]^+$; LCMS RT = 1.632 min, 100% (214 nm).

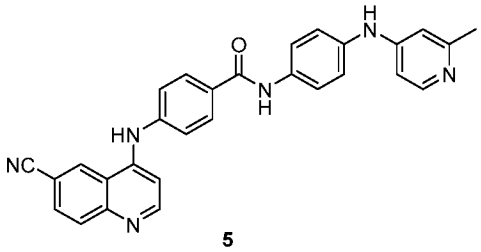
Example 4: Compound 4 (4-((4-(5-(pyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)amino)quinoline-6-carbonitrile)



4

[0475] **Compound 4** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 4** (4-((4-(5-(pyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)amino)quinoline-6-carbonitrile): $C_{28}H_{19}N_7$; 453.51 g/mol; 48 mg; yellow solid; ESI-LCMS m/z = 454 $[M+H]^+$; LCMS RT = 1.508 min, 100% (214 nm).

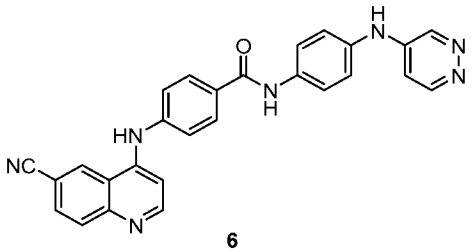
Example 5: Compound 5 (4-((6-cyanoquinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide)



5

[0476] **Compound 5** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 5** (4-((6-cyanoquinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide): $C_{29}H_{22}N_6O$; 470.54 g/mol; 33 mg; yellow solid; ESI-LCMS m/z = 471 $[M+H]^+$; LCMS RT = 1.597 min, 95.63 % (214 nm).

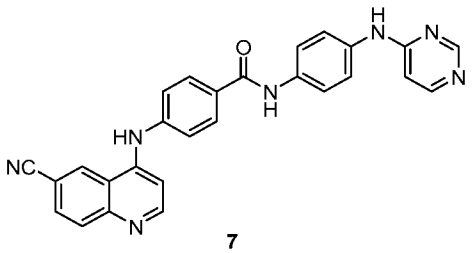
Example 6: Compound 6 (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridazin-4-ylamino)phenyl)benzamide)



6

[0477] **Compound 6** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 6** (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridazin-4-ylamino)phenyl)benzamide): $C_{27}H_{19}N_7O$; 457.50 g/mol; 9.8 mg; white solid; ESI-LCMS m/z = 458.2 $[M+H]^+$; LCMS RT = 1.568min, 100% (214 nm).

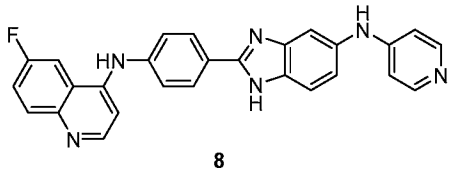
Example 7: Compound 7 (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyrimidin-4-ylamino)phenyl)benzamide)



7

[0478] **Compound 7** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 7** (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyrimidin-4-ylamino)phenyl)benzamide): $C_{27}H_{19}N_7O$; 457.50 g/mol; 22 mg; yellow solid; ESI-LCMS m/z = 458 $[M+H]^+$; LCMS RT = 1.588 min, 100% (214nm).

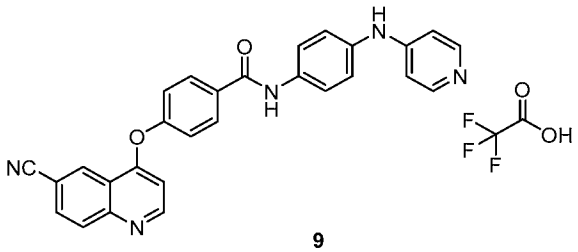
Example 8: Compound 8 (6-fluoro-N-(4-(5-(pyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine)



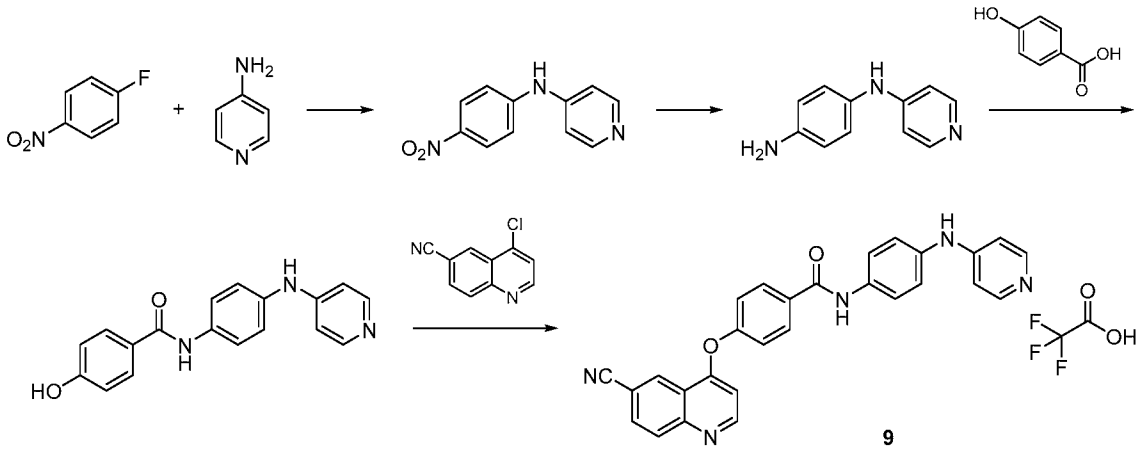
8

[0479] **Compound 8** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 8** (6-fluoro-N-(4-(5-(pyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine): $C_{27}H_{19}FN_6$; 446.49 g/mol; 25 mg; yellow solid; ESI-LCMS m/z = 447 $[M+H]^+$; LCMS RT = 1.549min, 100% (214 nm and 254 nm).

Example 9: Compound 9 (4-((6-cyanoquinolin-4-yl)oxy)-N-(4-(pyridin-4-ylamino)phenyl)benzamide 2,2,2-trifluoroacetate)



9

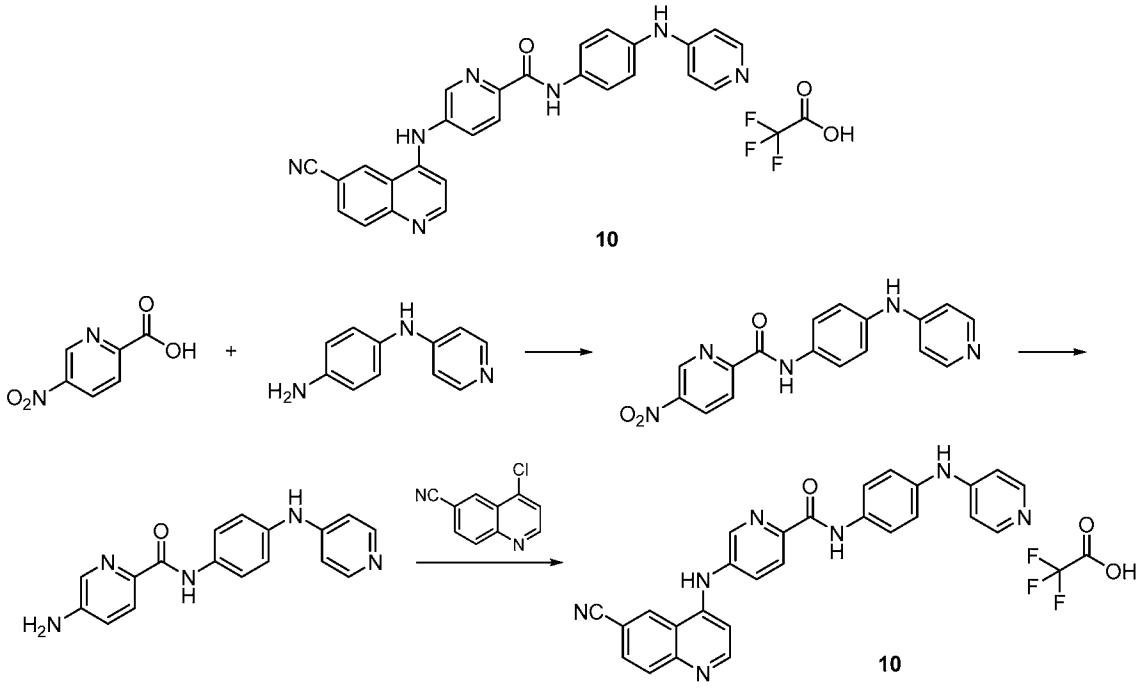


9

Scheme 6

[0480] **Compound 9** was prepared by the method shown in Scheme 6. **Compound 9** (4-((6-cyanoquinolin-4-yl)oxy)-N-(4-(pyridin-4-ylamino)phenyl)benzamide 2,2,2-trifluoroacetate) was prepared as shown in Scheme 6: $C_{30}H_{20}F_3N_5O_4$; 571.52 g/mol; ESI-LCMS m/z = 458.1 $[M+H]^+$; LCMS RT = 2.753min, 96.8% (210 nm).

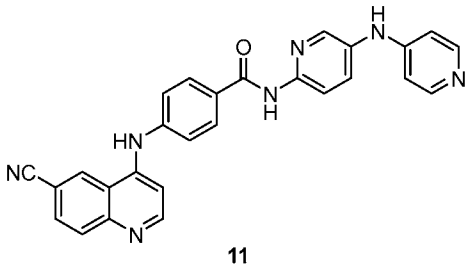
Example 10: Compound 10 (5-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide 2,2,2-trifluoroacetate)

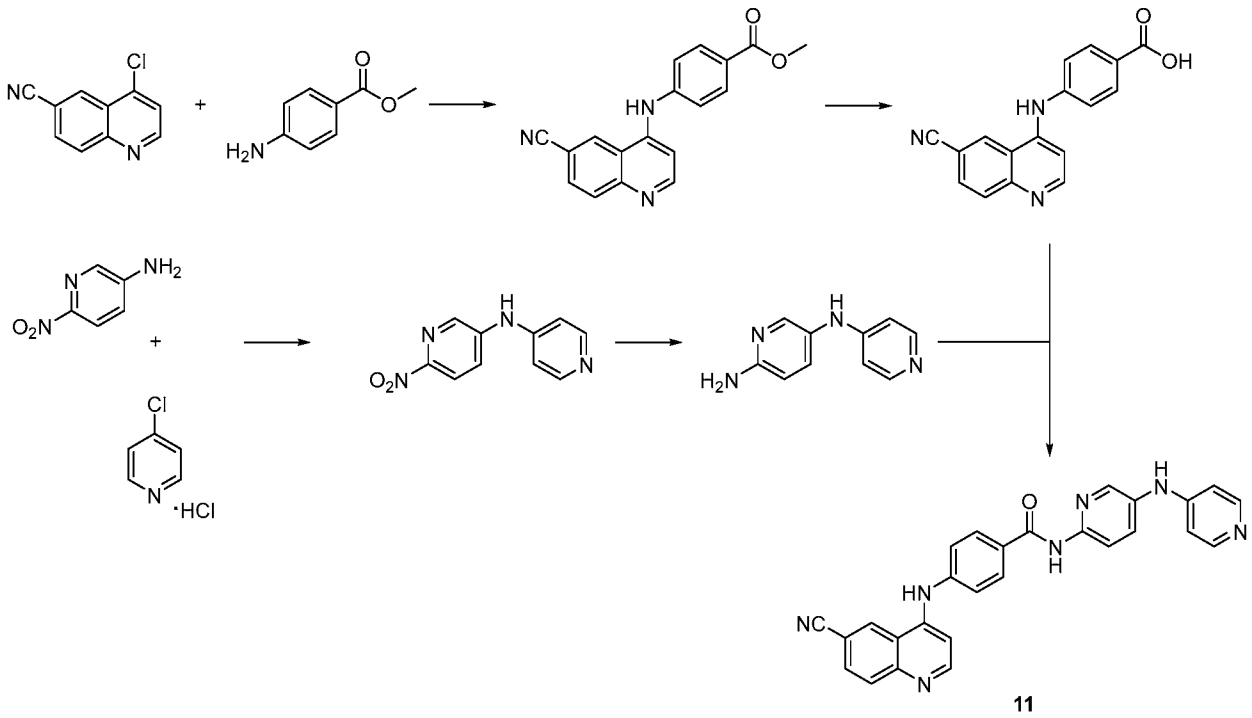


Scheme 7

[0481] **Compound 10** was prepared by the method shown in Scheme 7. **Compound 10** (5-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide 2,2,2-trifluoroacetate) was prepared as shown in Scheme 7: $C_{29}H_{20}F_3N_7O_3$; 571.52 g/mol; ESI-LCMS m/z = 458.1 $[M+H]^+$; LCMS RT = 2.408min, >95% (210 nm).

Example 11: Compound 11 (4-((6-cyanoquinolin-4-yl)amino)-N-(5-(pyridin-4-ylamino)pyridin-2-yl)benzamide)

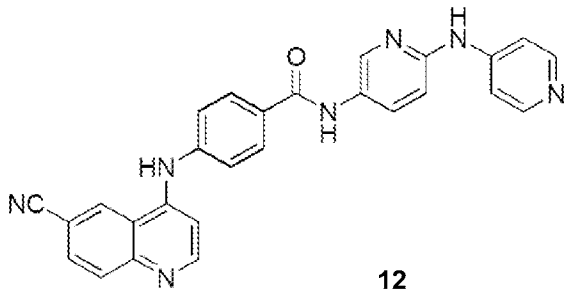




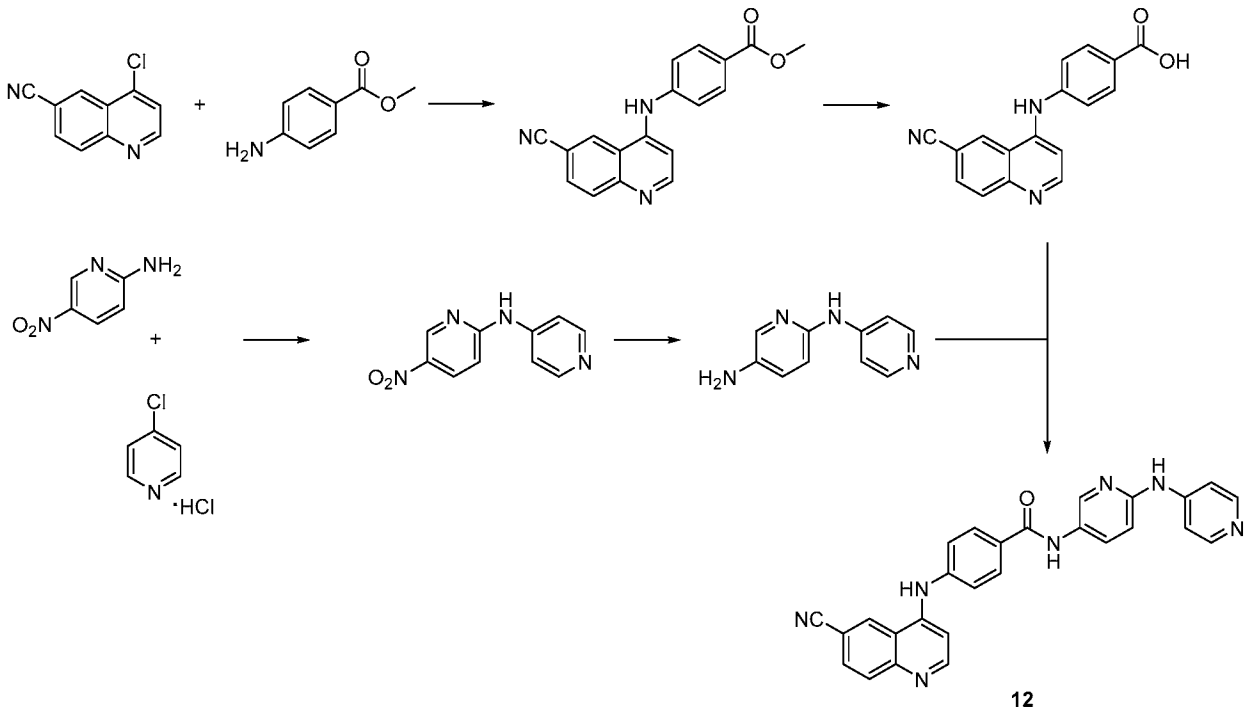
Scheme 8

[0482] **Compound 11** was prepared by the method shown in Scheme 8. **Compound 11** (4-((6-cyanoquinolin-4-yl)amino)-N-(5-(pyridin-4-ylamino)pyridin-2-yl)benzamide) was prepared as shown in Scheme 8: $C_{27}H_{19}N_7O$; 457.49 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 458 $[M+H]^+$; LCMS RT = 1.44 min, >95.00% (214 nm).

Example 12: Compound 12 (4-(6-cyanoquinolin-4-ylamino)-N-(6-(pyridin-4-ylamino)pyridin-3-yl)benzamide)



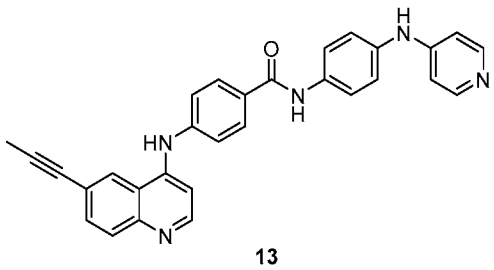
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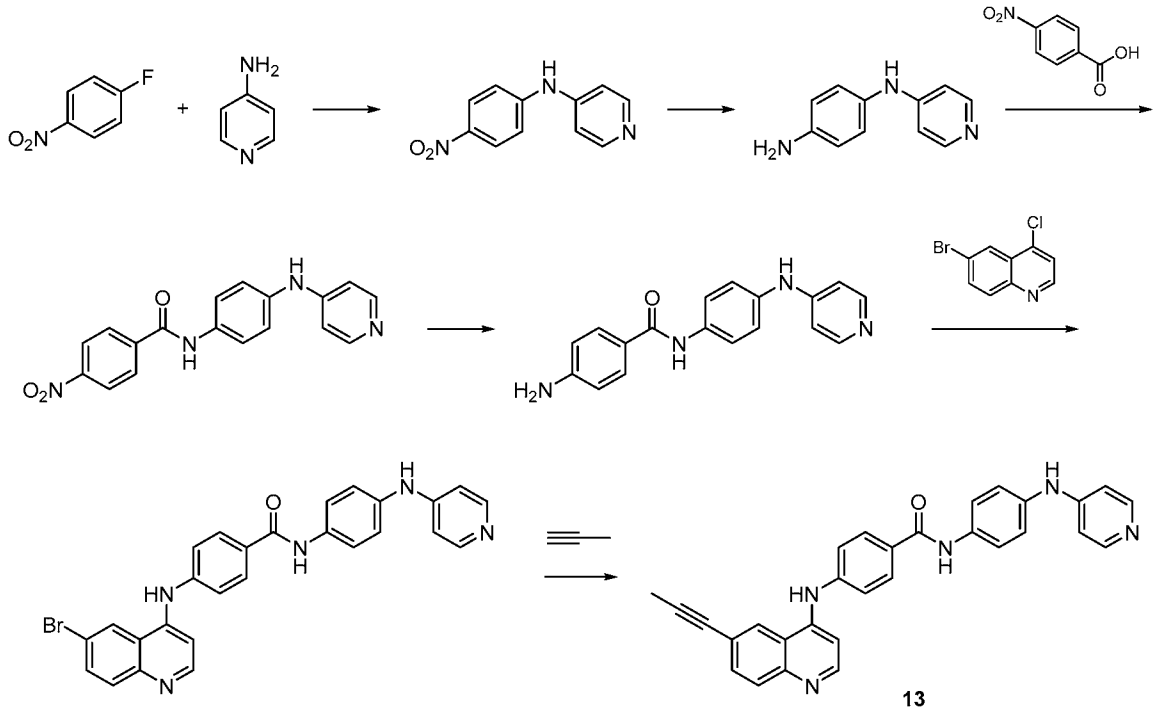


Scheme 9

[0483] **Compound 12** was prepared by the method shown Scheme 9. **Compound 12** (4-(6-cyanoquinolin-4-ylamino)-N-(6-(pyridin-4-ylamino)pyridin-3-yl)benzamide) was prepared as shown in Scheme 9: $C_{27}H_{19}N_7O$; 457.49 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 458 $[M+H]^+$; LCMS RT = 1.36 min, >95.00% (214 nm).

Example 13: Compound 13 (4-((6-(prop-1-yn-1-yl)quinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



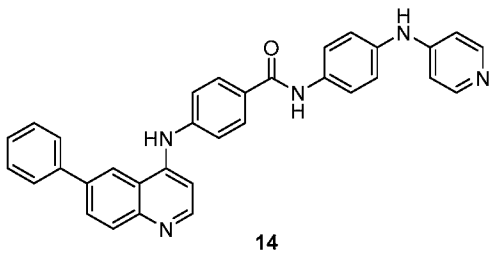


13

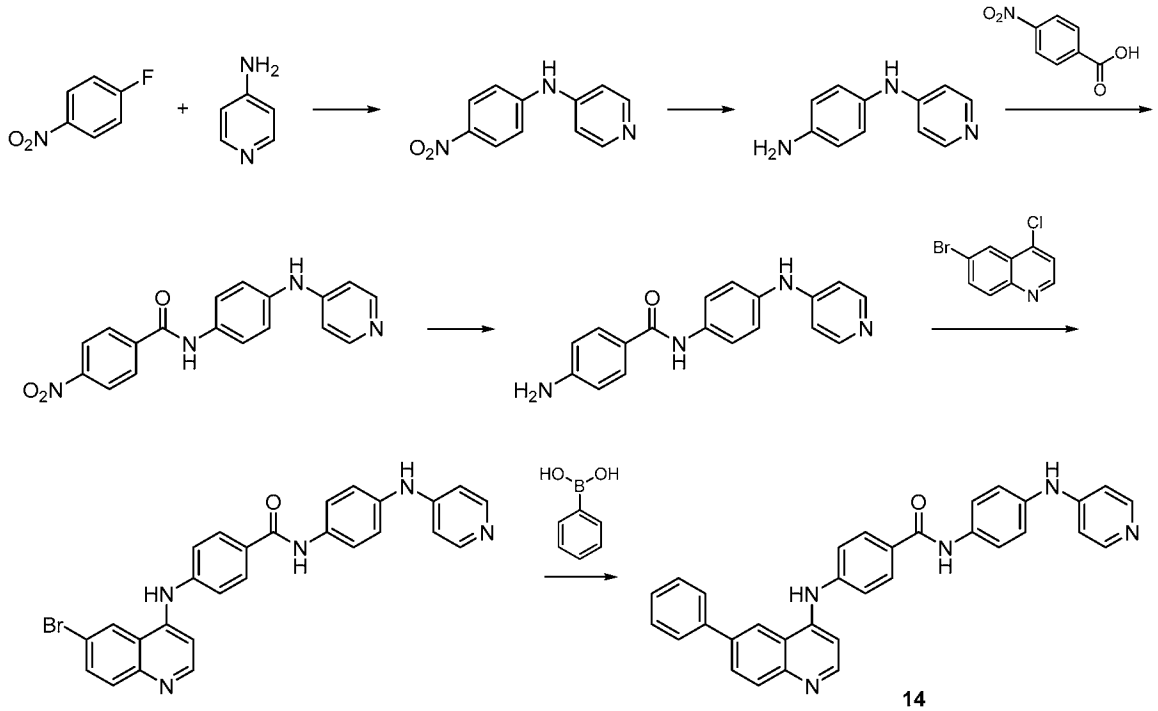
Scheme 10

[0484] **Compound 13** was prepared by the method shown in Scheme 10. **Compound 13** (4-((6-(prop-1-yn-1-yl)quinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Scheme 10: $C_{30}H_{23}N_5O$; 469.55 g/mol; ESI-LCMS m/z = 470.1 $[M+H]^+$; LCMS RT = 2.889 min, 98.6% (210 nm).

Example 14: Compound 14 (4-((6-phenylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



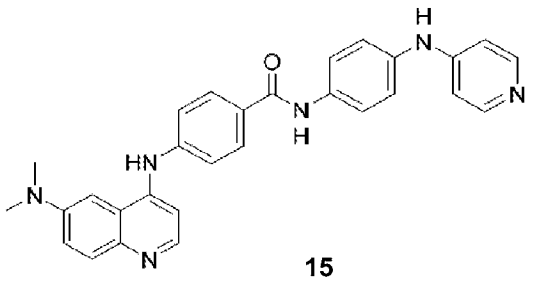
14

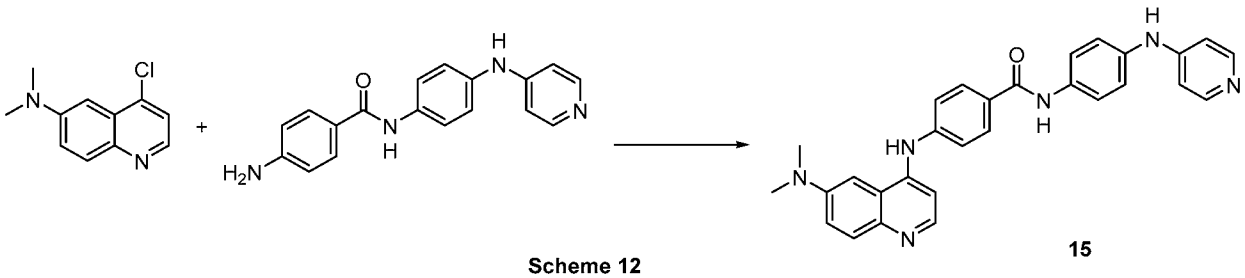


Scheme 11

[0485] **Compound 14** was prepared by the method shown in Scheme 11. **Compound 14** (4-((6-phenylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Scheme 11: $C_{33}H_{25}N_5O$; 507.60 g/mol; ESI-LCMS m/z =508.2 $[M+H]^+$; LCMS RT = 3.199 min, 98.3% (210 nm).

Example 15: Compound 15 (4-((6-(dimethylamino)quinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



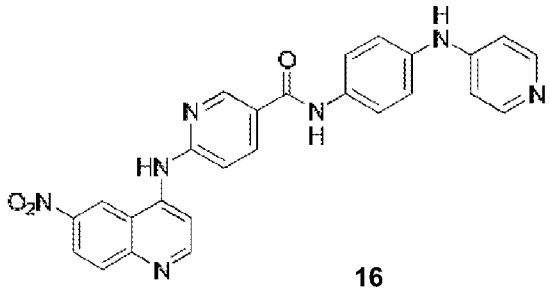


Scheme 12

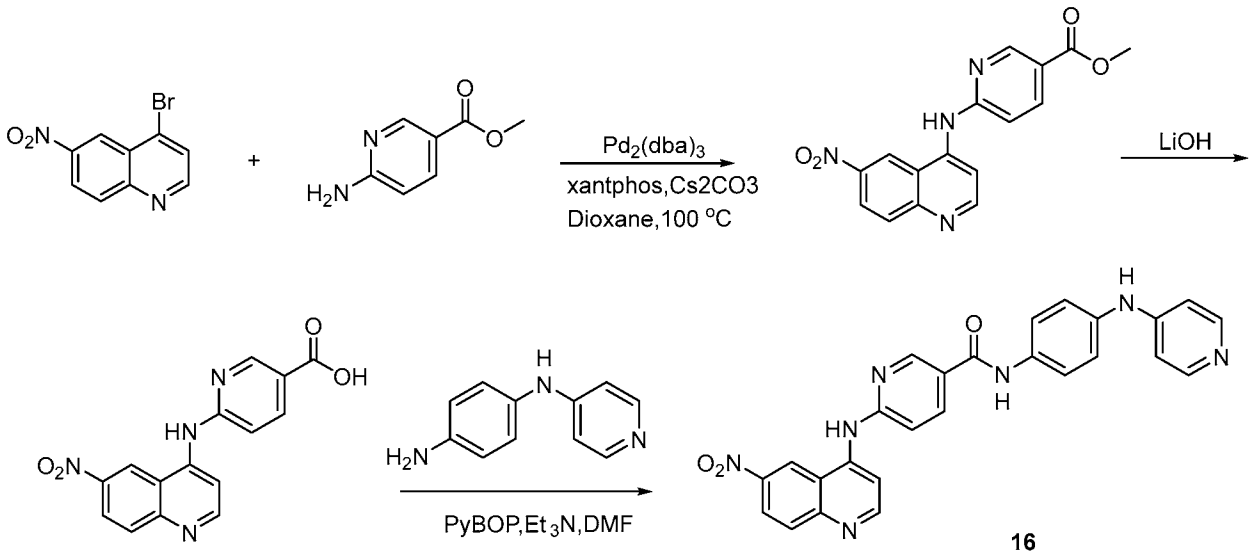
[0486] **Compound 15** was prepared by the method shown in Scheme 12. **Compound 15** (4-((6-(dimethylamino)quinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)

was prepared as shown in Scheme 12: $C_{29}H_{26}N_6O$; 474.57 g/mol; 18 mg; pale yellow solid; ESI-LCMS m/z = 475 $[M+H]^+$; LCMS RT = 1.42 min, >95.00% (214 nm).

Example 16: Compound 16 (6-(6-nitroquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide)



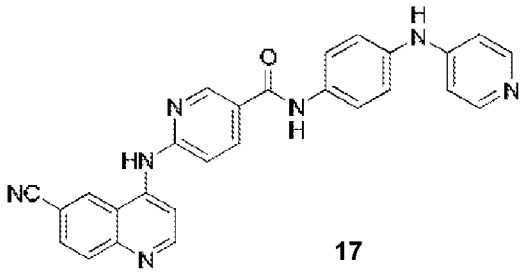
16



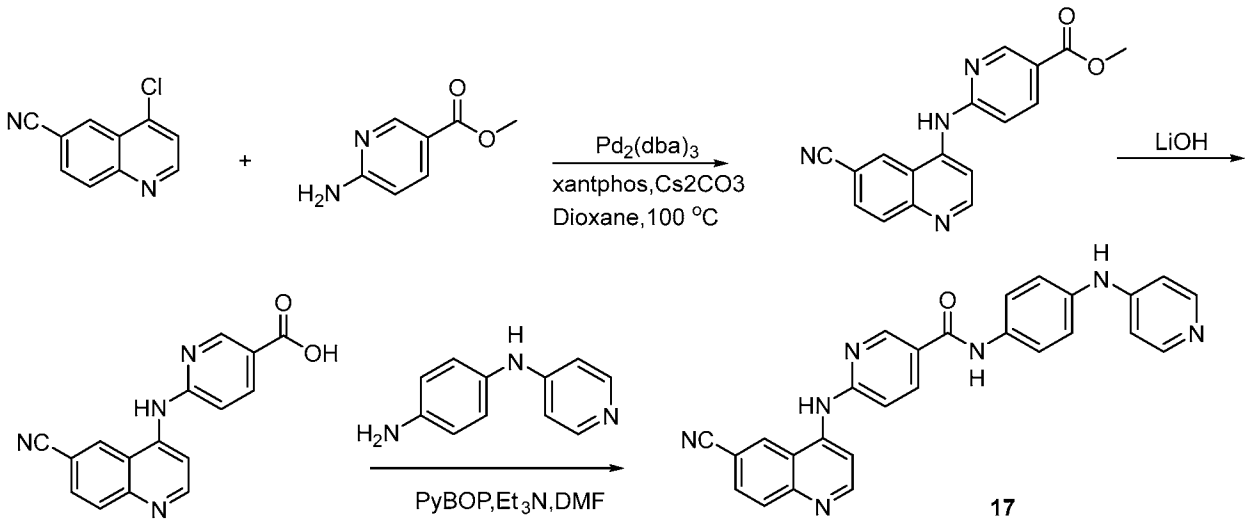
Scheme 13

[0487] **Compound 16** was prepared by the method shown in Scheme 13. **Compound 16** (6-(6-nitroquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 13: $C_{26}H_{19}N_7O_3$; 477.47 g/mol; 24 mg; pale yellow solid; ESI-LCMS m/z = 478 $[M+H]^+$; LCMS RT = 1.65 min, >95.00% (214 nm).

Example 17: Compound 17 (6-(6-cyanoquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide)



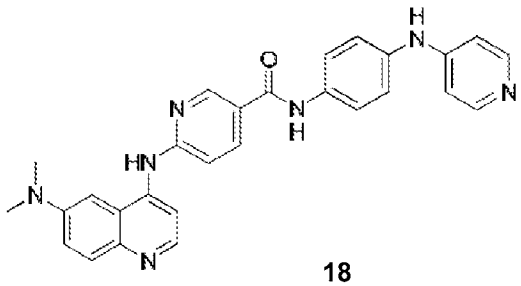
17

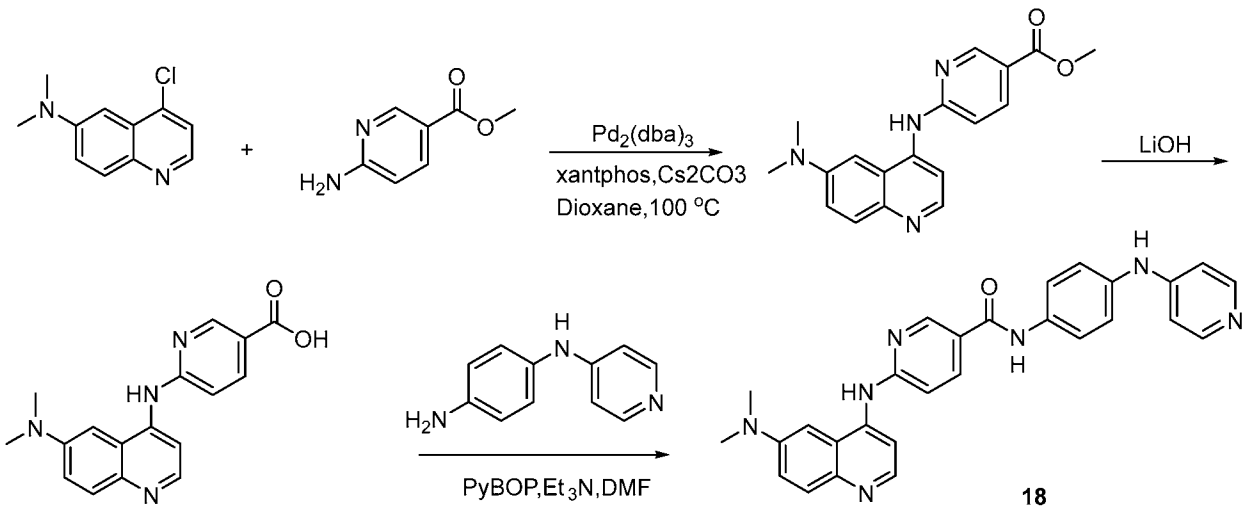


Scheme 14

[0488] **Compound 17** was prepared by the method shown in Scheme 14. **Compound 17** (6-(6-cyanoquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 14: $C_{27}H_{19}N_7O$; 457.49 g/mol; 14 mg; pale yellow solid; ESI-LCMS m/z = 458 $[M+H]^+$; LCMS RT = 1.63 min, >95.00% (214 nm).

Example 18: Compound 18 (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide)

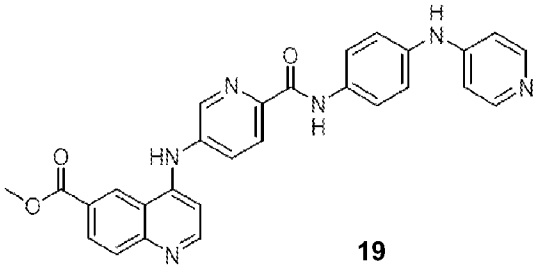




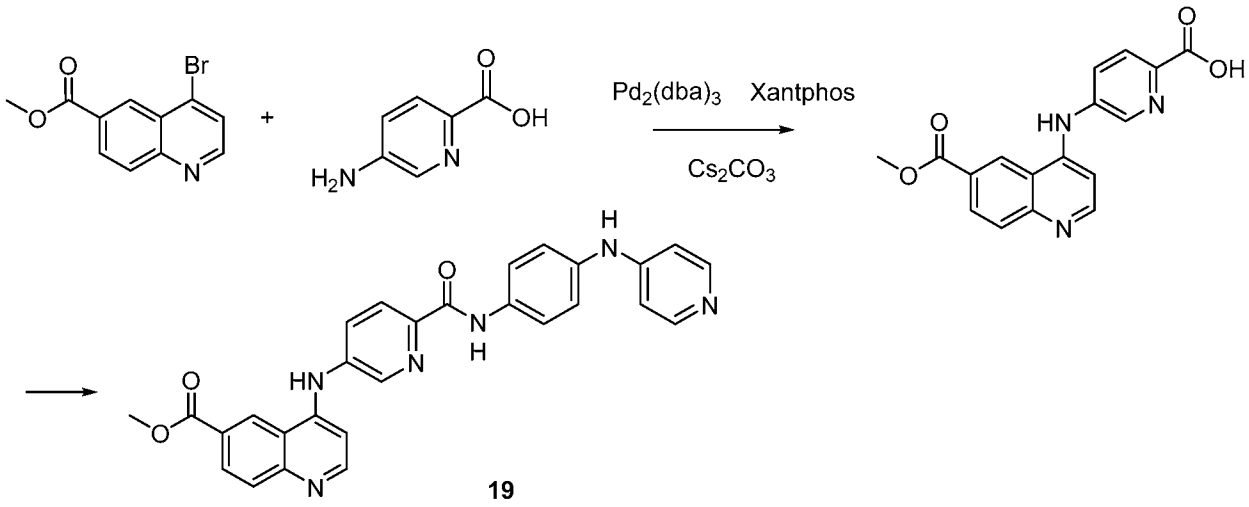
Scheme 15

[0489] **Compound 18** was prepared by the method shown in Scheme 15. **Compound 18** (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 15: $C_{28}H_{25}N_7O$; 475.54 g/mol; 17 mg; yellow solid; ESI-LCMS m/z = 476 $[M+H]^+$; LCMS RT = 1.73 min, >95.00% (214 nm).

Example 19: Compound 19 (4-(6-(4-(pyridin-4-ylamino)phenylcarbamoyl)pyridin-3-ylamino)quinoline-6-carboxylate)



19

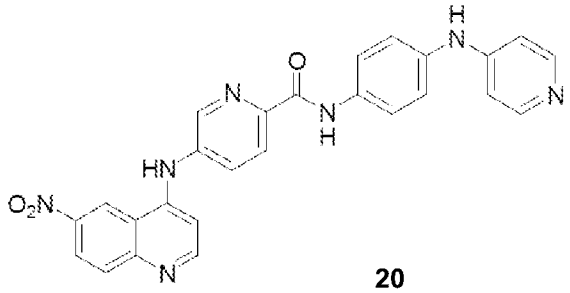


19

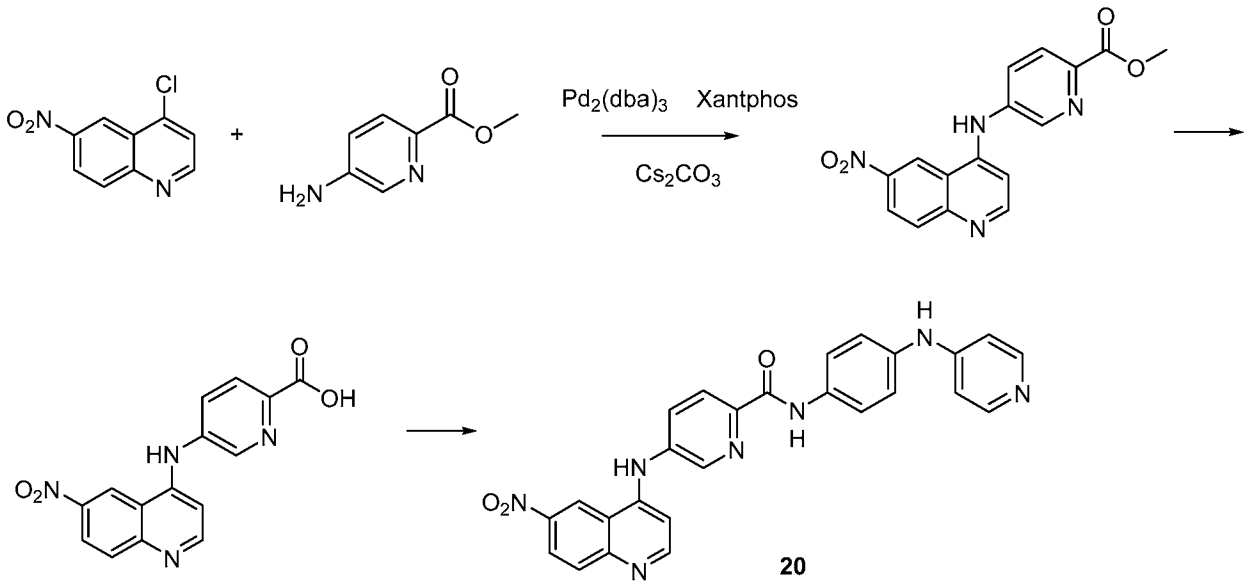
Scheme 16

[0490] **Compound 19** was prepared by the method shown in Scheme 16. **Compound 19** (4-(6-(4-(pyridin-4-ylamino)phenylcarbamoyl)pyridin-3-ylamino)quinoline-6-carboxylate) was prepared as shown in Scheme 16: $C_{28}H_{22}N_6O_3$; 490.51 g/mol; 13 mg; pale yellow solid; ESI-LCMS m/z = 491 $[M+H]^+$; LCMS RT = 1.38 min, >95.00% (214 nm).

Example 20: Compound 20 (5-(6-nitroquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide)



20

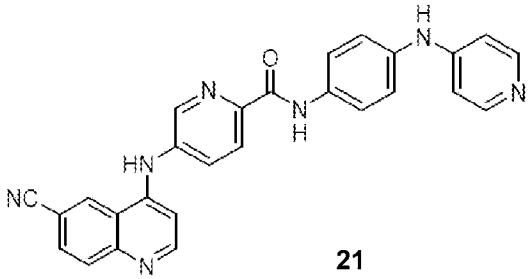


20

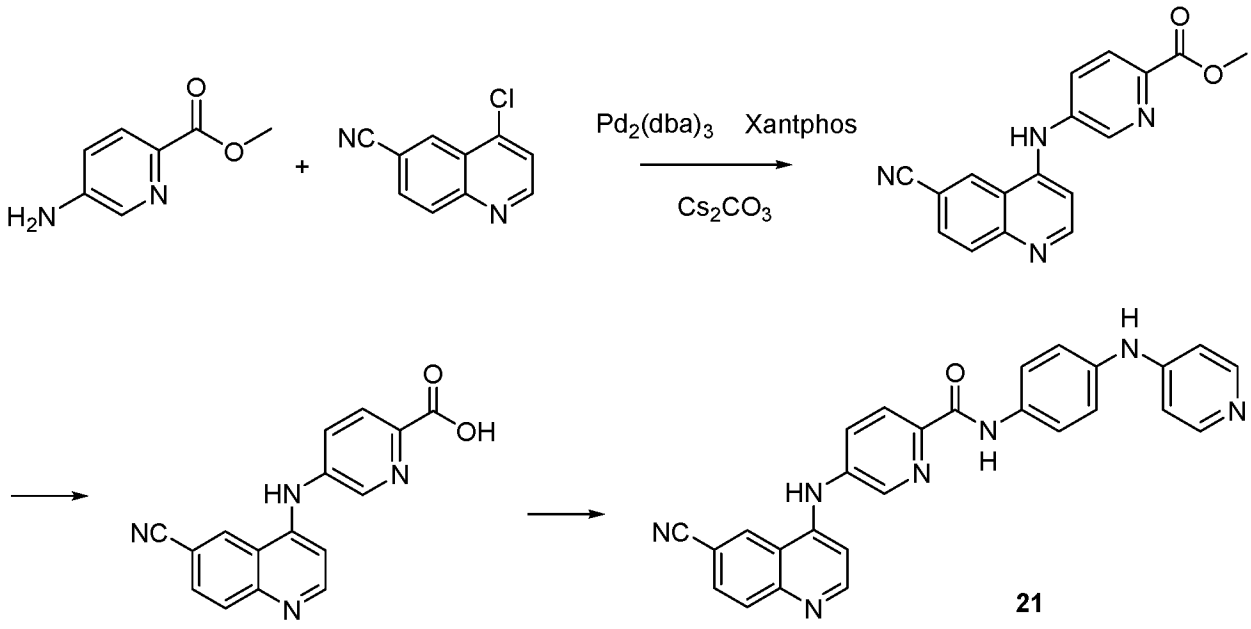
Scheme 17

[0491] **Compound 20** was prepared by the method shown in Scheme 17. **Compound 20** (5-(6-nitroquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide) was prepared as shown in Scheme 17: $C_{26}H_{19}N_7O_3$; 477.47 g/mol; 12 mg; yellow brown solid; ESI-LCMS m/z = 478 $[M+H]^+$; LCMS RT = 1.39 min, >95.00% (214 nm).

Example 21: Compound 21 (5-(6-cyanoquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide)



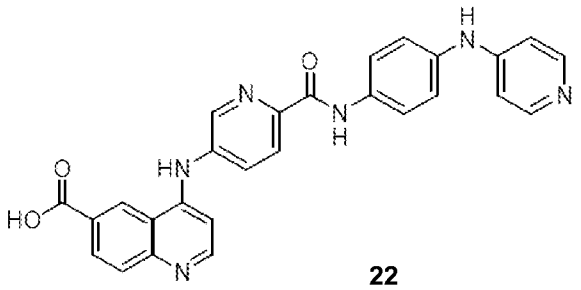
21



Scheme 18

[0492] **Compound 21** was prepared by the method shown in Scheme 18. **Compound 21** (5-(6-cyanoquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide) was prepared as shown in Scheme 18: $C_{27}H_{19}N_7O$; 457.49 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 458 $[M+H]^+$; LCMS RT = 1.37 min, >95.00% (214 nm).

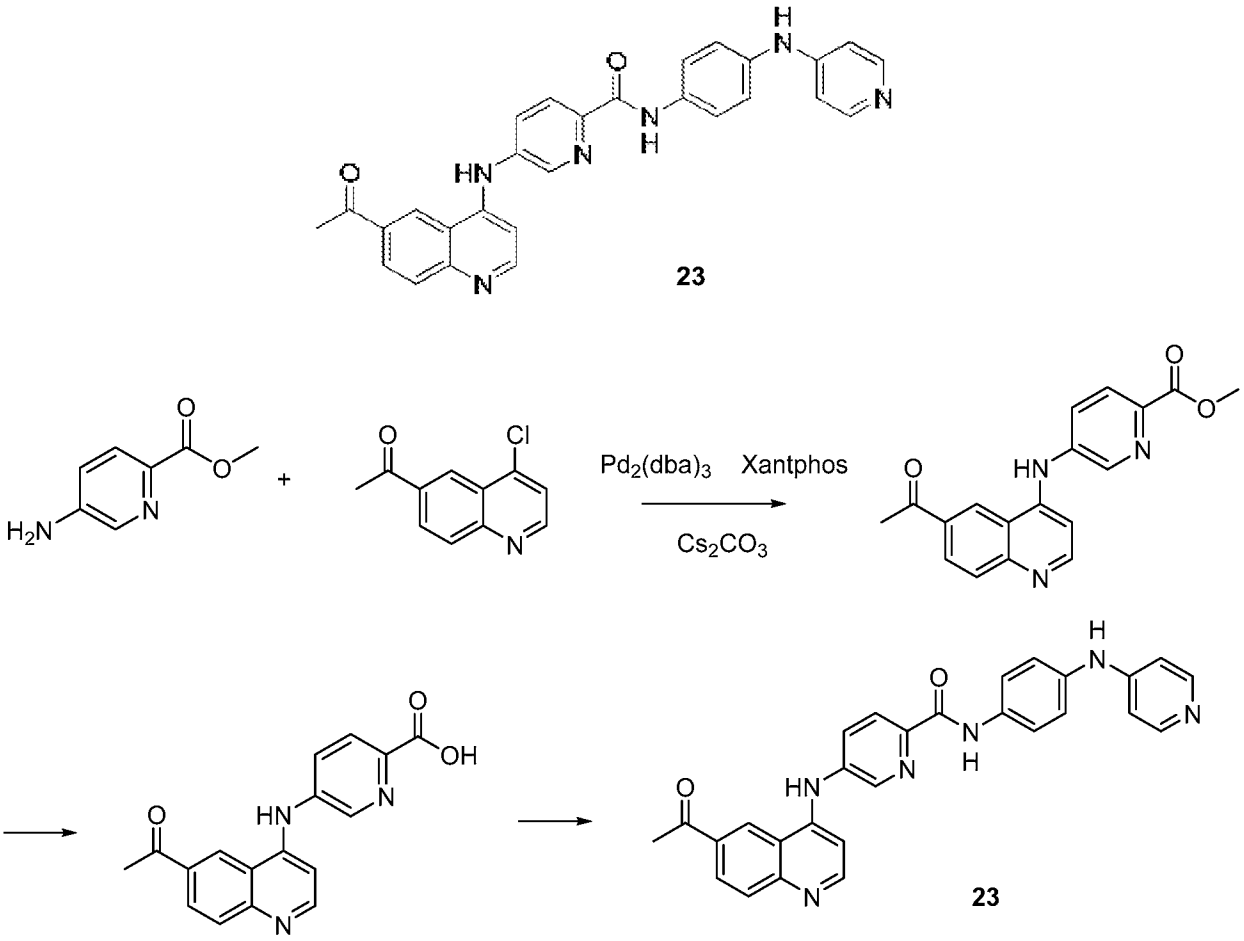
Example 22: Compound 22 (4-(6-(4-(pyridin-4-ylamino)phenylcarbamoyl)pyridin-3-ylamino)quinoline-6-carboxylic acid)



22

[0493] **Compound 22** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 22** (4-(6-(4-(pyridin-4-ylamino)phenylcarbamoyl)pyridin-3-ylamino)quinoline-6-carboxylic acid): $C_{27}H_{20}N_6O_3$; 476.49 g/mol; 19 mg; pale yellow solid; ESI-LCMS m/z = 477 $[M+H]^+$; LCMS RT = 1.33 min, >95.00% (214 nm).

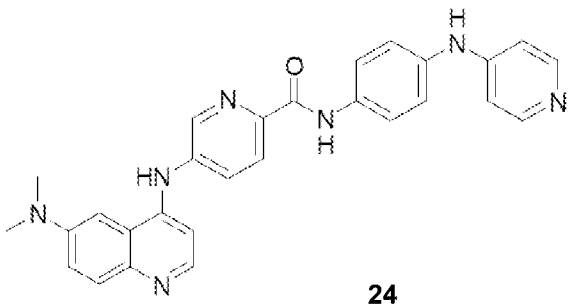
Example 23: Compound 23 (5-(6-acetylquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide)

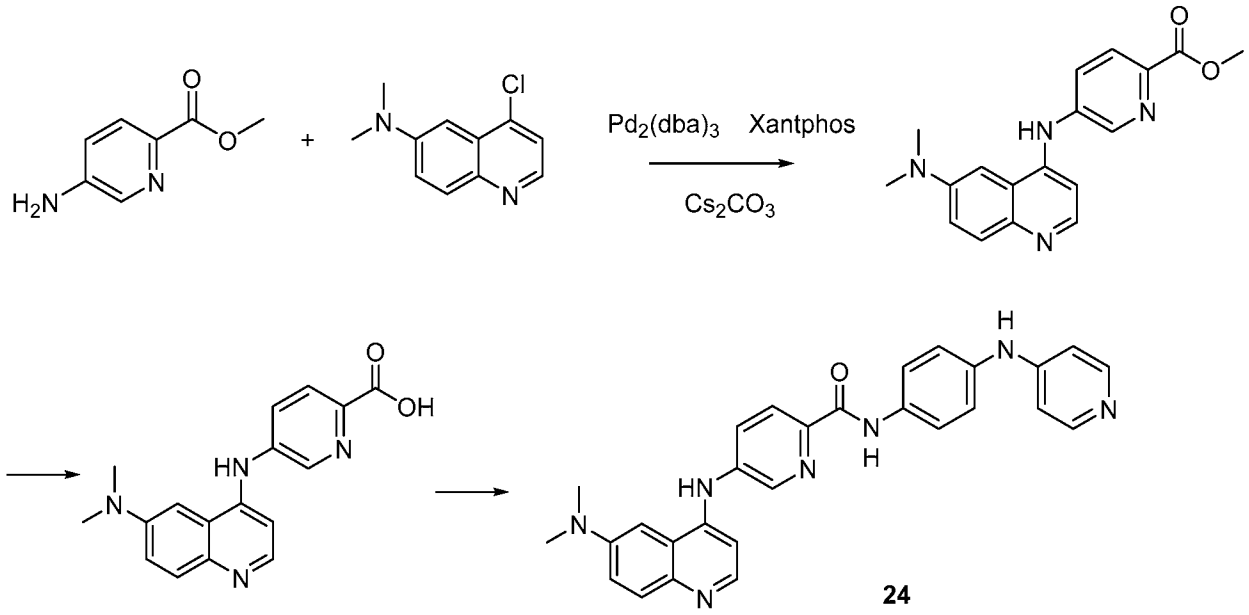


Scheme 19

[0494] **Compound 23** was prepared by the method shown in Scheme 19. **Compound 23** (5-(6-acetylquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide) was prepared as shown in Scheme 19: $C_{28}H_{22}N_6O_2$; 474.51 g/mol; 20 mg; pale yellow solid; ESI-LCMS m/z = 475 $[M+H]^+$; LCMS RT = 1.38 min, >95.00% (214 nm).

Example 24: Compound 24 (5-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide)

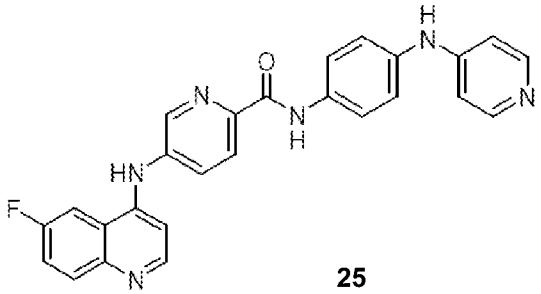


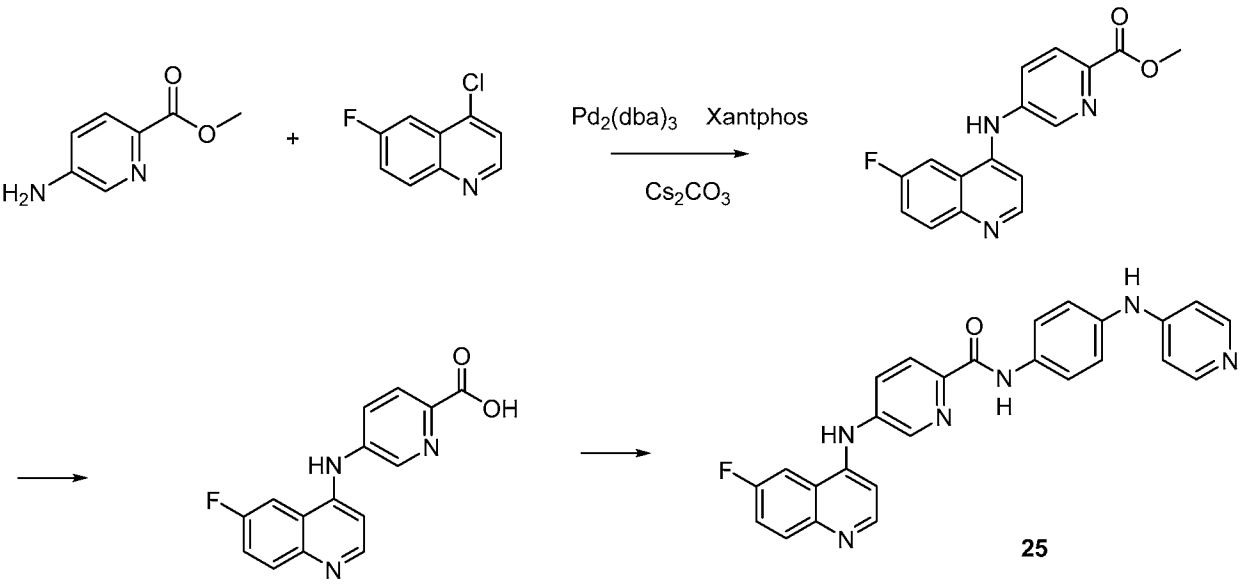


Scheme 20

[0495] **Compound 24** was prepared by the method shown in Scheme 20. **Compound 24** (5-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(pyridin-4- ylamino)phenyl)picolinamide) was prepared as shown in Scheme 20: $C_{28}H_{25}N_7O$; 475.54 g/mol; 18 mg; pale yellow solid; ESI-LCMS m/z = 476 $[M+H]^+$; LCMS RT = 1.52 min, >95.00% (214 nm).

Example 25: Compound 25 (5-(6-fluoroquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide)

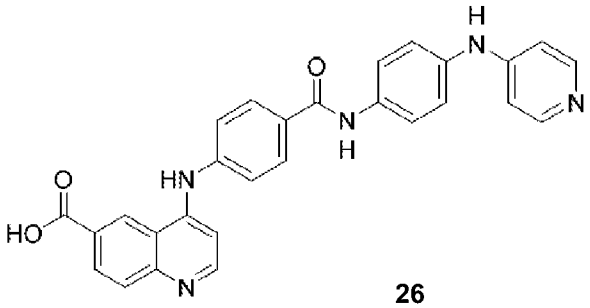




Scheme 21

[0496] **Compound 25** was prepared by the method shown in Scheme 21. **Compound 25** (5-(6-fluoroquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)picolinamide) was prepared as shown in Scheme 21: $C_{26}H_{19}FN_6O$; 450.47 g/mol; 10 mg; pale yellow solid; ESI-LCMS m/z = 451 $[M+H]^+$; LCMS RT = 1.38 min, >95.00% (214 nm).

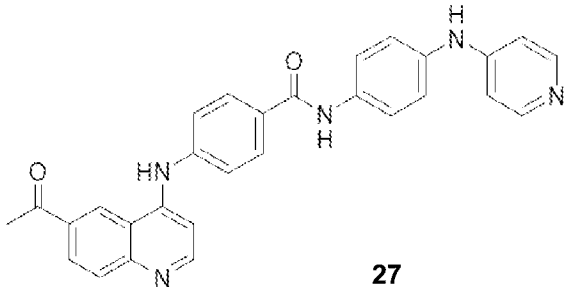
Example 26: Compound 26 (4-((4-((4-(pyridin-4-ylamino)phenyl)carbamoyl)phenyl)amino)quinoline-6-carboxylic acid)



26

[0497] **Compound 26** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 26** (4-((4-((4-(pyridin-4-ylamino)phenyl)carbamoyl)phenyl)amino)quinoline-6-carboxylic acid): $C_{28}H_{21}N_5O_3$; 475.51 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 476 $[M+H]^+$; LCMS RT = 1.34 min, >95.00% (214 nm).

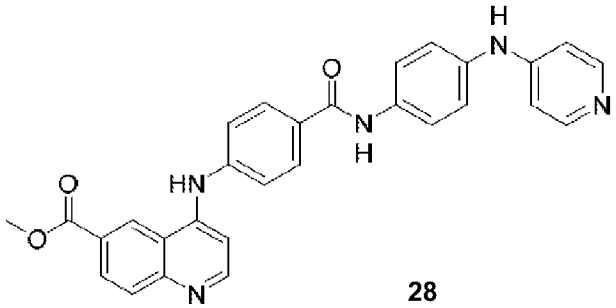
Example 27: Compound 27 (4-(6-acetylquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



27

[0498] **Compound 27** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 27** (4-(6-acetylquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide): $C_{29}H_{23}N_5O_2$; 473.53 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 474 $[M+H]^+$; LCMS RT = 1.44 min, >95.00% (214 nm).

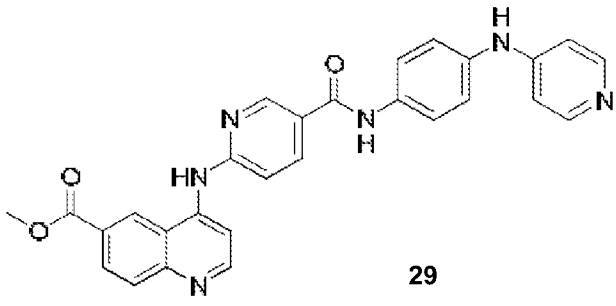
Example 28: Compound 28 (methyl 4-((4-((4-(pyridin-4-ylamino)phenyl)carbamoyl)phenyl)amino)quinoline-6-carboxylate)



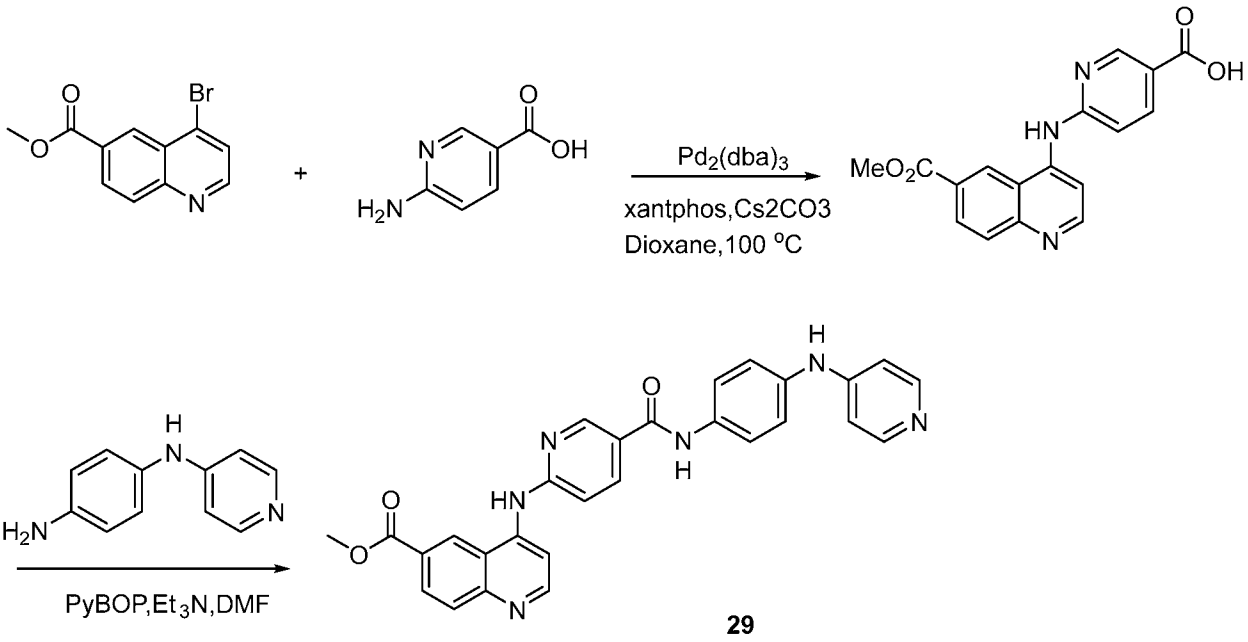
28

[0499] **Compound 28** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 28** (methyl 4-((4-((4-(pyridin-4-ylamino)phenyl)carbamoyl)phenyl)amino)quinoline-6-carboxylate): $C_{29}H_{23}N_5O_3$; 489.54 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 490 $[M+H]^+$; LCMS RT = 1.43 min, >95.00% (214 nm).

Example 29: Compound 29 (methyl 4-(5-(4-(pyridin-4-ylamino)phenylcarbamoyl)pyridin-2-ylamino)quinoline-6-carboxylate)



29

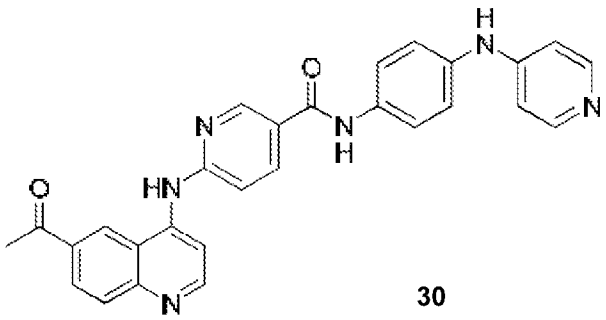


29

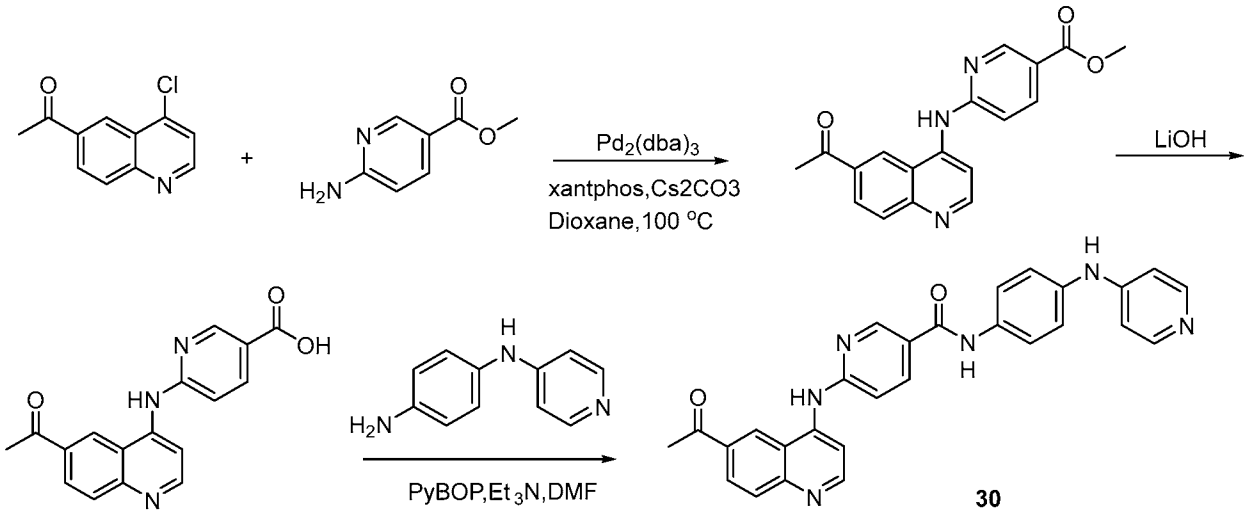
Scheme 22

[0500] **Compound 29** was prepared by the method shown in Scheme 22. **Compound 29** (methyl 4-(5-(4-(pyridin-4-ylamino)phenylcarbamoyl)pyridin-2-ylamino)quinoline-6-carboxylate) was prepared as shown in Scheme 22: $C_{28}H_{22}N_6O_3$; 490.51 g/mol; 15 mg; yellow solid; ESI-LCMS m/z = 491 $[M+H]^+$; LCMS RT = 1.39 min, >95.00% (214 nm).

Example 30: Compound 30 (6-(6-acetylquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide)



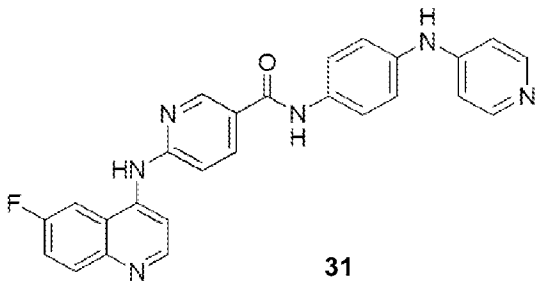
30

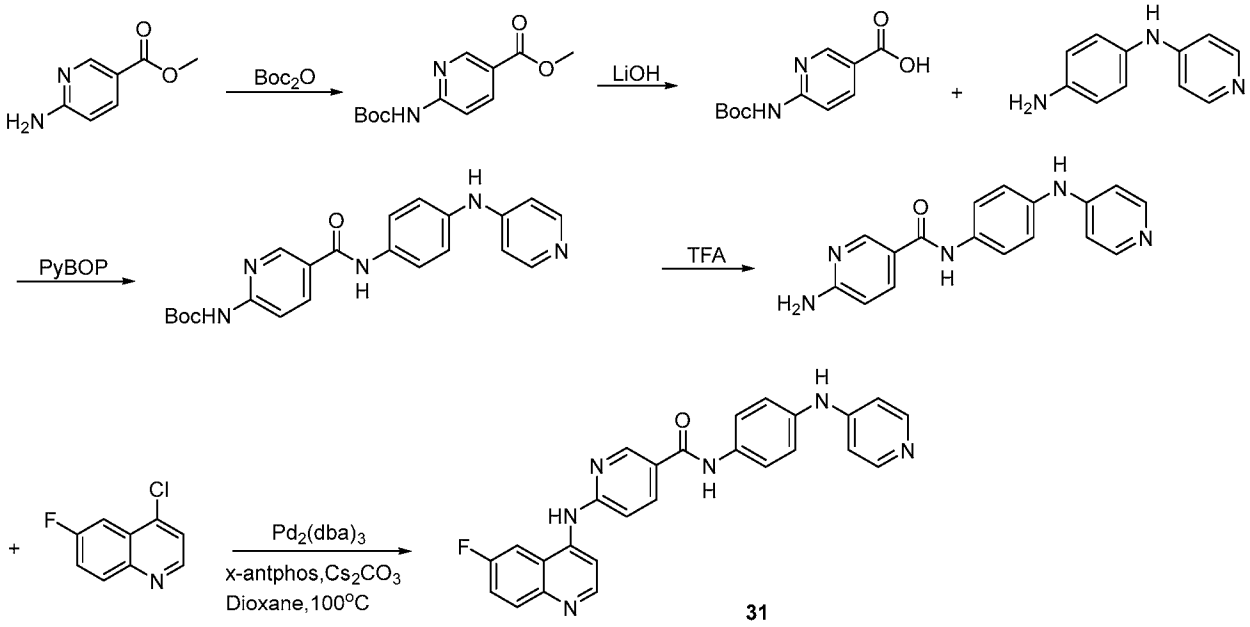


Scheme 23

[0501] **Compound 30** was prepared by the method shown in Scheme 23. **Compound 30** (6-(6-acetylquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 23: $C_{28}H_{22}N_6O_2$; 474.51 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 475 $[M+H]^+$; LCMS RT = 1.49 min, >95.00% (214 nm).

Example 31: Compound 31 (6-(6-fluoroquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide)

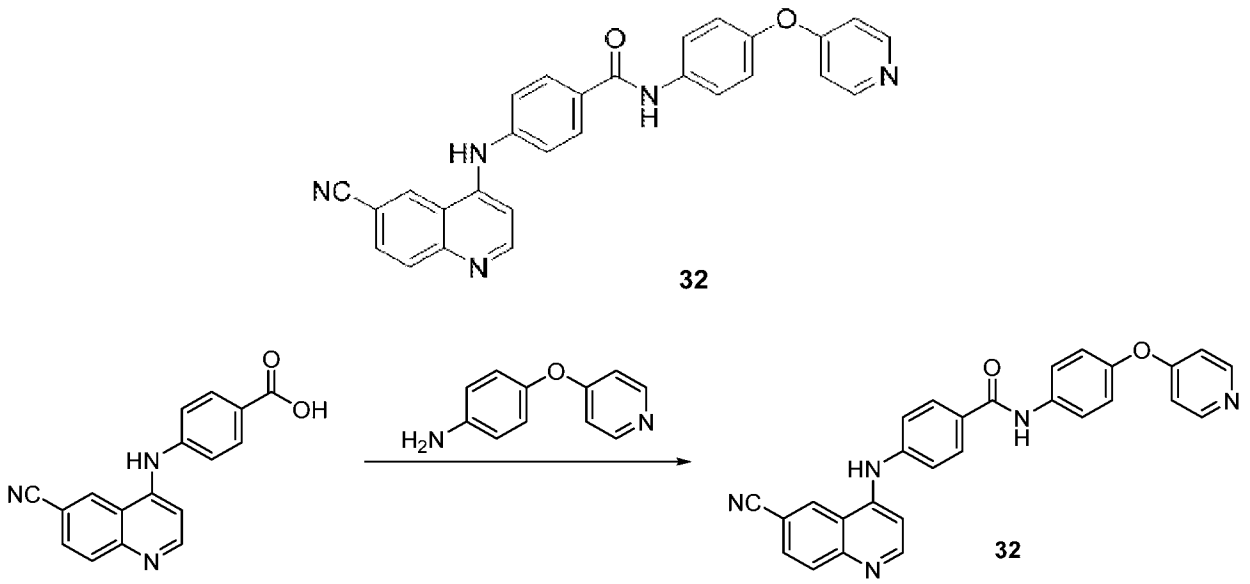




Scheme 24

[0502] **Compound 31** was prepared by the method shown in Scheme 24. **Compound 31** (6-(6-fluoroquinolin-4-ylamino)-N-(4-(pyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 24: $C_{26}H_{19}FN_6O$; 450.47 g/mol; 13 mg; pale yellow solid; ESI-LCMS m/z = 451 $[M+H]^+$; LCMS RT = 1.60 min, >95.00% (214 nm).

Example 32: Compound 32 (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-yloxy)phenyl)benzamide)

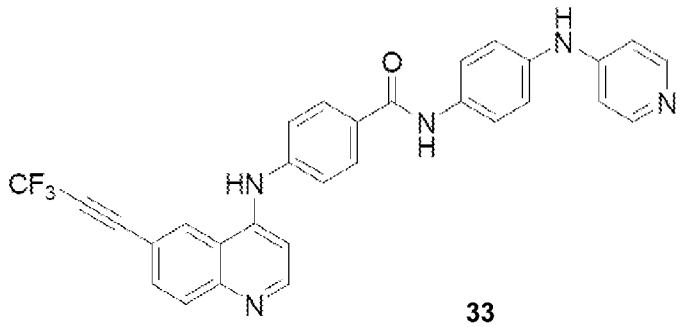


Scheme 25

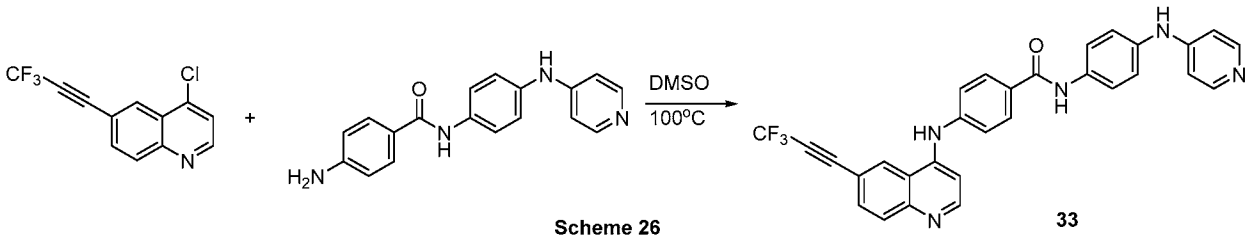
[0503] **Compound 32** was prepared by the method shown in Scheme 25. **Compound 32** (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-yloxy)phenyl)benzamide) was prepared as

shown in Scheme 25: $C_{26}H_{19}FN_6O$; 457.49 g/mol; 14 mg; pale yellow solid; ESI-LCMS m/z = 458 $[M+H]^+$; LCMS RT = 1.38 min, >95.00% (214 nm).

Example 33: Compound 33 (N-(4-(pyridin-4-ylamino)phenyl)-4-((6-(3,3,3-trifluoroprop-1-yn-1-yl)quinolin-4-yl)amino)benzamide)



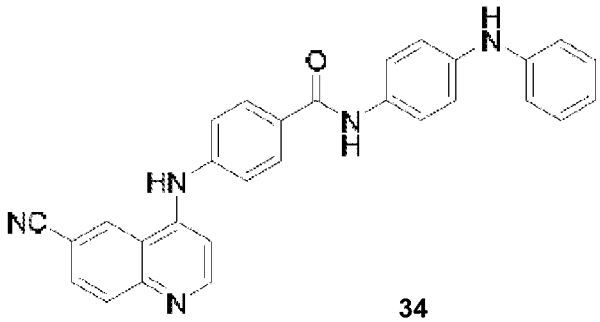
33



Scheme 26

[0504] **Compound 33** was prepared by the method shown in Scheme 26. **Compound 33** (N-(4-(pyridin-4-ylamino)phenyl)-4-((6-(3,3,3-trifluoroprop- 1-yn-1-yl)quinolin-4-yl)amino)benzamide) was prepared as shown in Scheme 26: $C_{30}H_{20}F_3N_5O$; 523.52 g/mol; 15 mg; pale yellow solid; ESI-LCMS m/z = 524 $[M+H]^+$; LCMS RT = 1.94 min, >95.00% (214 nm).

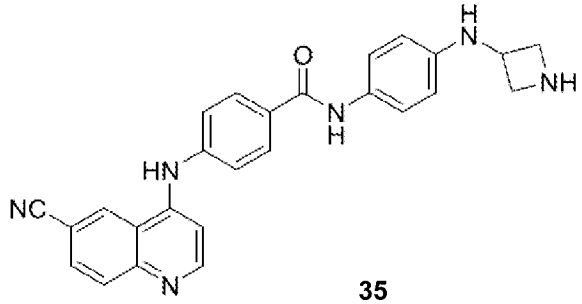
Example 34: Compound 34 (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(phenylamino)phenyl)benzamide)



34

[0505] **Compound 34** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 34** (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(phenylamino)phenyl)benzamide): $C_{29}H_{21}N_5O$; 455.52 g/mol; 15 mg; pale yellow solid; ESI-LCMS m/z = 456 $[M+H]^+$; LCMS RT = 1.19 min, >95.00% (214 nm).

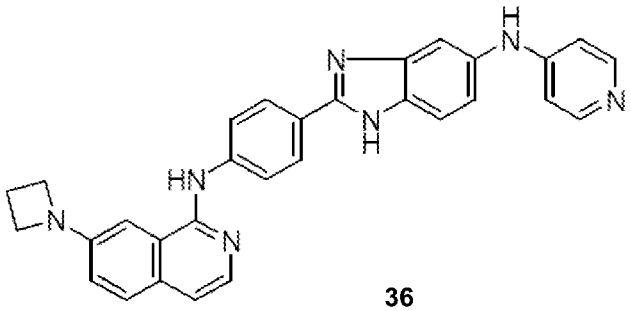
Example 35: Compound 35 (N-(4-(azetidin-3-ylamino)phenyl)-4-((6-cyanoquinolin-4-yl) amino)benzamide)



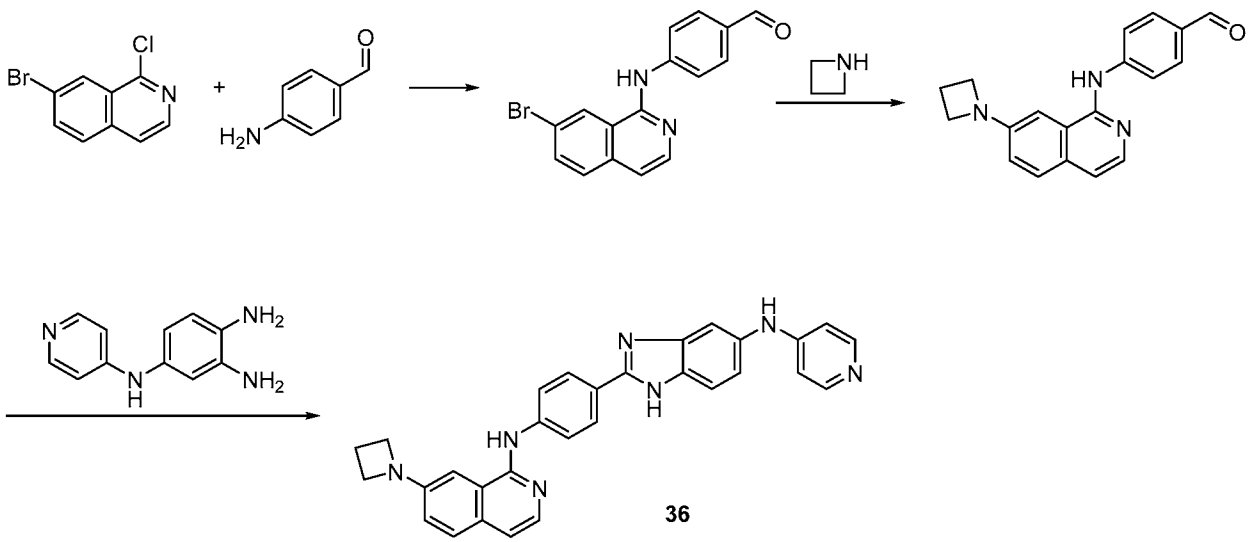
35

[0506] **Compound 35** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 35** (N-(4-(azetidin-3-ylamino)phenyl)-4-((6-cyanoquinolin-4-yl) amino)benzamide): $C_{26}H_{22}N_6O$; 434.50 g/mol; 13 mg; pale yellow solid; ESI-LCMS m/z = 435 $[M+H]^+$; LCMS RT = 1.33 min, >95.00% (214 nm).

Example 36: Compound 36 (7-(azetidin-1-yl)-N-(4-(5-(pyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)isoquinolin-1-amine)



36



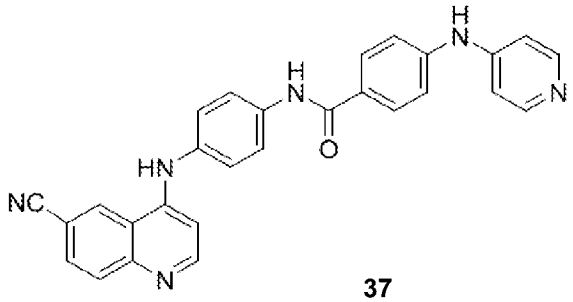
36

Scheme 27

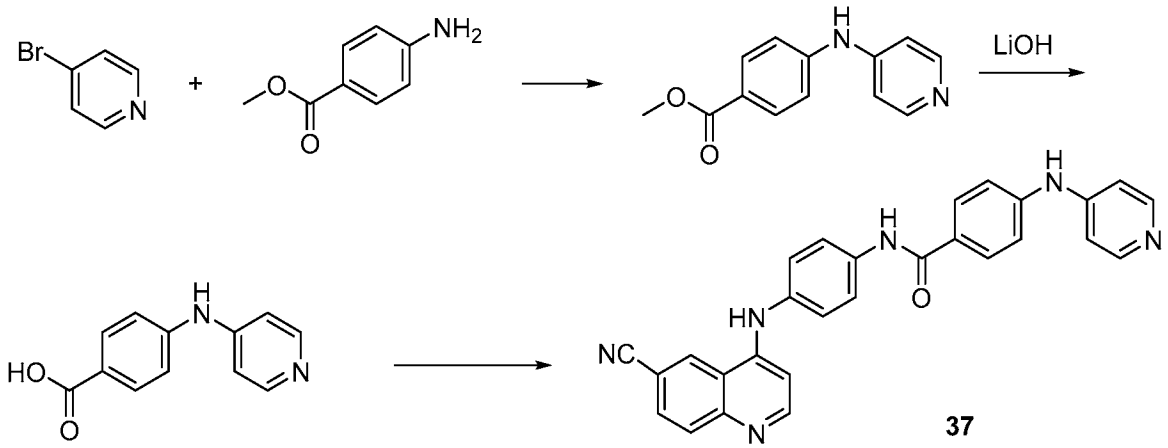
[0507] **Compound 36** was prepared by the method shown in Scheme 27. **Compound 36** (7-(azetidin-1-yl)-N-(4-(5-(pyridin-4-ylamino)-1H-benzo[d]imidazol-2-

yl)phenyl)isoquinolin-1-amine) was prepared as shown in Scheme 26: $C_{30}H_{25}N_7$; 483.58 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 484 $[M+H]^+$; LCMS RT = 1.71 min, >95.00% (214 nm).

Example 37: Compound 37 (N-(4-((6-cyanoquinolin-4-yl)amino)phenyl)-4-(pyridin-4-ylamino)benzamide)



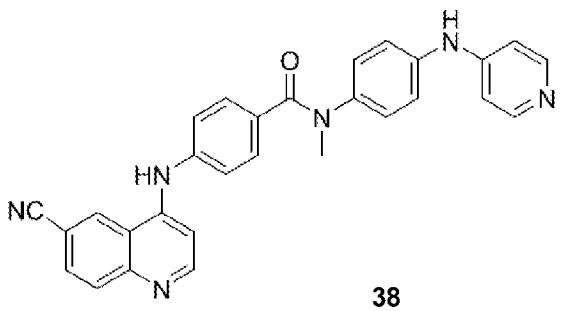
37



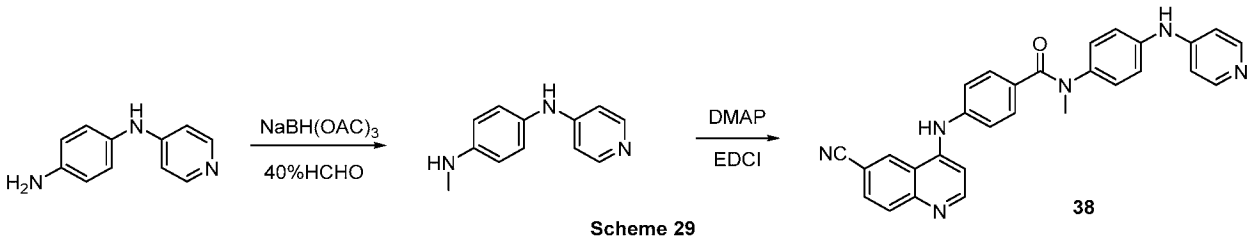
Scheme 28

[0508] **Compound 37** was prepared by the method shown in Scheme 28. **Compound 37** (N-(4-((6-cyanoquinolin-4-yl)amino)phenyl)-4-(pyridin-4-ylamino)benzamide) was prepared as shown in Scheme 28: $C_{28}H_{20}N_6O$; 456.51 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 457 $[M+H]^+$; LCMS RT = 1.39 min, >95.00% (214 nm).

Example 38: Compound 38 (4-((6-cyanoquinolin-4-yl)amino)-N-methyl-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



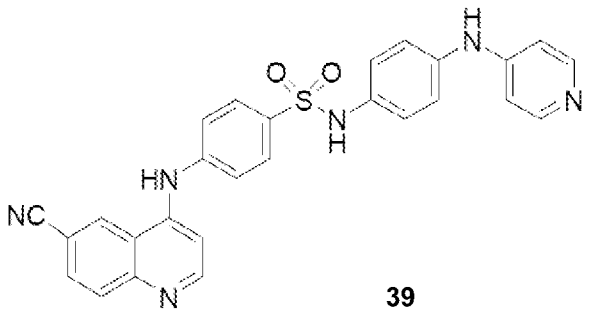
38



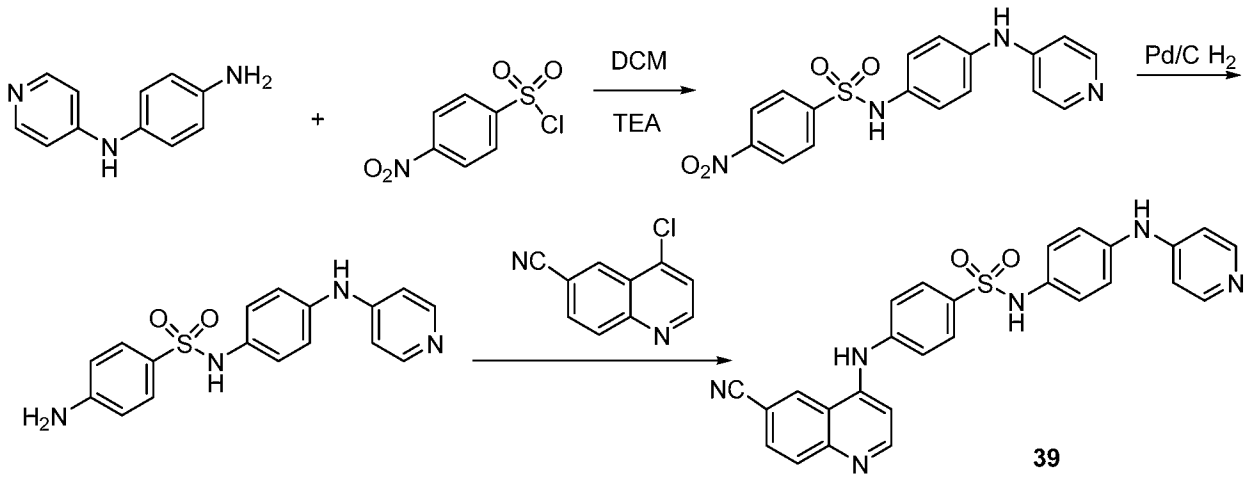
Scheme 29

[0509] **Compound 38** was prepared by the method shown in Scheme 29. **Compound 38** (4-((6-cyanoquinolin-4-yl)amino)-N-methyl-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Scheme 29: $C_{29}H_{22}N_6O$; 470.54 g/mol; 14 mg; pale yellow solid; ESI-LCMS m/z = 471 $[M+H]^+$; LCMS RT = 1.36 min, >95.00% (214 nm).

Example 39: Compound 39 (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzenesulfonamide)



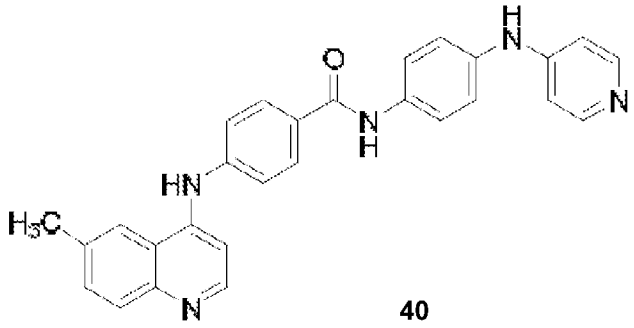
39



Scheme 30

[0510] **Compound 39** was prepared by the method shown in Scheme 30. **Compound 39** (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzenesulfonamide) was prepared as shown in Scheme 30: $C_{27}H_{20}N_6O_2S$; 492.56 g/mol; 16 mg; pale yellow solid; ESI-LCMS m/z = 493 $[M+H]^+$; LCMS RT = 0.96 min, >95.00% (214 nm).

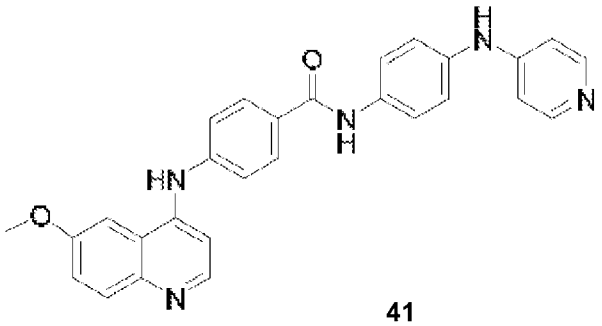
Example 40: Compound 40 (4-((6-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide)



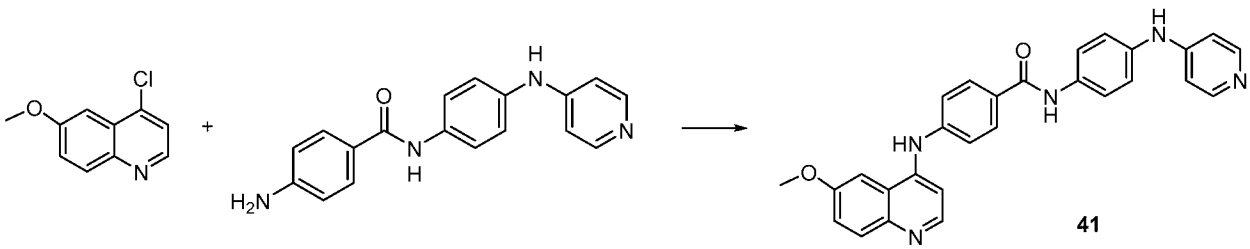
40

[0511] **Compound 40** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 40** (4-((6-methylquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide): $C_{28}H_{23}N_5O$; 445.53 g/mol; 13 mg; pale yellow solid; ESI-LCMS m/z = 446 $[M+H]^+$; LCMS RT = 1.44 min, >95.00% (214 nm).

Example 41: Compound 41 (4-((6-methoxyquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



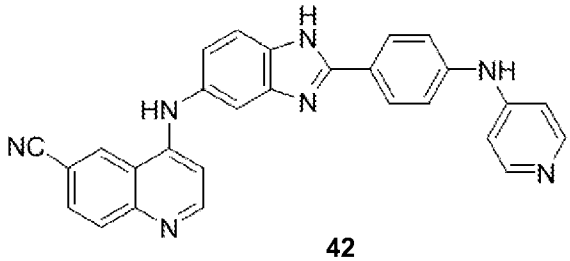
41



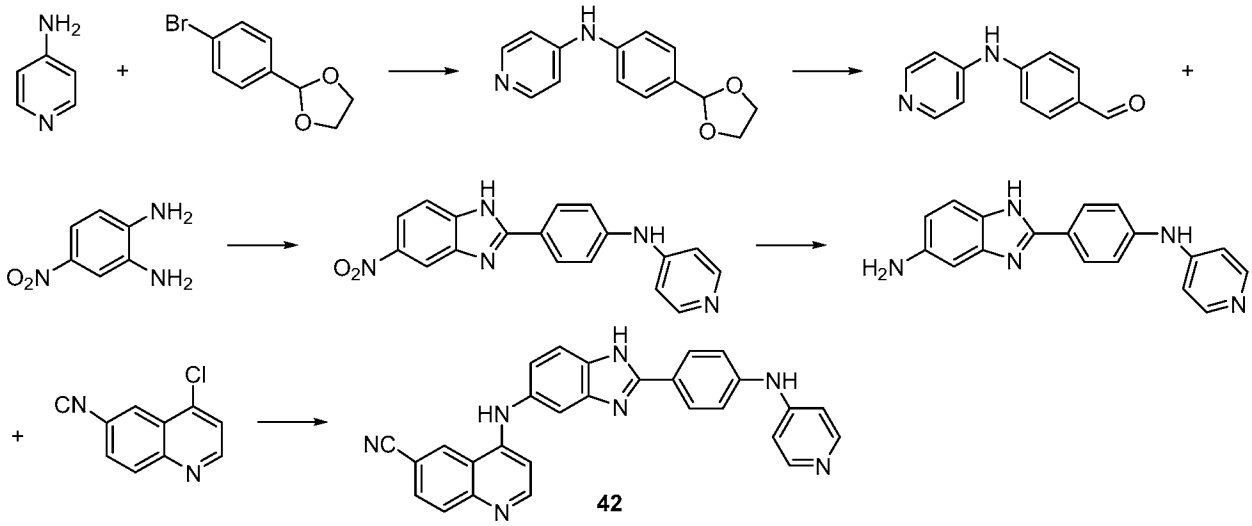
Scheme 31

[0512] **Compound 41** was prepared by the method shown in Scheme 31. **Compound 41** (4-((6-methoxyquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Scheme 31: $C_{28}H_{23}N_5O_2$; 461.53 g/mol; 16 mg; pale yellow solid; ESI-LCMS m/z = 462 $[M+H]^+$; LCMS RT = 1.40 min, >95.00% (214 nm).

Example 42: Compound 42 (4-((2-(4-(pyridin-4-ylamino)phenyl)-1H-benzo[d]imidazol-5-yl)amino)quinoline-6-carbonitrile)



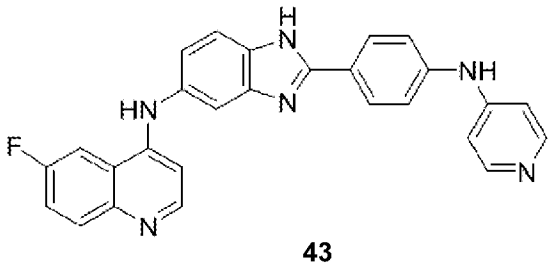
42



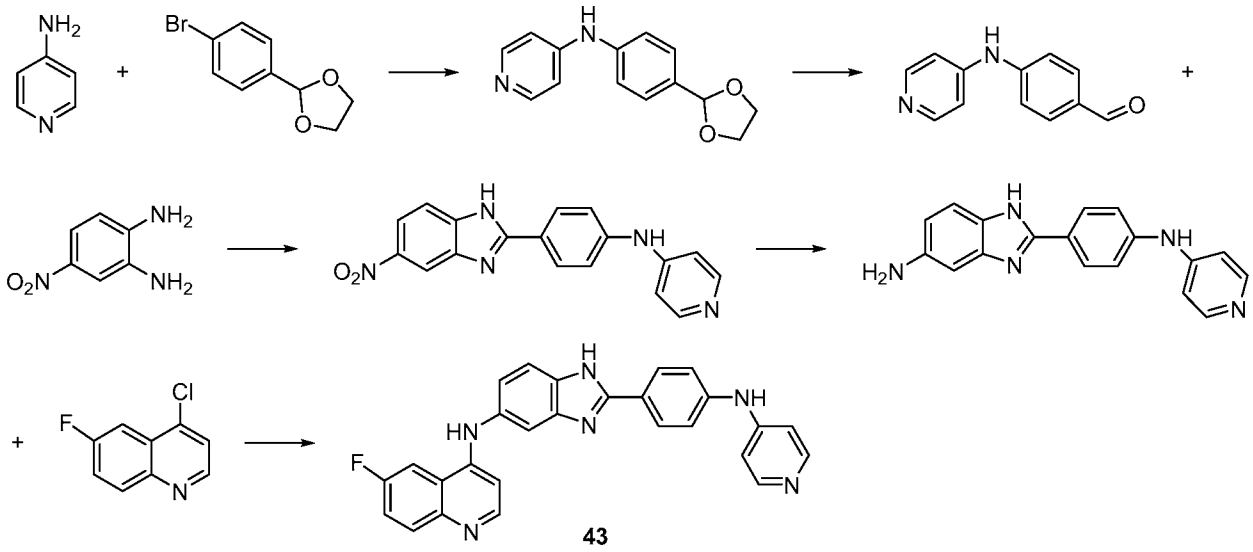
Scheme 32

[0513] **Compound 42** was prepared by the method shown in Scheme 32. **Compound 42** (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 43: Compound 43 (6-fluoro-N-(2-(4-(pyridin-4-ylamino)phenyl)-1H-benzo[d]imidazol-5-yl)quinolin-4-amine)



43

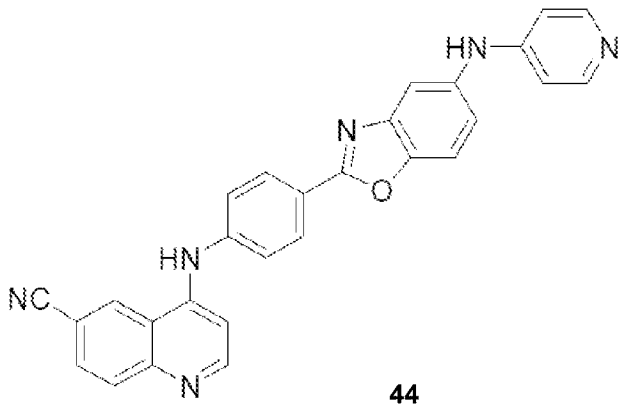


43

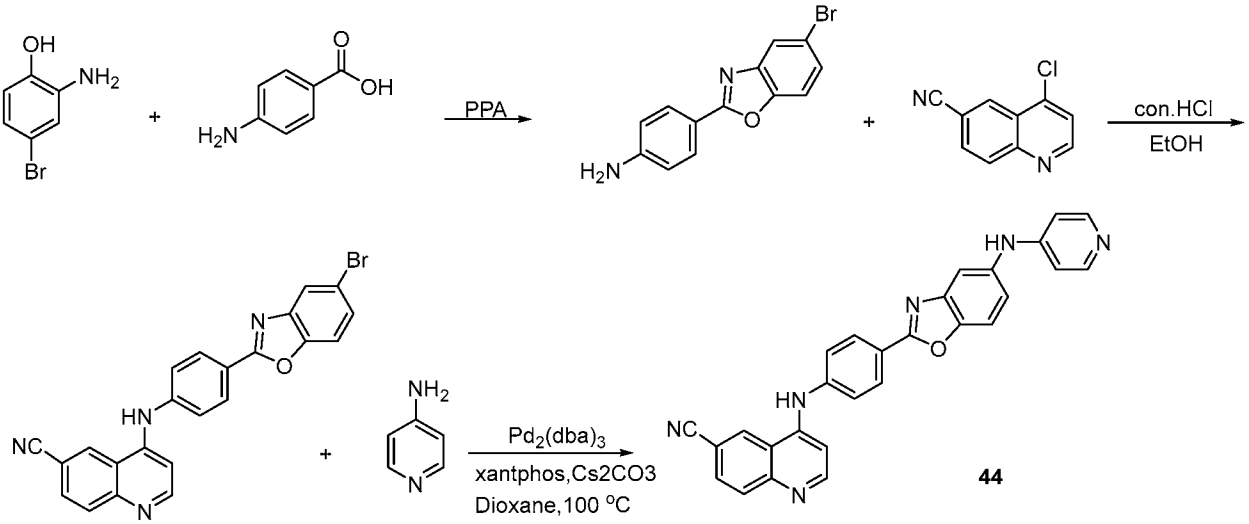
Scheme 33

[0514] **Compound 43** was prepared by the method shown in Scheme 33. **Compound 43** (6-fluoro-N-(2-(4-(pyridin-4-ylamino)phenyl)-1H-benzo[d]i midazol-5-yl)quinolin-4-amine) was prepared as shown in Scheme 33: $C_{27}H_{19}FN_6$; 446.49 g/mol; 13 mg; pale yellow solid; ESI-LCMS m/z = 447 $[M+H]^+$; LCMS RT = 1.38 min, >95.00% (214 nm).

Example 44: Compound 44 (4-(4-(5-(pyridin-4-ylamino)benzo[d]oxazol-2-yl)phenylamino)quinoline-6-carbonitrile)



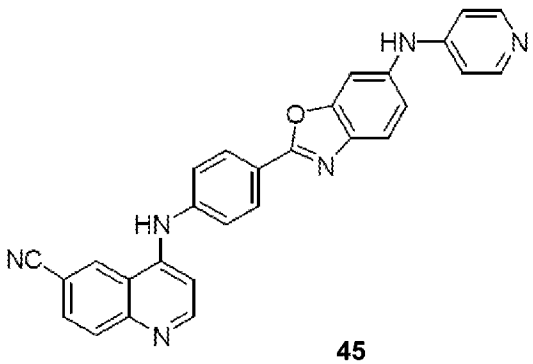
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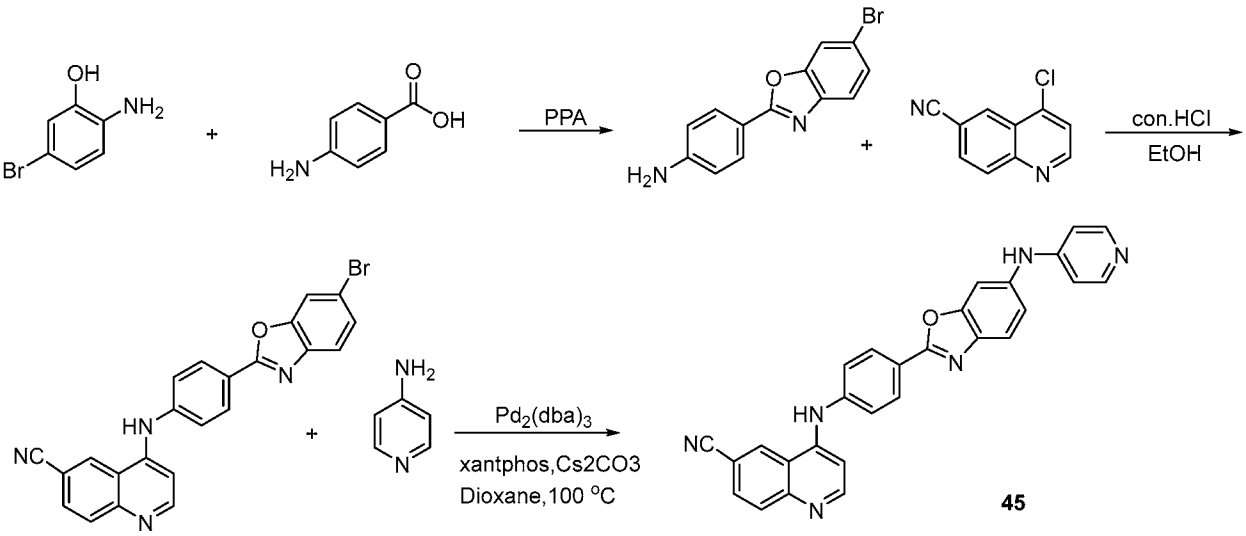
Scheme 34

[0515] **Compound 44** was prepared by the method shown Scheme 34. **Compound 44** (4-(4-(5-(pyridin-4-ylamino)benzo[d]oxazol-2-yl)phenylamino)quinoline-6-carbonitrile) was prepared as shown in Scheme 34: $C_{28}H_{18}N_6O$; 454.48 g/mol; 12 mg; yellow solid; ESI-LCMS m/z = 455 $[M+H]^+$; LCMS RT = 1.88 min, >95.00% (214 nm).

Example 45: Compound 45 (4-(4-(6-(pyridin-4-ylamino)benzo[d]oxazol-2-yl)phenylamino)quinoline-6-carbonitrile)



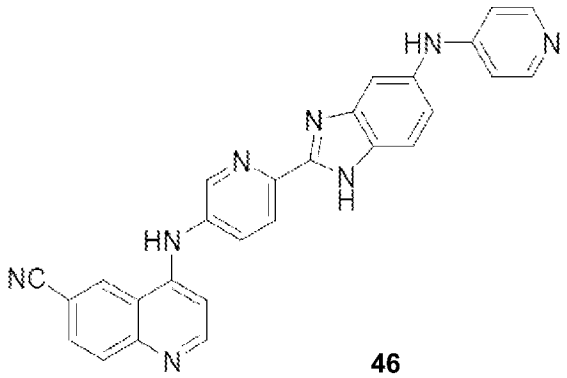
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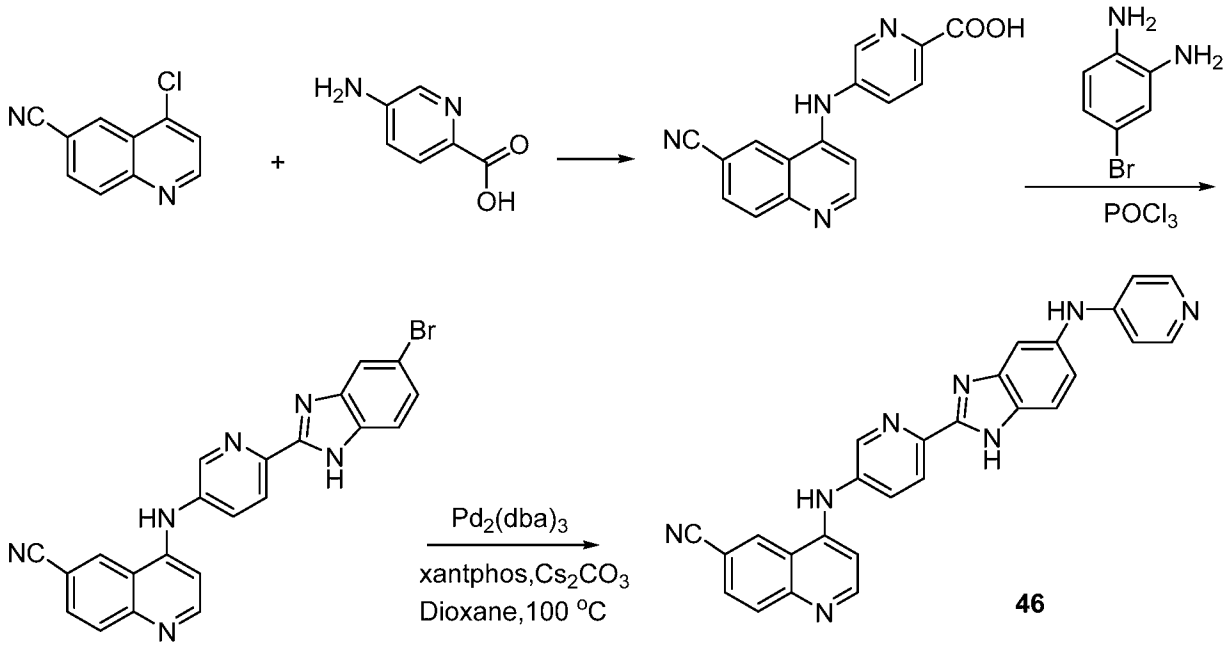


Scheme 35

[0516] **Compound 45** was prepared by the method shown in Scheme 35. **Compound 45** (4-(4-(6-(pyridin-4-ylamino)benzo[d]oxazol-2-yl)phenylamino)quinoline-6-carbonitrile) was prepared as shown in Scheme 35: $C_{28}H_{18}N_6O$; 454.48 g/mol; 14 mg; yellow solid; ESI-LCMS m/z = 455 $[M+H]^+$; LCMS RT = 1.85 min, >95.00% (214 nm).

Example 46: Compound 46 (4-(6-(5-(pyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-3-ylamino)quinoline-6-carbonitrile)

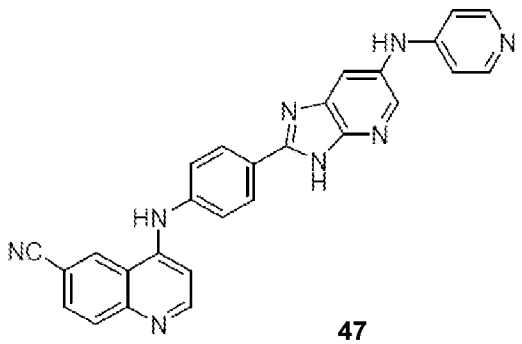




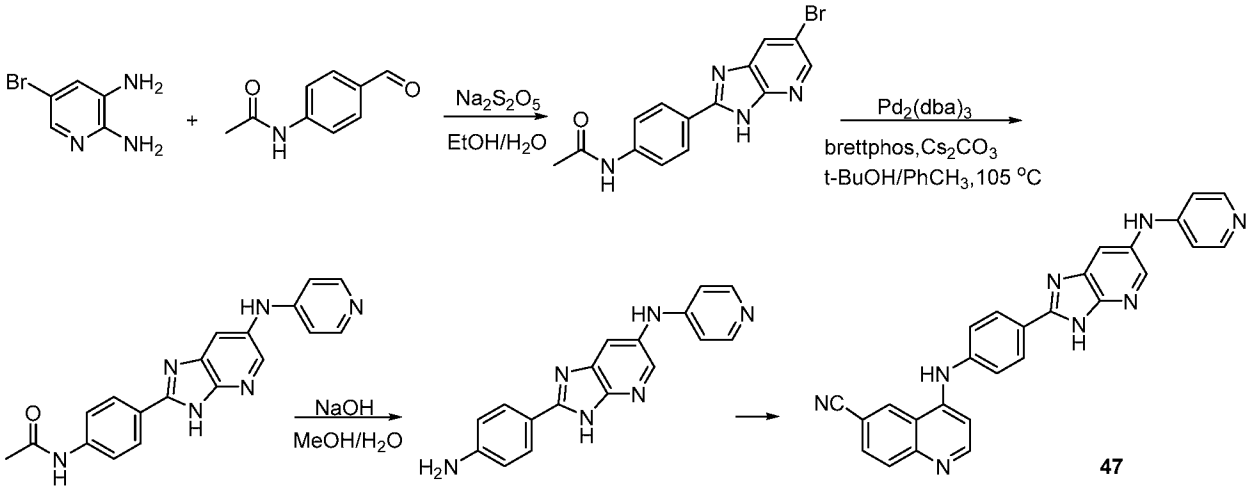
Scheme 36

[0517] **Compound 46** was prepared by the method shown in Scheme 36. **Compound 46** (4-(6-(5-(pyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-3-ylamino)quinoline-6-carbonitrile) was prepared as shown in Scheme 36: $C_{27}H_{18}N_8$; 454.49 g/mol; 12 mg; yellow solid; ESI-LCMS m/z = 455 $[M+H]^+$; LCMS RT = 1.41 min, >95.00% (214 nm).

Example 47: Compound 47 (4-(4-(6-(pyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl) phenylamino)quinoline-6-carbonitrile)



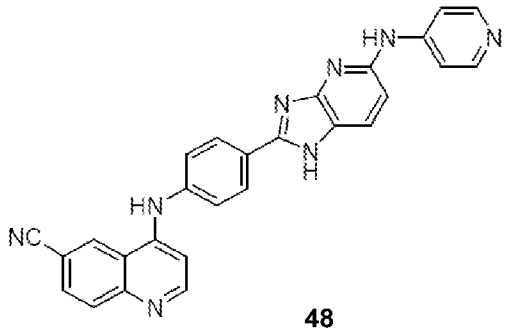
47



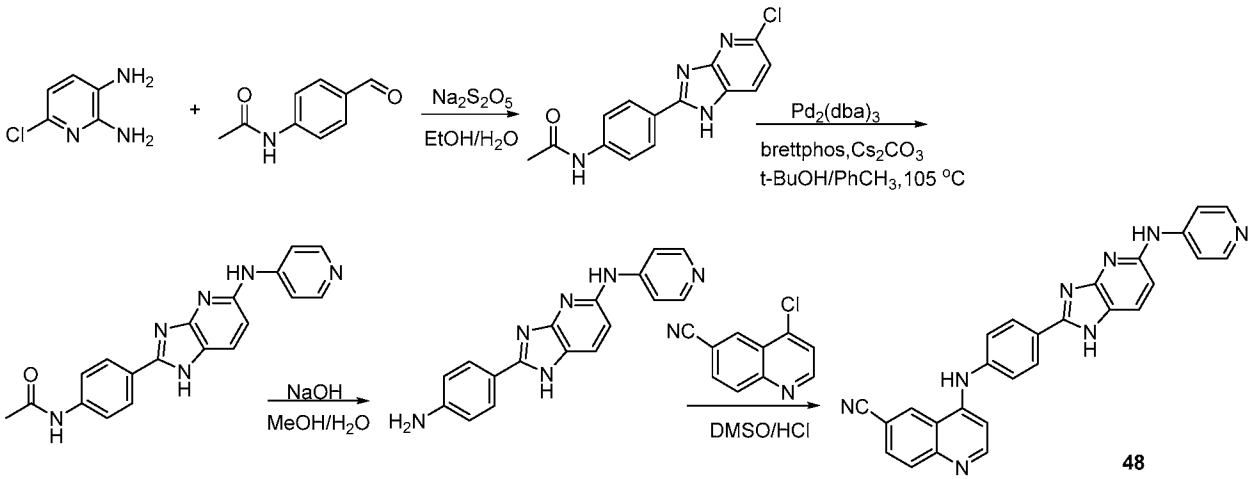
Scheme 37

[0518] **Compound 47** was prepared by the method shown in Scheme 37. **Compound 47** (4-(4-(6-(pyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl) phenylamino)quinoline-6-carbonitrile) was prepared as shown in Scheme 37: $C_{27}H_{18}N_8$; 454.49 g/mol; 12 mg; yellow solid; ESI-LCMS m/z = 455 $[M+H]^+$; LCMS RT = 1.66 min, >95.00% (214 nm).

Example 48: Compound 48 (4-(4-(5-(pyridin-4-ylamino)-1H-imidazo[4,5-b]pyridin-2-yl) phenylamino)quinoline-6-carbonitrile)



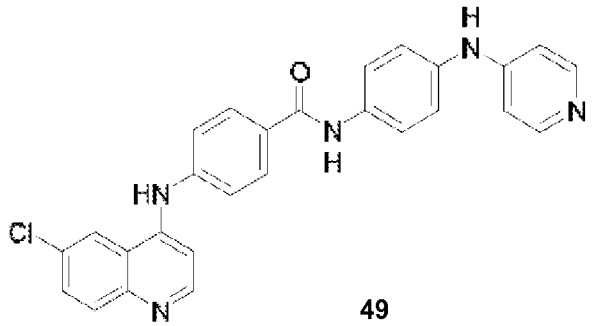
48



Scheme 38

[0519] **Compound 48** was prepared by the method shown in Scheme 38. **Compound 48** (4-(4-(5-(pyridin-4-ylamino)-1H-imidazo[4,5-b]pyridin-2-yl) phenylamino)quinoline-6-carbonitrile) was prepared as shown in Scheme 38: $C_{27}H_{18}N_8$; 454.49 g/mol; 11 mg; yellow solid; ESI-LCMS m/z = 455 $[M+H]^+$; LCMS RT = 1.66 min, >95.00% (214 nm).

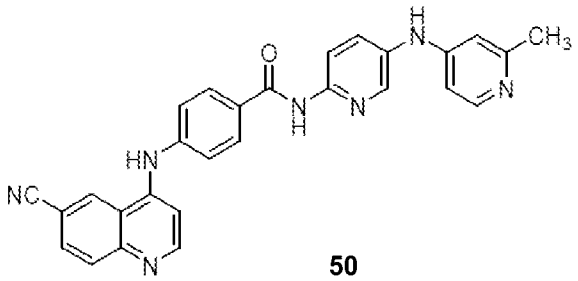
Example 49: Compound 49 (4-((6-chloroquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide)



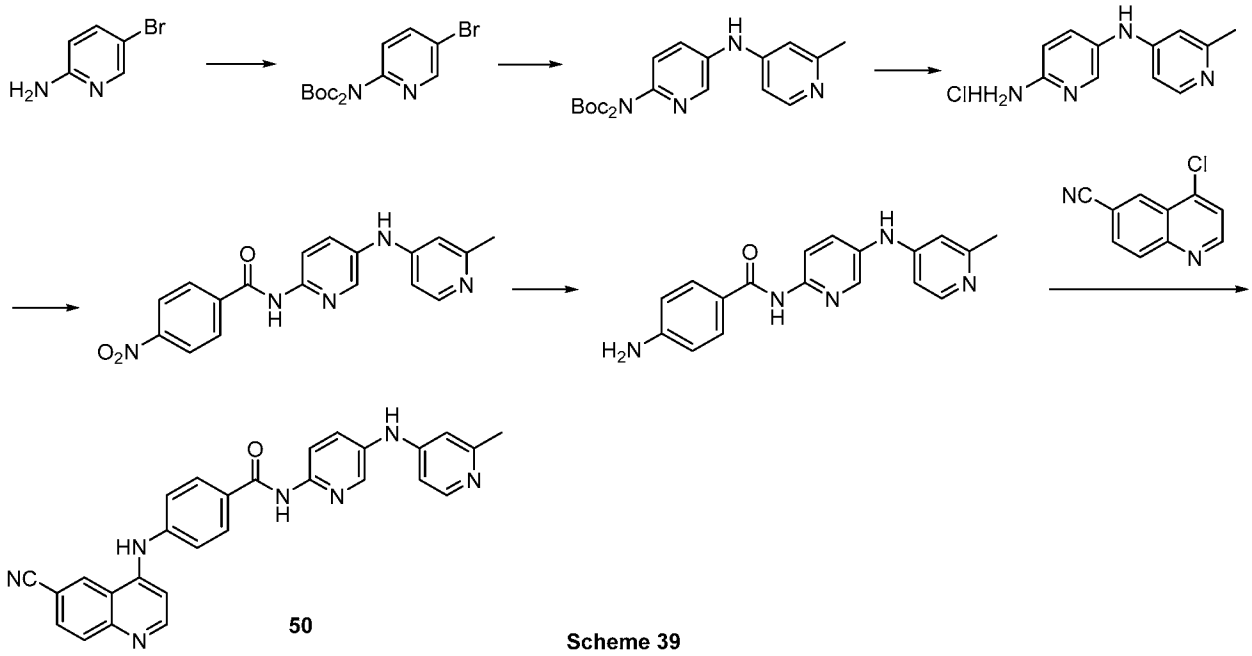
49

[0520] **Compound 49** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 49** (4-((6-chloroquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino) phenyl)benzamide): $C_{27}H_{20}ClN_5O$; 465.94 g/mol; 17 mg; pale yellow solid; ESI-LCMS m/z = 466 $[M+H]^+$; LCMS RT = 1.49 min, >95.00% (214 nm).

Example 50: Compound 50 (4-(6-cyanoquinolin-4-ylamino)-N-(5-(2-methylpyridin-4-yl amino)pyridin-2-yl)benzamide)



50

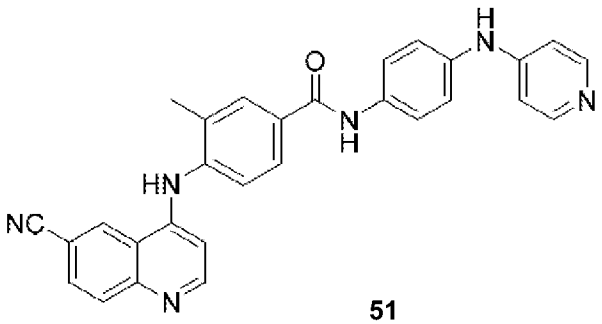


50

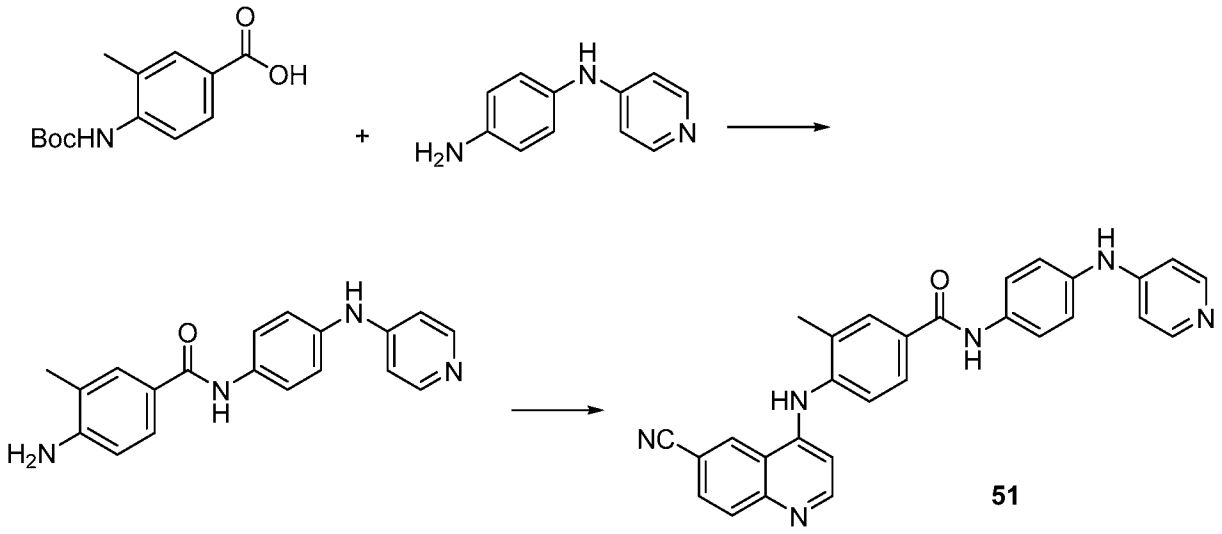
Scheme 39

[0521] **Compound 50** was prepared by the method shown in Scheme 39. **Compound 50** (4-(6-cyanoquinolin-4-ylamino)-N-(5-(2-methylpyridin-4-yl amino)pyridin-2-yl)benzamide) was prepared as shown in Scheme 39: $C_{28}H_{21}N_7O$; 471.51 g/mol; 25 mg; pale yellow solid; ESI-LCMS m/z = 472 $[M+H]^+$; LCMS RT = 1.38 min, >95.00% (214 nm).

Example 51: Compound 51 (4-((6-cyanoquinolin-4-yl)amino)-3-methyl-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



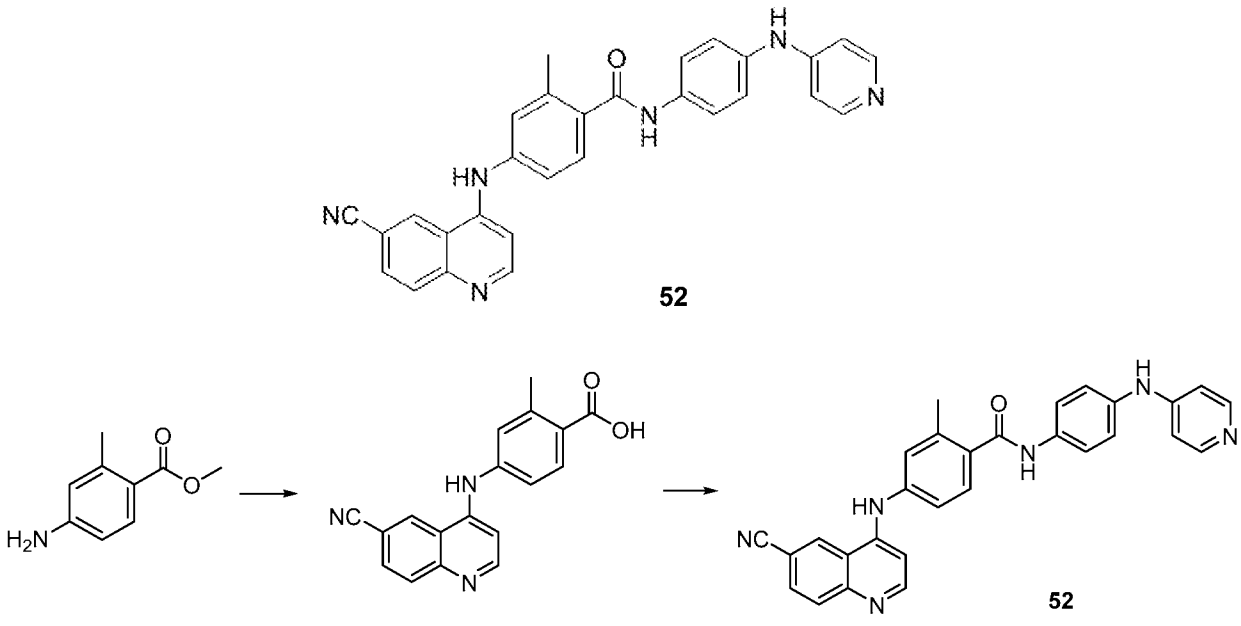
51



Scheme 40

[0522] **Compound 51** was prepared by the method shown in Scheme 40. **Compound 51** (4-((6-cyanoquinolin-4-yl)amino)-3-methyl-N-(4-(pyridin-4- ylamino)phenyl)benzamide) was prepared as shown in Scheme 40: $C_{29}H_{22}N_6O$; 470.54 g/mol; 15 mg; pale yellow solid; ESI-LCMS m/z = 471 $[M+H]^+$; LCMS RT = 1.39 min, >95.00% (214 nm).

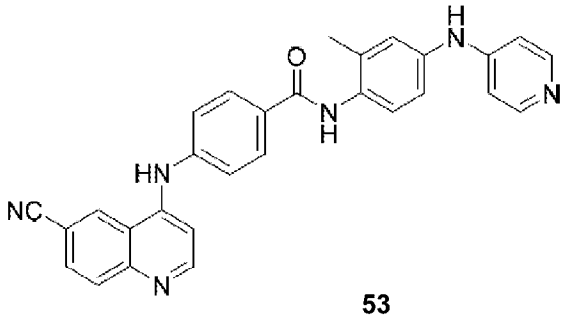
Example 52: Compound 52 (4-((6-cyanoquinolin-4-yl)amino)-2-methyl-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



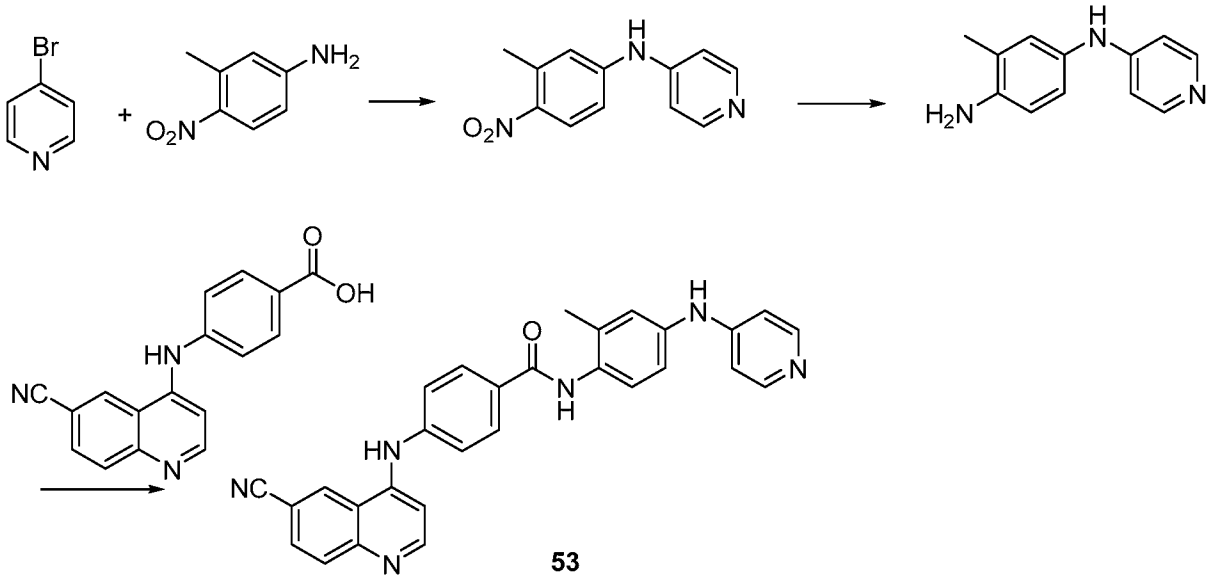
Scheme 41

[0523] **Compound 52** was prepared by the method shown in Scheme 41. **Compound 52** (4-((6-cyanoquinolin-4-yl)amino)-2-methyl-N-(4-(pyridin-4- ylamino)phenyl)benzamide) was prepared as shown in Scheme 41: $C_{29}H_{22}N_6O$; 470.54 g/mol; 20 mg; pale yellow solid; ESI-LCMS m/z = 471 $[M+H]^+$; LCMS RT = 1.49 min, >95.00% (214 nm).

Example 53: Compound 53 (4-((6-cyanoquinolin-4-yl)amino)-N-(2-methyl-4-(pyridin-4-ylamino)phenyl)benzamide)



53

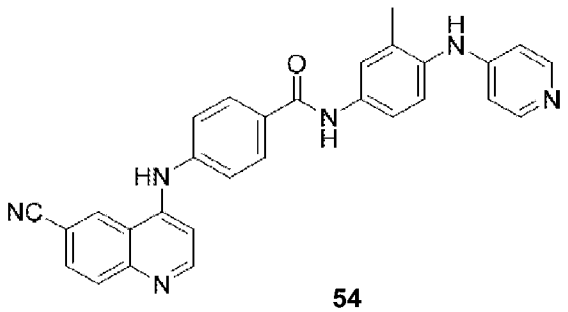


53

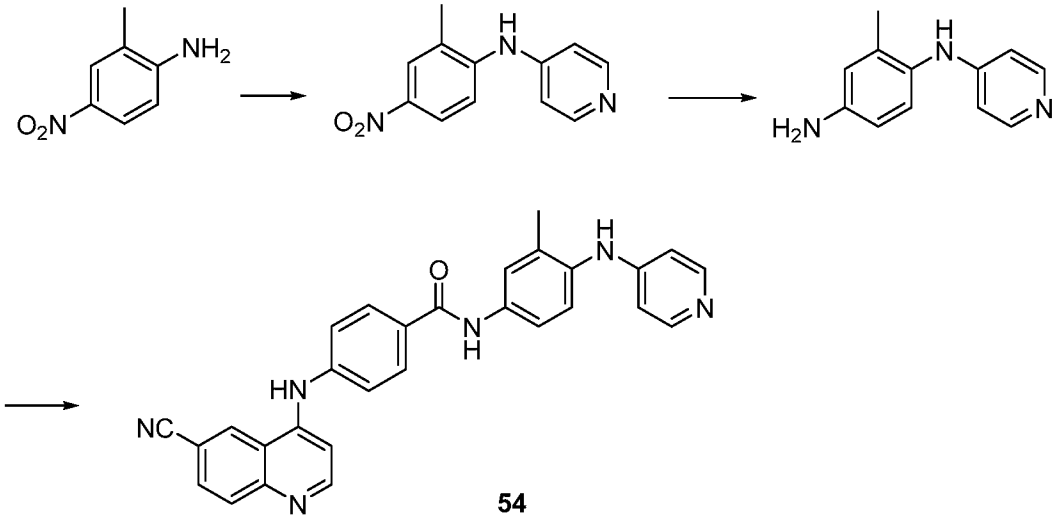
Scheme 42

[0524] **Compound 53** was prepared by the method shown in Scheme 42. **Compound 53** (4-((6-cyanoquinolin-4-yl)amino)-N-(2-methyl-4-(pyridin-4- ylamino)phenyl)benzamide) was prepared as shown in Scheme 42: $C_{29}H_{22}N_6O$; 470.54 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 471 $[M+H]^+$; LCMS RT = 1.37 min, >95.00% (214 nm).

Example 54: Compound 54 (4-((6-cyanoquinolin-4-yl)amino)-N-(3-methyl-4-(pyridin-4-ylamino)phenyl)benzamide)



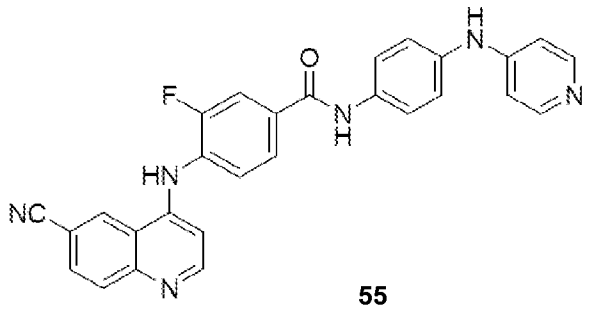
54

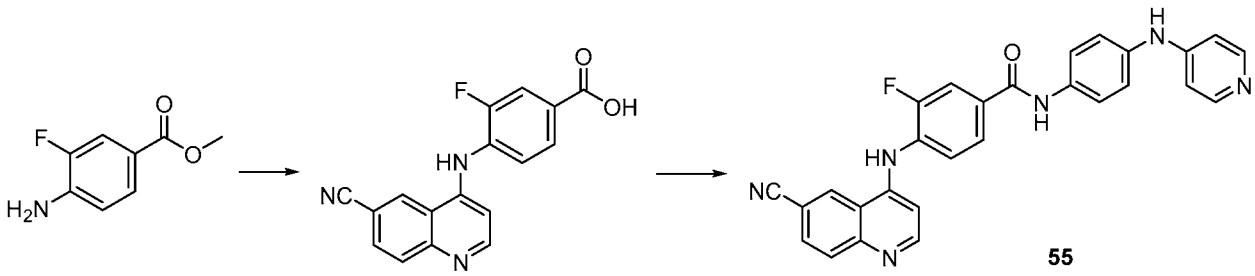


Scheme 43

[0525] **Compound 54** was prepared by the method shown in Scheme 43. **Compound 54** (4-((6-cyanoquinolin-4-yl)amino)-N-(3-methyl-4-(pyridin-4- ylamino)phenyl)benzamide) was prepared as shown in Scheme 43: $C_{29}H_{22}N_6O$; 470.54 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 471 $[M+H]^+$; LCMS RT = 1.39 min, >95.00% (214 nm).

Example 55: Compound 55 (4-(6-cyanoquinolin-4-ylamino)-3-fluoro-N-(4-(pyridin-4-yl amino)phenyl)benzamide)

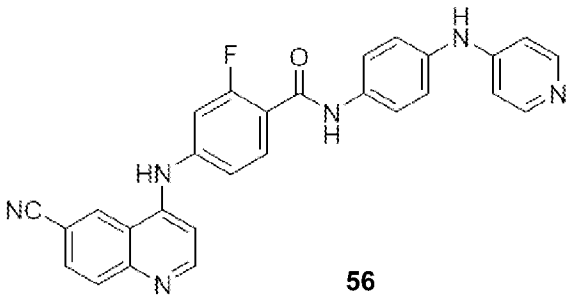




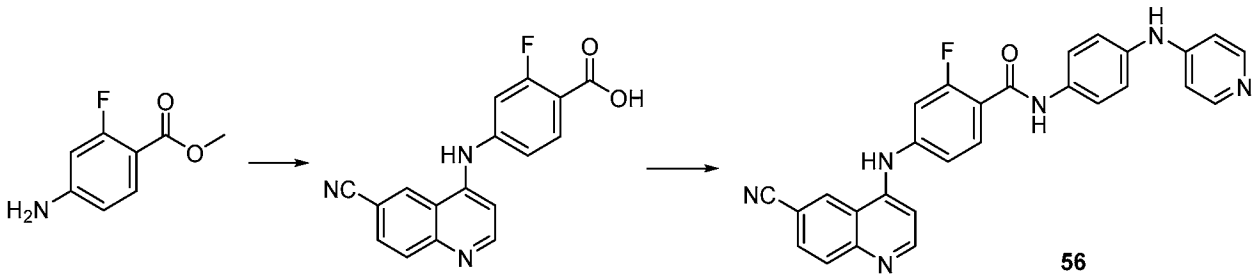
Scheme 44

[0526] **Compound 55** was prepared by the method shown in Scheme 44. **Compound 55** (4-(6-cyanoquinolin-4-ylamino)-3-fluoro-N-(4-(pyridin-4-yl amino)phenyl)benzamide) was prepared as shown in Scheme 44: $C_{28}H_{19}FN_6O$; 474.49 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 475 $[M+H]^+$; LCMS RT = 1.40 min, >95.00% (214 nm).

Example 56: Compound 56 (4-(6-cyanoquinolin-4-ylamino)-2-fluoro-N-(4-(pyridin-4-yl amino)phenyl)benzamide)



56

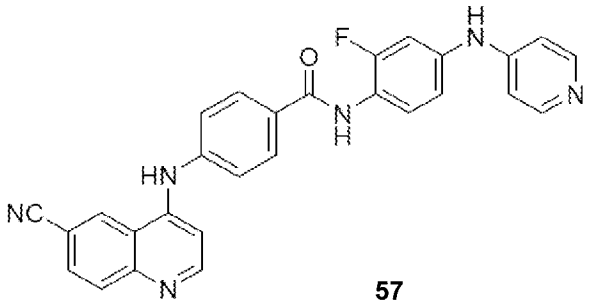


56

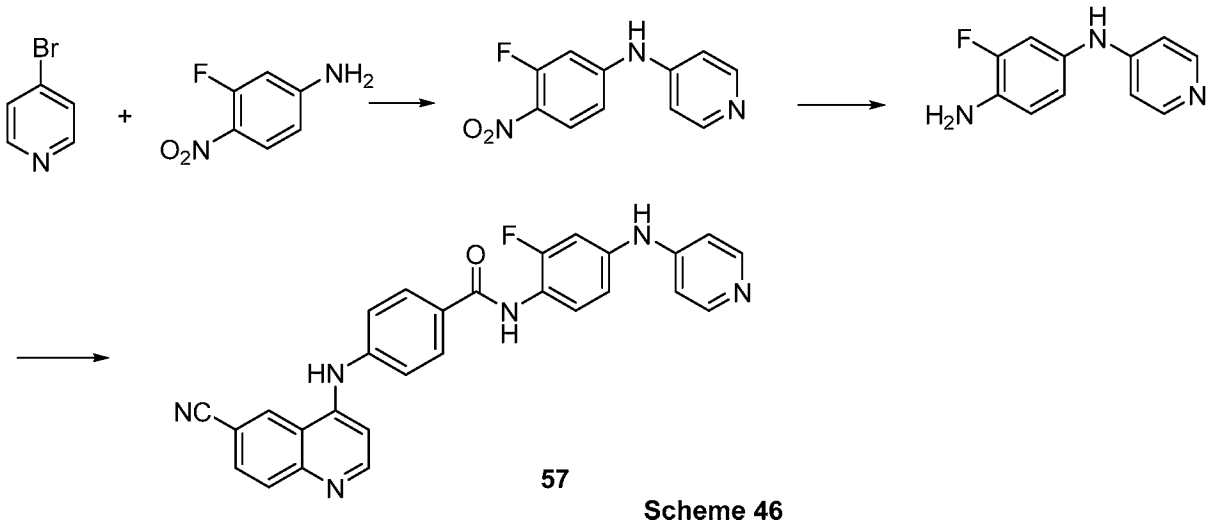
Scheme 45

[0527] **Compound 56** was prepared by the method shown in Scheme 45. **Compound 56** (4-(6-cyanoquinolin-4-ylamino)-2-fluoro-N-(4-(pyridin-4-yl amino)phenyl)benzamide) was prepared as shown in Scheme 45: $C_{28}H_{19}FN_6O$; 474.49 g/mol; 13 mg; pale yellow solid; ESI-LCMS m/z = 475 $[M+H]^+$; LCMS RT = 1.36 min, >95.00% (214 nm).

Example 57: Compound 57 (4-(6-cyanoquinolin-4-ylamino)-N-(2-fluoro-4-(pyridin-4-yl amino)phenyl)benzamide)



57

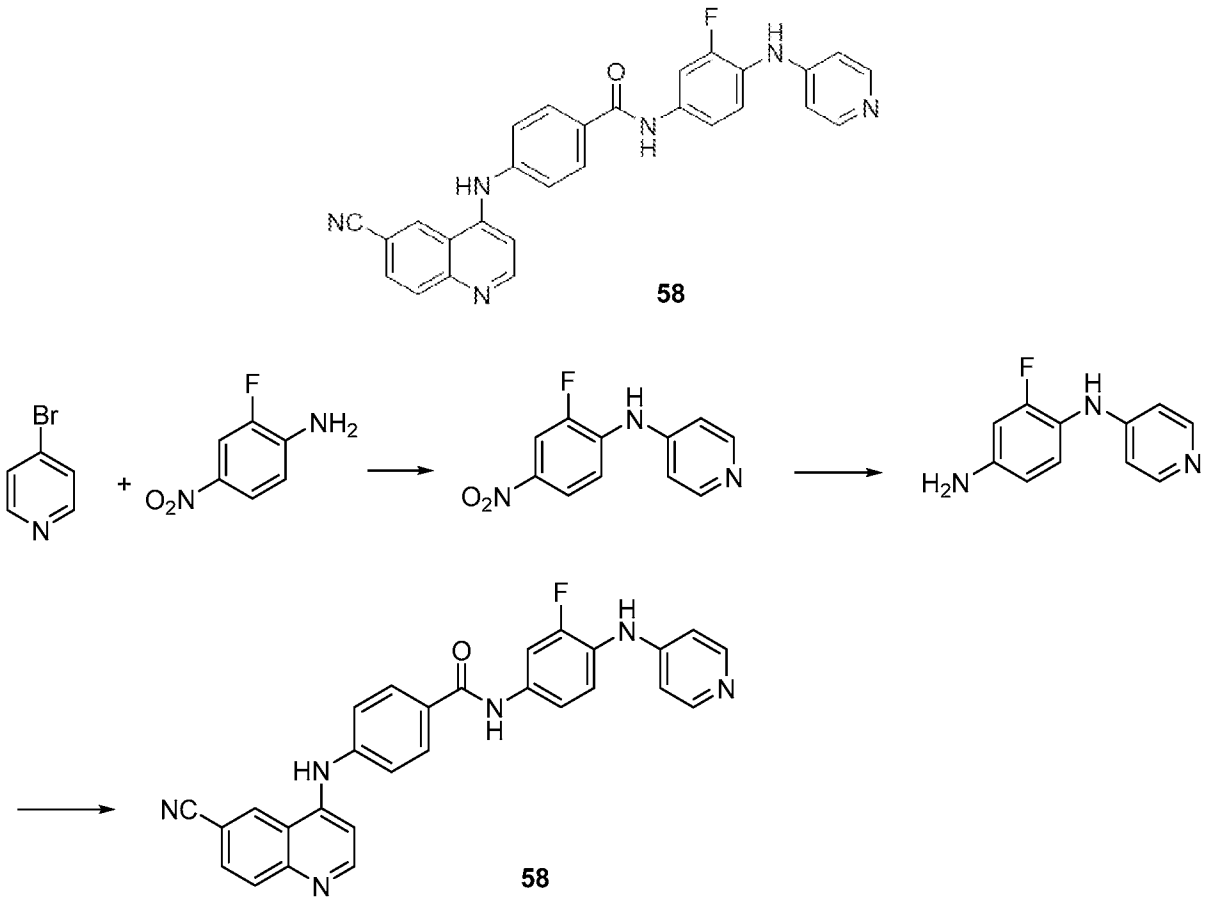


57

Scheme 46

[0528] **Compound 57** was prepared by the method shown in Scheme 46. **Compound 57** (4-(6-cyanoquinolin-4-ylamino)-N-(2-fluoro-4-(pyridin-4-yl amino)phenyl)benzamide) was prepared as shown in Scheme 46: $C_{28}H_{19}FN_6O$; 474.49 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 475 $[M+H]^+$; LCMS RT = 1.36 min, >95.00% (214 nm).

Example 58: Compound 58 (4-(6-cyanoquinolin-4-ylamino)-N-(3-fluoro-4-(pyridin-4-yl amino)phenyl)benzamide)



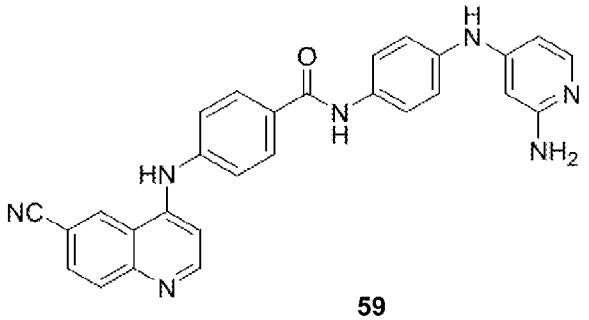
58

58

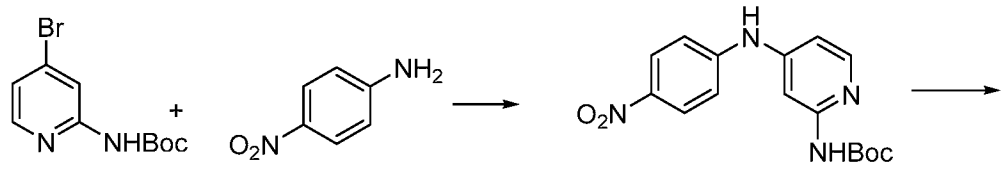
Scheme 47

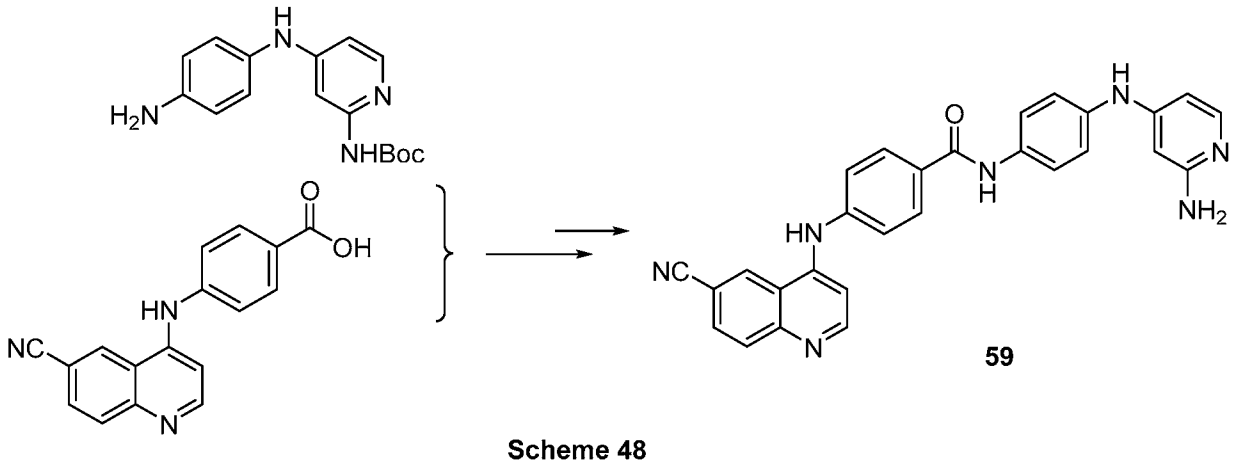
[0529] **Compound 58** was prepared by the method shown in Scheme 47. **Compound 58** (4-(6-cyanoquinolin-4-ylamino)-N-(3-fluoro-4-(pyridin-4-yl amino)phenyl)benzamide) was prepared as shown in Scheme 47: $C_{28}H_{19}FN_6O$; 474.49 g/mol; 14 mg; pale yellow solid; ESI-LCMS m/z = 475 $[M+H]^+$; LCMS RT = 1.38 min, >95.00% (214 nm).

Example 59: Compound 59 (N-(4-((2-aminopyridin-4-yl)amino)phenyl)-4-((6-cyanoquinolin-4-yl)amino)benzamide)



59



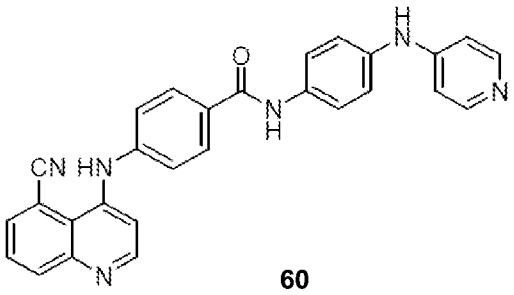


59

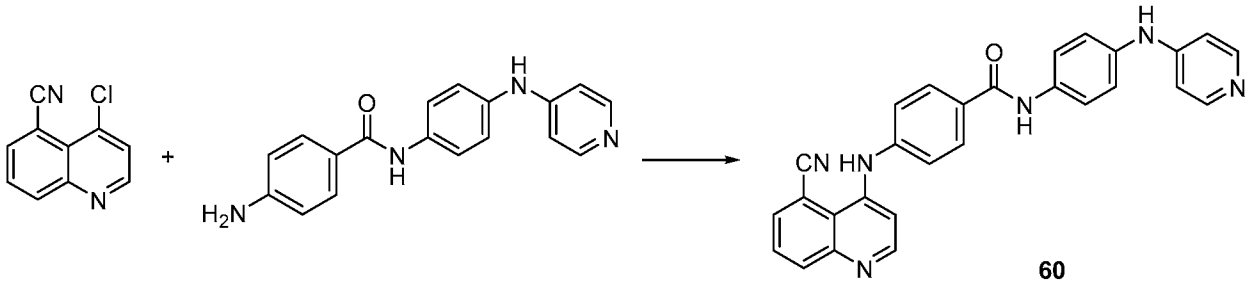
Scheme 48

[0530] **Compound 59** was prepared by the method shown in Scheme 48. **Compound 59** (N-(4-((2-aminopyridin-4-yl)amino)phenyl)-4-((6-cyanoquinolin-4-yl)amino)benzamide) was prepared as shown in Scheme 48: $C_{28}H_{21}N_7O$; 471.52 g/mol; 10 mg; pale yellow solid; ESI-LCMS m/z = 472 $[M+H]^+$; LCMS RT = 0.99 min, >95.00% (214 nm).

Example 60: Compound 60 (4-((5-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



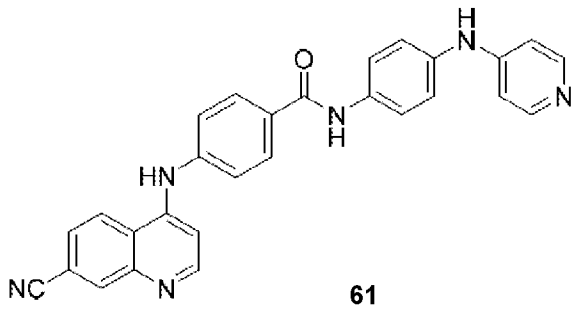
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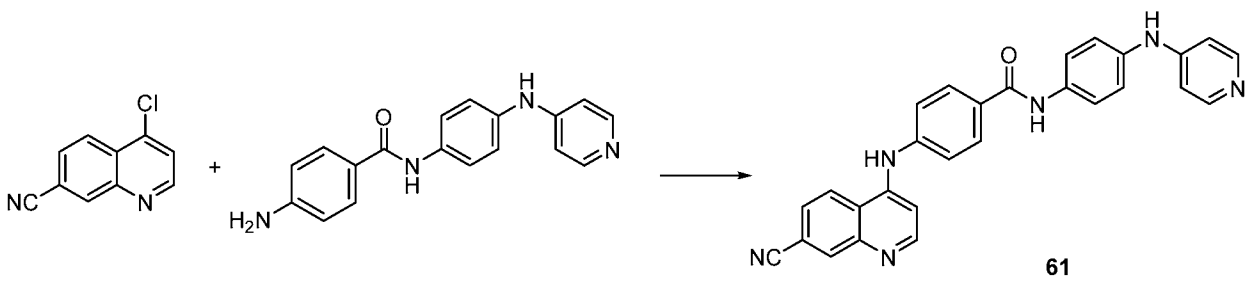
Scheme 49

[0531] **Compound 60** was prepared by the method shown in Scheme 49. **Compound 60** (4-((5-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Scheme 49: $C_{28}H_{20}N_6O$; 456.51 g/mol; 11 mg; yellow solid; ESI-LCMS m/z = 457 $[M+H]^+$; LCMS RT = 1.34 min, >95.00% (214 nm).

Example 61: Compound 61 (4-((7-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



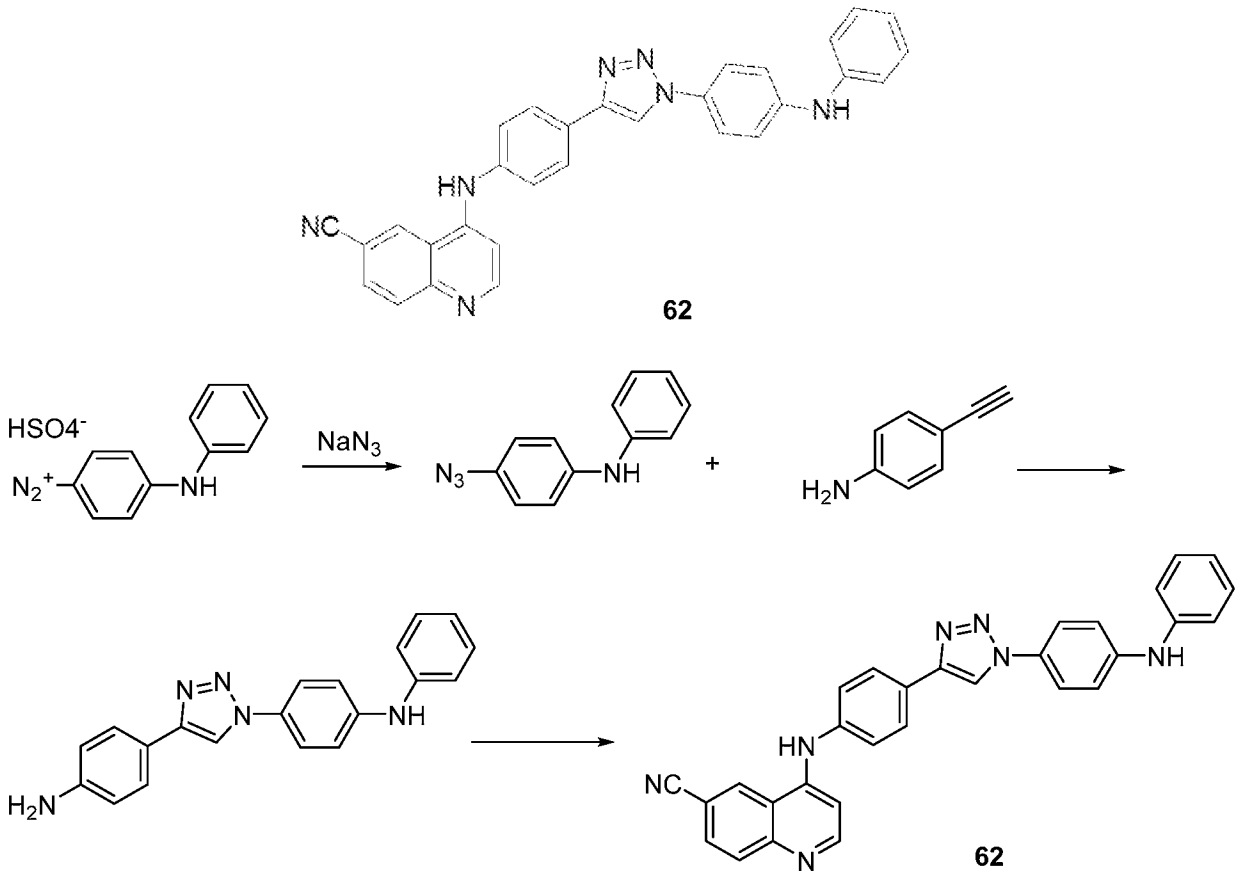
61



Scheme 50

[0532] **Compound 61** was prepared by the method shown in Scheme 50. **Compound 61** (4-((7-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Scheme 50: $C_{28}H_{20}N_6O$; 456.51 g/mol; 13 mg; pale yellow solid; ESI-LCMS m/z = 457 $[M+H]^+$; LCMS RT = 1.37 min, >95.00% (214 nm).

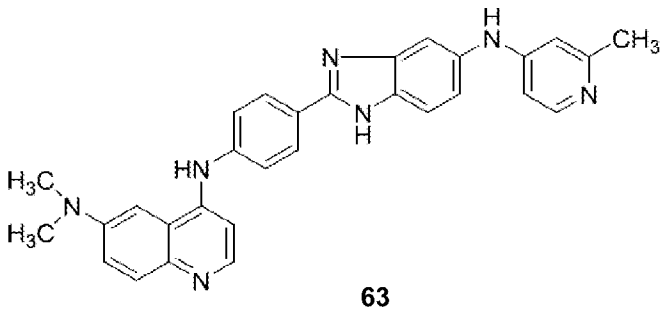
Example 62: Compound 62 (4-((4-(1-(4-(phenylamino)phenyl)-1H-1,2,3-triazol-4-yl)phenyl)amino)quinoline-6-carbonitrile)



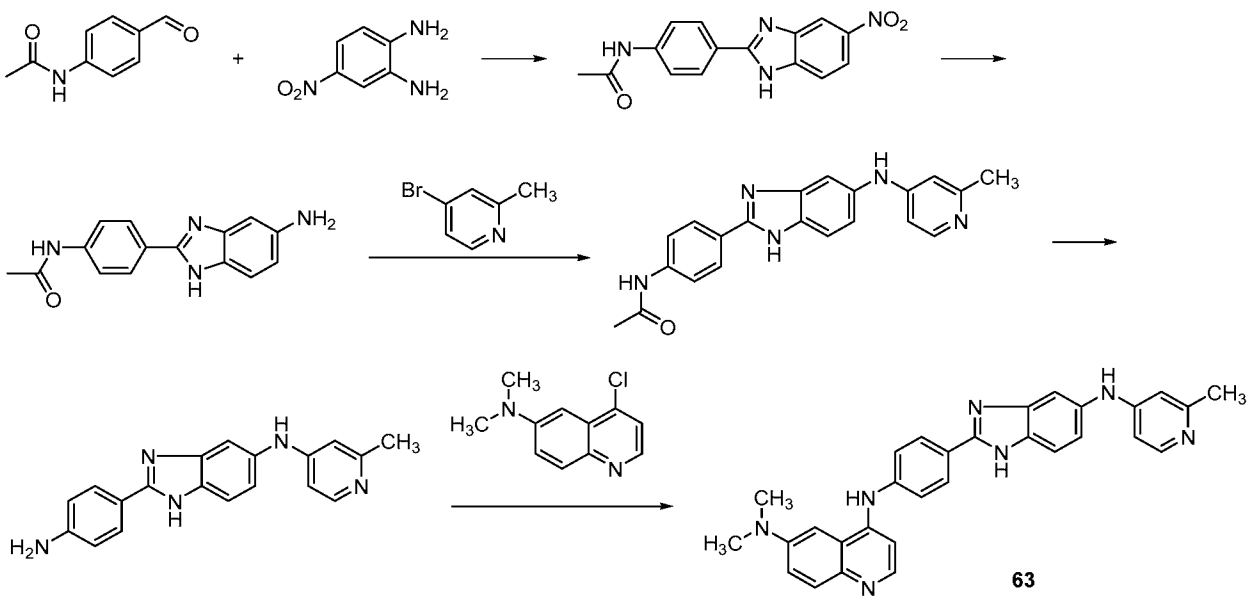
Scheme 51

[0533] **Compound 62** was prepared by the method shown in Scheme 51. **Compound 62** (4-((4-(1-(4-(phenylamino)phenyl)-1H-1,2,3-triazol-4-yl)phenyl)amino)quinoline-6-carbonitrile) was prepared as shown in Scheme 51: $C_{30}H_{21}N_7$; 479.55 g/mol; 13 mg; yellow solid; ESI-LCMS m/z = 480 $[M+H]^+$; LCMS RT = 1.70 min, >95.00% (214 nm).

Example 63: Compound 63 (N^6,N^6-dimethyl-N^4-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinoline-4,6-diamine)



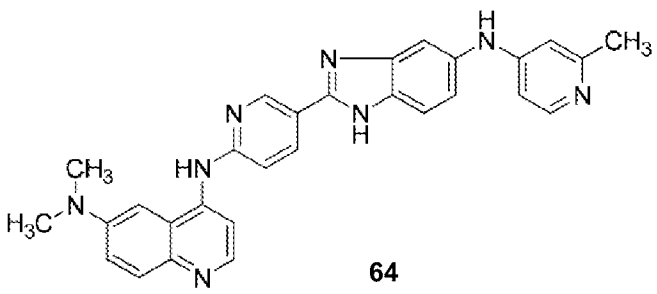
63



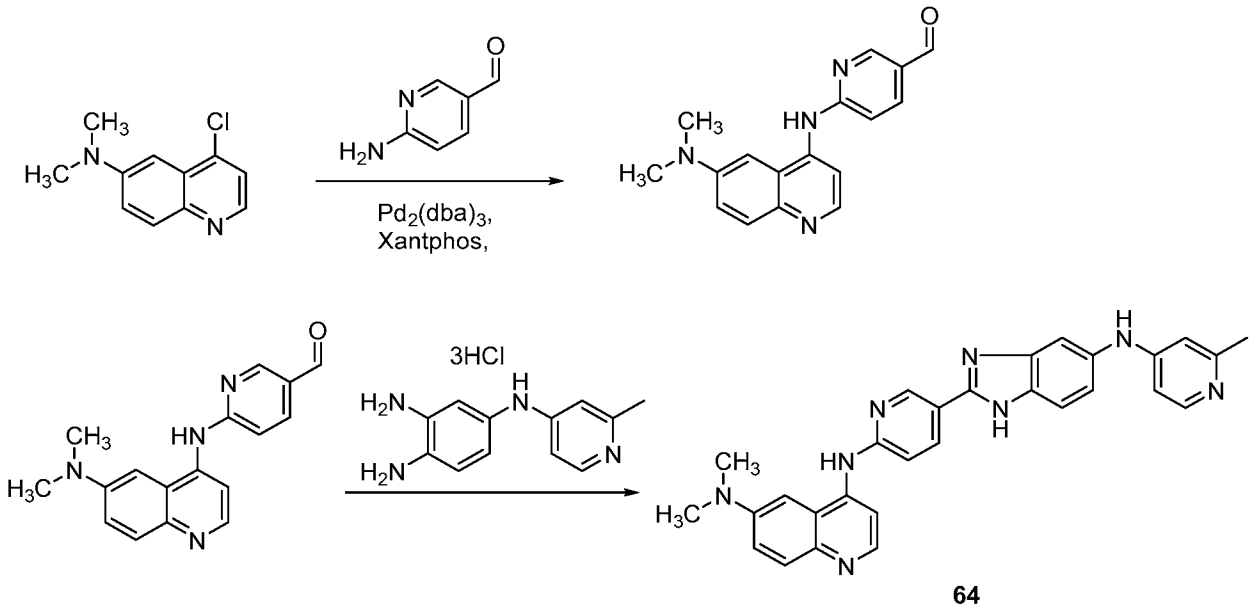
Scheme 52

[0534] **Compound 63** was prepared by the method shown in Scheme 52. **Compound 63** (N^6,N^6-dimethyl-N^4-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinoline-4,6-diamine) was prepared as shown in Scheme 52: $C_{30}H_{27}N_7$; 485.60 g/mol; 10 mg; yellow solid; ESI-LCMS m/z = 486 $[M+H]^+$; LCMS RT = 1.58 min, >95.00% (214 nm).

Example 64: Compound 64 (N^6,N^6-dimethyl-N^4-(5-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)quinoline-4,6-diamine)



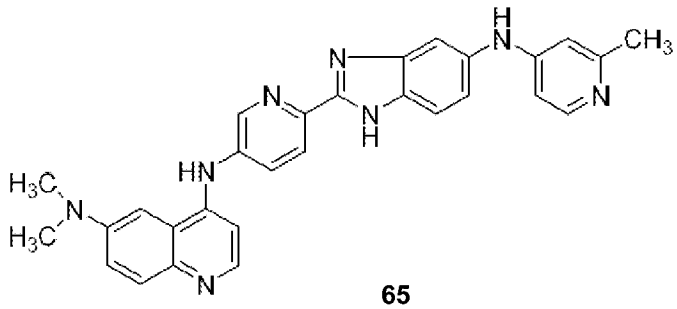
64



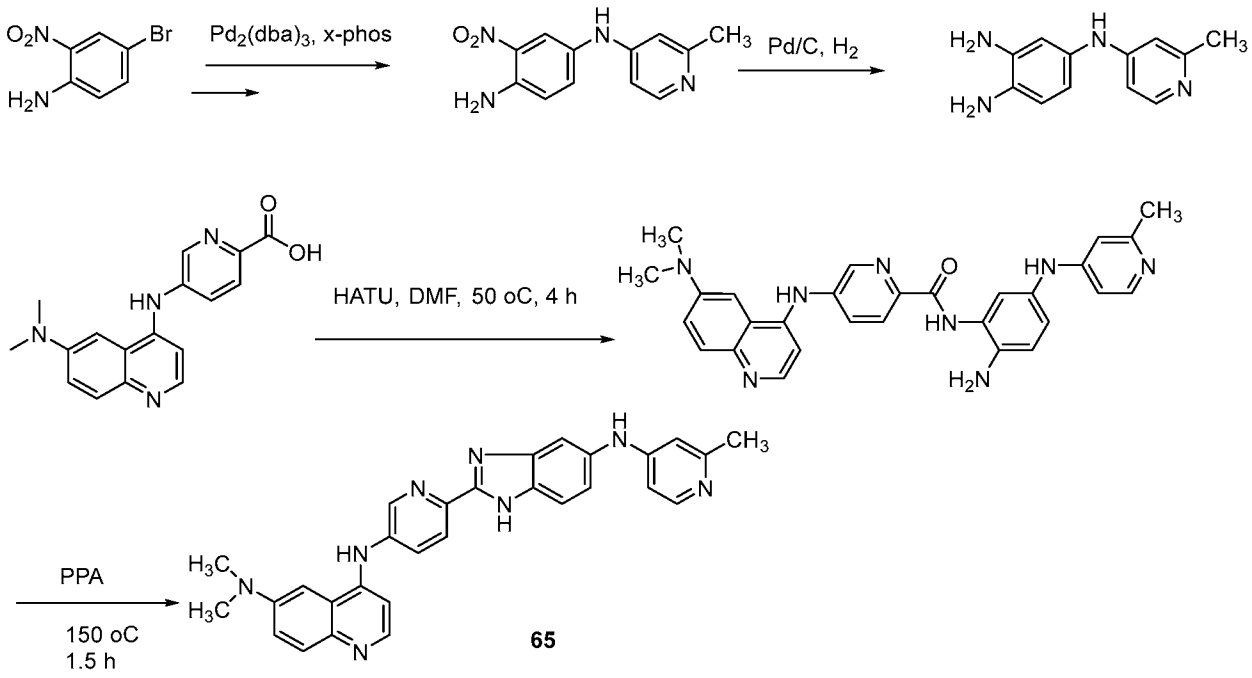
Scheme 53

[0535] **Compound 64** was prepared by the method shown in Scheme 53. **Compound 64** (N^6,N^6-dimethyl-N^4-(5-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)quinoline-4,6-diamine) was prepared as shown in Scheme 53: $C_{29}H_{26}N_8$; 486.57 g/mol; 11 mg; dark yellow solid; ESI-LCMS m/z = 487.0 $[M+H]^+$; LCMS RT = 1.39 min, >95.00% (214 nm).

Example 65: Compound 65 (N^6,N^6-dimethyl-N^4-(6-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinoline-4,6-diamine)



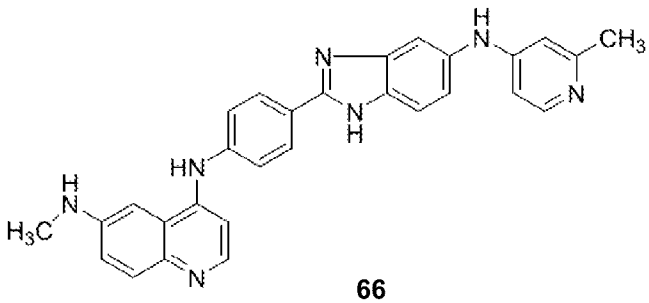
65



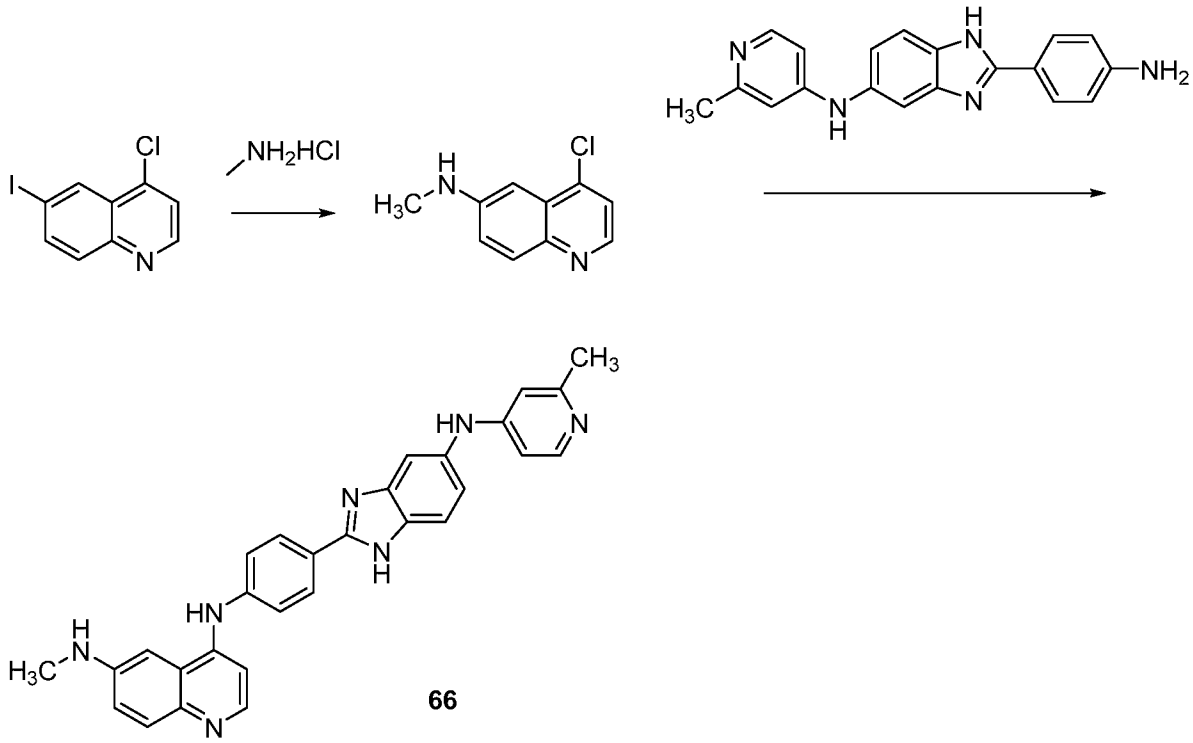
Scheme 54

[0536] **Compound 65** was prepared by the method shown in Scheme 54. **Compound 65** (N^6,N^6-dimethyl-N^4-(6-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinoline-4,6-diamine) was prepared as shown in Scheme 54: $C_{29}H_{26}N_8$; 486.58 g/mol; 18 mg; yellow solid; ESI-LCMS m/z = 487 $[M+H]^+$; LCMS RT = 1.38 min, >95.00% (214 nm).

Example 66: Compound 66 (N^6-methyl-N^4-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinoline-4,6-diamine)



66

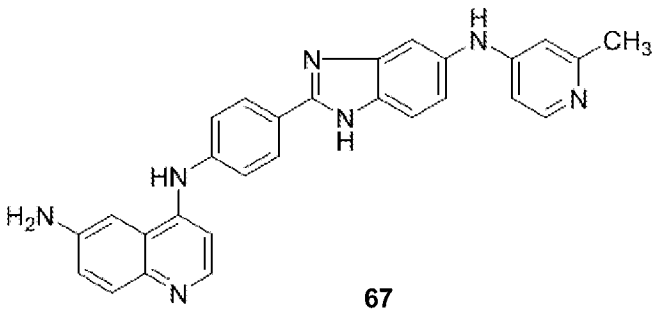


66

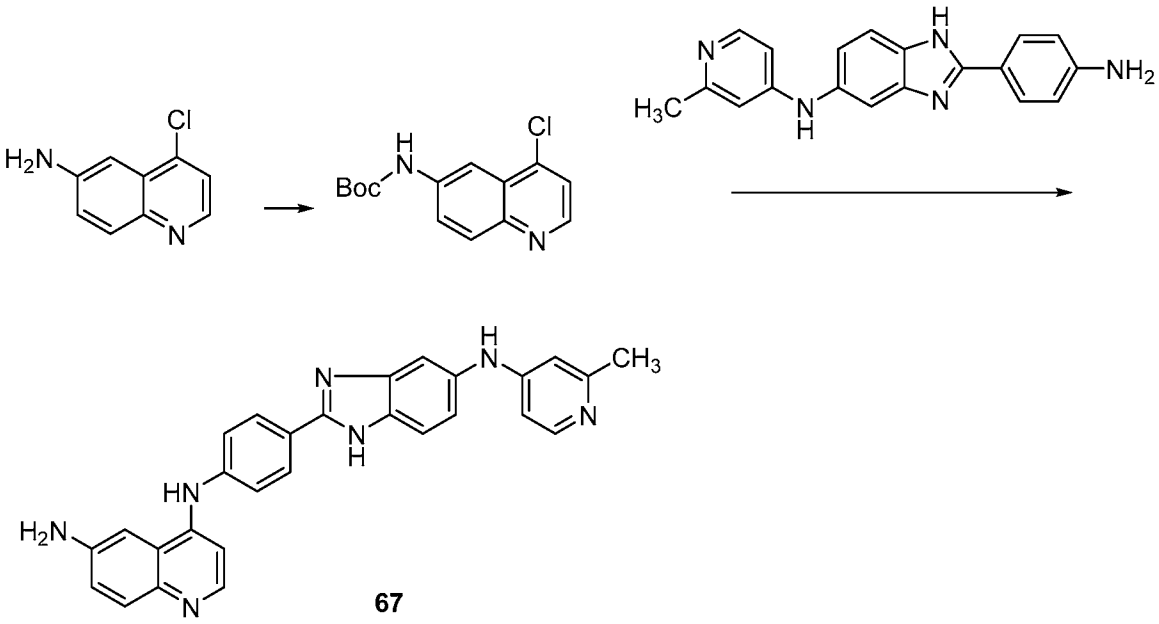
Scheme 55

[0537] **Compound 66** was prepared by the method shown in Scheme 55. **Compound 66** (N^6-methyl-N^4-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinoline-4,6-diamine) was prepared as shown in Scheme 55: $C_{29}H_{25}N_7$; 471.57 g/mol; 10 mg; yellow solid; ESI-LCMS m/z = 472 $[M+H]^+$; LCMS RT = 1.51 min, >95.00% (214 nm).

Example 67: Compound 67 (N^4-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinoline-4,6-diamine)



67

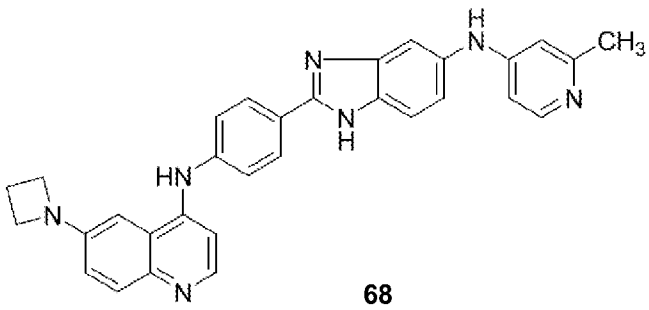


67

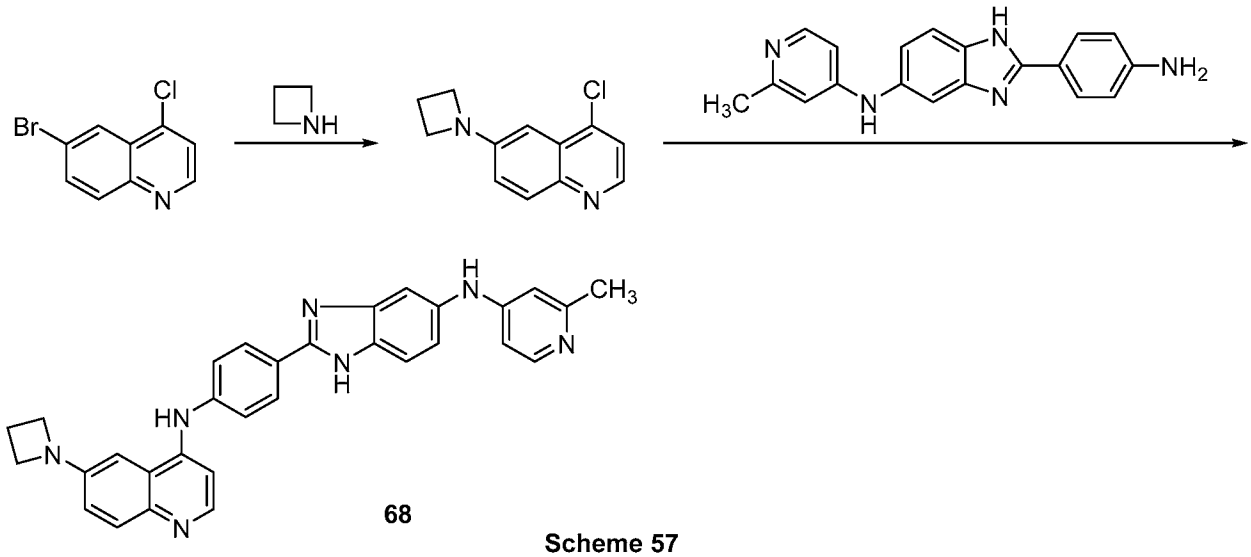
Scheme 56

[0538] **Compound 67** was prepared by the method shown in Scheme 56. **Compound 67** (N^4-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinoline-4,6-diamine) was prepared as shown in Scheme 56: $C_{28}H_{23}N_7$; 457.54 g/mol; 11 mg; yellow solid; ESI-LCMS m/z = 458 $[M+H]^+$; LCMS RT = 1.47 min, >95.00% (214 nm).

Example 68: Compound 68 (6-(azetidin-1-yl)-N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine)



68

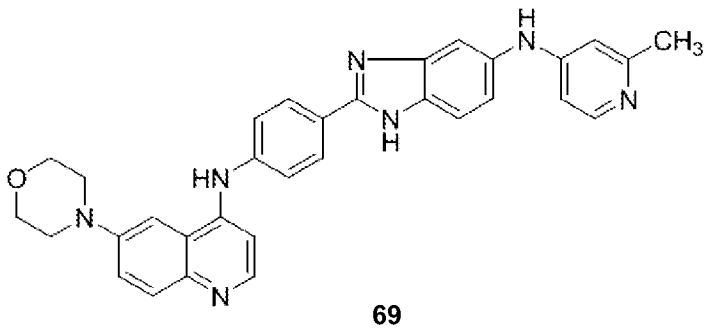


68

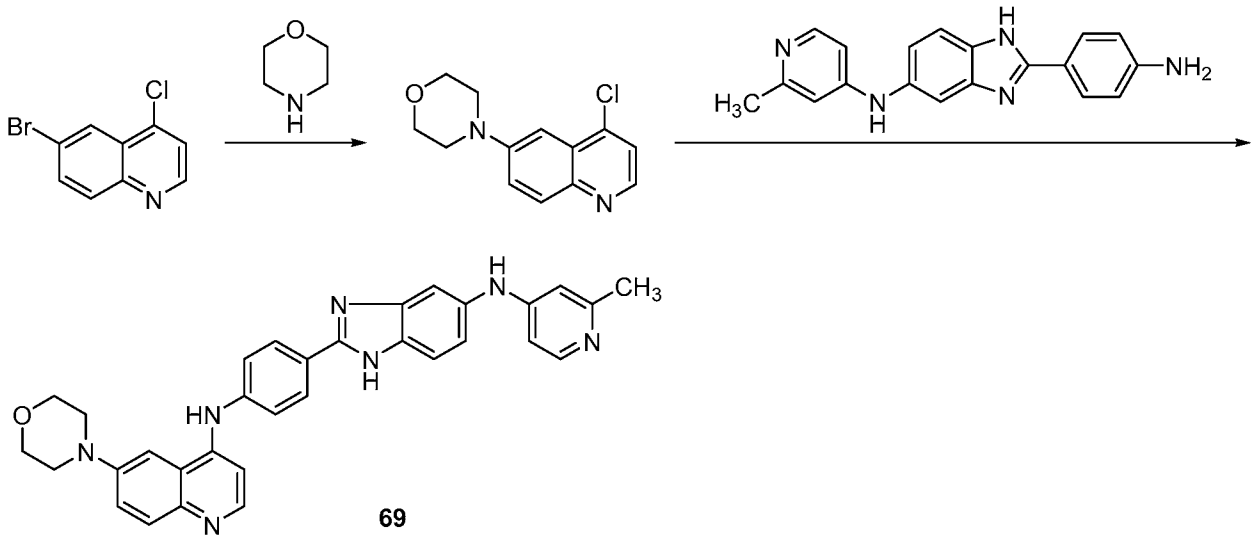
Scheme 57

[0539] **Compound 68** was prepared by the method shown in Scheme 57. **Compound 68** (6-(azetidin-1-yl)-N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine) was prepared as shown in Scheme 57: $C_{31}H_{27}N_7$; 497.61 g/mol; 15 mg; yellow solid; ESI-LCMS m/z = 498 $[M+H]^+$; LCMS RT = 1.50 min, >95.00% (214 nm).

Example 69: Compound 69 (N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)-6-morpholinoquinolin-4-amine)



69

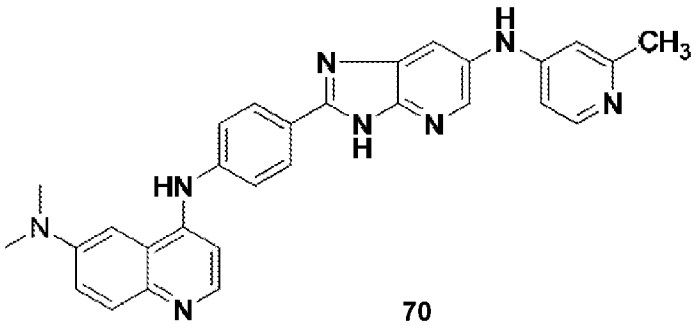


69

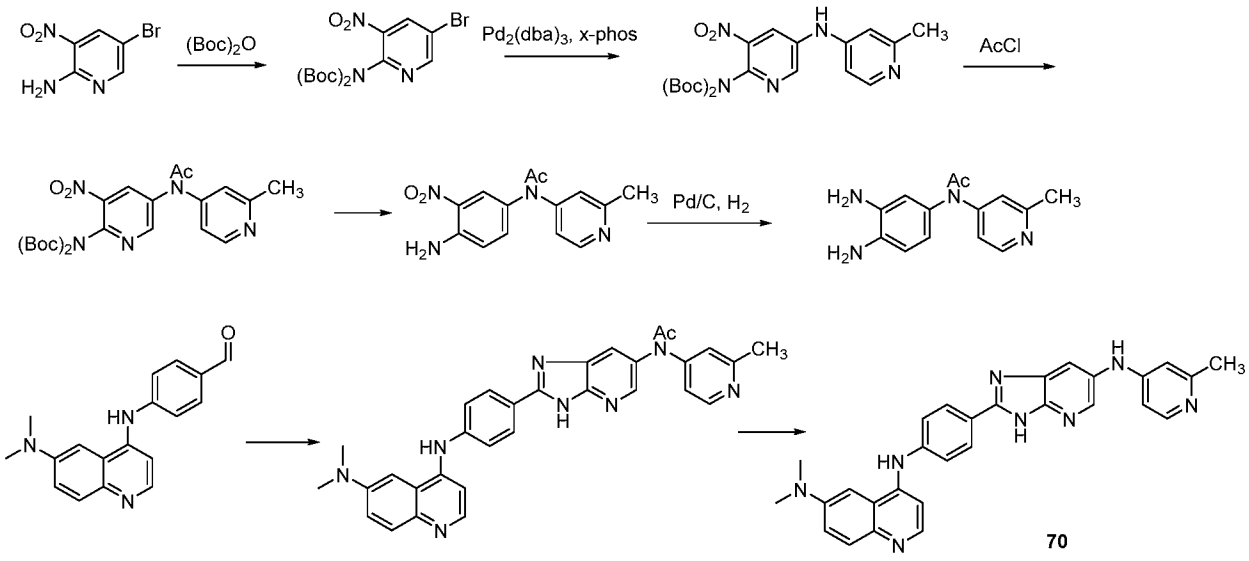
Scheme 58

[0540] **Compound 69** was prepared by the method shown in Scheme 58. **Compound 69** (N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)-6-morpholinoquinolin-4-amine) was prepared as shown in Scheme 58: $C_{32}H_{29}N_7O$; 527.63 g/mol; 16 mg; yellow solid; ESI-LCMS m/z = 528 $[M+H]^+$; LCMS RT = 1.51 min, >95.00% (214 nm).

Example 70: Compound 70 (N^6,N^6-dimethyl-N^4-(4-(6-(2-methylpyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)phenyl)quinoline-4,6-diamine)



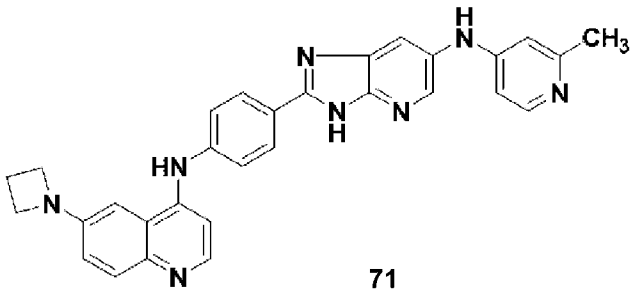
70



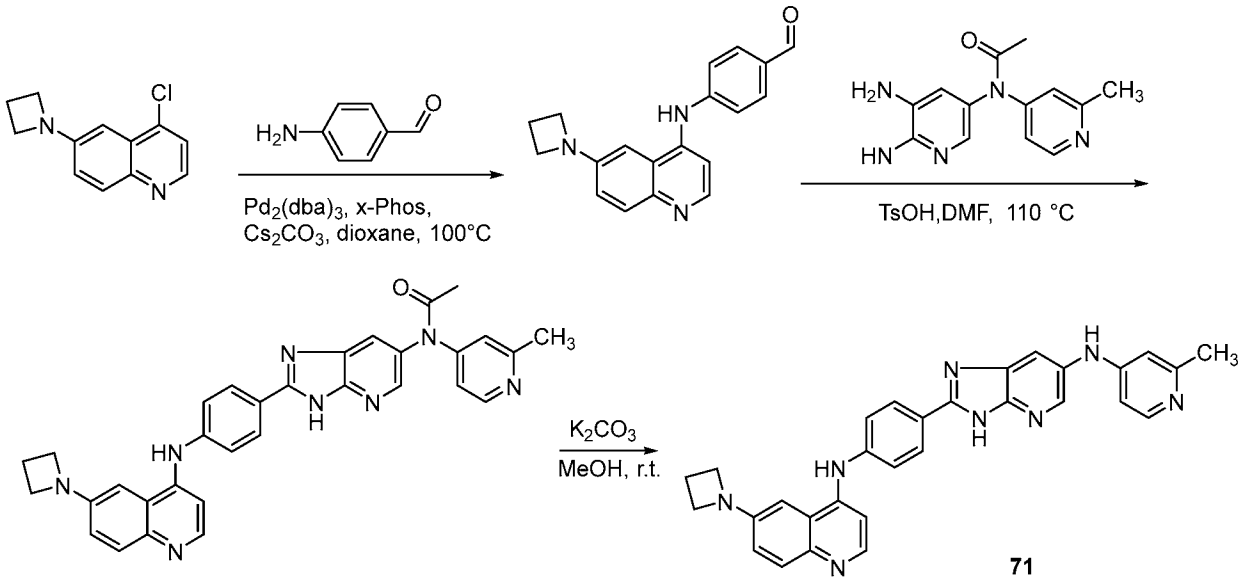
Scheme 59

[0541] **Compound 70** was prepared by the method shown in Scheme 59. **Compound 70** (N^6,N^6-dimethyl-N^4-(4-(6-(2-methylpyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)phenyl)quinoline-4,6-diamine) was prepared as shown in Scheme 59: $C_{29}H_{26}N_8$; 486.57 g/mol; 20 mg; yellow solid; ESI-LCMS m/z = 487 $[M+H]^+$; LCMS RT = 1.37 min, >95.00% (214 nm).

Example 71: Compound 71 (6-(azetidin-1-yl)-N-(4-(6-((2-methylpyridin-4-yl)amino)-3H-imidazo[4,5-b]pyridin-2-yl)phenyl)quinolin-4-amine)



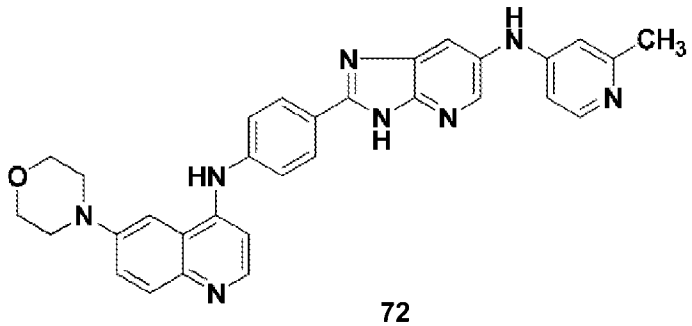
71



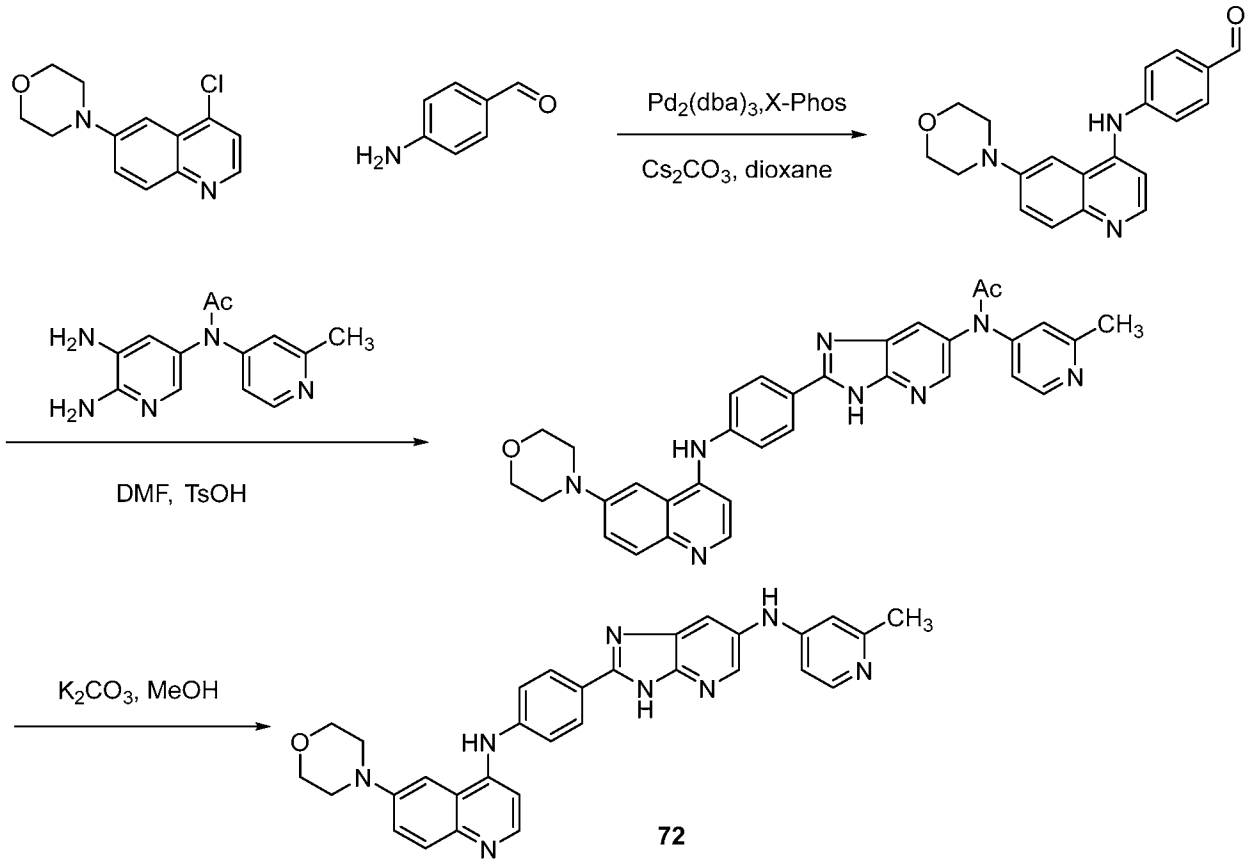
Scheme 60

[0542] **Compound 71** was prepared by the method shown in Scheme 60. **Compound 71** (6-(azetidin-1-yl)-N-(4-(6-((2-methylpyridin-4-yl)amino)-3H-imidazo[4,5-b]pyridin-2-yl)phenyl)quinolin-4-amine) was prepared as shown in Scheme 60: $C_{30}H_{26}N_8$; 498.594 g/mol; 15 mg; yellow solid; ESI-LCMS m/z = 499.0 $[M+H]^+$; LCMS RT = 1.22 min, >95.00% (214 nm).

Example 72: Compound 72 (N-(4-(6-(2-methylpyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)phenyl)-6-morpholinoquinolin-4-amine)



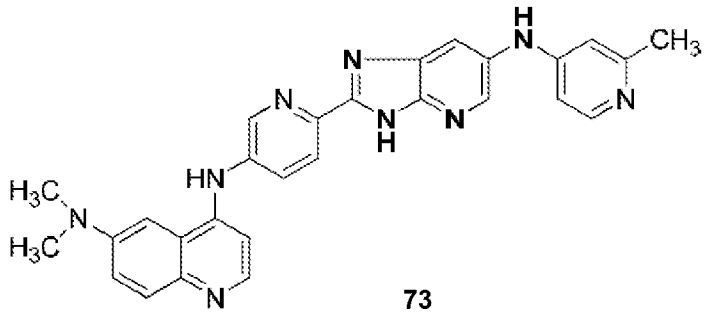
72

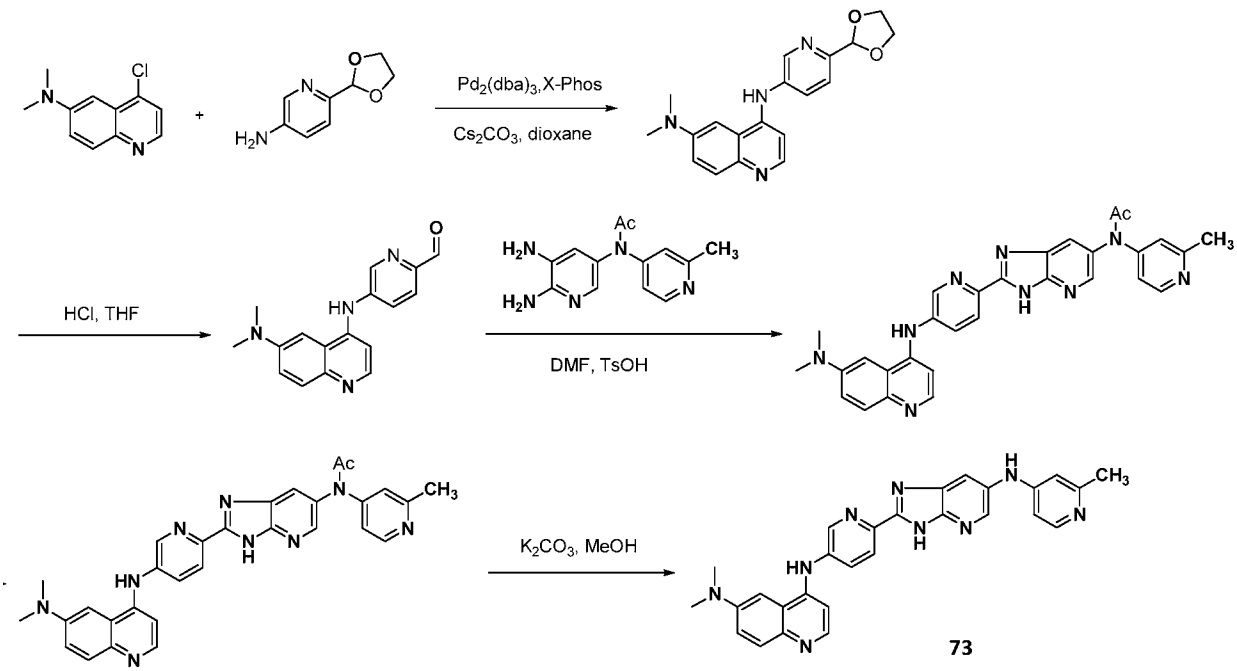


Scheme 61

[0543] **Compound 72** was prepared by the method shown in Scheme 61. **Compound 72** (N-(4-(6-(2-methylpyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)phenyl)-6-morpholinoquinolin-4-amine) was prepared as shown in Scheme 61: $C_{31}H_{28}N_8O$; 528.61 g/mol; 20 mg; yellow solid; ESI-LCMS m/z = 529 $[M+H]^+$; LCMS RT = 1.32 min, >95.00% (214 nm).

Example 73: Compound 73 (N^6,N^6-dimethyl-N^4-(6-(6-(2-methylpyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-3-yl)quinoline-4,6-diamine)

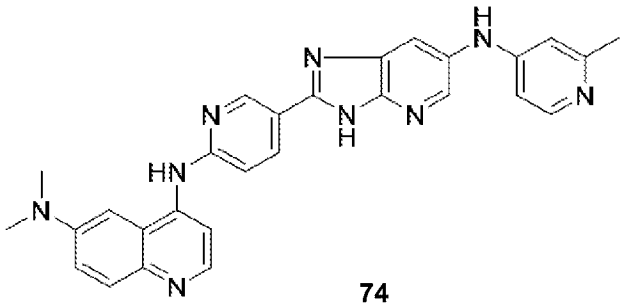




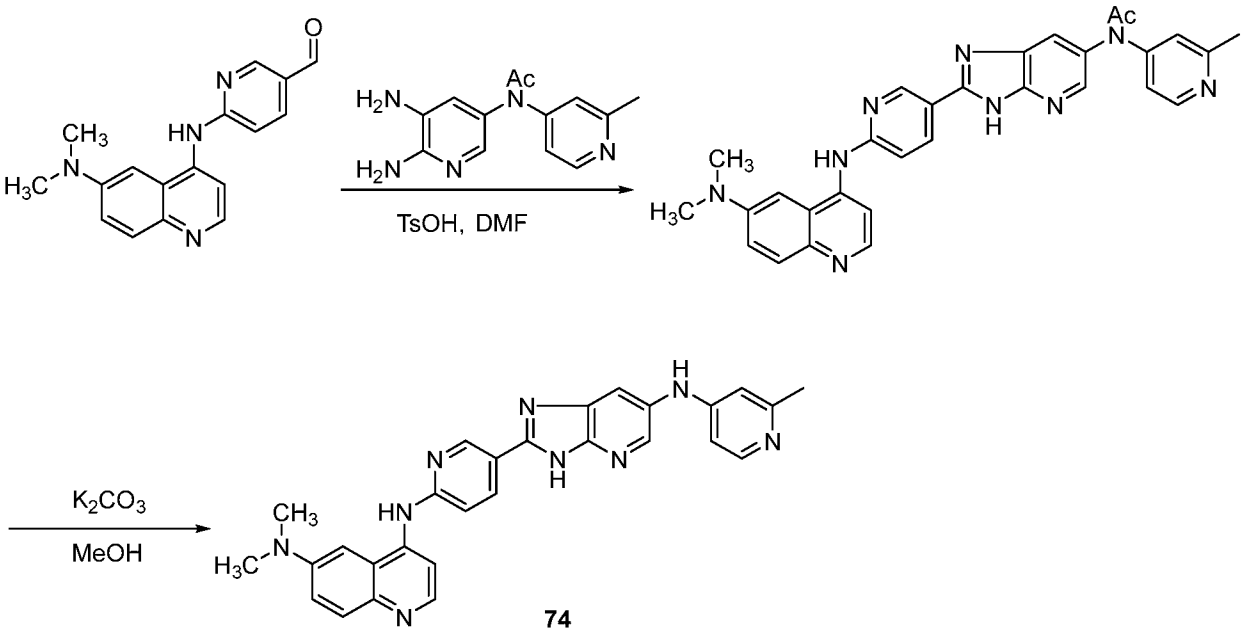
Scheme 62

[0544] **Compound 73** was prepared by the method shown in Scheme 62. **Compound 73** (N^6,N^6-dimethyl-N^4-(6-(6-(2-methylpyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-3-yl)quinoline-4,6-diamine) was prepared as shown in Scheme 62: $C_{28}H_{25}N_9$; 487.56 g/mol; 15 mg; yellow solid; ESI-LCMS m/z = 488 $[M+H]^+$; LCMS RT = 1.35 min, >95.00% (214 nm).

Example 74: Compound 74 (N^6,N^6-dimethyl-N^4-(5-(6-((2-methylpyridin-4-yl)amino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-yl)quinoline-4,6-diamine)



74

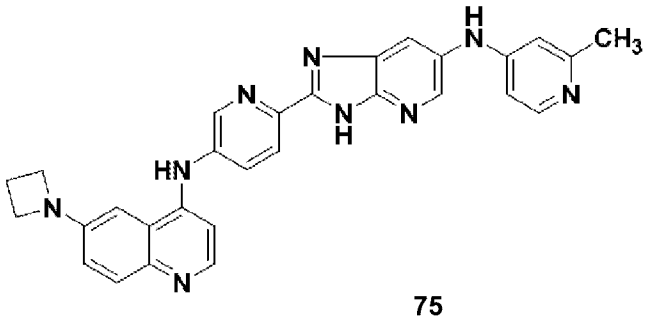


74

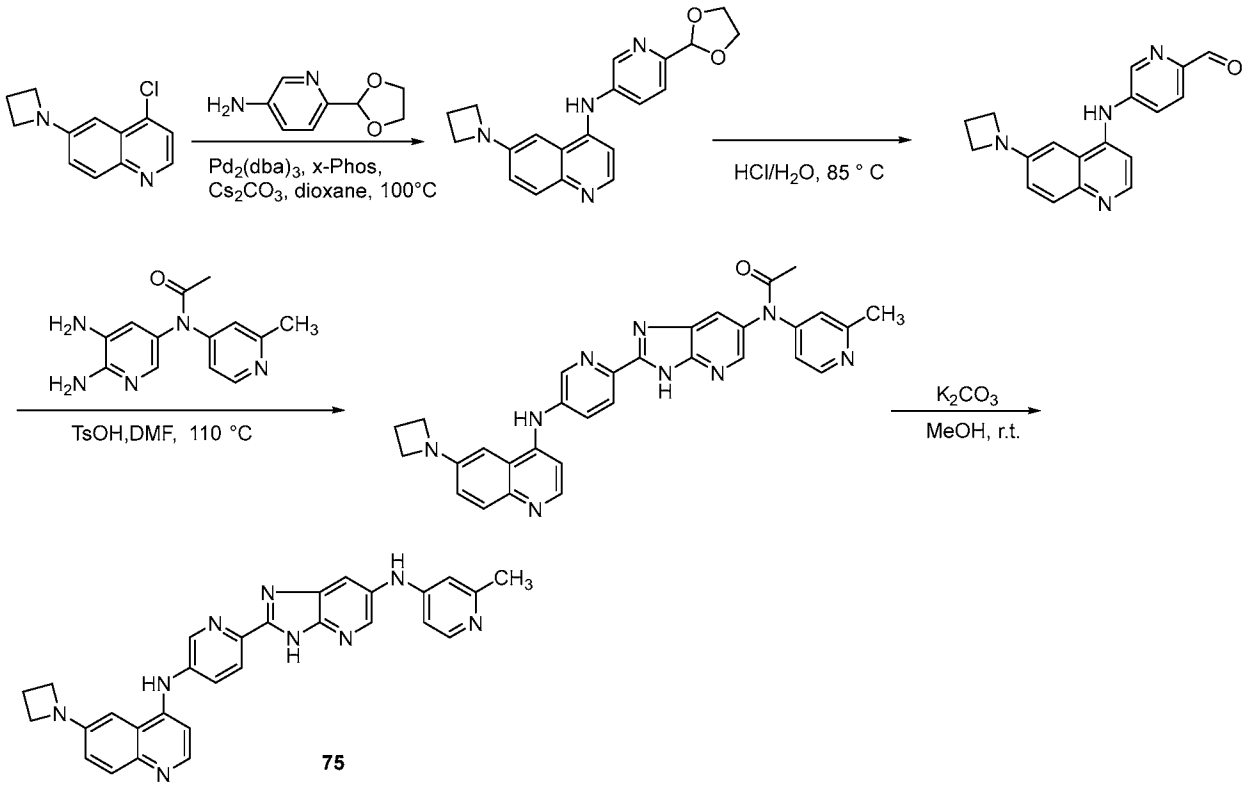
Scheme 63

[0545] **Compound 74** was prepared by the method shown in Scheme 63. **Compound 74** (N^6,N^6-dimethyl-N^4-(5-(6-((2-methylpyridin-4-yl)amino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-yl)quinoline-4,6-diamine) was prepared as shown in Scheme 63: $C_{28}H_{25}N_9$; 487.57 g/mol; 11 mg; yellow solid; ESI-LCMS m/z = 488 $[M+H]^+$; LCMS RT = 1.23 min, >95.00% (214 nm).

Example 75: Compound 75 (6-(azetidin-1-yl)-N-(6-(6-((2-methylpyridin-4-yl)amino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-3-yl)quinolin-4-amine)



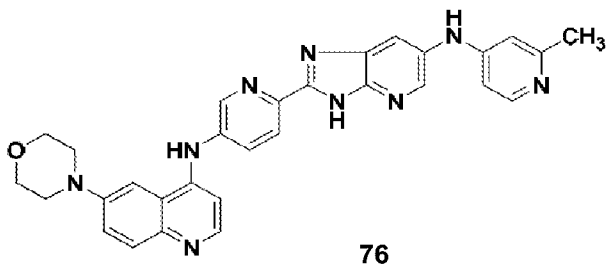
75



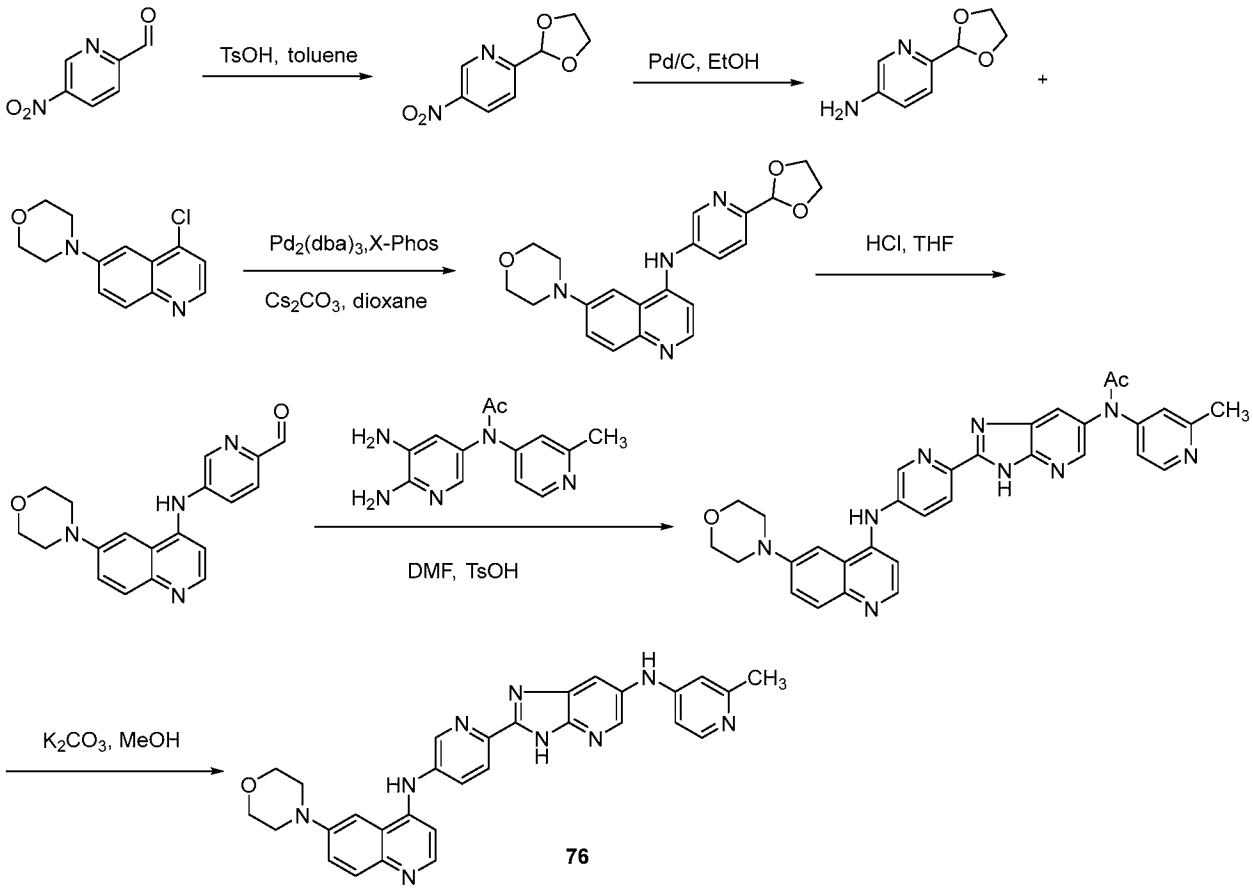
Scheme 64

[0546] **Compound 75** was prepared by the method shown in Scheme 64. **Compound 75** (6-(azetidin-1-yl)-N-(6-(6-((2-methylpyridin-4-yl)amino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-3-yl)quinolin-4-amine) was prepared as shown in Scheme 64: $C_{29}H_{25}N_9$; 499.582 g/mol; 13 mg; yellow solid; ESI-LCMS m/z = 500.1 $[M+H]^+$; LCMS RT = 1.35 min, >95.00% (214 nm).

Example 76: Compound 76 (N-(6-(6-(2-methylpyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine)



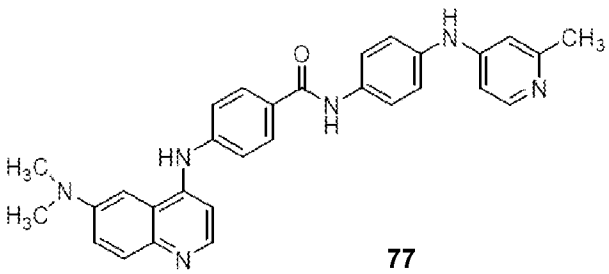
76



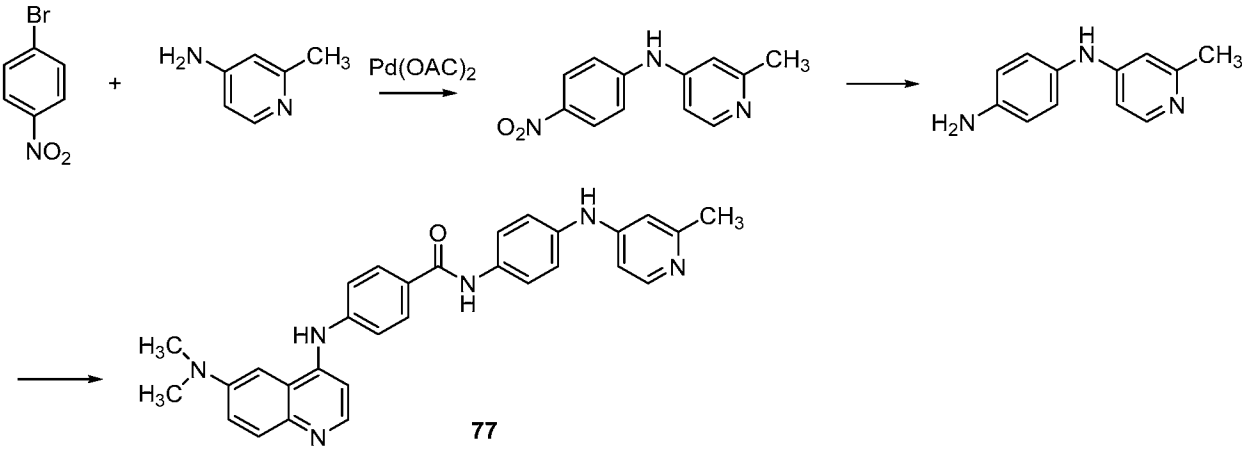
Scheme 65

[0547] **Compound 76** was prepared by the method shown in Scheme 65. **Compound 76** (N-(6-(6-(2-methylpyridin-4-ylamino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine) was prepared as shown in Scheme 65: $C_{30}H_{27}N_9O$; 529.60 g/mol; 20 mg; yellow solid; ESI-LCMS m/z = 530 $[M+H]^+$; LCMS RT = 1.31 min, >95.00% (214 nm).

Example 77: Compound 77 (4-((6-(dimethylamino)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide)



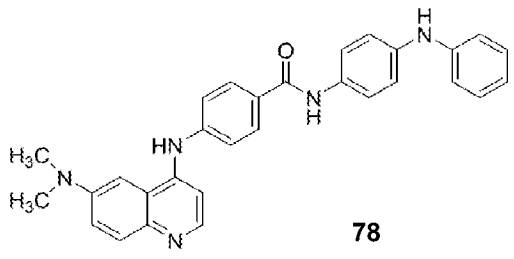
77

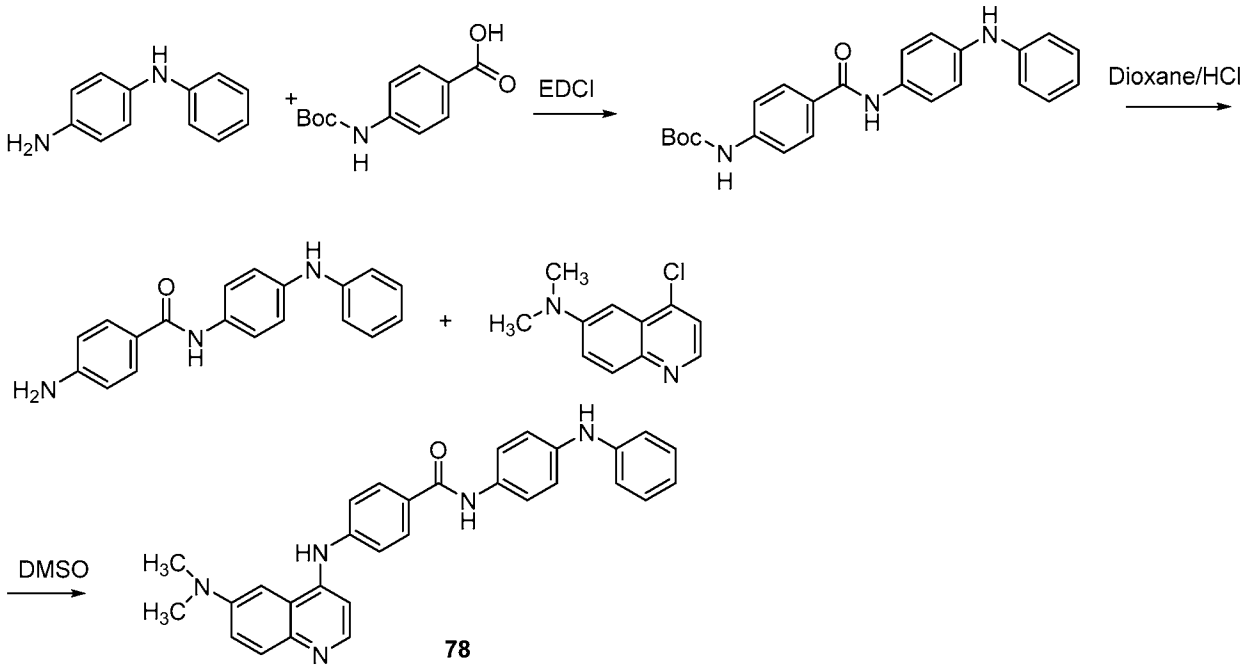


Scheme 66

[0548] **Compound** 77 was prepared by the method shown in Scheme 66. **Compound** 77 (4-((6-(dimethylamino)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide) was prepared as shown in Scheme 66: $C_{30}H_{28}N_6O$; 488.60 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 489 $[M+H]^+$; LCMS RT = 1.63 min, >95.00% (214 nm).

Example 78: Compound 78 (4-((6-(dimethylamino)quinolin-4-yl)amino)-N-(4-(phenylamino)phenyl)benzamide)

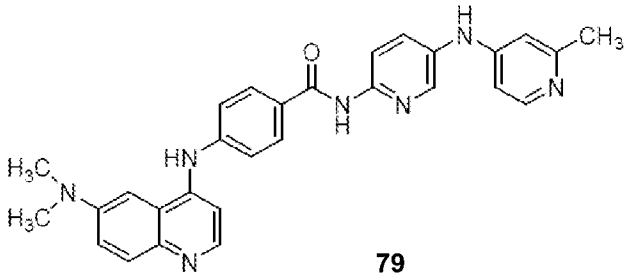




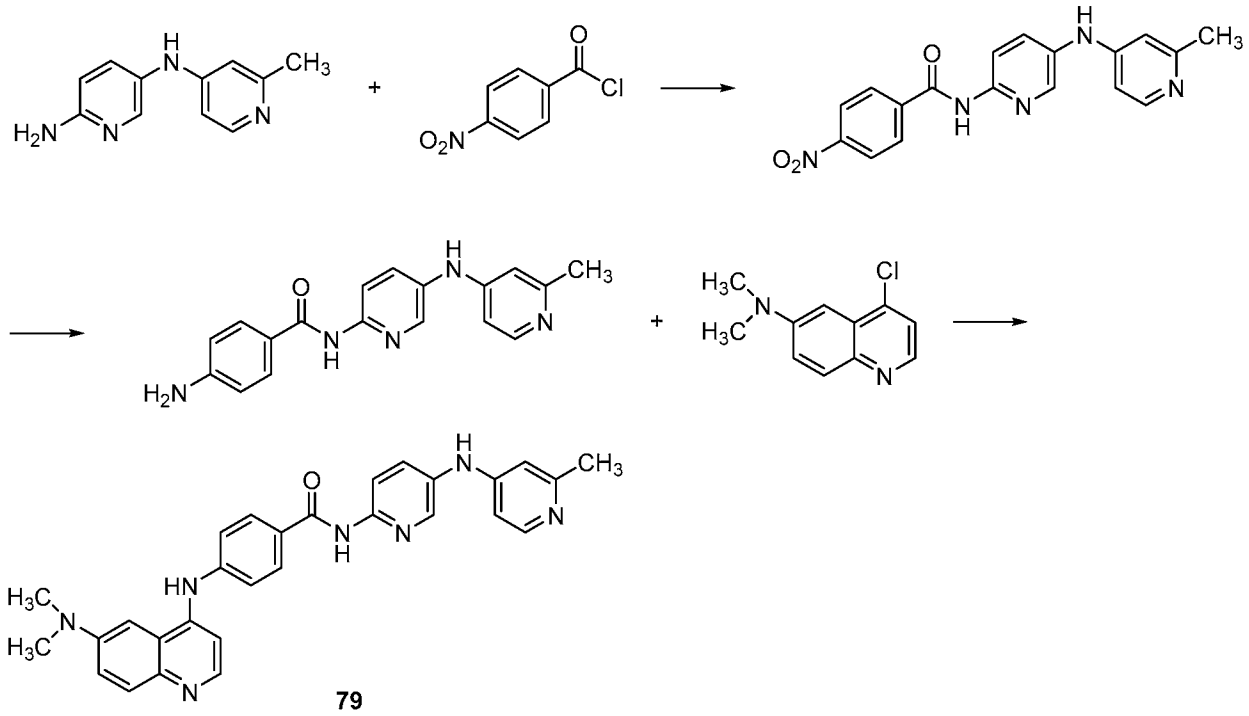
Scheme 67

[0549] **Compound 78** was prepared by the method shown in Scheme 67. **Compound 78** (4-((6-(dimethylamino)quinolin-4-yl)amino)-N-(4-(phenylamino)phenyl)benzamide) was prepared as shown in Scheme 67: $C_{30}H_{27}N_5O$; 473.58 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 474 $[M+H]^+$; LCMS RT = 1.76 min, >95.00% (214 nm).

Example 79: Compound 79 (4-(6-(dimethylamino)quinolin-4-ylamino)-N-(5-(2-methylpyridin-4-ylamino)pyridin-2-yl)benzamide)



79

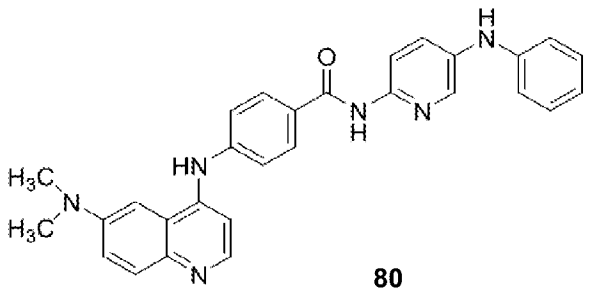


79

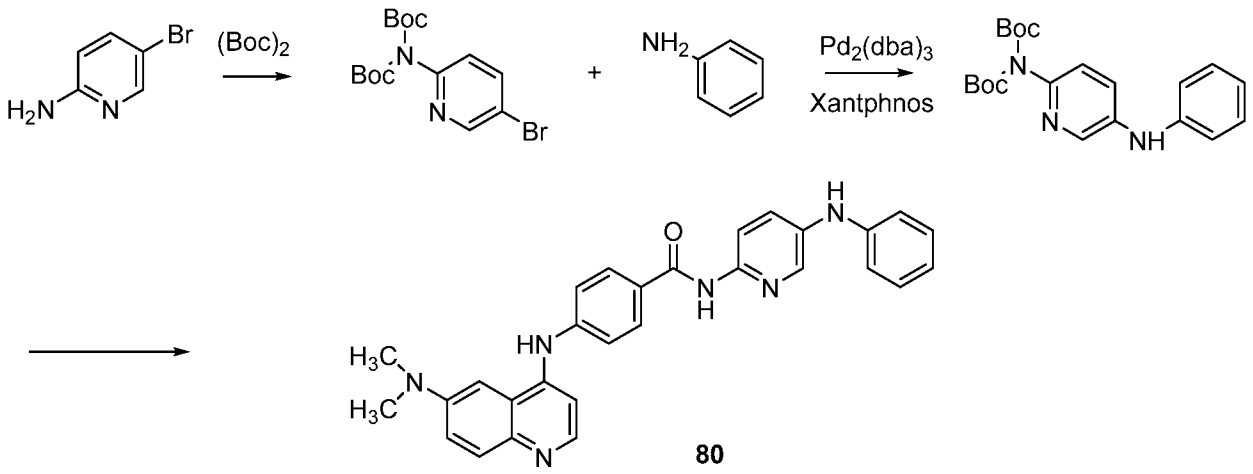
Scheme 68

[0550] **Compound 79** was prepared by the method shown in Scheme 68. **Compound 79** (4-(6-(dimethylamino)quinolin-4-ylamino)-N-(5-(2-methylpyridin-4-ylamino)pyridin-2-yl)benzamide) was prepared as shown in Scheme 68: $C_{29}H_{27}N_7O$; 489.57 g/mol; 23 mg; yellow solid; ESI-LCMS m/z = 490 $[M+H]^+$; LCMS RT = 1.48 min, >95.00% (214 nm).

Example 80: Compound 80 (4-((6-(dimethylamino)quinolin-4-yl)amino)-N-(5-(phenylamino)pyridin-2-yl)benzamide)



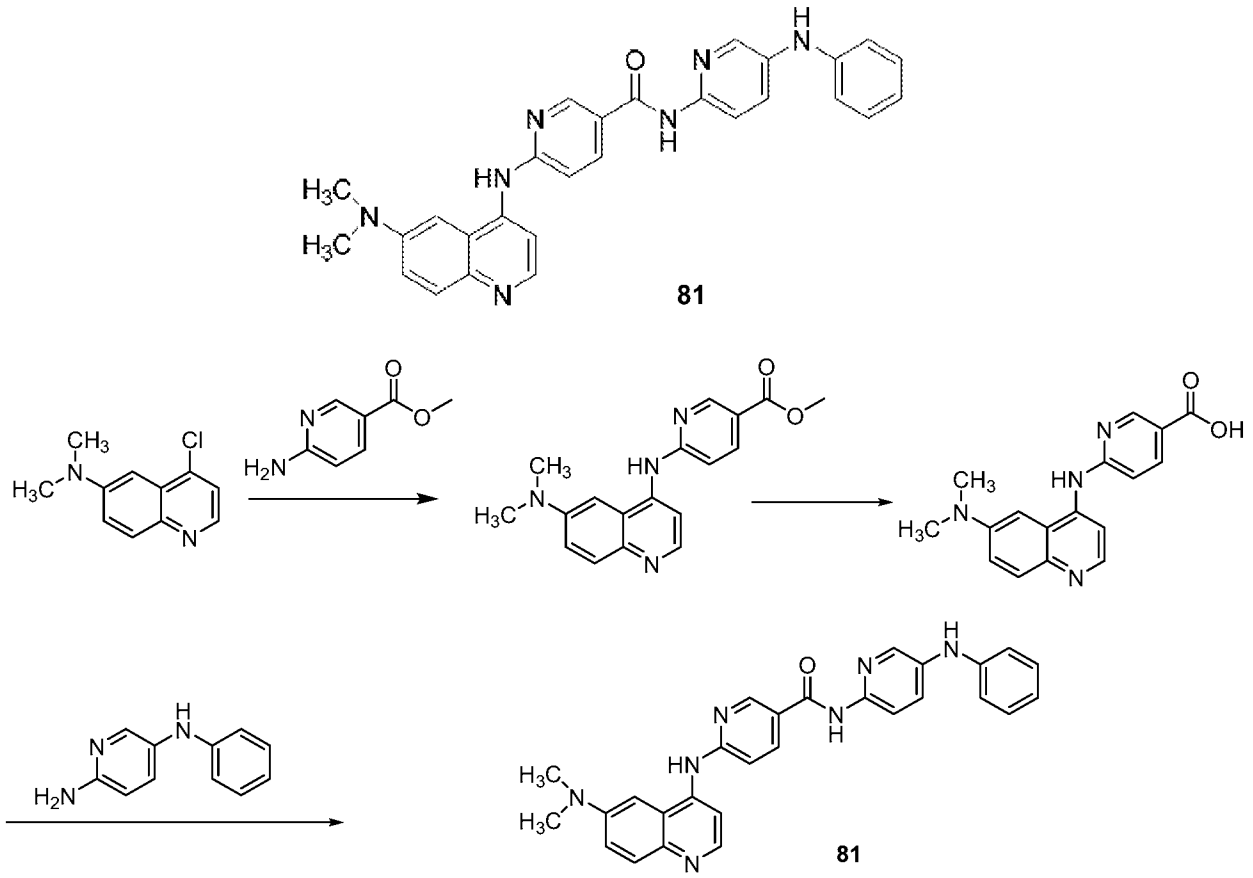
80



Scheme 69

[0551] **Compound 80** was prepared by the method shown in Scheme 69. **Compound 80** (4-((6-(dimethylamino)quinolin-4-yl)amino)-N-(5-(phenylamino)pyridin-2-yl)benzamide) was prepared as shown in Scheme 69: $C_{29}H_{26}N_6O$; 474.57 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 475 $[M+H]^+$; LCMS RT = 1.79 min, >95.00% (214 nm).

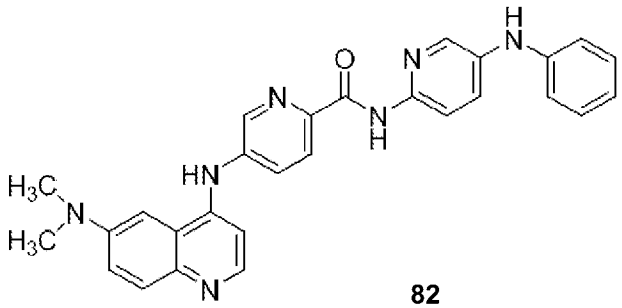
Example 81: Compound 81 (6-((6-(dimethylamino)quinolin-4-yl)amino)-N-(5-(phenylamino)pyridin-2-yl)nicotinamide)



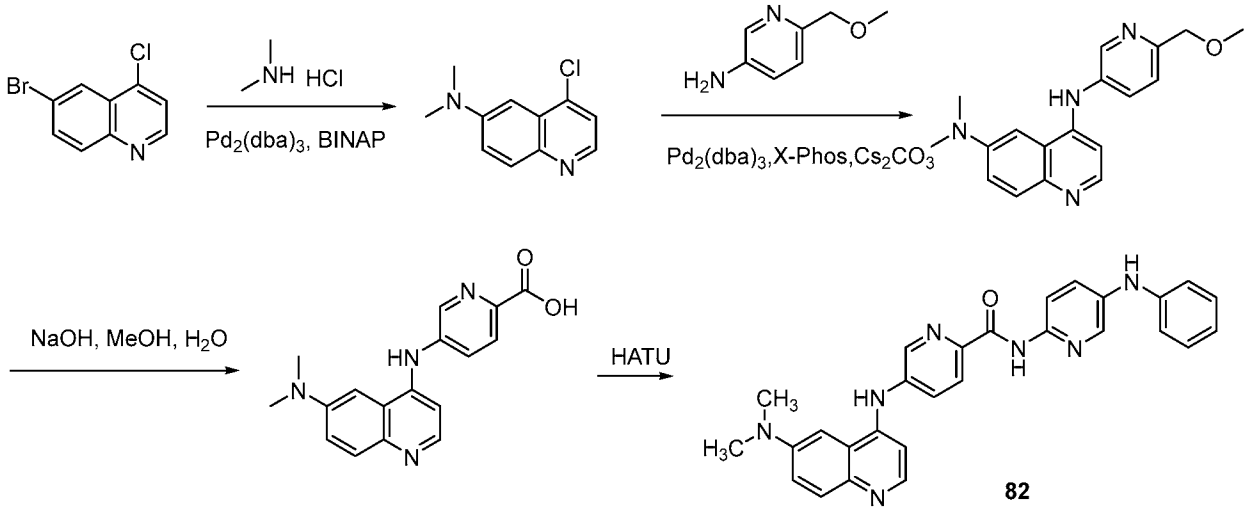
Scheme 70

[0552] **Compound 81** was prepared by the method shown in Scheme 70. **Compound 81** (6-((6-(dimethylamino)quinolin-4-yl)amino)-N-(5-(phenylamino)pyridin-2-yl)nicotinamide) was prepared as shown in Scheme 70: $C_{28}H_{25}N_7O$; 475.56 g/mol; 19 mg; pale yellow solid; ESI-LCMS m/z = 476 $[M+H]^+$; LCMS RT = 1.71 min, >95.00% (214 nm).

Example 82: Compound 82 (5-((6-(dimethylamino)quinolin-4-yl)amino)-N-(5-(phenylamino)pyridin-2-yl)picolinamide)



82

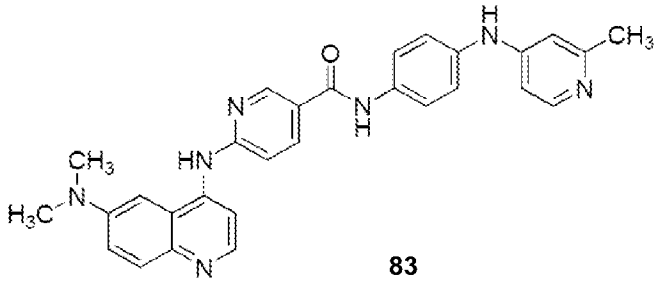


82

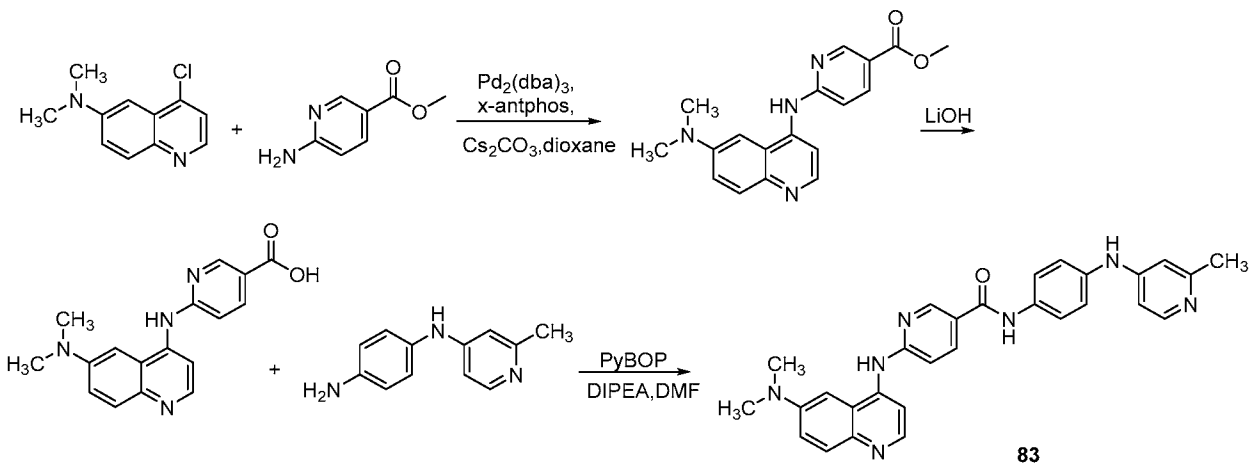
Scheme 71

[0553] **Compound 82** was prepared by the method shown in Scheme 71. **Compound 82** (5-((6-(dimethylamino)quinolin-4-yl)amino)-N-(5-(phenylamino)pyridin-2-yl)picolinamide) was prepared as shown in Scheme 71: $C_{28}H_{25}N_7O$; 475.56 g/mol; 19 mg; yellow solid; ESI-LCMS m/z = 476 $[M+H]^+$; LCMS RT = 1.78 min, >95.00% (214 nm).

Example 83: Compound 83 (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)nicotinamide)



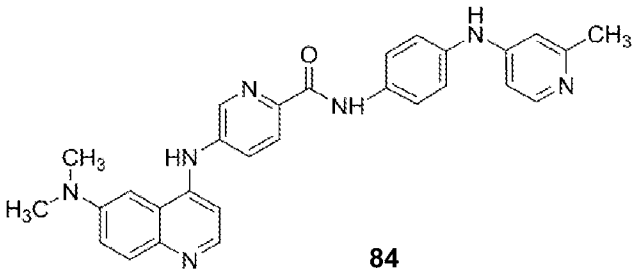
83



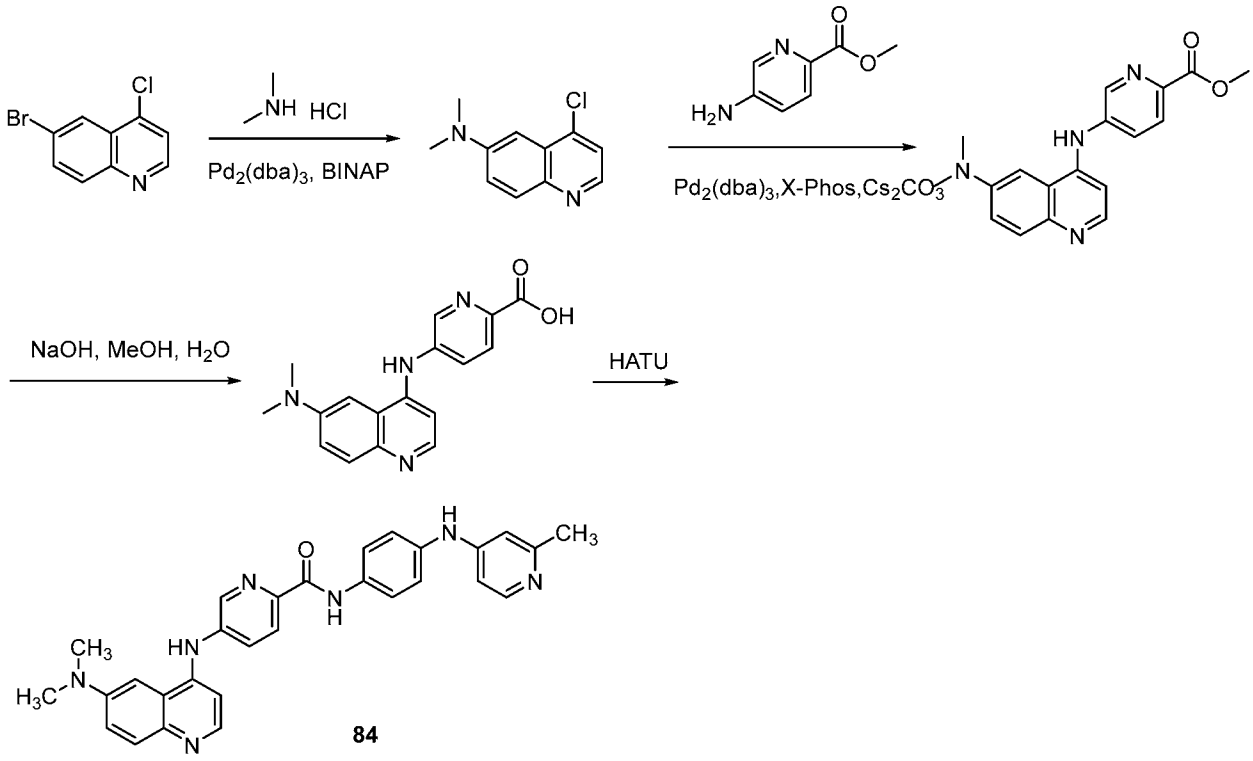
Scheme 72

[0554] **Compound 83** was prepared by the method shown in Scheme 72. **Compound 83** (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 72: $C_{29}H_{27}N_7O$; 489.57 g/mol; 16 mg; yellow solid; ESI-LCMS m/z = 490 $[M+H]^+$; LCMS RT = 1.50 min, >95.00% (214 nm).

Example 84: Compound 84 (5-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)picolinamide)



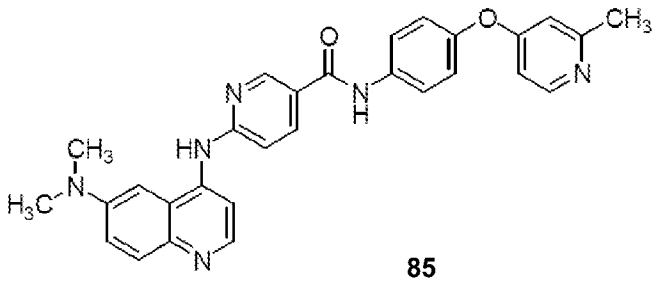
84



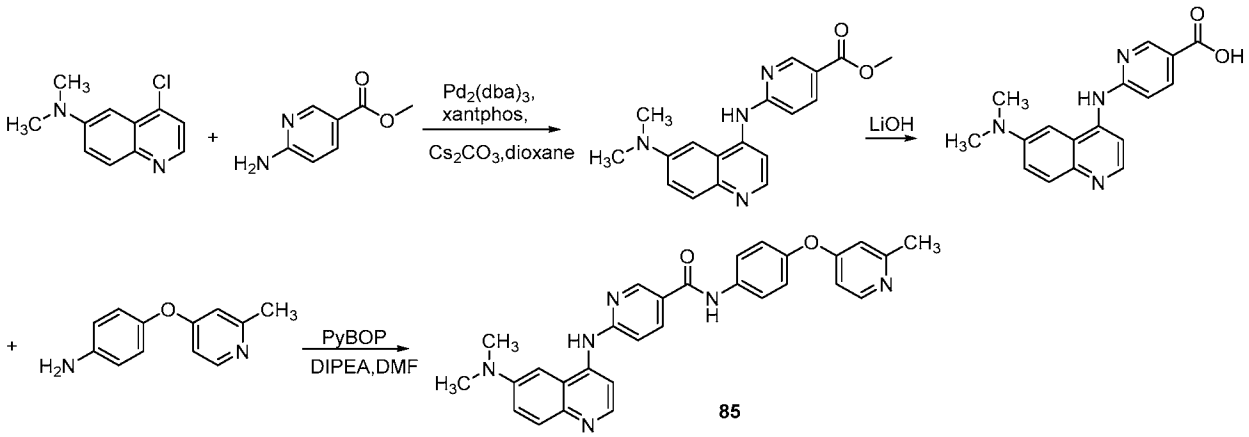
Scheme 73

[0555] **Compound 84** was prepared by the method shown in Scheme 73. **Compound 84** (5-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)picolinamide) was prepared as shown in Scheme 73: $C_{29}H_{27}N_7O$; 489.57 g/mol; 24 mg; pale yellow solid; ESI-LCMS m/z = 490 $[M+H]^+$; LCMS RT = 1.42 min, >95.00% (214 nm).

Example 85: Compound 85 (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-yloxy)phenyl)nicotinamide)



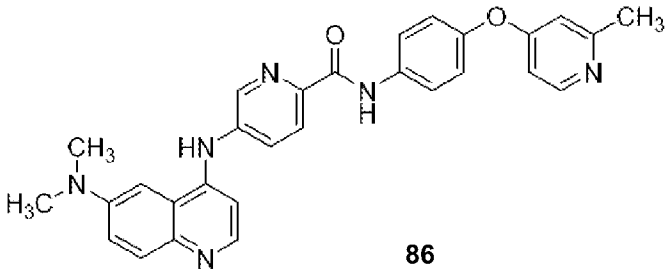
85



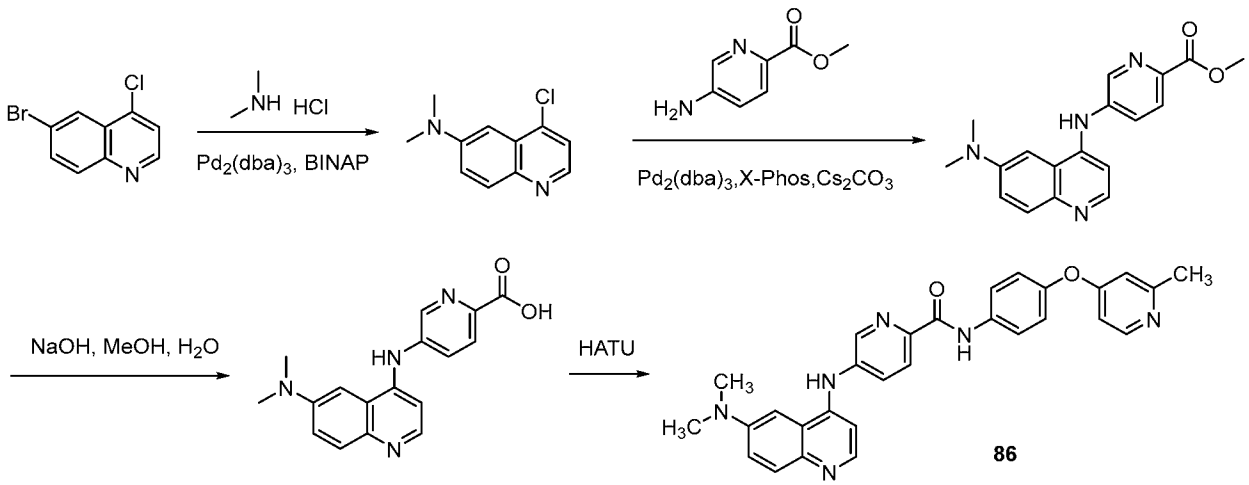
Scheme 74

[0556] **Compound 85** was prepared by the method shown in Scheme 74. **Compound 85** (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-yloxy)phenyl)nicotinamide) was prepared as shown in Scheme 74: $C_{29}H_{26}N_6O_2$; 490.56 g/mol; 20 mg; yellow solid; ESI-LCMS m/z = 491 $[M+H]^+$; LCMS RT = 1.51 min, >95.00% (214 nm).

Example 86: Compound 86 (5-((6-(dimethylamino)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)oxy)phenyl)picolinamide)



86

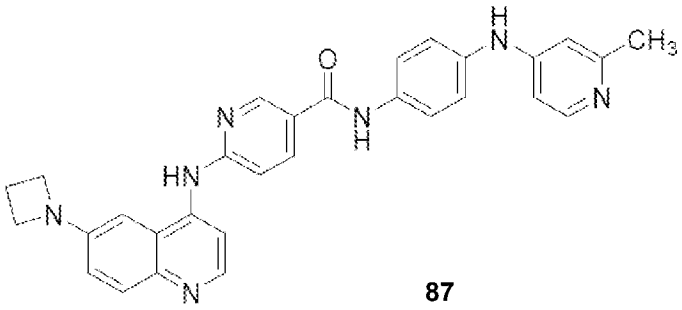


Scheme 75

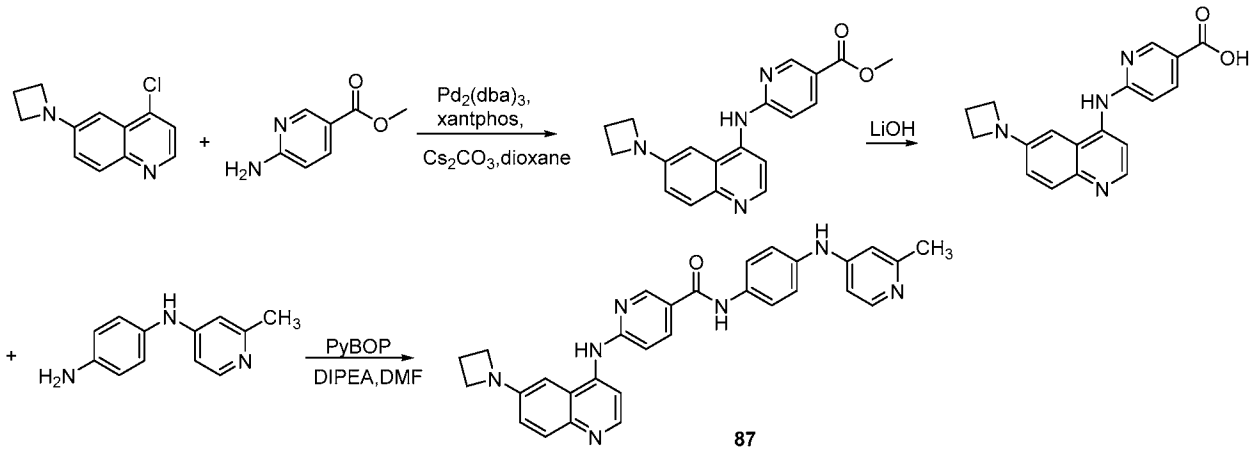
[0557] **Compound 86** was prepared by the method shown in Scheme 75. **Compound 86** (5-((6-(dimethylamino)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-

yl)oxy)phenyl)picolinamide) was prepared as shown in Scheme 75: $C_{29}H_{26}N_6O_2$; 490.56 g/mol; 20 mg; yellow solid; ESI-LCMS m/z = 491 $[M+H]^+$; LCMS RT = 1.78 min, >95.00% (214 nm).

Example 87: Compound 87 (6-(6-(azetidin-1-yl)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)nicotinamide)



87

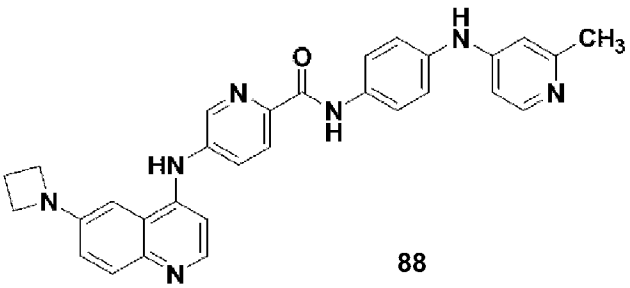


87

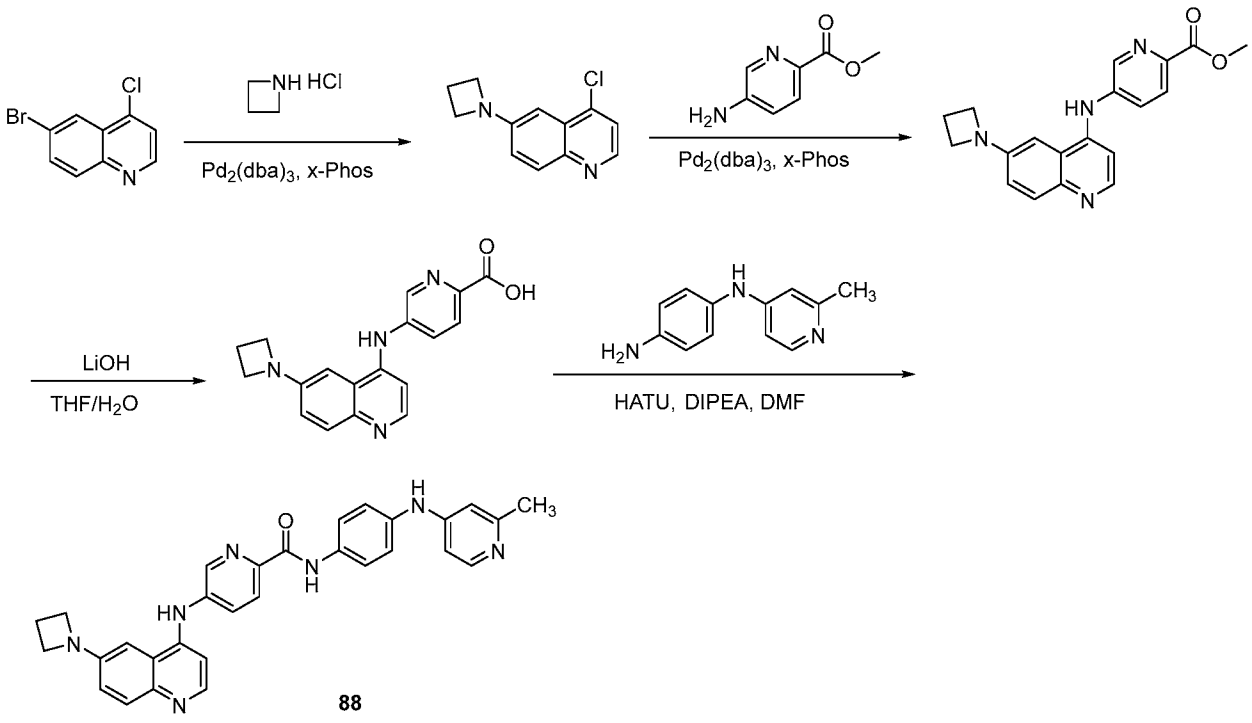
Scheme 76

[0558] **Compound 87** was prepared by the method shown in Scheme 76. **Compound 87** (6-(6-(azetidin-1-yl)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 76: $C_{30}H_{27}N_7O$; 501.58 g/mol; 24 mg; yellow solid; ESI-LCMS m/z = 502 $[M+H]^+$; LCMS RT = 1.78 min, >95.00% (214 nm).

Example 88: Compound 88 (5-((6-(azetidin-1-yl)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)picolinamide)



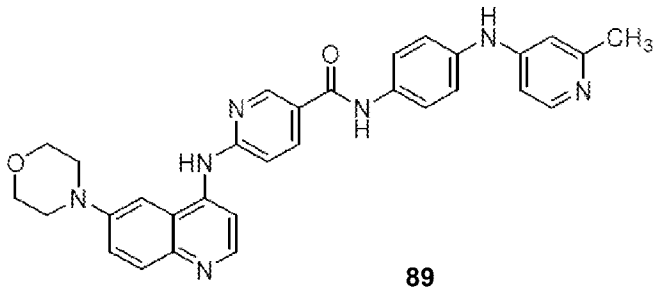
88



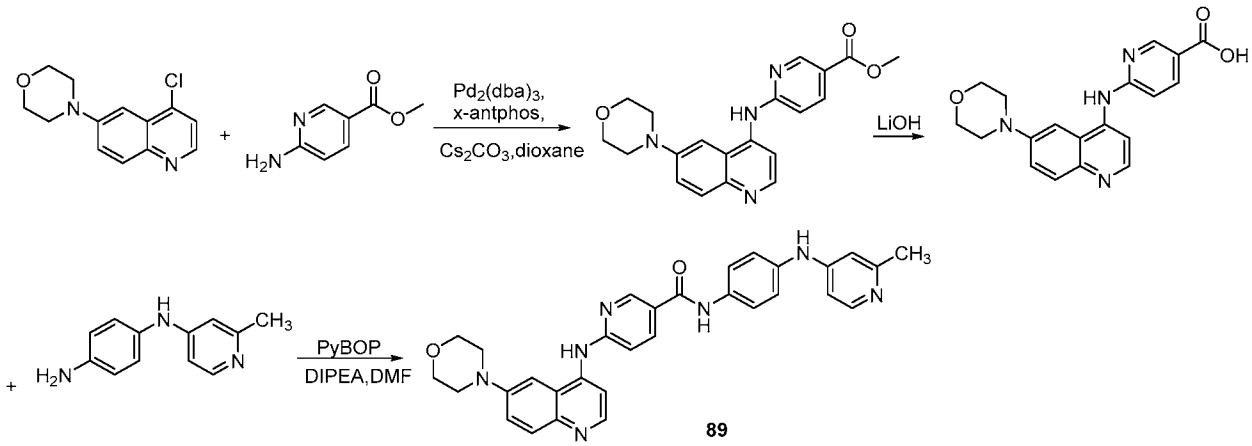
Scheme 77

[0559] **Compound 88** was prepared by the method shown in Scheme 77. **Compound 88** (5-((6-(azetidin-1-yl)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)picolinamide) was prepared as shown in Scheme 77: $C_{30}H_{27}N_7O$; 501.594 g/mol; 20 mg; yellow solid; ESI-LCMS m/z = 502 $[M+H]^+$; LCMS RT = 1.74 min, >95.00% (214 nm).

Example 89: Compound 89 (N-(4-(2-methylpyridin-4-ylamino)phenyl)-6-(6-morpholinoquinolin-4-ylamino)nicotinamide)



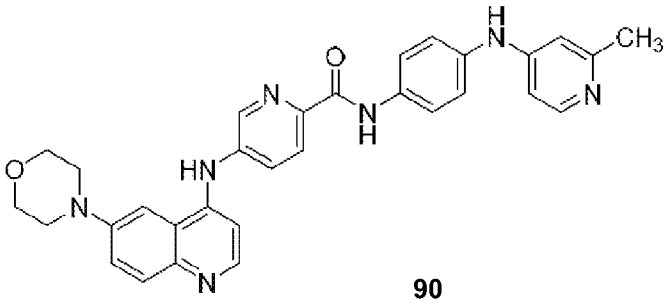
89



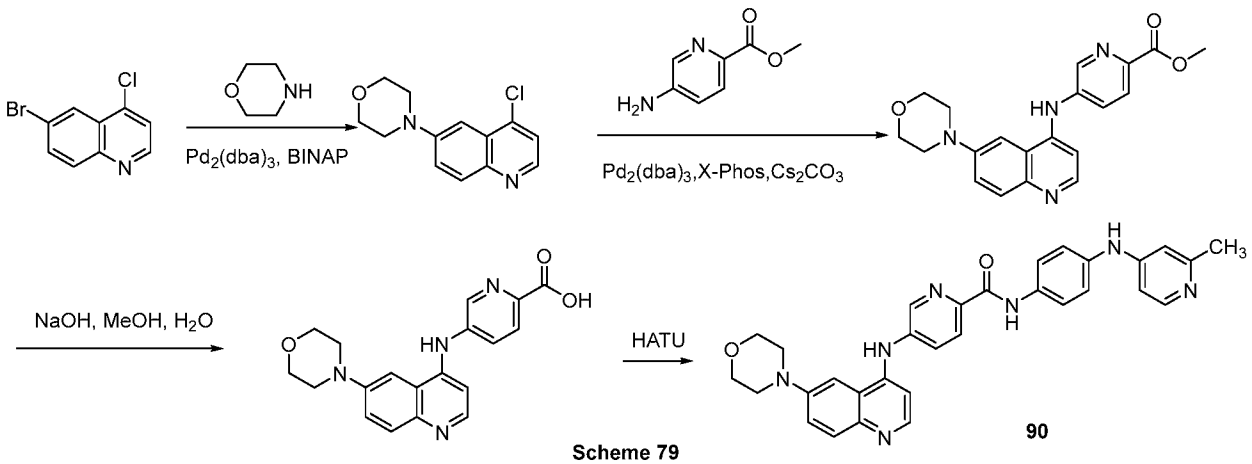
Scheme 78

[0560] **Compound 89** was prepared by the method shown in Scheme 78. **Compound 89** (N-(4-(2-methylpyridin-4-ylamino)phenyl)-6-(6-morpholinoquinolin-4-ylamino)nicotinamide) was prepared as shown in Scheme 78: $C_{31}H_{29}N_7O_2$; 531.61 g/mol; 17 mg; yellow solid; ESI-LCMS m/z = 532 $[M+H]^+$; LCMS RT = 1.51 min, >95.00% (214 nm).

Example 90: Compound 90 (N-(4-((2-methylpyridin-4-yl)amino)phenyl)-5-((6-morpholinoquinolin-4-yl)amino)picolinamide)



90

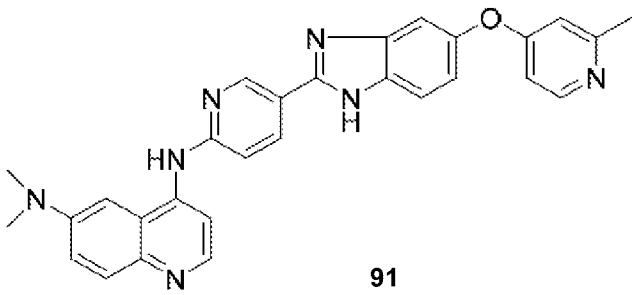


Scheme 79

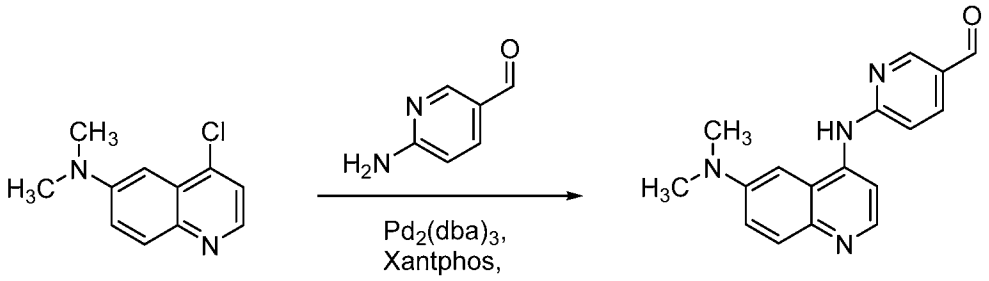
[0561] **Compound 90** was prepared by the method shown in Scheme 79. **Compound 90** (N-(4-((2-methylpyridin-4-yl)amino)phenyl)-5-((6-morpholinoquinolin-4-

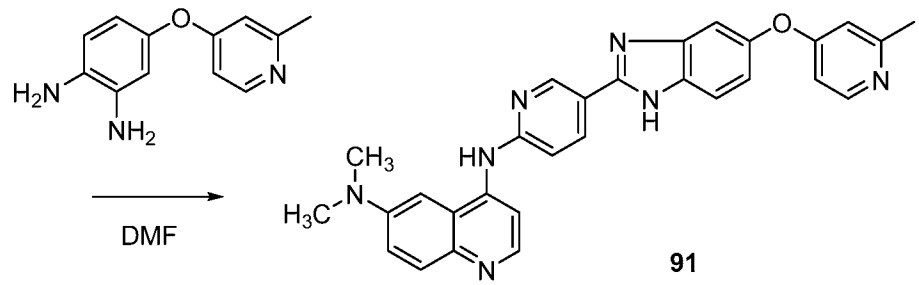
yl)amino)picolinamide) was prepared as shown in Scheme 79: $C_{31}H_{29}N_7O_2$; 531.62 g/mol; 13 mg; grey solid; ESI-LCMS m/z = 532.2 $[M+H]^+$; LCMS RT = 1.49 min, >95.00% (214 nm).

Example 91: Compound 91 (N^6,N^6-dimethyl-N^4-(5-(5-((2-methylpyridin-4-yl)oxy)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)quinoline-4,6-diamine)



91



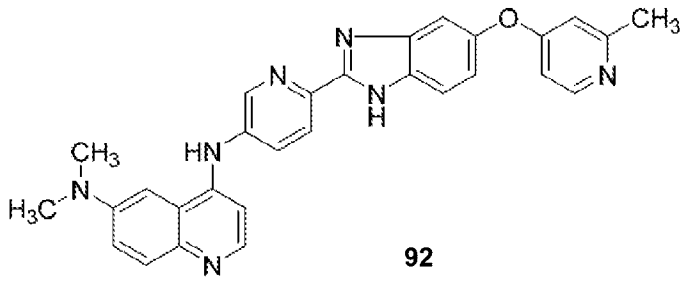


91

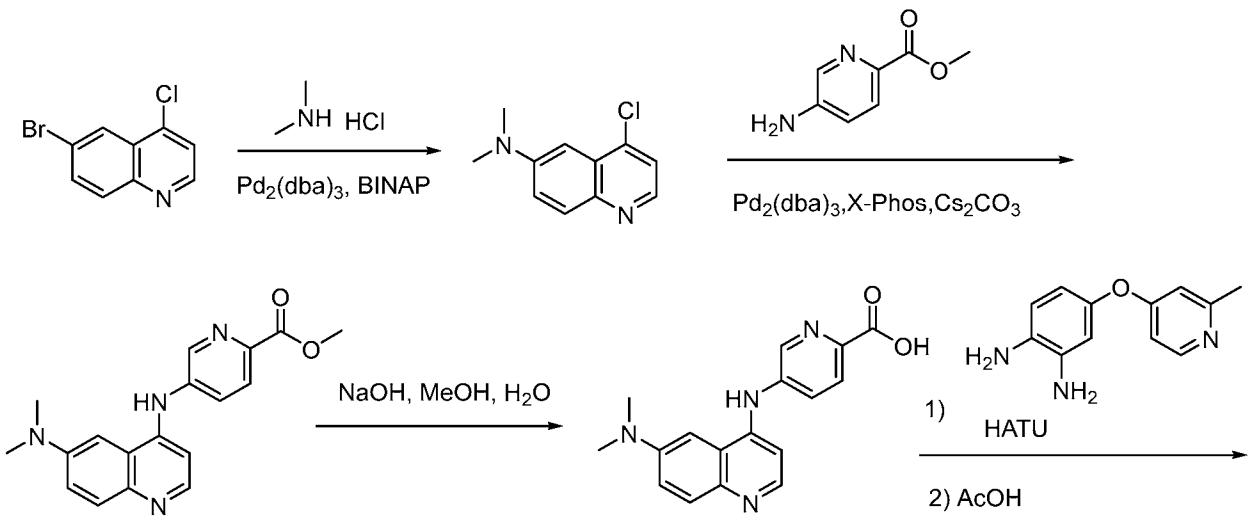
Scheme 80

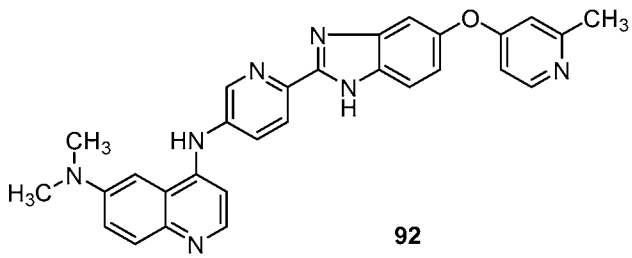
[0562] **Compound 91** was prepared by the method shown in Scheme 80. **Compound 91** (N^6,N^6-dimethyl-N^4-(5-(5-((2-methylpyridin-4-yl)oxy)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)quinoline-4,6-diamine) was prepared as shown in Scheme 80: $C_{29}H_{25}N_7O$; 487.57 g/mol; 13 mg; yellow solid; ESI-LCMS m/z = 488 $[M+H]^+$; LCMS RT = 1.66 min, >95.00% (214 nm).

Example 92: Compound 92 (N^6,N^6-dimethyl-N^4-(6-(5-((2-methylpyridin-4-yl)oxy)-1H benzo[d]imidazol-2-yl)pyridin-3-yl)quinoline-4,6-diamine)



92



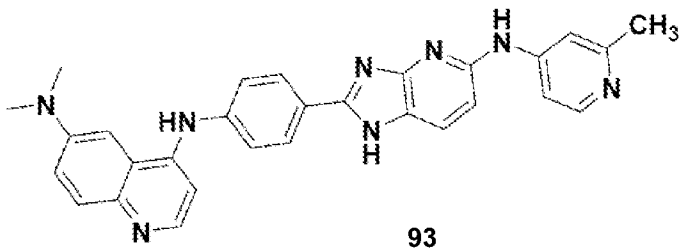


92

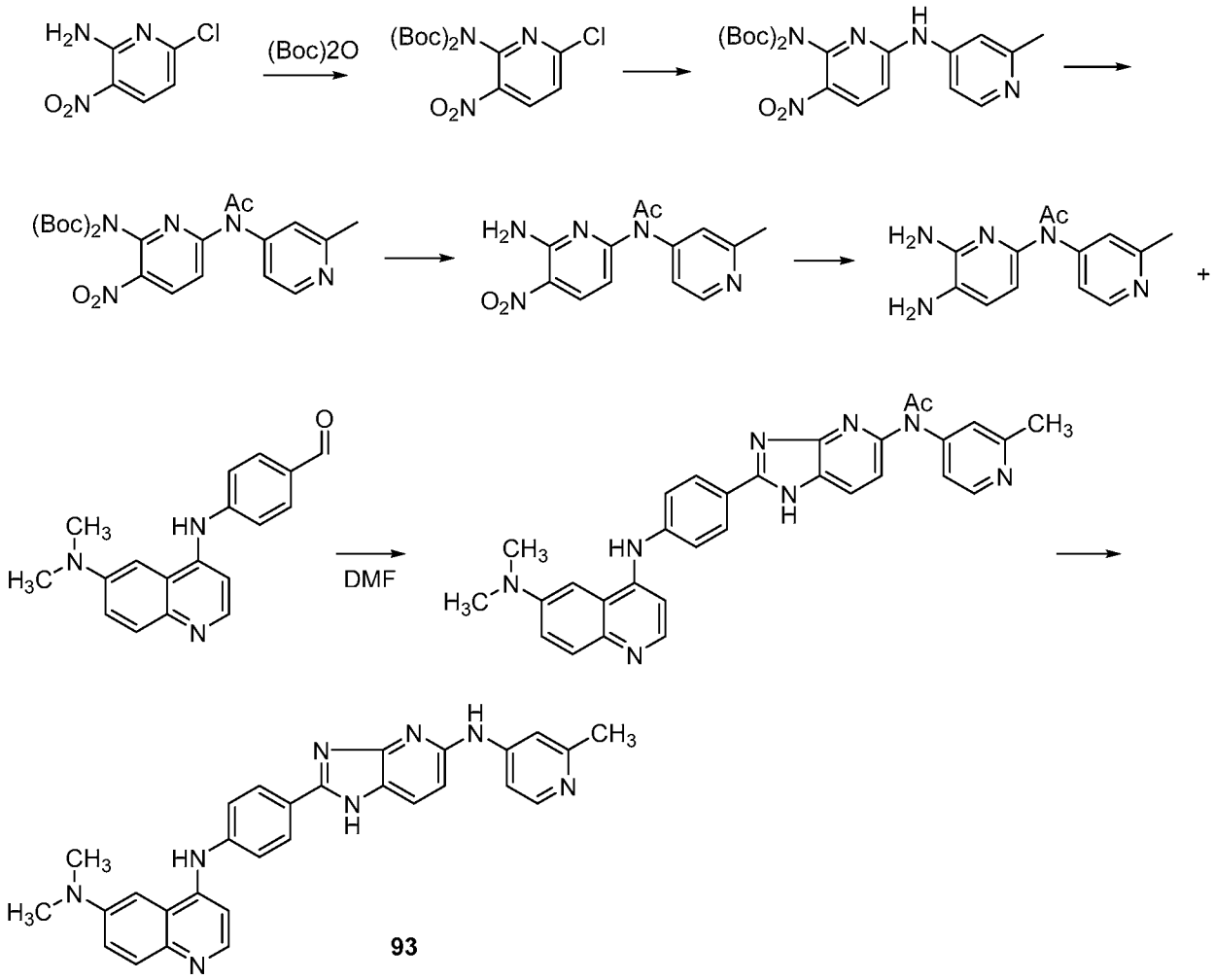
Scheme 81

[0563] **Compound 92** was prepared by the method shown in Scheme 81. **Compound 92** (N^6,N^6-dimethyl-N^4-(6-(5-((2-methylpyridin-4-yl)oxy)-1H benzo[d]imidazol-2-yl)pyridin-3-yl)quinoline-4,6-diamine) was prepared as shown in Scheme 81: $C_{29}H_{25}N_7O$; 487.57 g/mol; 25 mg; yellow solid; ESI-LCMS m/z = 488 $[M+H]^+$; LCMS RT = 1.78 min, >95.00% (214 nm).

Example 93: Compound 93 (N^6,N^6-dimethyl-N^4-(4-(5-((2-methylpyridin-4-yl)amino)-1H-imidazo[4,5-b]pyridin-2-yl)phenyl)quinoline-4,6-diamine)



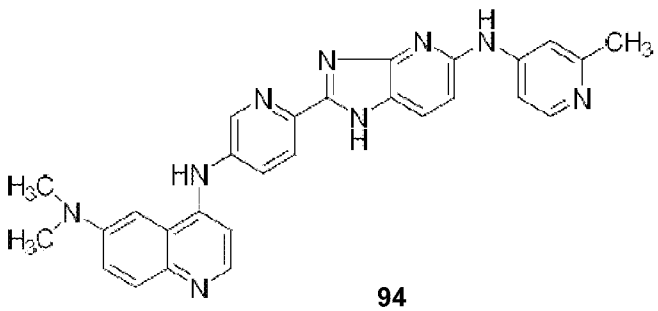
93



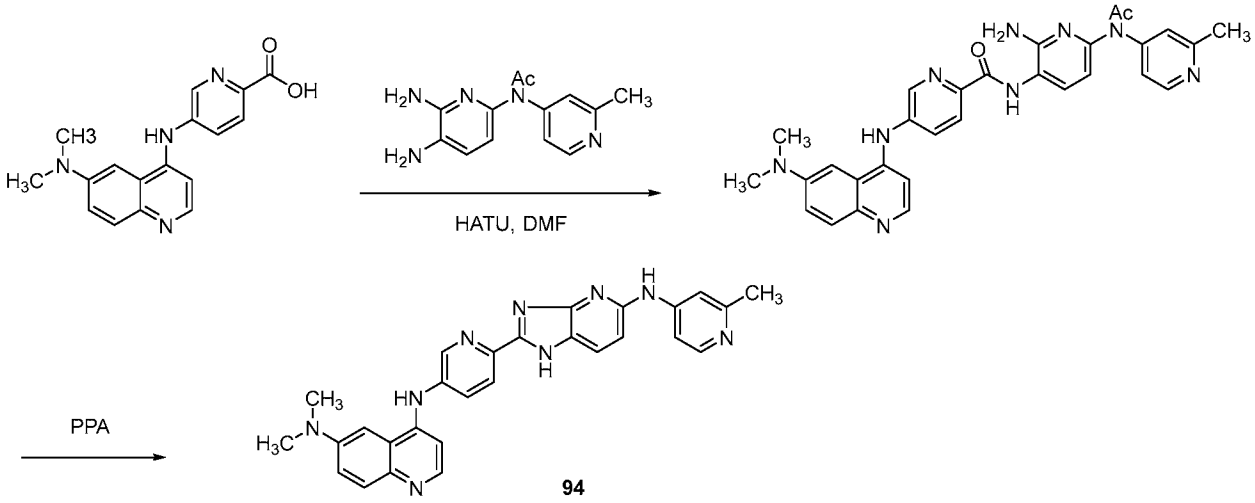
Scheme 82

[0564] **Compound 93** was prepared by the method shown in Scheme 82. **Compound 93** (N^6,N^6-dimethyl-N^4-(4-(5-((2-methylpyridin-4-yl)amino)-1H-imidazo[4,5-b]pyridin-2-yl)phenyl)quinoline-4,6-diamine) was prepared as shown in Scheme 82: $C_{29}H_{26}N_8$; 486.58 g/mol; 18 mg; yellow-brown solid; ESI-LCMS m/z = 487 $[M+H]^+$; LCMS RT = 1.401 min, >95.00% (214 nm).

Example 94: Compound 94 (N^6,N^6-dimethyl-N^4-(6-(5-((2-methylpyridin-4-yl)amino)-1H imidazo[4,5-b]pyridin-2-yl)pyridin-3-yl)quinoline-4,6-diamine)



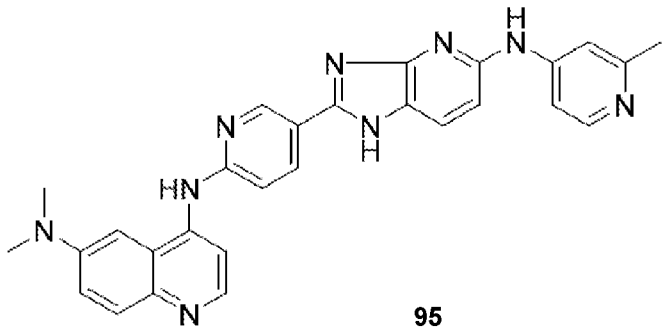
94

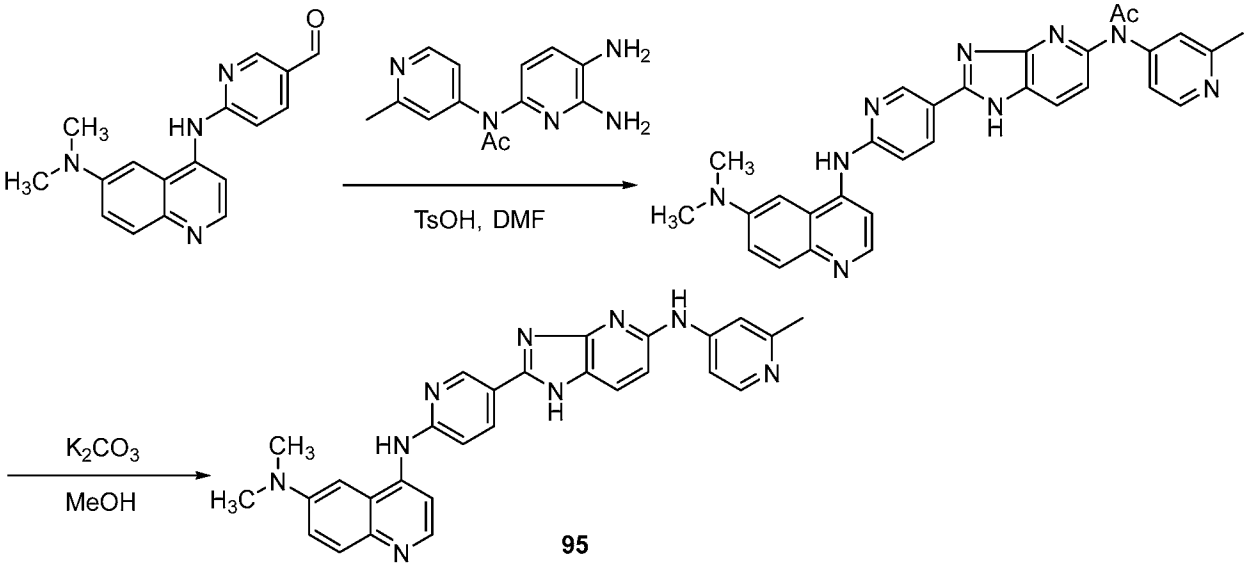


Scheme 83

[0565] **Compound 94** was prepared by the method shown in Scheme 83. **Compound 94** (N^6,N^6-dimethyl-N^4-(6-(5-((2-methylpyridin-4-yl)amino)-1H imidazo[4,5-b]pyridin-2-yl)pyridin-3-yl)quinoline-4,6-diamine) was prepared as shown in Scheme 83: $C_{28}H_{25}N_9$; 487.57 g/mol; 14 mg; grey solid; ESI-LCMS m/z = 488 $[M+H]^+$; LCMS RT = 1.39 min, >95.00% (214 nm).

Example 95: Compound 95 (N^6,N^6-dimethyl-N^4-(5-(5-((2-methylpyridin-4-yl)amino)-1H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-yl)quinoline-4,6-diamine)



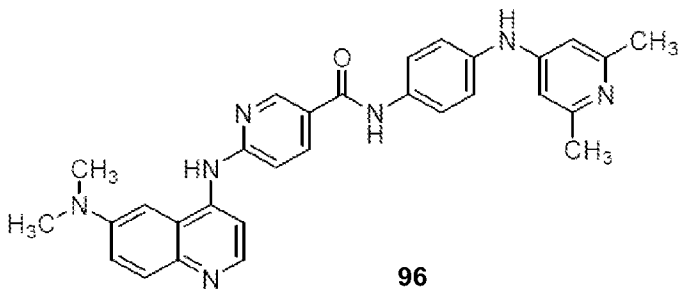


95

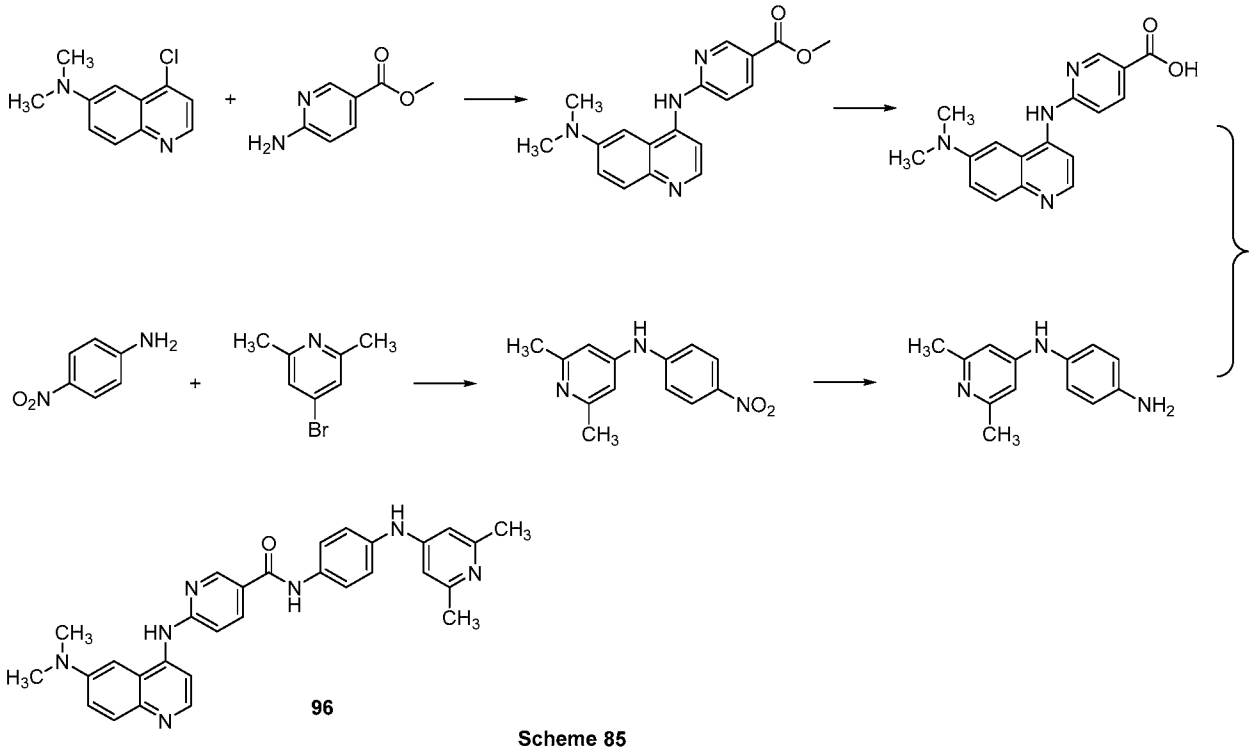
Scheme 84

[0566] **Compound 95** was prepared by the method shown in Scheme 84. **Compound 95** (N^6,N^6-dimethyl-N^4-(5-(5-((2-methylpyridin-4-yl)amino)-1H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-yl)quinoline-4,6-diamine) was prepared as shown in Scheme 84: $C_{28}H_{25}N_9$; 487.57 g/mol; 10.3 mg; green solid; ESI-LCMS m/z = 488 $[M+H]^+$; LCMS RT = 1.403 min, >95.00% (214 nm).

Example 96: Compound 96 (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2,6-dimethylpyridin-4-ylamino)phenyl)nicotinamide)



96

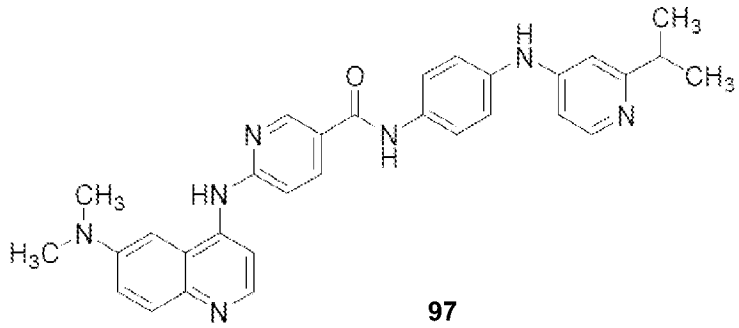


96

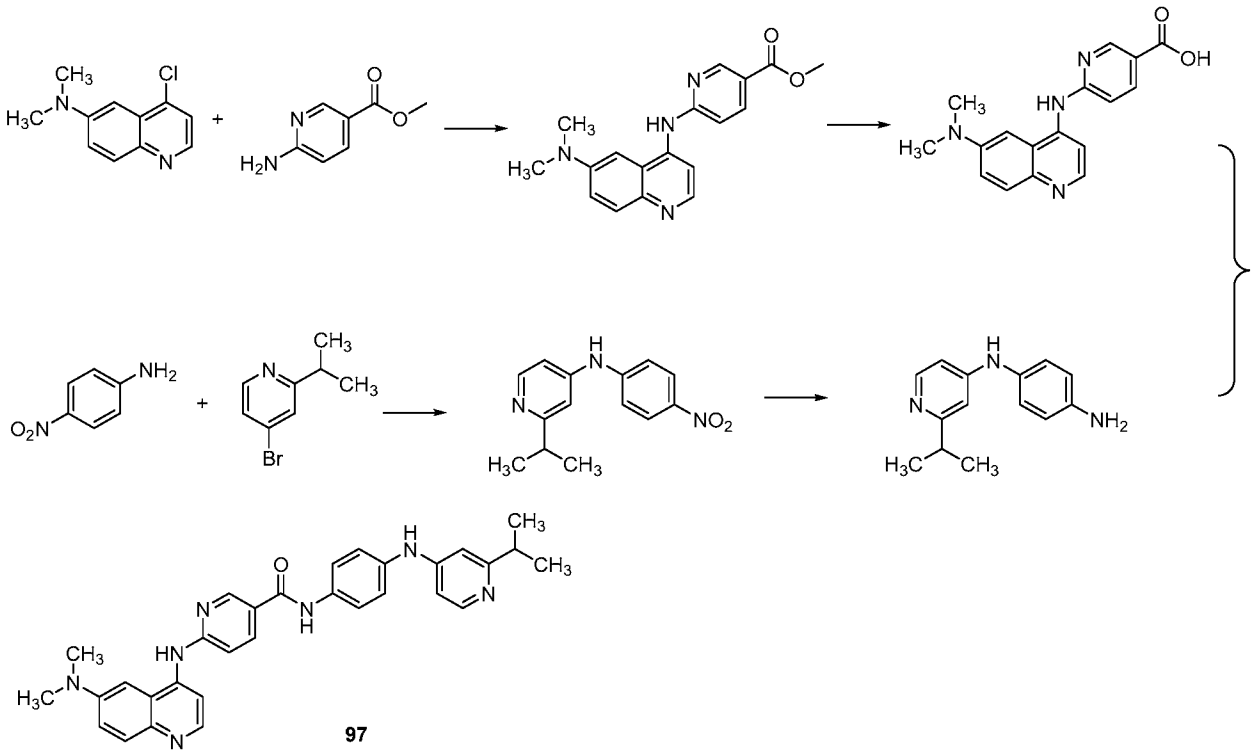
Scheme 85

[0567] **Compound 96** was prepared by the method shown in Scheme 85. **Compound 96** (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2,6-dimethylpyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 85: $C_{30}H_{29}N_7O$; 503.60 g/mol; 17 mg; yellow solid; ESI-LCMS m/z = 504 $[M+H]^+$; LCMS RT = 1.54 min, >95.00% (214 nm).

Example 97: Compound 97 (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2-isopropylpyridin-4-ylamino)phenyl)nicotinamide)



97

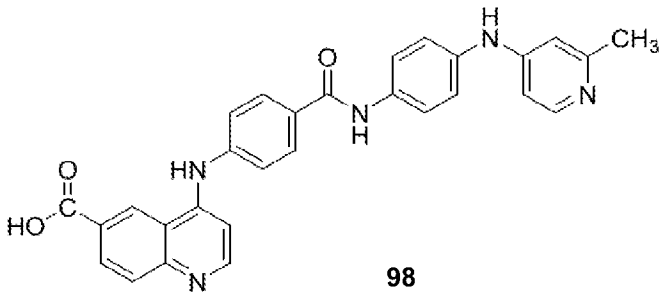


97

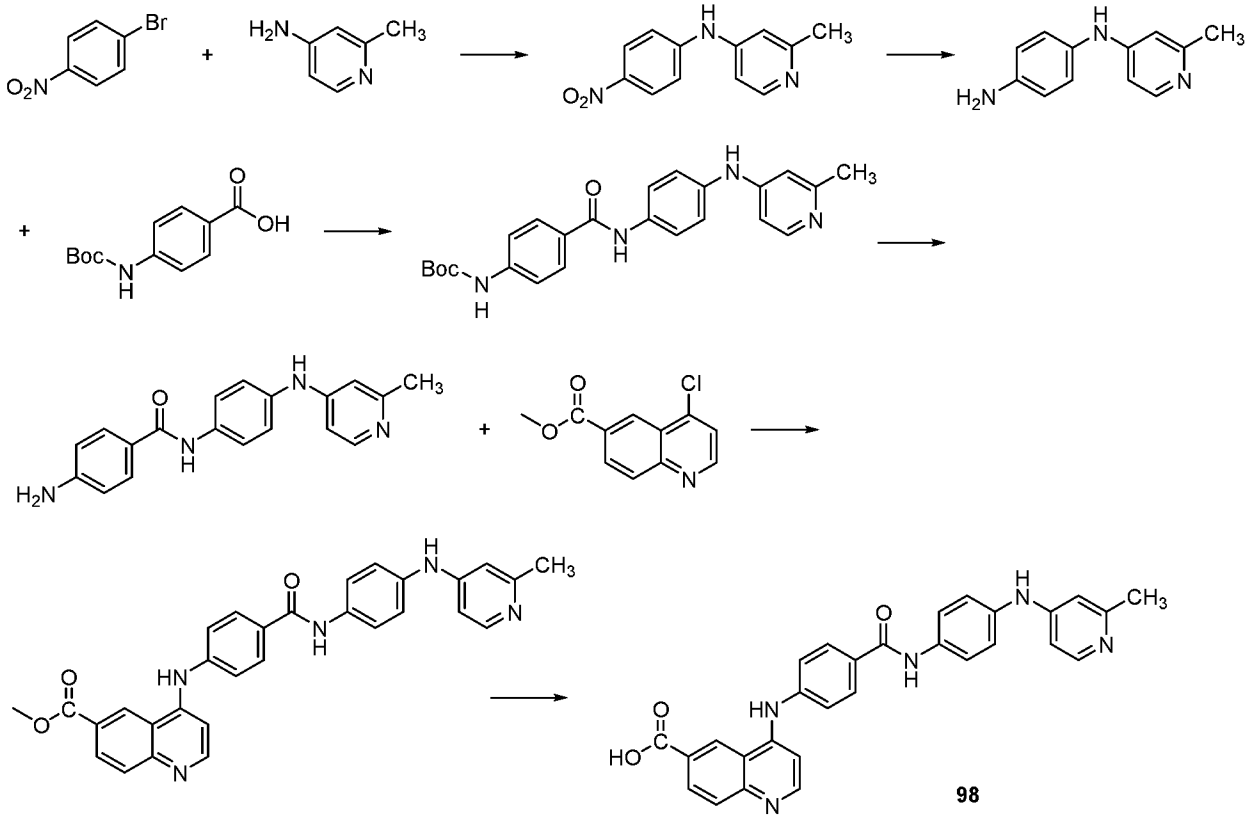
Scheme 86

[0568] **Compound 97** was prepared by the method shown in Scheme 86. **Compound 97** (6-(6-(dimethylamino)quinolin-4-ylamino)-N-(4-(2-isopropylpyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 86: $C_{31}H_{31}N_7O$; 517.62 g/mol; 20 mg; yellow solid; ESI-LCMS m/z = 518 $[M+H]^+$; LCMS RT = 1.59 min, >95.00% (214 nm).

Example 98: Compound 98 (4-((4-((4-((2-methylpyridin-4-yl)amino)phenyl)carbamoyl)phenyl)amino)quinoline-6-carboxylic acid)



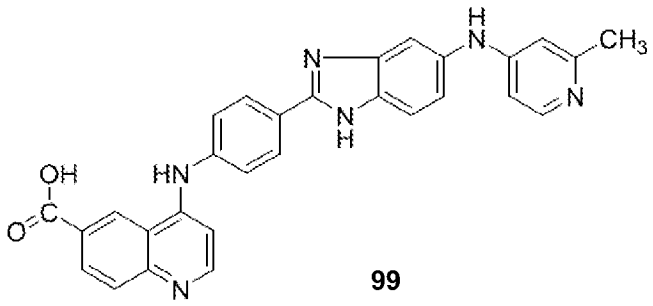
98



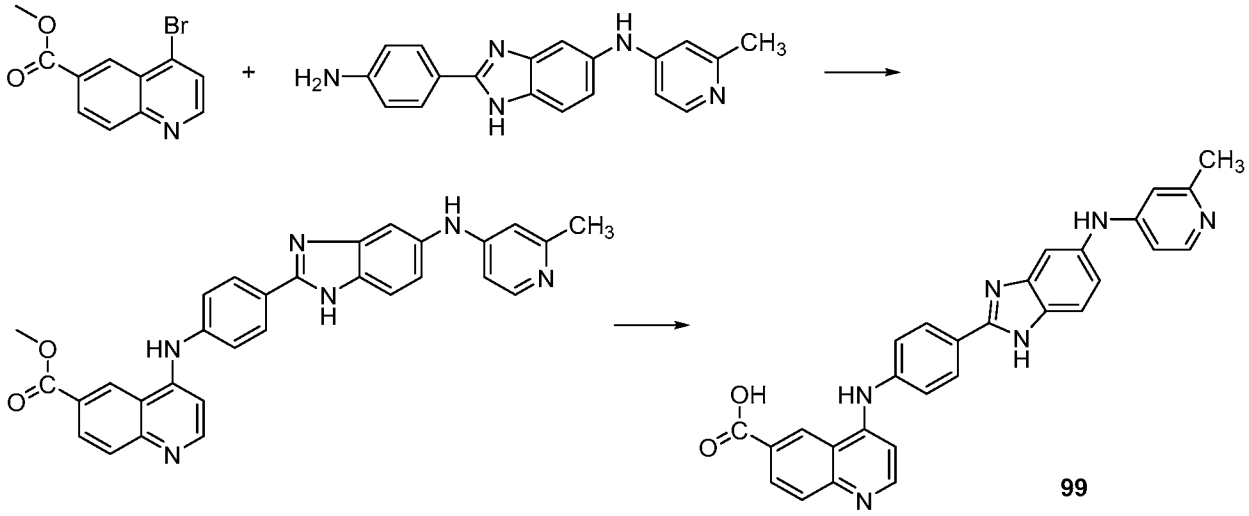
Scheme 87

[0569] **Compound 98** was prepared by the method shown in Scheme 87. **Compound 98** (4-((4-((4-((2-methylpyridin-4-yl)amino)phenyl)carbamoyl)phenyl)amino)quinoline-6-carboxylic acid) was prepared as shown in Scheme 87: $C_{29}H_{23}N_5O_3$; 489.54 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 490 $[M+H]^+$; LCMS RT = 1.07 min, >95.00% (214 nm).

Example 99: Compound 99 (4-((4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)amino)quinoline-6-carboxylic acid)



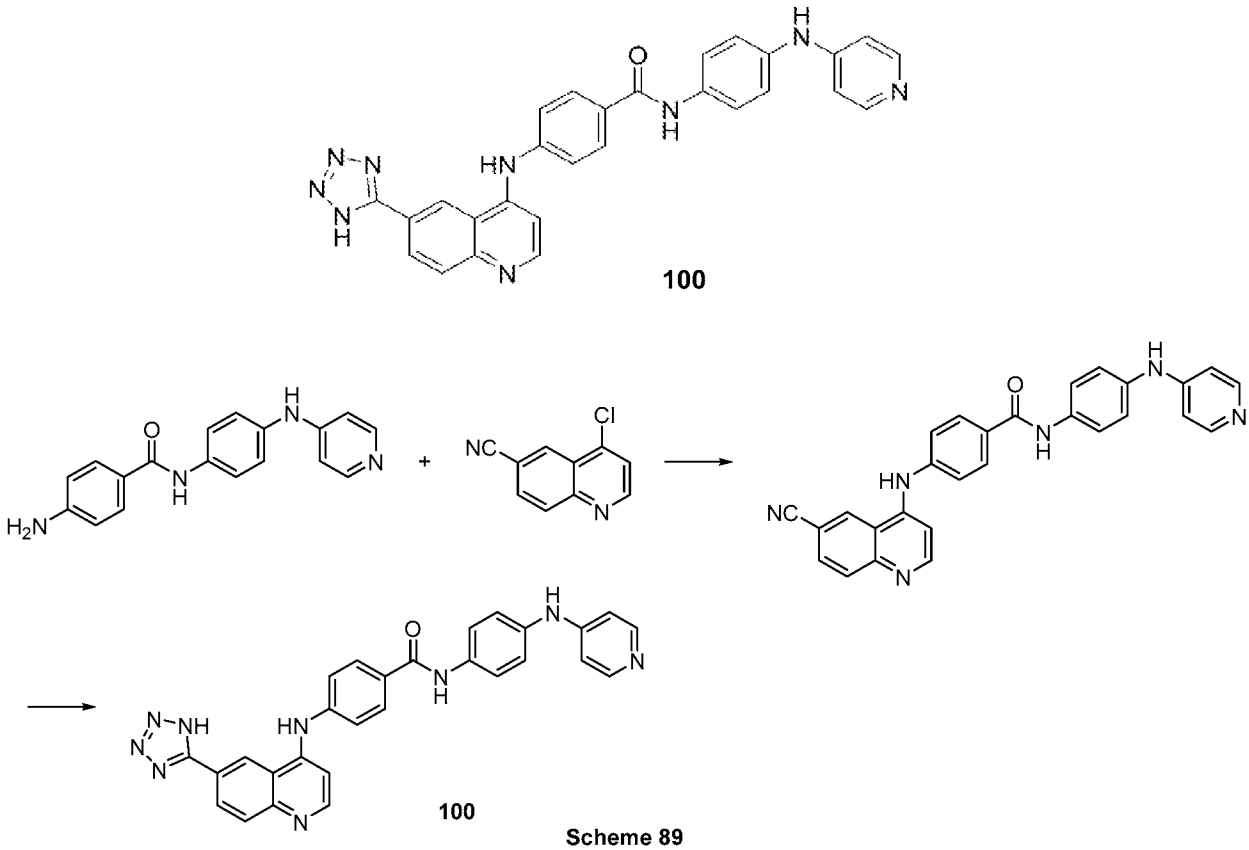
99



Scheme 88

[0570] **Compound 99** was prepared by the method shown in Scheme 88. **Compound 99** (4-((4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)amino)quinoline-6-carboxylic acid) was prepared as shown in Scheme 88: $C_{29}H_{22}N_6O_2$; 486.54 g/mol; 11 mg; yellow solid; ESI-LCMS m/z = 487 $[M+H]^+$; LCMS RT = 1.39 min, >95.00% (214 nm).

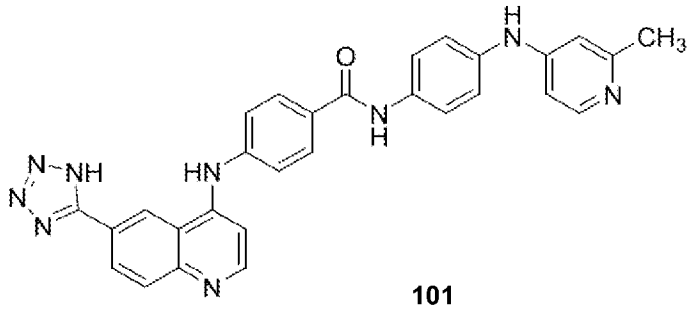
Example 100: Compound 100 (4-((6-(1H-tetrazol-5-yl)quinolin-4-yl)amino)-N-(4-(pyridin- 4-ylamino)phenyl)benzamide)



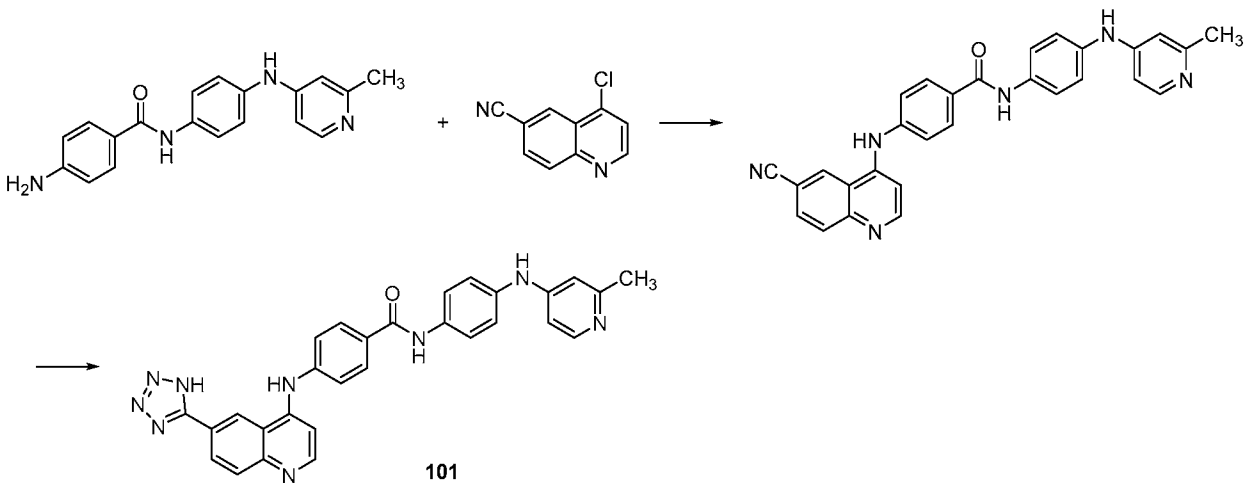
Scheme 89

[0571] **Compound 100** was prepared by the method shown in Scheme 89. **Compound 100** (4-((6-(1H-tetrazol-5-yl)quinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide) was prepared as shown in Scheme 89: $C_{28}H_{21}N_9O$; 499.54 g/mol; 16 mg; pale yellow solid; ESI-LCMS m/z = 500 $[M+H]^+$; LCMS RT = 1.14 min, >95.00% (214 nm).

Example 101: Compound 101 (4-((6-(1H-tetrazol-5-yl)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide)



101

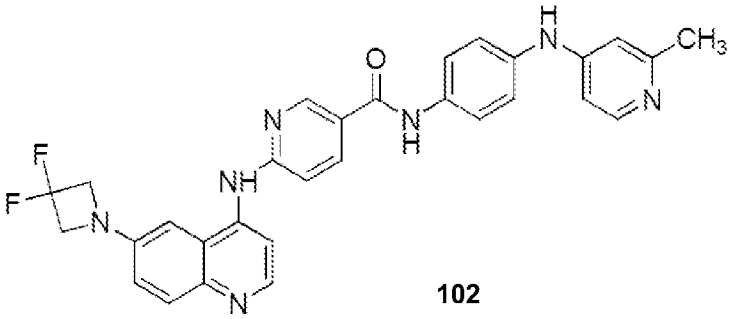


101

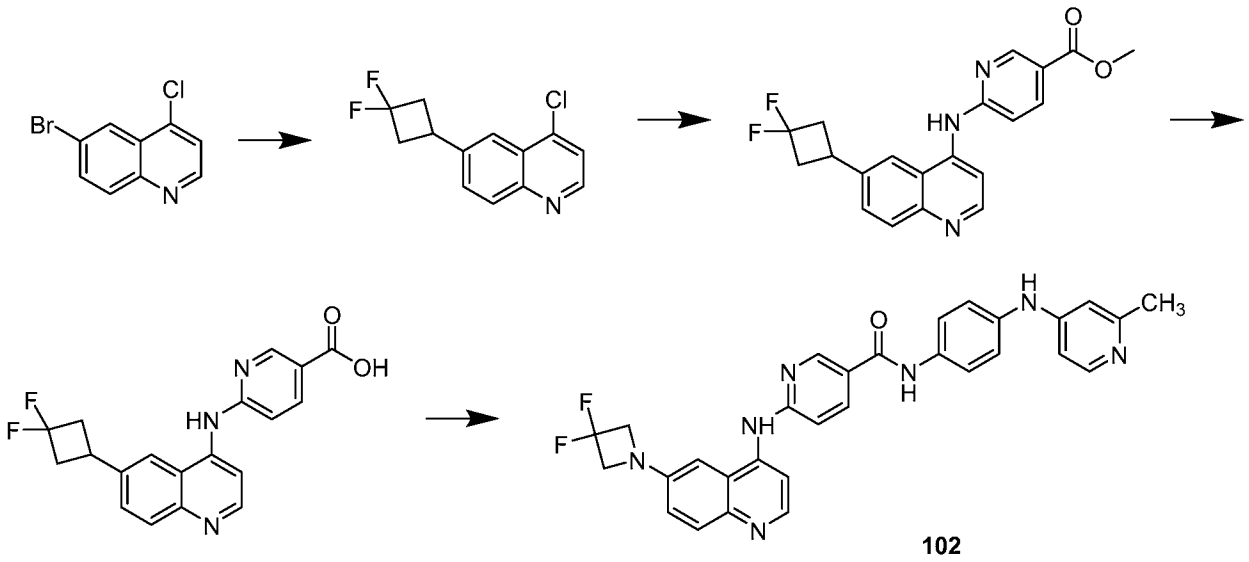
Scheme 90

[0572] **Compound 101** was prepared by the method shown in Scheme 90. **Compound 101** (4-((6-(1H-tetrazol-5-yl)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide) was prepared as shown in Scheme 90: $C_{29}H_{23}N_9O$; 513.57 g/mol; 18 mg; pale yellow solid; ESI-LCMS m/z = 514 $[M+H]^+$; LCMS RT = 1.11 min, >95.00% (214 nm).

Example 102: Compound 102 (6-(6-(3,3-difluoroazetidin-1-yl)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)nicotinamide)



102

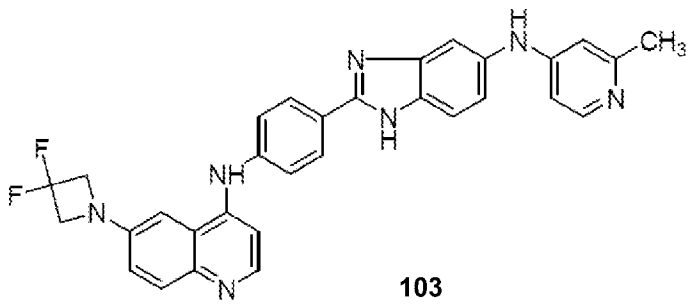


102

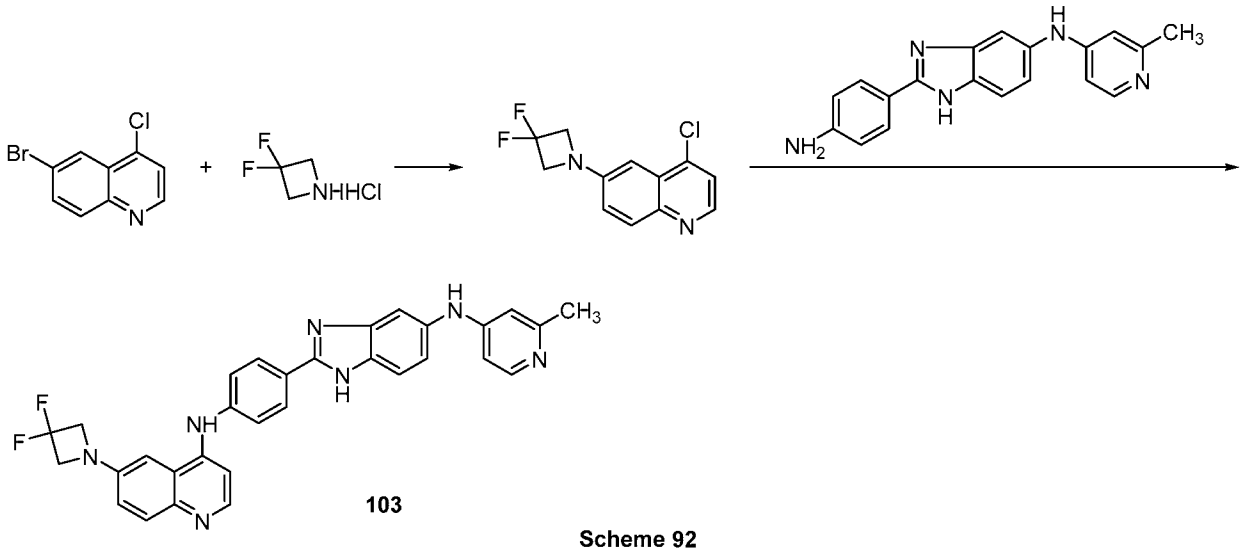
Scheme 91

[0573] **Compound 102** was prepared by the method shown in Scheme 91. **Compound 102** (6-(6-(3,3-difluoroazetidin-1-yl)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 91: $C_{30}H_{25}F_2N_7O$; 537.56 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 538 $[M+H]^+$; LCMS RT = 1.54 min, >95.00% (214 nm).

Example 103: Compound 103 (6-(3,3-difluoroazetidin-1-yl)-N-(4-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine)



103

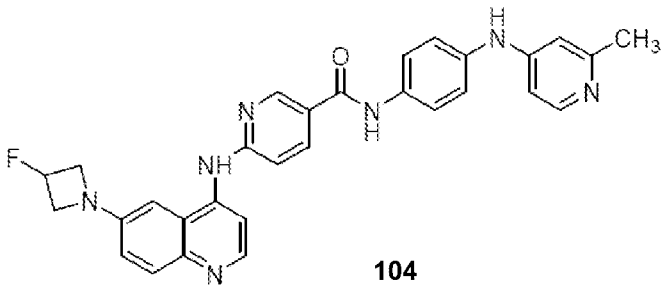


103

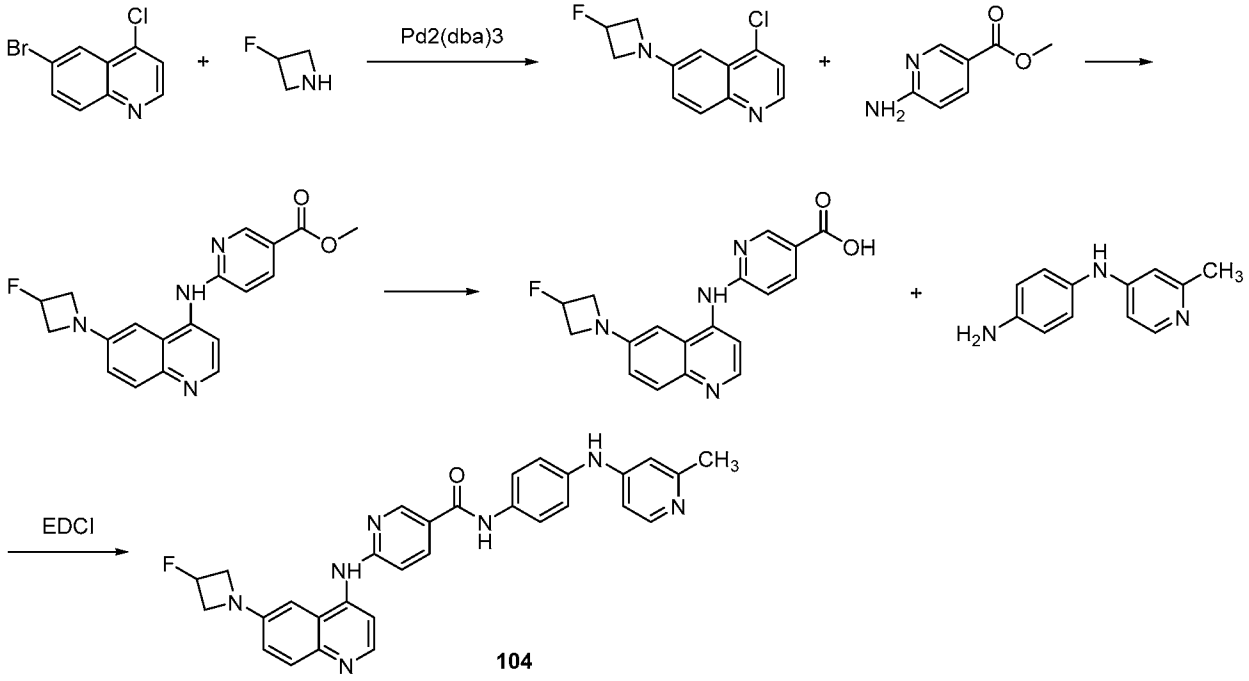
Scheme 92

[0574] **Compound 103** was prepared by the method shown in Scheme 92. **Compound 103** (6-(3,3-difluoroazetidin-1-yl)-N-(4-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine) was prepared as shown in Scheme 92: $C_{31}H_{25}F_2N_7$; 533.57 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 534 $[M+H]^+$; LCMS RT = 1.55 min, >95.00% (214 nm).

Example 104: Compound 104 (6-((6-(3-fluoroazetidin-1-yl)quinolin-4-yl)amino)-N-(4-((2- methylpyridin-4-yl)amino)phenyl)nicotinamide)



104

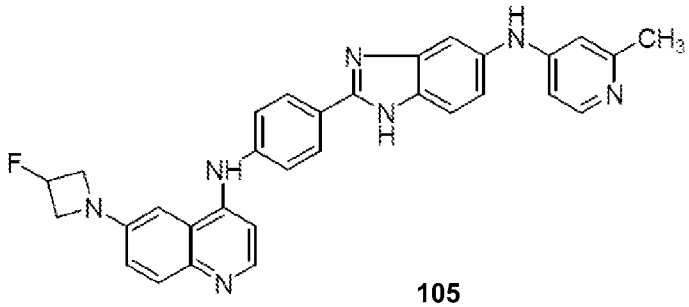


104

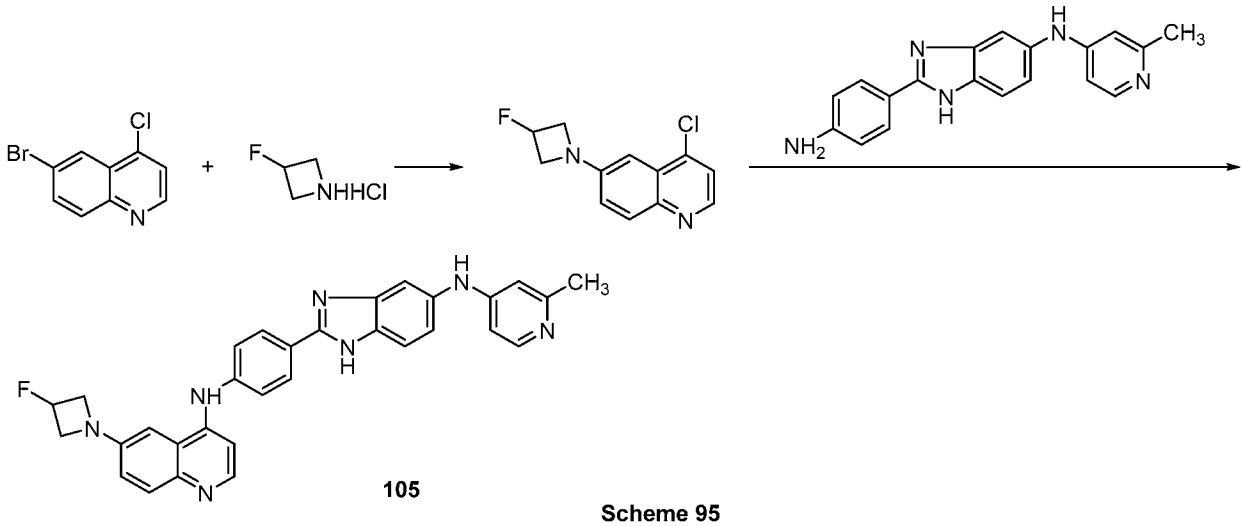
Scheme 94

[0575] **Compound 104** was prepared by the method shown in Scheme 94. **Compound 104** (6-((6-(3-fluoroazetidin-1-yl)quinolin-4-yl)amino)-N-(4-((2- methylpyridin-4-yl)amino)phenyl)nicotinamide) was prepared as shown in Scheme 94: $C_{30}H_{26}FN_7O$; 519.58 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 520 $[M+H]^+$; LCMS RT = 1.51 min, >95.00% (214 nm).

Example 105: Compound 105 (6-(3-fluoroazetidin-1-yl)-N-(4-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine)



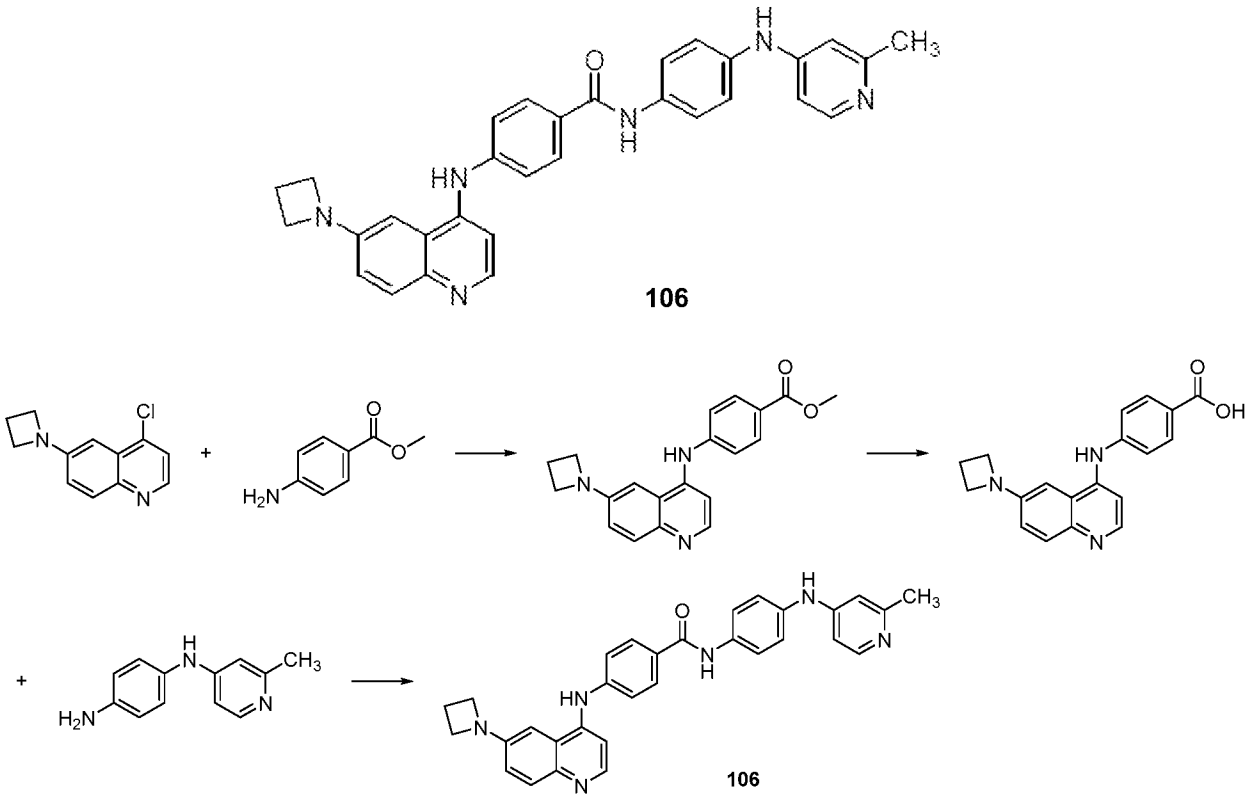
105



Scheme 95

[0576] **Compound 105** was prepared by the method shown in Scheme 95. **Compound 105** (6-(3-fluoroazetidin-1-yl)-N-(4-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine) was prepared as shown in Scheme 95: $C_{31}H_{26}FN_7$; 515.58 g/mol; 18 mg; pale yellow solid; ESI-LCMS m/z = 516 $[M+H]^+$; LCMS RT = 1.49 min, >95.00% (214 nm).

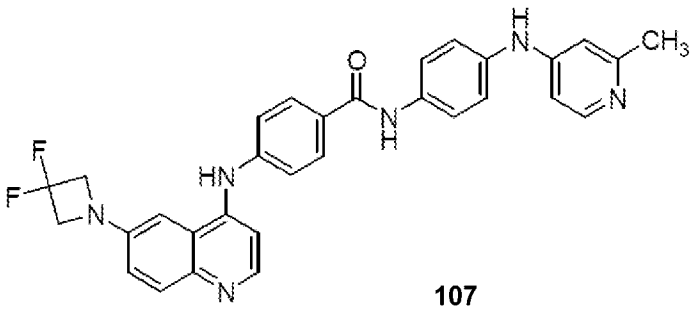
Example 106: Compound 106 (4-((6-(azetidin-1-yl)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide)



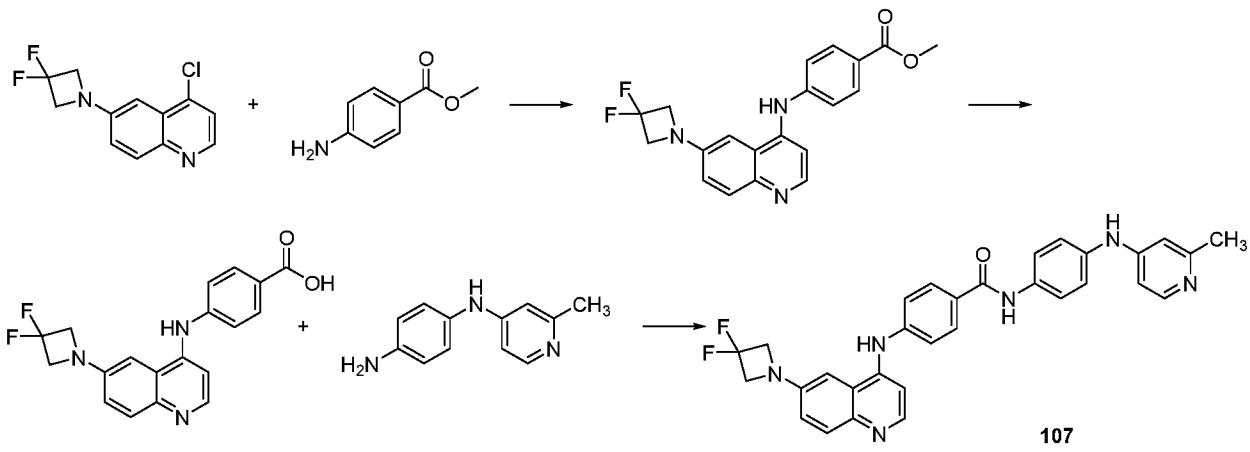
Scheme 96

[0577] **Compound 106** was prepared by the method shown in Scheme 96. **Compound 106** (4-((6-(azetidin-1-yl)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide) was prepared as shown in Scheme 96: $C_{31}H_{28}FN_6O$; 500.61 g/mol; 20 mg; pale yellow solid; ESI-LCMS m/z = 501 $[M+H]^+$; LCMS RT = 1.53 min, >95.00% (214 nm).

Example 107: Compound 107 (4-((6-(3,3-difluoroazetidin-1-yl)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide)



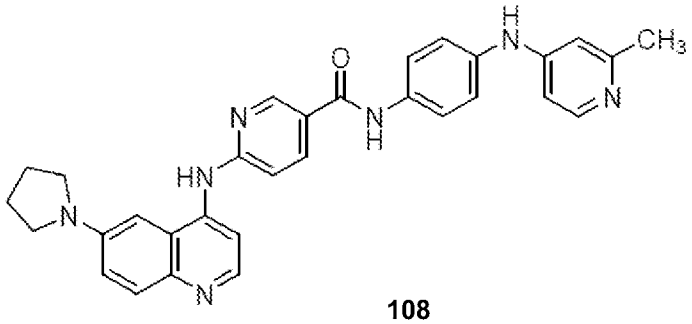
107



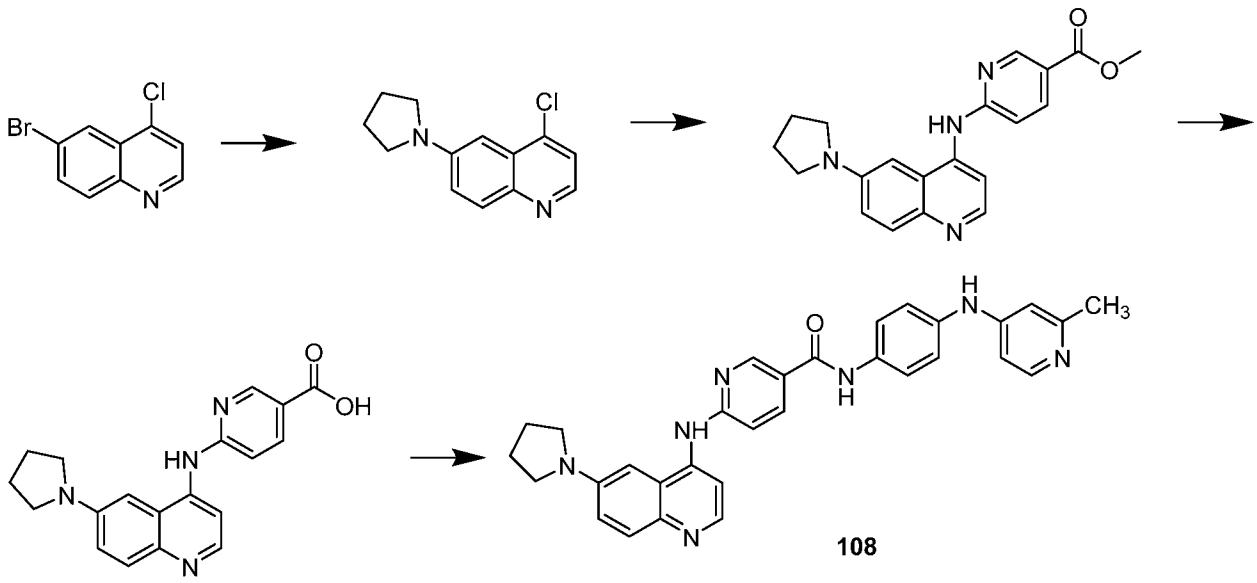
Scheme 97

[0578] **Compound 107** was prepared by the method shown in Scheme 97. **Compound 107** (4-((6-(3,3-difluoroazetidin-1-yl)quinolin-4-yl)amino)-N-(4-((2-methylpyridin-4-yl)amino)phenyl)benzamide) was prepared as shown in Scheme 97: $C_{31}H_{26}F_2N_6O$; 536.59 g/mol; 15 mg; pale yellow solid; ESI-LCMS m/z = 537 $[M+H]^+$; LCMS RT = 1.52 min, >95.00% (214 nm).

Example 108: Compound 108 (N-(4-(2-methylpyridin-4-ylamino)phenyl)-6-(6-(pyrrolidin-1-yl)quinolin-4-ylamino)nicotinamide)



108

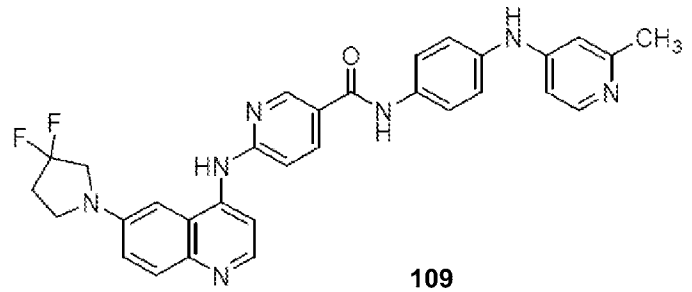


108

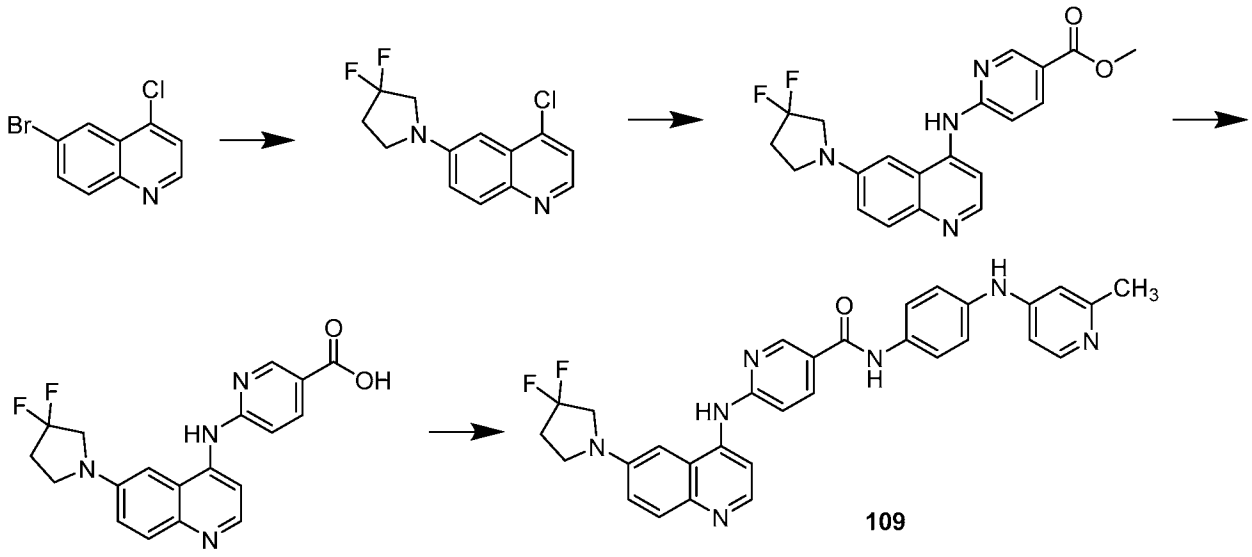
Scheme 98

[0579] **Compound 108** was prepared by the method shown in Scheme 98. **Compound 108** (N-(4-(2-methylpyridin-4-ylamino)phenyl)-6-(6-(pyrrolidin-1-yl)quinolin-4-ylamino)nicotinamide) was prepared as shown in Scheme 98: $C_{31}H_{29}N_7O$; 515.61 g/mol; 10 mg; pale yellow solid; ESI-LCMS m/z = 516 $[M+H]^+$; LCMS RT = 1.61 min, >95.00% (214 nm).

Example 109: Compound 109 (6-(6-(3,3-difluoropyrrolidin-1-yl)quinolin-4-ylamino)-N-(4- (2-methylpyridin-4-ylamino)phenyl)nicotinamide)



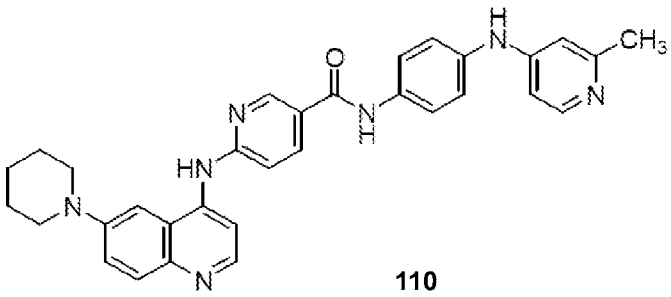
109



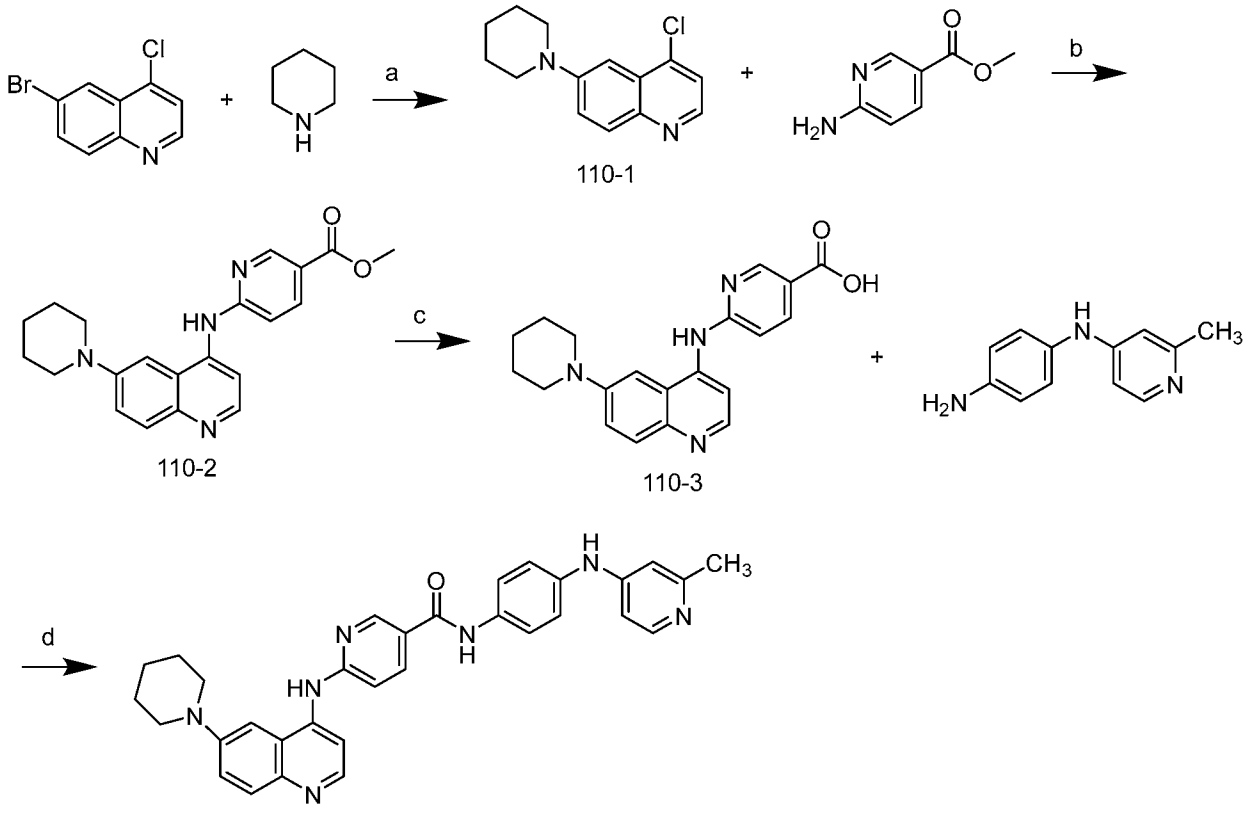
Scheme 99

[0580] **Compound 109** was prepared by the method shown in Scheme 99. **Compound 109** (6-(6-(3,3-difluoropyrrolidin-1-yl)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)nicotinamide) was prepared as shown in Scheme 99: $C_{31}H_{27}F_2N_7O$; 551.59 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 552 $[M+H]^+$; LCMS RT = 1.56 min, >95.00% (214 nm).

Example 110: Compound 110 (N-(4-(2-methylpyridin-4-ylamino)phenyl)-6-(6-(piperidin-1-yl)quinolin-4-ylamino)nicotinamide)



110



Scheme 100

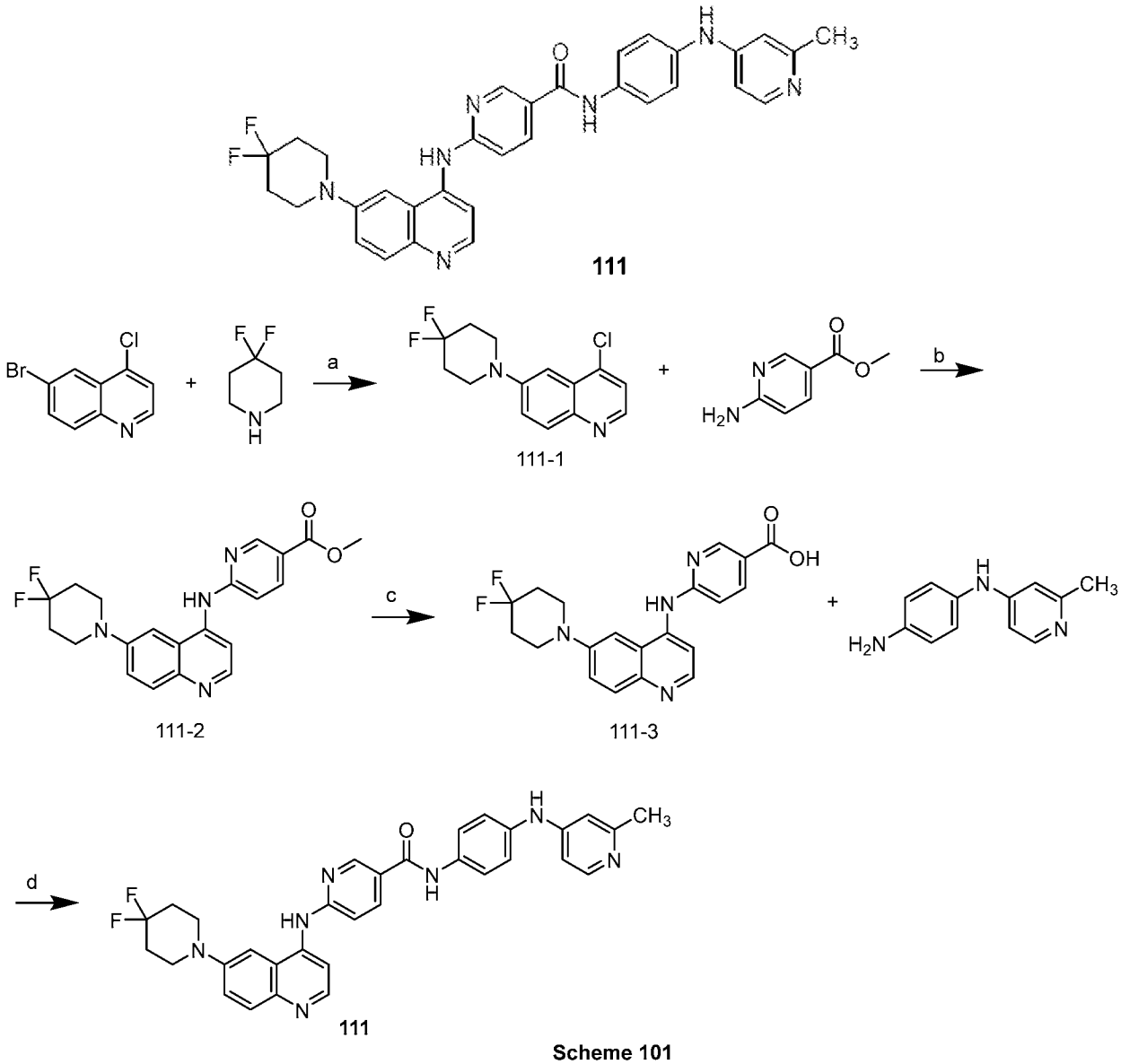
[0581] Step a: To a solution of 6-bromo-4-chloroquinoline (362 mg, 1.5 mmol) and piperidine (127 mg, 1.5 mmol) in 1,4-dioxane (4 mL) was added Cs_2CO_3 (716mg, 2.2 mmol), $Pd_2(dba)_3$ (30 mg), and Xantphos(30 mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 110-1 (250 mg, 67.8%).

[0582] Step b: To a solution of Compound 110-1 (250 mg, 1.0 mmol) and methyl 6-aminonicotinate (154 mg, 1.0 mmol) in 1,4-dioxane (4 mL) was added Cs_2CO_3 (487 mg, 1.5 mmol), $Pd_2(dba)_3$ (20 mg), and Xantphos (20 mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 110-2 (200 mg, 55.2%).

[0583] Step c: To a stirring solution of Compound 110-2 (200 mg, 0.55 mmol) in MeOH (3 mL) was added NaOH (1 mL, 2 N). The resulting mixture was stirred at room temperature for 2 hours. The reaction was concentrated, the pH adjusted to 4 with 1 N HCl, and filtered to give Compound 110-3 (167 mg, 87%).

[0584] Step d: To a stirring solution of Compound 110-3 (164 mg, 0.47 mmol) and N1-(2-methylpyridin-4-yl)benzene-1,4-diamine (94 mg, 0.47 mmol) in DMF (2 mL) was added EDCI (135 mg, 0.7 mmol) and DMAP (85 mg, 0.7 mmol). The mixture was stirred at room temperature for 8 hours. The reaction was purified by prep-HPLC to afford **Compound 110** (N-(4-(2-methylpyridin-4-ylamino)phenyl)-6-(6-(piperidin-1-yl)quinolin-4-ylamino)nicotinamide) as a pale yellow solid (18 mg, 7.2%): $C_{32}H_{31}N_7O$; 529.63 g/mol; ESI-LCMS m/z = 530 $[M+H]^+$; LCMS RT = 1.60 min, >95.00% (214 nm).

Example 111: Compound 111 (6-(6-(4,4-difluoropiperidin-1-yl)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)nicotinamide



[0585] Step a: To a solution of 6-bromo-4-chloroquinoline (362 mg, 1.5 mmol) and piperidine (181 mg, 1.5 mmol) in 1,4-dioxane (4 mL) was added Cs_2CO_3 (716 mg, 2.2

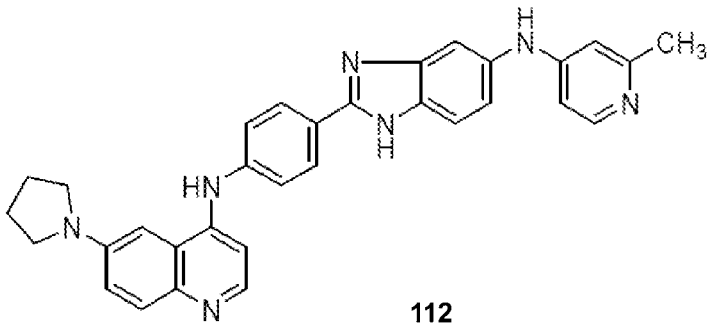
mmol), $Pd_2(dba)_3$ (30 mg), and Xantphos (30 mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 111-1 (275 mg, 65%).

[0586] Step b: To a solution of Compound 111-1 (275 mg, 0.97 mmol) and methyl 6-aminonicotinate (154 mg, 1.0 mmol) in 1,4-dioxane (4 mL) was added Cs_2CO_3 (487 mg, 1.5 mmol), $Pd_2(dba)_3$ (20 mg), and Xantphos (20 mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 111-2 (216 mg, 56%).

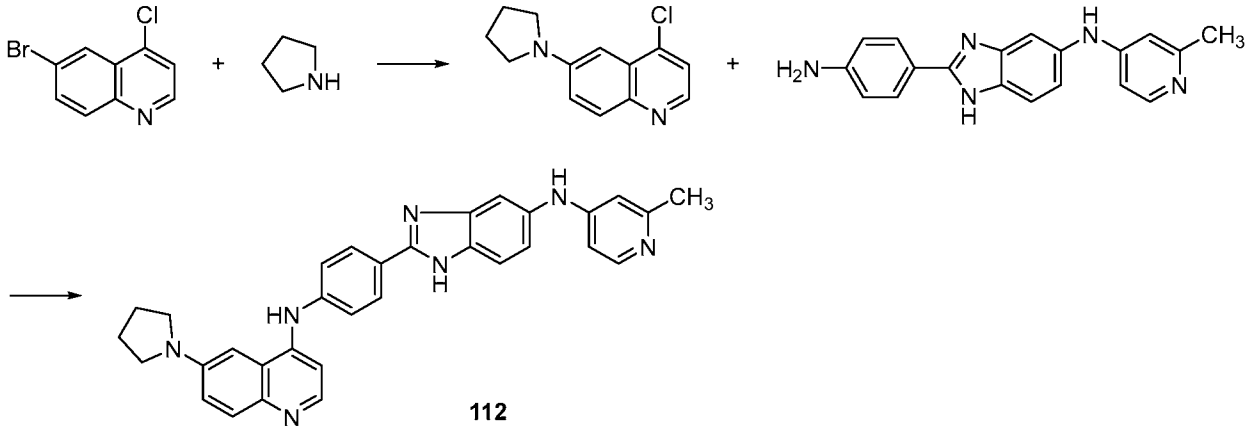
[0587] Step c: To a stirring solution of Compound 111-2 (216 mg, 0.54 mmol) in MeOH (3 mL) was added NaOH (1 mL, 2 N). The resulting mixture was stirred at room temperature for 2 hours. The reaction was concentrated, the pH adjusted to 4 with 1 N HCl, and filtered to give Compound 111-3 (190 mg, 92%).

[0588] Step d: To a stirring solution of Compound 111-3 (180 mg, 0.47 mmol) and N1-(2-methylpyridin-4-yl)benzene-1,4-diamine (94 mg, 0.47 mmol) in DMF (2 mL) was added EDCI (135 mg, 0.7 mmol) and DMAP (85 mg, 0.7 mmol). The mixture was stirred at room temperature for 8 hours. The reaction was purified by prep-HPLC to afford **Compound 111** (6-(6-(4,4-difluoropiperidin-1-yl)quinolin-4-ylamino)-N-(4-(2-methylpyridin-4-ylamino)phenyl)nicotinamide) as a pale yellow solid (20 mg, 7.5%): $C_{32}H_{29}F_2N_7O$; 565.62 g/mol; ESI-LCMS m/z = 566 $[M+H]^+$; LCMS RT = 1.58 min, >95.00% (214 nm).

Example 112: Compound 112 (N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)-6-(pyrrolidin-1-yl)quinolin-4-amine)



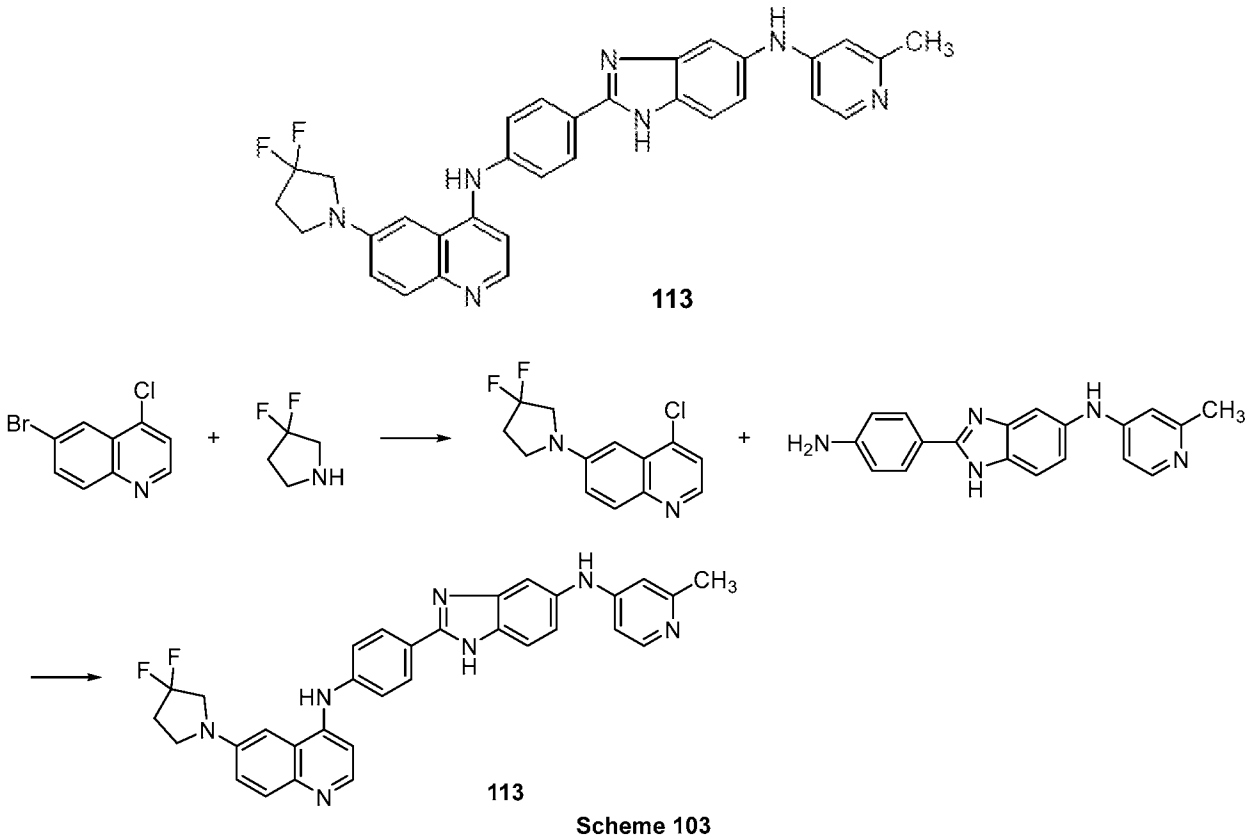
112



Scheme 102

[0589] **Compound 112** was prepared by the method shown in Scheme 102. **Compound 112** (N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)-6-(pyrrolidin-1-yl)quinolin-4-amine) was prepared as shown in Scheme 102: $C_{32}H_{29}N_7$; 511.63 g/mol; 11 mg; pale yellow solid; ESI-LCMS m/z = 512 $[M+H]^+$; LCMS RT = 1.57 min, >95.00% (214 nm).

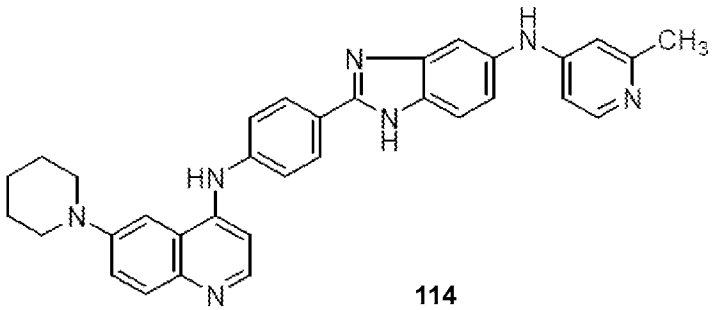
Example 113: Compound 113 (6-(3,3-difluoropyrrolidin-1-yl)-N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine)



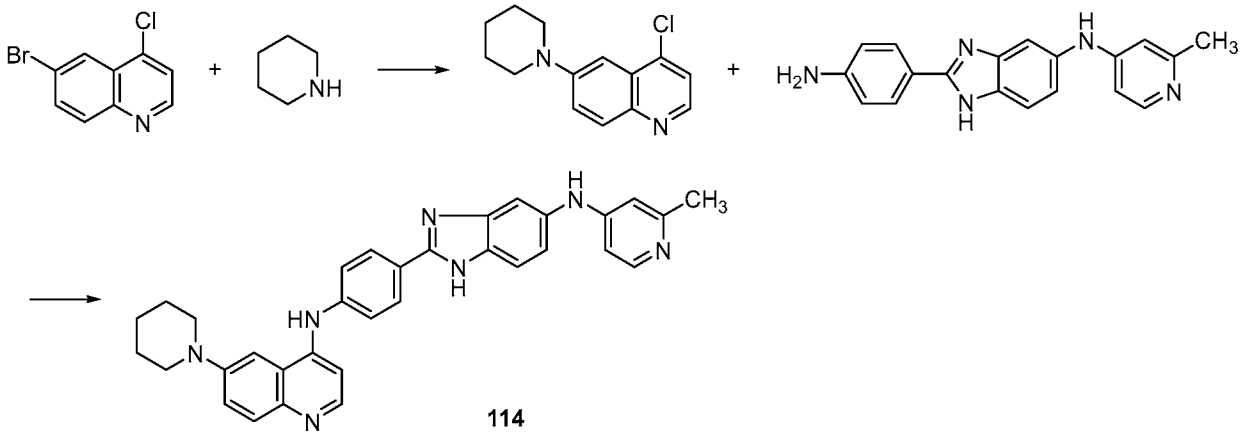
Scheme 103

[0590] **Compound 113** was prepared by the method shown in Scheme 103. **Compound 113** (6-(3,3-difluoropyrrolidin-1-yl)-N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine) was prepared as shown in Scheme 103: $C_{32}H_{27}F_2N_7$; 547.61 g/mol; 10 mg; pale yellow solid; ESI-LCMS m/z = 548 $[M+H]^+$; LCMS RT = 1.55 min, >95.00% (214 nm).

Example 114: Compound 114 (N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)-6-(piperidin-1-yl)quinolin-4-amine)



114

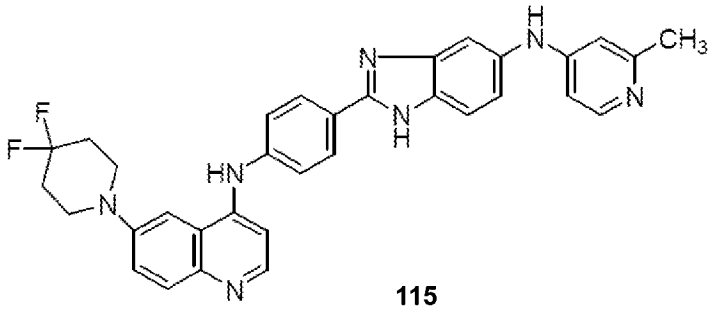


114

Scheme 104

[0591] **Compound 114** was prepared by the method shown in Scheme 104. **Compound 114** (N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)-6-(piperidin-1-yl)quinolin-4-amine) was prepared as shown in Scheme 104: $C_{33}H_{31}N_7$; 525.66 g/mol; 10 mg; pale yellow solid; ESI-LCMS m/z = 526 $[M+H]^+$; LCMS RT = 1.57 min, >95.00% (214 nm).

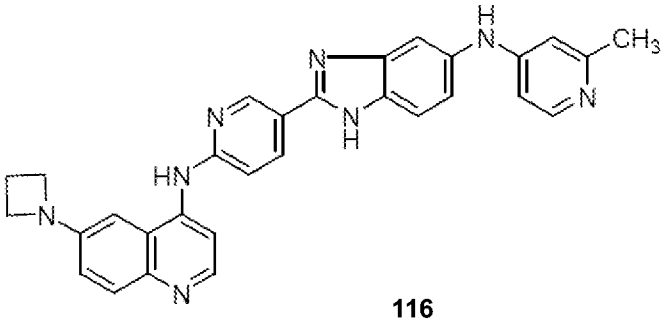
Example 115: Compound 115 (6-(4,4-difluoropiperidin-1-yl)-N-(4-(5-((2-methylpyridin-4- yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine)



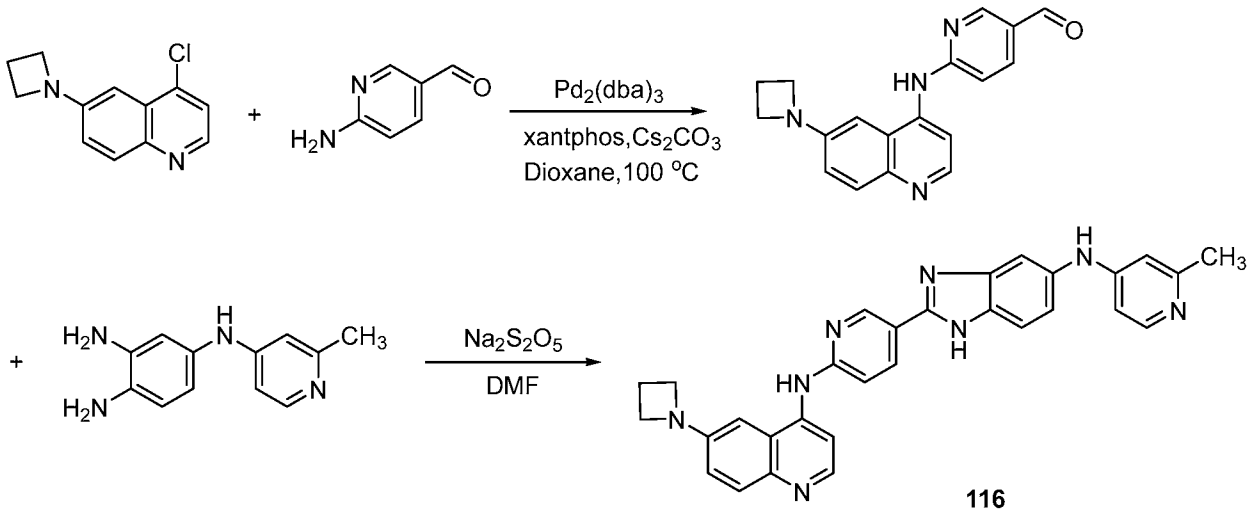
115

[0592] **Compound 115** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 115** (6-(4,4-difluoropiperidin-1-yl)-N-(4-(5-((2-methylpyridin-4- yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine) was prepared as shown in Scheme 105: $C_{33}H_{31}F_2N_7$; 561.64 g/mol; 13 mg; pale yellow solid; ESI-LCMS m/z = 562 $[M+H]^+$; LCMS RT = 1.65 min, >95.00% (214 nm).

Example 116: Compound 116 (6-(azetidin-1-yl)-N-(5-(5-(2-methylpyridin-4-ylamino)-1H benzo[d]imidazol-2-yl)pyridin-2-yl)quinolin-4-amine)



116

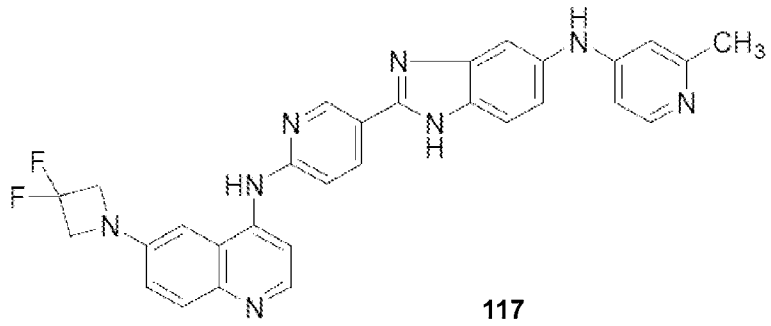


116

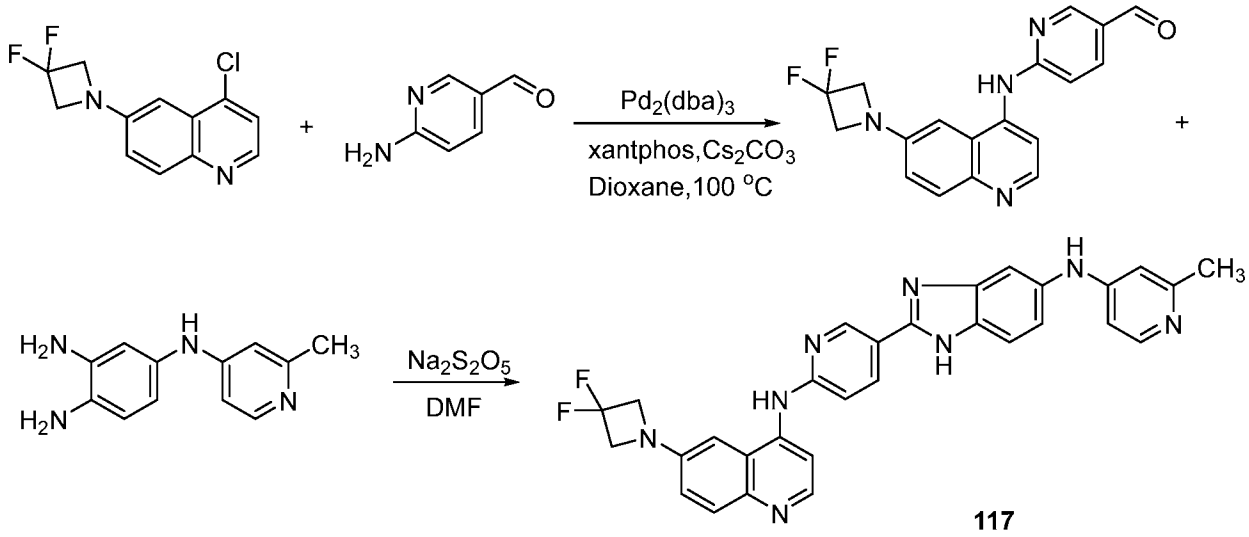
Scheme 106

[0593] **Compound 116** was prepared by the method shown in Scheme 106. **Compound 116** (6-(azetidin-1-yl)-N-(5-(5-(2-methylpyridin-4-ylamino)-1H benzo[d]imidazol-2-yl)pyridin-2-yl)quinolin-4-amine) was prepared as shown in Scheme 106: $C_{30}H_{26}N_8$; 498.58 g/mol; 13 mg; yellow solid; ESI-LCMS m/z = 499 $[M+H]^+$; LCMS RT = 1.91 min, >95.00% (214 nm).

Example 117: Compound 117 (6-(3,3-difluoroazetidin-1-yl)-N-(5-(5-(2-methylpyridin-4-yl amino)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)quinolin-4-amine)



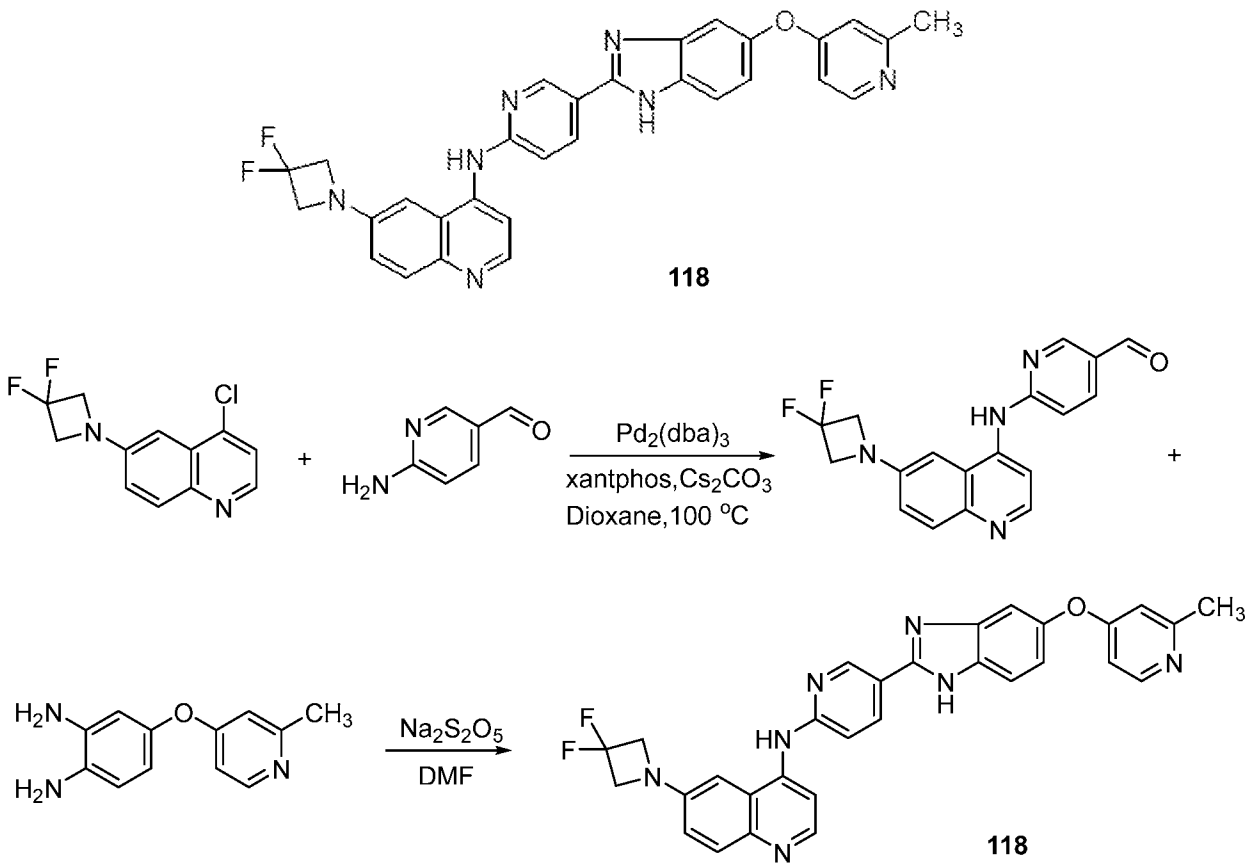
117



Scheme 107

[0594] **Compound 117** was prepared by the method shown in Scheme 107. **Compound 117** (6-(3,3-difluoroazetidin-1-yl)-N-(5-(5-(2-methylpyridin-4-yl amino)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)quinolin-4-amine) was prepared as shown in Scheme 107: $C_{30}H_{24}F_2N_8$; 534.56 g/mol; 28 mg; yellow solid; ESI-LCMS m/z = 535 $[M+H]^+$; LCMS RT = 1.52 min, >95.00% (214 nm).

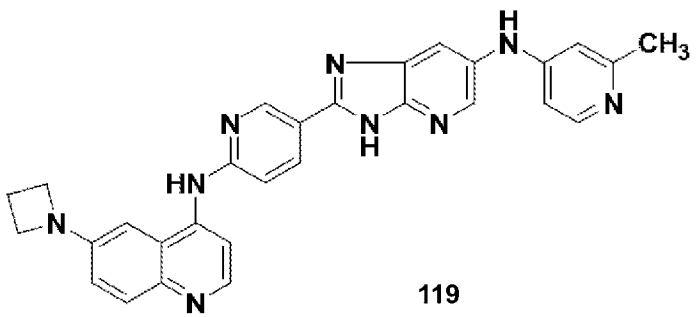
Example 118: Compound 118 (6-(3,3-difluoroazetidin-1-yl)-N-(5-(5-(2-methylpyridin-4-yloxy)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)quinolin-4-amine)

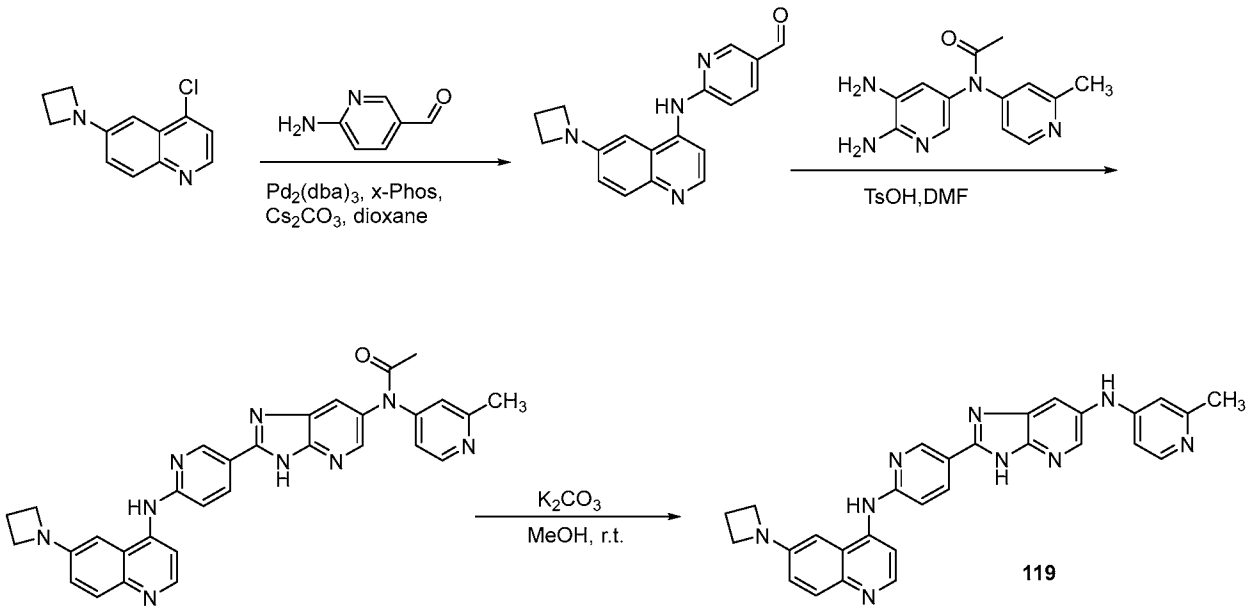


Scheme 108

[0595] **Compound 118** was prepared by the method shown in Scheme 108. **Compound 118** (6-(3,3-difluoroazetidin-1-yl)-N-(5-(5-(2-methylpyridin-4-yloxy)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)quinolin-4-amine) was prepared as shown in Scheme 108: $C_{30}H_{23}F_2N_7O$; 535.55 g/mol; 22 mg; pale yellow solid; ESI-LCMS m/z = 536 $[M+H]^+$; LCMS RT = 1.56 min, >95.00% (214 nm).

Example 119: Compound 119 (6-(azetidin-1-yl)-N-(5-(6-((2-methylpyridin-4-yl)amino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-yl)quinolin-4-amine)

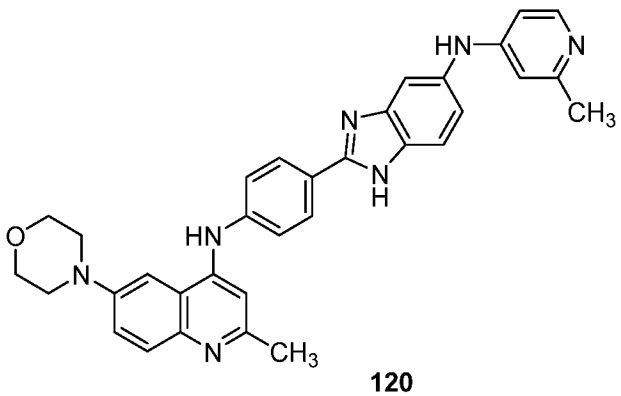




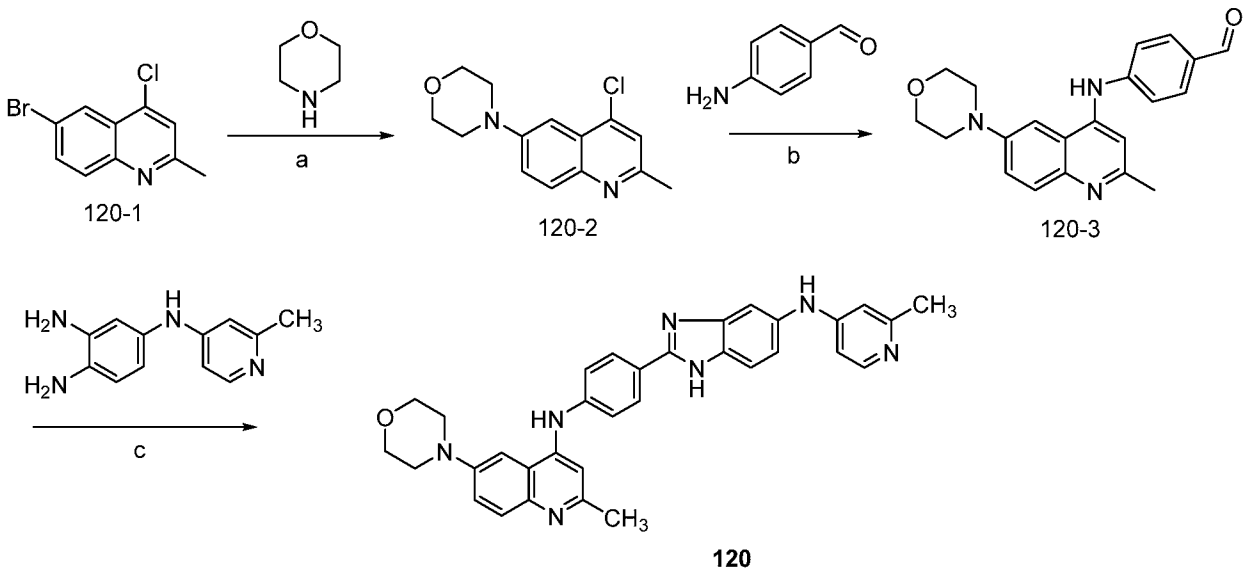
Scheme 109

[0596] **Compound 119** was prepared by the method shown in Scheme 109. **Compound 119** (6-(azetidin-1-yl)-N-(5-(6-((2-methylpyridin-4-yl)amino)-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-yl)quinolin-4-amine) was prepared as shown in Scheme 109: $C_{29}H_{25}N_9$; 499.582 g/mol; 11 mg; yellow solid; ESI-LCMS m/z = 500.1 $[M+H]^+$; LCMS RT = 1.11 min, >95.00% (214 nm).

Example 120: Compound 120 (2-methyl-N-(4-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)-6-morpholinoquinolin-4-amine)



120



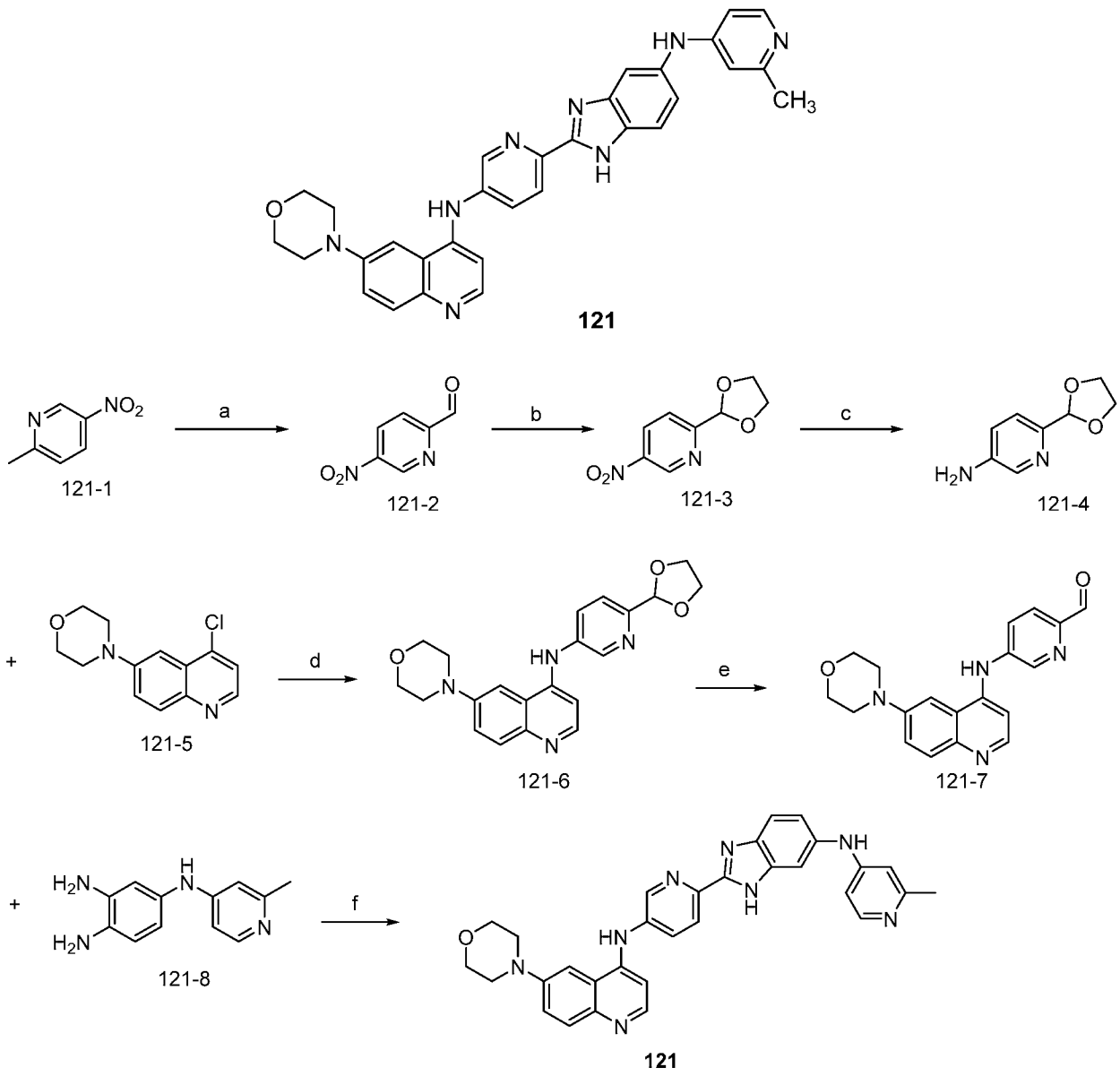
Scheme 110

[0597] Step a: To a solution of Compound 120-1 (765 mg, 3 mmol) and morpholine (261 mg, 3 mmol) in 1,4-dioxane (8 mL) was added Cs_2CO_3 (1.3g, 4.5 mmol), $Pd_2(dba)_3$ (80mg), and Xantphos (80mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 120-2 (518 mg, 66%).

[0598] Step b: To a solution of Compound 120-2 (259 mg, 0.99 mmol) and 4-aminobenzaldehyde (120 mg, 0.99 mmol) in 1,4-dioxane (4 mL) was added Cs_2CO_3 (487mg, 1.5mmol), $Pd_2(dba)_3$ (20mg), and Xantphos (20mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 120-3 (190 mg, 55.5%).

[0599] Step c: To a stirring solution of Compound 120-3 (150 mg, 0.43mmol) in DMF (3mL) was added N4-(2-methylpyridin-4-yl)benzene-1,2,4-triamine (92 mg, 0.43 mmol). The resulting mixture was stirred at 130 °C for 2 hours and purified by prep-HPLC to afford **Compound 120** (2-methyl-N-(4-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)-6-morpholinoquinolin-4-amine) as a yellow solid (20 mg, 8.5%): $C_{33}H_{31}N_7O$; 541.65 g/mol; ESI-LCMS m/z = 552 $[M+H]^+$; LCMS RT = 1.56 min, >95.00% (214 nm).

Example 121: Compound 121 (N-(6-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine)



Scheme 111

[0600] Step a: To a mixture of Compound 121-1 (1.4 g, 10.0 mmol) in 1,4-dioxane (30 mL) was added SeO_2 (1.1 g, 10.0 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and the crude residue was purified by silica-gel column chromatography (PE/EA = 5/1) to give Compound 121-2 as yellow solid (1.2 g, 80%).

[0601] Step b: To a mixture of Compound 121-2 (1.2 g, 8.0 mmol) in toluene (20 mL) was added ethane-1,2-diol (1.0 g, 16.0 mmol) and TosOH (138 mg, 0.8 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and the crude residue was purified by silica-gel column chromatography (PE/EA = 5/1) to give Compound 121-3 as yellow solid (1.4 g, 90%).

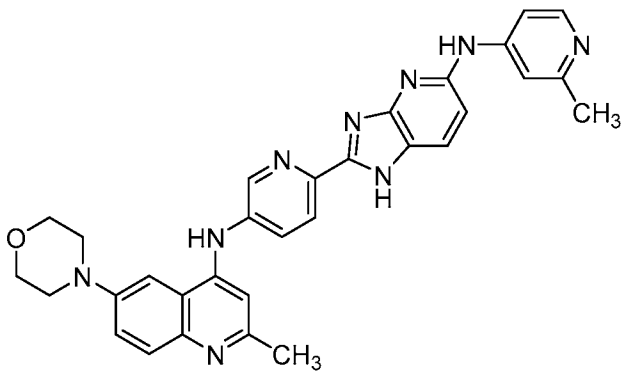
[0602] Step c: To a mixture of Compound 121-3 (1.4 g, 7.1 mmol) in MeOH (20 mL) was added Pd/C (140 mg), and the mixture was stirred at room temperature for 12 hours under H_2. The mixture was filtered and concentrated to give Compound 121-4 (1.2 g, 100%), which was used in the next step without further purification.

[0603] Step d: To a mixture of Compound 121-5 (50 mg, 0.2 mmol) in 1,4-dioxane (1 mL) was added Compound 121-4 (33 mg, 0.2 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and the crude residue was purified by silica-gel column chromatography (MeOH/EA = 1/20) to give Compound 121-6 as yellow solid (53 mg, 70%).

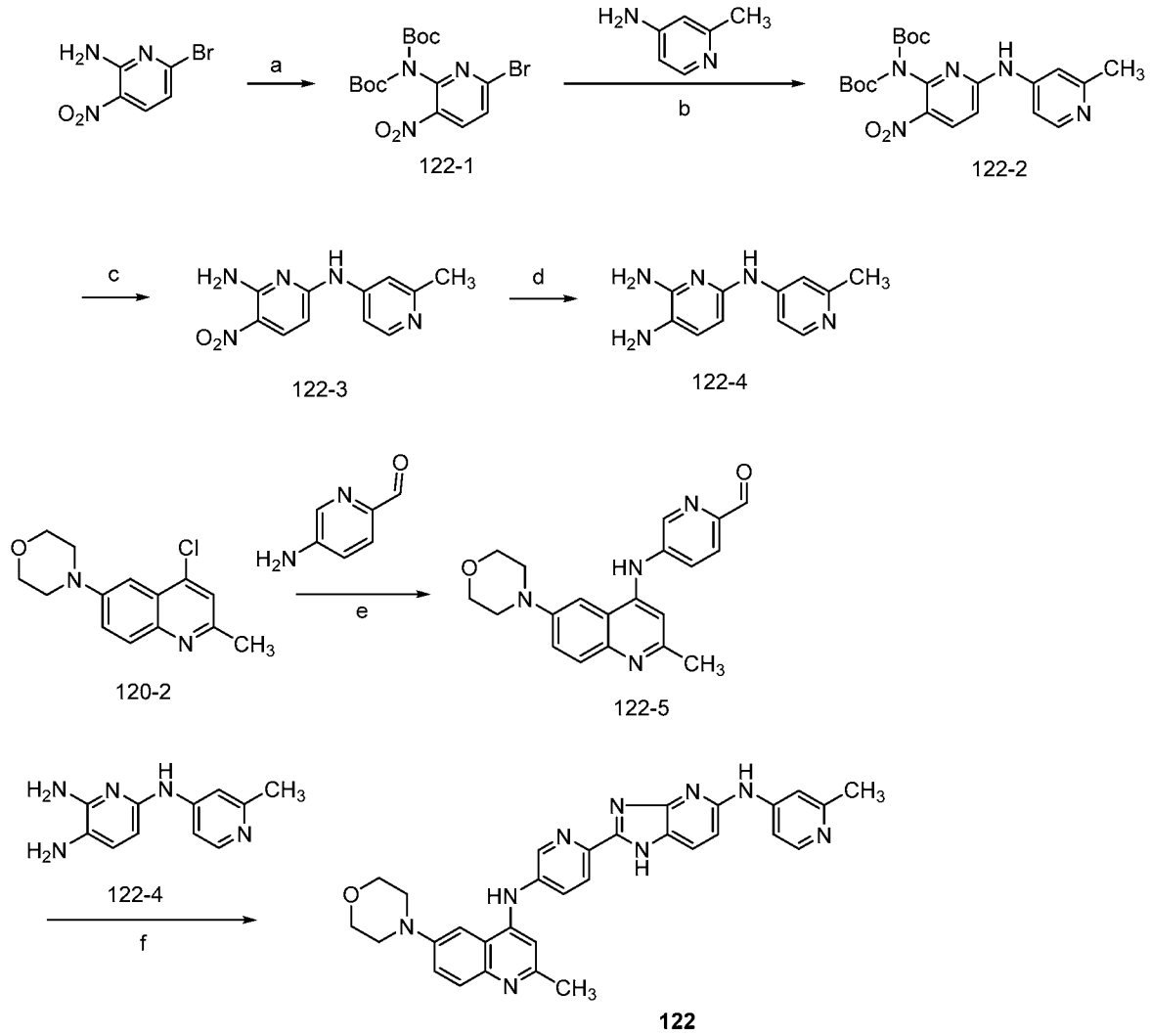
[0604] Step e: A mixture of Compound 121-6 (50 mg, 0.13 mmol) in HCOOH (2 mL) was stirred at 80 °C for 1 hour under N_2. The mixture was concentrated to give Compound 121-7 as yellow solid (44 mg, 100%).

[0605] Step f: A mixture of Compound 121-7 (40 mg, 0.12 mmol) and Compound 121-8 (39 mg, 0.18 mmol) in DMF (1 mL) was stirred at 130 °C for 1 hour. The mixture was purified by prep-HPLC to give **Compound 121** (N-(6-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidaz ol-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine) as a yellow solid (33 mg, 53%): $C_{31}H_{28}N_8O$; 528.62 g/mol; ESI-LCMS m/z = 529 $[M+H]^+$; LCMS RT = 1.37 min, >95.00% (214 nm).

Example 122: Compound 122 (2-methyl-N-(6-(5-(2-methylpyridin-4-ylamino)-1H-imidazo [4,5-b]pyridin-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine)



122



Scheme 112

[0606] Compound 120-2 was synthesized in analogous fashion to that described in Example 120.

[0607] Step a: To a mixture of 6-bromo-3-nitropyridin-2-amine (10 g, 46 mmol) in THF (20 mL) was added $(Boc)_2$ (30 g, 138 mmol) and TEA (14 g, 138 mmol), and the mixture was stirred at room temperature for 6 hours. The residue was purified by flash chromatography on silica gel (0-30% EA in PE) to afford Compound 122-1 (18 g, 94%) as a white solid.

[0608] Step b: To a stirred mixture of Compound 122-1 (18 g, 43 mmol) in 1,4-dioxane (500 mL) was added 2-methylpyridin-4-amine (4.6 g, 0.1 mol), Cs_2CO_3 (28 g, 86 mmol), $Pd_2(dba)_3$ (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 122-2 (16 g, 83.6%) as a white solid.

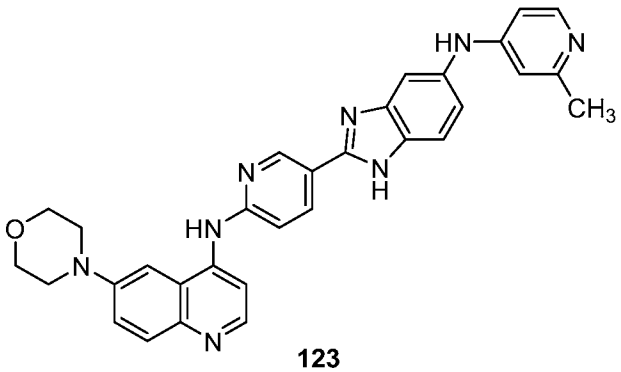
[0609] Step c: A mixture of Compound 122-2 (16 g, 36 mmol) in dioxane hydrochloride (1000 mL, 4 M) was stirred at room temperature for 4 hours. The combined organic phase was concentrated to give Compound 122-3 as white solid (8 g, 90.7%).

[0610] Step d: To a mixture of Compound 122-3 (8 g, 32 mmol) in MeOH (300 mL) was added Pd/C (270 mg, 0.26 mmol), 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 122-4 as yellow solid (6.7 g, 97%).

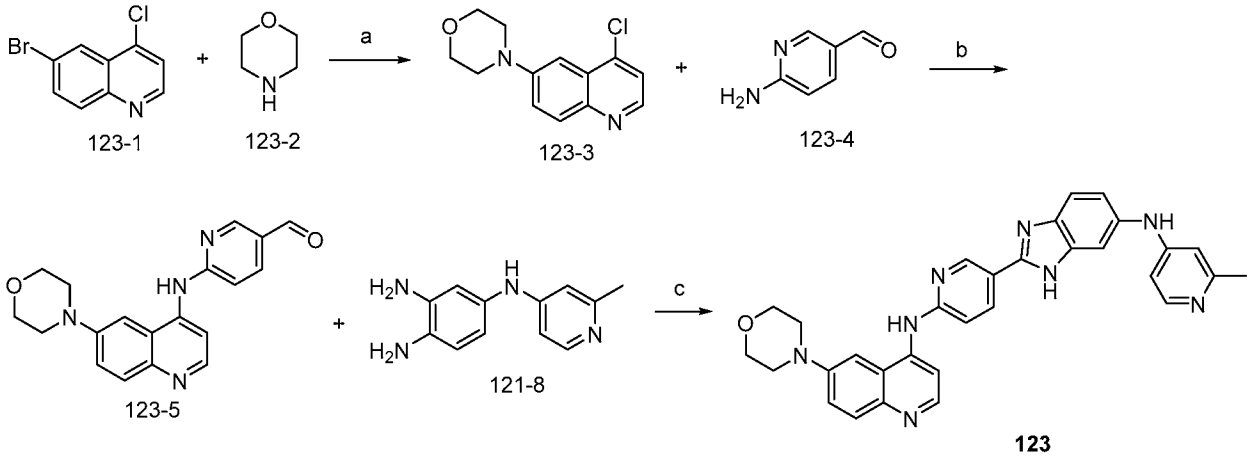
[0611] Step e: To a mixture Compound 120-2 (200 mg, 0.763 mmol) in 1,4-dioxane (5 mL) was added 5-aminopicolinaldehyde (93 mg, 0.763 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), Xantphos (60 mg, 0.1 mmol), and Cs_2CO_3 (500 mg, 1.5 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and the crude residue was purified by silica-gel column chromatography (MeOH/EA = 1/20) to give Compound 122-5 as yellow solid (160 mg, 60%).

[0612] Step f: A mixture of Compound 122-5 (50 mg, 0.14mmol) and Compound 122-4 (31 mg, 0.14 mmol) in DMF (1 mL) was stirred at 130 °C for 1 hour. The mixture was purified by prep-HPLC to give **Compound 122** (2-methyl-N-(6-(5-(2-methylpyridin-4-ylamino)-1H-imidazo [4,5-b]pyridin-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine) as yellow solid (15 mg, 20%): $C_{31}H_{29}N_9O$; 543.62 g/mol; ESI-LCMS m/z = 544 $[M+H]^+$; LCMS RT = 1.52 min, >95.00% (214 nm).

Example 123: Compound 123 (N-(5-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidaz ol-2-yl)pyridin-2-yl)-6-morpholinoquinolin-4-amine)



123



Scheme 113

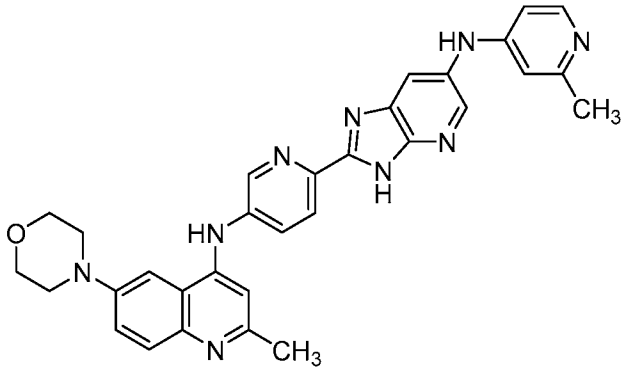
[0613] Compound 121-8 was synthesized in analogous fashion to that described in Example 121.

[0614] Step a: To a mixture of Compound 123-1 (482 mg, 2.0 mmol) in 1,4-dioxane (10 mL) was added Compound 123-2 (174 mg, 2.0 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), Xantphos (58 mg, 0.1 mmol), and Cs_2CO_3 (1.3 g, 4.0 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and the crude residue was purified by silica-gel column chromatography (PE/EA = 2/1) to give Compound 123-3 as yellow solid (406 mg, 82%).

[0615] Step b: To a mixture of Compound 123-3 (50 mg, 0.2 mmol) in 1,4-dioxane (1 mL) was added Compound 123-4 (25 mg, 0.2 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and the crude residue was purified by silica-gel column chromatography (MeOH/EA = 1/20) to give Compound 123-5 as yellow solid (47 mg, 70%).

[0616] Step c: A mixture of Compound 123-5 (40 mg, 0.12 mmol) and Compound 121-8 (39 mg, 0.18 mmol) in DMF (1 mL) was stirred at 130 °C for 1 hour. The mixture was purified by prep-HPLC to give **Compound 123** (N-(5-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidaz ol-2-yl)pyridin-2-yl)-6-morpholinoquinolin-4-amine) as yellow solid (31 mg, 50%): $C_{31}H_{28}N_8O$; 528.62 g/mol; ESI-LCMS m/z = 529 $[M+H]^+$; LCMS RT = 1.40 min, >95.00% (214 nm).

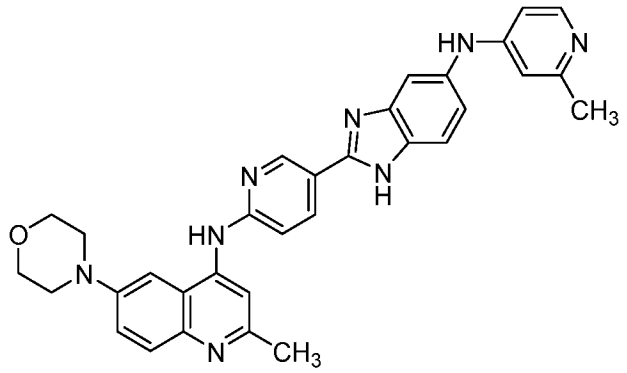
Example 124: Compound 124 (2-methyl-N-(6-(6-(2-methylpyridin-4-ylamino)-3H-imidazo [4,5-b]pyridin-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine)



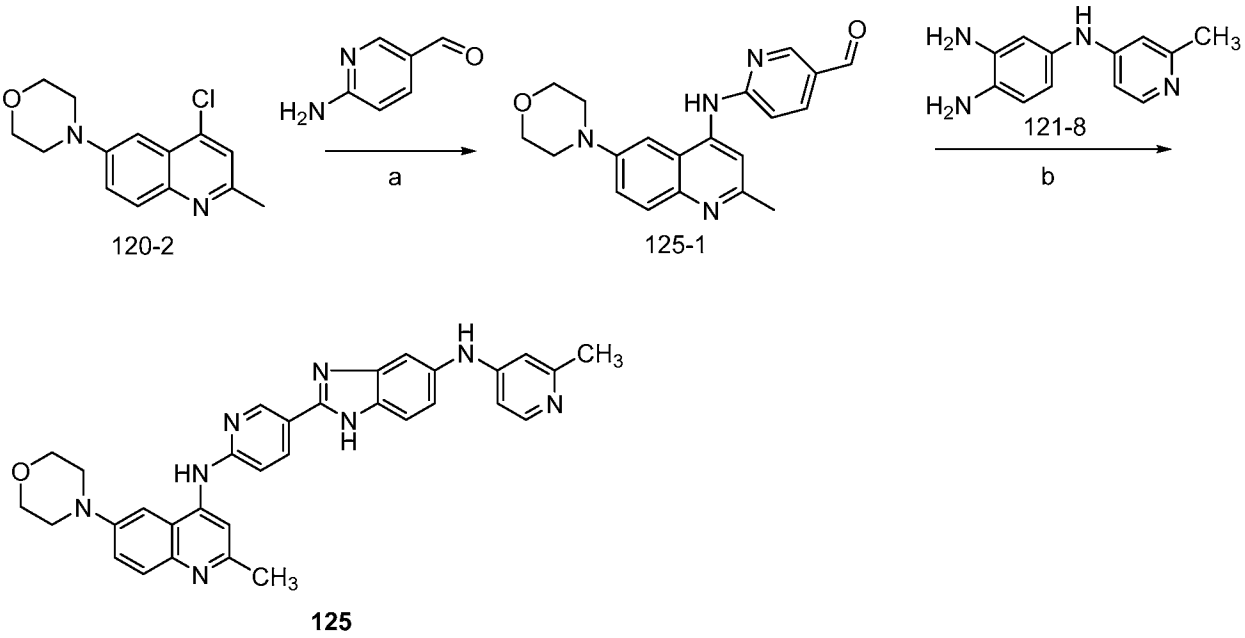
124

[0617] **Compound 124** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 124** (2-methyl-N-(6-(6-(2-methylpyridin-4-ylamino)-3H-imidazo [4,5-b]pyridin-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine): $C_{31}H_{29}N_9O$; 543.62 g/mol; 11 mg; yellow solid; ESI-LCMS m/z = 544 $[M+H]^+$; LCMS RT = 1.45 min, >95.00% (214 nm).

Example 125: Compound 125 (2-methyl-N-(5-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)-6-morpholinoquinolin-4-amine)



125



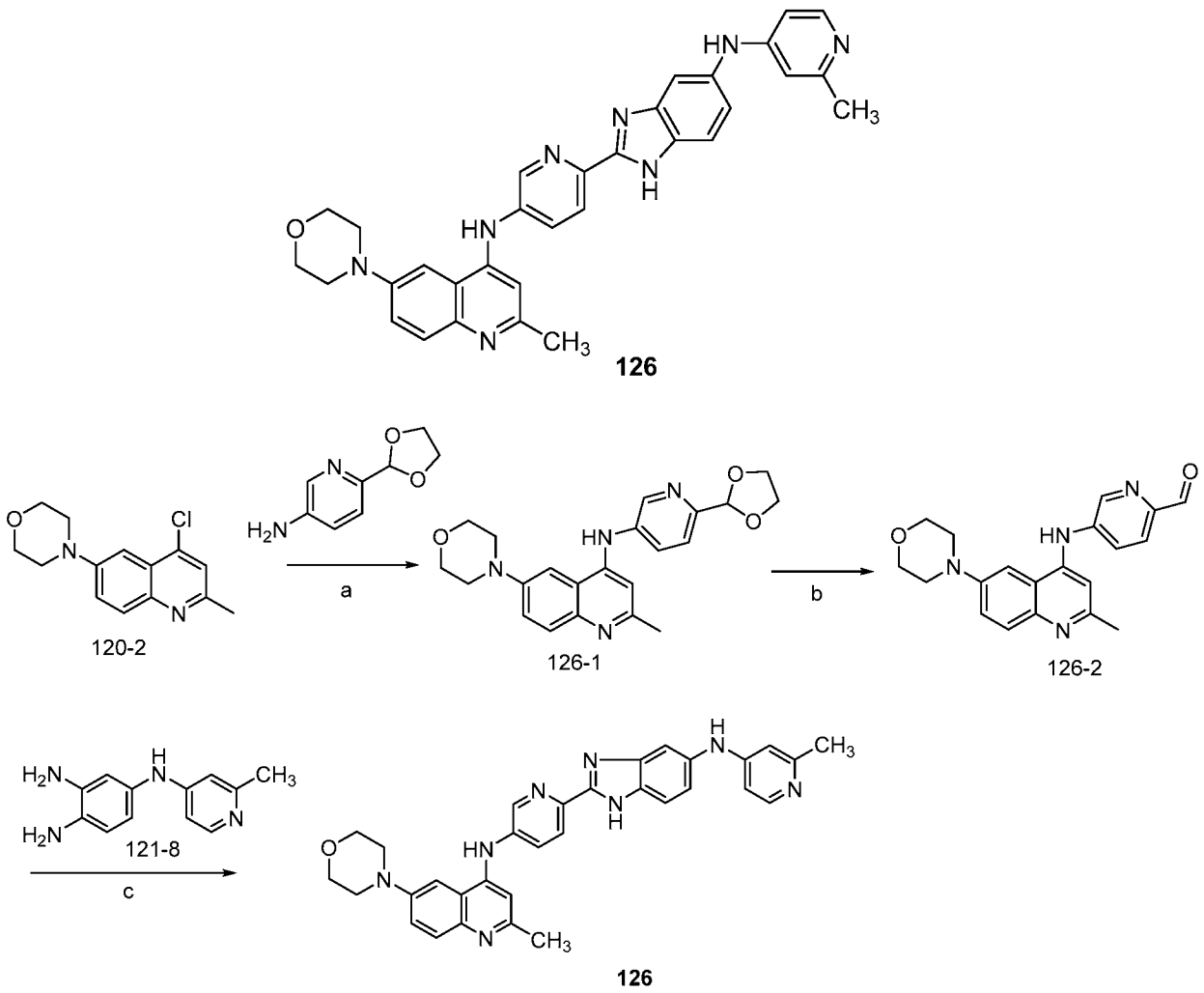
Scheme 114

[0618] Compound 120-2 was synthesized in analogous fashion to that described in Example 120. Compound 121-8 was synthesized in analogous fashion to that described in Example 121.

[0619] Step a: To a solution of Compound 120-2 (259 mg, 0.99 mmol) and 6-aminonicotinaldehyde (120 mg, 0.99 mmol) in 1,4-dioxane (4 mL) was added Cs_2CO_3 (487 mg, 1.5 mmol), $Pd_2(dba)_3$ (20 mg), Xantphos (20 mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 125-1 (186mg, 53%).

[0620] Step b: To a stirring solution of Compound 125-1 (150 mg, 0.43 mmol) in DMF (3 mL) was added N4-(2-methylpyridin-4-yl)benzene-1,2,4-triamine (Compound 121-8) (92 mg, 0.43 mmol). The resulting mixture was stirred at 130 °C for 2 hours and purified by prep-HPLC to afford **Compound 125** (2-methyl-N-(5-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-2-yl)-6-morpholinoquinolin-4-amine as a yellow solid (20 mg, 8.5%): $C_{32}H_{30}N_8O$; 542.63 g/mol; ESI-LCMS m/z = 543 $[M+H]^+$; LCMS RT = 1.43 min, >95.00% (214 nm).

Example 126: Compound 126 (2-methyl-N-(6-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine)



Scheme 115

[0621] Compound 120-2 was synthesized in analogous fashion to that described in Example 120. Compound 121-8 was synthesized in analogous fashion to that described in Example 121.

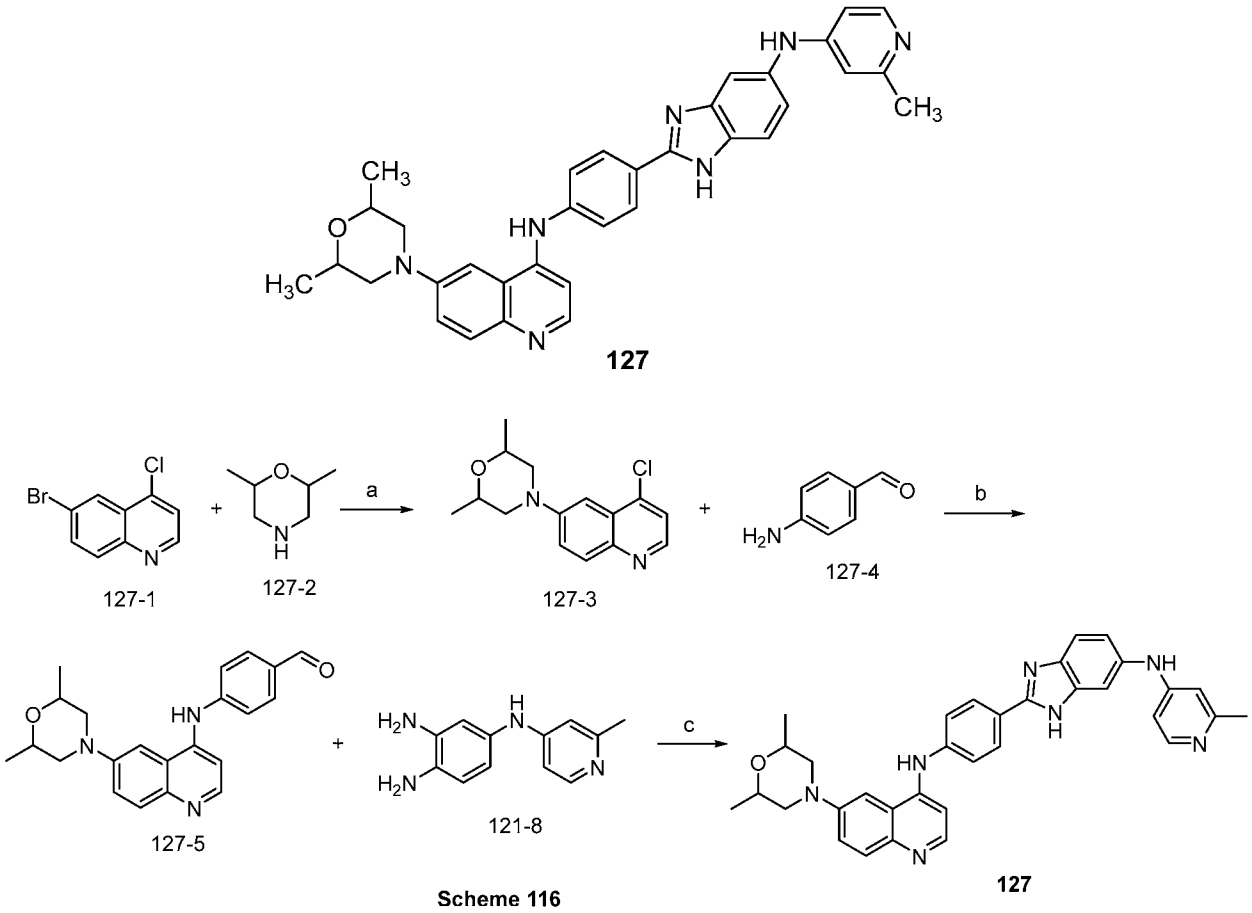
[0622] Step a: To a solution of Compound 120-2 (259 mg, 0.99 mmol) and 6-(1,3-dioxolan-2-yl)pyridin-3-amine (164 mg, 0.99 mmol) in 1,4-dioxane (4 mL) was added Cs_2CO_3 (487mg, 1.5mmol), $Pd_2(dba)_3$ (20 mg), and Xantphos (20 mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 126-1 (209 mg, 54%).

[0623] Step b: To a stirring solution of Compound 126-1 (209 mg, 0.53 mmol) in DCM (3 mL) was added HCOOH (1 mL). The resulting mixture was stirred at 40 °C for 2 hours,

quenched with $NaHCO_3$, extracted with DCM, dried, and concentrated to give Compound 126-2 (169 mg, 92%) as an oil.

[0624] Step b: To a stirring solution of Compound 126-2 (150 mg, 0.43 mmol) in DMF (3 mL) was added N4-(2-methylpyridin-4-yl)benzene-1,2,4-triamine (Compound 121-8) (92 mg, 0.43 mmol). The resulting mixture was stirred at 130 °C for 2 hours and purified by prep-HPLC to afford **Compound 126** (2-methyl-N-(6-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)-6-morpholinoquinolin-4-amine) as a yellow solid (20 mg, 8.5%): $C_{32}H_{30}N_8O$; 542.63 g/mol; ESI-LCMS m/z = 543 $[M+H]^+$; LCMS RT = 1.44 min, >95.00% (214 nm).

Example 127: Compound 127 (6-(2,6-dimethylmorpholino)-N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine)



Scheme 116

[0625] Compound 121-8 was synthesized in analogous fashion to that described in Example 121.

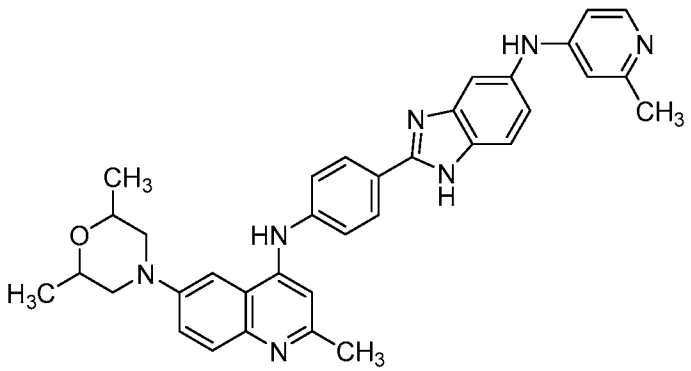
[0626] Step a: To a mixture of Compound 127-1 (482 mg, 2.0 mmol) in 1,4-dioxane (10 mL) was added Compound 127-2 (230 mg, 2.0 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), Xantphos (58 mg, 0.1 mmol), and Cs_2CO_3 (1.3 g, 4.0 mmol), and the mixture was stirred at

100 °C for 12 hours under N_2. The mixture was concentrated and the crude residue was purified by silica-gel column chromatography (PE/EA = 2/1) to give Compound 127-3 as yellow solid (414 mg, 75%).

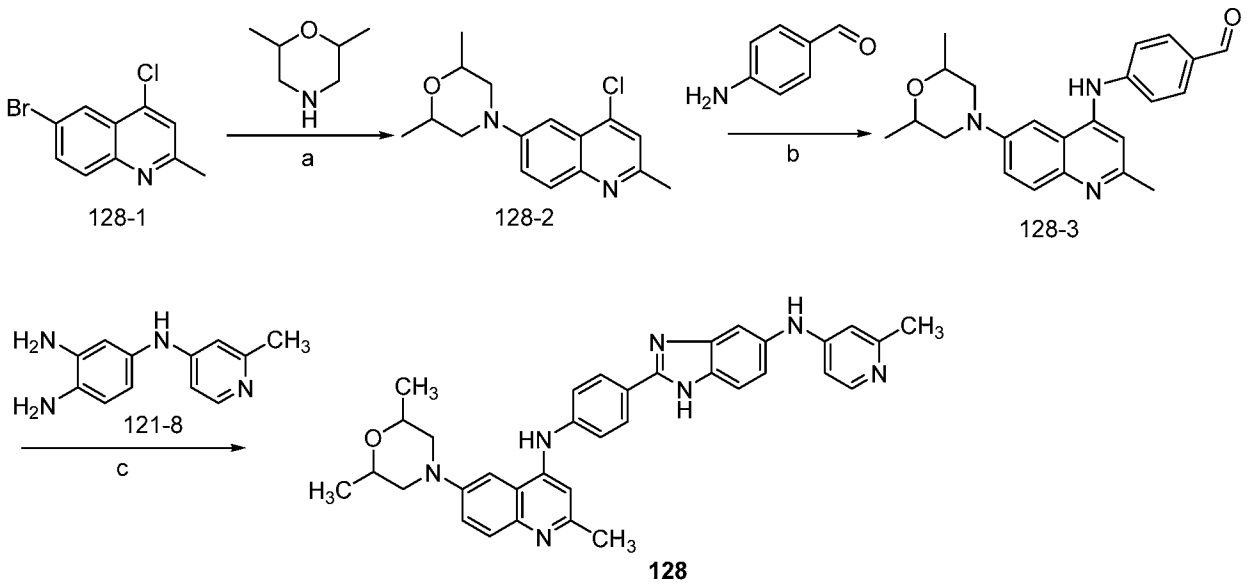
[0627] Step b: To a mixture of Compound 127-3 (55 mg, 0.2 mmol) in 1,4-dioxane (1 mL) was added Compound 127-4 (24 mg, 0.2 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and the crude residue was purified by silica-gel column chromatography (MeOH/EA = 1/20) to give Compound 127-5 as yellow solid (45 mg, 62%).

[0628] Step c: A mixture of Compound 127-5 (40 mg, 0.11 mmol) and Compound 121-8 (39 mg, 0.18 mmol) in DMF (1 mL) was stirred at 130 °C for 1 hour. The mixture was purified by prep-HPLC to give **Compound 127** (6-(2,6-dimethylmorpholino)-N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine) as yellow solid (35 mg, 57%): $C_{34}H_{33}N_7O$; 555.69 g/mol; ESI-LCMS m/z = 556 $[M+H]^+$; LCMS RT = 1.47 min, >95.00% (214 nm).

Example 128: Compound 128 (6-(2,6-dimethylmorpholino)-2-methyl-N-(4-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine)



128



Scheme 117

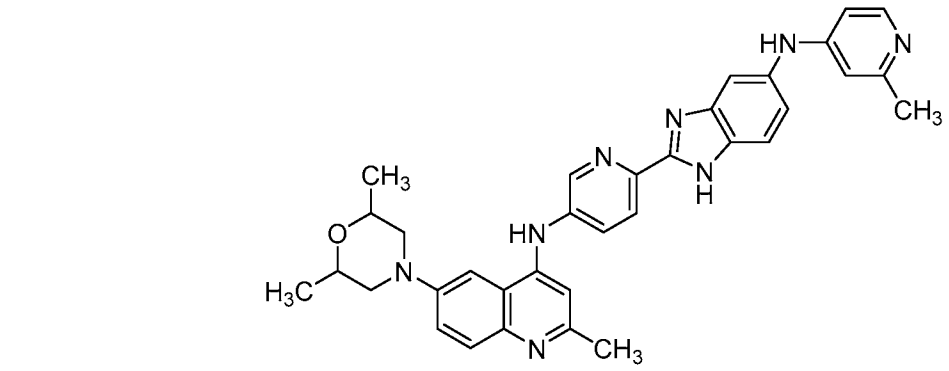
[0629] Compound 121-8 was synthesized in analogous fashion to that described in Example 121.

[0630] Step a: To a solution of Compound 128-1 (765 mg, 3 mmol) and 2,6-dimethylmorpholine (345 mg, 3 mmol) in 1,4-dioxane (8 mL) was added Cs_2CO_3 (1.3 g, 4.5 mmol), $Pd_2(dba)_3$ (80mg), and Xantphos (80mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 128-2 (583 mg, 67%).

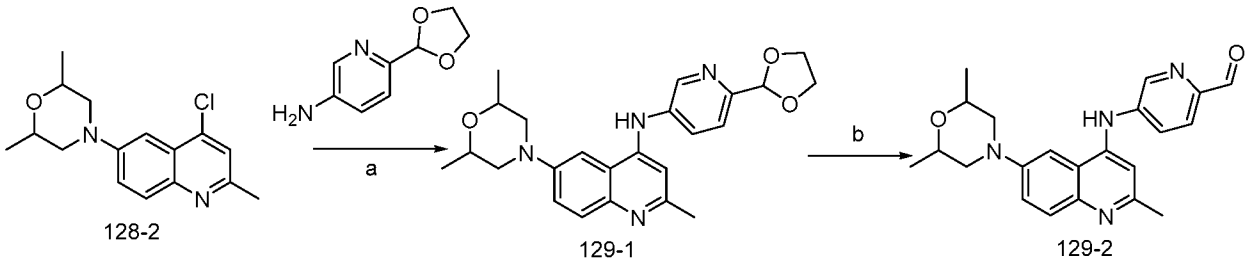
[0631] Step b: To a solution of Compound 128-2 (287 mg, 0.99 mmol) and 4-aminobenzaldehyde (120 mg, 0.99 mmol) in 1,4-dioxane (4 mL) was added Cs_2CO_3 (487mg, 1.5 mmol), $Pd_2(dba)_3$ (20 mg), and Xantphos (20 mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 128-3 (200 mg, 54%).

[0632] Step c: To a stirring solution of Compound 128-3 (160 mg, 0.43 mmol) in DMF (3 mL) was added N4-(2-methylpyridin-4-yl)benzene-1,2,4-triamine (Compound 121-8) (92 mg, 0.43 mmol). The resulting mixture was stirred at 130 °C for 2 hours and purified by prep-HPLC to give **Compound 128** (6-(2,6-dimethylmorpholino)-2-methyl-N-(4-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine) as a yellow solid (20 mg, 8.2%): $C_{35}H_{35}N_7O$; 569.70 g/mol; ESI-LCMS m/z = 570 $[M+H]^+$; LCMS RT = 1.50 min, >95.00% (214 nm).

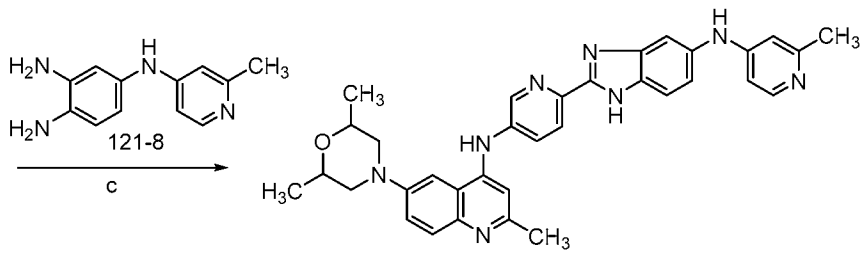
Example 129: Compound 129 (6-(2,6-dimethylmorpholino)-2-methyl-N-(6-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine)



129



128-2 129-1 129-2



121-8 129

Scheme 118

[0633] Compound 121-8 was synthesized in analogous fashion to that described in Example 121. Compound 128-2 was synthesized in analogous fashion to that described in Example 128.

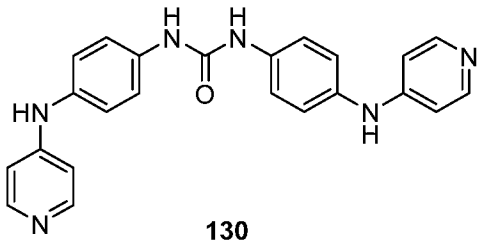
[0634] Step a: To a solution of Compound 128-2 (287 mg, 0.99 mmol) and 4-aminobenzaldehyde (164 mg, 0.99 mmol) in 1,4-dioxane (4 mL) was added Cs_2CO_3 (487 mg, 1.5mmol), $Pd_2(dba)_3$ (20mg), and Xantphos (20 mg). The reaction mixture was stirred at 100 °C overnight, quenched with water, extracted with EA, washed with water and brine, dried, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH:DCM = 1:20) to afford Compound 129-1 (228 mg, 55%).

[0635] Step b: To a stirring solution of Compound 129-1 (228 mg, 0.54 mmol) in DCM (3 mL) was added HCOOH (1 mL). The resulting mixture was stirred at 40 °C for 2 hours,

quenched with $NaHCO_3$, extracted with DCM, dried, and concentrated to give Compound 129-2 (182 mg, 90%) as an oil.

[0636] Step c: To a stirring solution of Compound 129-2 (161 mg, 0.43 mmol) in DMF (3 mL) was added N4-(2-methylpyridin-4-yl)benzene-1,2,4-triamine (Compound 121-8) (92 mg, 0.43 mmol). The resulting mixture was stirred at 130 °C for 2 hours and purified by prep-HPLC to afford **Compound 129** (6-(2,6-dimethylmorpholino)-2-methyl-N-(6-(5-(2-methylpyridin-4-ylamino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine) as a yellow solid (21 mg, 8.5%): $C_{34}H_{34}N_8O$; 570.69 g/mol; ESI-LCMS m/z = 571 $[M+H]^+$; LCMS RT = 1.50 min, >95.00% (214 nm).

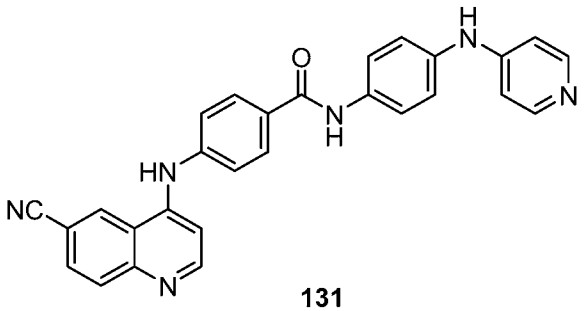
Example 130: Compound 130 (1,3-bis(4-(pyridin-4-ylamino)phenyl)urea)



130

[0637] **Compound 130** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 130** (1,3-bis(4-(pyridin-4-ylamino)phenyl)urea); $C_{23}H_{20}N_6O$; 396.44 g/mol; 11 mg; white solid; ESI-LCMS m/z = 397 $[M+H]^+$; LCMS RT = 1.36 min, >95.00% (214 nm).

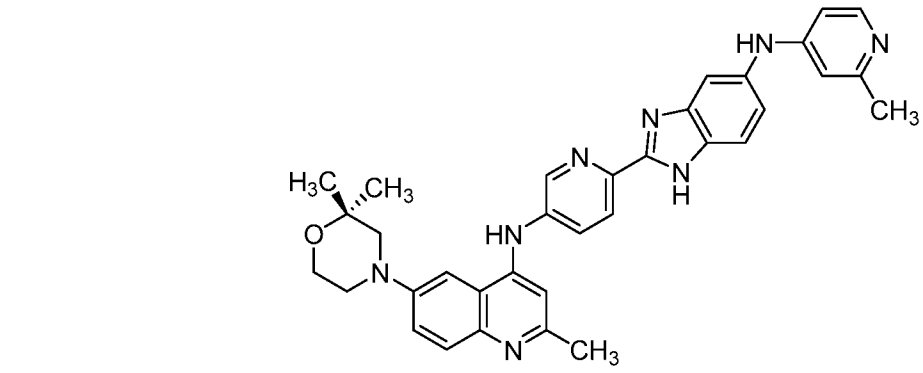
Example 131: Compound 131 (4-((6-cyanoquinolin-4-yl)amino)-N-(4-(pyridin-4-ylamino)phenyl)benzamide)



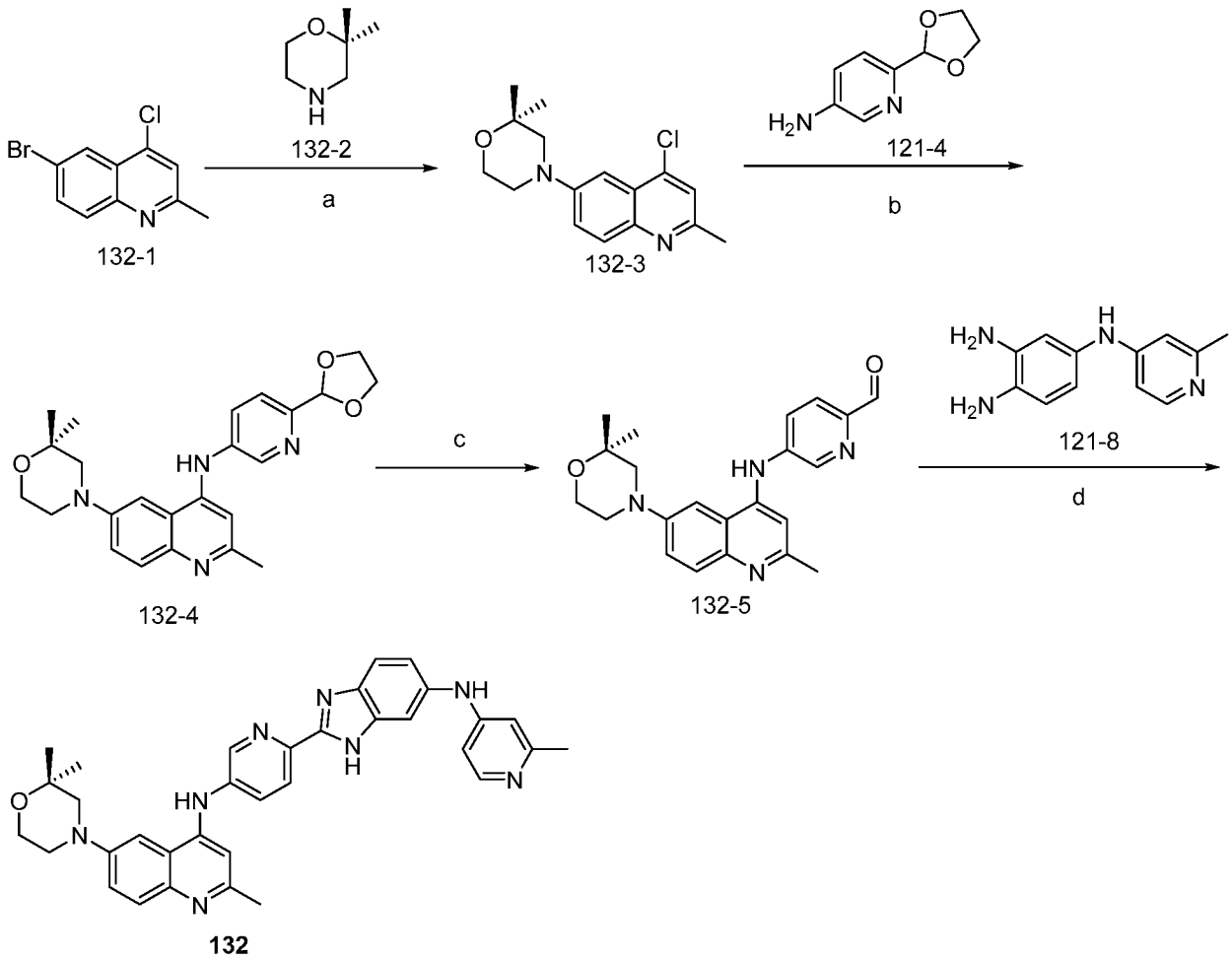
131

[0638] **Compound 131** was prepared by a method known in the art and/or a method analogous to those described herein.

Example 132: Compound 132 (6-(2,2-dimethylmorpholino)-2-methyl-N-(6-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine)



132



Scheme 119

[0639] Compounds 121-4 and 121-8 were synthesized in analogous fashion to that described in Example 121.

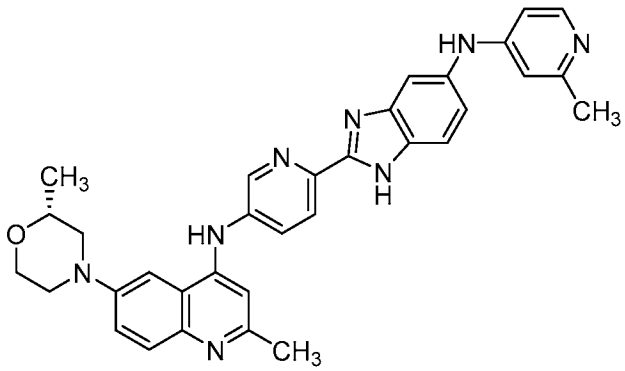
[0640] Step a: To the mixture of Compound 132-1 (510 mg, 2.0 mmol) in 1,4-dioxane (10 mL) was added Compound 132-2 (230 mg, 2.0 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), Xantphos (58 mg, 0.1 mmol), and t-BuONa (384 mg, 4.0 mmol) and the mixture was stirred at 100 °C for 12 h under N_2. The mixture was concentrated and the crude was purified by silica-gel column (PE/EA=2/1) to get the Compound 132-3 as yellow solid (476 mg, yield: 82%).

[0641] Step b: To the mixture of Compound 132-3 (58 mg, 0.2 mmol) in 1,4-dioxane (1 mL) was added Compound 132-4 (33 mg, 0.2 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol) and the mixture was stirred at 100 °C for 12 h under N_2. The mixture was concentrated and the crude was purified by silica-gel column (MeOH/EA=1/20) to get the Compound 132-4 as yellow solid (57 mg, yield: 68%).

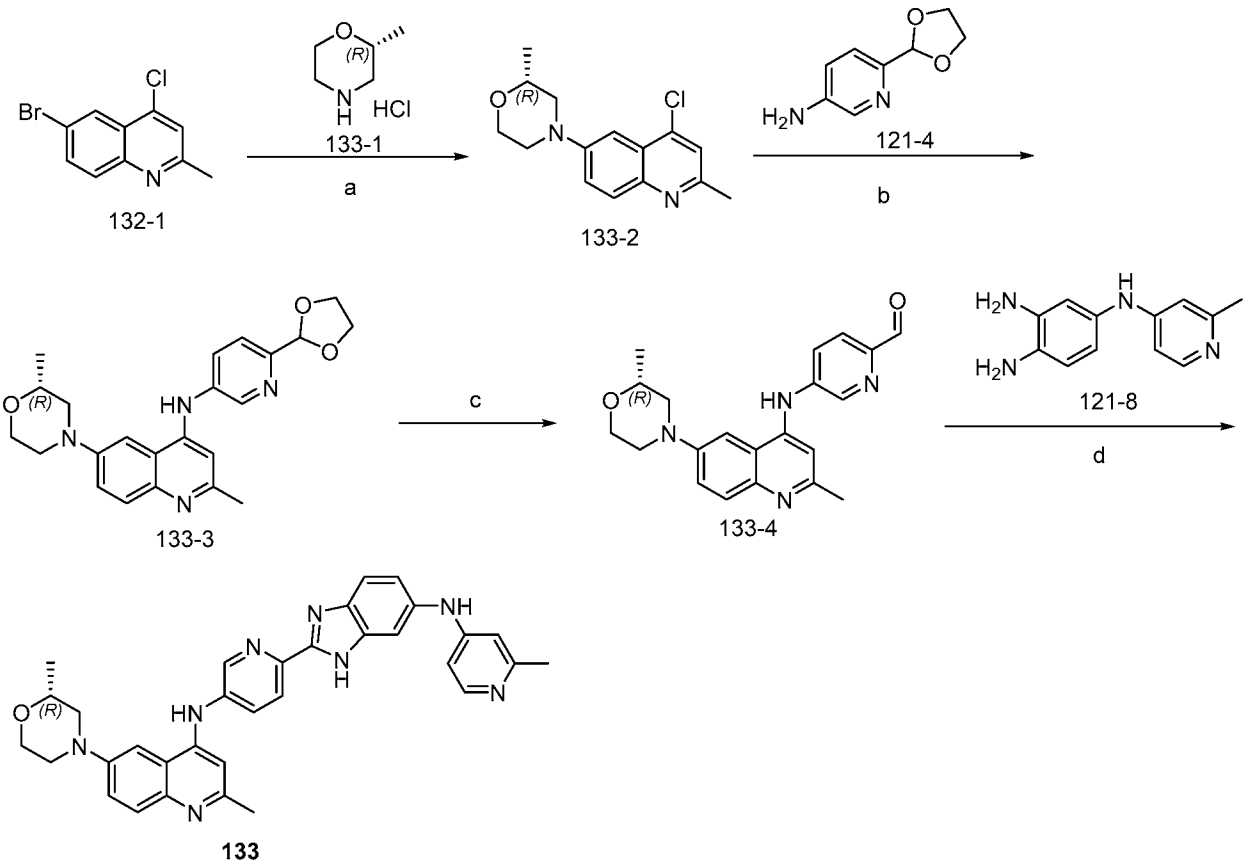
[0642] Step c: The mixture of Compound 132-4 (50 mg, 0.12 mmol) in HCOOH (2 mL) was stirred at 80 °C for 1 h under N_2. The mixture was concentrated to get the Compound 132-5 as yellow solid (45 mg, yield: 100%).

[0643] Step d: The mixture of Compound 132-5 (42 mg, 0.11 mmol) and Compound 121-8 (39 mg, 0.18 mmol) in DMF (1 mL) was stirred at 130 °C for 1 h. The mixture was purified by Prep-HPLC to give **Compound 132** (6-(2,2-dimethylmorpholino)-2-methyl-N-(6-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine) as yellow solid (39 mg, yield: 63%): $C_{34}H_{34}N_8O$; 570.70 g/mol; ESI-LCMS m/z = 571 $[M+H]^+$; RT = 1.51 min, >98.00% (214 nm).

Example 133: Compound 133 ((R)-2-methyl-6-(2-methylmorpholino)-N-(6-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine)



133



Scheme 120

[0644] Compounds 121-4 and 121-8 were synthesized in analogous fashion to that described in Example 121.

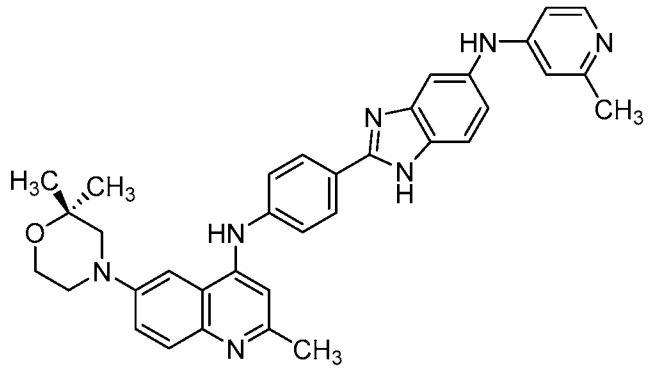
[0645] Step a: To the mixture of Compound 132-1 (510 mg, 2.0 mmol) in 1,4-dioxane (10 mL) was added Compound 133-1 (274 mg, 2.0 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), Xantphos (58 mg, 0.1 mmol), and t-BuONa (384 mg, 4.0 mmol) and the mixture was stirred at 100 °C for 12 h under N_2. The mixture was concentrated and the crude was purified by silica-gel column (PE/EA=2/1) to get the Compound 133-2 as yellow solid (342 mg, yield: 62%).

[0646] Step b: To the mixture of Compound 133-2 (55 mg, 0.2 mmol) in 1,4-dioxane (1 mL) was added Compound 121-4 (33 mg, 0.2 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol) and the mixture was stirred at 100 °C for 12 h under N_2. The mixture was concentrated and the crude was purified by silica-gel column (MeOH/EA=1/20) to get the Compound 133-3 as yellow solid (47 mg, yield: 58%).

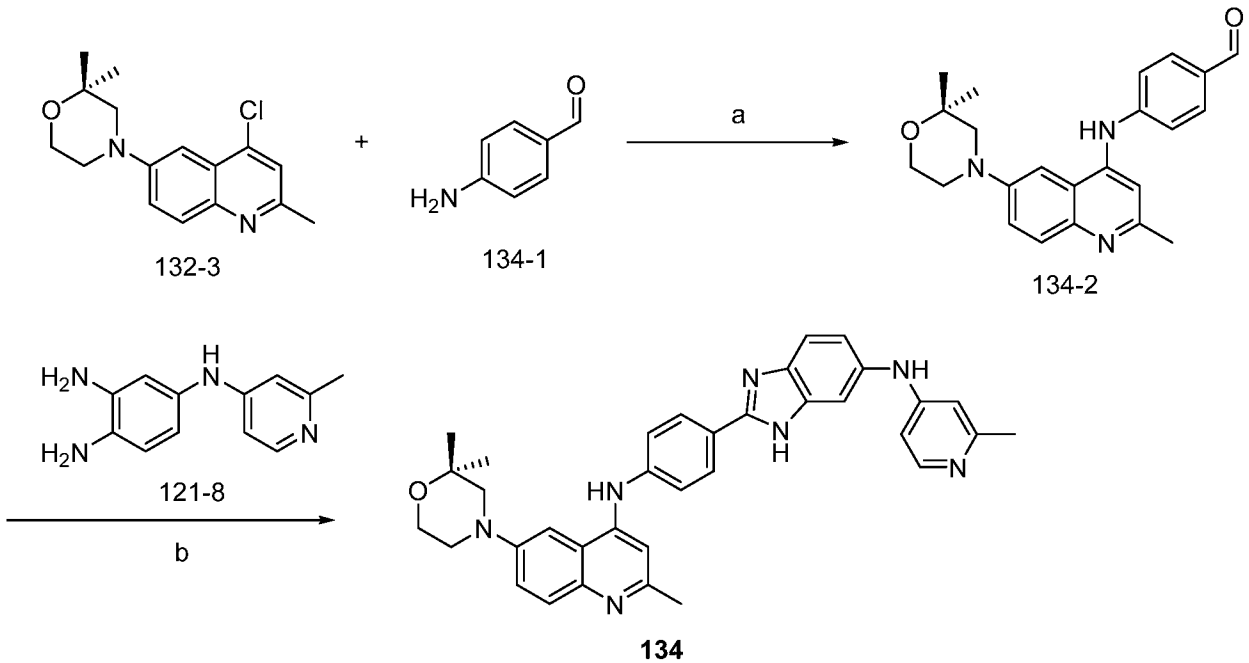
[0647] Step c: The mixture of Compound 133-3 (47 mg, 0.12 mmol) in HCOOH (2 mL) was stirred at 80 °C for 1 h under N_2. The mixture was concentrated to get the Compound 133-4 as yellow solid (42 mg, yield: 100%).

[0648] Step d: The mixture of Compound 133-4 (40 mg, 0.11 mmol) and Compound 121-8 (39 mg, 0.18 mmol) in DMF (1 mL) was stirred at 130 °C for 1 h. The mixture was purified by Prep-HPLC to give **Compound 133** ((R)-2-methyl-6-(2-methylmorpholino)-N-(6-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine) as yellow solid (30 mg, yield: 50%): $C_{33}H_{32}N_8O$; 556.67 g/mol; ESI-LCMS m/z = 557 $[M+H]^+$; RT = 1.48 min, >98.00% (214 nm).

Example 134: Compound 134 (6-(2,2-dimethylmorpholino)-2-methyl-N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine)



134



Scheme 121

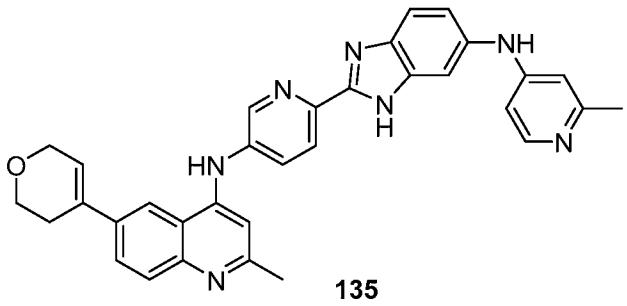
[0649] Compound 121-8 was synthesized in analogous fashion to that described in Example 121.

[0650] Compounds 132-3 was synthesized in analogous fashion to that described in Example 132.

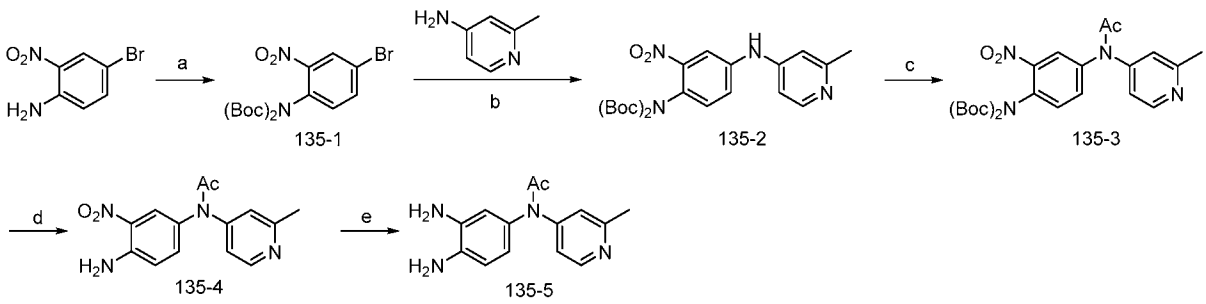
[0651] Step a: To the mixture of Compound 132-3 (58 mg, 0.2 mmol) in 1,4-dioxane (1 mL) was added Compound 134-1 (24 mg, 0.2 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol) and the mixture was stirred at 100 °C for 12 h under N_2. The mixture was concentrated and the crude was purified by silica-gel column (MeOH/EA=1/20) to get the Compound 134-2 as yellow solid (53 mg, yield: 71%).

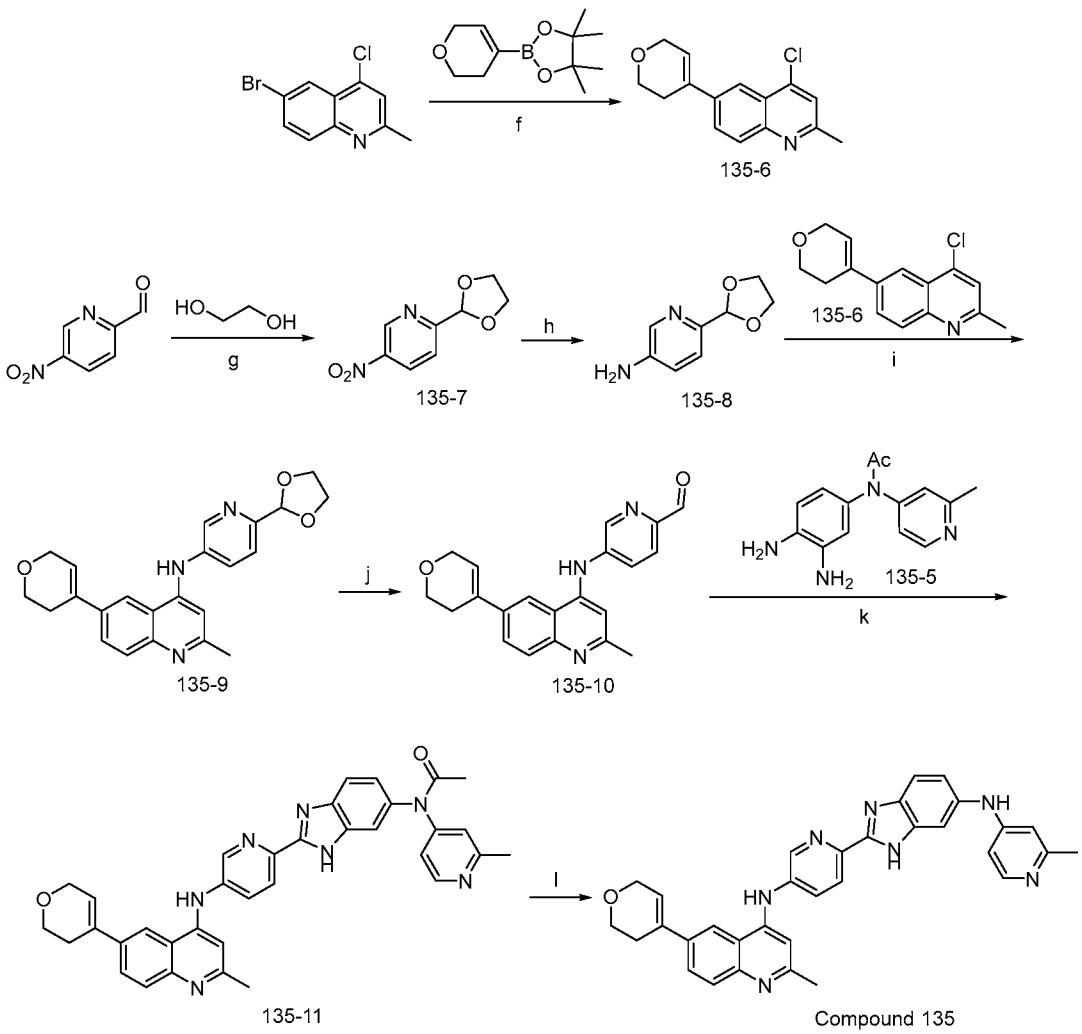
[0652] Step b: The mixture of Compound 134-2 (45 mg, 0.12 mmol) and Compound 121-8 (39 mg, 0.18 mmol) in DMF (1 mL) was stirred at 130 °C for 1 h. The mixture was purified by Prep-HPLC to give **Compound 134** (6-(2,2-dimethylmorpholino)-2-methyl-N-(4-(5-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)phenyl)quinolin-4-amine) as yellow solid (42 mg, yield: 62%): $C_{35}H_{35}N_7O$; 569.71 g/mol; ESI-LCMS m/z = 570 $[M+H]^+$; RT = 1.48 min, >98.00% (214 nm).

Example 135: Compound 135 (6-(3,6-dihydro-2H-pyran-4-yl)-2-methyl-N-(6-(6-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine)



135





Scheme 122

[0653] **Compound 135** was prepared by a method shown in Scheme 122.

[0654] Step a: A mixture of 4-bromo-2-nitroaniline (1.5 g, 6.9 mmol), $(Boc)_2O$ (4.5 g, 20.8 mmol), and Et_3N (2.1 g, 20.8 mmol) in 30 mL of DCM was stirred at room temperature for 16 hours. The mixture was concentrated and purified by silica gel chromatography (0-30% EtOAc/petroleum ether) to give Compound 135-1 (2 g, 69% yield) as a yellow solid.

[0655] Step b: A mixture of Compound 135-1 (2 g, 4.8 mmol), 2-methylpyridin-4-amine (778 mg, 7.2 mmol), $Pd_2(dba)_3$ (550 mg, 0.6 mmol), x-phos (476 mg, 1 mmol), and Cs_2CO_3 (3.12 g, 9.6 mmol) in 20 mL of toluene was stirred at 100 °C for 4 hours. The mixture was concentrated and purified by silica gel chromatography (10-60% EtOAc/petroleum ether) to give Compound 135-2 (1.2 g, 56% yield) as a yellow solid.

[0656] Step c: To a mixture of Compound 135-2 (1.2 g, 2.7 mmol) and Et_3N (818 mg, 8.1 mmol) in 15 mL of DCM was added acetyl chloride (316 mg, 5 mmol) at 0 °C. The

mixture was stirred at room temperature for 5 hours, quenched with water (10 mL), and extracted with DCM (3 × 20 mL). The combined organic solvents were concentrated and purified by silica gel chromatography (0-40% EtOAc/petroleum ether) to give Compound 135-3 (1g, 76% yield) as a yellow solid.

[0657] Step d: TFA (2 mL) was added to a stirred mixture of Compound 135-3 (1 g, 2 mmol) in DCM (8 mL). The mixture was stirred at room temperature for 1 hour and then concentrated to dryness. The residue was dissolved in water (10 mL) and neutralized with K_2CO_3 aqueous solution to a pH of 8. The mixture was extracted with EtOAc (3 × 15 mL). The combined organic solvents were dried over Na_2SO_4 and concentrated to give Compound 135-4 (450 mg, 78% yield) as a yellow solid.

[0658] Step e: A mixture of Compound 135-4 (450 mg, 1.6 mmol) and Pd/C (100 mg, 10% on activated carbon) was stirred under H_2 for 3 hours. The mixture was filtered and then the filtrate was concentrated to give Compound 135-5 (380 mg, 74% yield) as a yellow solid.

[0659] Step f: A mixture of 6-bromo-4-chloro-2-methylquinoline (256 mg, 1.0 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (137 mg, 1.0 mmol), $Pd_2(dba)_3$ (183 mg, 0.2 mmol), BINAP (248 mg, 0.4 mmol), and t-BuONa (168 mg, 1.5 mmol) in 20 mL of dioxane was stirred at 100 °C for 1 hour. The mixture was concentrated and purified by silica gel chromatography (0-40% EtOAc/petroleum ether) to give Compound 135-6 (220 mg, 75% yield) as a yellow oil.

[0660] Step g: A mixture of 4-nitrobenzaldehyde (1.0 g, 6.67 mmol), ethane-1,2-diol (0.62 g, 10.0 mmol), and TsOH (0.19 g, 1.0 mmol) in 30 mL of toluene was stirred at 110 °C for 16 hours. The mixture was concentrated and purified by silica gel chromatography (0-25% EtOAc/petroleum ether) to give Compound 135-7 (1.2g, 93% yield) as a yellow oil.

[0661] Step h: A mixture of Compound 135-7 (1.2 g, 6.12 mmol), Pd/C (0.6 g), and TsOH (0.19 g, 1.0 mmol) in 30 mL of ethanol was stirred at room temperature for 16 hours under H_2. The catalyst was filtered, and the filtration concentrated to give Compound 135-8 (800 mg, 79% yield).

[0662] Step i: A mixture of Compound 135-6 (200 mg, 0.69 mmol), Compound 135-8 (115 mg, 0.69 mmol), $Pd_2(dba)_3$ (146 mg, 0.16 mmol), X-Phos (152 mg, 0.32 mmol), and Cs_2CO_3 (522 mg, 1.6 mmol) in 10 mL of dioxane was stirred at 110 °C for 2 hours. The mixture was concentrated and purified by silica gel chromatography (0-60% MeOH/EtOAc) to give Compound 135-9 (160 mg, 55% yield) as a yellow solid.

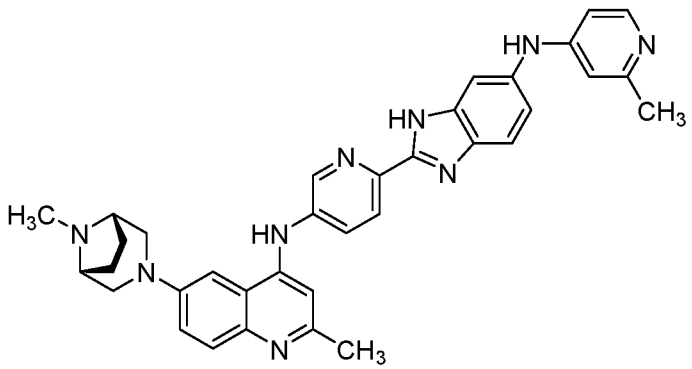
[0663] Step j: A mixture of Compound 135-9 (160 mg, 0.38 mmol) in 6 mL of THF and 6 mL of 3 N HCl was stirred at 60 °C for 2 hours. The mixture was concentrated, the pH was adjusted to 8 by K_2CO_3, extracted with EtOAc, and the organic phase was dried and concentrated to give Compound 135-10 (140 mg, 97% yield) as a yellow solid.

[0664] Step k: A mixture of Compound 135-10 (70 mg, 0.19 mmol), Compound 135-5 (48 mg, 0.19 mmol), and TsOH (19 mg, 0.1 mmol) in 5 mL of DMF was stirred at 100 °C for 2 hours. The mixture was purified by reverse phase HPLC (NH_4HCO_3) to give Compound 135-11 (60 mg, 52% yield) as a yellow solid.

[0665] Step l: A mixture of Compound 135-11 (60 mg, 0.1 mmol) and K_2CO_3 (45 mg, 0.326 mmol) in 2 mL of MeOH was stirred room temperature for 2 hours. Water (20 mL) was added and the solid was collected and dried under vacuum to give Compound 135 (20 mg, 35% yield) as a yellow solid.

Compound 135 (6-(3,6-dihydro-2H-pyran-4-yl)-2-methyl-N-(6-(6-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine): $C_{33}H_{29}N_7O$; 539.64 g/mol; 12 mg; pale yellow solid; ESI-LCMS m/z = 540.3 $[M+H]^+$; LCMS RT = 1.49 min, >95.00% (214 nm).

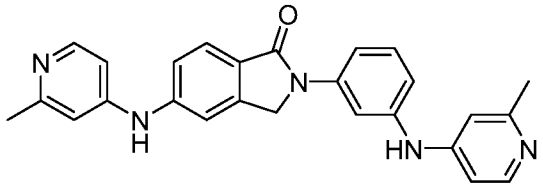
Example 136: Compound 136 (2-methyl-6-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-N-(6-(6-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine)



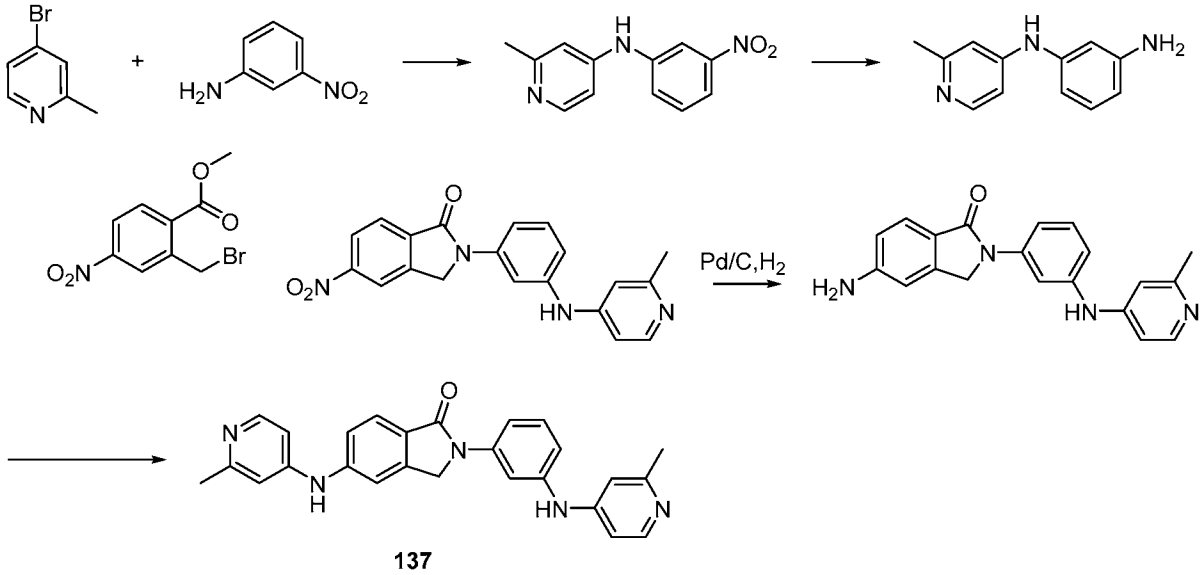
136

[0666] **Compound 136** was prepared by a method known in the art and/or a method analogous to those described herein. **Compound 136** (2-methyl-6-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-N-(6-(6-((2-methylpyridin-4-yl)amino)-1H-benzo[d]imidazol-2-yl)pyridin-3-yl)quinolin-4-amine): $C_{35}H_{35}N_9$; 581.73 g/mol; 16 mg; yellow solid; ESI-LCMS m/z = 582 $[M+H]^+$; LCMS RT = 1.16 min, >95.00% (214 nm).

Example 137: Compound 137 (5-((2-methylpyridin-4-yl)amino)-2-(3-((2-methylpyridin-4-yl)amino)phenyl)isoindolin-1-one)



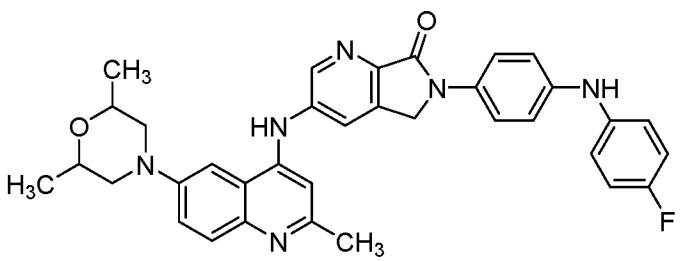
137



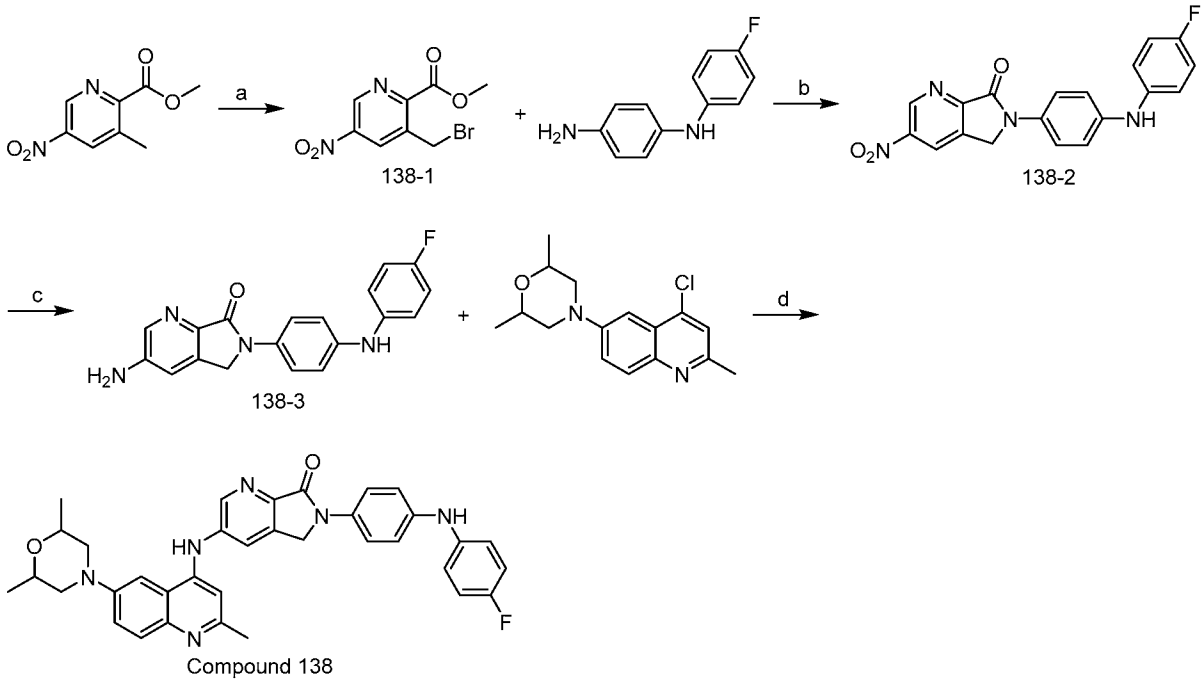
Scheme 123

[0667] **Compound 137** was prepared by a method shown in Scheme 123. **Compound 137** (5-((2-methylpyridin-4-yl)amino)-2-(3-((2-methylpyridin-4-yl)amino)phenyl)isoindolin-1-one): $C_{26}H_{23}N_5O$; 421.49 g/mol; 7.1 mg; yellow solid; ESI-LCMS m/z = 422 $[M+H]^+$; LCMS RT = 1.29 min, >95.00% (214 nm).

Example 138: Compound 138 (3-((6-(2,6-dimethylmorpholino)-2-methylquinolin-4-yl)amino)-6-(4-((4-fluorophenyl)amino)phenyl)-5,6-dihydro-7H-pyrrolo[3,4-b]pyridin-7-one)



138



Scheme 124

[0668] **Compound 138** was prepared by a method shown in Scheme 124.

[0669] Step a: To a solution of methyl 3-methyl-5-nitropicolinate (5 g, 25.5 mmol) in DCM (20 mL) was added NBS (4.54 g, 25.5 mmol) and AIBN (4.18 g, 25.5 mmol) at room temperature, and the mixture stirred at 80 °C for 6 hours. The mixture was cooled to room temperature, quenched with water, and extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. After removal of solvent, the crude product was purified by silica gel chromatography (20% EtOAc/petroleum ether) to afford Compound 138-1 (5.0 g, 30% yield) as a yellow solid.

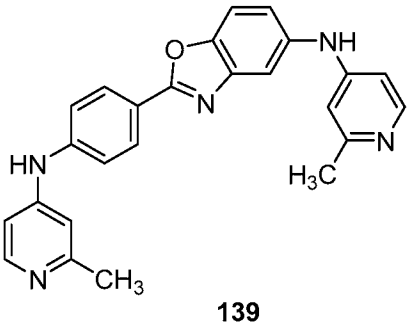
[0670] Step b: To a solution of Compound 138-1 (1.05 g, 2.00 mmol) in EtOH (20 mL) was added N1-(4-fluorophenyl)benzene-1,4-diamine (480 mg, 2.37 mmol) and pyridine (2 mL). The mixture was stirred at 80° C for 4 hours and then filtered to afford Compound 138-2 (580 mg, 80% yield) as a yellow solid.

[0671] Step c: To a solution of Compound 138-2 (260 mg, 0.71 mmol) in MeOH (30 mL) was added Pd/C (10%, 130 mg). The mixture was stirred for 2 hours at room temperature and then filtered to afford Compound 138-3 (169 mg, 71% yield) as a yellow solid.

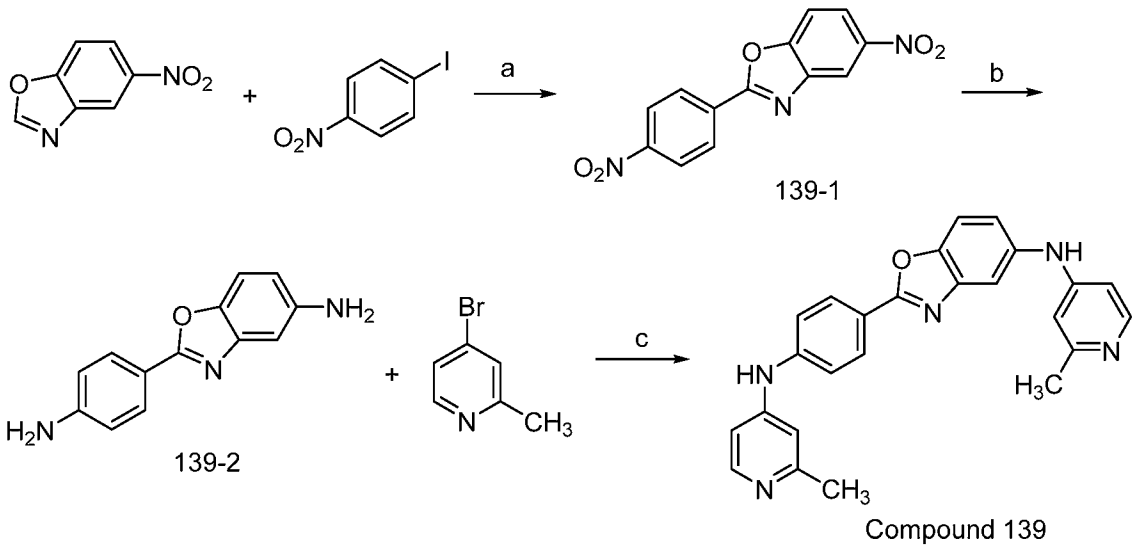
[0672] Step d: A mixture of Compound 138-3 (100 mg, 0.30 mmol), 4-(4-chloro-2-methylquinolin-6-yl)-2,6-dimethylmorpholine (87 mg, 0.30 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol), xantphos (69 mg, 0.12 mmol), and Cs_2CO_3 (195 mg, 0.60 mmol) in 1,4-dioxnae (10 mL) was stirred at 100 °C for 3 hours, and then concentrated. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. After removal of solvent, the crude product was purified by silica gel chromatography (10% MeOH/EtOAc) to afford Compound 138 (12 mg, 7% yield) as a light-yellow solid.

Compound 138 (3-((6-(2,6-dimethylmorpholino)-2-methylquinolin-4-yl)amino)-6-(4-((4-fluorophenyl)amino)phenyl)-5,6-dihydro-7H-pyrrolo[3,4-b]pyridin-7-one): $C_{35}H_{33}FN_6O_2$; 588.67 g/mol; 12 mg; light-yellow solid. ESI-LCMS m/z = 589.0 $[M+H]^+$; LCMS RT = 1.56 min, >95.00% (214 and 254 nm).

Example 139: Compound 139 (N-(2-methylpyridin-4-yl)-2-(4-((2-methylpyridin-4-yl)amino)phenyl)benzo[d]oxazol-5-amine)



139



Scheme 125

[0673] **Compound 139** was prepared by the method shown in Scheme 125.

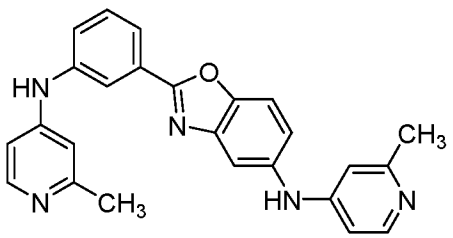
[0674] Step a: To a solution of 5-nitrobenzo[d]oxazole (500 mg, 3.05 mmol) in 1,4-dioxane (20 mL) was added 1-iodo-4-nitrobenzene (910 mg, 3.65 mmol), lithium t-butoxide (490 mg, 6.10 mmol), and $Pd(PPh_3)_4$ (175 mg, 0.15 mmol). The mixture was stirred at 100 °C overnight under Ar. Water (60 mL) was added and the mixture extracted with DCM (3 × 60 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude Compound 139-1. The crude (1.2 g) was used directly in next step.

[0675] Step b: To a solution of crude Compound 139-1 (1.2 g) in ethanol (15 mL) was added a spoonful of Raney Nickel and $N_2H_4 \cdot H_2O$ (3 mL). The mixture was stirred at room temperature for 1 hour under N_2. The mixture was filtered and the solvent was removed in vacuo. The crude was purified by prep-TLC (petroleum ether: ethyl acetate = 1:1, 254 nm, silica) to afford Compound 139-2 (500 mg, 35% yield) as a brown solid.

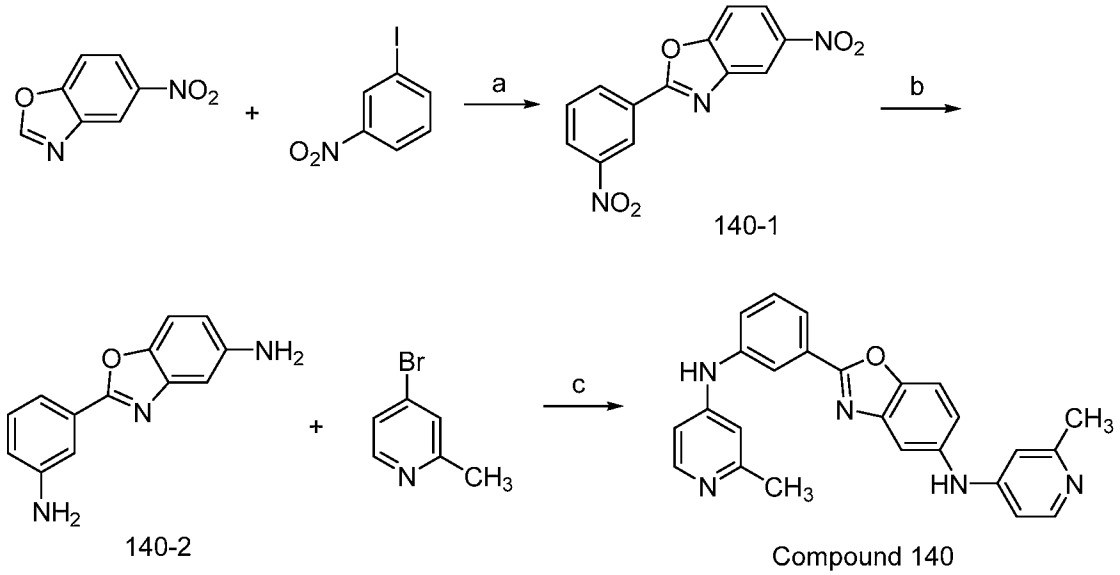
[0676] Step c: To a solution of Compound 139-2 (140 mg, 0.62 mmol) in ethanol (6 mL) was added 4-bromo-2-methylpyridine (0.03 mL, 0.62 mmol), Pd_2dba_3 (56 mg, 0.062 mmol), K_2CO_3 (95 mg, 0.64 mmol), and X-Phos (146 mg, 0.29 mmol). The mixture was stirred at 100° C overnight. Water (20 mL) was added and the mixture extracted with ethyl acetate (2 × 20 mL). The combined organic phased were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford the crude product. The crude was purified by prep-HPLC to afford Compound 139 (60 mg, 63% yield) as a white solid.

[0677] **Compound 139** (N-(2-methylpyridin-4-yl)-2-(4-((2-methylpyridin-4-yl)amino)phenyl)benzo[d]oxazol-5-amine): $C_{25}H_{21}N_5O$; 407.47 g/mol; 60 mg; white solid; ESI-LCMS m/z = 408 $[M+H]^+$; LCMS RT = 1.67 min, >95.00% (214 and 254 nm).

Example 140: Compound 140 (N-(2-methylpyridin-4-yl)-2-(3-((2-methylpyridin-4-yl)amino)phenyl)benzo[d]oxazol-5-amine)



140



Scheme 126

[0678] **Compound 140** was prepared by the method shown in Scheme 126.

[0679] Step a: To a solution of 5-nitrobenzo[d]oxazole (500 mg, 3.05 mmol) in 1,4-dioxane (20 mL) was added 1-iodo-4-nitrobenzene (910 mg, 3.65 mmol), lithium t-butoxide (490 mg, 6.10 mmol) and $Pd(PPh_3)_4$ (175 mg, 0.15 mmol). The mixture was stirred at 100 °C overnight under Ar. Water (60 mL) was added and the mixture extracted with DCM (3 × 60 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude Compound 140-1. The crude (1.1 g) was used directly in next step.

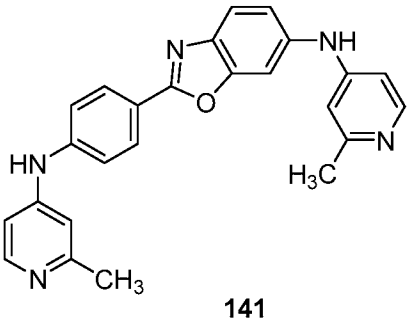
[0680] Step b: To a solution of crude Compound 140-1 (1.1 g) in ethanol (15 mL) was added a spoonful of Raney Nickel and $N_2H_4 \cdot H_2O$ (3 mL). The mixture was stirred at room temperature for 1 hour under N_2. The mixture was filtered and the solvent was removed in vacuo. The crude was purified by prep-TLC (petroleum ether: ethyl acetate = 1:1, 254 nm, silica) to afford Compound 140-2 (475 mg, 33% yield) as a brown solid.

[0681] Step c: To a solution of Compound 140-2 (250 mg, 1.1 mmol) in ethanol (60 mL) was added 4-bromo-2-methylpyridine (0.06 mL, 1.1 mmol), Pd_2dba_3 (100 mg, 0.11 mmol), K_2CO_3 (170 mg, 1.2 mmol), and X-Phos (261 mg, 0.55 mmol). The mixture was stirred at 100° C overnight. Water (150 mL) was added and the mixture extracted with ethyl acetate (2 × 150 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford the crude product.

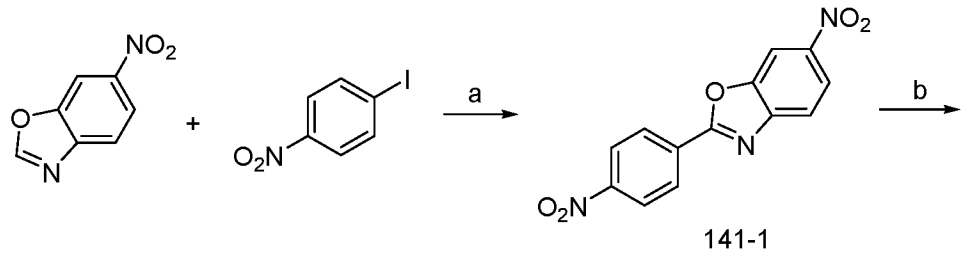
The crude was purified by prep-HPLC to afford Compound 140 (80 mg, 67% yield) as a white solid.

[0682] **Compound 140** (N-(2-methylpyridin-4-yl)-2-(3-((2-methylpyridin-4-yl)amino)phenyl)benzo[d]oxazol-5-amine): $C_{25}H_{21}N_5O$; 407.47 g/mol; 80 mg; white solid; ESI-LCMS m/z = 408 $[M+H]^+$; LCMS RT = 1.75 min, >95.00% (214 and 254 nm).

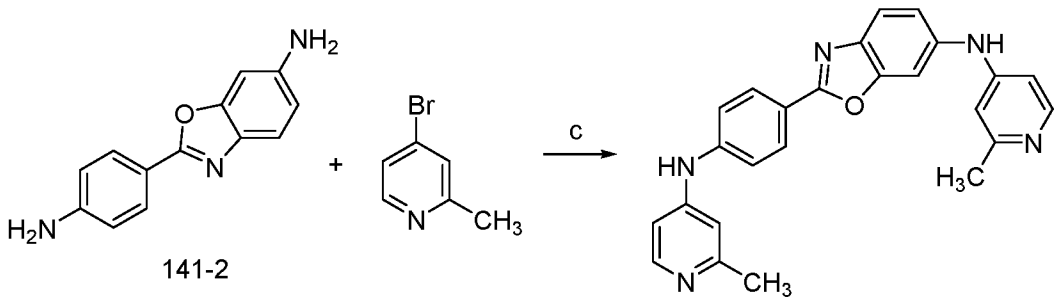
Example 141: Compound 141 (N-(2-methylpyridin-4-yl)-2-(4-((2-methylpyridin-4-yl)amino)phenyl)benzo[d]oxazol-6-amine)



141



141-1



141-2

Compound 141

Scheme 127

[0683] **Compound 141** was prepared by the method shown in Scheme 127.

[0684] Step a: To a solution of 6-nitrobenzo[d]oxazole (500 mg, 3.05 mmol) in 1,4-dioxane (20 mL) was added 1-iodo-4-nitrobenzene (910 mg, 3.65 mmol), lithium t-butoxide (490 mg, 6.10 mmol), and $Pd(PPh_3)_4$ (175 mg, 0.15 mmol). The mixture was stirred at 100 °C overnight under Ar. Water (60 mL) was added and the mixture extracted with DCM (3 × 60 mL). The combined organic phases were washed with brine (10 mL), dried over

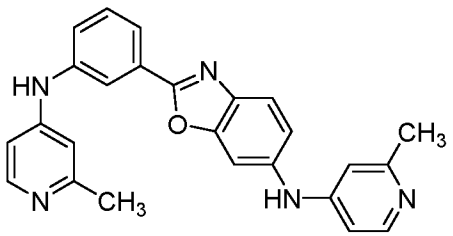
anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude Compound 141-1. The crude (1.5 g) was used directly in next step.

[0685] Step b: To a solution of crude Compound 141-1 (1.5 g) in ethanol (15 mL) was added a spoonful of Raney Nickel and $N_2H_4 \cdot H_2O$ (3 mL). The mixture was stirred at room temperature for 1 hour under N_2. The mixture was filtered and the solvent was removed in vacuo. The crude was purified by prep-TLC (petroleum ether: ethyl acetate = 1:1, 254 nm, silica) to afford Compound 141-2 (321 mg, 30% yield) as a brown solid.

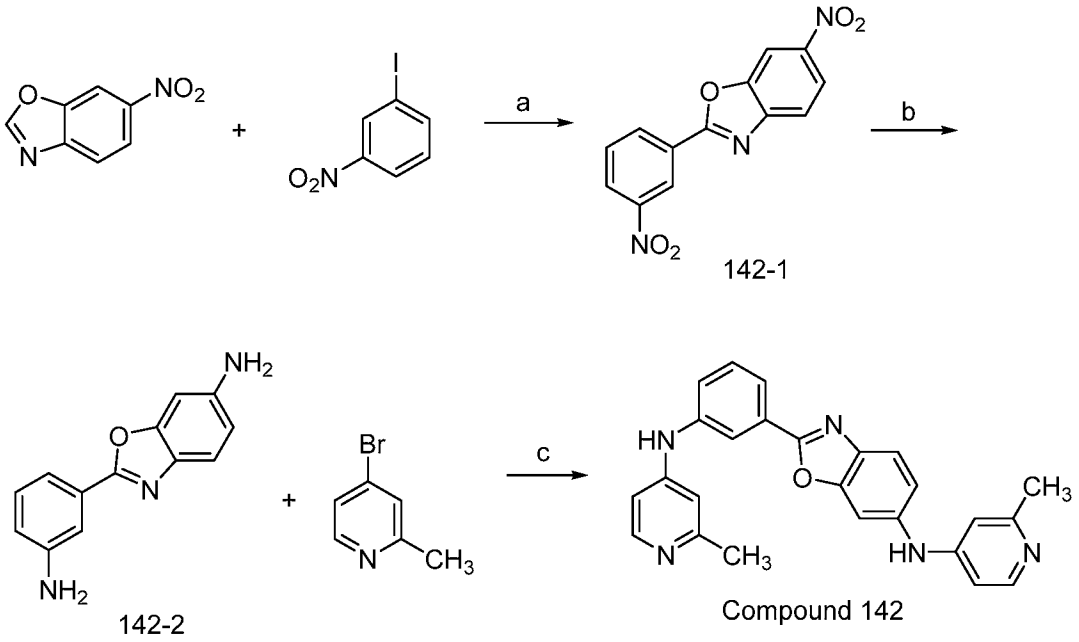
[0686] Step c: To a solution of Compound 141-2 (170 mg, 0.60 mmol) in ethanol (8 mL) was added 4-bromo-2-methylpyridine (0.04 mL, 0.60 mmol), Pd_2dba_3 (68 mg, 0.060 mmol), K_2CO_3 (116 mg, 0.71 mmol), and X-Phos (177 mg, 0.32 mmol). The mixture was stirred at 100° C overnight. Water (20 mL) was added and the mixture extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford the crude product. The crude was purified by prep-HPLC to afford Compound 141 (32 mg, 57% yield) as a white solid.

[0687] **Compound 141** (N-(2-methylpyridin-4-yl)-2-(4-((2-methylpyridin-4-yl)amino)phenyl)benzo[d]oxazol-6-amine): $C_{25}H_{21}N_5O$; 407.47 g/mol; 32 mg; white solid; ESI-LCMS m/z = 408 $[M+H]^+$; LCMS RT = 1.65 min, >95.00% (214 and 254 nm).

Example 142: Compound 142 (N-(2-methylpyridin-4-yl)-2-(3-((2-methylpyridin-4-yl)amino)phenyl)benzo[d]oxazol-6-amine)



142



Scheme 128

[0688] **Compound 142** was prepared by the method shown in Scheme 128.

[0689] Step a: To a solution of 6-nitrobenzo[d]oxazole (500 mg, 3.05 mmol) in 1,4-dioxane (20 mL) was added 1-iodo-4-nitrobenzene (910 mg, 3.65 mmol), lithium t-butoxide (490 mg, 6.10 mmol) and $Pd(PPh_3)_4$ (175 mg, 0.15 mmol). The mixture was stirred at 100 °C overnight under Ar. Water (60 mL) was added and the mixture extracted with DCM (3 × 60 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude Compound 142-1. The crude (1.2 g) was used directly in next step.

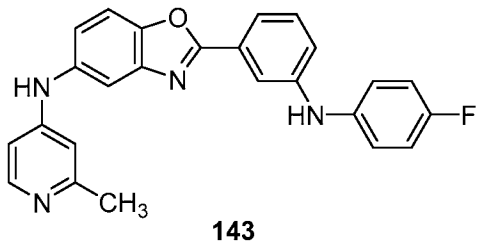
[0690] Step b: To a solution of crude Compound 142-1 (1.2 g) in ethanol (15 mL) was added a spoonful of Raney Nickel and $N_2H_4 \cdot H_2O$ (3 mL). The mixture was stirred at room temperature for 1 hour under N_2. The mixture was filtered and the solvent was removed in vacuo. The crude was purified by prep-TLC (petroleum ether: ethyl acetate = 1:1, 254 nm, silica) to afford Compound 142-2 (563 mg, 42% yield) as a brown solid.

[0691] Step c: To a solution of Compound 142-2 (250 mg, 1.1 mmol) in ethanol (60 mL) was added 4-bromo-2-methylpyridine (0.06 mL, 1.1 mmol), Pd_2dba_3 (100 mg, 0.11 mmol), K_2CO_3 (170 mg, 1.2 mmol), and X-Phos (261 mg, 0.55 mmol). The mixture was stirred at 100° C overnight. Water (150 mL) was added and the mixture extracted with ethyl acetate (2 × 150 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford the crude product.

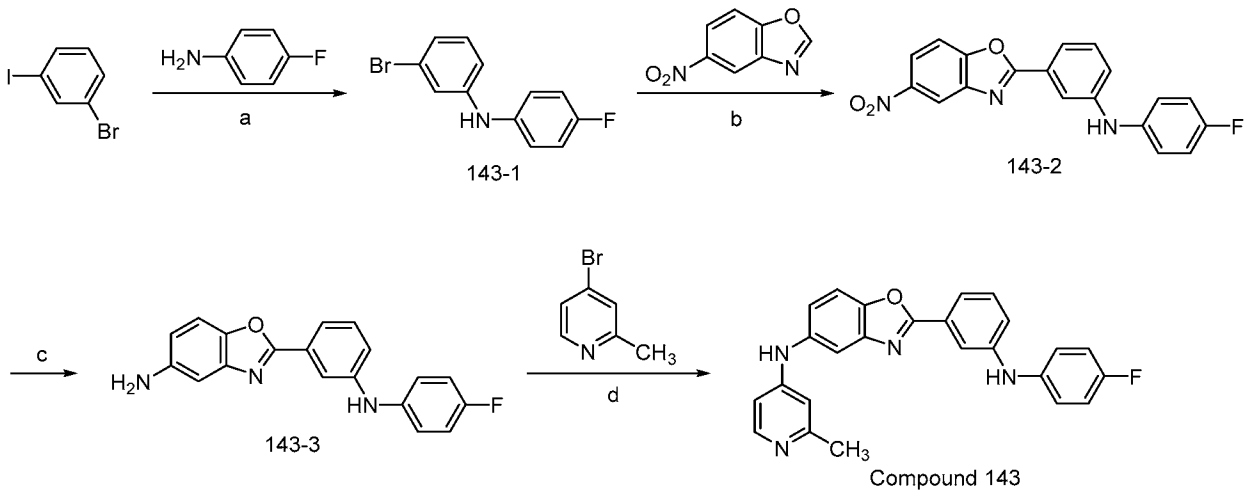
The crude was purified by prep-HPLC to afford Compound 142 (40 mg, 53% yield) as a white solid.

[0692] **Compound 142** (N-(2-methylpyridin-4-yl)-2-(3-((2-methylpyridin-4-yl)amino)phenyl)benzo[d]oxazol-6-amine): $C_{25}H_{21}N_5O$; 407.47 g/mol; 40 mg; white solid; ESI-LCMS m/z = 408 $[M+H]^+$; LCMS RT = 1.53 min, >95.00% (214 and 254 nm).

Example 143: Compound 143 (2-(3-((4-fluorophenyl)amino)phenyl)-N-(2-methylpyridin-4-yl)benzo[d]oxazol-5-amine)



143



Scheme 129

[0693] **Compound 143** was prepared by the method shown in Scheme 129.

[0694] Step a: To a solution of 1-bromo-3-iodobenzene (200 mg, 0.7 mmol) in xylene (10 mL) was added 4-fluoroaniline (40 mg, 0.36 mmol), $Pd(PPh_3)_2Cl_2$ (25 mg, 0.036 mmol), PPh (10 mg, 0.07 mmol), and t-BuONa (120 mg, 1.08 mmol) under Ar. The mixture was stirred at 140 °C for 16 hours under Ar. The mixture was concentrated and the residue was purified by EA/PE (0%-10%) to give Compound 143-1 (150 mg, 80% yield) as a yellow solid.

[0695] Step b: To a solution of Compound 143-1 (160 mg, 0.6 mmol) in 1,4-dioxane (5 mL) was added 5-nitrobenzo[d]oxazole (75 mg, 0.5 mmol), $Pd(Ph_3)_4$ (57 mg, 0.05 mmol) and t-BuLi (60 mg, 1.0 mmol) at room temperature under Ar. The mixture was stirred at 100 °C

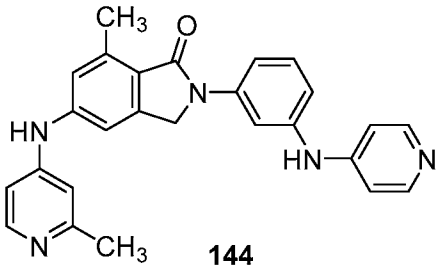
under Ar overnight. The mixture was concentrated and the residue was purified by EA/PE (0%-10%) to give Compound 143-2 (50 mg, 50% yield) as a yellow solid.

[0696] Step c: To a solution of Compound 143-2 (50 mg, 0.28 mmol) in EtOH (6 mL) and DCM (3 mL) was added $NH_2NH_2•H_2O$ (14 mg, 0.28 mmol) and Raney-Ni (10 mg) at room temperature under H_2. The mixture was stirred at room temperature for 16 hours. The mixture was filtered. The filtrate was concentrated to give Compound 143-3 (50 mg, 100% yield) as a yellow solid.

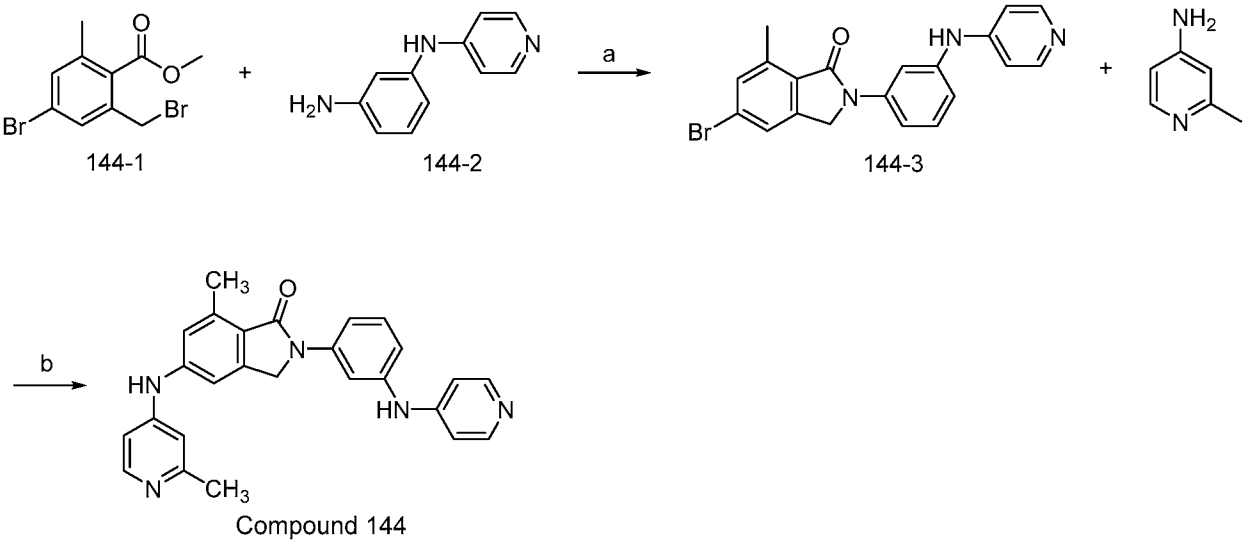
[0697] Step d: To a solution of Compound 143-3 (100 mg, 0.31 mmol) in EtOH (3 mL) was added 4-bromo-2-methylpyridine (100 mg, 0.6 mmol), X-phos (74 mg, 0.062 mmol), $Pd_2(dba)_3$ (30 mg, 0.031 mmol), and K_2CO_3 (200 mg, 1.55 mmol) at room temperature under Ar. The mixture was stirred at 100°C under Ar overnight. The reaction was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (NH_4HCO_3/H_2O/MeCN) to give Compound 143 (38.2 mg, 30% yield) as a yellow solid.

[0698] **Compound 143** (2-(3-((4-fluorophenyl)amino)phenyl)-N-(2-methylpyridin-4-yl)benzo[d]oxazol-5-amine): $C_{25}H_{19}FN_4O$; 410.45 g/mol; 38.2 mg; yellow solid; ESI-LCMS m/z = 411 $[M+H]^+$; LCMS RT = 1.106 min, >95.00% (214 and 254 nm).

Example 144: Compound 144 (7-methyl-5-((2-methylpyridin-4-yl)amino)-2-(3-(pyridin-4-ylamino)phenyl)isoindolin-1-one)



144



Scheme 130

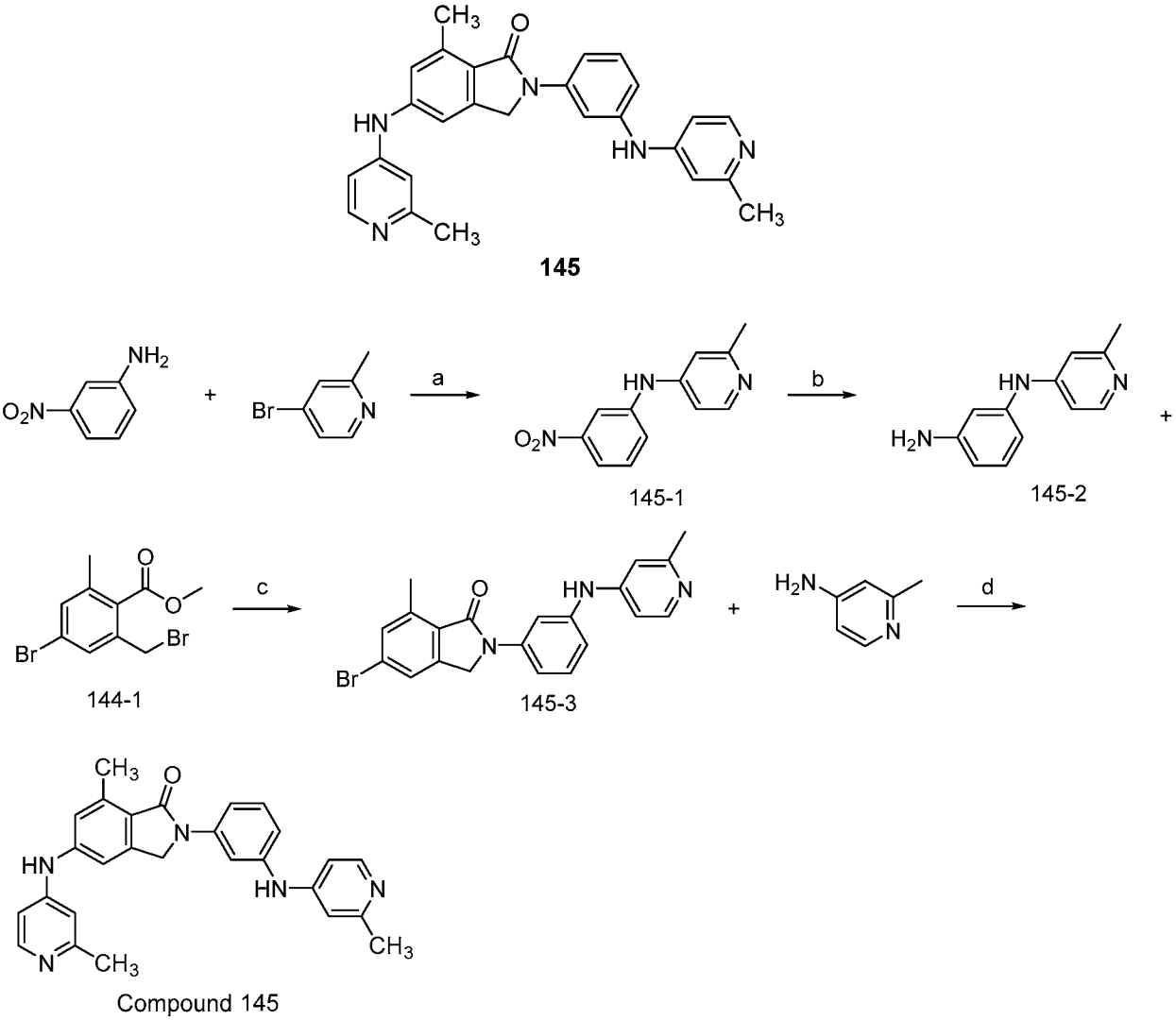
[0699] **Compound 144** was prepared by the method shown in Scheme 130.

[0700] Step a: To a mixture of Compound 144-1 (640 mg, 2 mmol) and Compound 144-2 (407 mg, 2.2 mmol) in MeOH (10 mL) was added TEA (606 mg, 6 mmol), and the mixture was stirred at 85° C for 16 hours. The combined organic phases were concentrated. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) to afford Compound 144-3 (400 mg, 50.8% yield) as a solid.

[0701] Step b: To a mixture of Compound 144-3 (150 mg, 0.38 mmol) in t-BuOH (5mL) /toluene (5 mL) was added 2-methylpyridin-4-amine (50 mg, 0.45 mmol), $Pd_2(dba)_3$ (20 mg, 0.02 mmol), Brettphos (20 mg, 0.02 mmol), and Cs_2CO_3 (247 mg, 0.76 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and the crude was purified by prep-HPLC to give Compound 144 as a yellow solid (15 mg, 10% yield).

[0702] **Compound 144** (7-methyl-5-((2-methylpyridin-4-yl)amino)-2-(3-(pyridin-4-ylamino)phenyl)isoindolin-1-one): $C_{26}H_{23}N_5O$; 421.49 g/mol; 15 mg; yellow solid; ESI-LCMS m/z = 422 $[M+H]^+$; LCMS RT = 1.30 min, >95.00% (214 and 254 nm).

Example 145: Compound 145 (7-methyl-5-((2-methylpyridin-4-yl)amino)-2-(3-((2-methylpyridin-4-yl)amino)phenyl)isoindolin-1-one)



Scheme 131

[0703] **Compound 145** was prepared by the method shown in Scheme 131.

[0704] Step a: To a stirred mixture of 3-nitroaniline (2.76 g, 0.02 mol) in 1,4-dioxane (30 mL) was added 4-bromo-2-methylpyridine (3.42 g, 0.02 mol), Cs_2CO_3 (13g, 0.04 mol), $Pd_2(dba)_3$ (280 mg, 0.25 mmol), and Xantphos (280 mg, 0.4 mmol) under N_2. The resulting mixture was stirred at 100° C for 3 hours. The reaction was quenched with water (60 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford Compound 145-1 (4 g, 87% yield) as a yellow solid.

[0705] Step b: To a mixture of Compound 145-1 (4 g, 17.5 mmol) in MeOH (100 mL) was added Pd/C (400mg), and the mixture was stirred at room temperature for 4 hours under

H_2. The combined organic phases were filtered by diatomite to give Compound 145-2 as a yellow solid (3 g, 88.7% yield).

[0706] Step c: To a mixture of Compound 144-1 (400 mg, 1.25 mmol) and Compound 145-2 (273 mg, 1.3 mmol) in MeOH (10 mL) was added TEA (253 mg, 2.5 mmol), and the mixture was stirred at 85° C for 16 hours. The combined organic phases were concentrated. The residue was purified by flash chromatography on silica gel (0-20% MeOH in DCM) to afford Compound 145-3 (300 mg, 59% yield) as a solid.

[0707] Step d: To a mixture of Compound 145-3 (150 mg, 0.36 mmol) in t-BuOH (5mL) /toluene (5 mL) was added 2-methylpyridin-4-amine (39 mg, 0.45 mmol), $Pd_2(dba)_3$ (20 mg, 0.02 mmol), Brettphos (20 mg, 0.02 mmol), and Cs_2CO_3 (234 mg, 0.72 mmol), and the mixture was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and the crude was purified by prep-HPLC to give Compound 145 as a yellow solid (18 mg, 11% yield).

[0708] **Compound 145** (7-methyl-5-((2-methylpyridin-4-yl)amino)-2-(3-((2-methylpyridin-4-yl)amino)phenyl)isoindolin-1-one): $C_{27}H_{25}N_5O$; 435.53 g/mol; 18 mg; yellow solid; ESI-LCMS m/z = 436 $[M+H]^+$; LCMS RT = 1.41 min, >95.00% (214 and 254 nm).

Example 146. Biological Assays

Foxp3 induction assay

[0709] 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.

[0710] 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)

[0711] **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)

[0712] 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).

[0713] 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.

[0714] 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.

[0715] 4. Gently rock the plates for ≥15 minutes at room temperature. Measure firefly luminescence using a luminometer.

[0716] The Akt3 inhibition and activation activities of selected compounds disclosed herein are shown in Tables 1 and 2, respectively.

Phospho-Akt Isoform Specificity Assay

[0717] 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.

[0718] Data illustrated by Figure 6 was obtained at least partially using this assay protocol.

IL-10 ELISA Assay

[0719] 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.

[0720] Data illustrated by Figures 7 and 8 were obtained at least partially using this assay protocol.

FoxP3 ELISA Assay

[0721] 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.

[0722] Data illustrated by Figure 5 was obtained at least partially using this assay protocol.

iTreg Induction Assay

[0723] 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.

[0724] Data illustrated by Figures 1-4 were obtained at least partially using this assay protocol.

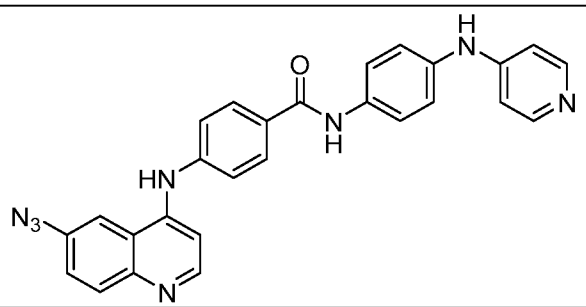
[0725] Figures 1-4 show evaluation of iTreg induction (FoxP3) from human CD4 T cells treated with certain compounds described herein in the presence of anti-CD3/anti-CD28/IL-2/TGFβ. Figure 5 shows evaluation of FoxP3 protein level in human CD4 T cells treated with Compounds 131, 24, 69, 70, 87, 90, 97, and 102 described herein. Figure 6 shows evaluation of Akt isoform specificity of Compounds 131, 24, 69, 87, 90, 97, and 102

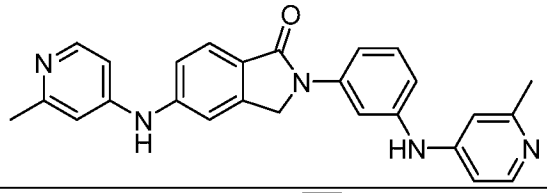
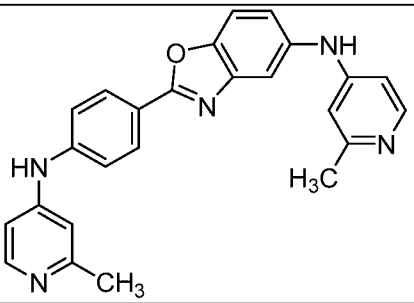
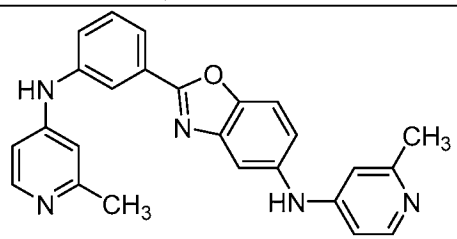
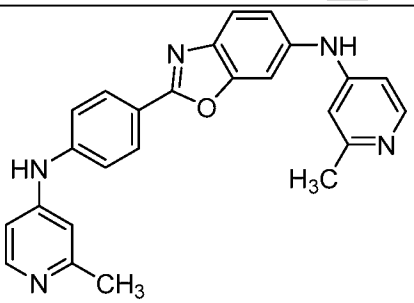
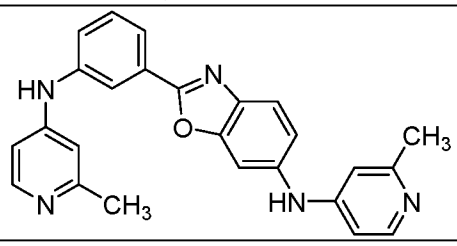
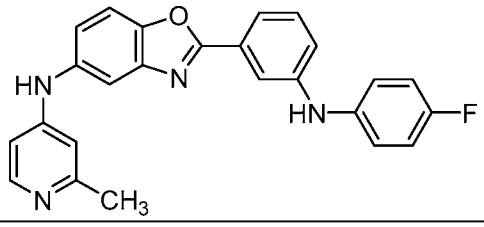
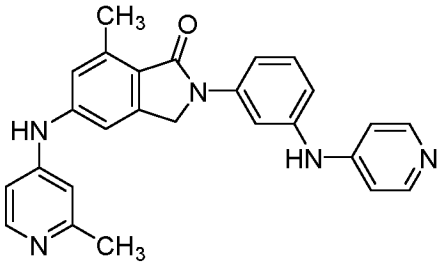
described herein. Figure 7 shows evaluation of IL-10 in supernatants from human nTreg cells treated with Compounds 131, 24, 69, 70, 87, 90, 97, and 102 described herein for 24 hours in the presence of anti-CD3/anti-CD28/IL-2 stimulation. Figure 8 shows evaluation of IL-10 in supernatants from human nTreg cells treated with Compounds 131, 24, 69, 70, 87, 90, 97, and 102 described herein for 48 hours in the presence of anti-CD3/anti-CD28/IL-2 stimulation. Figure 9 shows in vivo changes in Tregs in the spleen of mice on day 0 through day 4 post-PO treatment (10 mg/kg) with Compounds 131, 24, 69, 70, 87, 90, 97, and 102 described herein. Figure 10 shows in vivo changes in Tregs in the spleen of mice on day 0 through day 3 post-IV treatment (1 mg/kg) with Compounds 131, 24, 69, 70, 87, 90, 97, and 102 described herein.

[0726] TC-1 tumor bearing mice were treated via oral gavage with small molecules at indicated doses. Two days after single treatment spleens were isolated and % of Tregs were evaluated using flow cytometry. % Tregs were normalized to untreated controls. Figure 11 shows evaluation of Treg activation (normalized to untreated control; measured by flow cytometry) in isolated spleen of C57/Bl6 mice at two days post-treatment by single oral gavage with Compounds 131-134. Figure 12 shows evaluation of Treg activation (normalized to untreated control; measured by flow cytometry) in isolated spleen of C57/Bl6 mice at two days post-treatment by single oral gavage with Compounds 131, 121, and 127. Figure 13 shows evaluation of Treg activation (normalized to untreated control; measured by flow cytometry) in isolated spleen of C57/Bl6 mice at two days post-treatment (PO with Compounds 131, 123, 126, and 129).

[0727] 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		< 0.5

Compound No.	Structure	IC_{50} (μM)
137		< 0.5
139		<5
140		<2
141		<5
142		<5
143		<5
144		<1

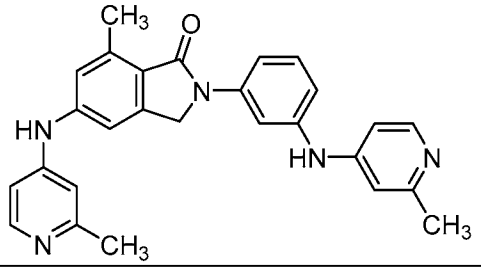
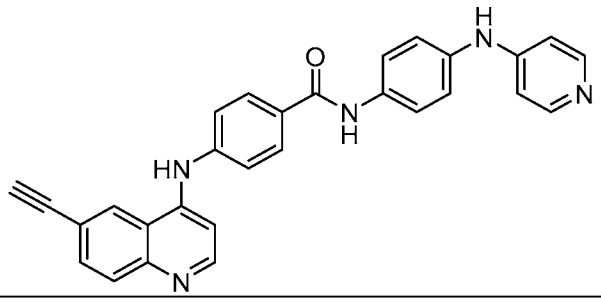
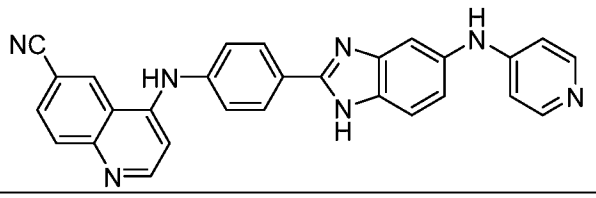
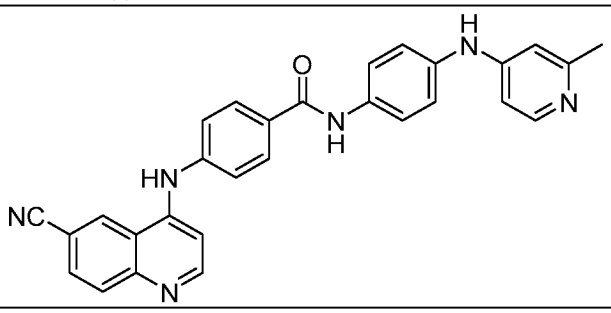
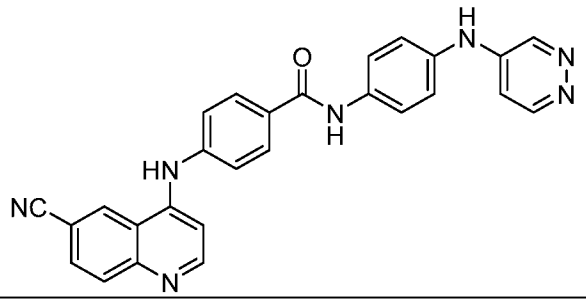
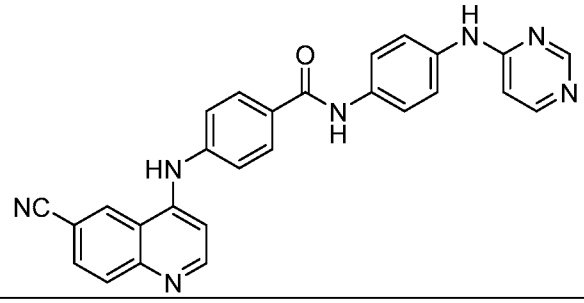
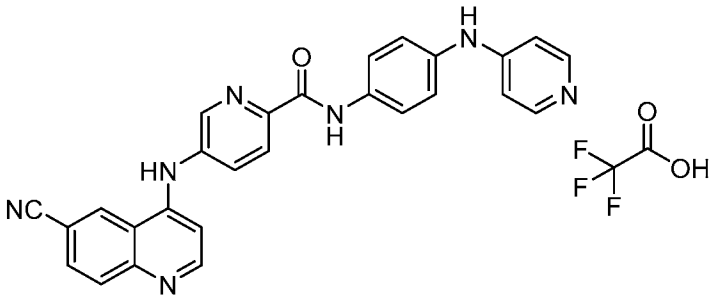
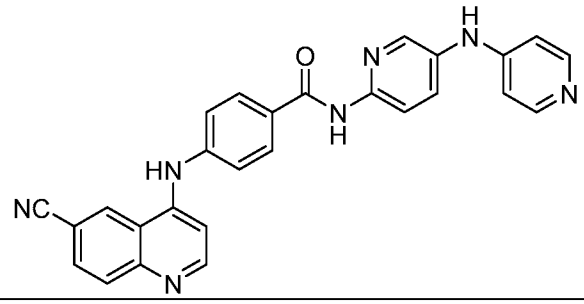
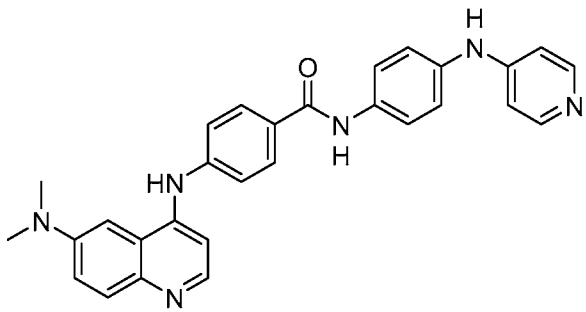
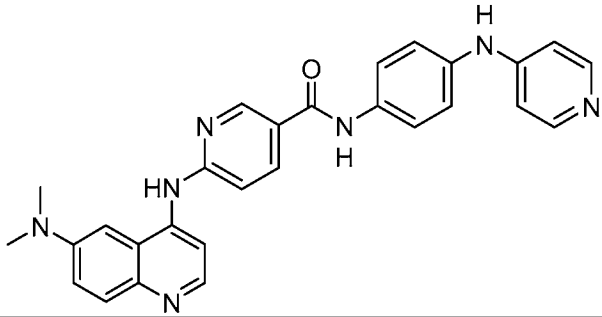
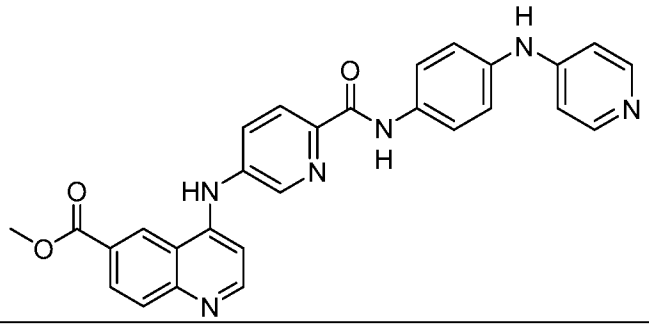
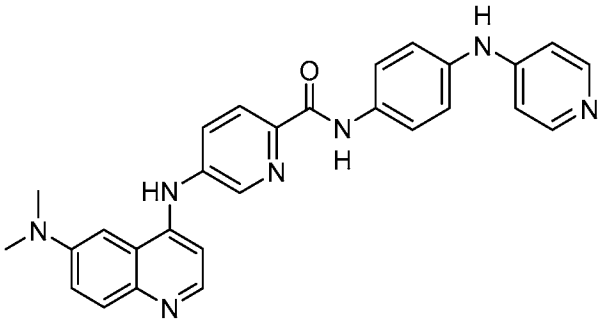
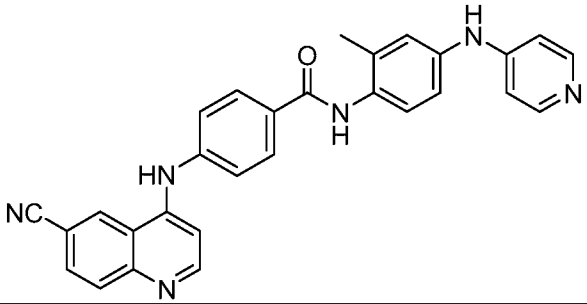
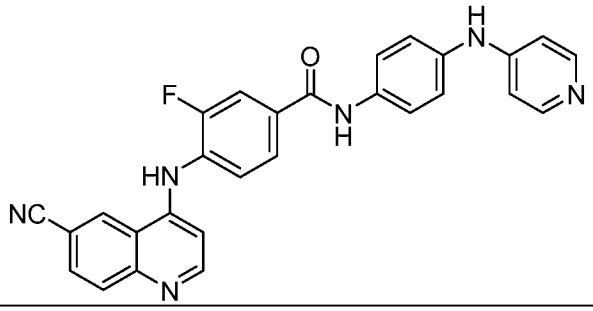
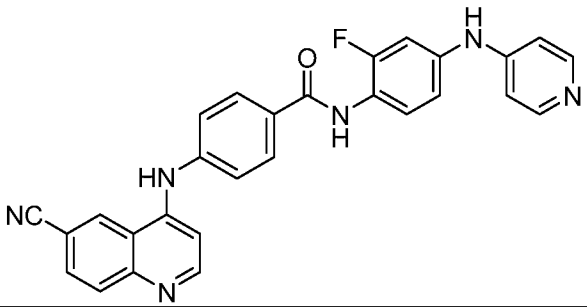
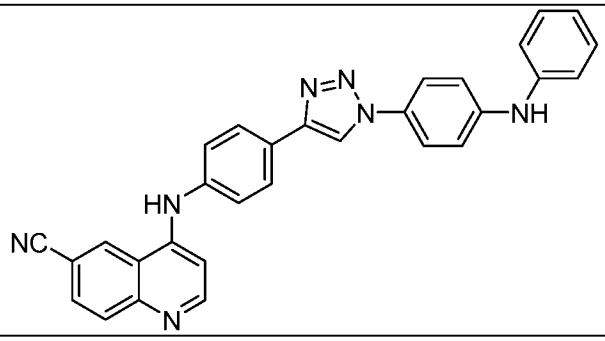
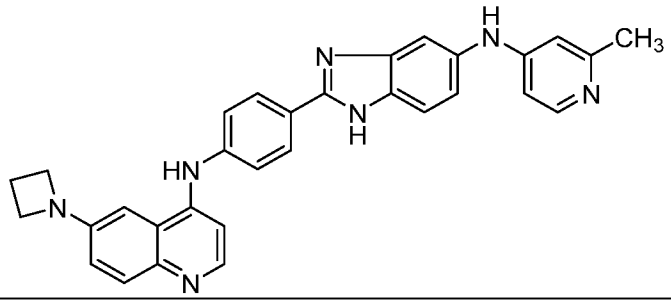
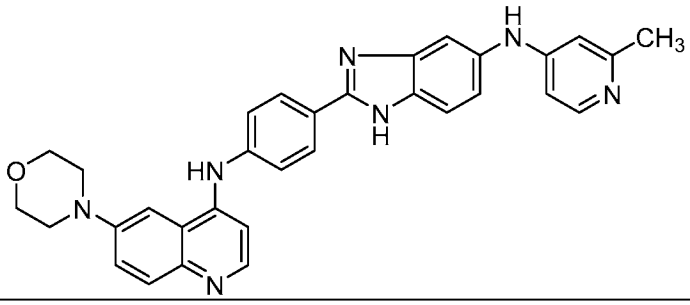
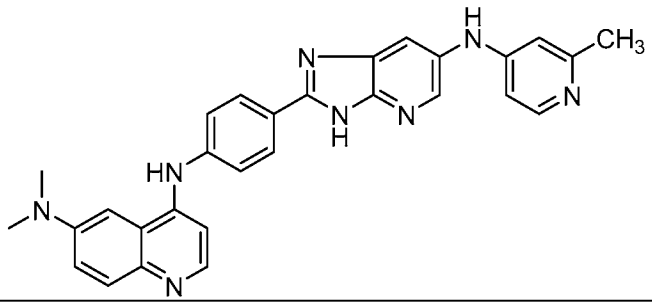
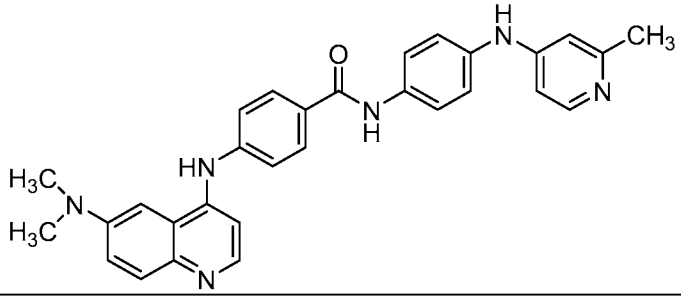
Compound No.	Structure	IC_{50} (μM)
145		<1

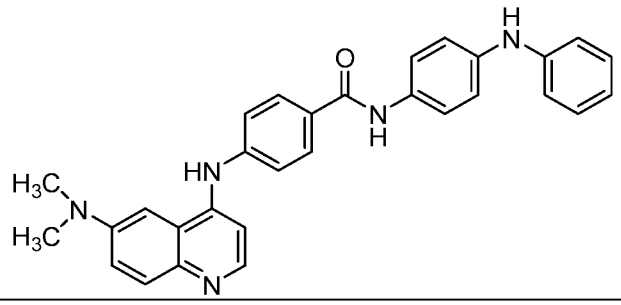
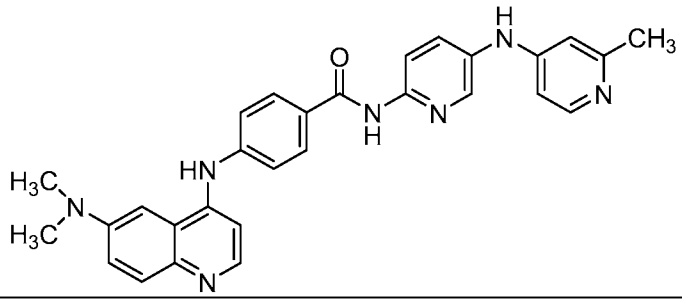
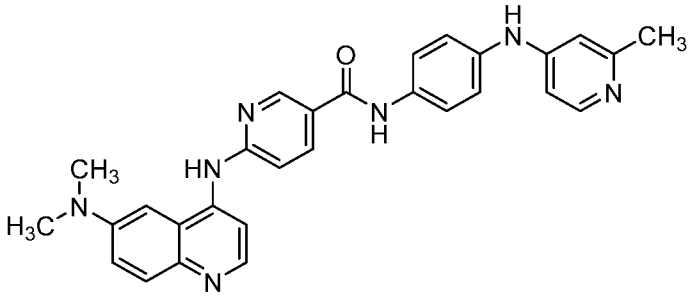
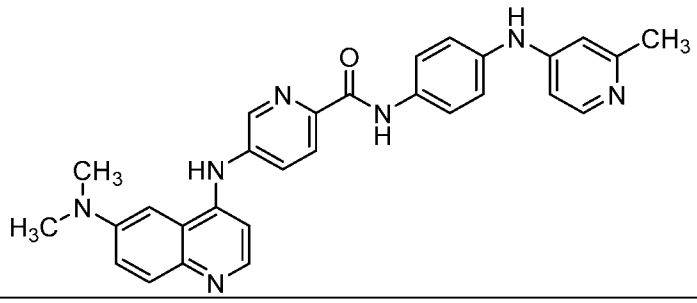
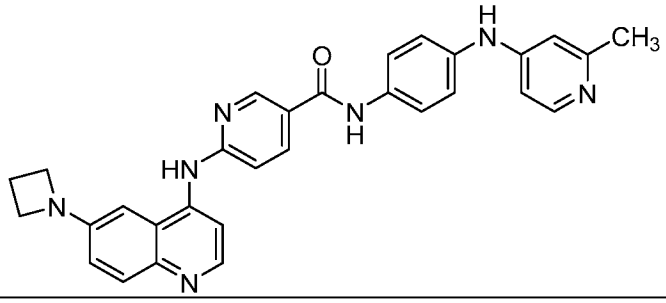
Table 2. Akt3 activation activity of selected compounds.

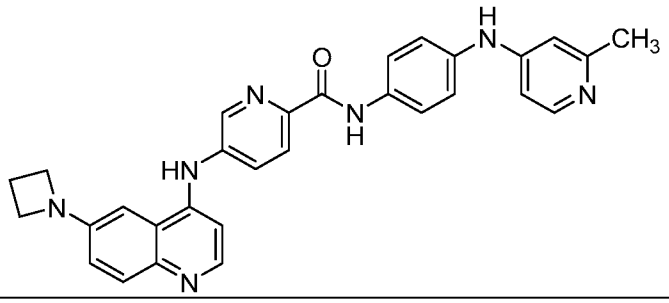
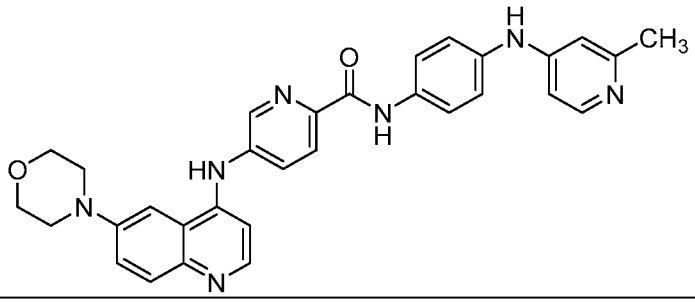
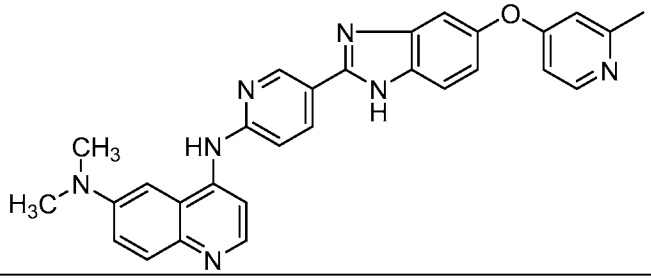
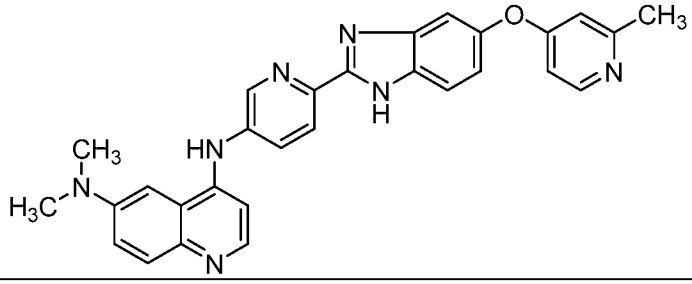
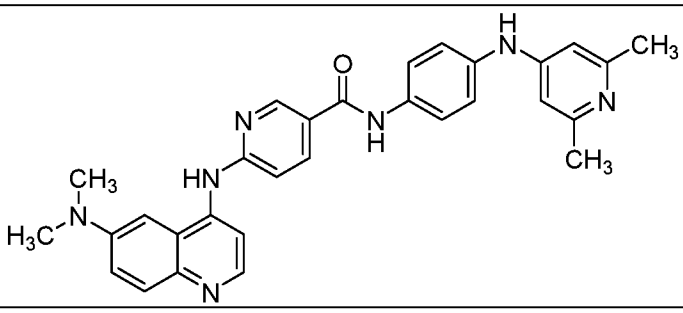
Compound No.	Structure	EC_{50} (μM)
2		< 2
4		< 5
5		< 5
6		< 5

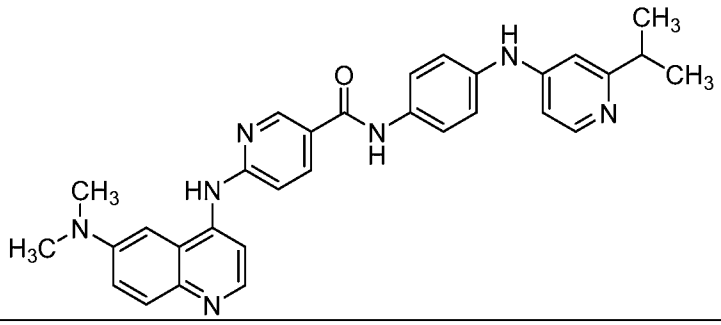
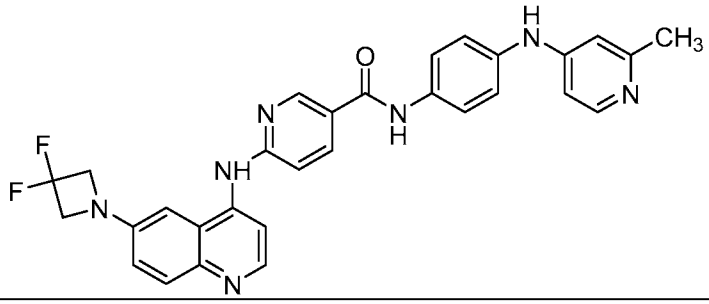
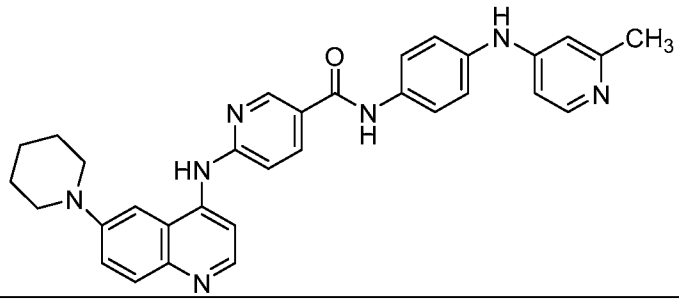
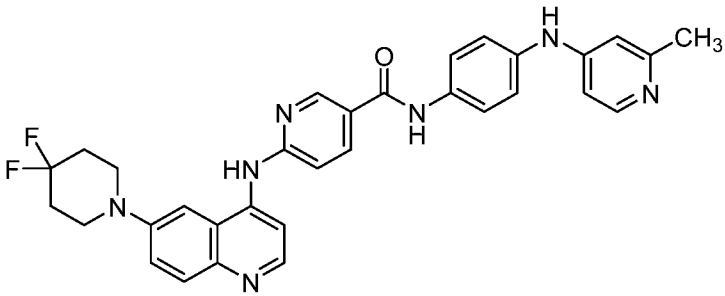
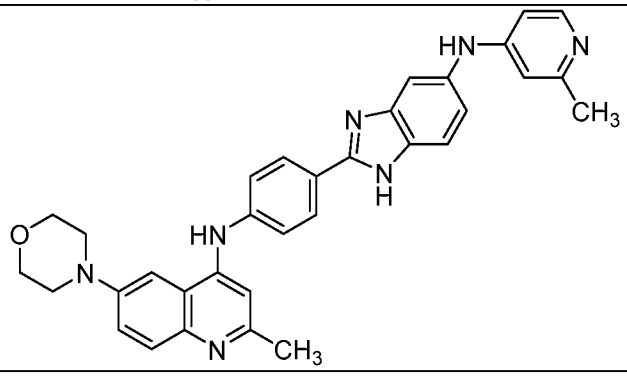
Compound No.	Structure	EC_{50} (μM)
7		< 5
10		< 2
11		< 0.5
15		< 1
18		< 0.5

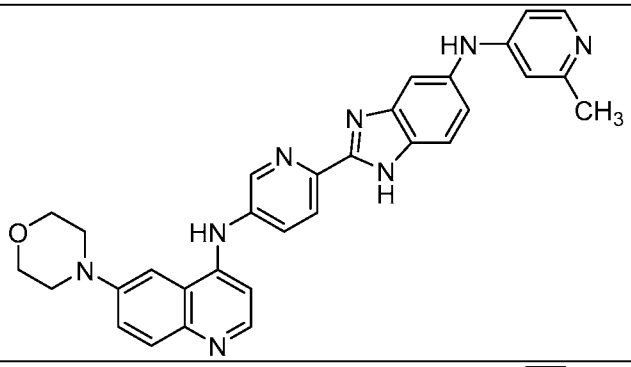
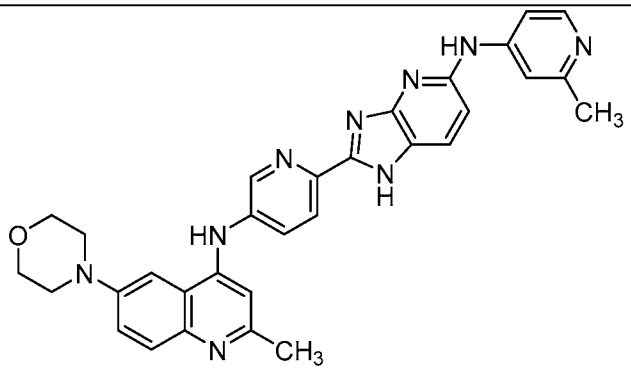
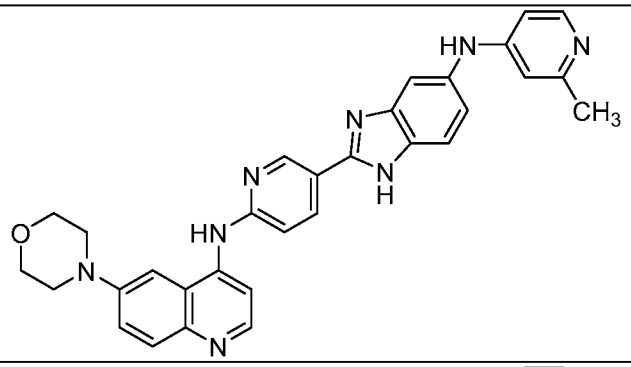
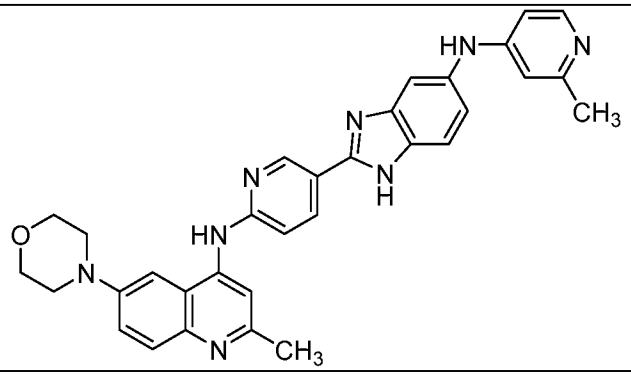
Compound No.	Structure	EC_{50} (μM)
19		< 1
24		< 0.5
53		< 2
55		< 5
57		< 1

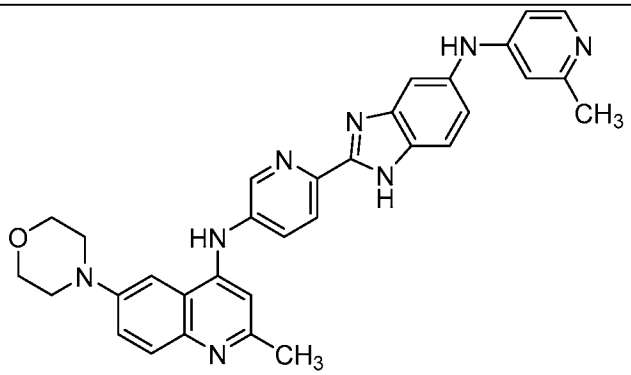
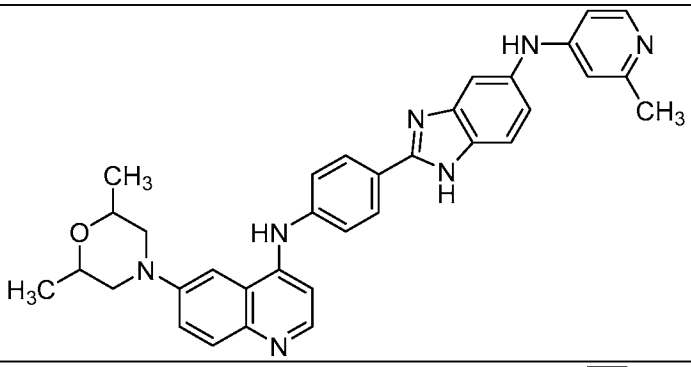
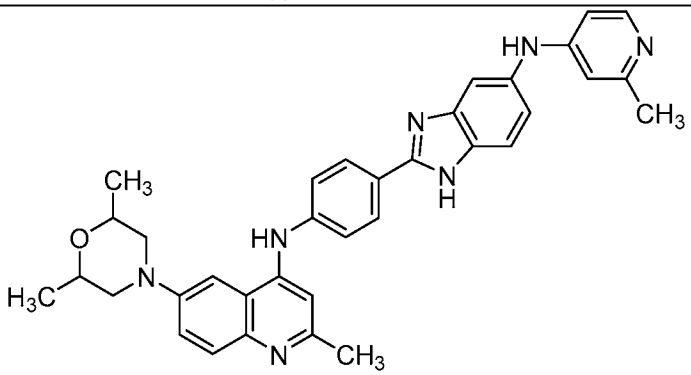
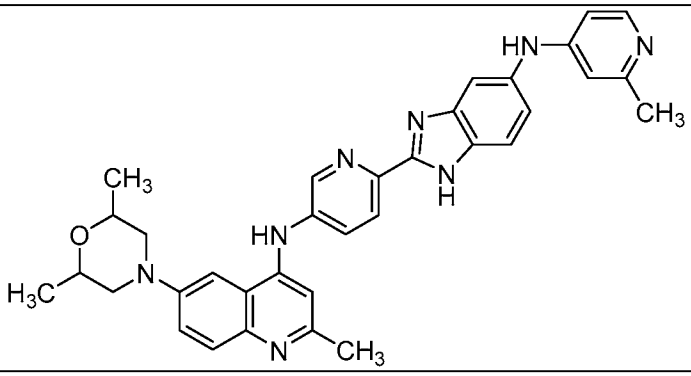
Compound No.	Structure	EC_{50} (μM)
62		< 0.5
68		< 1
69		< 0.5
70		< 1
77		< 1

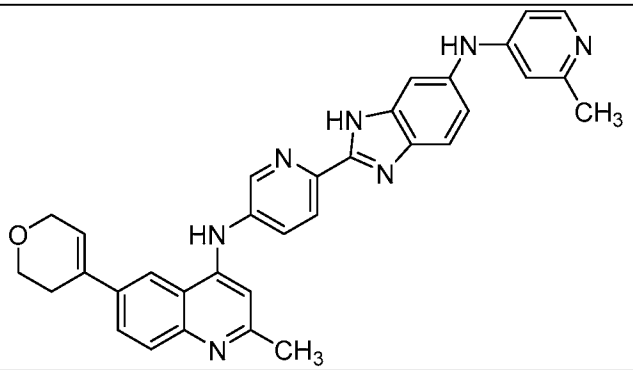
Compound No.	Structure	EC_{50} (μM)
78		< 0.5
79		< 1
83		< 0.5
84		< 0.5
87		< 0.5

Compound No.	Structure	EC_{50} (μM)
88		< 0.5
90		< 0.5
91		< 0.5
92		< 1
96		< 1

Compound No.	Structure	EC_{50} (μM)
97		< 0.5
102		< 0.5
110		< 0.5
111		< 0.5
120		< 0.1

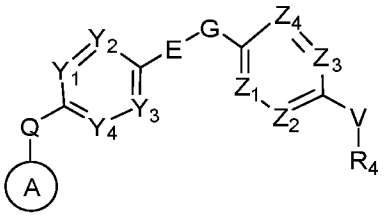
Compound No.	Structure	EC_{50} (μM)
121		< 0.02
122		< 2
123		< 0.05
125		< 0.05

Compound No.	Structure	EC_{50} (μM)
126		< 0.05
127		< 0.02
128		< 0.05
129		< 0.05

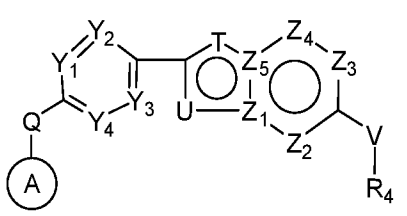
Compound No.	Structure	EC_{50} (μM)
135		< 0.5

CLAIMS

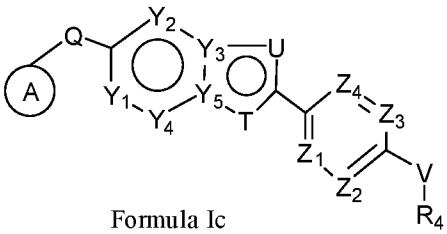
1. A compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc:



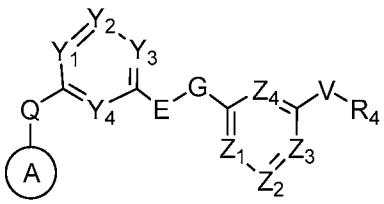
Formula Ia ;



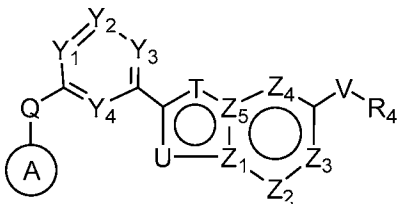
Formula Ib ;



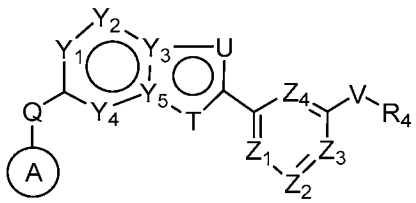
Formula Ic ;



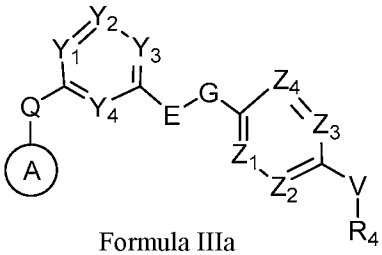
Formula IIa ;



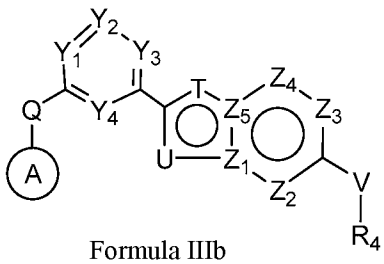
Formula IIb ;



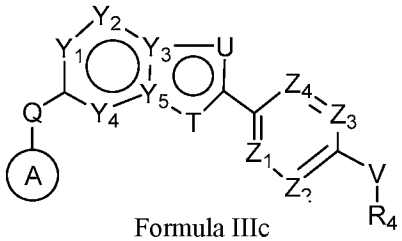
Formula IIc ;



Formula IIIa ;

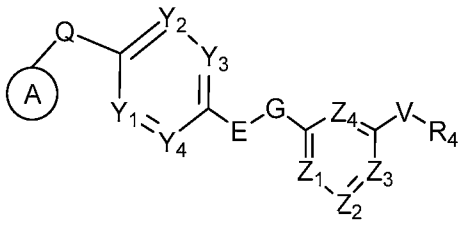


Formula IIIb ;



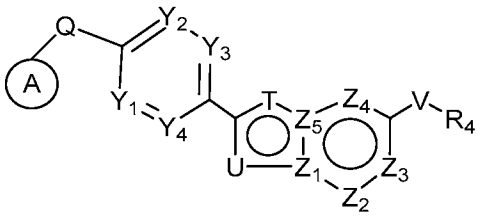
Formula IIIc

;



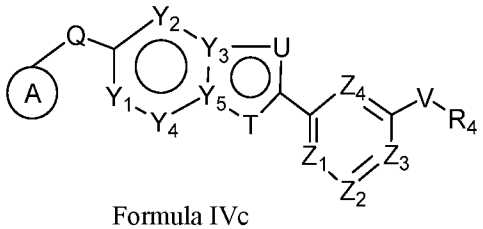
Formula IVa

;



Formula IVb

; or

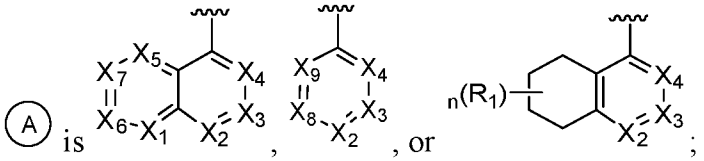


Formula IVc

;

or a pharmaceutically acceptable salt thereof;

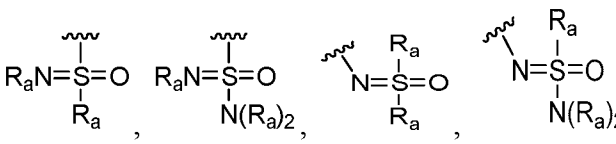
wherein:



is , , or ;

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

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, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, $(C_4\text{-}C_{14})$heterotricycloalkenyl, 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 $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, $-SO_2R_a$, or $-SO_2N(R_a)_2$;

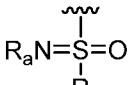
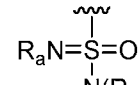
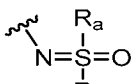
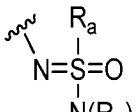
wherein the $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$bicycloalkyl, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}$

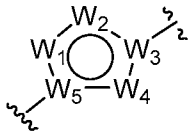
C_7)heterocycloalkenyl, (C_4-C_{10})bicycloalkenyl, (C_4-C_{10})heterobicycloalkenyl, (C_4-C_{14})tricycloalkenyl, (C_4-C_{14})heterotricycloalkenyl, aryl, and heteroaryl of R_1 are each optionally substituted by one or more (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, $-OR_a$, $-CN$, or $-N(R_a)_2$;

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, 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 ;

–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 ; wherein

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_2, R_x and Y_3, 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;

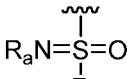
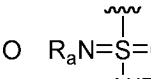
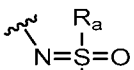
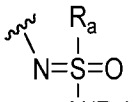
each occurrence of R_6 is independently selected from the group consisting of H, halogen, (C_1-C_6)alkyl, and (C_1-C_6)haloalkyl;

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-C_6)alkyl;

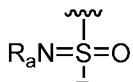
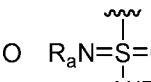
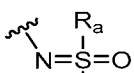
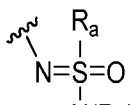
Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently N or CR_3 where valance permits;

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;

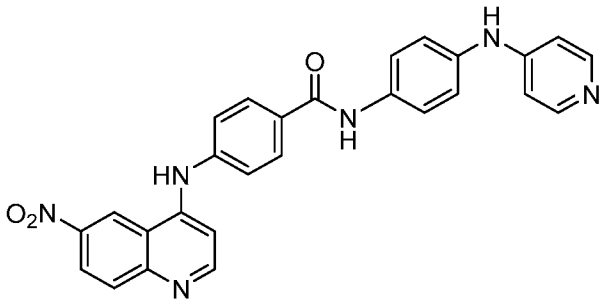
R_4 is selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (C_4-C_{10})heterospiroalkyl, aryl, and heteroaryl, each optionally substituted with one or more R_5;

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

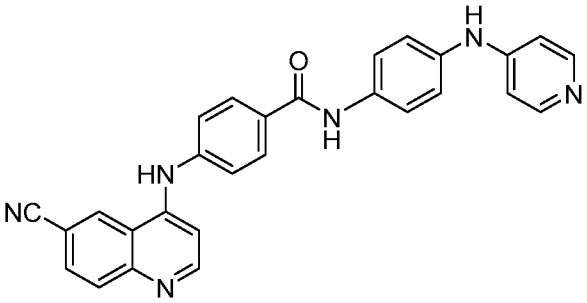
each occurrence of R_5 is independently selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)haloalkenyl, (C_2-C_6)alkynyl, (C_2-C_6)haloalkynyl, (C_3-C_7)cycloalkyl, (C_4-C_{10})bicycloalkyl, (C_3-C_7)heterocycloalkyl, (C_4-C_{10})heterobicycloalkyl, (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, $-SO_2R_a$, $-SO_2N(R_a)_2$, $-N(R_a)SO_2R_a$, $N(R_a)COR_a$, , , , 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;

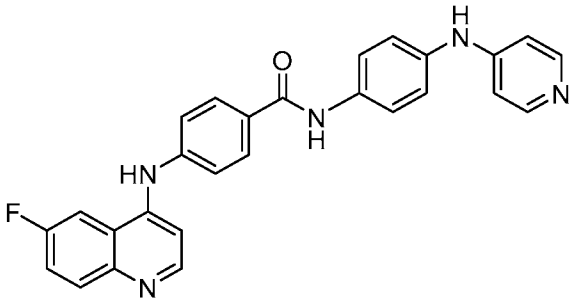
with the proviso that the compound is not



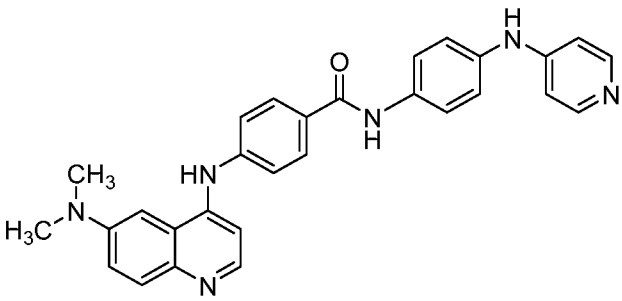
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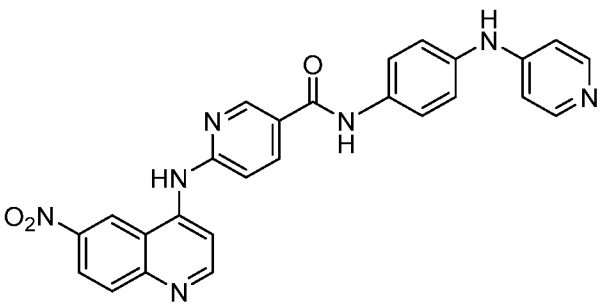
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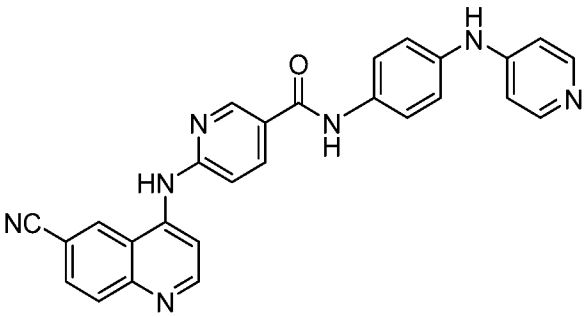
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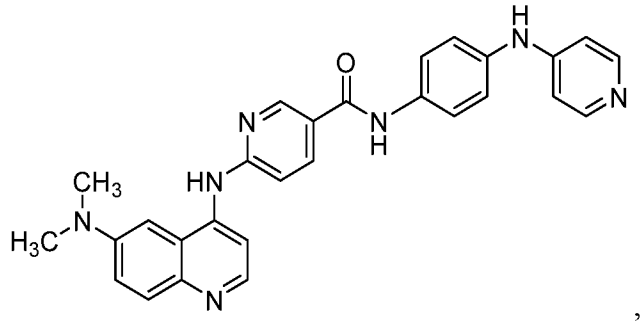
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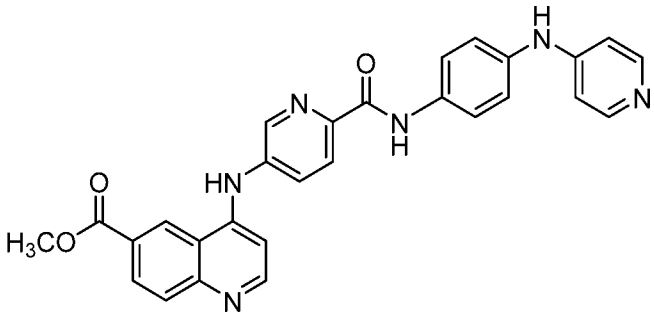
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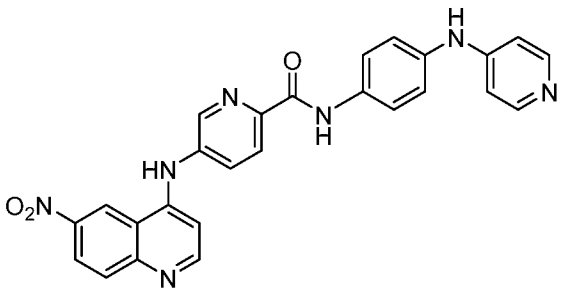
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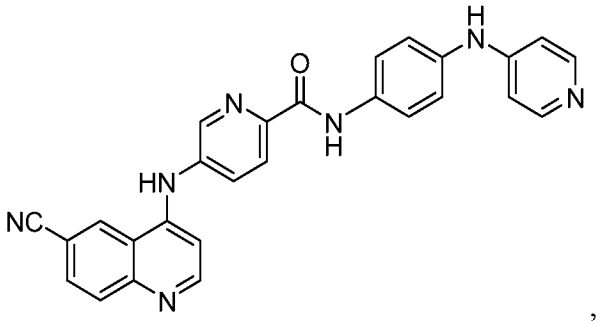
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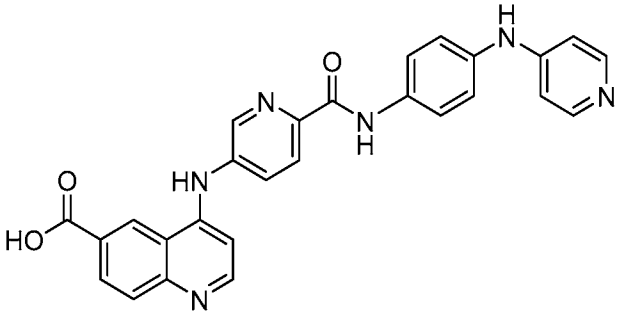
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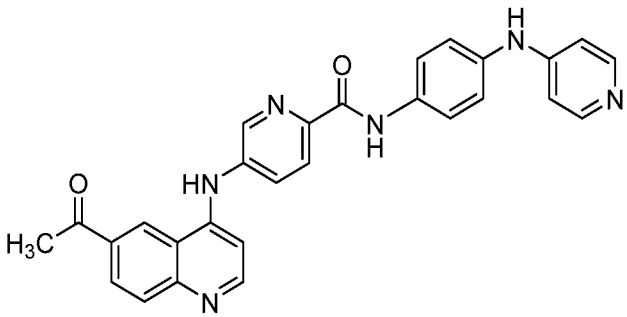
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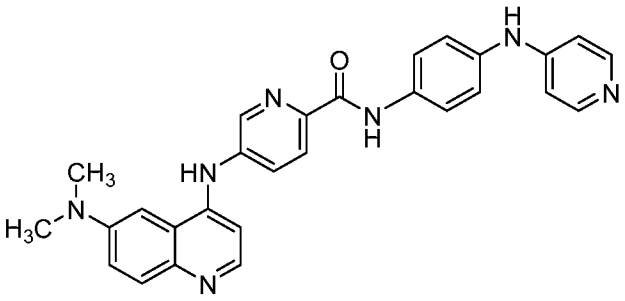
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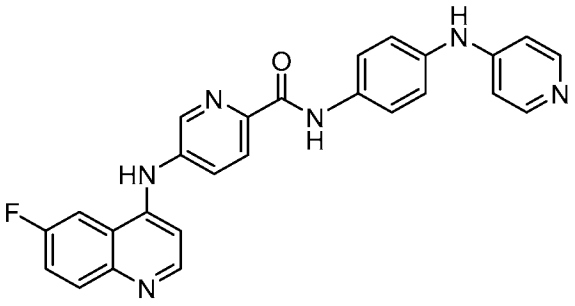
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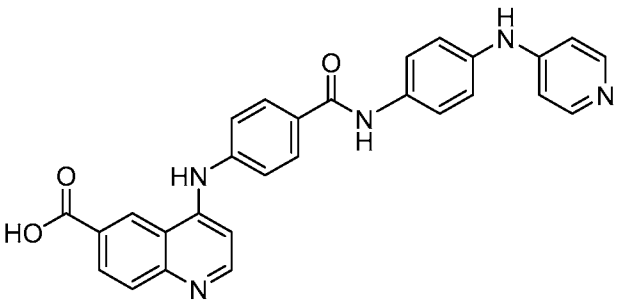
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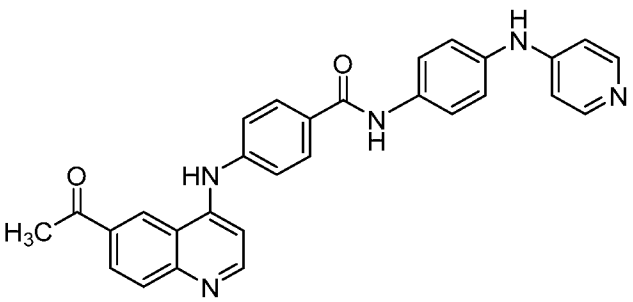
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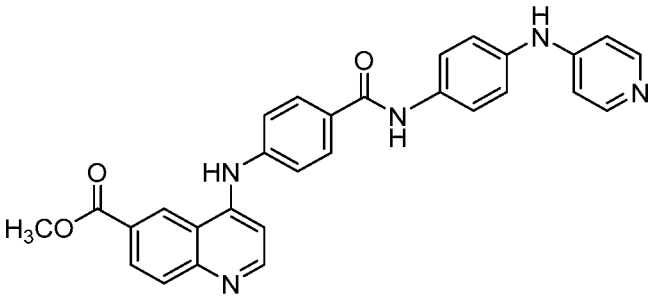
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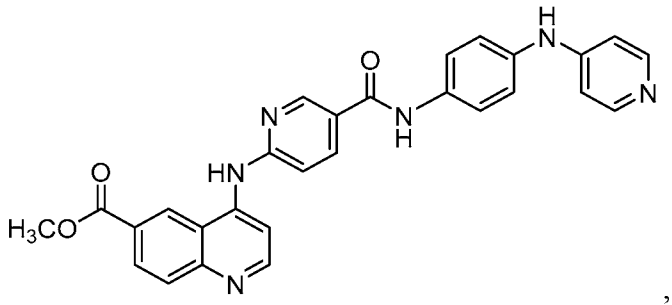
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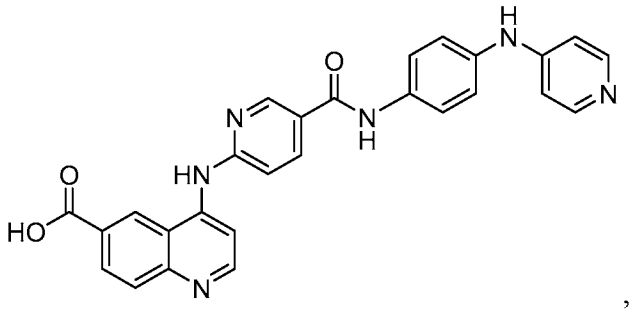
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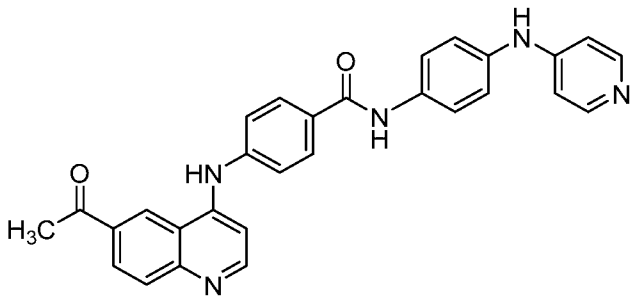
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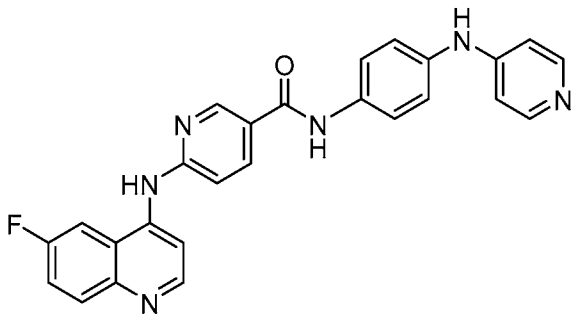
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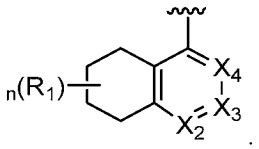
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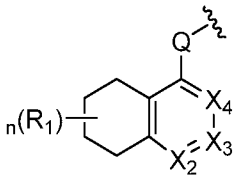
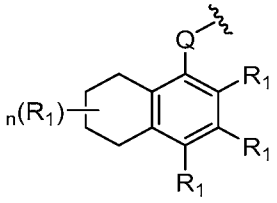
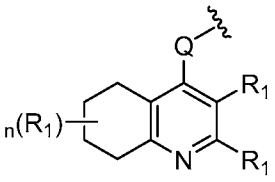
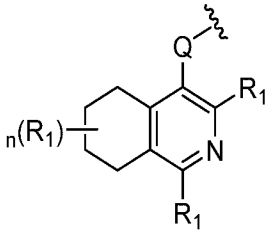
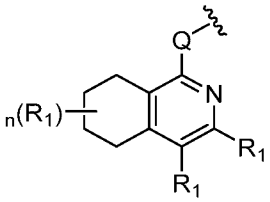
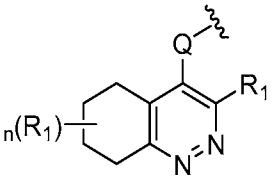
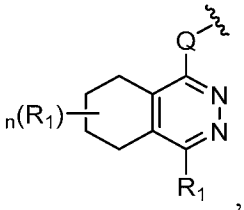
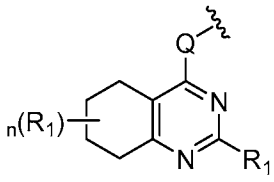


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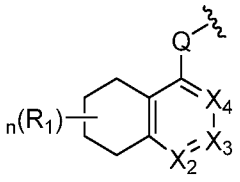
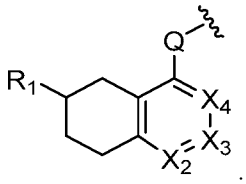
2. The compound of claim 1, wherein Q, T, and U are each independently O, NH, NCH_3, N(C=O)H, $N(C=O)CH_3$, $N(C=O)CH_2CH_3$, NSO_2CH_3, or $NSO_2CH_2CH_3$, where valence permits.

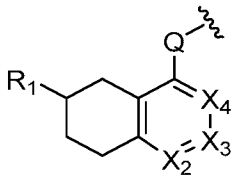
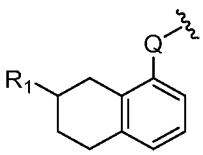
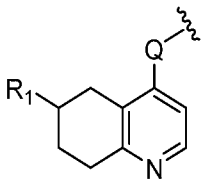
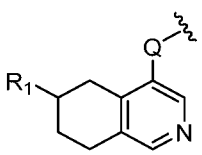
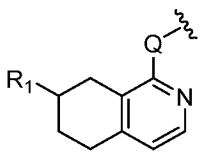
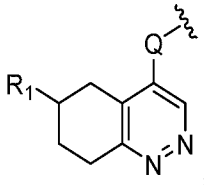
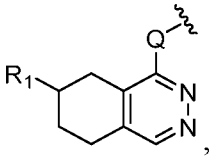
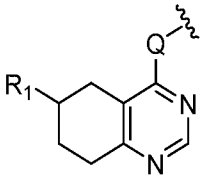
3. The compound of claim 1 or 2, wherein X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, Y_1, Y_2, Y_3, Y_4, Y_5, Z_1, Z_2, Z_3, Z_4, and Z_5 are each independently CH, C(halogen), or N.

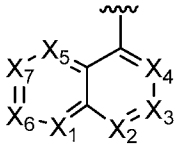
4. The compound of any one of claims 1-3, wherein (A) is .

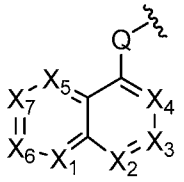
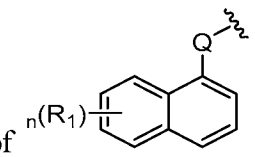
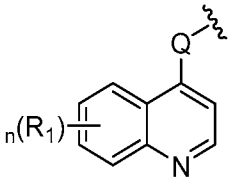
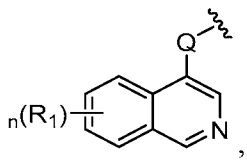
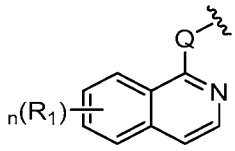
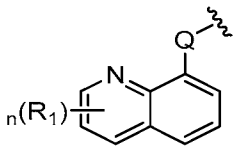
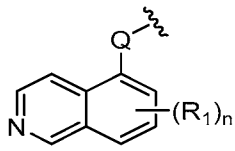
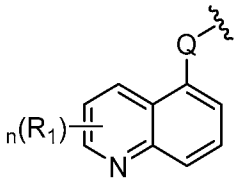
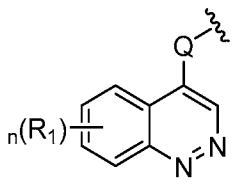
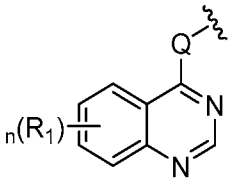
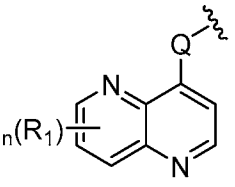
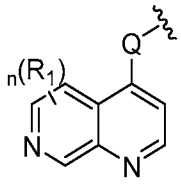
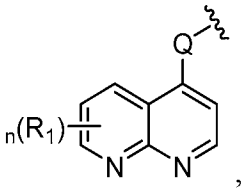
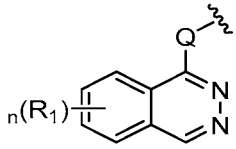
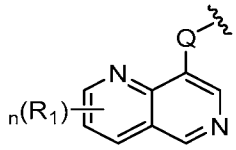
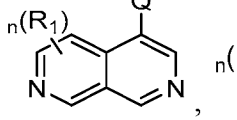
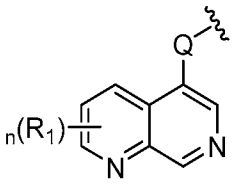
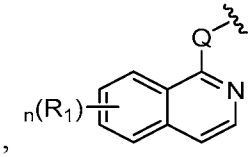
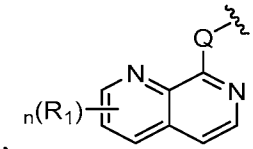
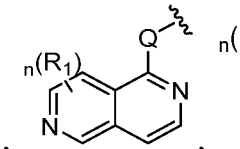
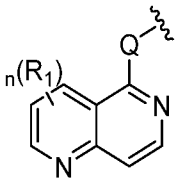
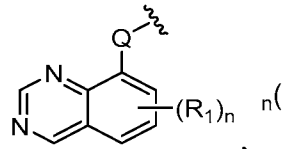
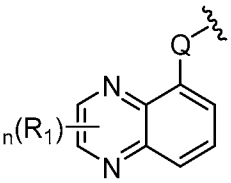
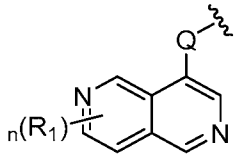
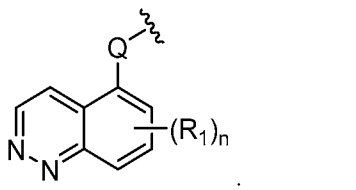
5. The compound of any one of claims 1-4, wherein the structural moiety  has the structure of , , , , , , or .

6. The compound of any one of claims 1-5, wherein n is 0, 1, or 2.

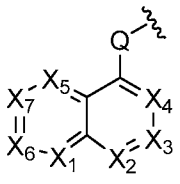
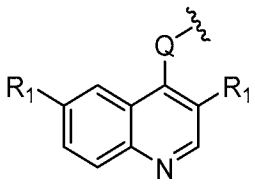
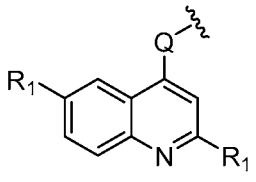
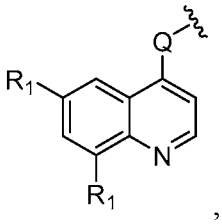
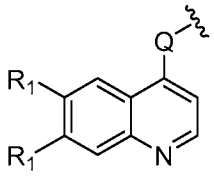
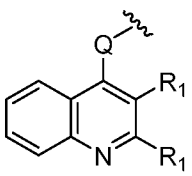
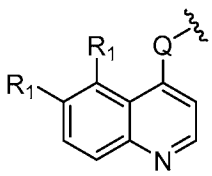
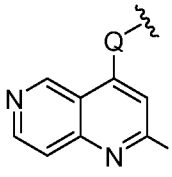
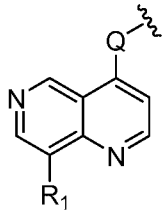
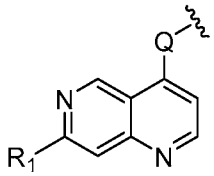
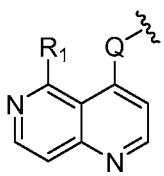
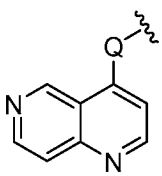
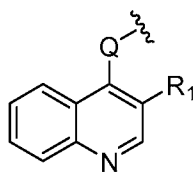
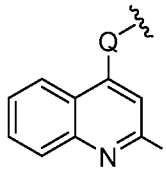
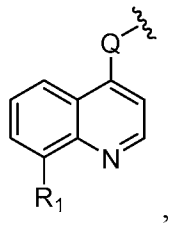
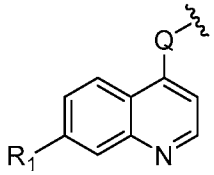
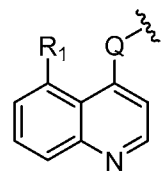
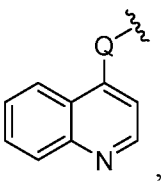
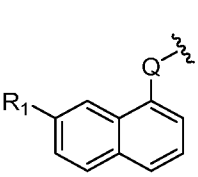
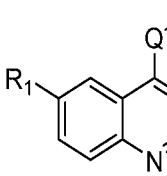
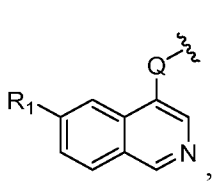
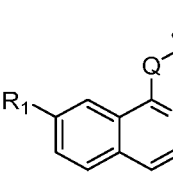
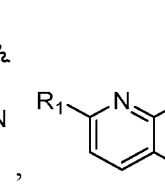
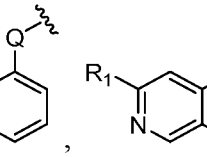
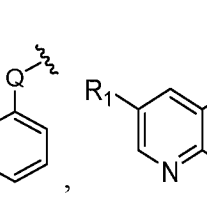
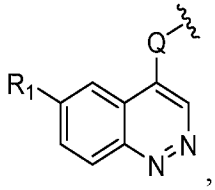
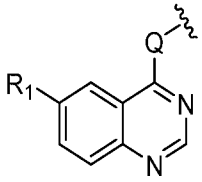
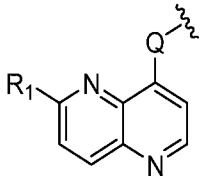
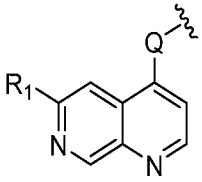
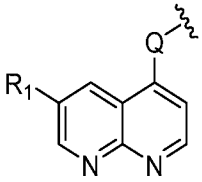
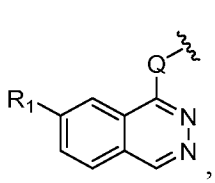
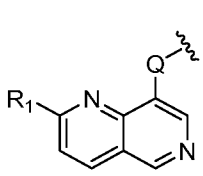
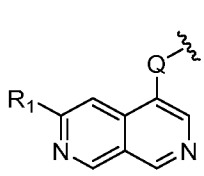
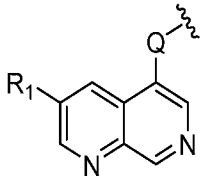
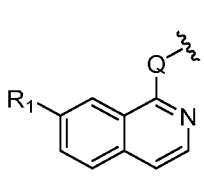
7. The compound of any one of claims 1-6, wherein the structural moiety  has the structure of .

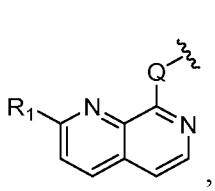
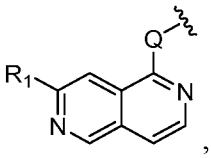
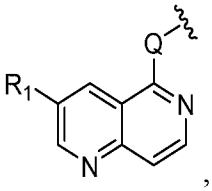
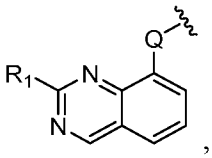
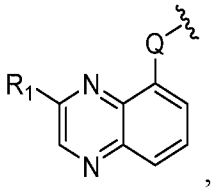
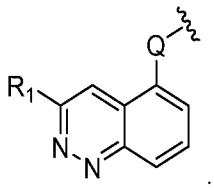
8. The compound of claim 7, wherein the structural moiety  has the structure of , , , , , , or .

9. The compound of any one of claims 1-3, wherein Ⓐ is .

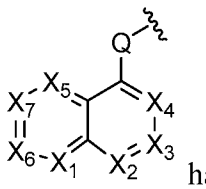
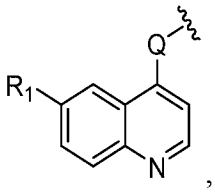
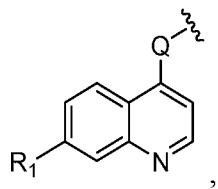
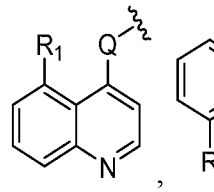
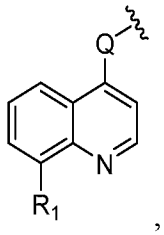
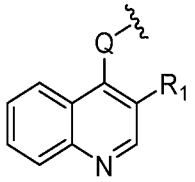
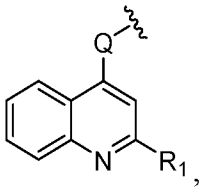
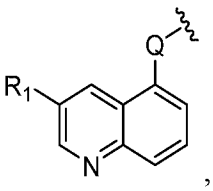
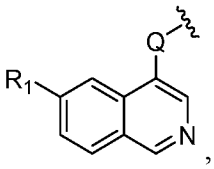
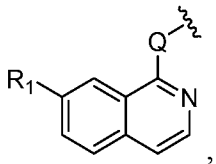
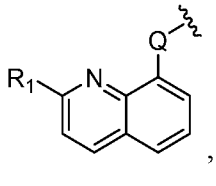
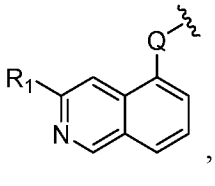
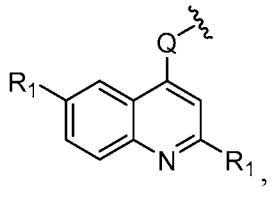
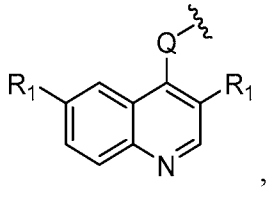
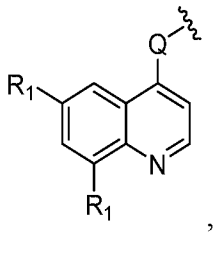
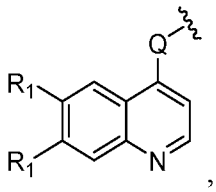
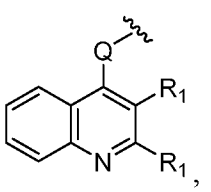
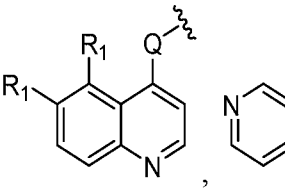
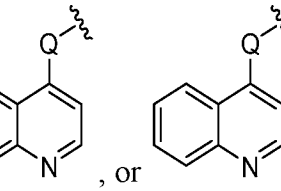
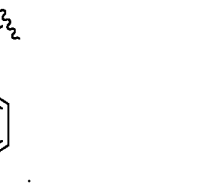
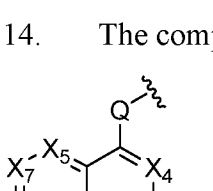
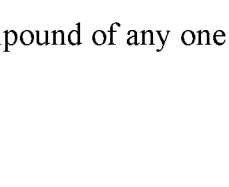
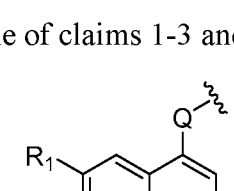
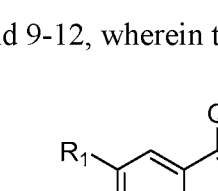
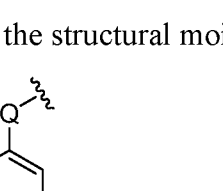
10. The compound of any one of claims 1-3 and 9, wherein the structural moiety  has the structure of , , , , , , , , , , , , , , , , , , , , , , , , , , , , or .

11. The compound of any one of claims 1-3 and 10, wherein n is 0, 1, or 2.

12. The compound of any one of claims 1-3 and 9-11, wherein the structural moiety  has the structure of , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , ,






, or

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13. The compound of any one of claims 1-3 and 9-12, wherein the structural moiety

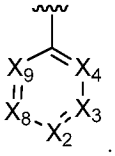

has the structure of




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, or

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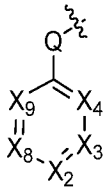
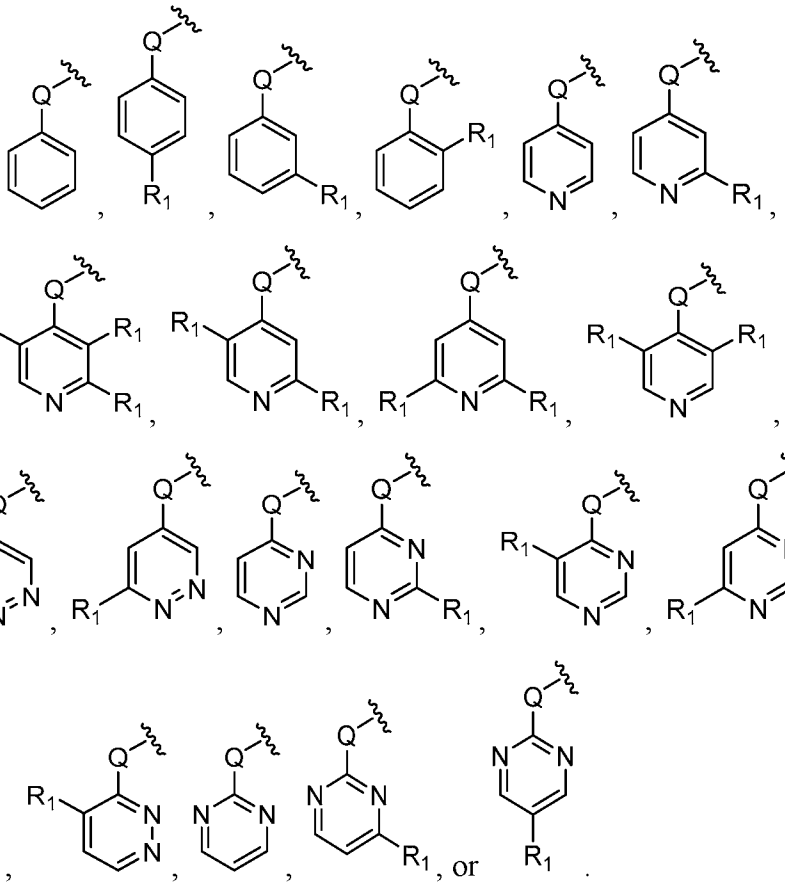
14. The compound of any one of claims 1-3 and 9-12, wherein the structural moiety

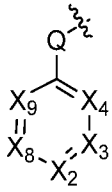
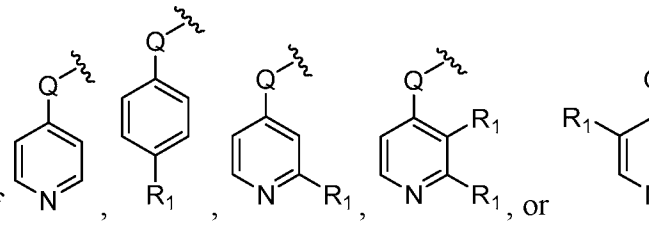
has the structure of

, or

.

15. The compound of any one of claims 1-3, wherein Ⓐ is .

16. The compound of any one of claims 1-3 and 15, wherein the structural moiety  has the structure of .

17. The compound of any one of claims 1-3 and 15-16, wherein the structural moiety  has the structure of .

18. The compound of any one of claims 1-17, wherein Q is O.

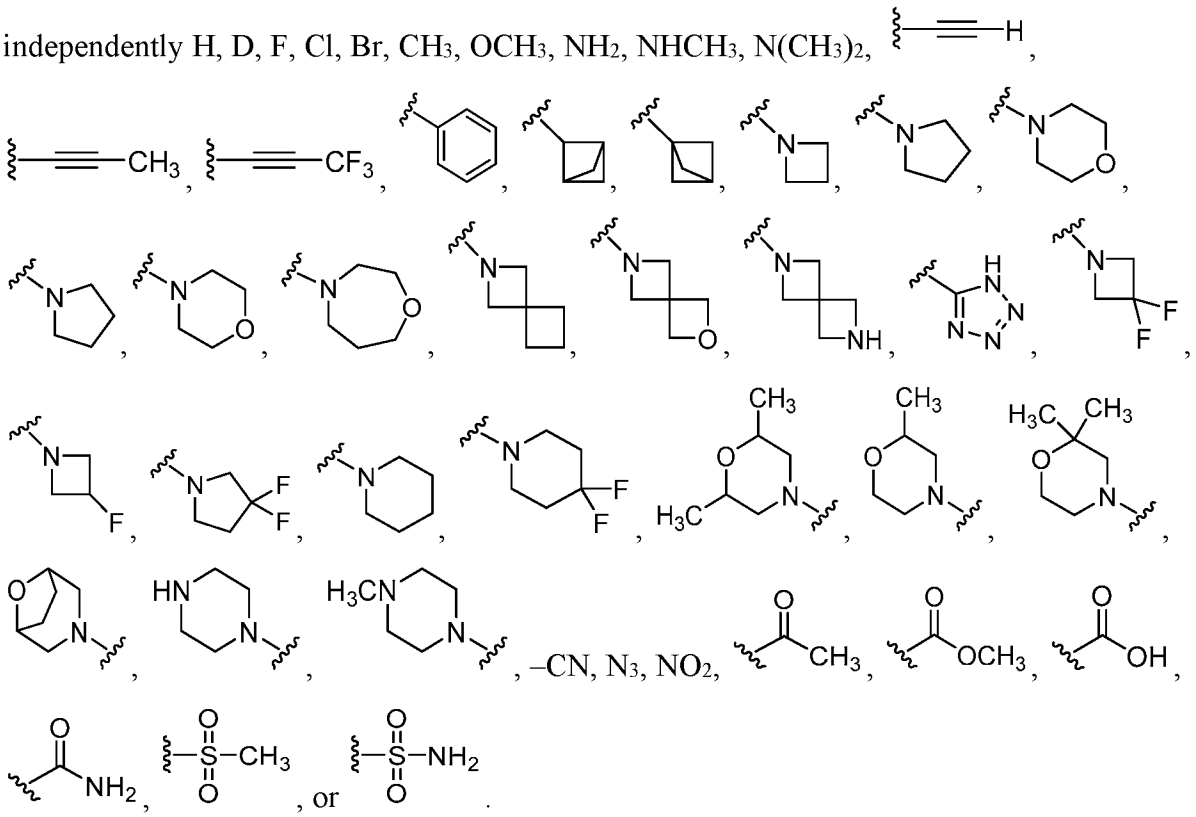
19. The compound of any one of claims 1-17, wherein Q is NR_a, $N(C{=}O)R_a$, or NSO_2R_a.

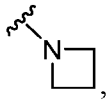
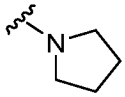
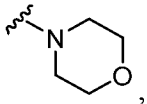
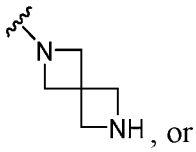
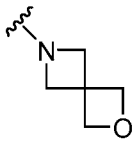
20. The compound of any one of claims 1-19, wherein each occurrence of R_1 is independently H, D, halogen, OR_a, $N(R_a)_2$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, aryl,

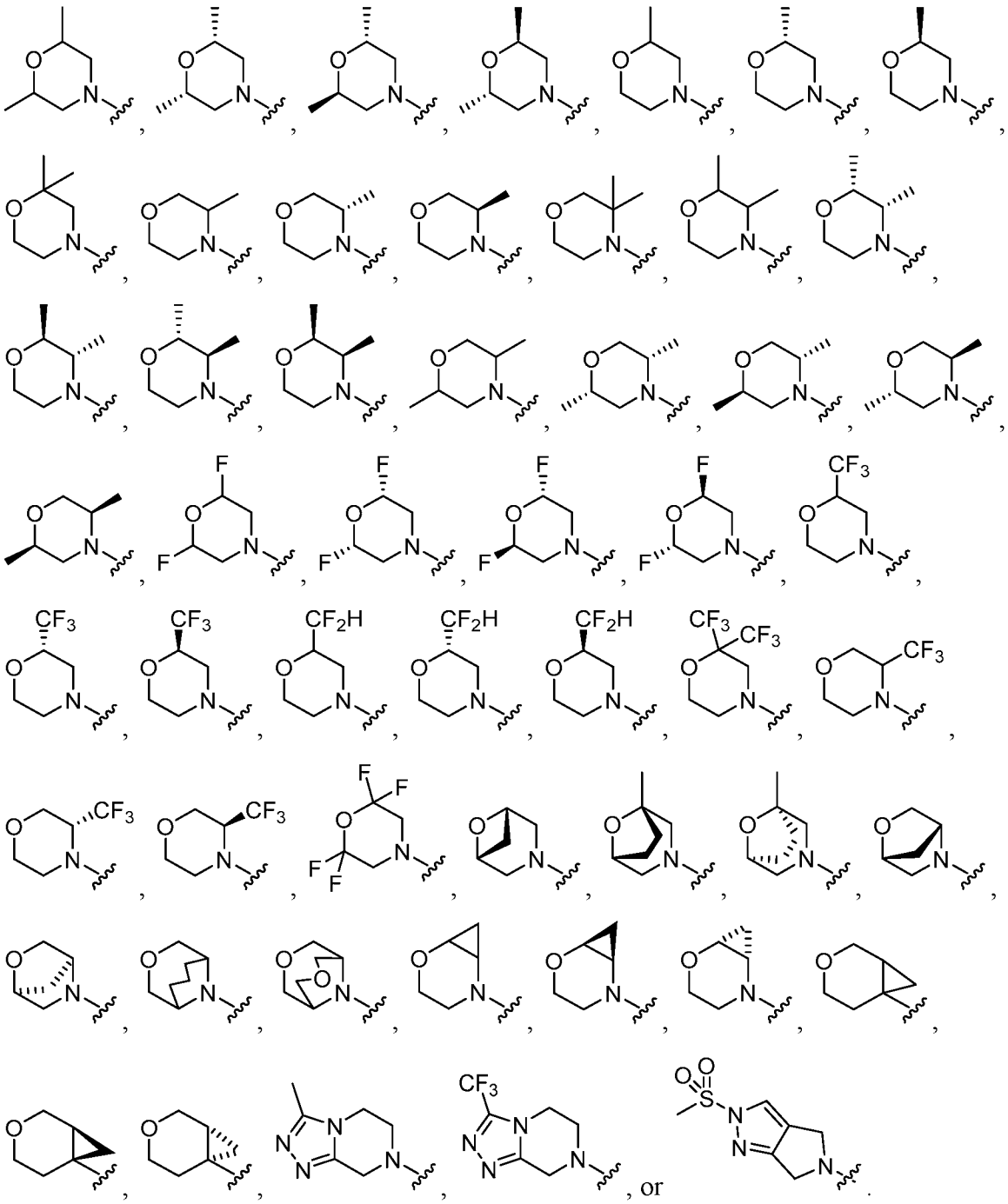
(C_4-C_{10})bicycloalkyl, –CN, N_3, NO_2, COR_a, CO_2R_a, $CON(R_a)_2$, $–SO_2R_a$, or $–SO_2N(R_a)_2$; wherein the (C_3-C_7)heterocycloalkyl is optionally substituted with one or more (C_1-C_6)alkyl.

21. The compound of any one of claims 1-20, wherein each occurrence of R_1 is independently H, 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 is optionally substituted with one or more (C_1-C_6)alkyl.

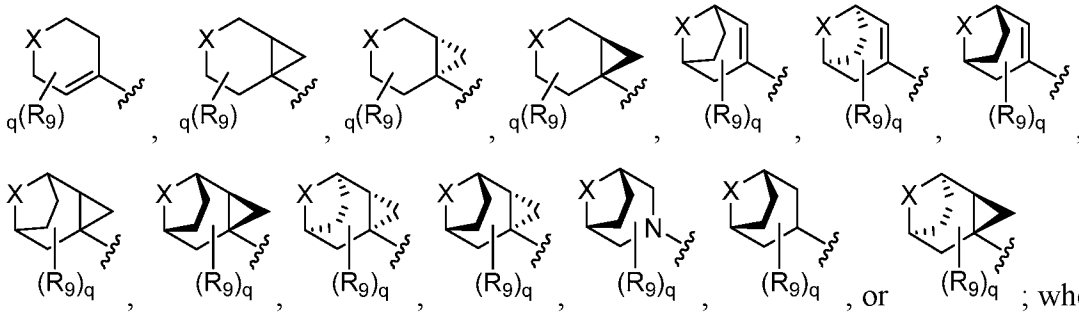
22. The compound of any one of claims 1-21, wherein each occurrence of R_1 is independently H, halogen, (C_1-C_6)alkyl, (C_3-C_7)heterocyclohaloalkyl, or (C_3-C_7)heterocycloalkyl; wherein the (C_3-C_7)heterocycloalkyl is optionally substituted with one or more (C_1-C_6)alkyl.

23. The compound of any one of claims 1-22, wherein each occurrence of R_1 is independently H, D, F, Cl, Br, CH_3, OCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, 

24. The compound of any one of claims 1-23, wherein each occurrence of R_1 is independently H, D, F, CH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, , , , , or .

25. The compound of any one of claims 1-21, wherein at least one occurrence of R_1 is .

26. The compound of any one of claims 1-21, wherein at least one occurrence of R_1 is



; wherein X is CR_{15} O, NR_{14}, or S; each occurrence of R_9 is independently H, $(C_1$-$C_6)$alkyl, halogenated $(C_1$-$C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; R_{14} is H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, $(C_3$-$C_7)$heterocycloalkyl, aryl, or heteroaryl; each occurrence of R_{15} is independently H, $(C_1$-$C_6)$alkyl, halogenated $(C_1$-$C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; and q is 0, 1, 2, or 3.

27. The compound of any one of claims 1-21 and 26, wherein X is O.

28. The compound of any one of claims 1-21, 26, and 27, wherein each occurrence of R_9 is independently H, $(C_1$-$C_6)$alkyl, halogenated $(C_1$-$C_6)$alkyl, or halogen.

29. The compound of any one of claims 1-21 and 26-28, wherein each occurrence of R_9 is independently H, F, Cl, Br, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$.

30. The compound of any one of claims 1-21 and 26-29, wherein each occurrence of R_9 is independently H, F, Cl, Br or CH_3.

31. The compound of any one of claims 1-21 and 26-30, wherein each occurrence of R_{15} is independently H, $(C_1$-$C_6)$alkyl, halogenated $(C_1$-$C_6)$alkyl, or halogen.

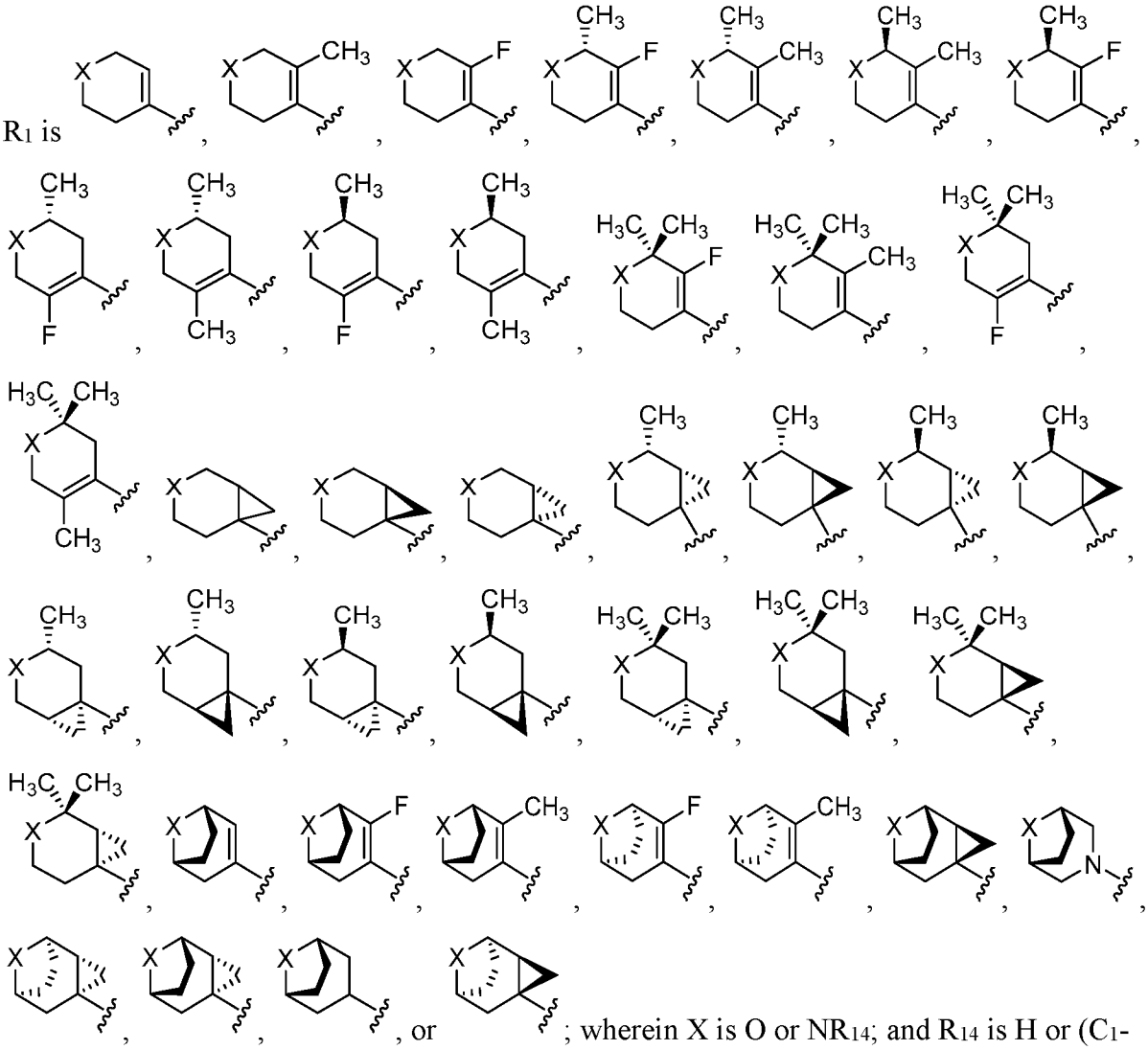
32. The compound of any one of claims 1-21 and 26-31, wherein each occurrence of R_{15} is independently H, F, Cl, Br or CH_3.

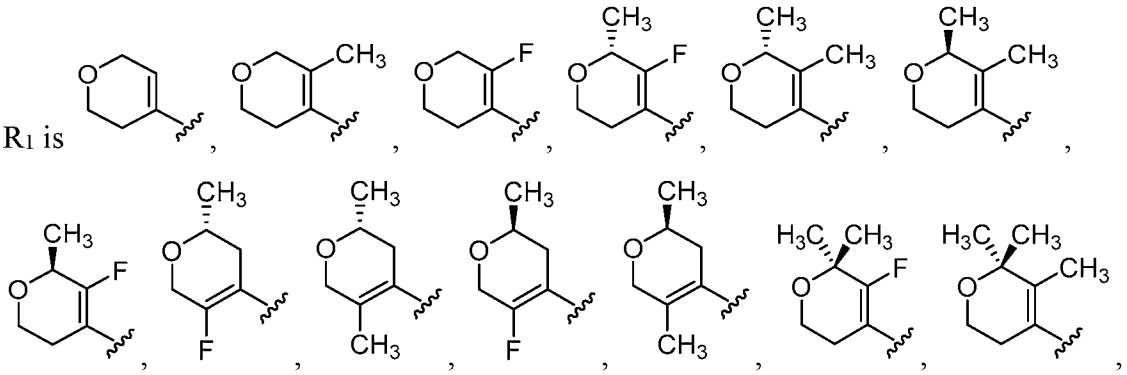
33. The compound of any one of claims 1-21 and 26-32, wherein q is 0.

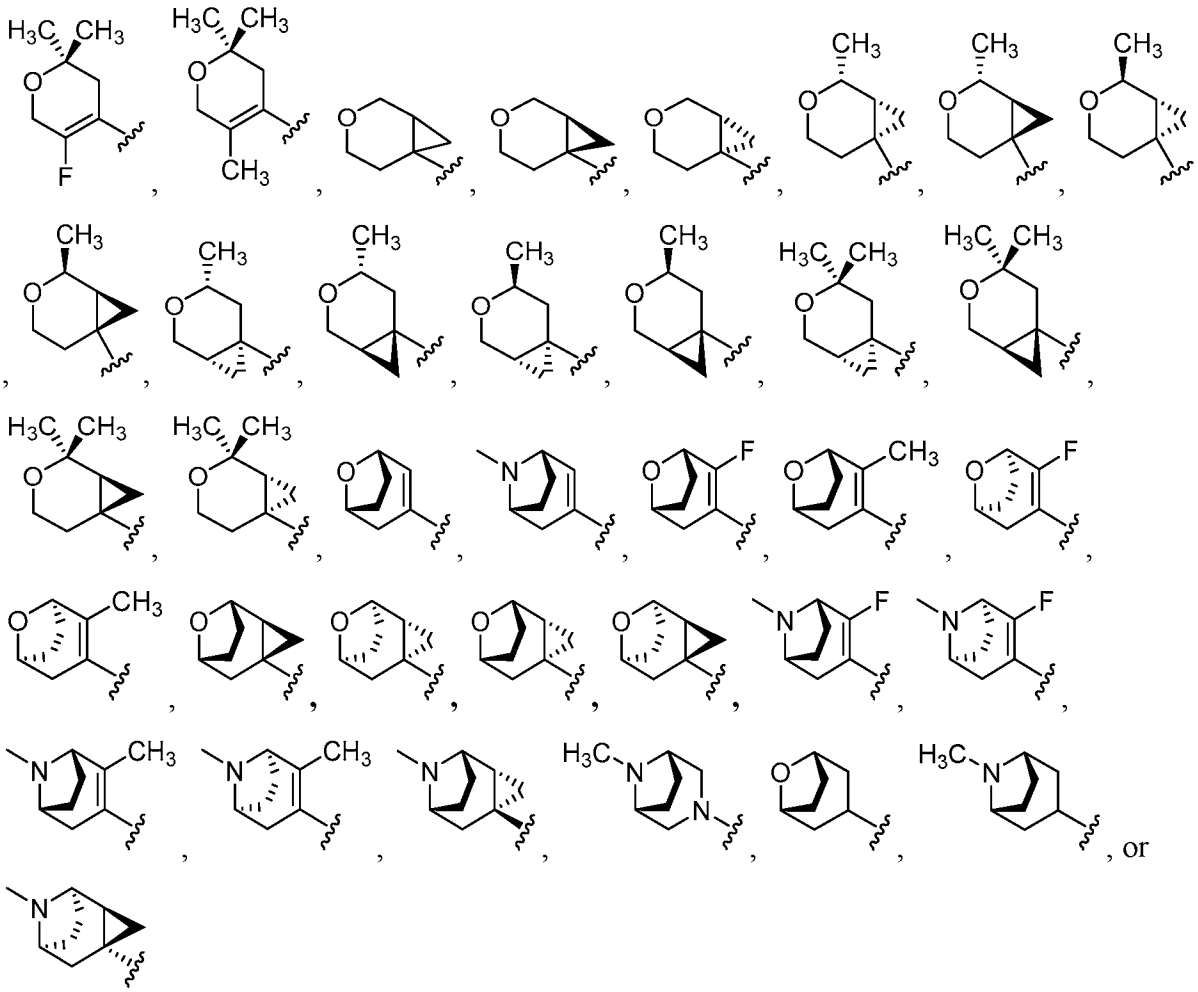
34. The compound of any one of claims 1-21 and 26-33, wherein q is 1.

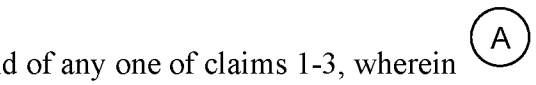
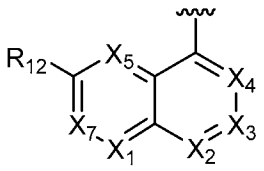
35. The compound of any one of claims 1-21 and 26-34, wherein q is 2 or 3.

36. The compound of any one of claims 1-21, 26, and 28-37, wherein X is NR_{14} and R_{14} is H or $(C_1$-$C_6)$alkyl.

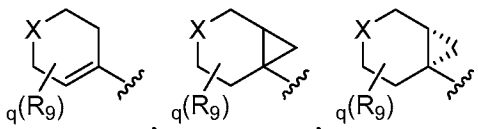
37. The compound of any one of claims 1-21 and 26, wherein at least one occurrence of R_1 is ; wherein X is O or NR_{14}; and R_{14} is H or (C_1-C_6)alkyl.

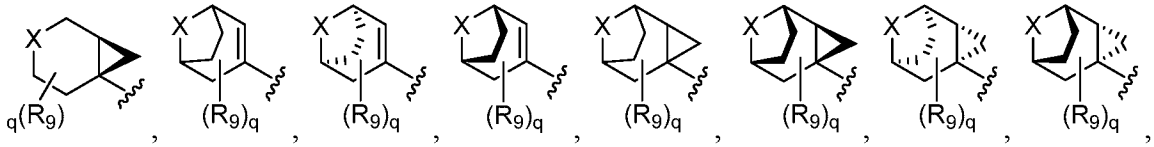
38. The compound of any one of claims 1-21 and 26, wherein at least one occurrence of R_1 is 

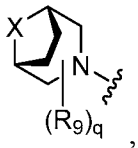
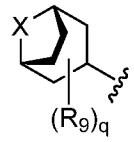
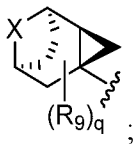


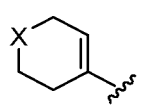
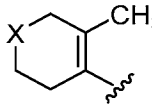
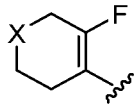
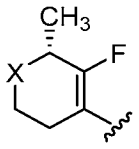
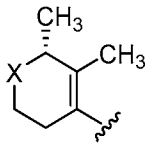
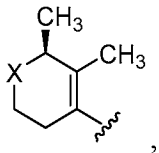
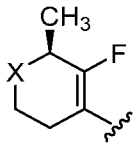
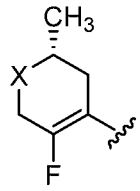
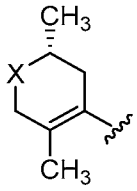
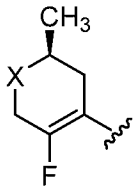
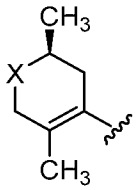
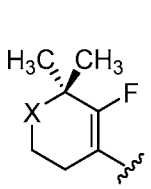
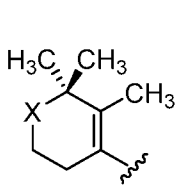
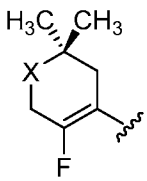
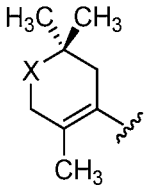
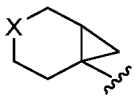
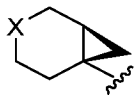
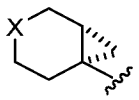
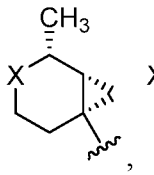
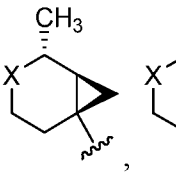
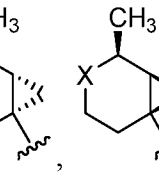
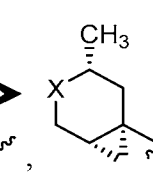
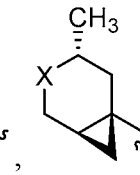
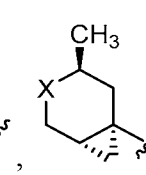
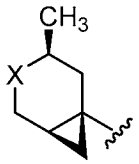
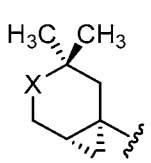
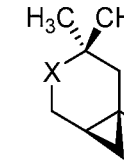
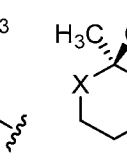
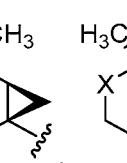
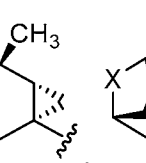
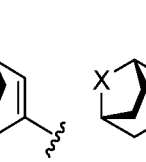
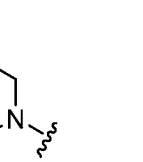
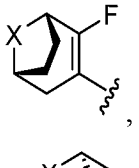
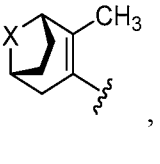
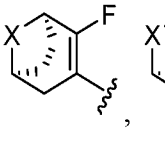
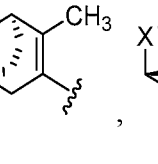
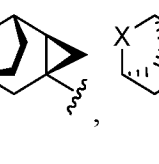
39. The compound of any one of claims 1-3, wherein  is 

wherein R_{12} is (C_3-C_7)cycloalkenyl, (C_3-C_7)heterocycloalkenyl, (C_4-C_{10})bicycloalkenyl, (C_4-C_{10})heterobicycloalkenyl, (C_4-C_{14})tricycloalkenyl, or (C_4-C_{14})heterotricycloalkenyl, each of which is optionally substituted by one or more (C_1-C_6)alkyl, halogenated (C_1-C_6)alkyl, halogen, $-OR_a$, $-CN$, or $-N(R_a)_2$.

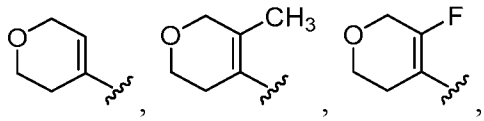
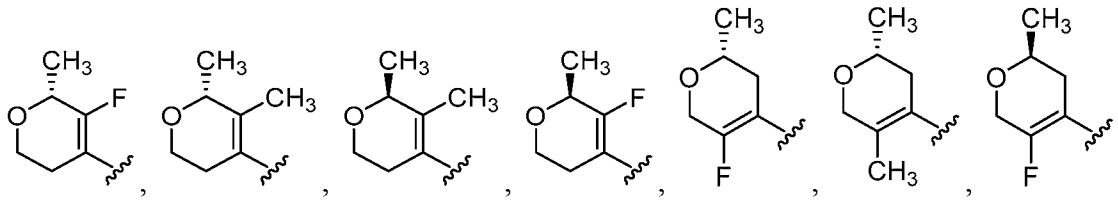
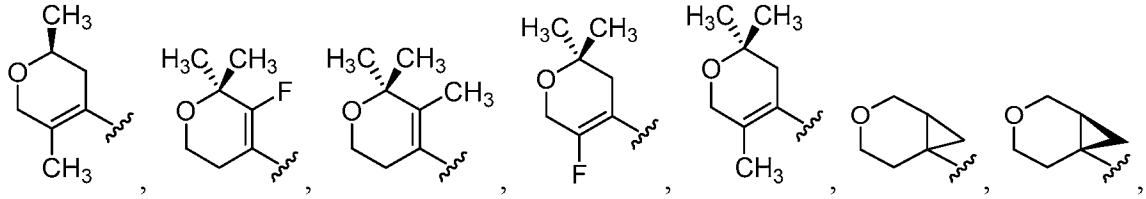
40. The compound of claim 39, wherein R_{12} is 

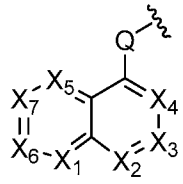
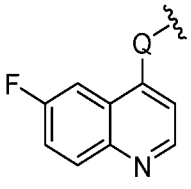
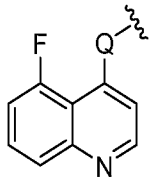
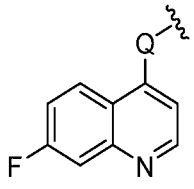
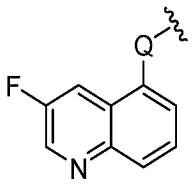
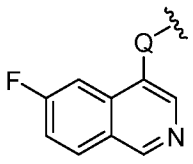
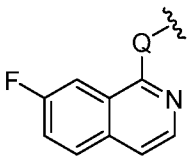
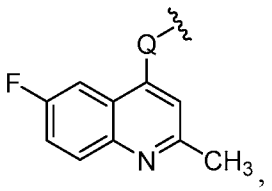
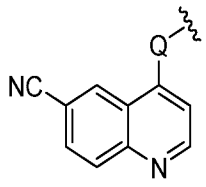
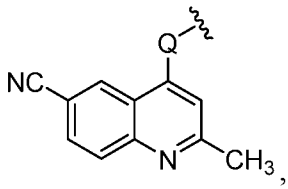
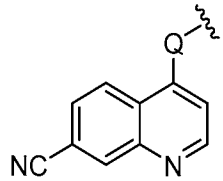
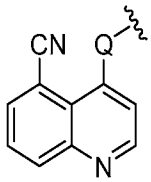
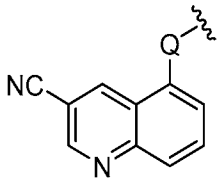
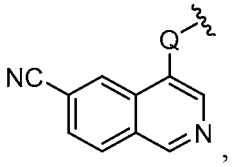
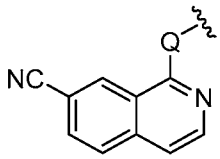
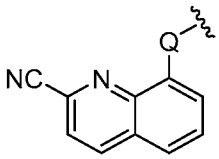
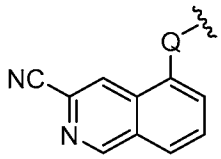
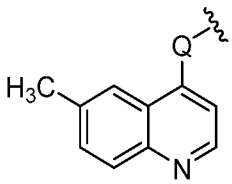
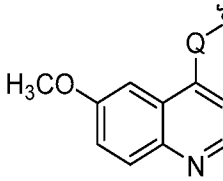
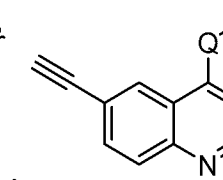
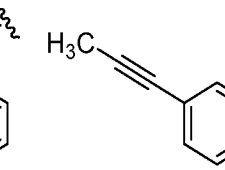
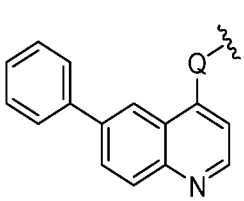
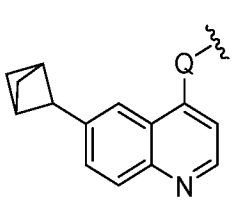
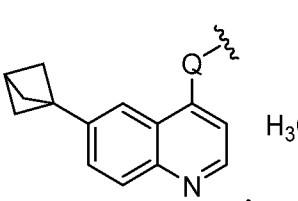
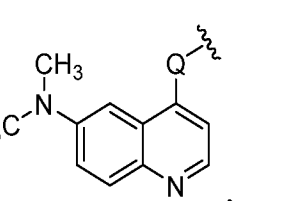
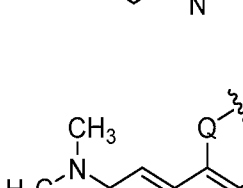
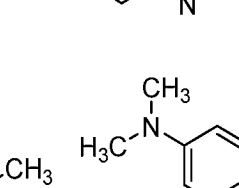
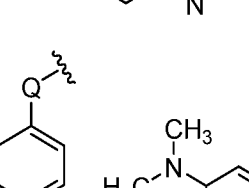
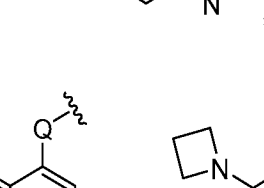
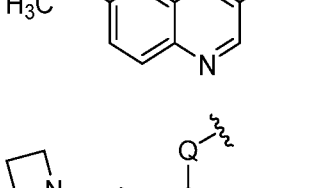
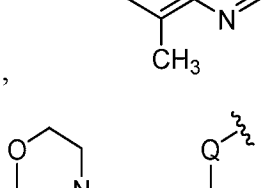
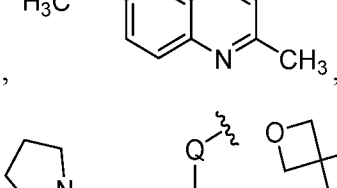
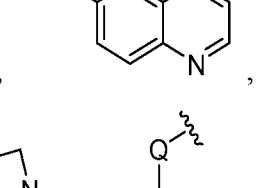
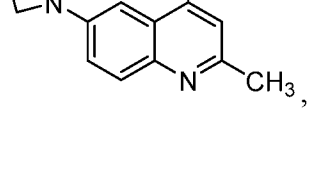
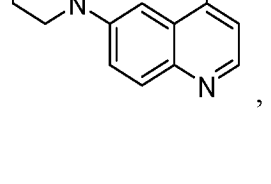
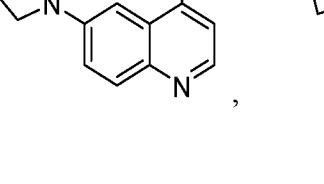
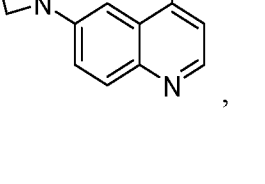


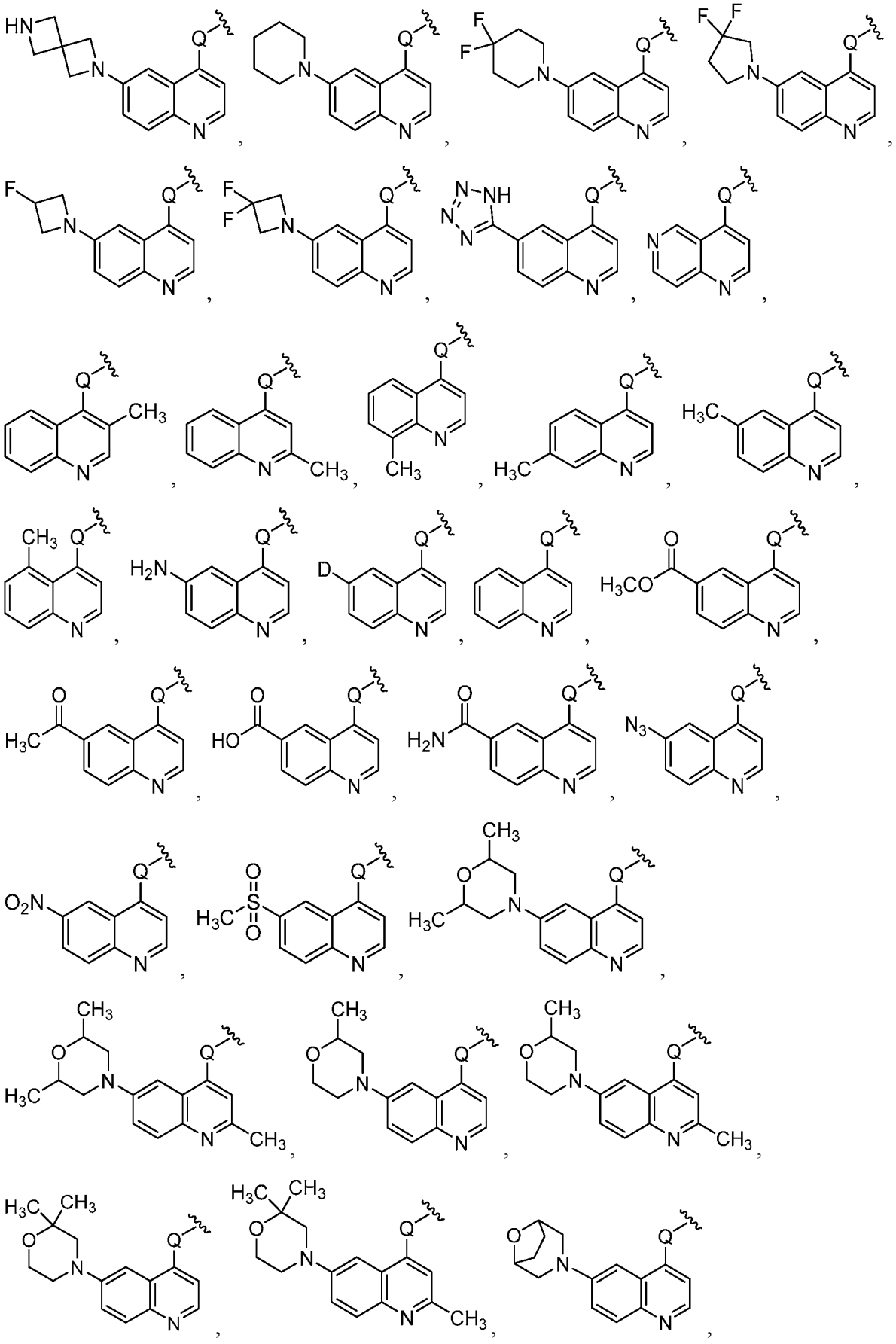



; wherein X is CR_{15}, O, NR_{14}, or S; each occurrence of R_9 is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; R_{14} is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, aryl, or heteroaryl; each occurrence of R_{15} is independently H, $(C_1\text{-}C_6)$alkyl, halogenated $(C_1\text{-}C_6)$alkyl, halogen, $-OR_a$, –CN, or $-N(R_a)_2$; and q is 0, 1, 2, or 3.

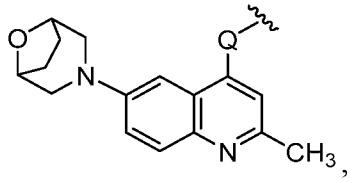
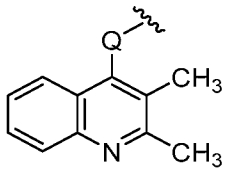
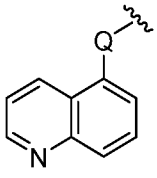
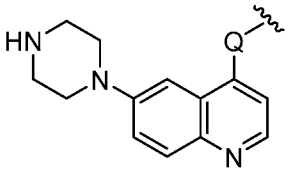
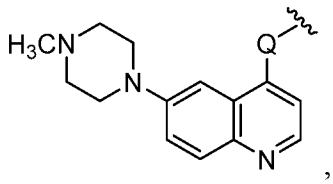
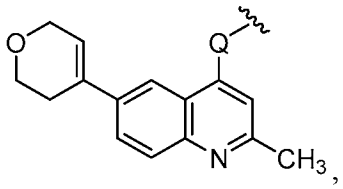
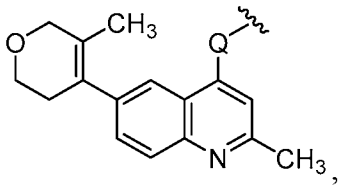
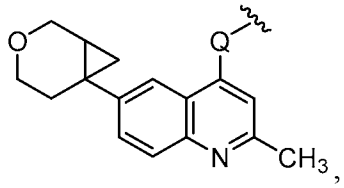
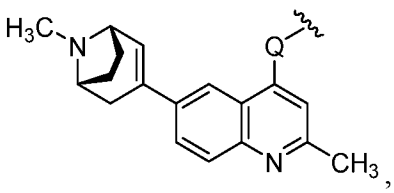
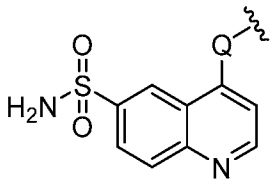
41. The compound of claim 39, wherein R_{12} is 





































or
; wherein X is O or NR_{14}; and R_{14} is H or $(C_1\text{-}C_6)$alkyl.

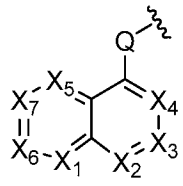
42. The compound of claim 39, wherein R_{12} is , , ,

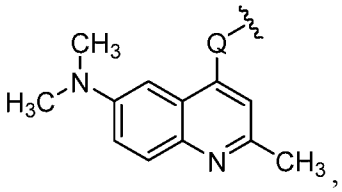
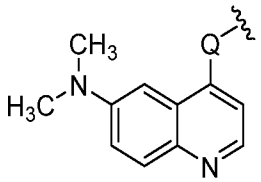
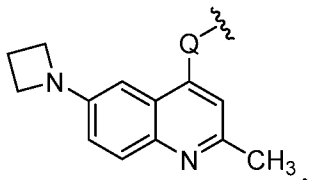
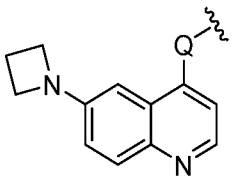
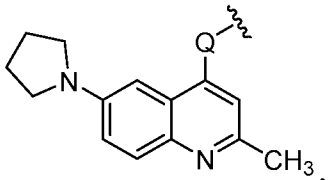
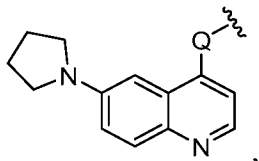
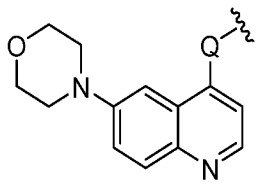
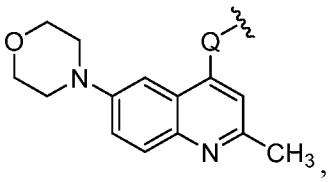
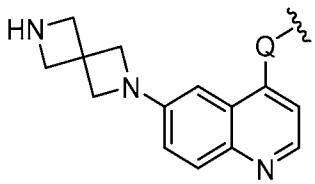
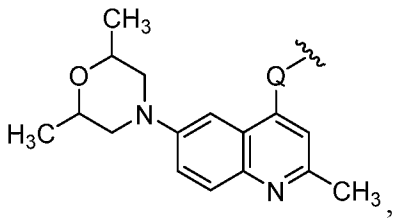
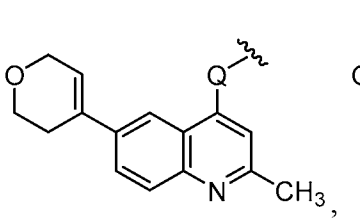
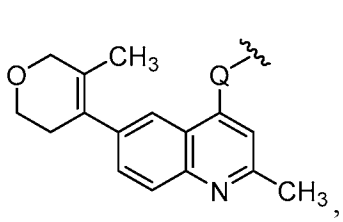
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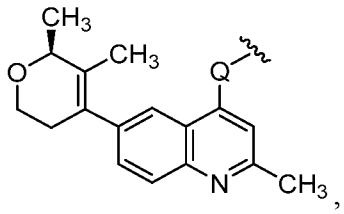
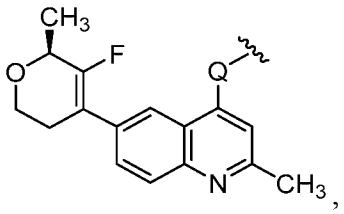
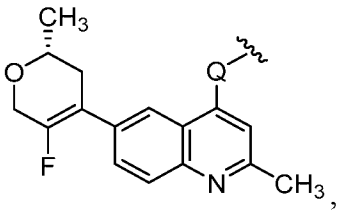
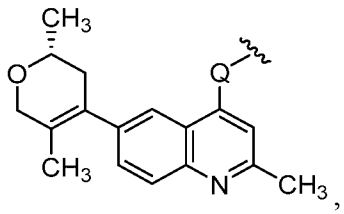
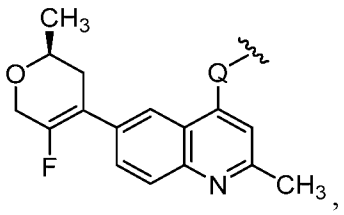
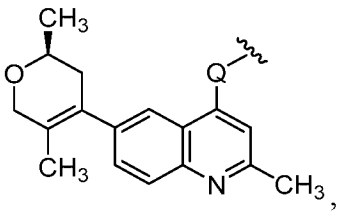
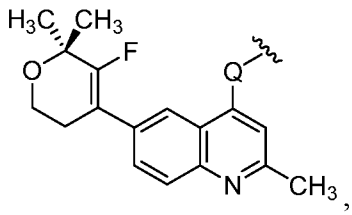
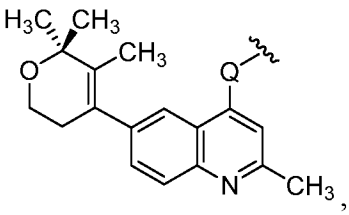
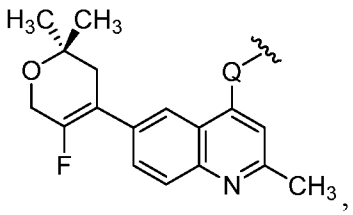
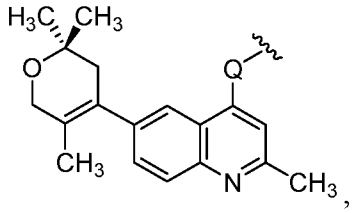
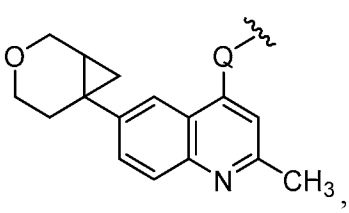
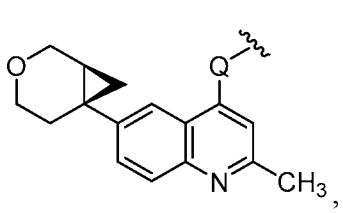
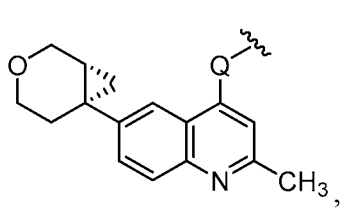
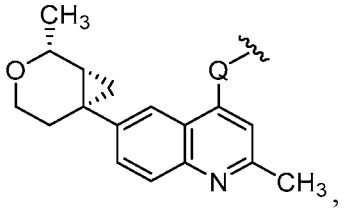
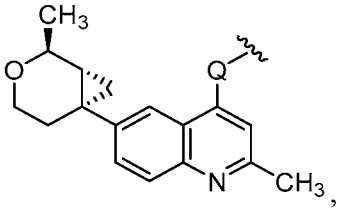
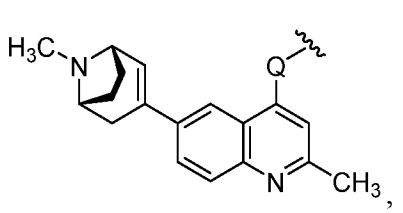
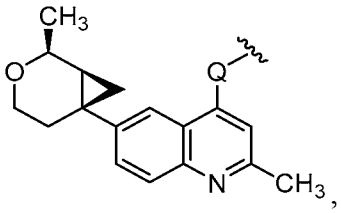
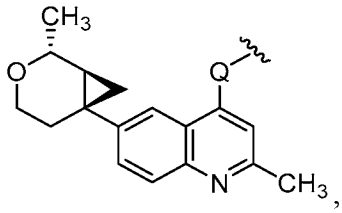
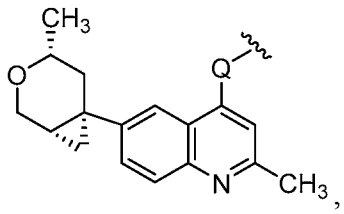
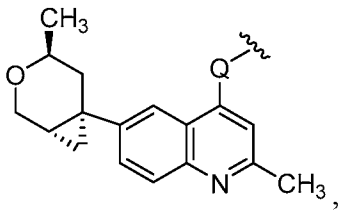
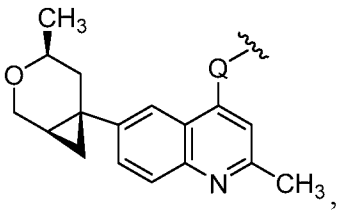
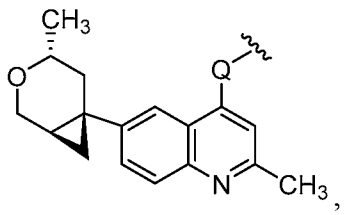
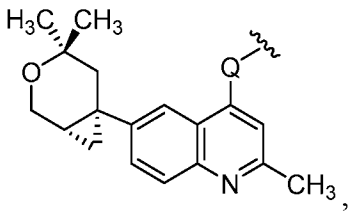
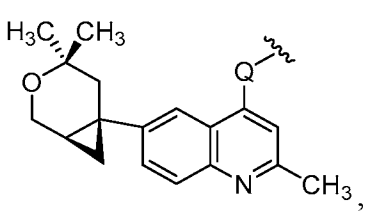


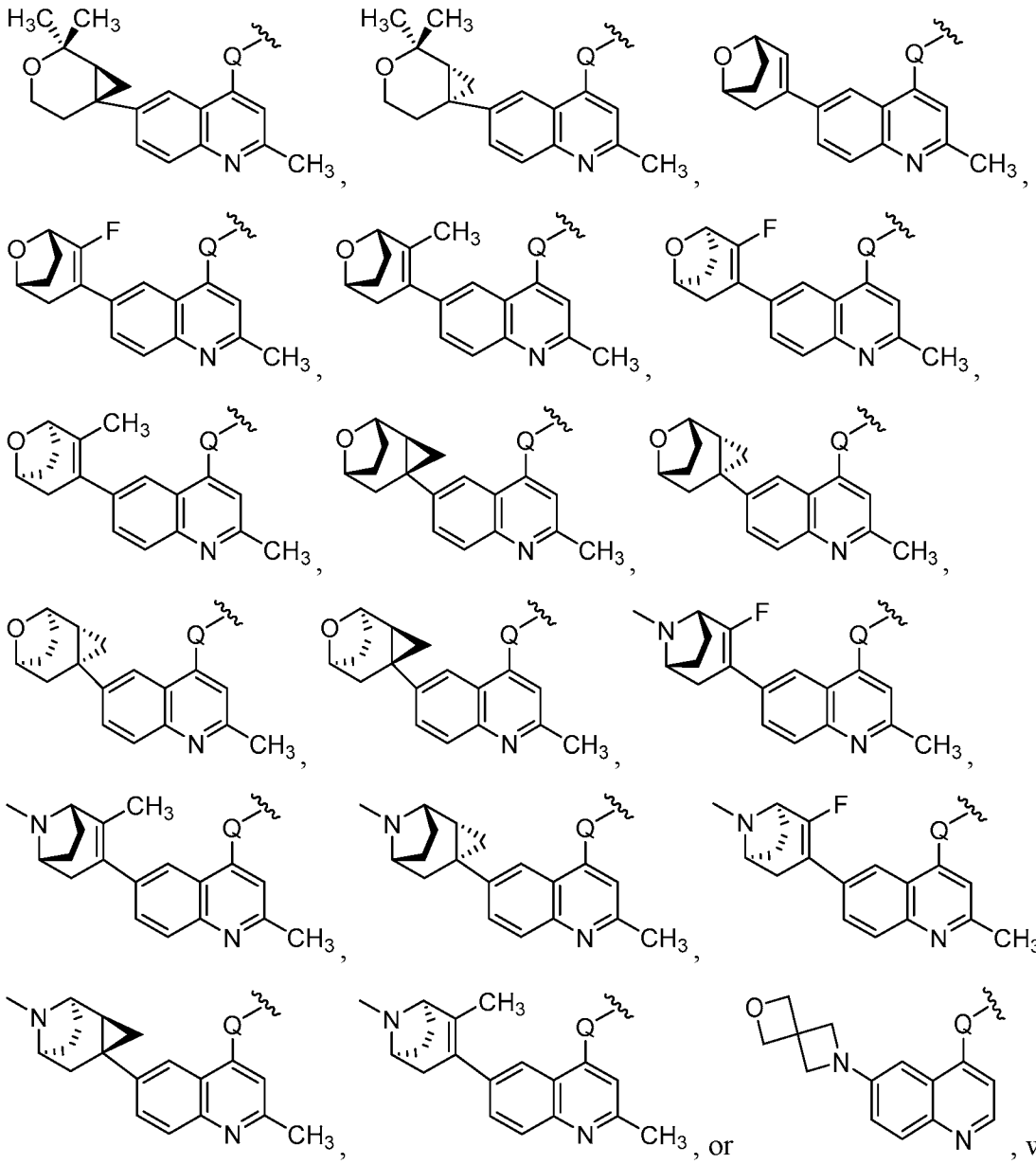











, wherein Q is O or NH.

45. The compound of any one of claims 1-3, 10-14, 18-24 and 44, wherein the structural moiety  has the structure of

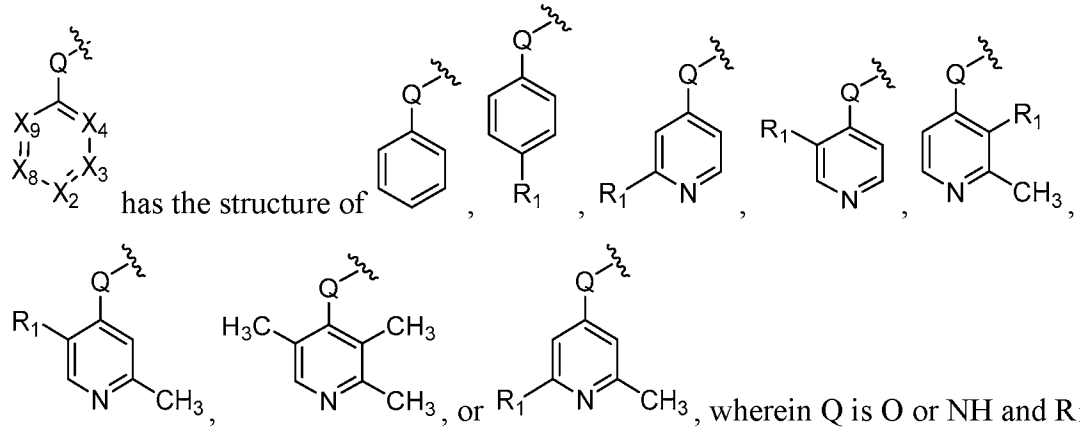















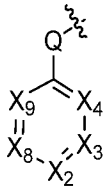
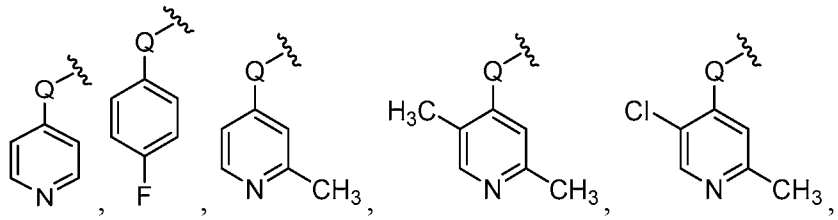
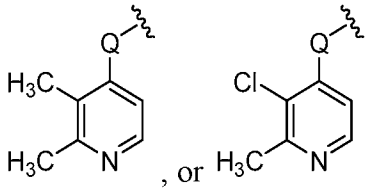
Q is O or NH.

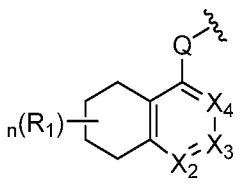
46. The compound of any one of claims 1-3 and 15-24, wherein the structural moiety

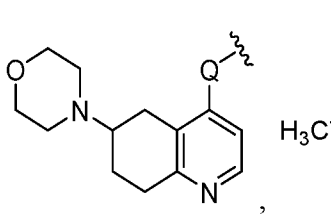
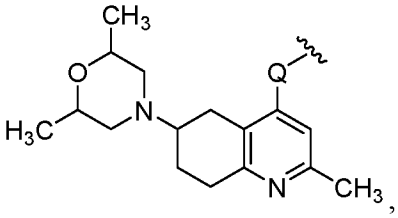
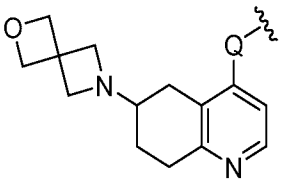
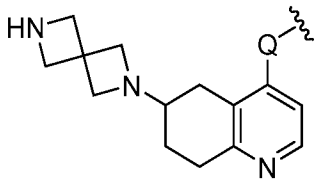


has the structure of , wherein Q is O or NH and R_1 is H,

(C_1-C_6)alkyl, (C_3-C_7)heterocycloalkyl, halogenated (C_3-C_7)heterocycloalkyl, or halogen.

47. The compound of any one of claims 1-3, 15-24, and 46, wherein the structural moiety  has the structure of , or  wherein Q is O or NH.

48. The compound of any one of claims 1-7 and 18-24, wherein the structural moiety  has the structure of

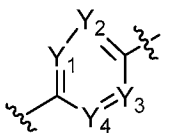
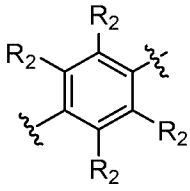
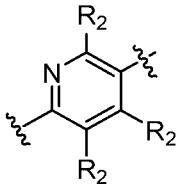
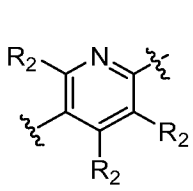
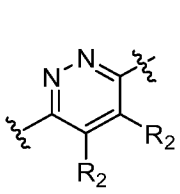
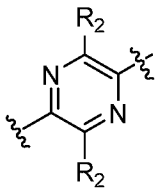
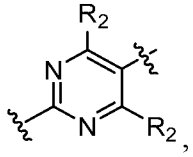
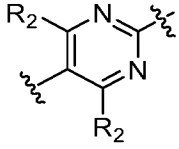
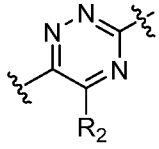
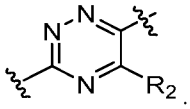

,

,

, or

, wherein Q is O or NH.

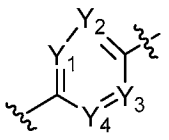
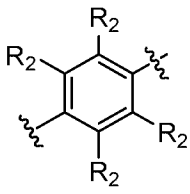
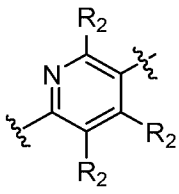
49. The compound of claim 1, having the formula of Formula Ia.

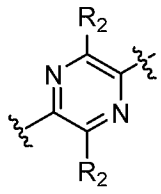
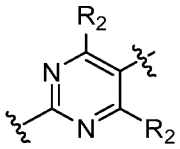
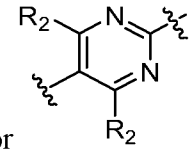
50. The compound of claim 1, having the formula of Formula IIa.

51. The compound of claim 1, having the formula of Formula IIIa.

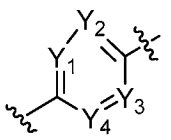
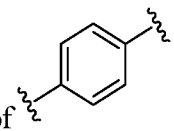
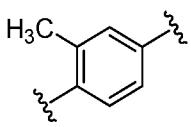
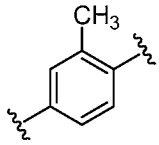
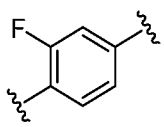
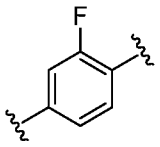
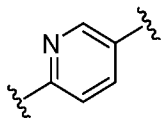
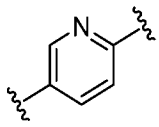
52. The compound of claim 1, having the formula of Formula IVa.

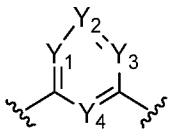
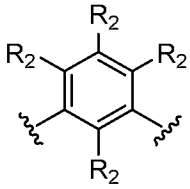
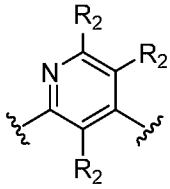
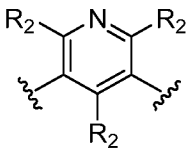
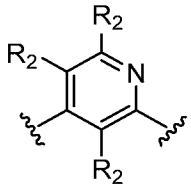
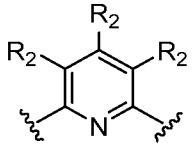
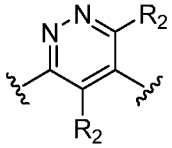
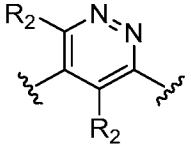
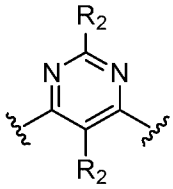
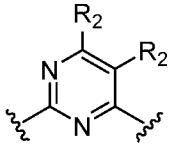
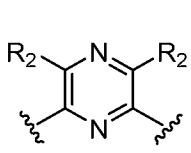
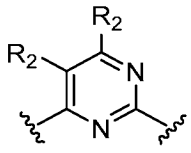
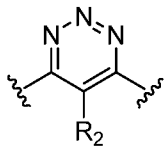
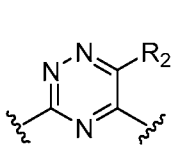
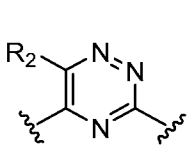
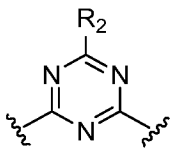
53. The compound of any one of claims 1, 49, and 52, wherein the structural moiety

has the structure of

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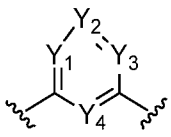
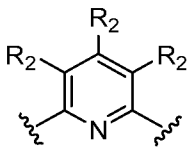
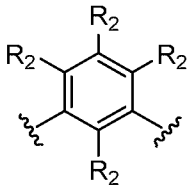
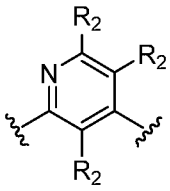
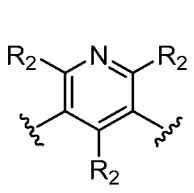
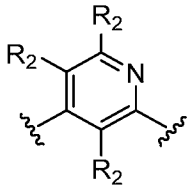
54. The compound of any one of claims 1, 49, and 52-53, wherein the structural moiety

has the structure of

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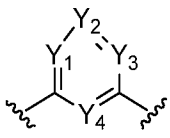
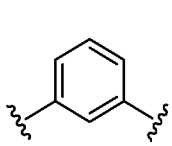
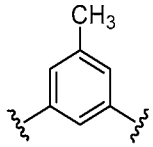
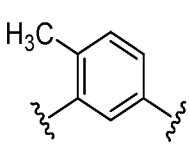
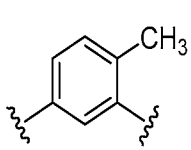
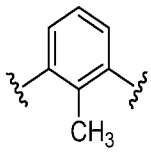
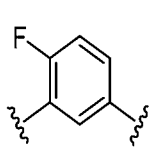
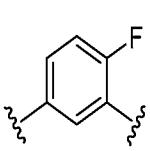
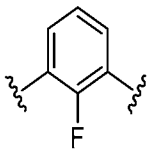
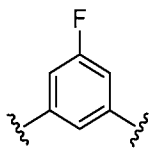
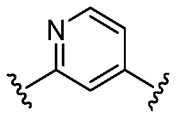
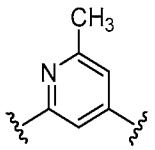
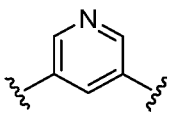
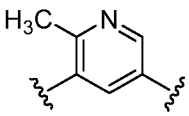
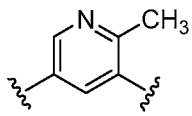
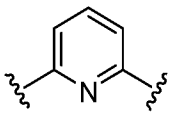
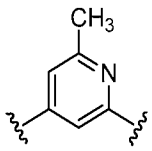
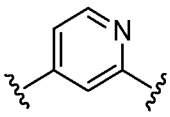
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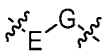
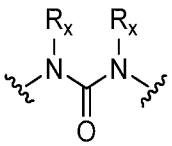
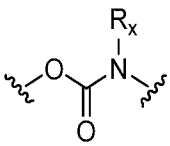
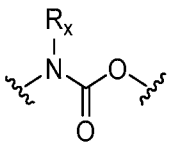
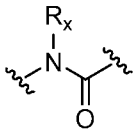
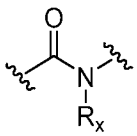
55. The compound of any one of claims 1, 49, and 52-54, wherein each occurrence of R_2 is independently H, halogen, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$.

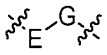
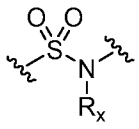
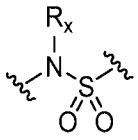
56. The compound of any one of claims 1, 49, and 52-55, wherein the structural moiety  has the structure of , , , , , , or .

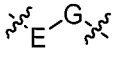
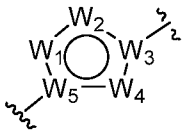
57. The compound of any one of claims 1 and 50-51, wherein the structural moiety  has the structure of , , , , , , , , , , , , , , or .

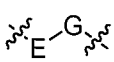
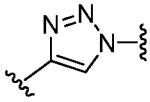
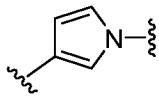
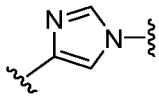
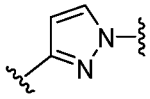
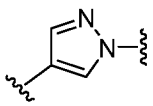
58. The compound of any one of claims 1, 50-51, and 57, wherein the structural moiety  has the structure of , , , , or .

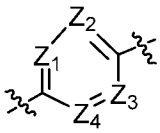
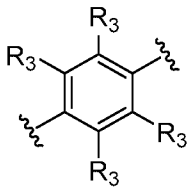
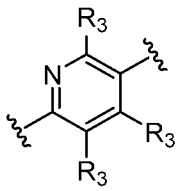
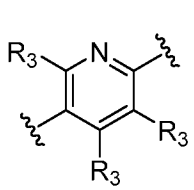
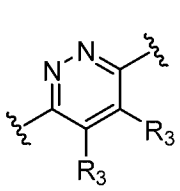
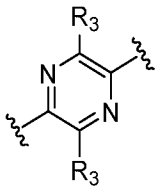
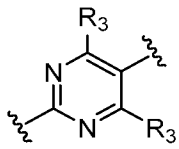
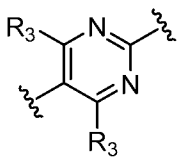
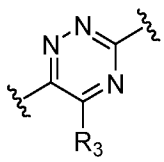
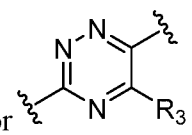
59. The compound of any one of claims 1, 50-51, and 57-58, wherein the structural moiety  has the structure of , , , , , , , , , , , , , , , , or .

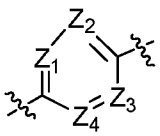
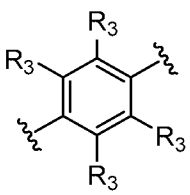
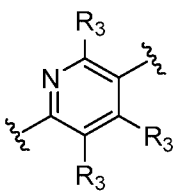
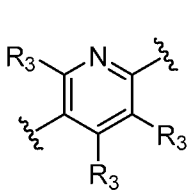
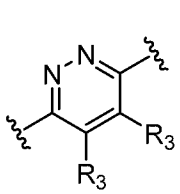
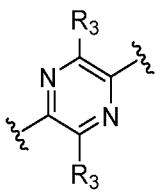
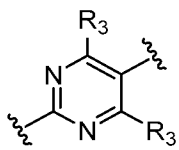
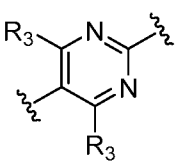
60. The compound of any one of claims 1 and 49-59, wherein the structural moiety  has the structure of , , , , or .

61. The compound of any one of claims 1 and 49-59, wherein the structural moiety  has the structure of  or .

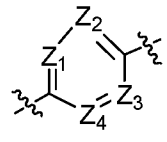
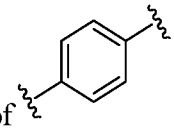
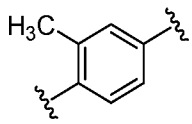
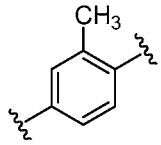
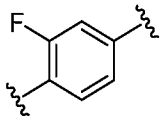
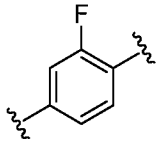
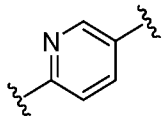
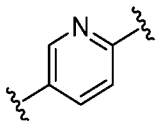
62. The compound of any one of claims 1 and 49-59, wherein the structural moiety  has the structure of .

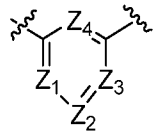
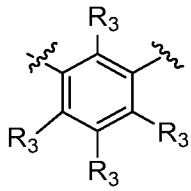
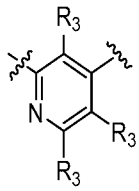
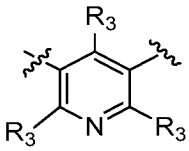
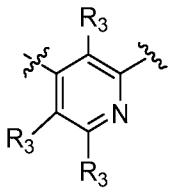
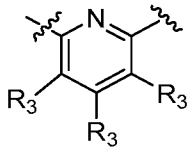
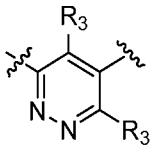
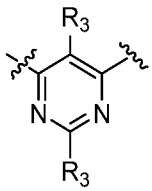
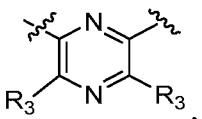
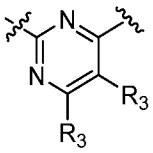
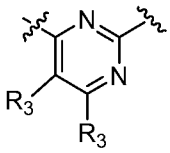
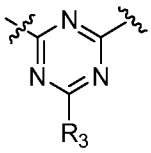
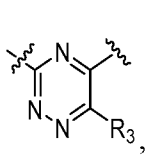
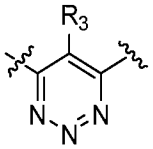
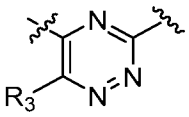
63. The compound of any one of claims 1, 49-59, and 62, wherein the structural moiety  has the structure of , , , , or .

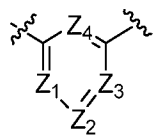
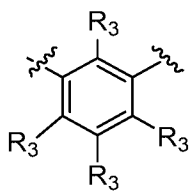
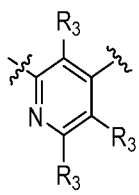
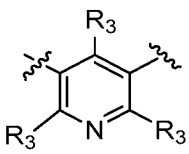
64. The compound of any one of claims 1, 49, 51 and 53-63, wherein the structural moiety  has the structure of , , , , , , , , or .

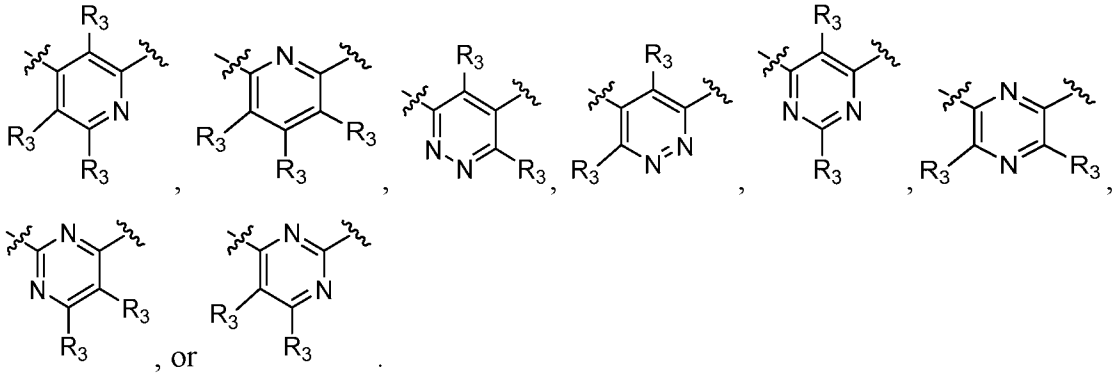
65. The compound of any one of claims 1, 49, 51 and 53-64, wherein the structural moiety  has the structure of , , , , , , or .

66. The compound of any one of claims 1, 49, 51 and 53-65, wherein each occurrence of R_3 is H, halogen, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$.

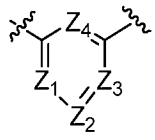
67. The compound of any one of claims 1, 49, 51 and 53-66, wherein the structural moiety  has the structure of , , , , , , or .

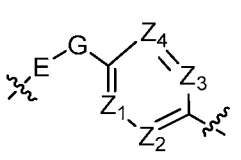
68. The compound of any one of claims 1, 50, 52 and 53-63, wherein the structural moiety  has the structure of , , , , , , , , , , , , , , or .

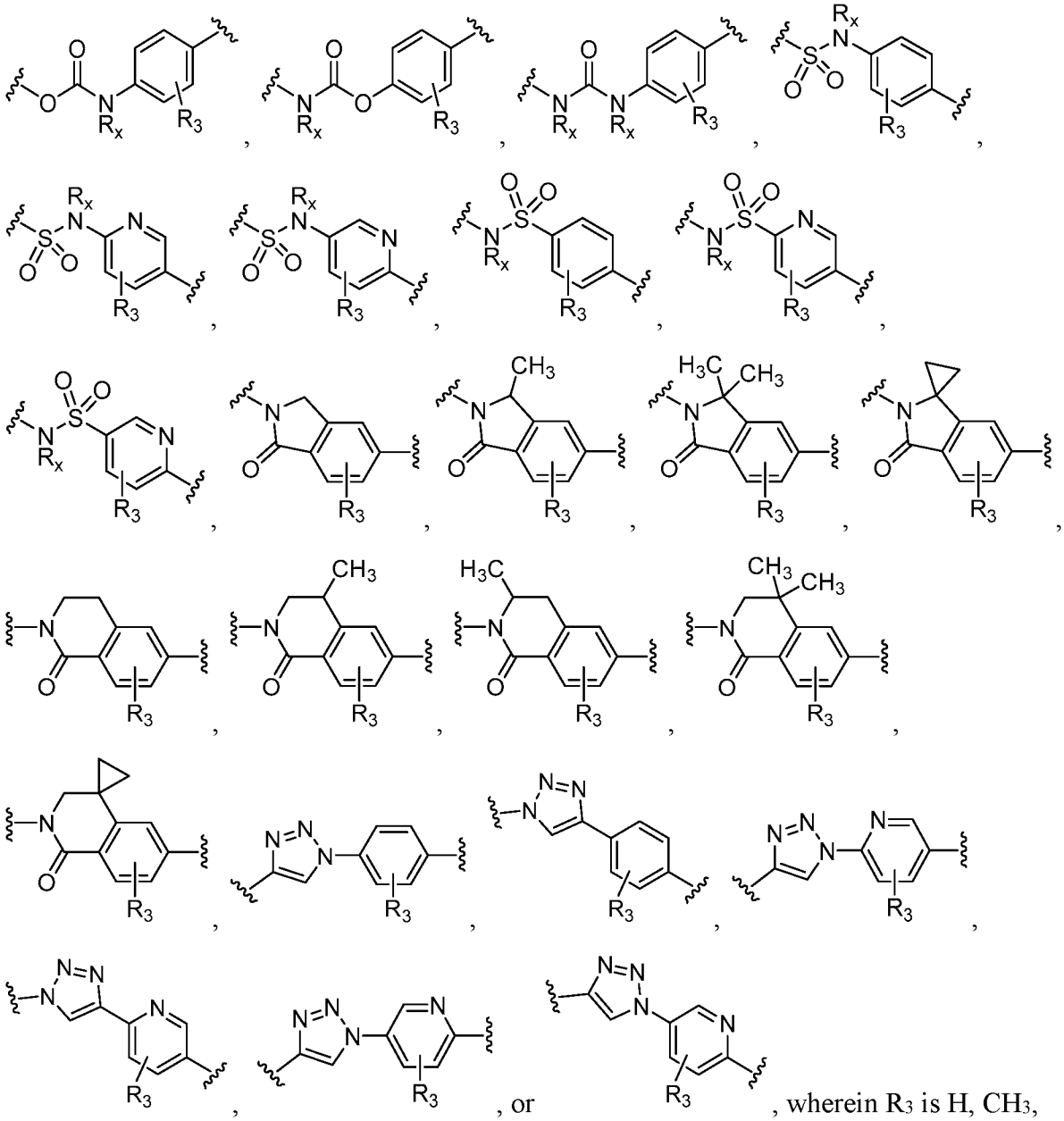
69. The compound of any one of claims 1, 50, 52, 53-63, and 68, wherein the structural moiety  has the structure of , , ,



70. The compound of any one of claims 1, 50, 52, 53-63, and 68-69, wherein each occurrence of R_3 is H, halogen, CH_3, CF_3, OH, NH_2, $-NHCH_3$, or $-N(CH_3)_2$.

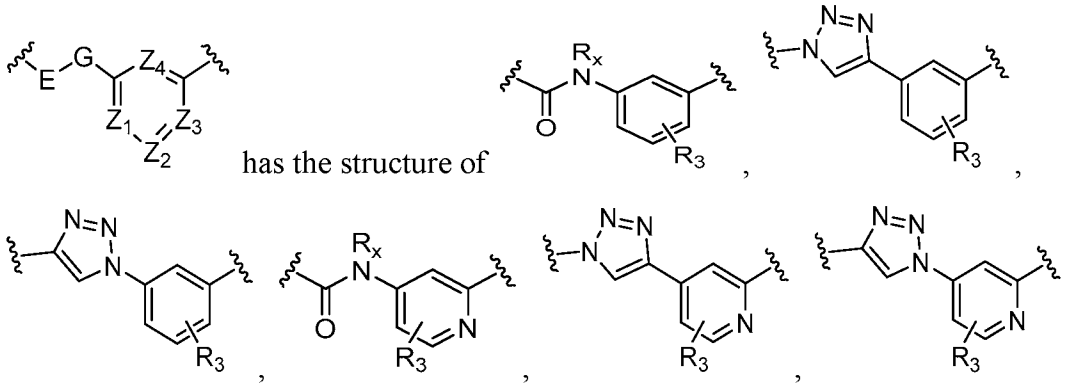
71. The compound of any one of claims 1, 50, 52, 53-63, and 68-70, wherein the structural moiety  has the structure of

72. The compound of any one of claims 1, 49 and 51, wherein the structural moiety  has the structure of

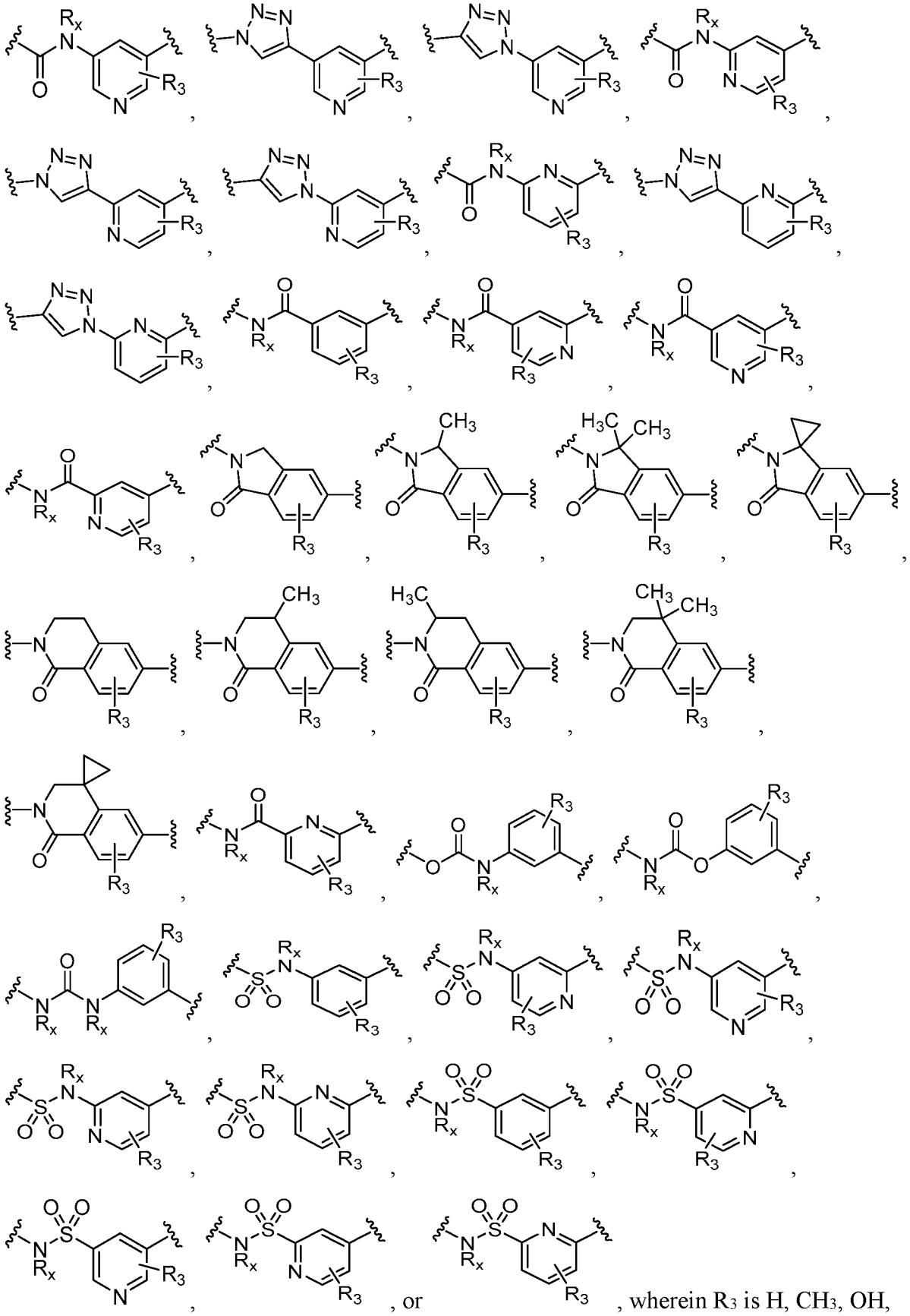


, wherein R_3 is H, CH_3, OH, halogen, or NH_2; and wherein R_x is H, CH_3, or CH_2CH_3.

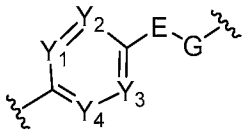
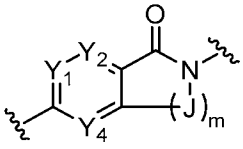
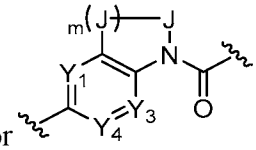
73. The compound of any one of claims 1, 50 and 52, wherein the structural moiety

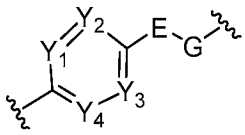
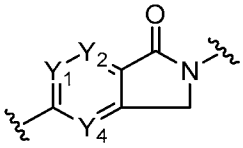
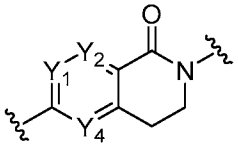
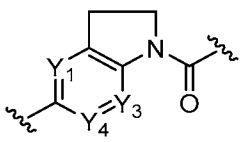
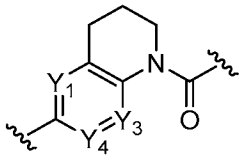


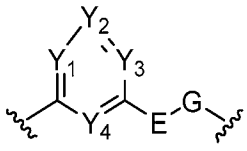
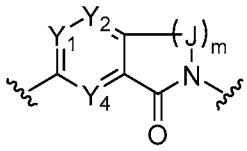
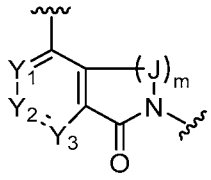
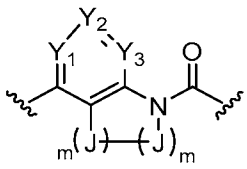
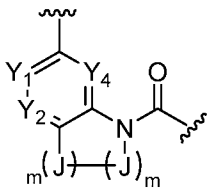
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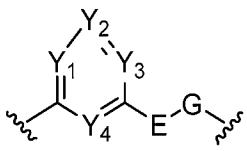
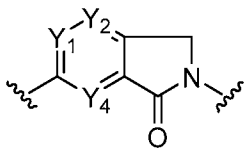
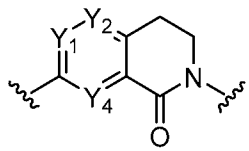


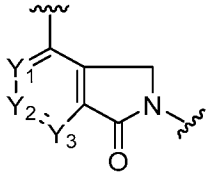
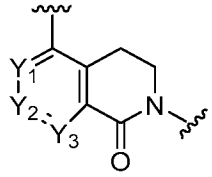
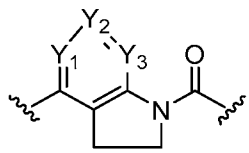
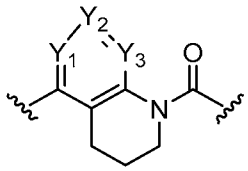
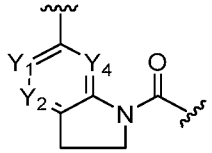
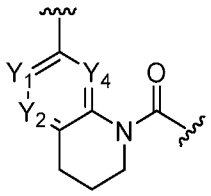
, wherein R_3 is H, CH_3, OH, halogen, or NH_2; and wherein R_x is H, CH_3, or CH_2CH_3.

74. The compound of any one of claims 1, 49, and 52, wherein the structural moiety  has the structure of  or , wherein 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.

75. The compound of any one of claims 1, 49, 52, and 74, wherein the structural moiety  has the structure of , , , or , wherein Y_1, Y_2, Y_3, and Y_4 are each independently N, CH, CCH_3, or CF.

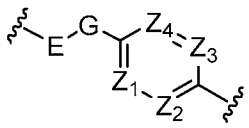
76. The compound of any one of claims 1 and 50-51, wherein the structural moiety  has the structure of , , , or , wherein each occurrence of m is independently 1 or 2, J is $C(R_y)_2$, and each occurrence of R_y is independently H, $(C_1\text{-}C_6)$alkyl, OH, $O(C_1\text{-}C_6)$alkyl, or halogen.

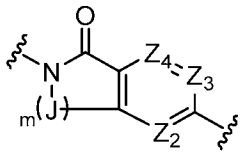
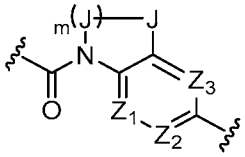
77. The compound of any one of claims 1, 50-51, and 76, wherein the structural moiety  has the structure of , ,

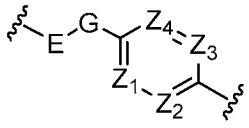
or , wherein Y_1, Y_2, Y_3, and Y_4 are each independently N, CH, CCH_3, or CF.

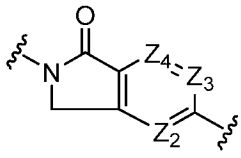
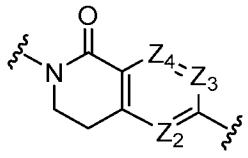
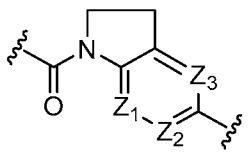
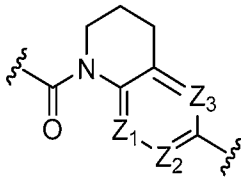
78. The compound of any one of claims 1, 49, and 51, wherein the structural moiety



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.

79. The compound of any one of claims 1, 49, 51, and 78, wherein the structural moiety



has the structure of , , , or , wherein Z_1, Z_2, Z_3, and Z_4 are each independently N, CH, CCH_3, or CF.

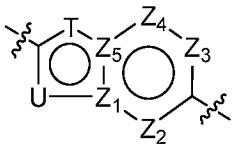
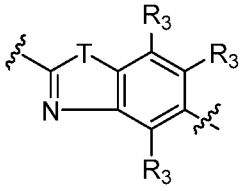
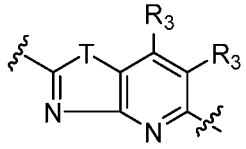
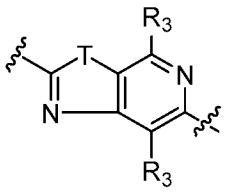
80. The compound of claim 1, having the formula of Formula Ib.

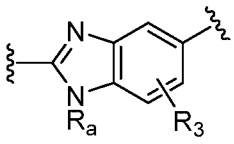
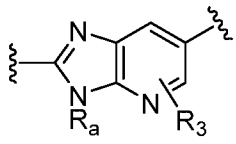
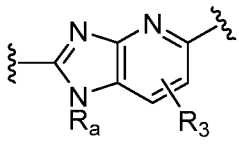
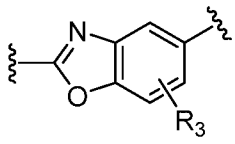
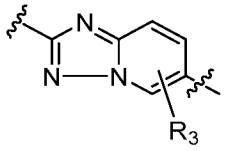
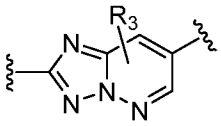
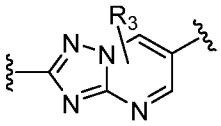
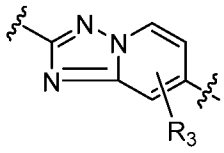
81. The compound of claim 1, having the formula of Formula IIb.

82. The compound of claim 1, having the formula of Formula IIIb.

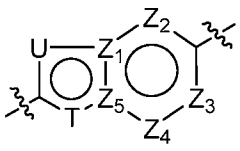
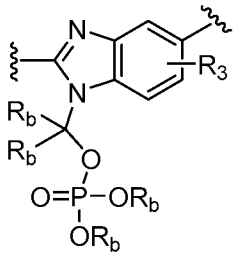
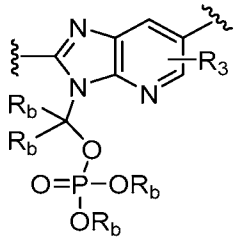
83. The compound of claim 1, having the formula of Formula IVb.

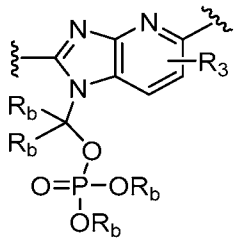
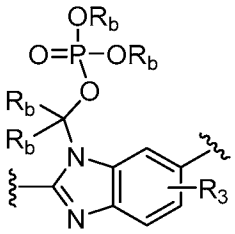
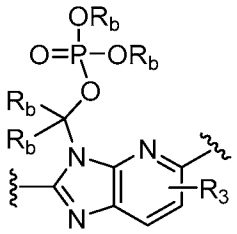
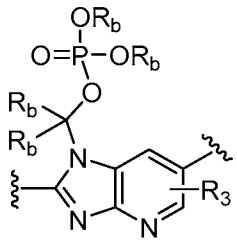
84. The compound any one of claims 1, 80, and 82, wherein the structural moiety


has the structure of

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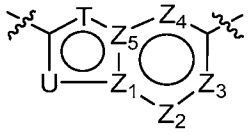
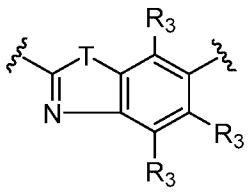
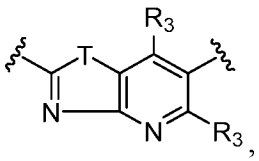









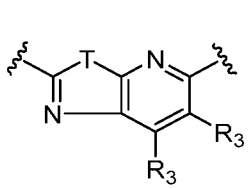
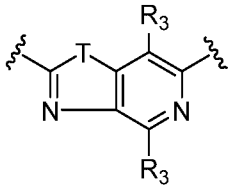
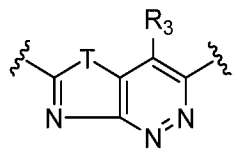
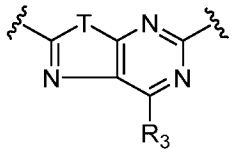
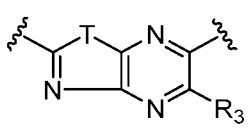
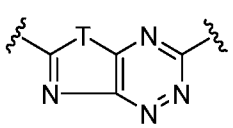
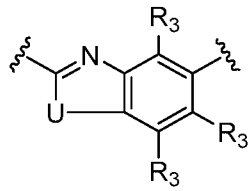
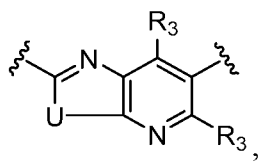
, wherein R_3 is H, CH_3, OH, halogen, or NH_2; and wherein R_a is H, CH_3, or CH_2CH_3.

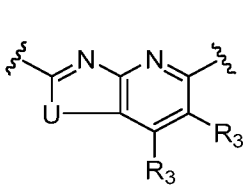
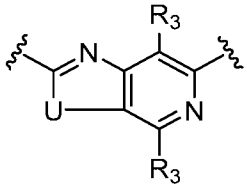
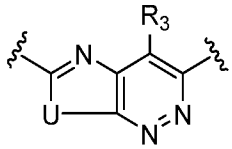
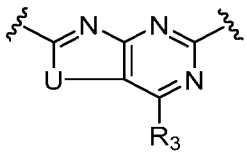
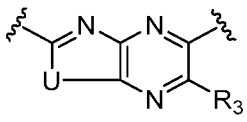
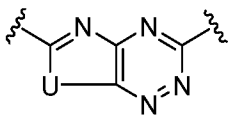
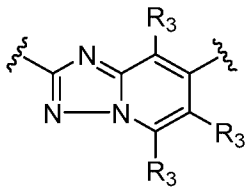
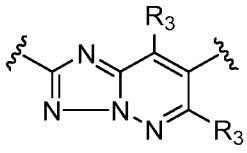
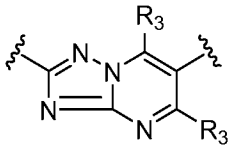
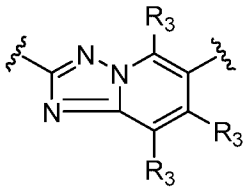
86. The compound of any one of claims 1, 80, 82, and 84-85, wherein the structural moiety  has the structure of  ,

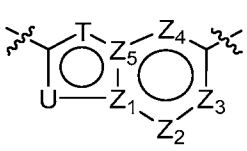
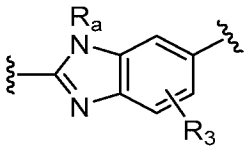
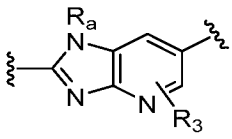
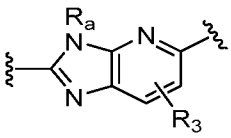
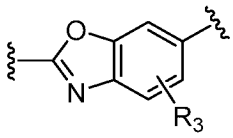
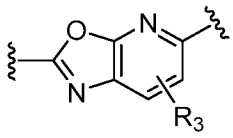
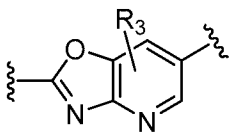
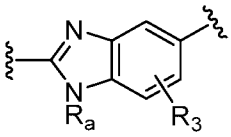
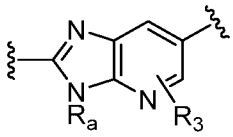
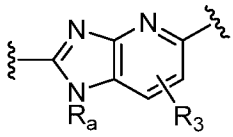
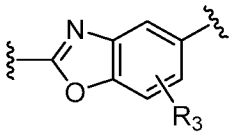
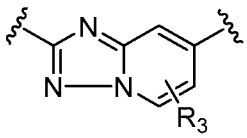
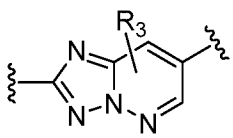
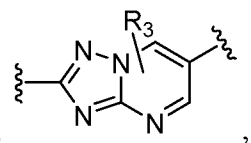
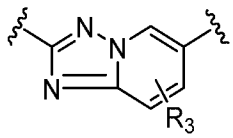
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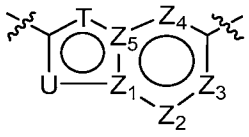
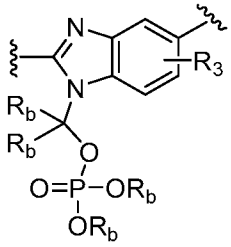
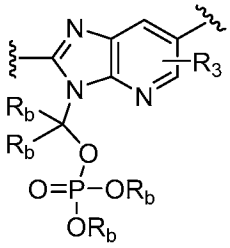
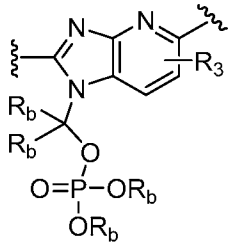
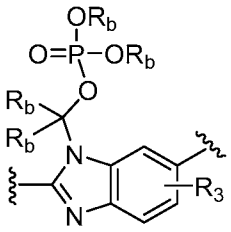
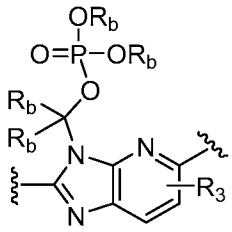
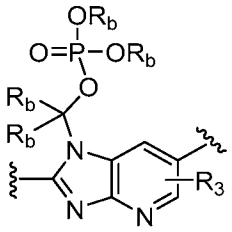
87. The compound of any one of claims 1, 81, and 83, wherein the structural moiety  has the structure of  ,











, or , wherein 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.

88. The compound of any one of claims 1, 81, 83, and 87, wherein the structural moiety


has the structure of














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

89. The compound of any one of claims 1, 81, 83, and 87-88, wherein the structural moiety  has the structure of , , , , , or .

90. The compound of any one of claims 84, 86, 87, and 88, wherein each occurrence of R_b is independently H or $(C_1\text{-}C_6)$alkyl.

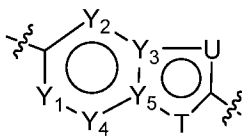
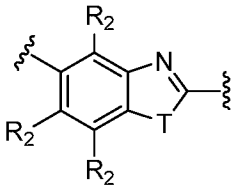
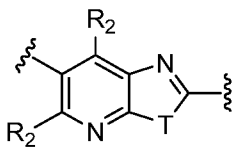
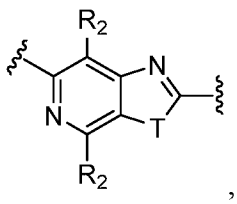
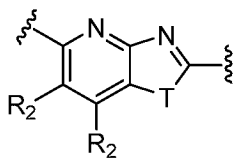
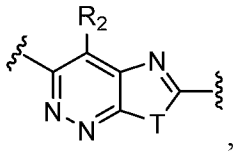
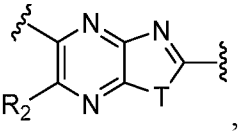
91. The compound of any one of claims 84, 86, 87, 88, and 90, wherein each occurrence of R_b is independently H, CH_3, CH_2CH_3, or $CH(CH_3)_2$.

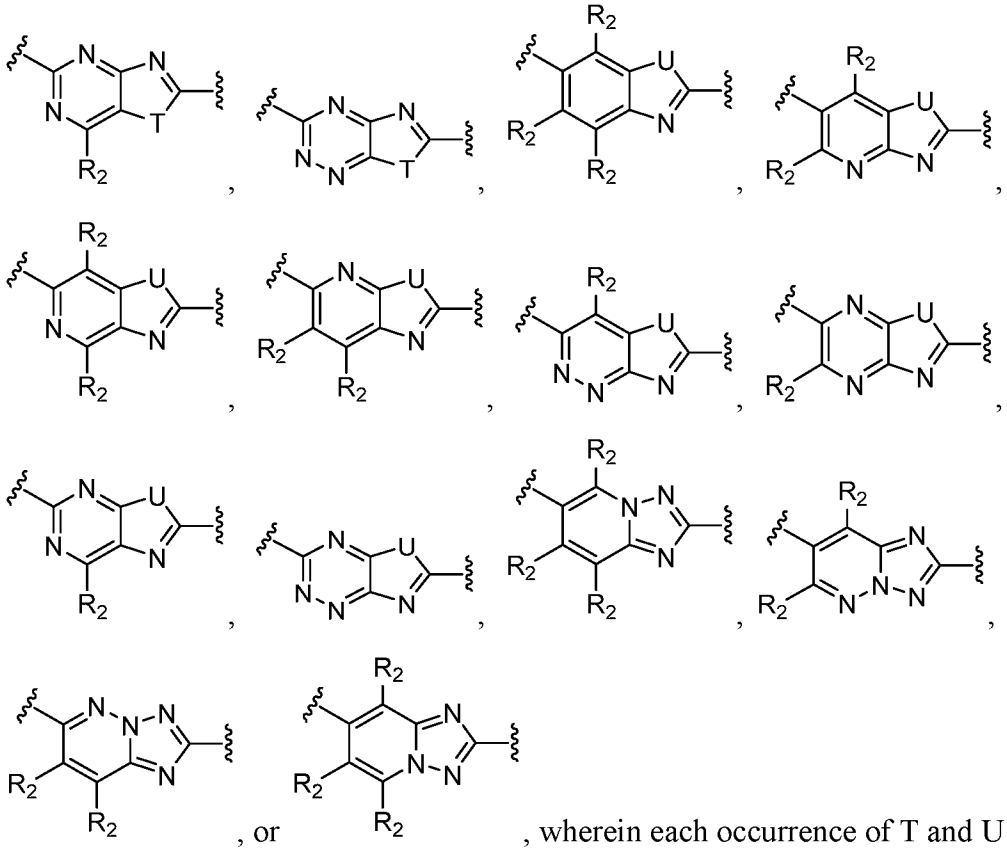
92. The compound of claim 1, having the formula of Formula Ic.

93. The compound of claim 1, having the formula of Formula IIc.

94. The compound of claim 1, having the formula of Formula IIIc.

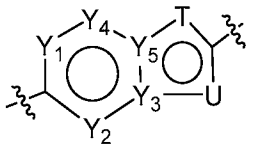
95. The compound of claim 1, having the formula of Formula IVc.

96. The compound of any one of claims 1, 92, and 95, wherein the structural moiety  has the structure of , , , , , .



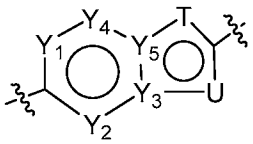
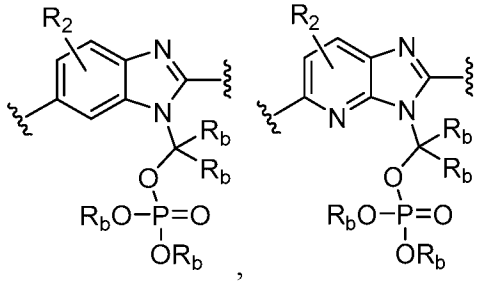
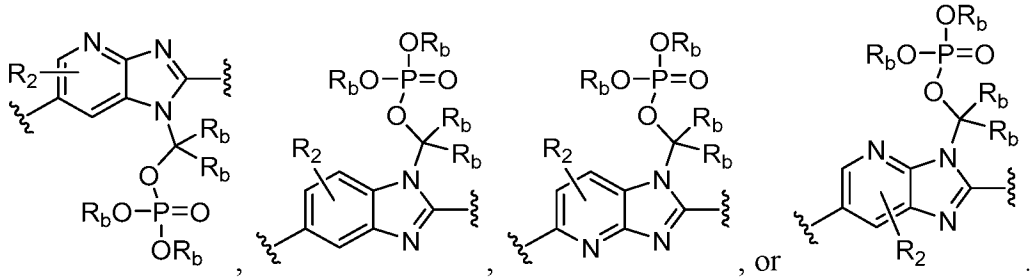
, wherein each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

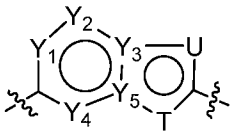
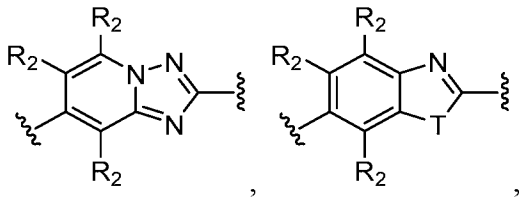
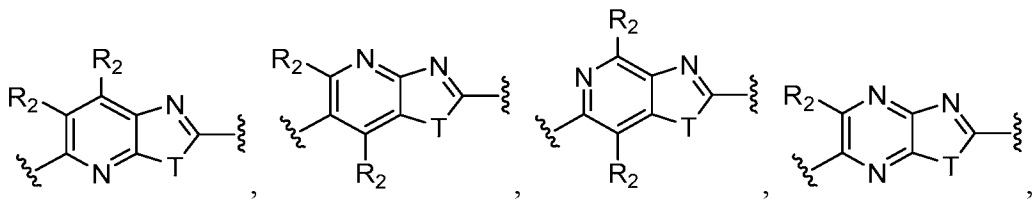
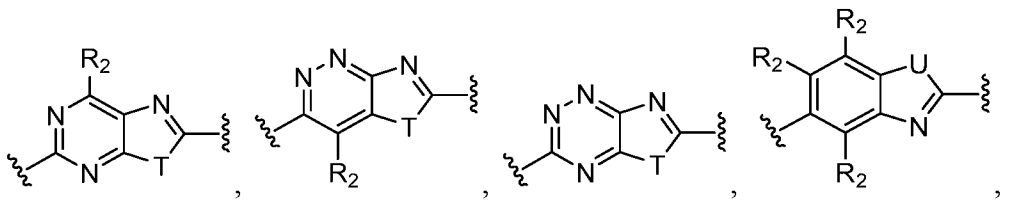
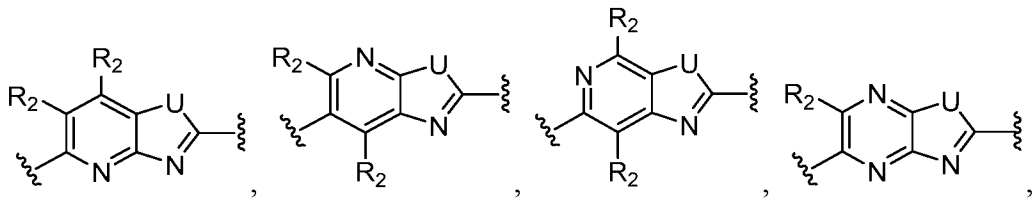
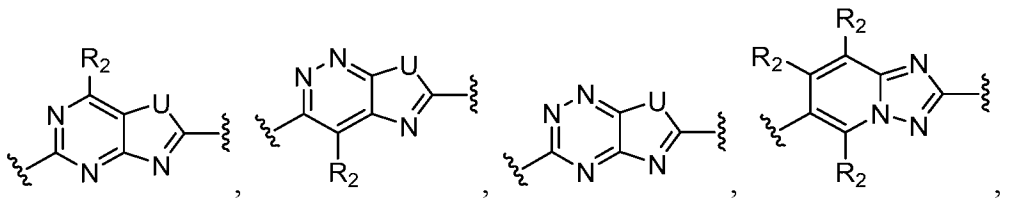
97. The compound of any one of claims 1, 92, and 95-96, wherein the structural moiety

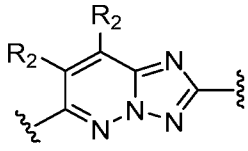
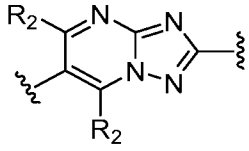
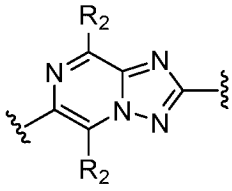


has the structure of

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

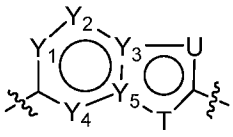
98. The compound of any one of claims 1, 92, and 95-97, wherein the structural moiety  has the structure of , , or .

99. The compound of any one of claims 1 and 93-94, wherein the structural moiety  has the structure of , , , , and .

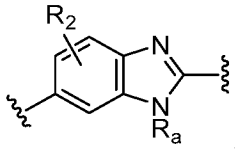
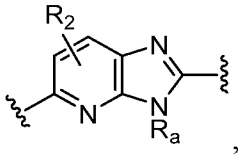
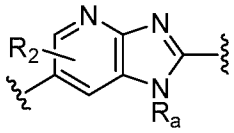
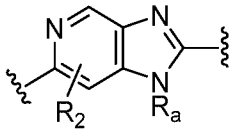
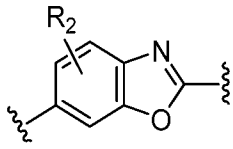
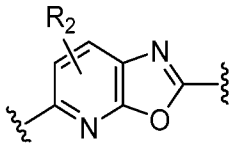
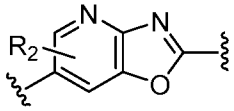
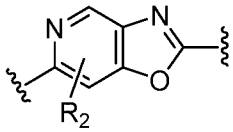
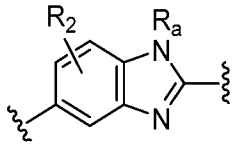
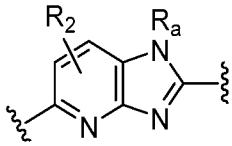
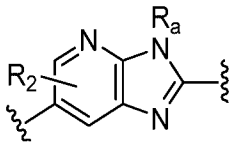
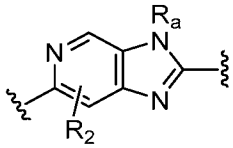
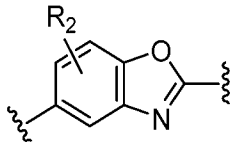




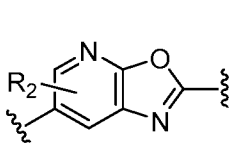
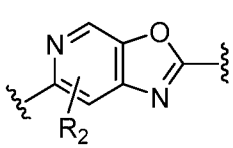
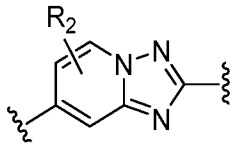
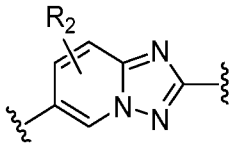
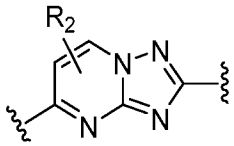
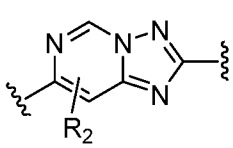
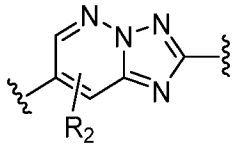
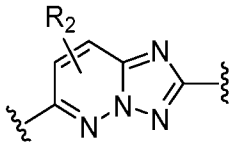
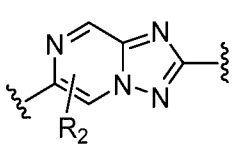
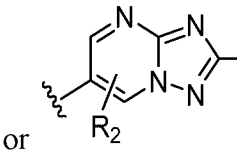
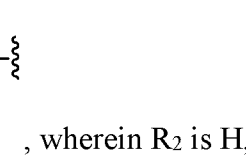
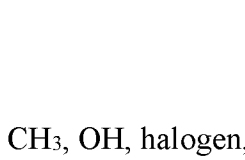
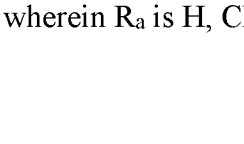
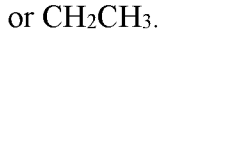
, wherein each occurrence of T and U is independently O, N, NR_a, $N(C=O)R_a$, $NC(R_b)_2OP(=O)(OR_b)_2$, or NSO_2R_a where valance permits.

100. The compound of any one of claims 1, 93-94, and 99, wherein the structural moiety

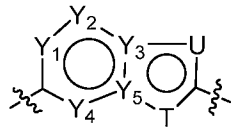
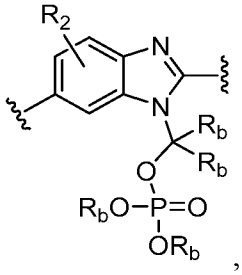
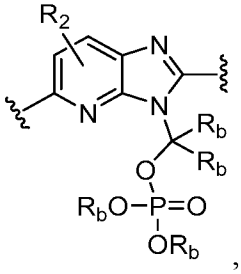
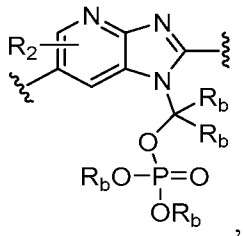
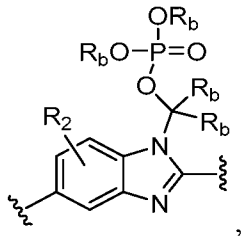
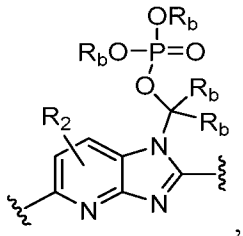
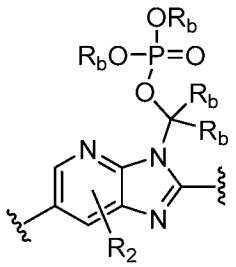


has the structure of

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

101. The compound of any one of claims 1, 93-94, and 99-100, wherein the structural moiety  has the structure of , , , , , or .

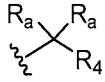
102. The compound of any one of claims 96, 98, 99, and 101, wherein each occurrence of R_b is independently H or (C_1-C_6)alkyl.

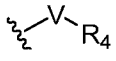
103. The compound of any one of claims 96, 98, 99, and 101-102, wherein each occurrence of R_b is independently H, CH_3, CH_2CH_3, or $CH(CH_3)_2$.

104. The compound of any one of claims 1 and 96-103, wherein each occurrence of R_2 is independently H, CH_3, OH, NH_2, or halogen.

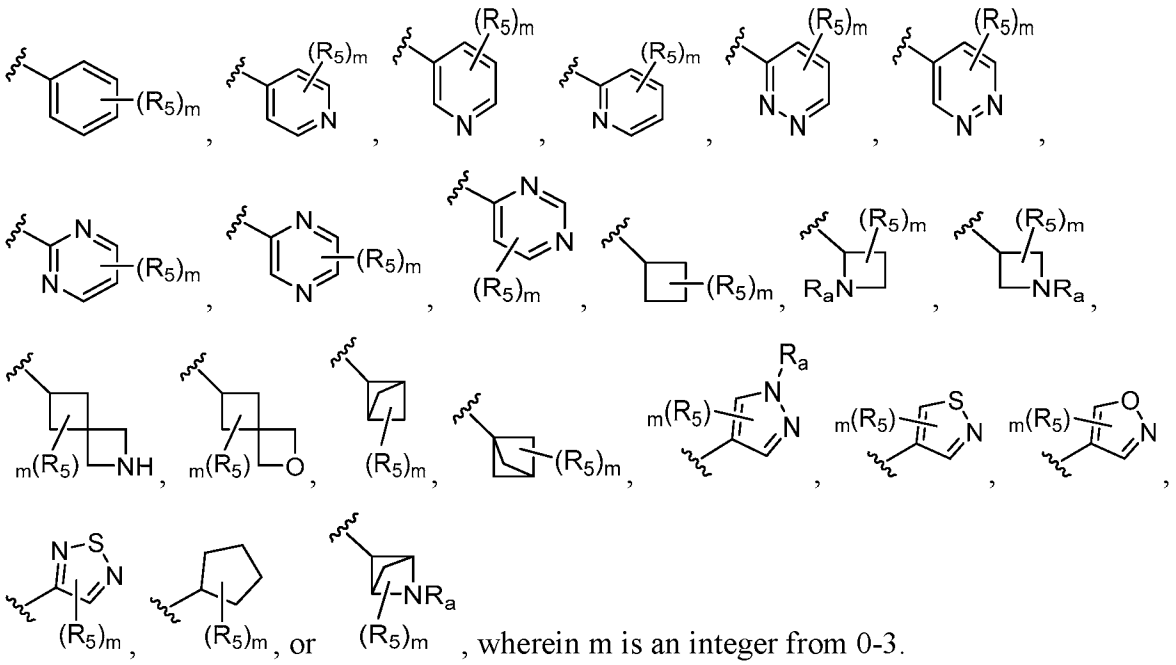
105. The compound of claim 1, wherein the structural moiety  has the structure of .

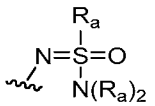
106. The compound of claim 1, wherein the structural moiety  has the structure of .

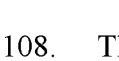
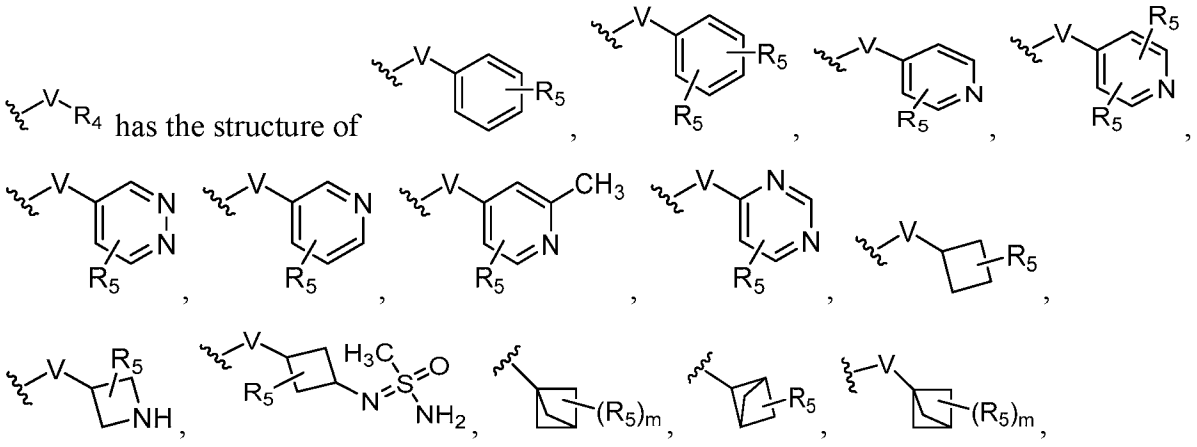
107. The compound of claim 1, wherein the structural moiety  has the structure of .

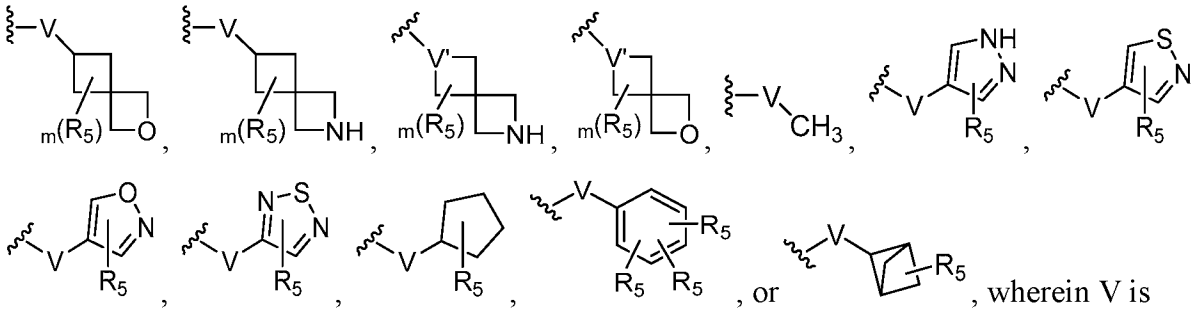
108. The compound of claim 1, wherein the V and R_4 of the structural moiety  taken together form a (C_4-C_{10})heterospiroalkyl.

109. The compound of claim 1, wherein V is absent.

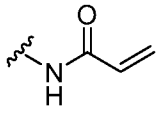
110. The compound of any one of claims 1 and 105-109, wherein R_4 is (C_1-C_6)alkyl, , wherein m is an integer from 0-3.

111. The compound of claim 1 or 110, wherein 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.

112. The compound of any one of claims 1 and 105-111, wherein the structural moiety  has the structure of 



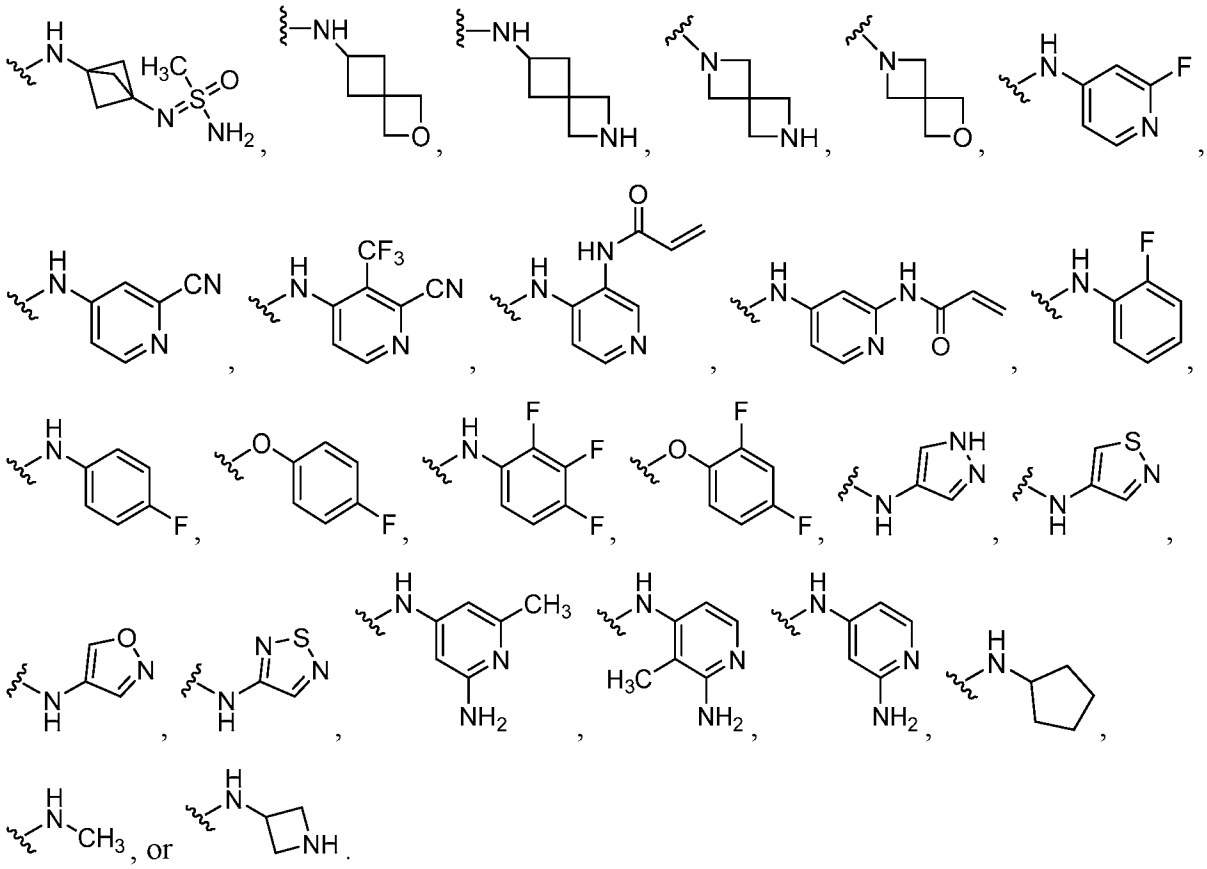
, wherein V is $C(R_a)_2$, O, NR_a, $N(C=O)R_a$, or NSO_2R_a and V' is CR_a or N.

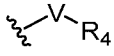
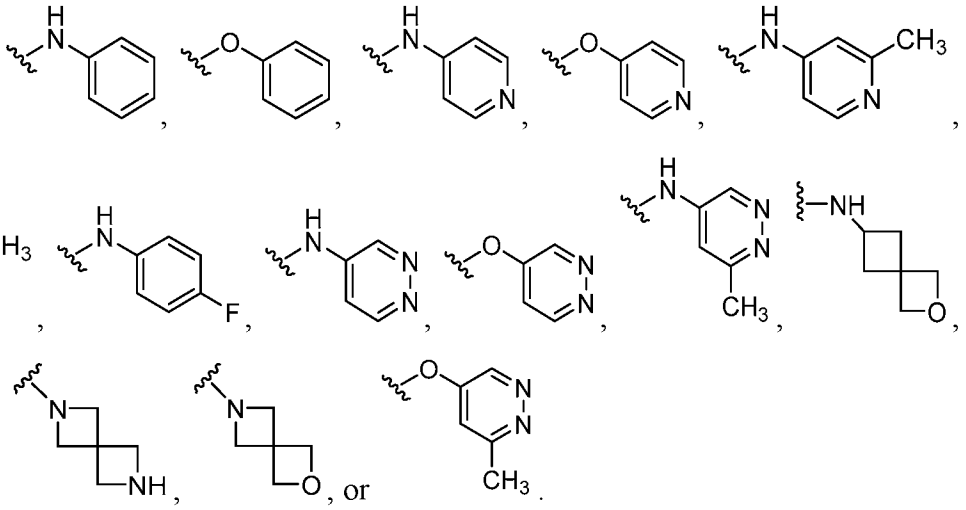
113. The compound of claim 1 or 112, wherein each occurrence of R_5 is independently H, CH_3, isopropyl, halogen, OH, CN, , CF_3, $(C_1\text{-}C_6)$haloalkyl, or NH_2.

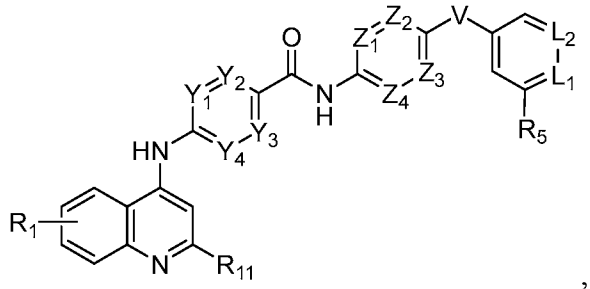
114. The compound of any one of the proceeding claims, wherein each occurrence of R_a is independently H, $(C_2\text{-}C_6)$alkenyl, or $(C_1\text{-}C_6)$alkyl.

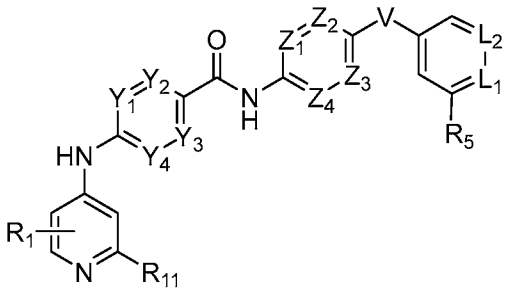
115. The compound of claim any one of the proceeding claims, wherein each occurrence of R_a is H, CH_3, or CH_2CH_3.

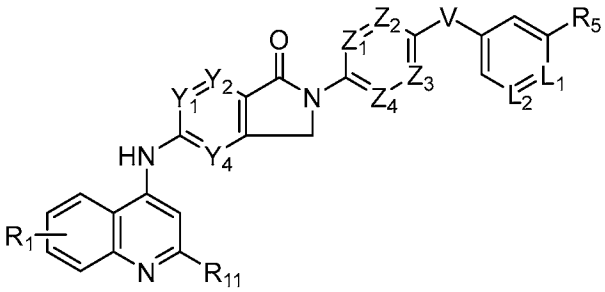
116. The compound of any one of claims 1 and 105-111, wherein the structural moiety has the structure of

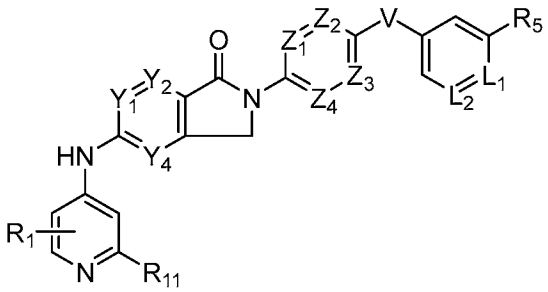


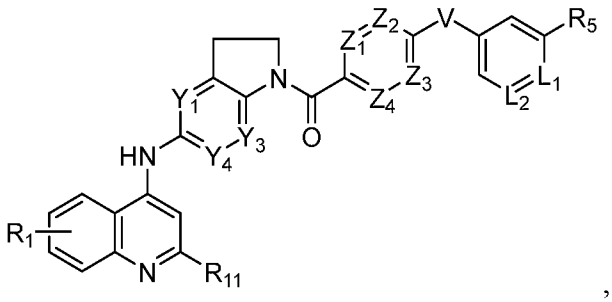
117. The compound of claim 1 and 105-111, wherein the structural moiety  has the structure of 

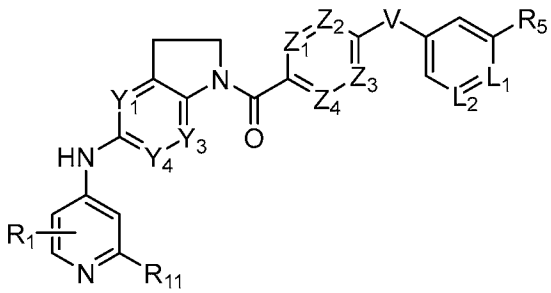
118. The compound of claim 1 or 49, wherein the compound of Formula Ia has the structure of ,

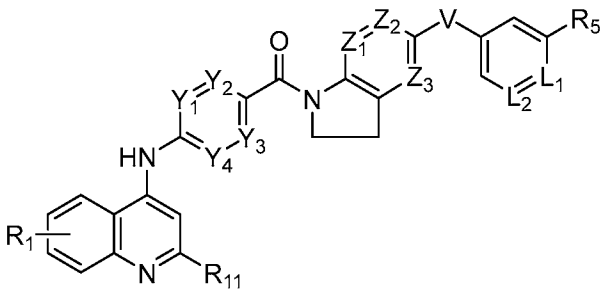
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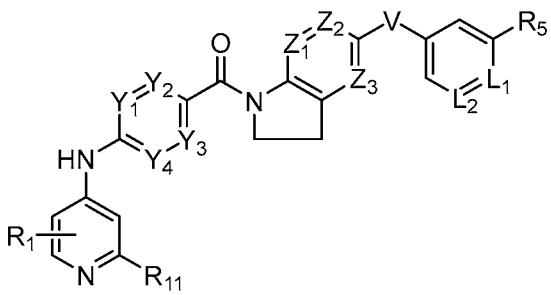
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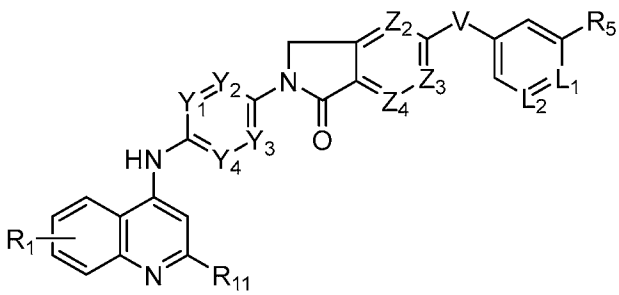
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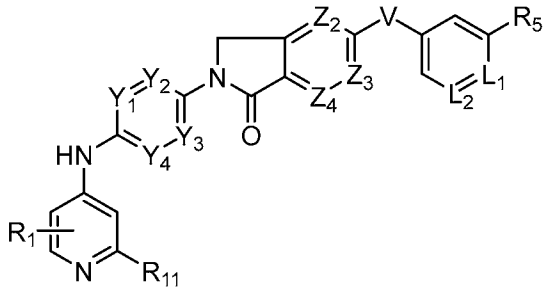
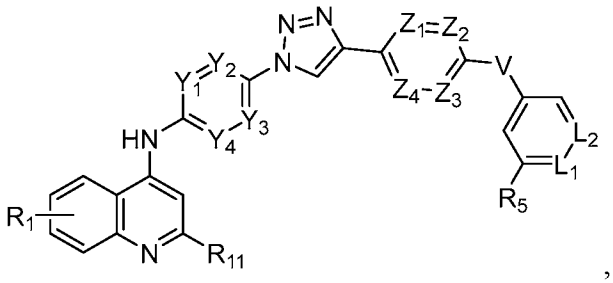
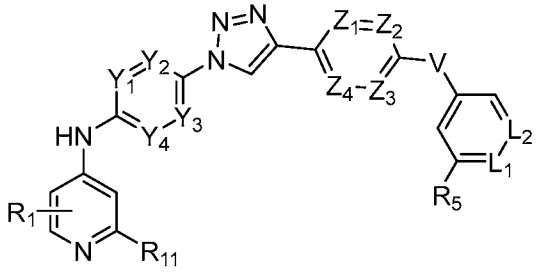
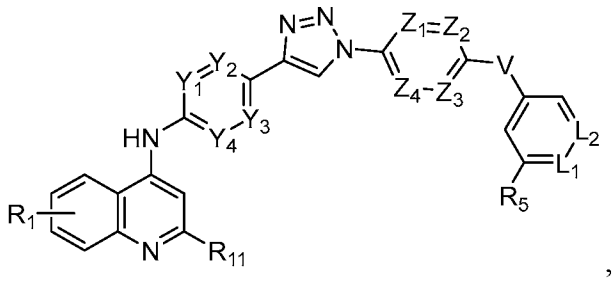
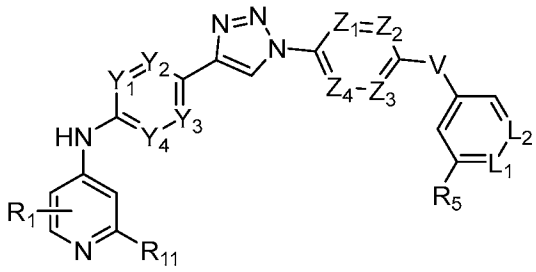
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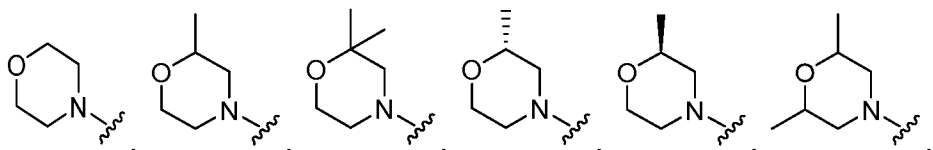
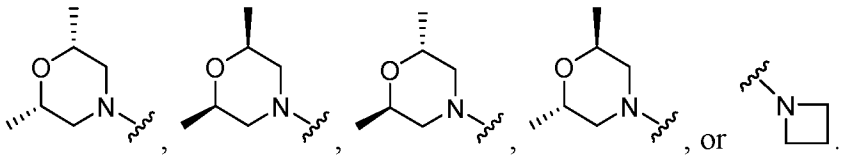
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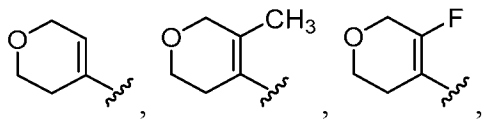
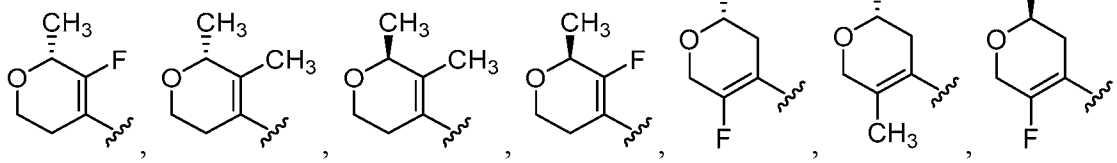
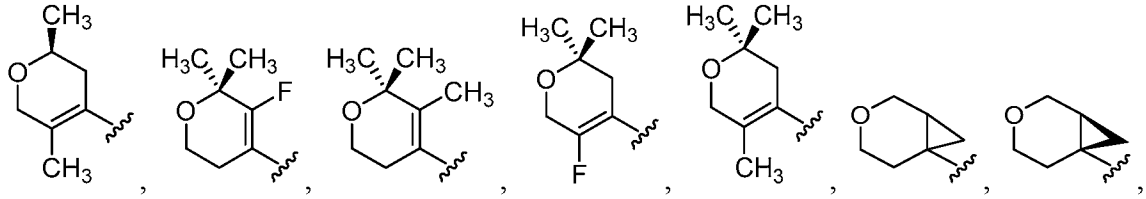
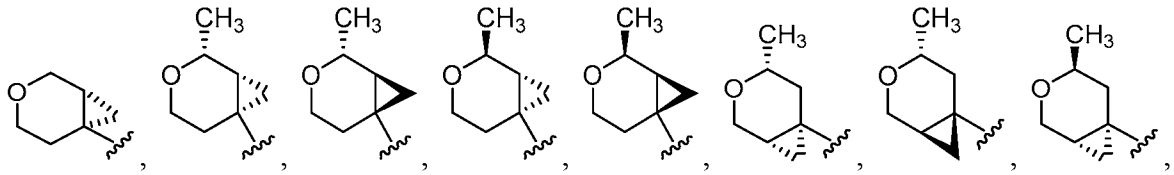
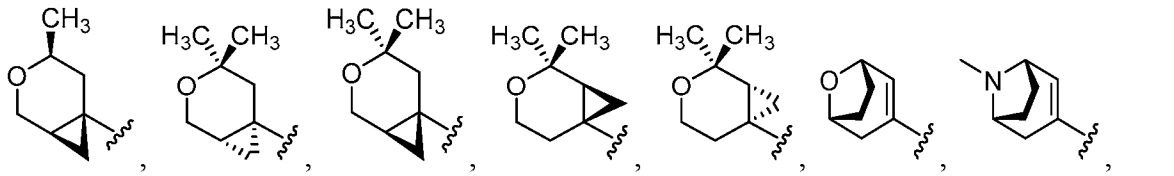
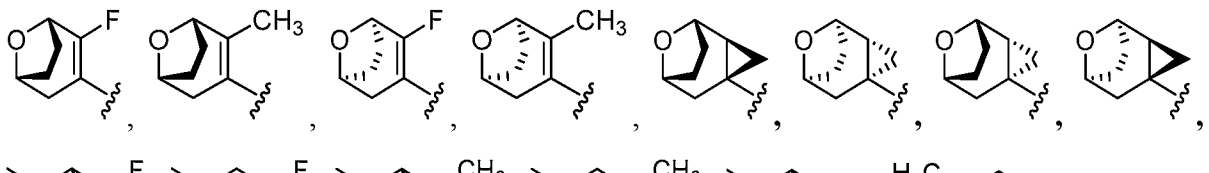
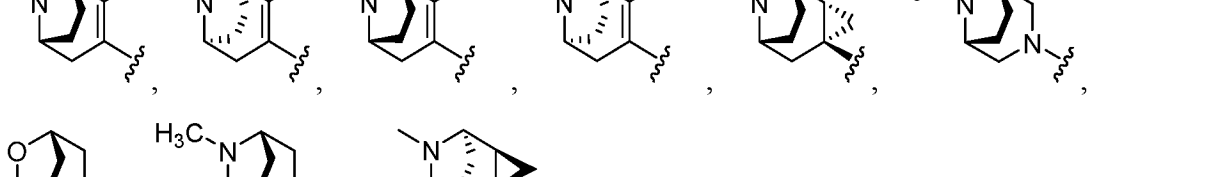
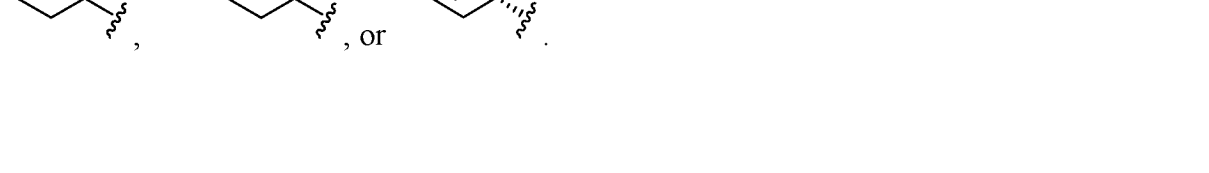
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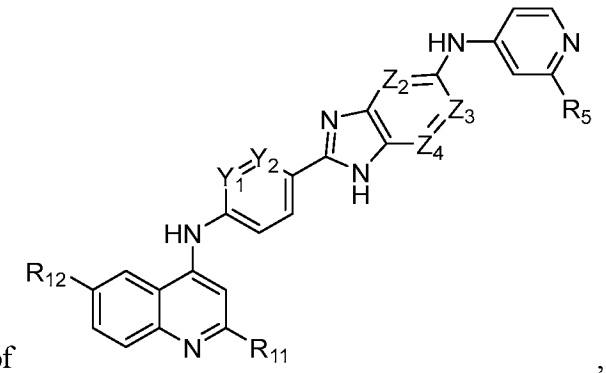
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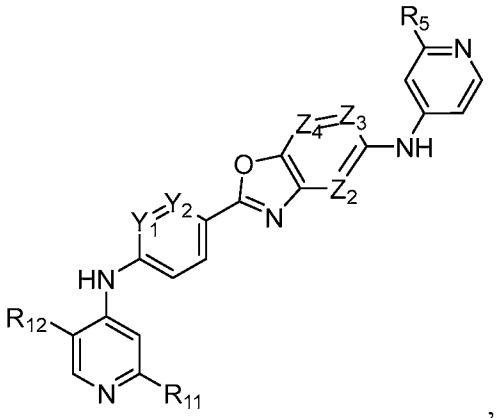

,

,

,

, or

, wherein R_1 is H, $(C_1\text{-}C_6)$alkyl, $N(R_a)_2$, $(C_3\text{-}C_7)$heterocycloalkyl, halogen, $(C_4\text{-}C_{14})$tricycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl, halogenated $(C_3\text{-}C_7)$heterocycloalkyl, $(C_4\text{-}C_{10})$heterobicycloalkyl, $(C_4\text{-}C_{14})$heterotricycloalkyl, $(C_4\text{-}C_{10})$heterospiroalkyl, $(C_3\text{-}C_7)$cycloalkenyl, $(C_3\text{-}C_7)$heterocycloalkenyl, $(C_4\text{-}C_{10})$bicycloalkenyl, $(C_4\text{-}C_{10})$heterobicycloalkenyl, $(C_4\text{-}C_{14})$tricycloalkenyl, or $(C_4\text{-}C_{14})$heterotricycloalkenyl; R_5 and R_{11} are each independently H, halogen, 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.

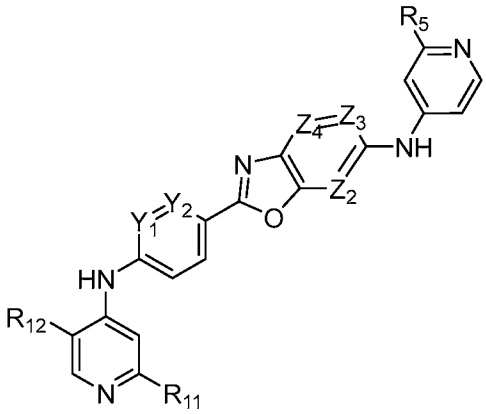
119. The compound of claim 118, wherein R_1 is H, F, Cl, Br, CH_3, CH_2CH_3, $CH(CH_3)_2$, NH_2, NMe_2,

,

, or

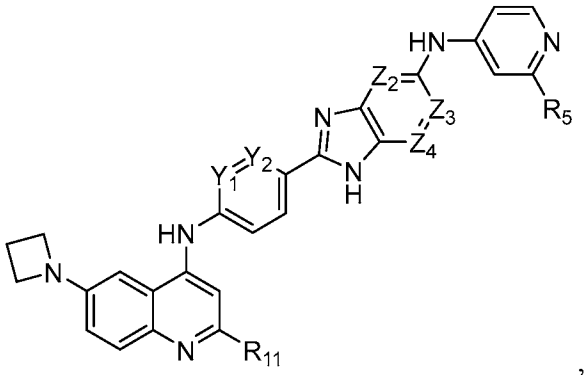
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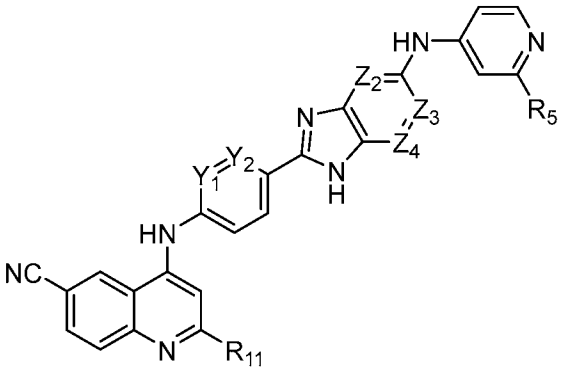
120. The compound of claim 118, wherein R_1 is , , , , , , , , , , , or .

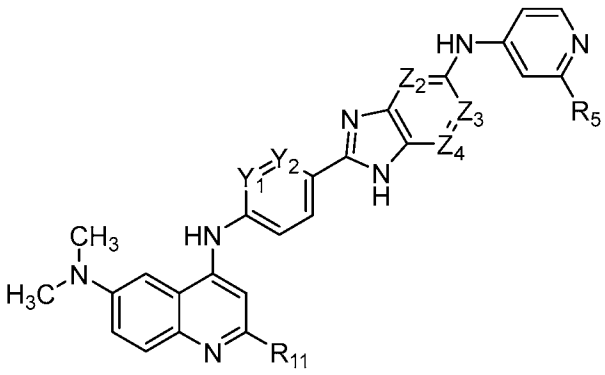
121. The compound of claim 1 or 80, wherein the compound of Formula Ib has the structure of ,

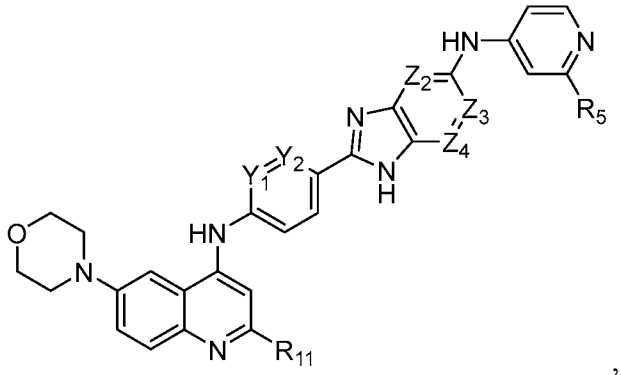
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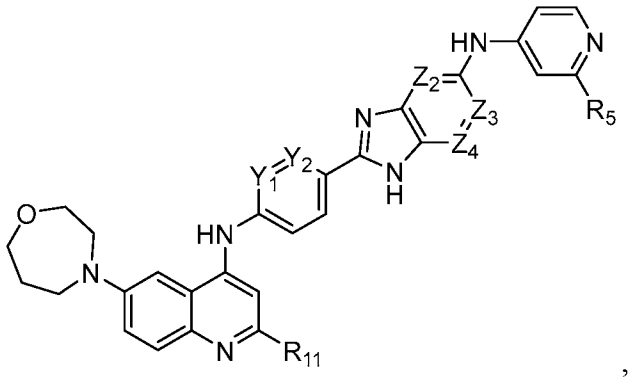
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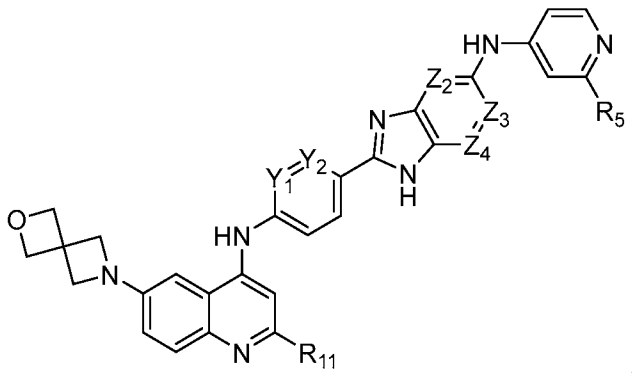
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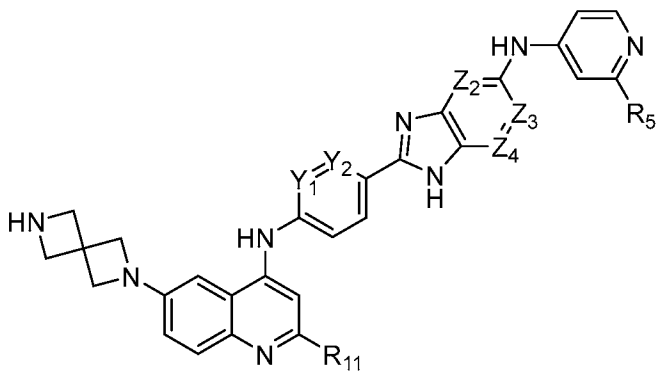
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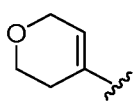
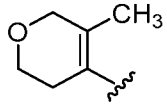


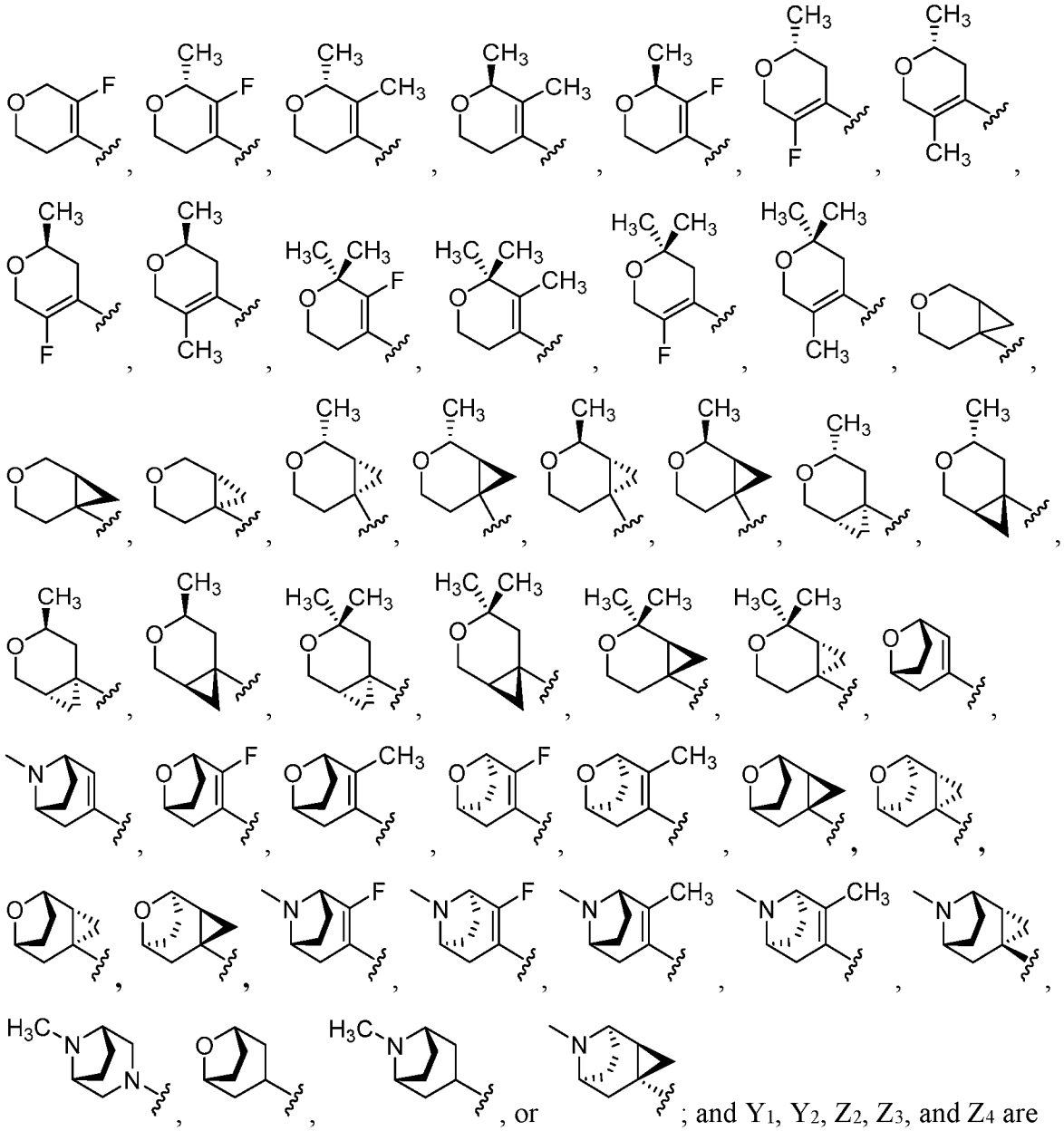
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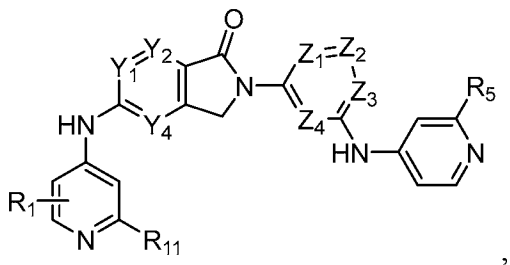


, wherein R_{11} and R_5 are each independently H, halogen, or CH_3; R_{12} is H, halogen, CH_3, , ,



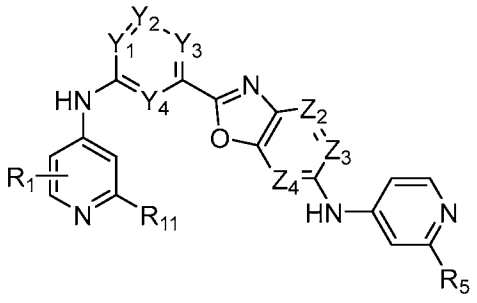
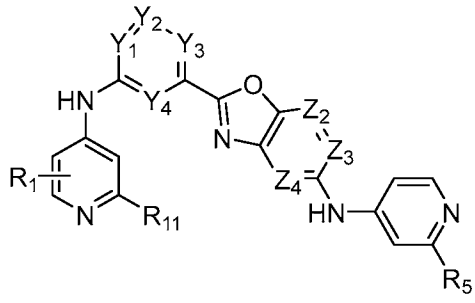
; and Y_1, Y_2, Z_2, Z_3, and Z_4 are each independently CH or N.

122. The compound of claim 1, wherein the compound of Formula IIa has the structure of

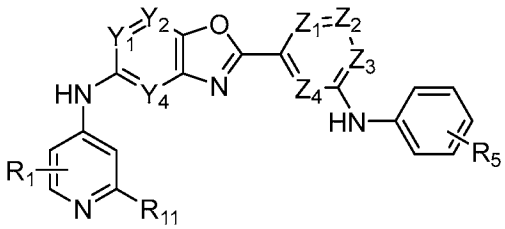
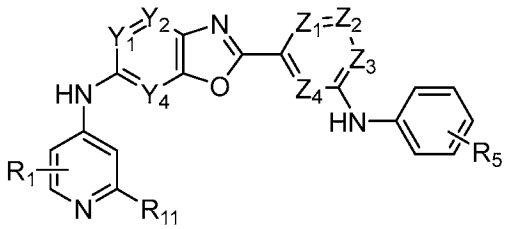


, wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_4, Z_1, Z_2, Z_3, and Z_4 are each independently CH or N.

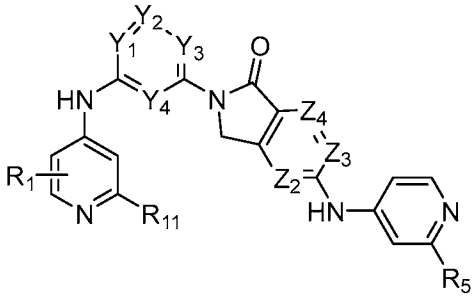
123. The compound of claim 1, wherein the compound of Formula IIb has the structure of


or

, wherein R_1, R_5, and R_{11} are each independently H, halogen, 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.

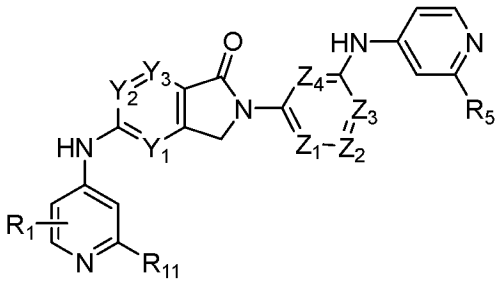
124. The compound of claim 1, wherein the compound of Formula IIc has the structure of


or

, wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_4, Z_1, Z_2, Z_3, and Z_4 are each independently CH or N.

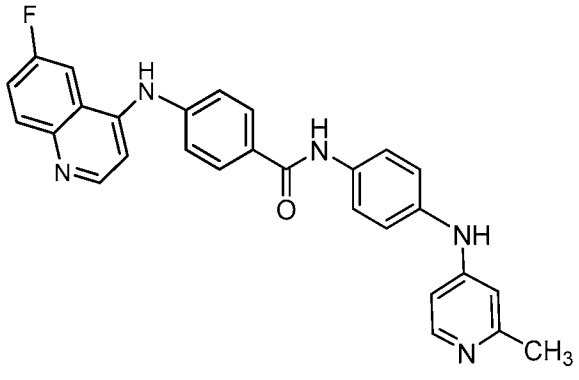
125. The compound of claim 1, wherein the compound of Formula IIIa has the structure of

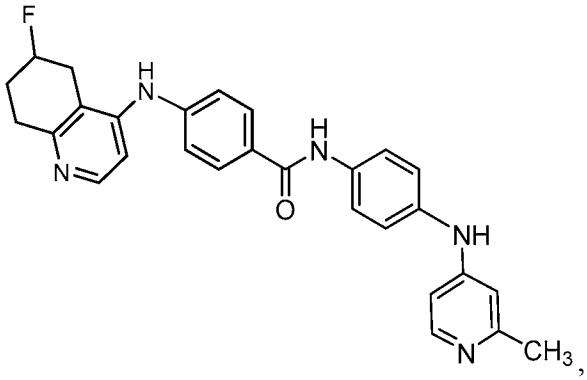

, wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_3, Y_4, Z_2, Z_3, and Z_4 are each independently CH or N.

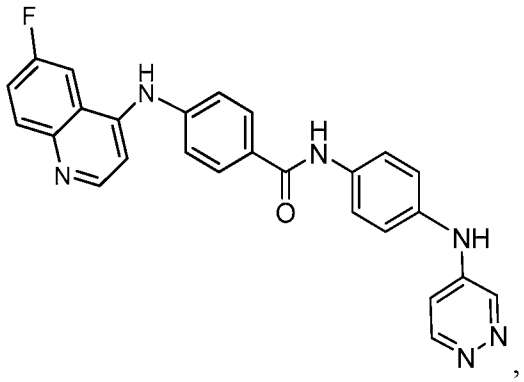
126. The compound of claim 1, wherein the compound of Formula IVa has the structure of

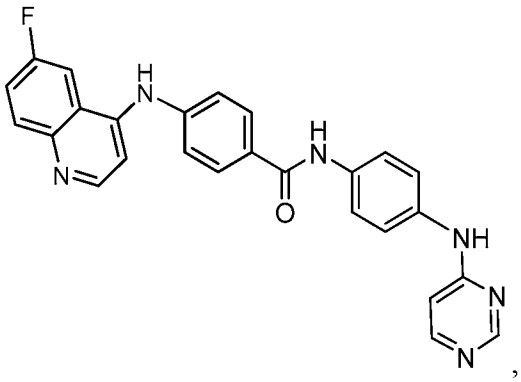

, wherein R_1, R_5, and R_{11} are each independently H, halogen, or CH_3; and Y_1, Y_2, Y_3, Z_1, Z_2, Z_3, and Z_4 are each independently CH or N.

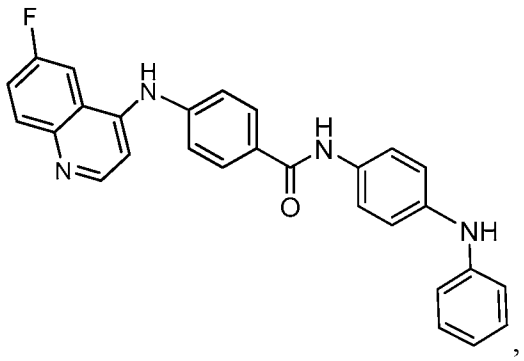
127. The compound of claim 1, wherein the compound of Formula Ia is

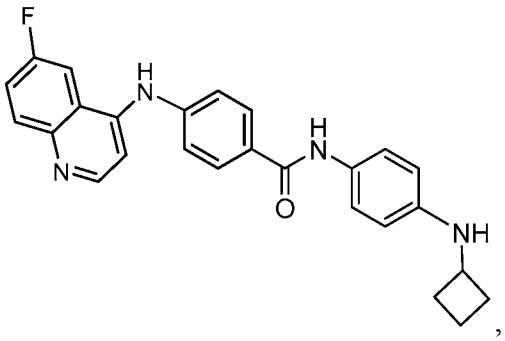

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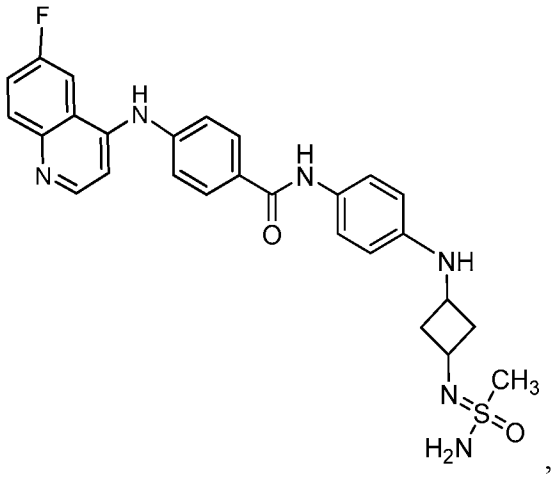

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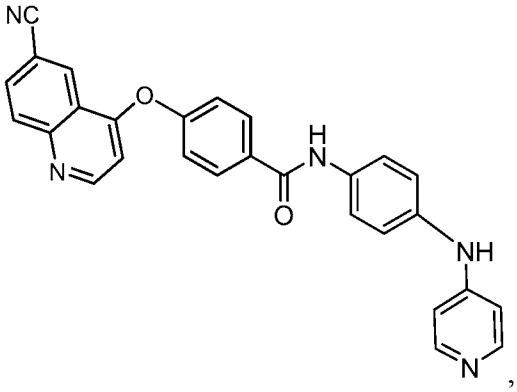

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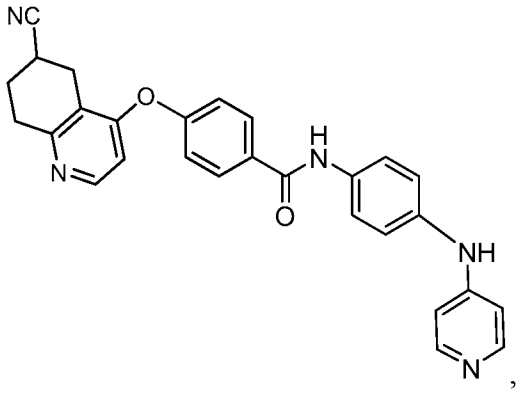

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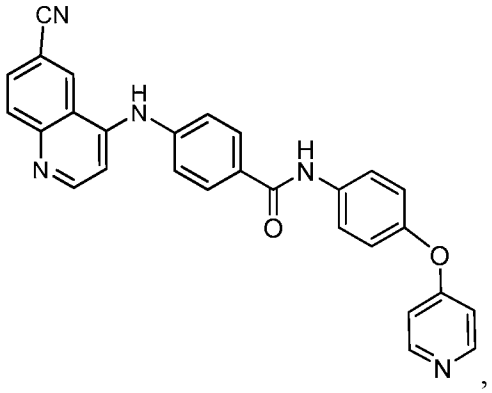

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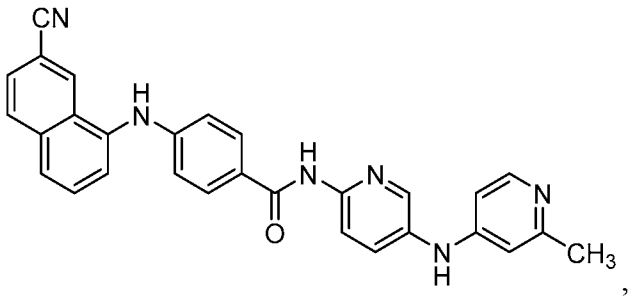

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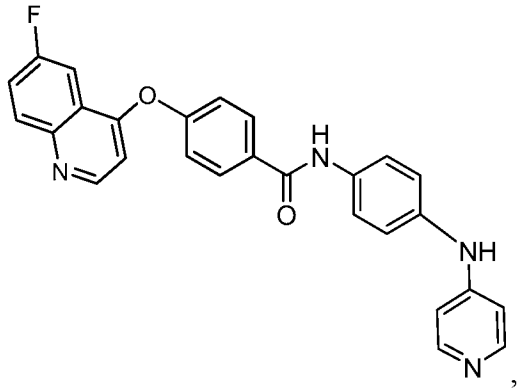

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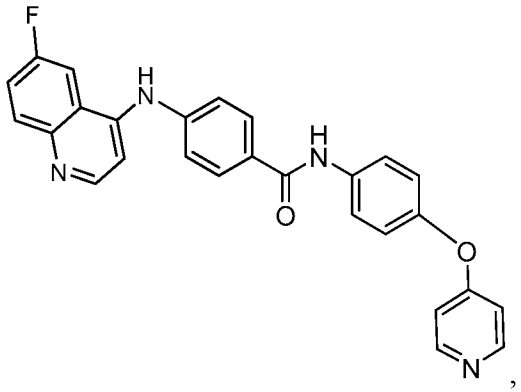

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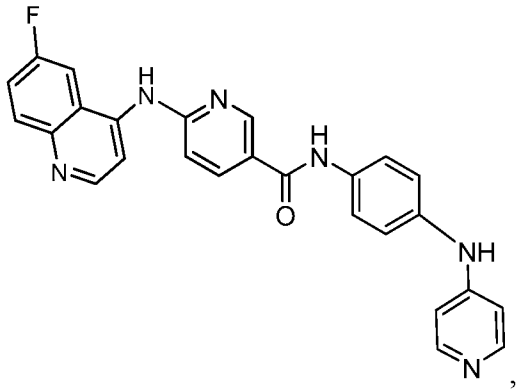


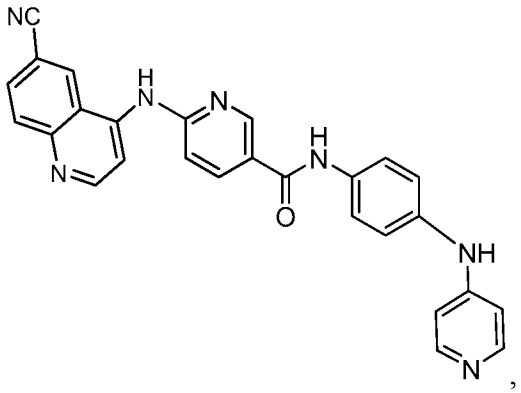


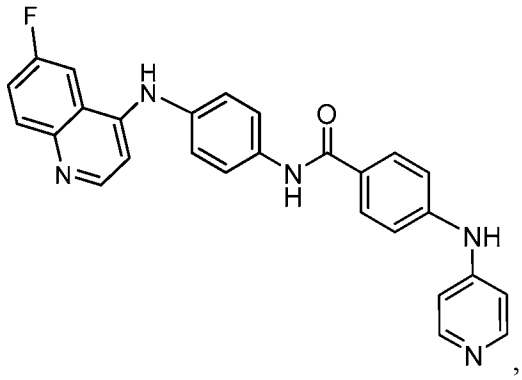


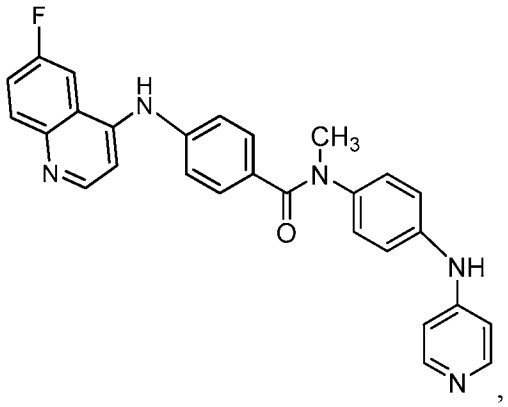


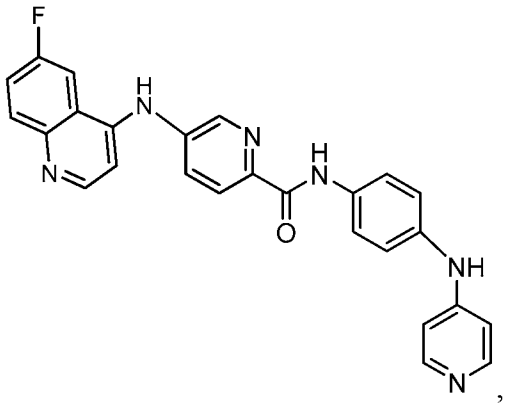


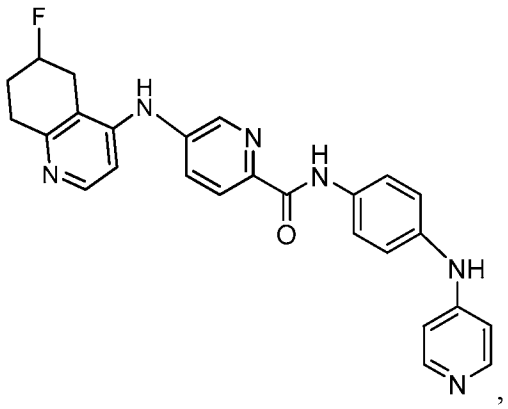


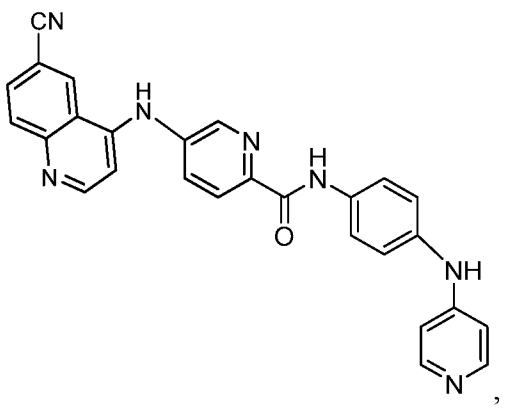


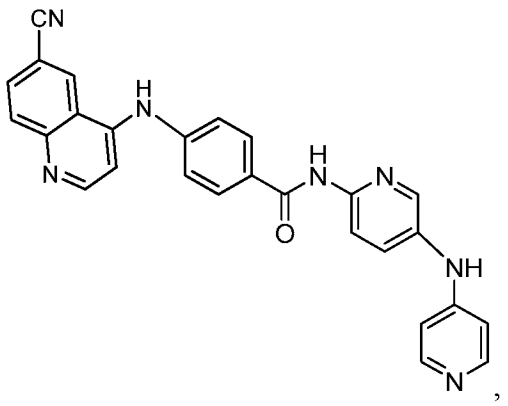


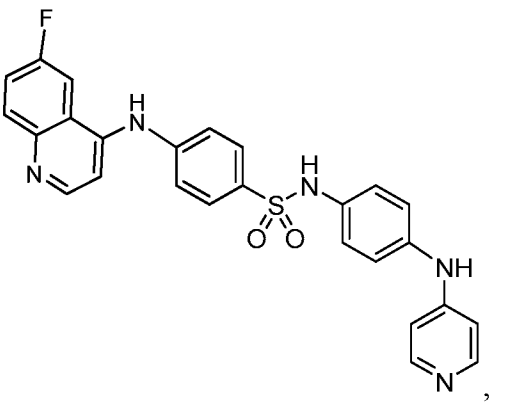


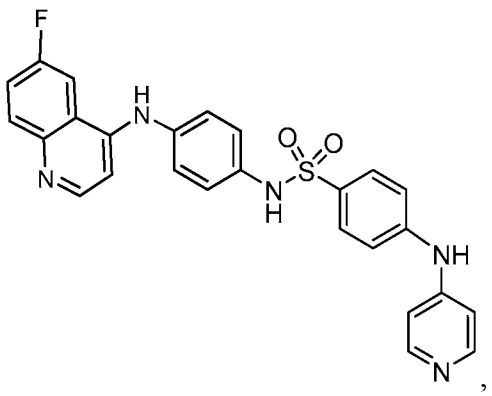


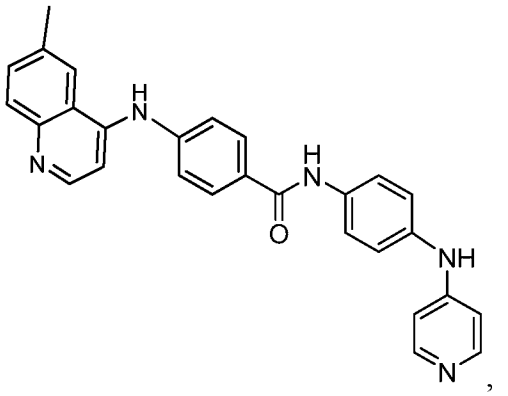


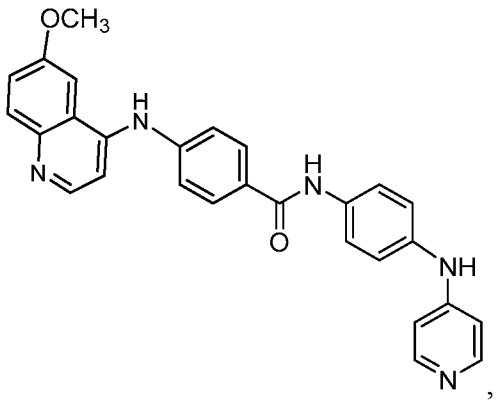


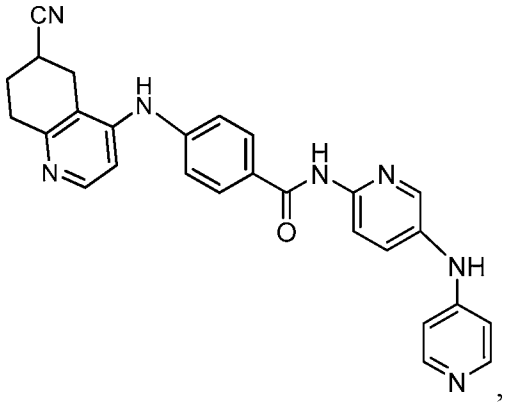


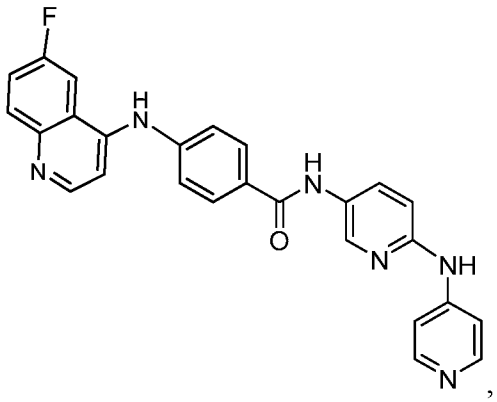


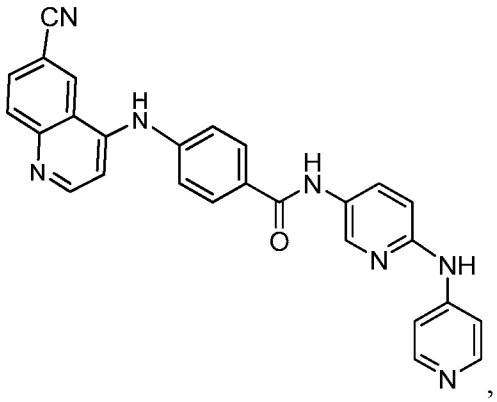


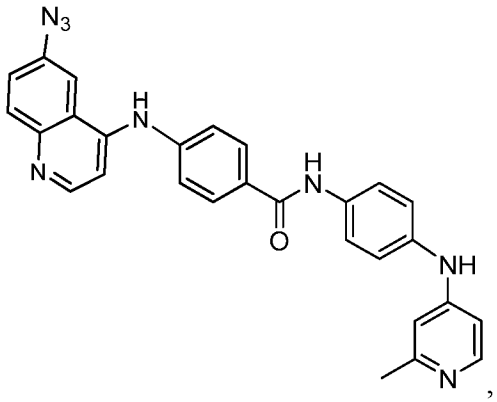


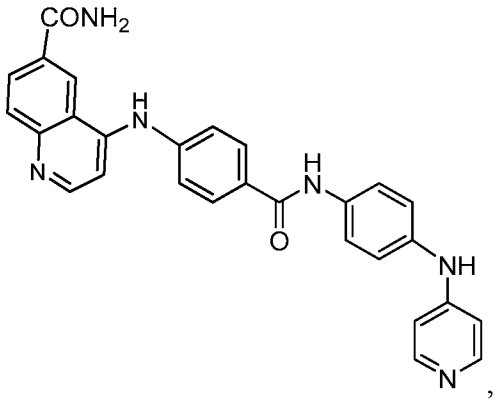

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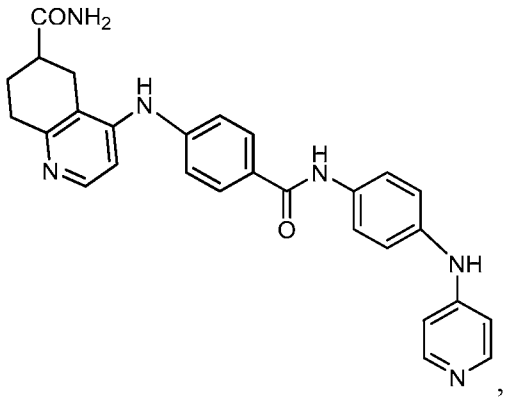

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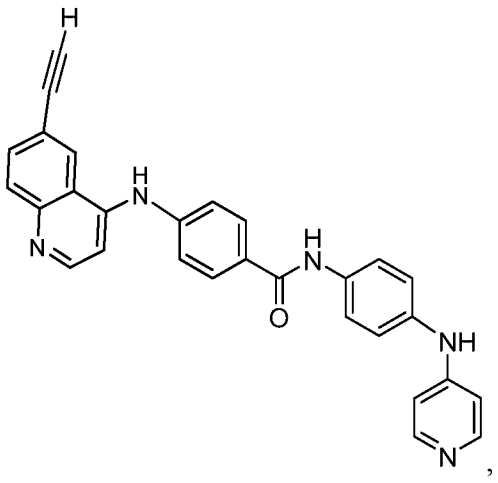

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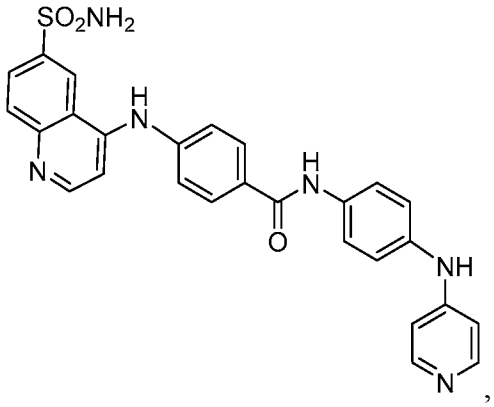

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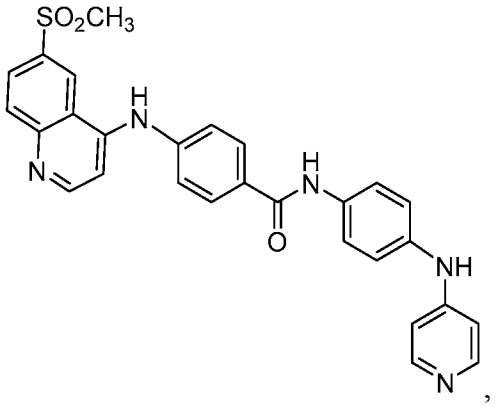

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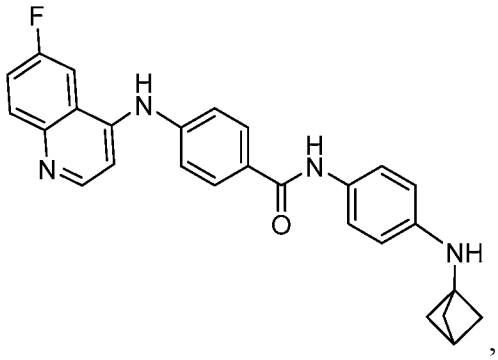

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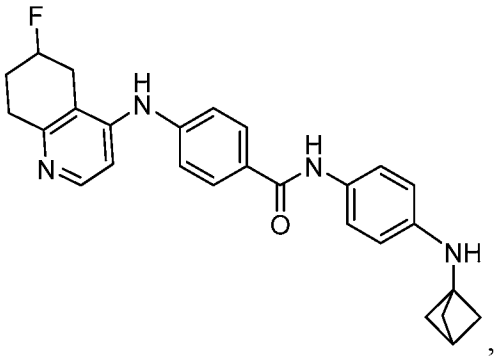

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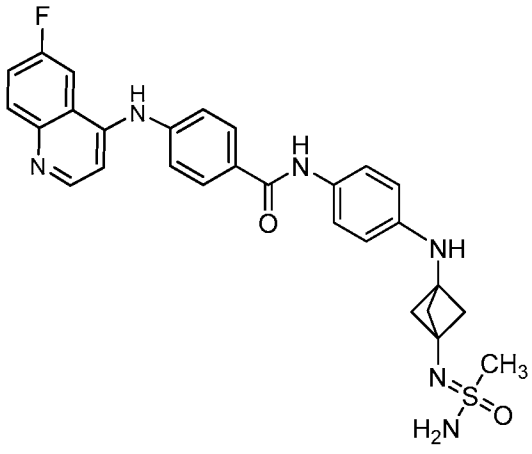

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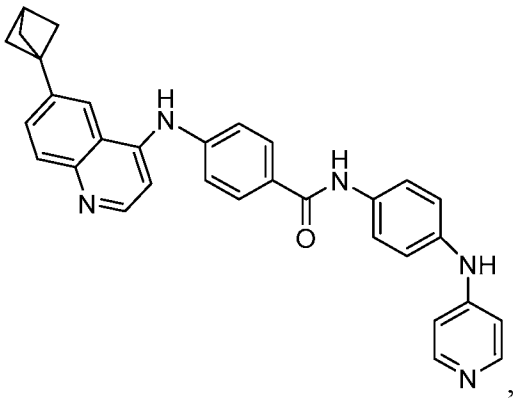

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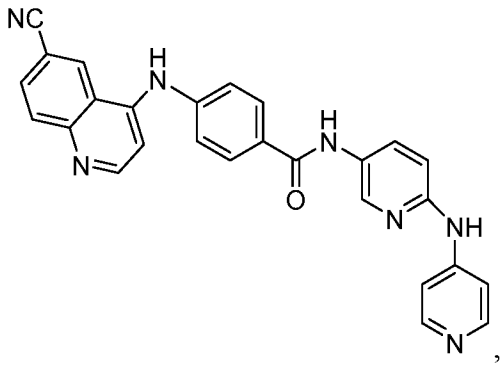

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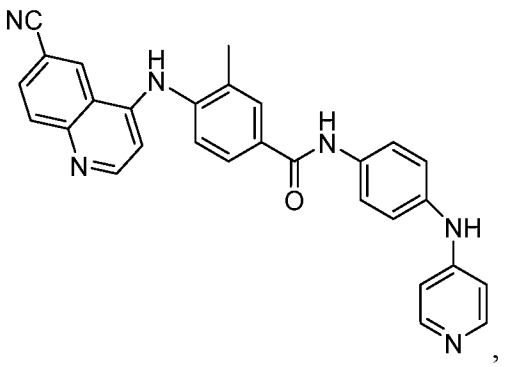

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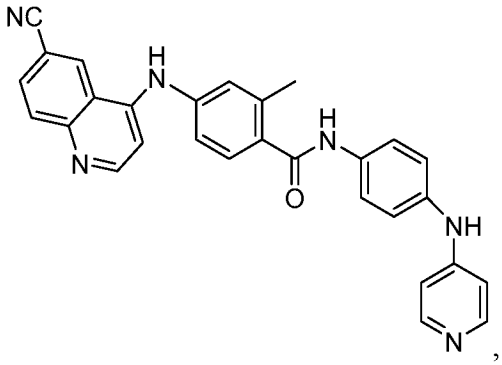
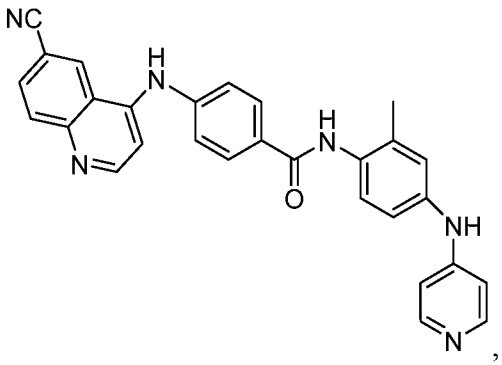
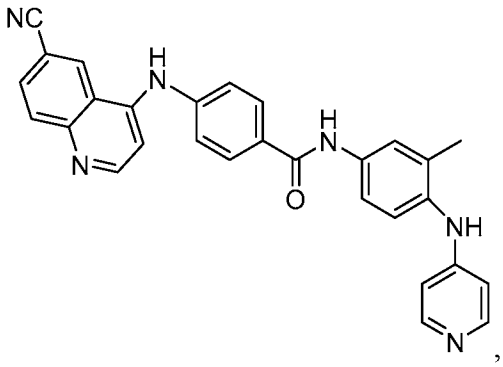
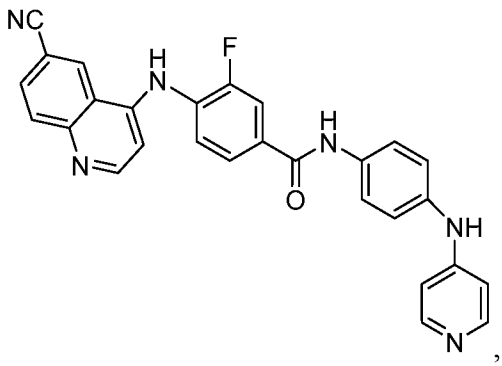
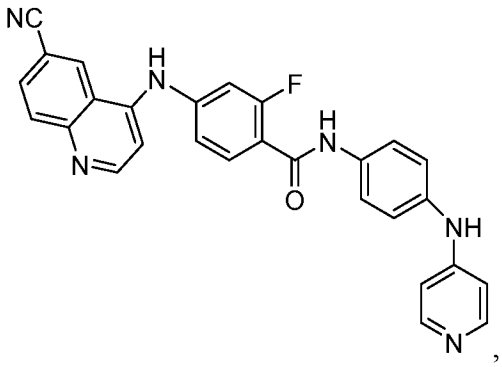
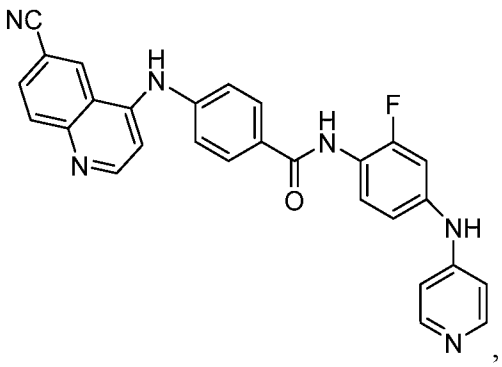
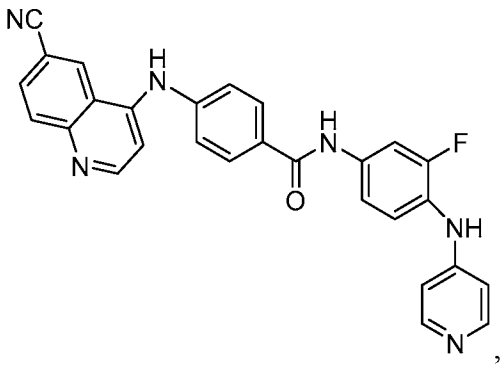
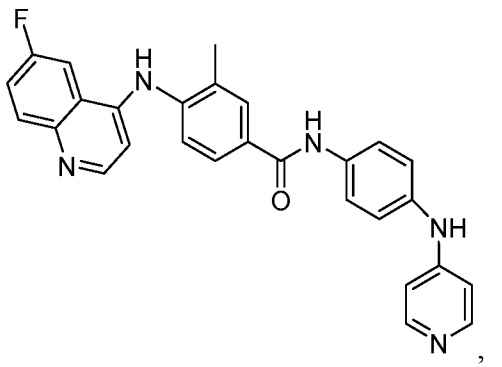

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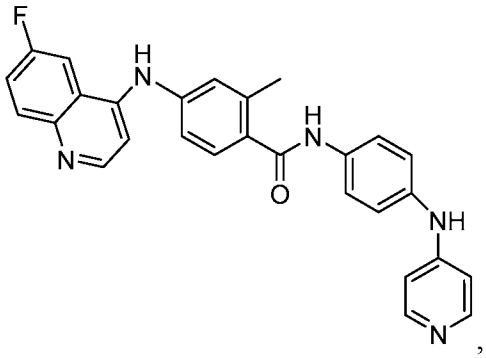
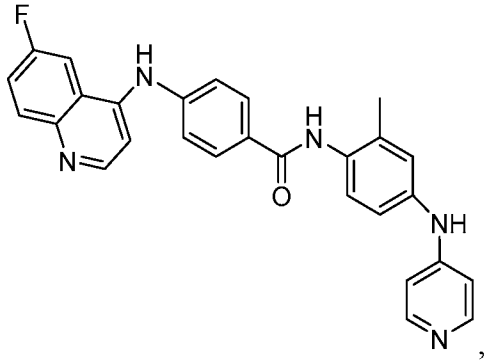
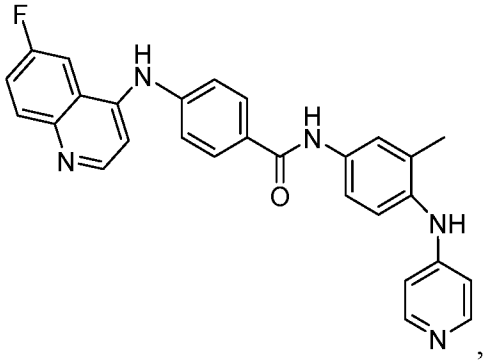
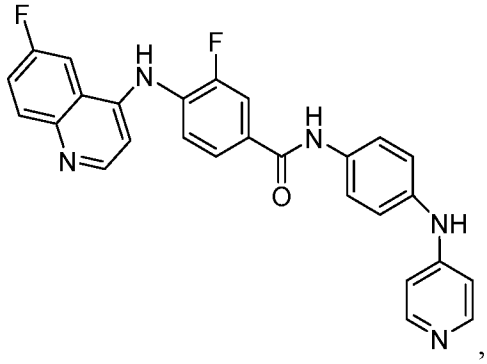
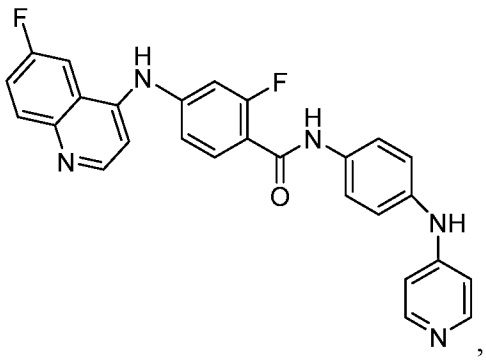
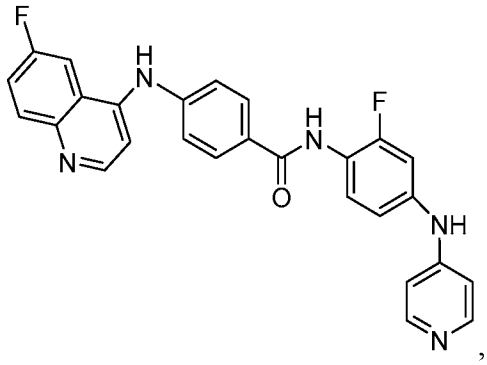
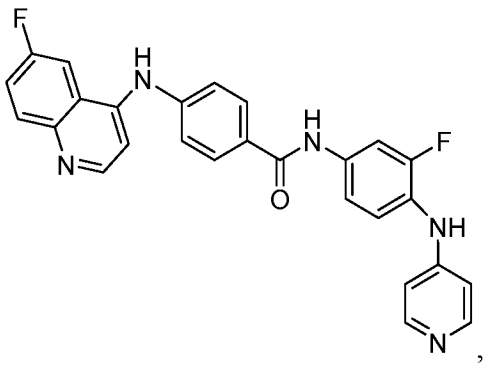
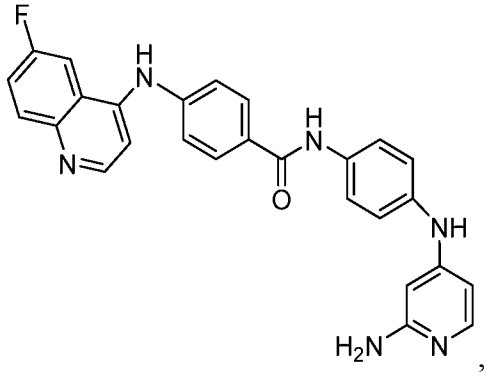

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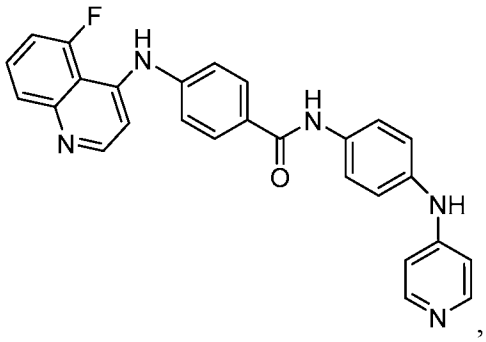

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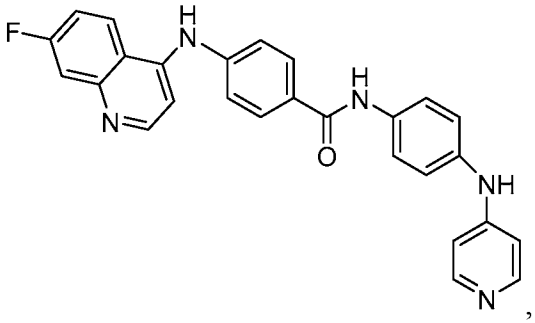

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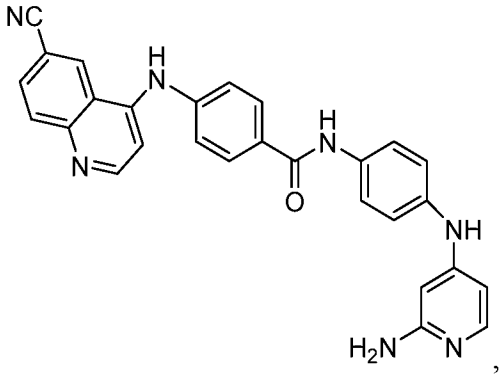

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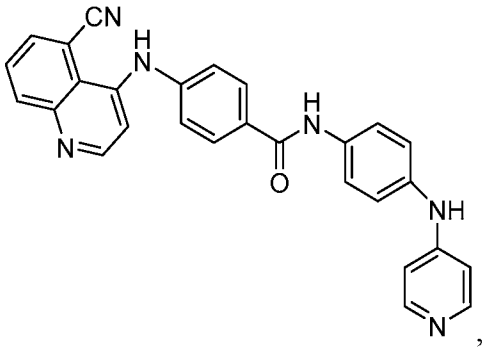

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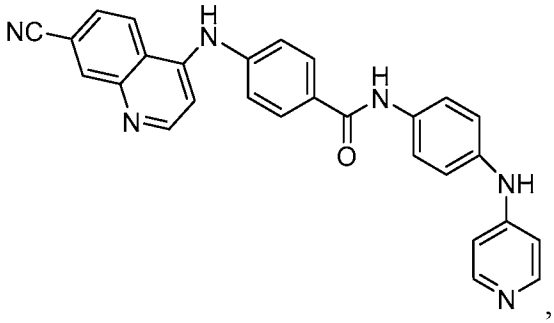

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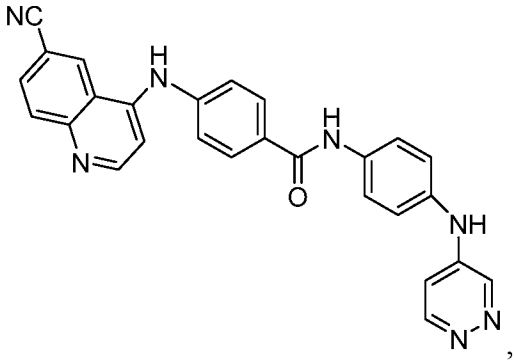


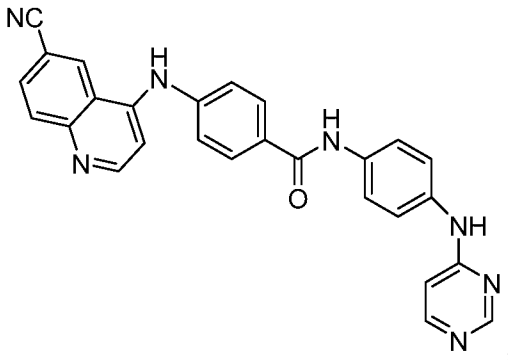


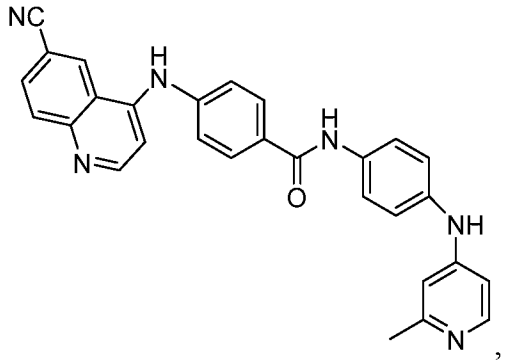
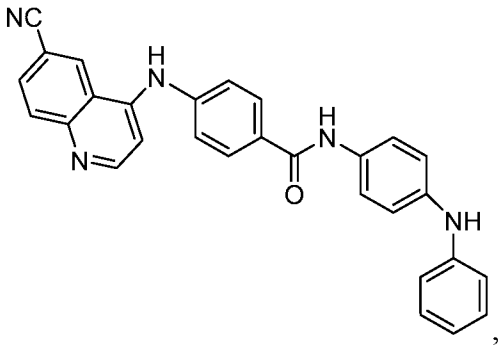
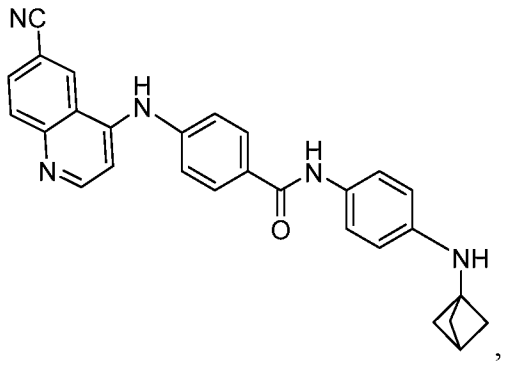
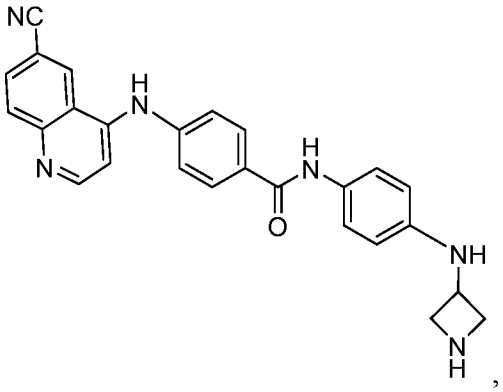
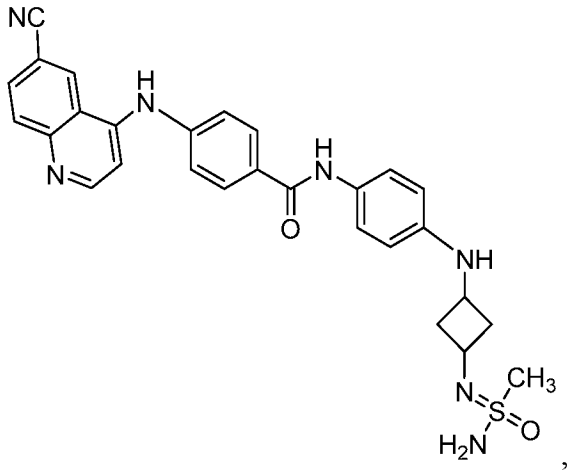
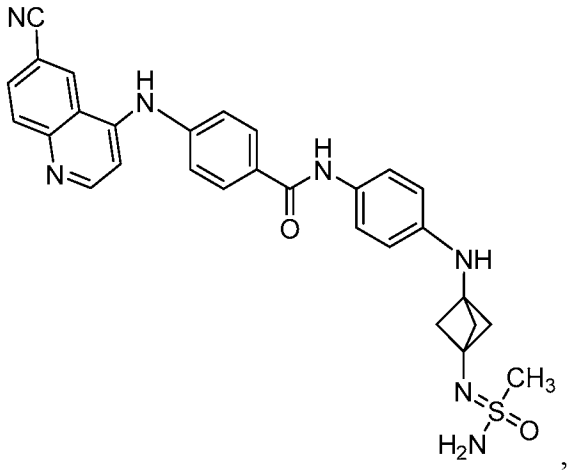
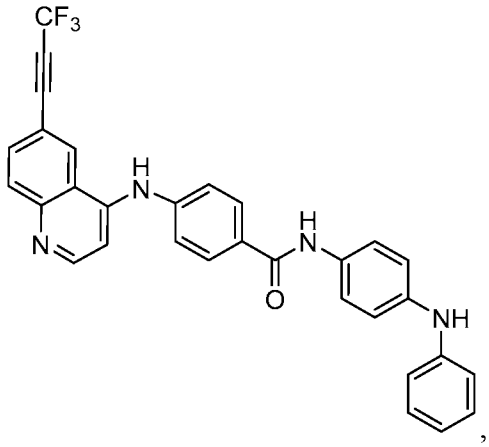
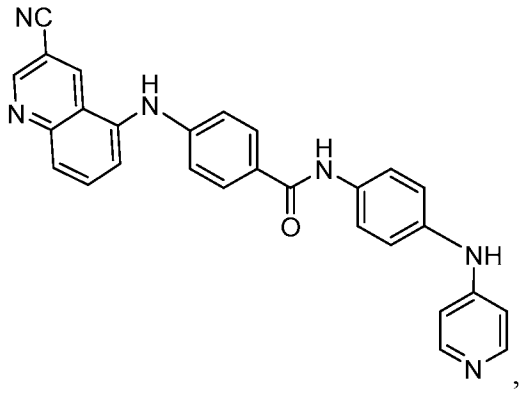


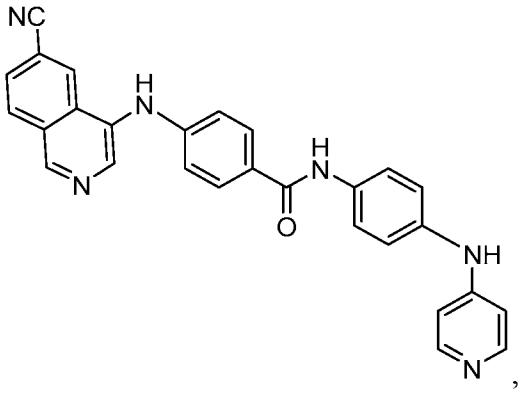


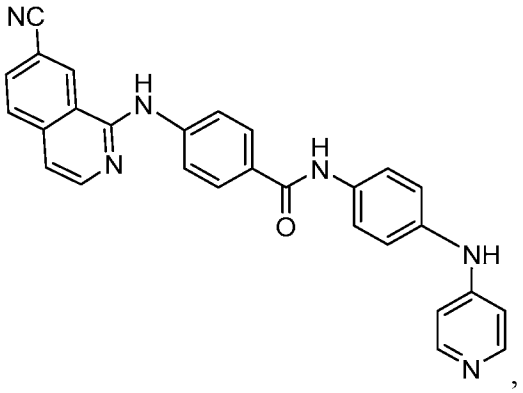


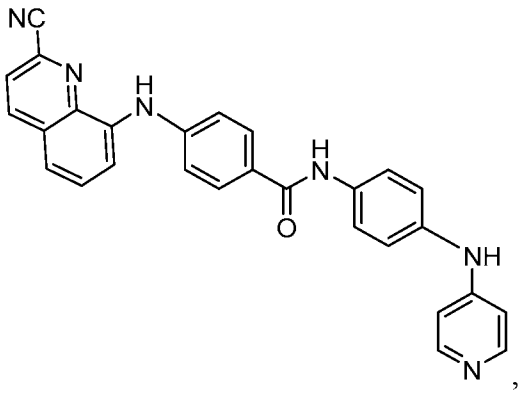


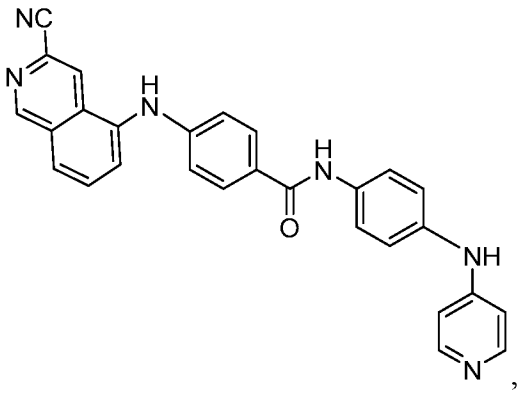


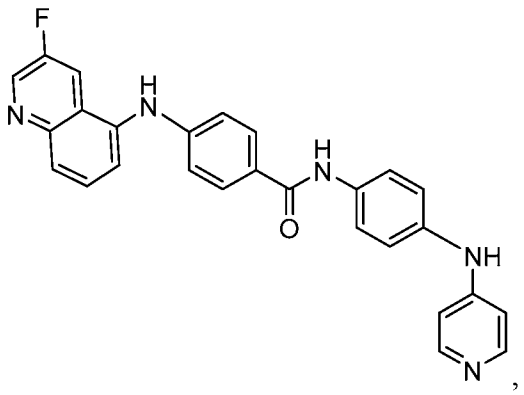

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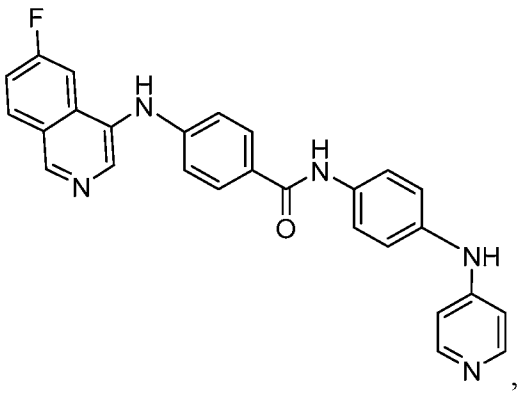


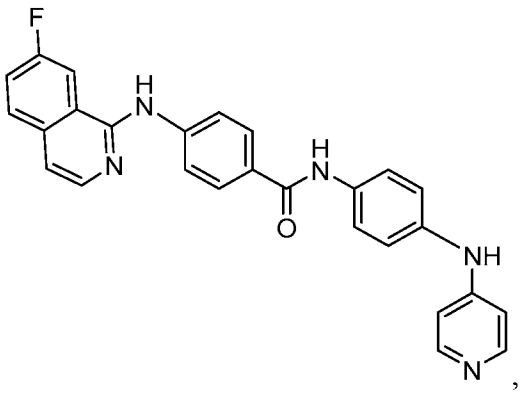


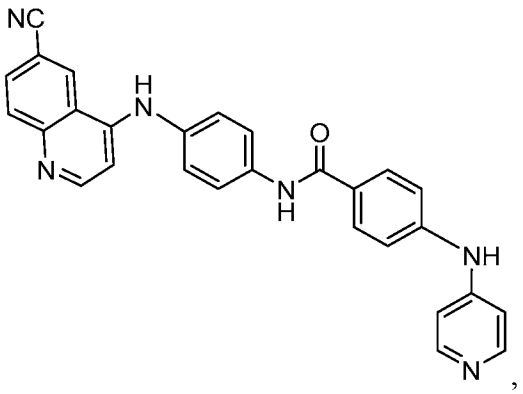


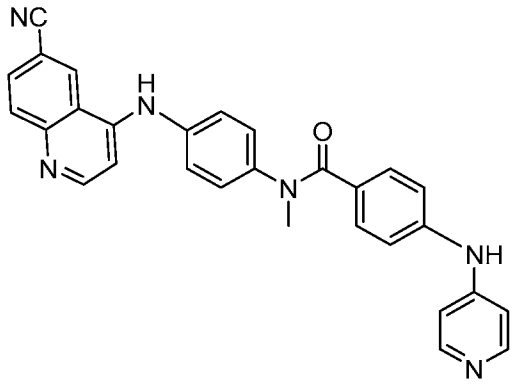


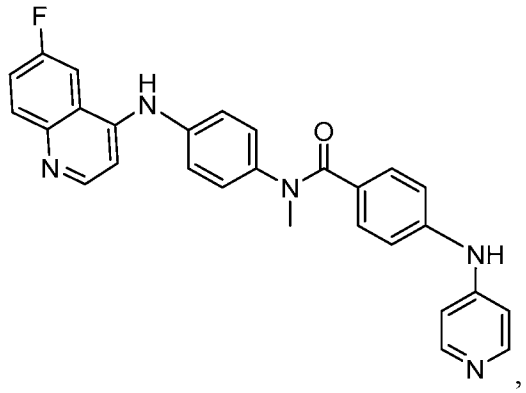


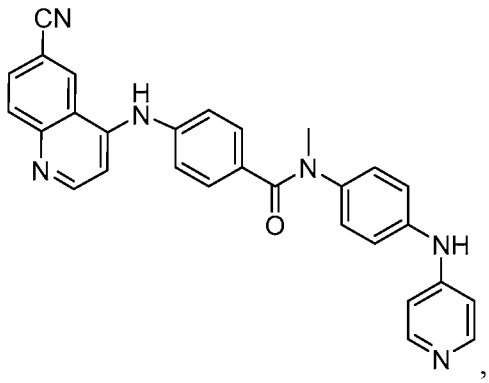


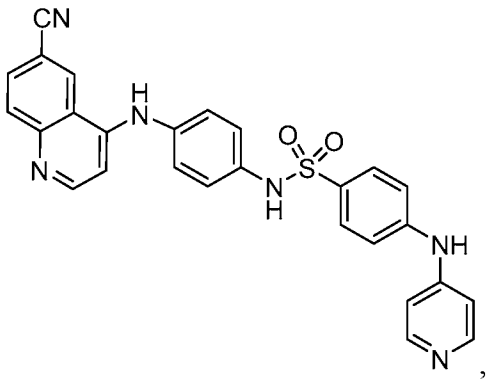


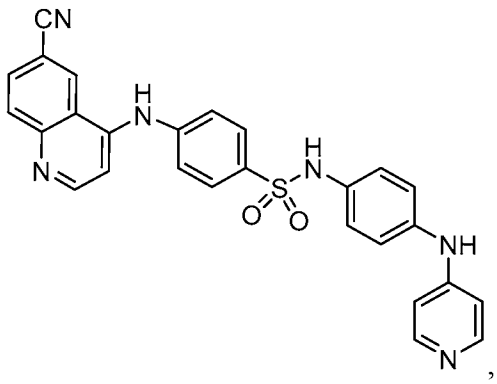


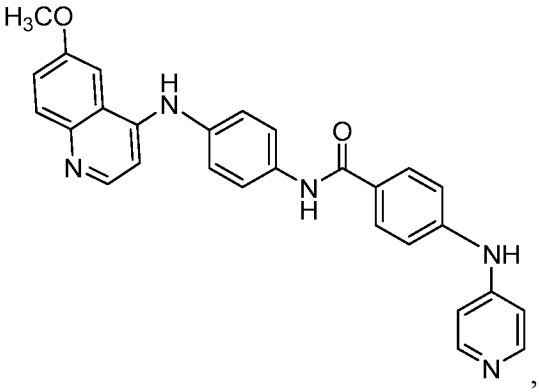


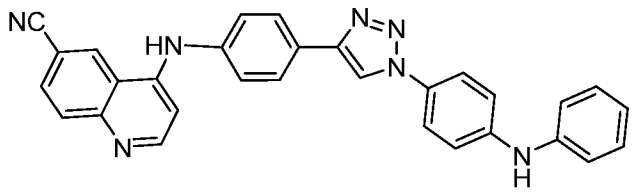


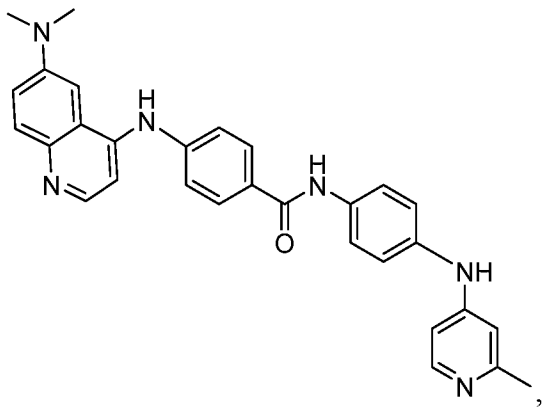


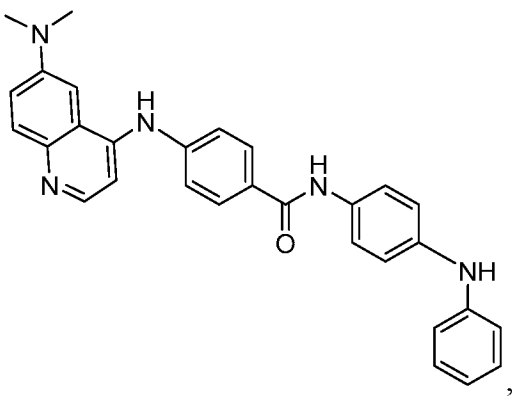


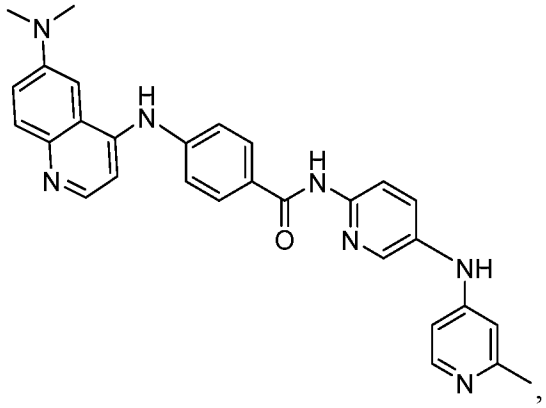


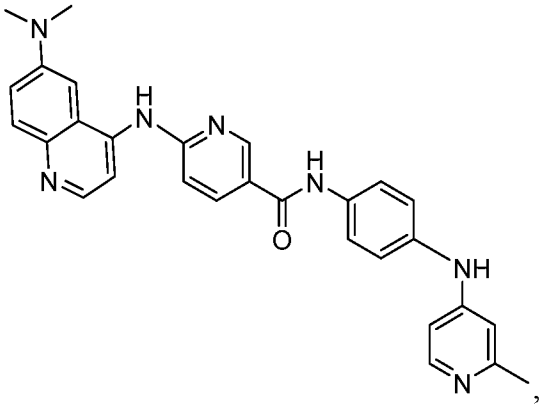


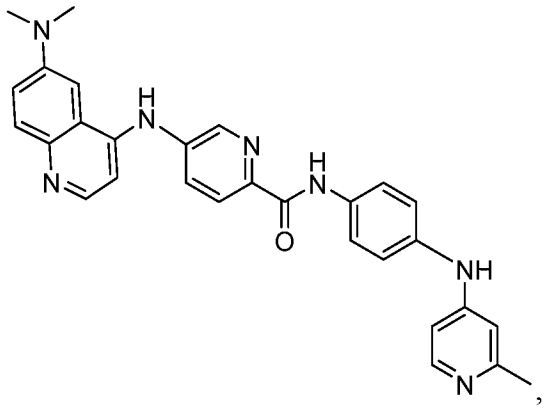


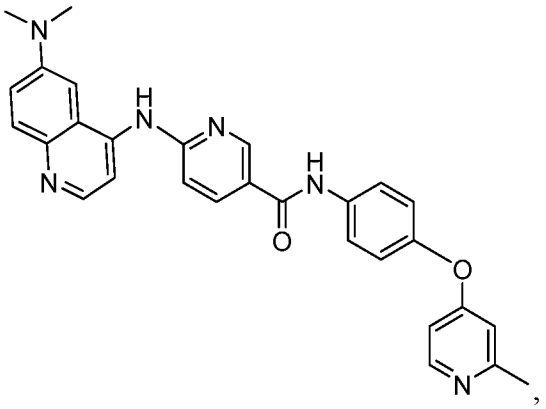


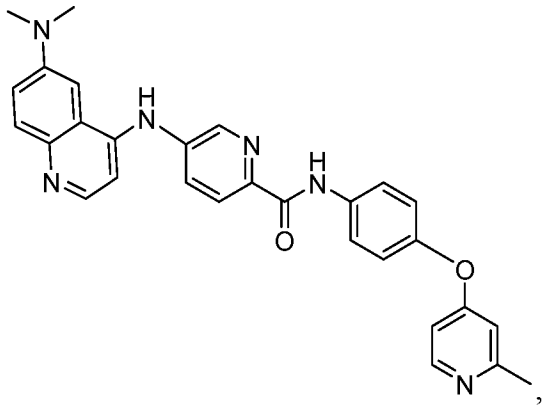


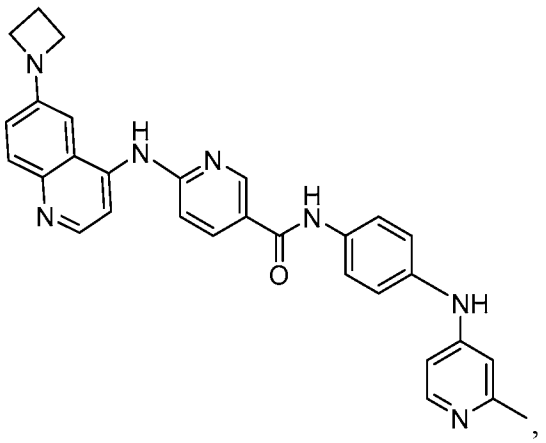


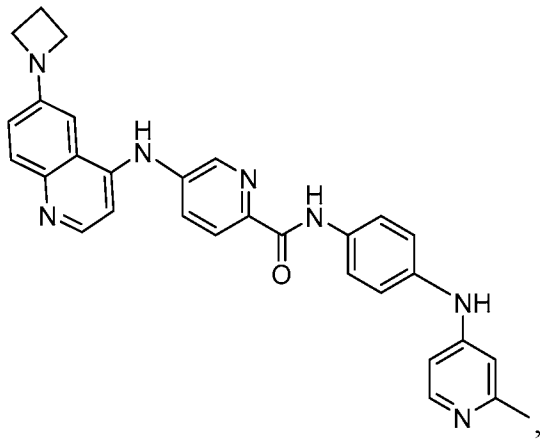


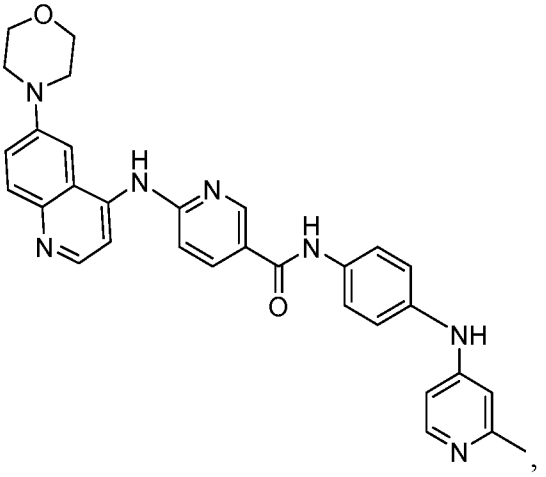


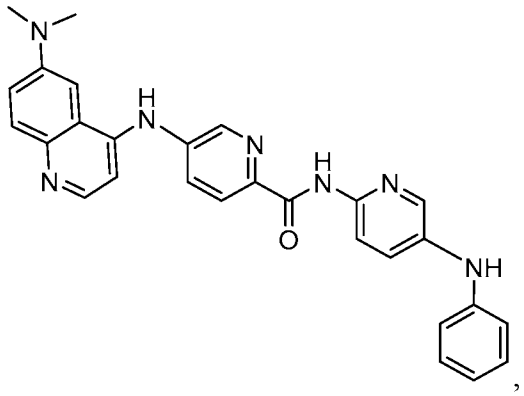


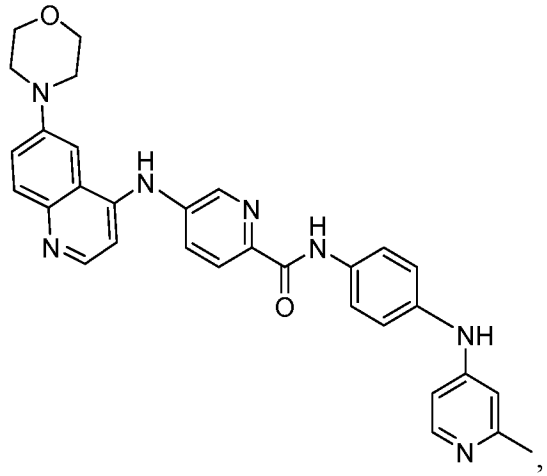


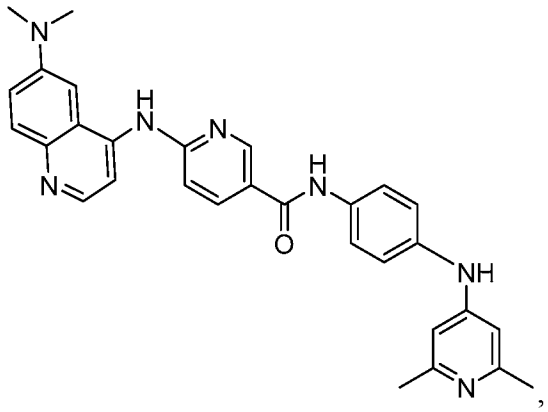


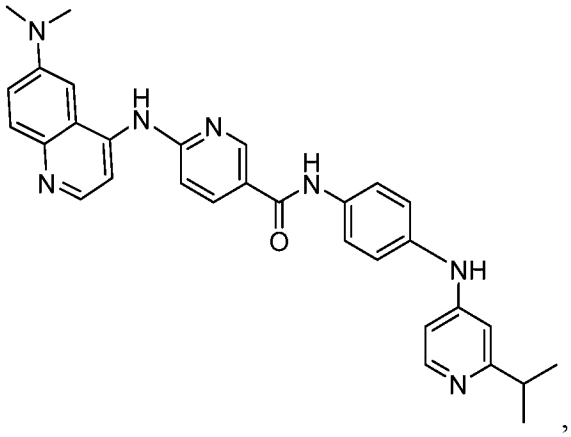


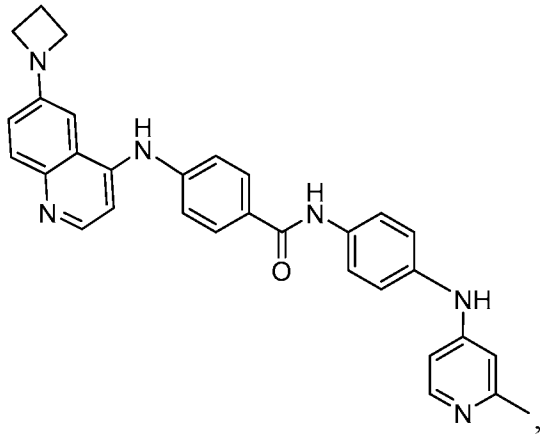


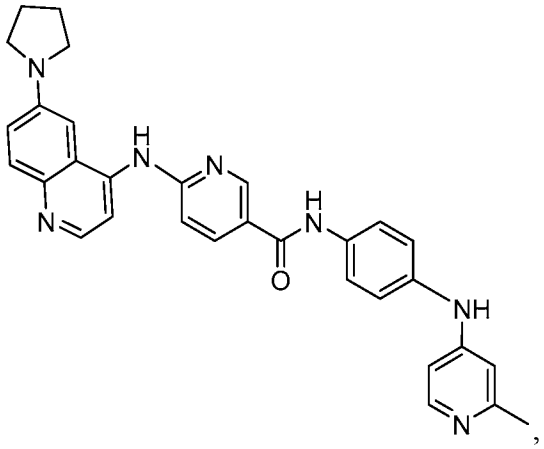


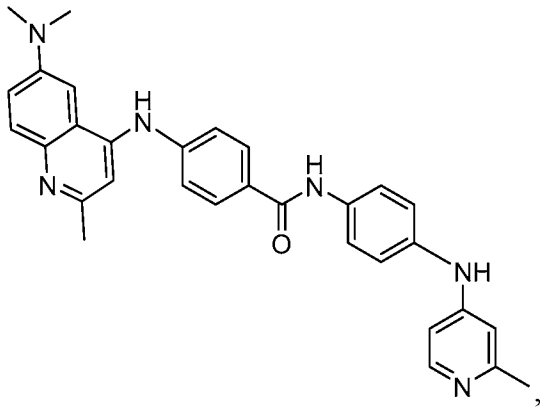


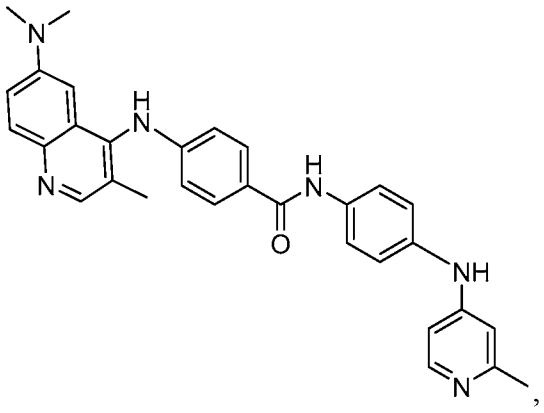


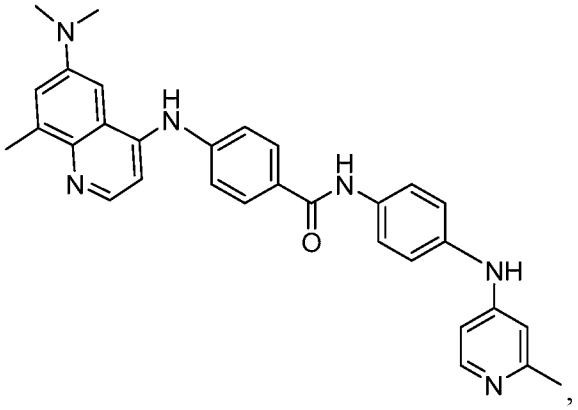


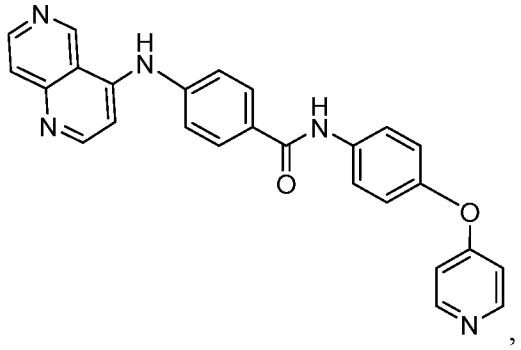


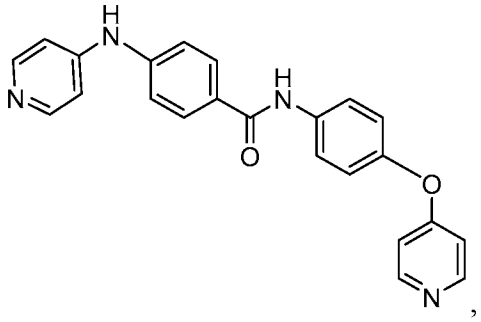


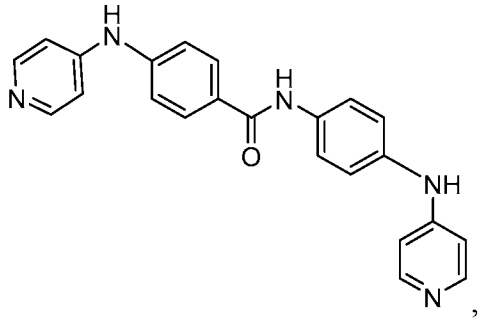


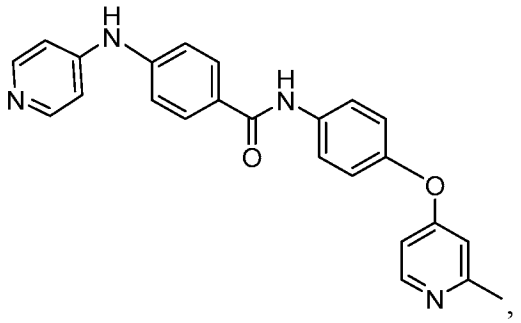


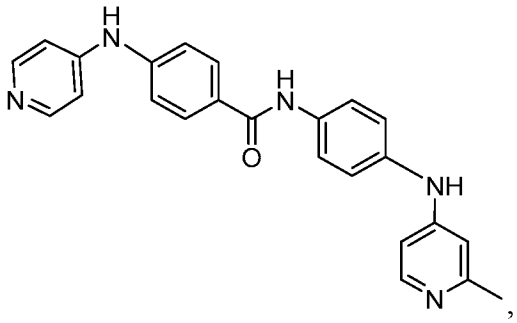


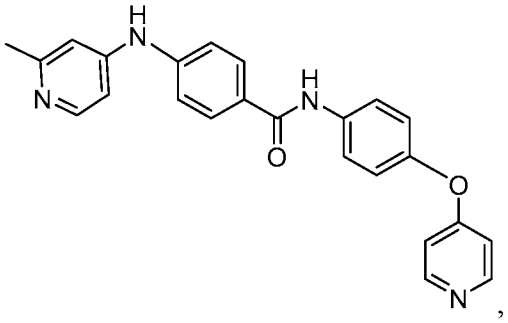


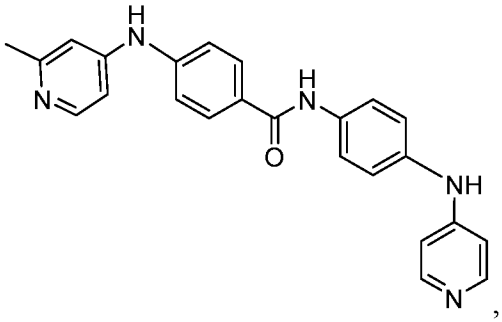


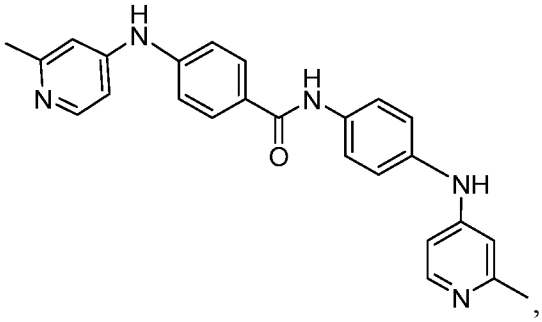


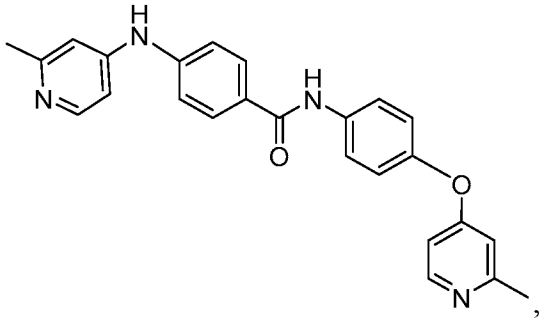


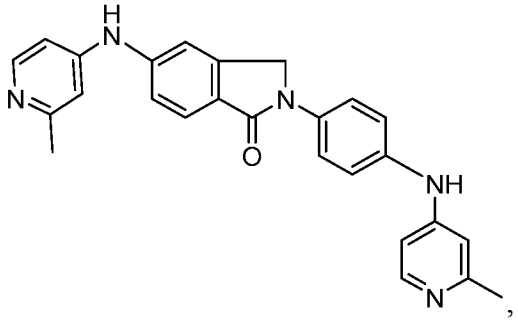


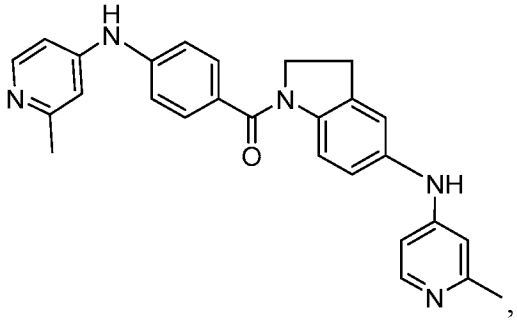


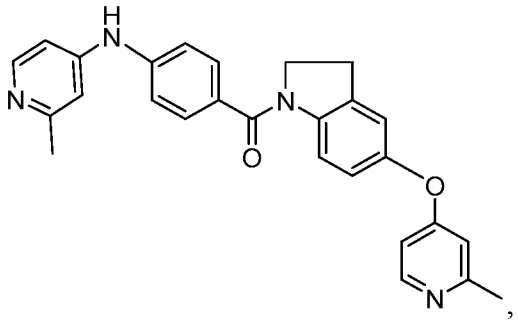


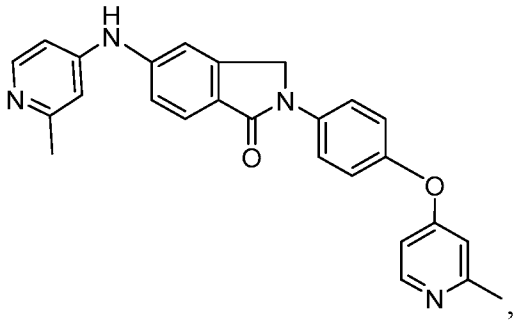


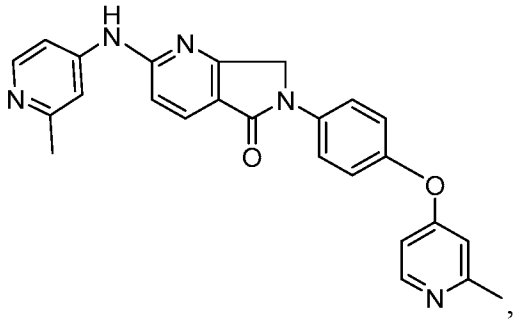


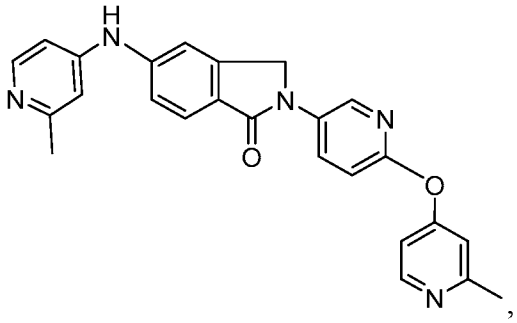


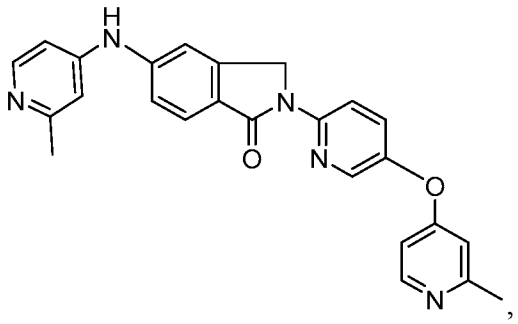


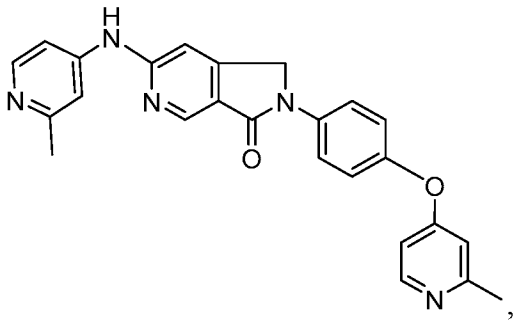


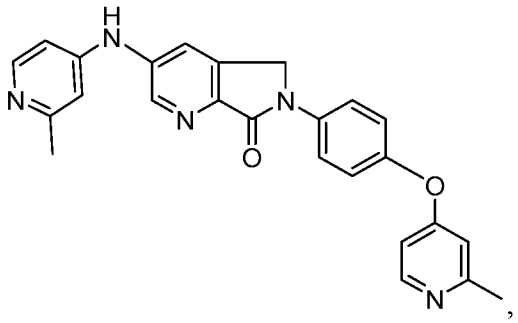


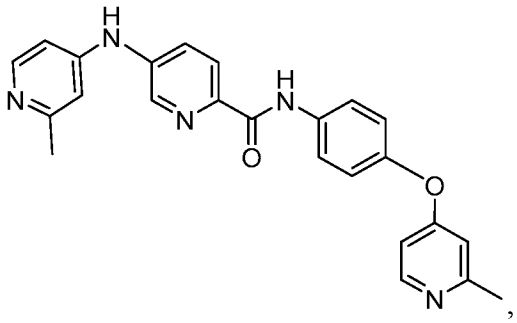


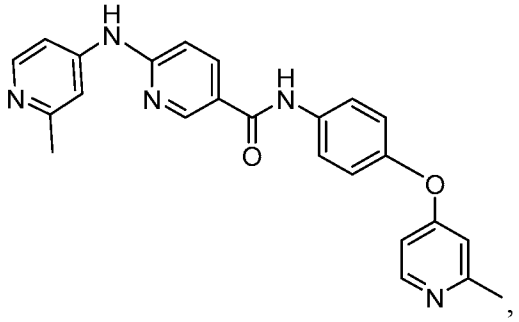
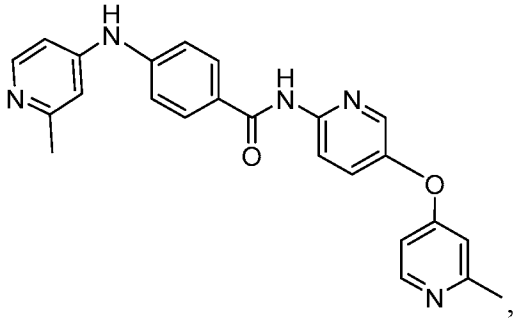
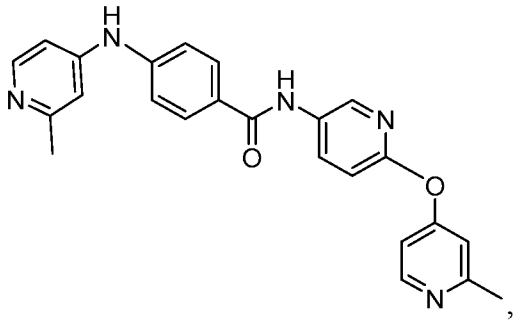
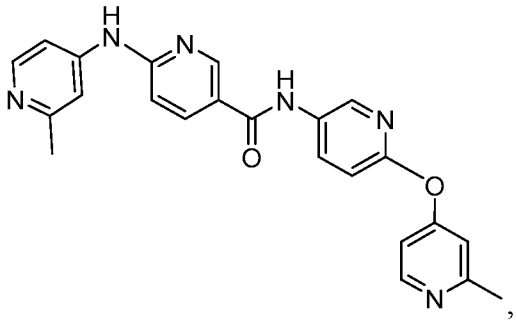
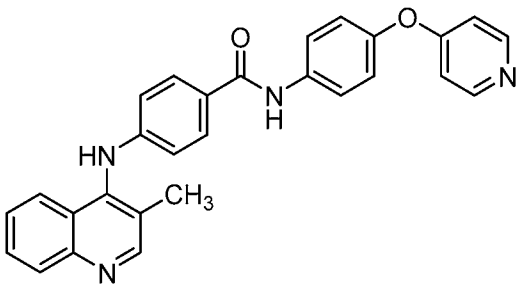
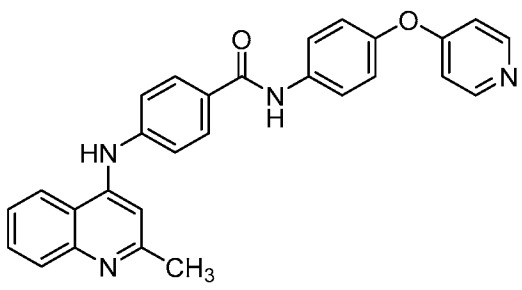
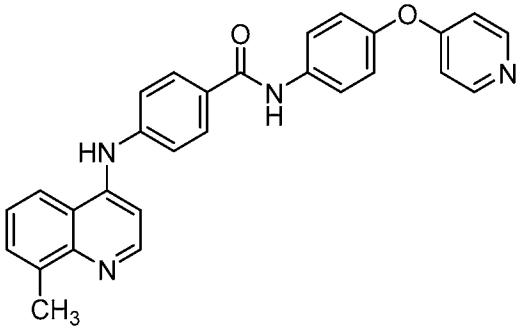
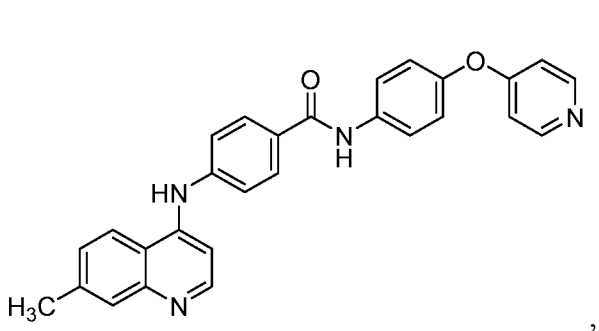
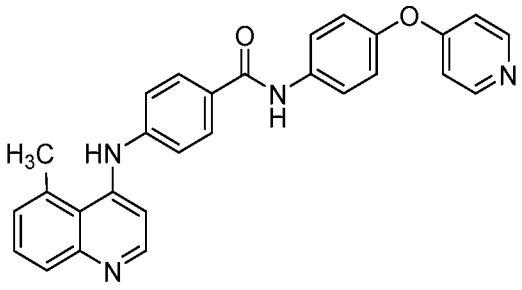
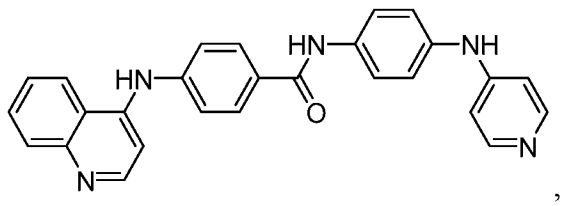


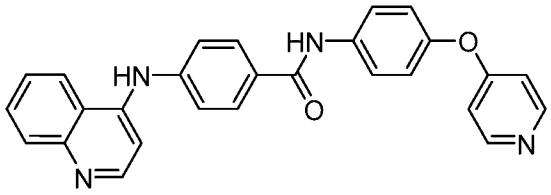
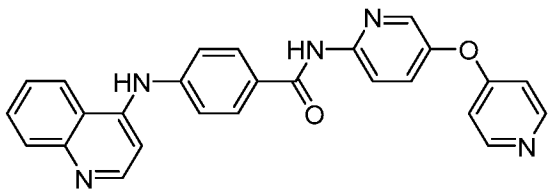
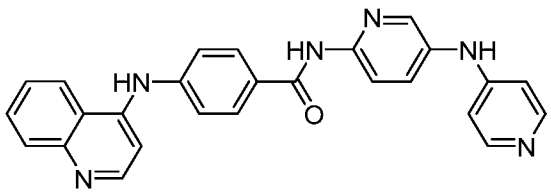
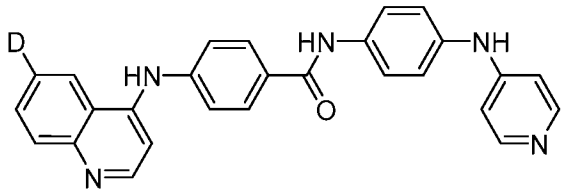
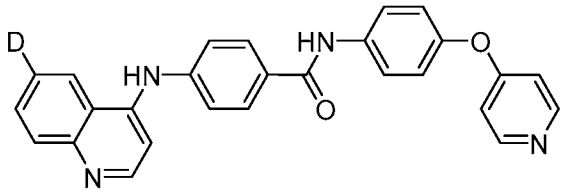
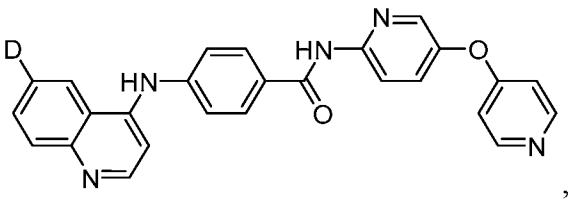
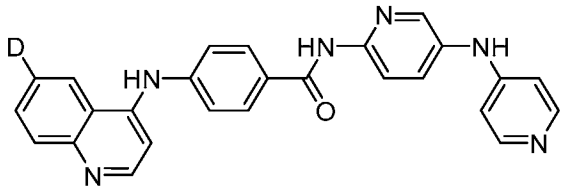
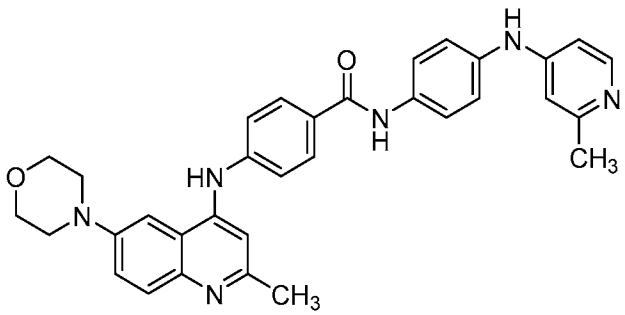
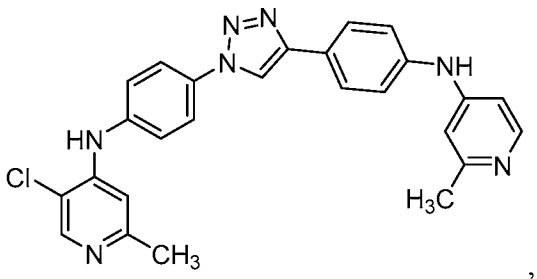
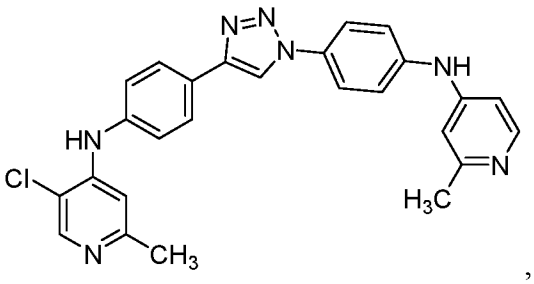
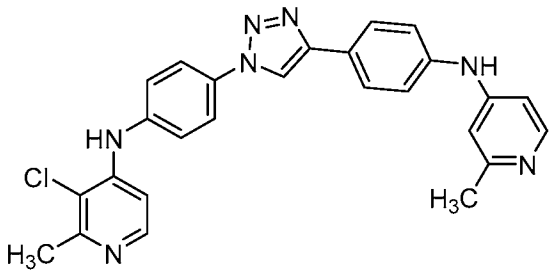
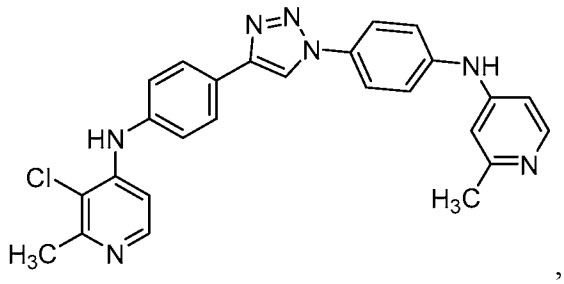


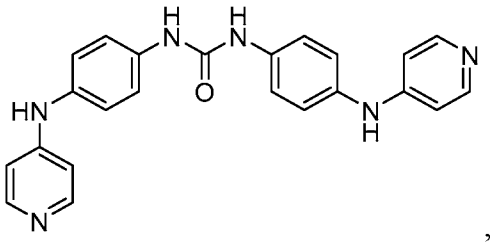
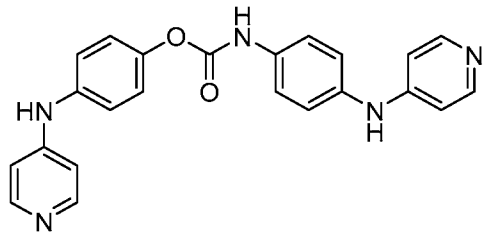
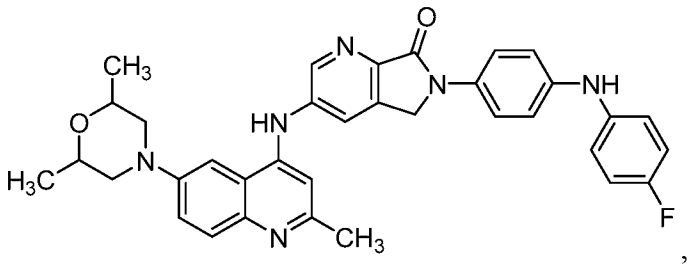
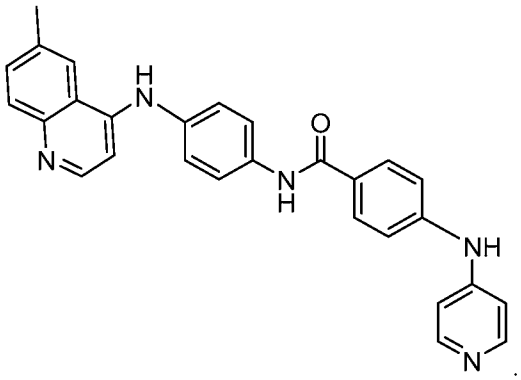




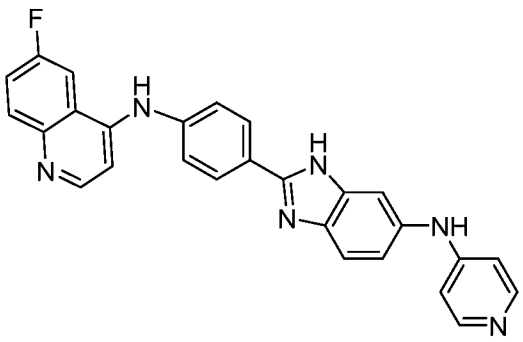
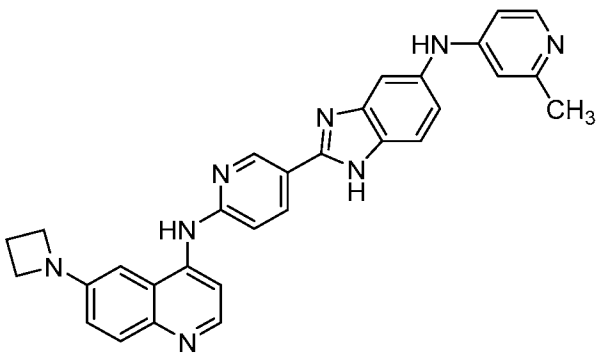
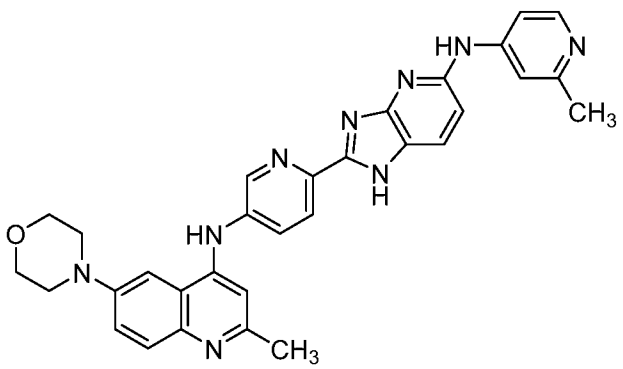


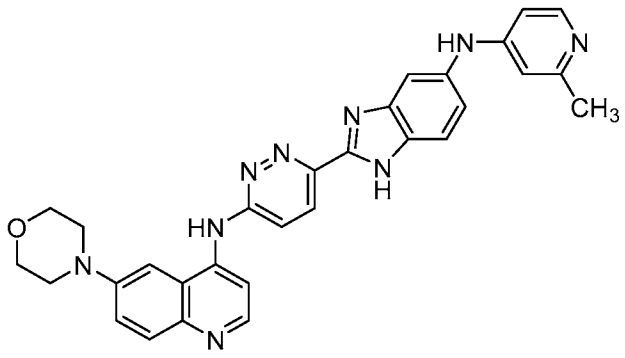

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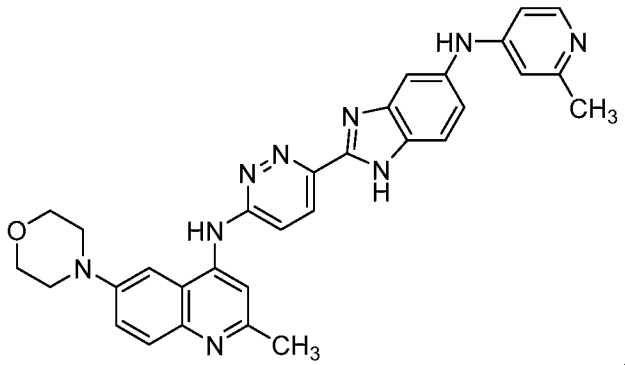

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128. The compound of claim 1, wherein the compound of Formula Ib is

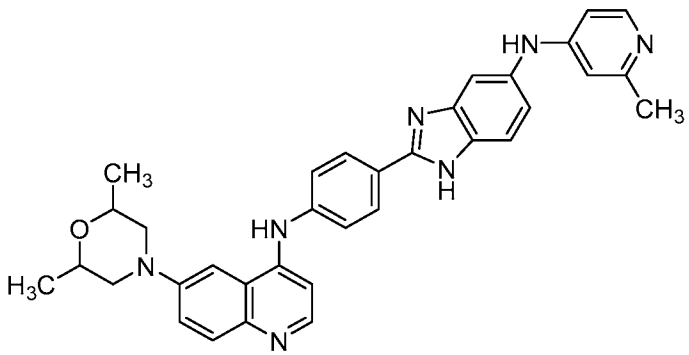

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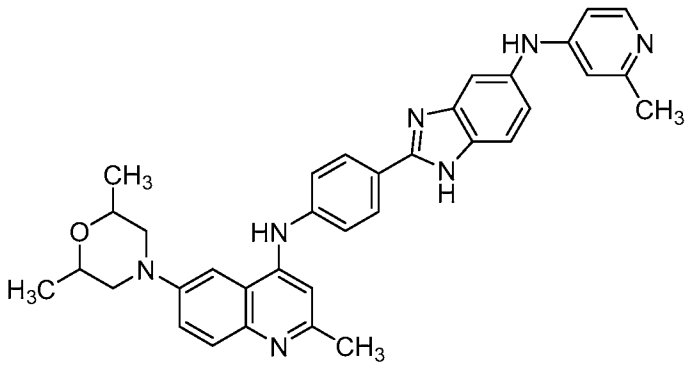
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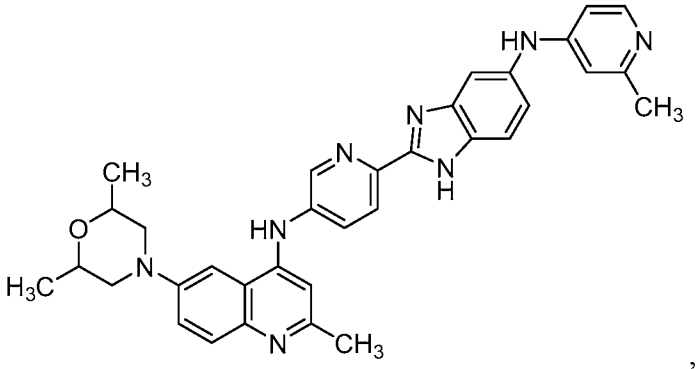
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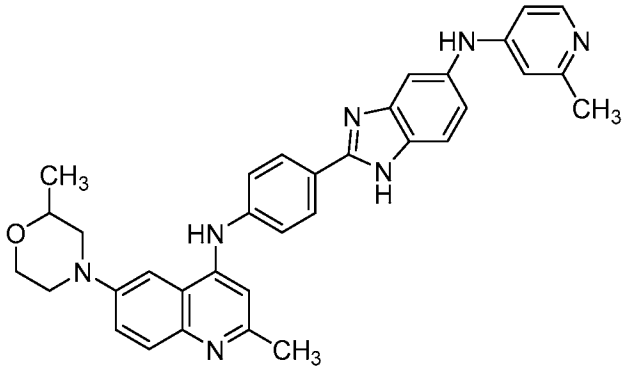
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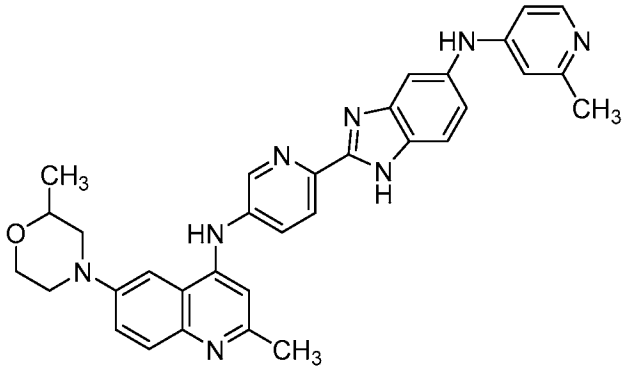
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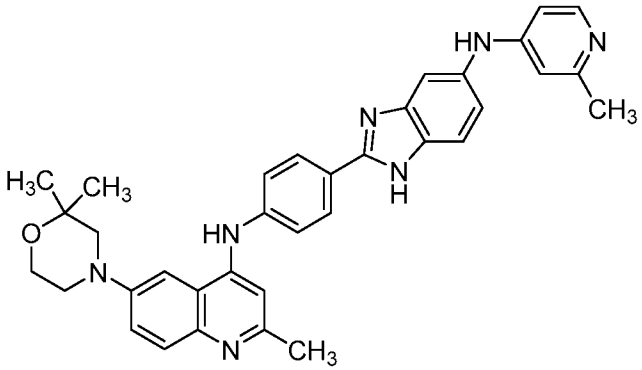
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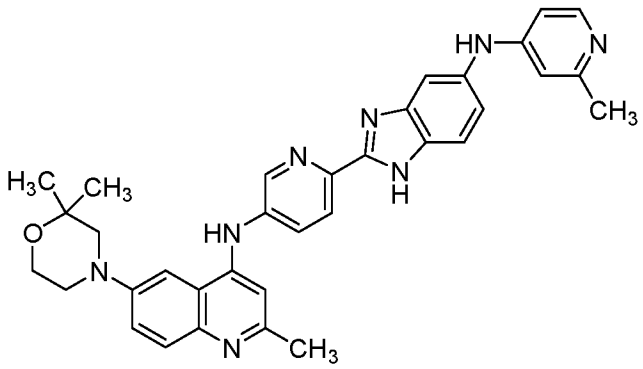
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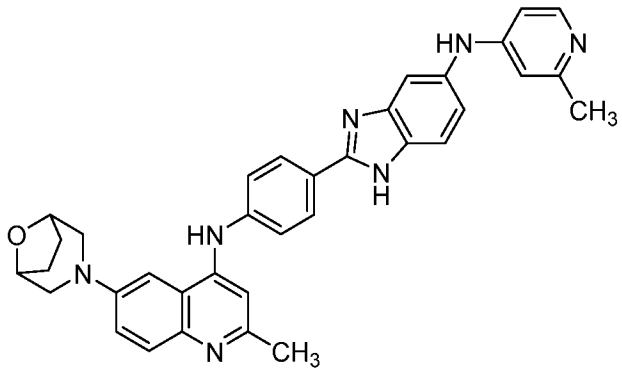
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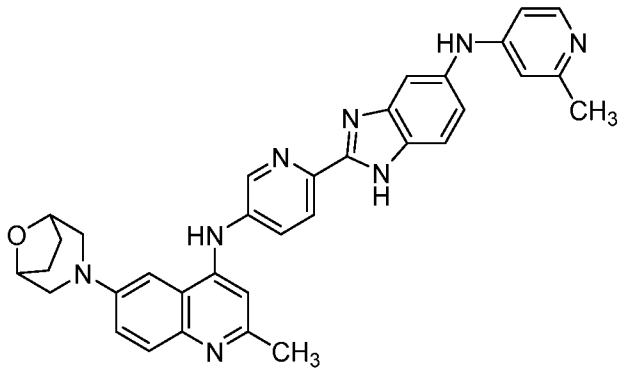
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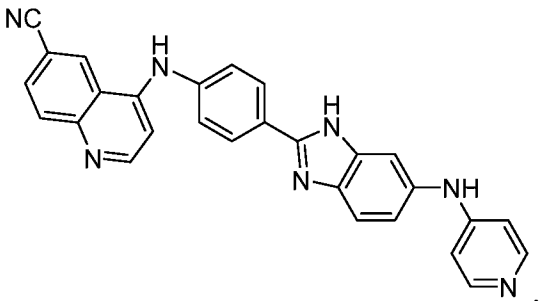
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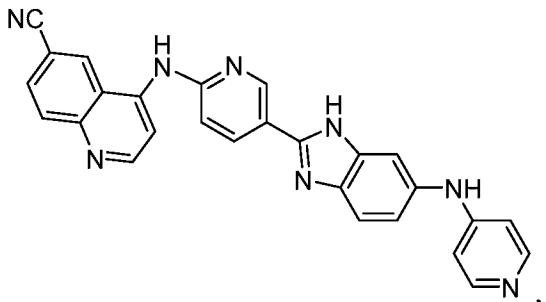
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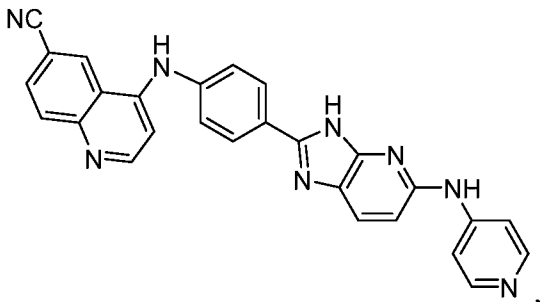
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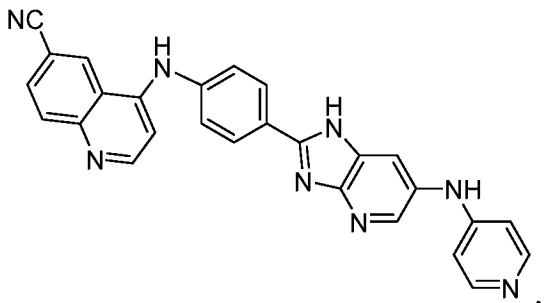
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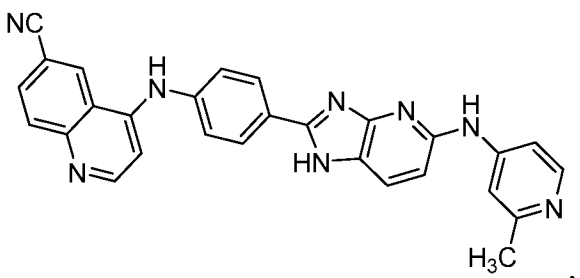
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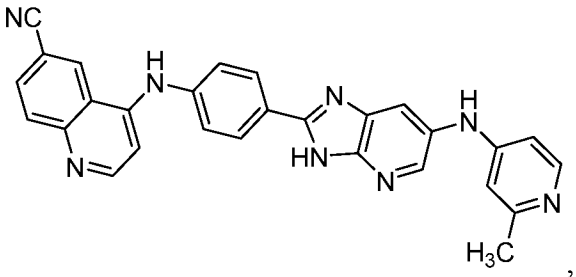
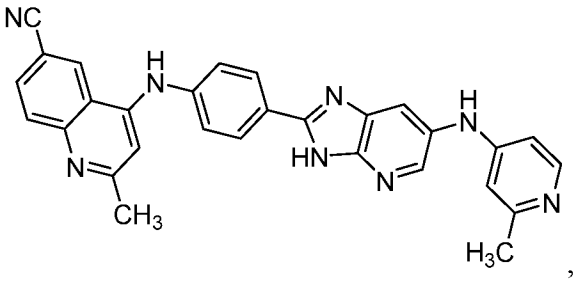
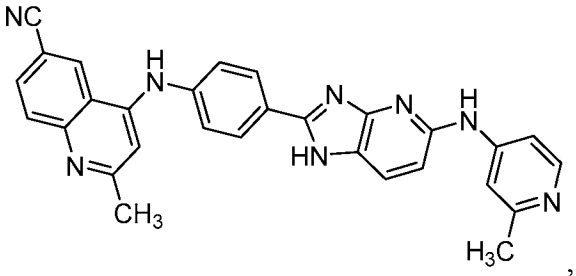
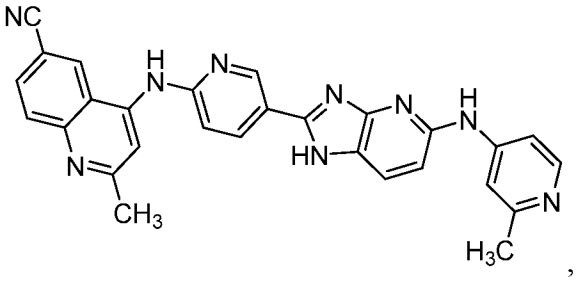
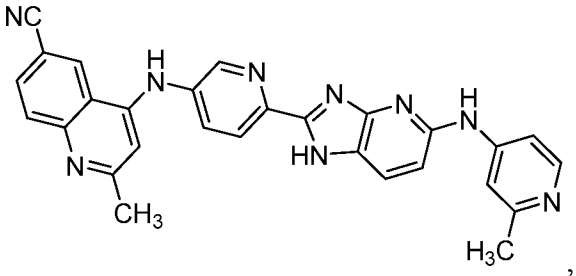
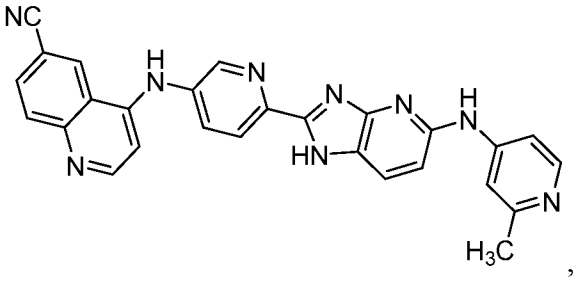
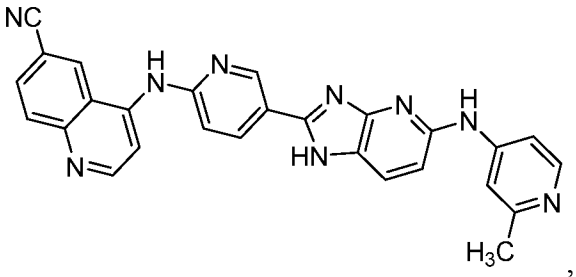
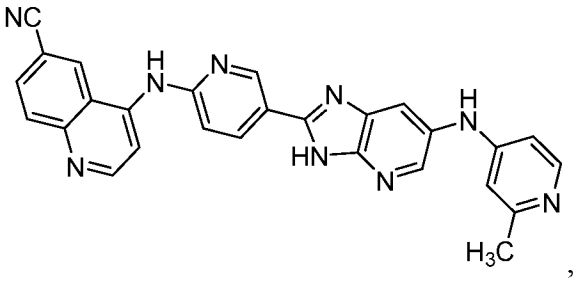
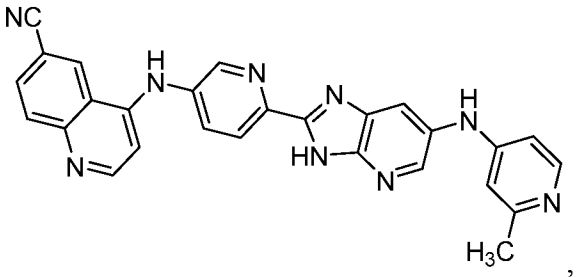
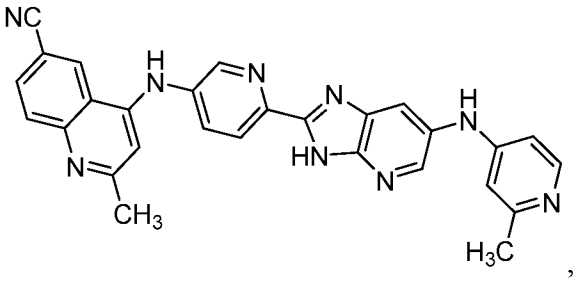
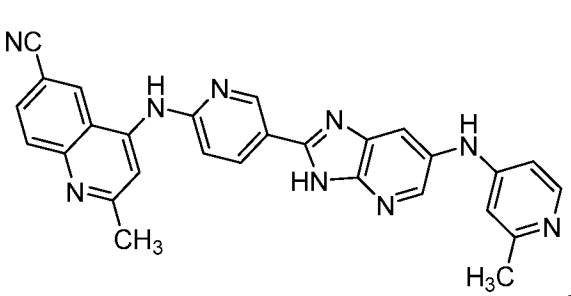
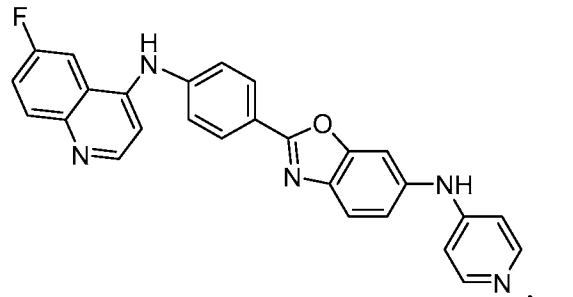
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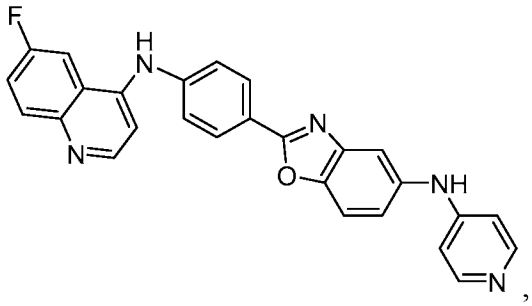


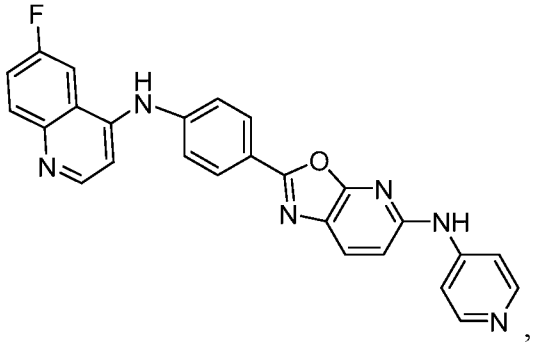
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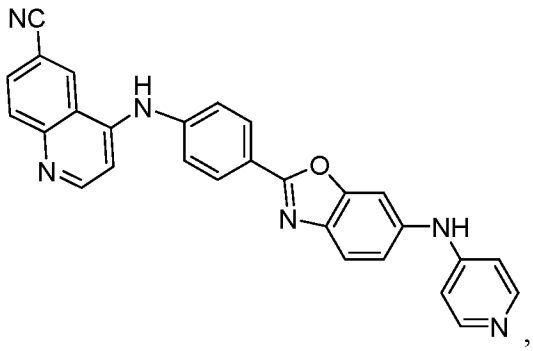


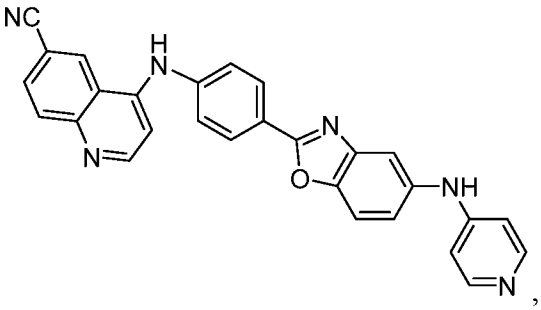
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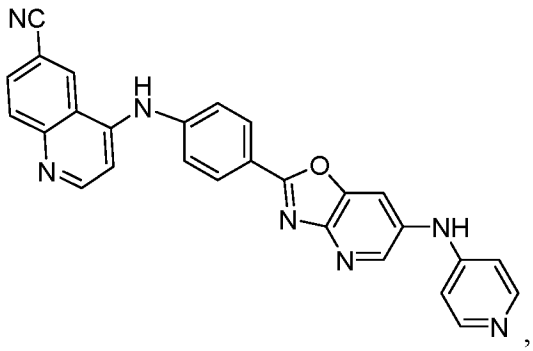

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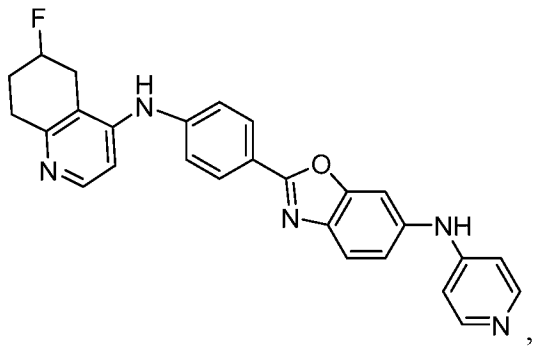


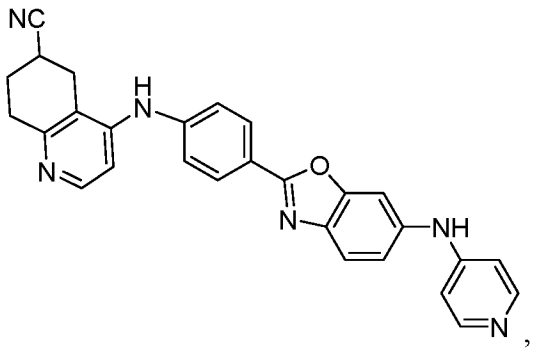


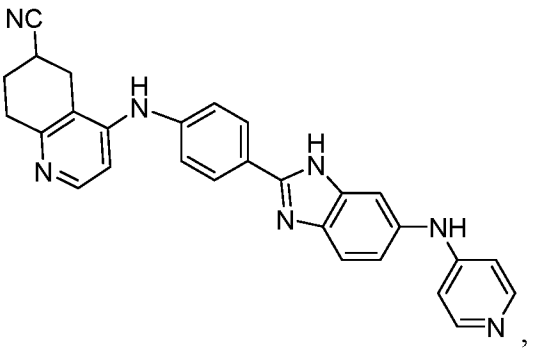


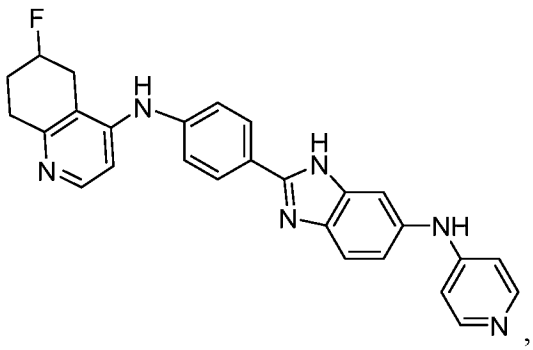


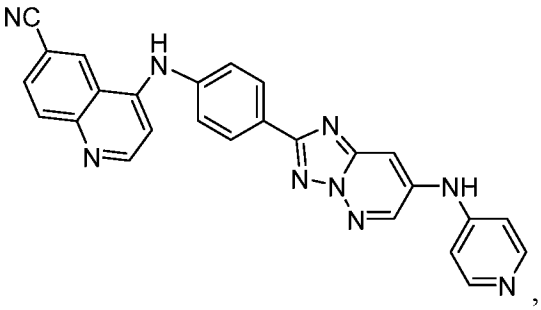


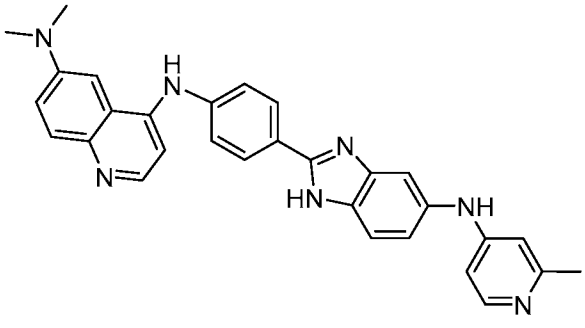
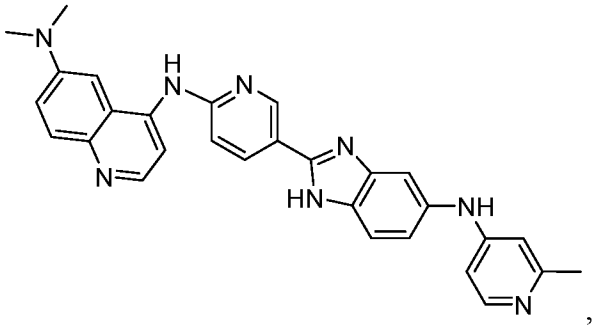
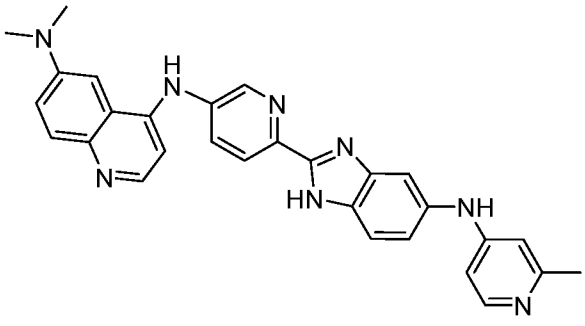
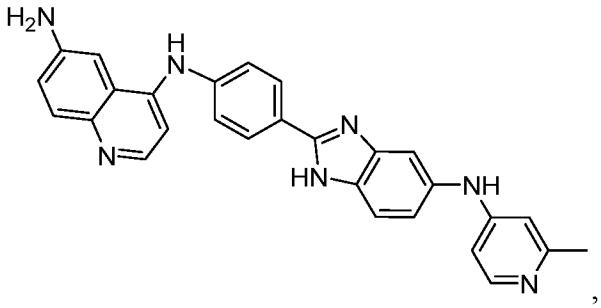
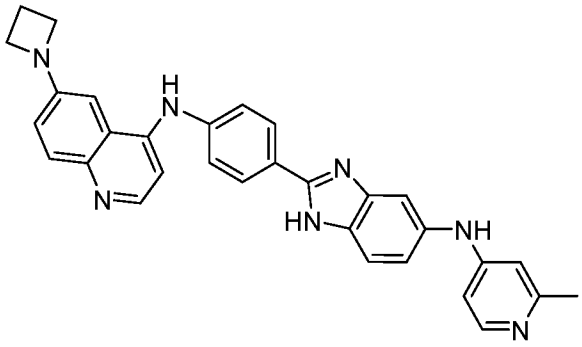
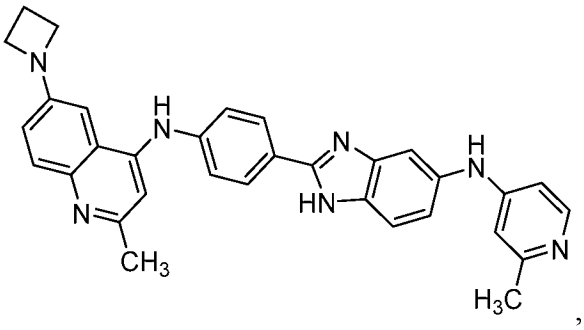
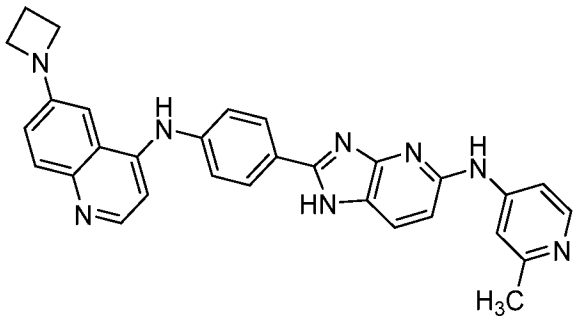
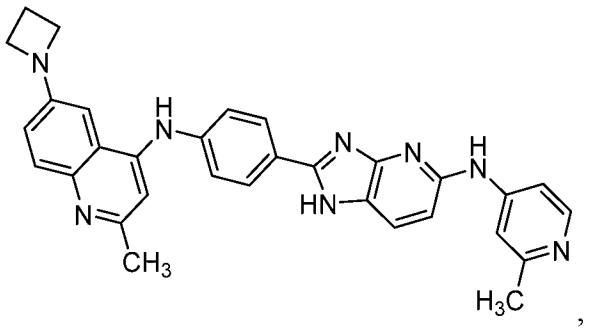
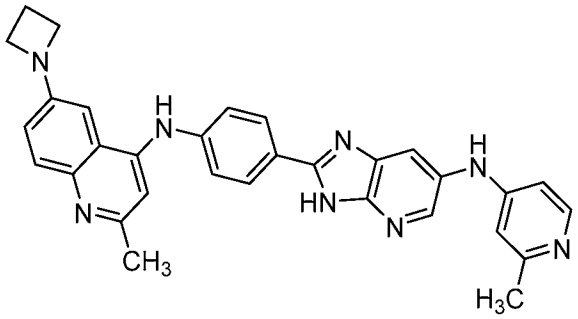
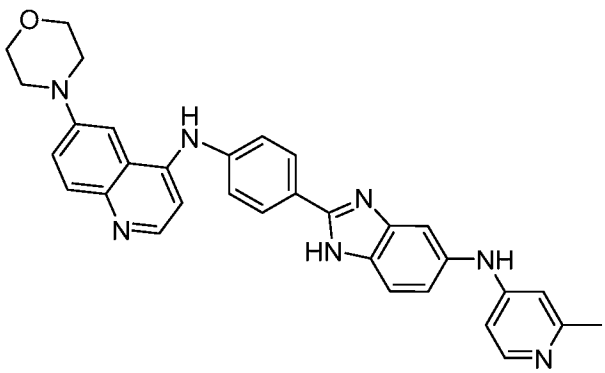


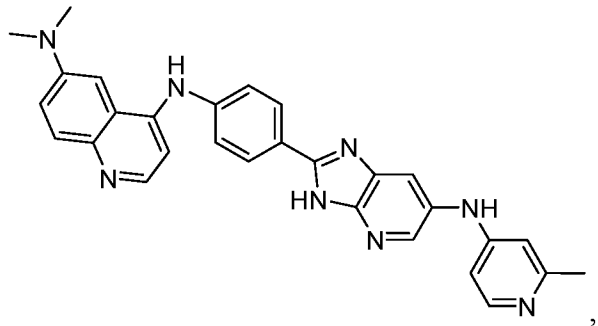
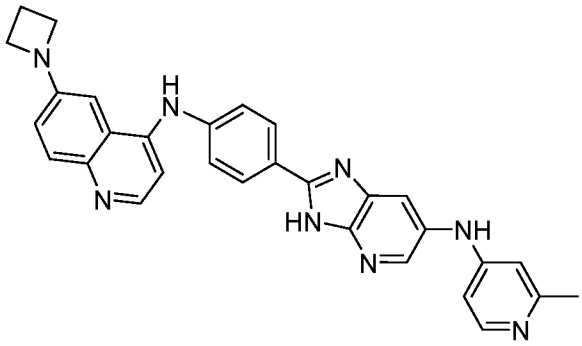
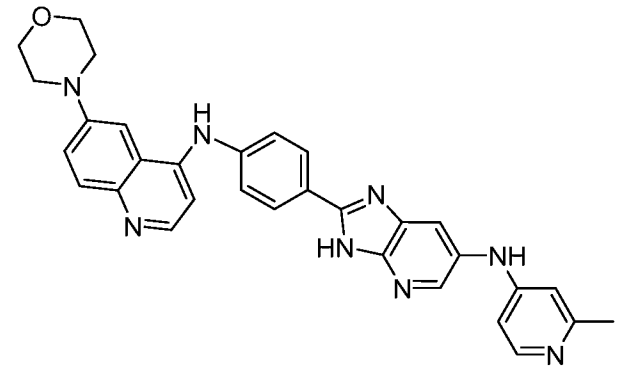
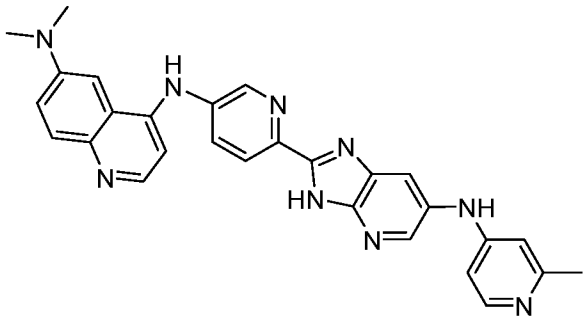
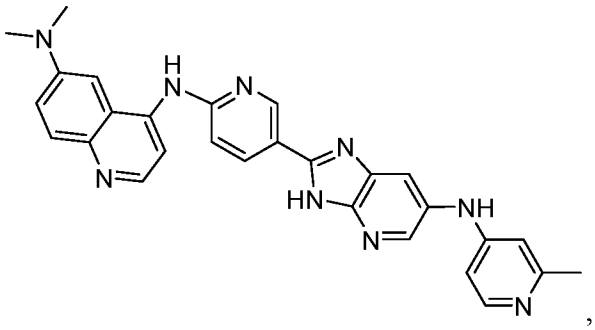
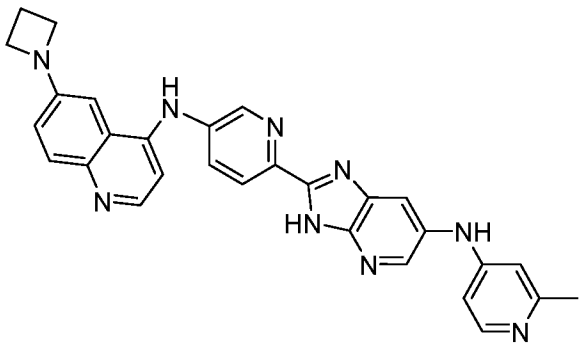
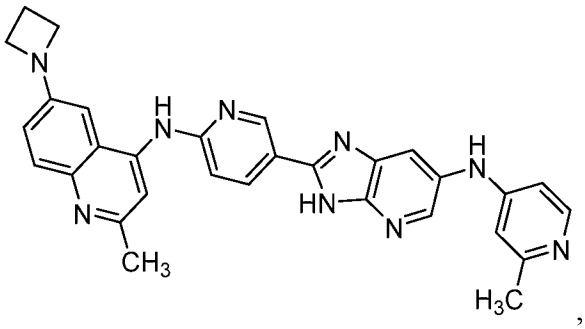
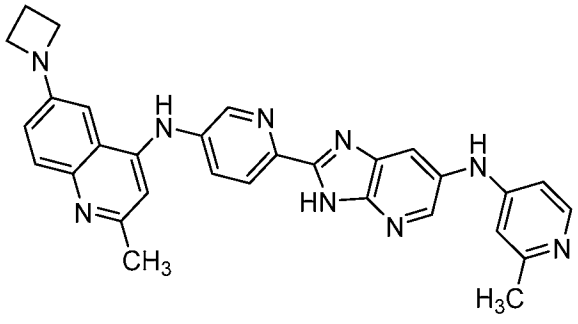
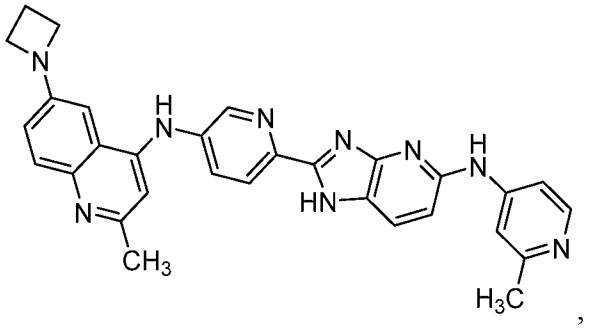


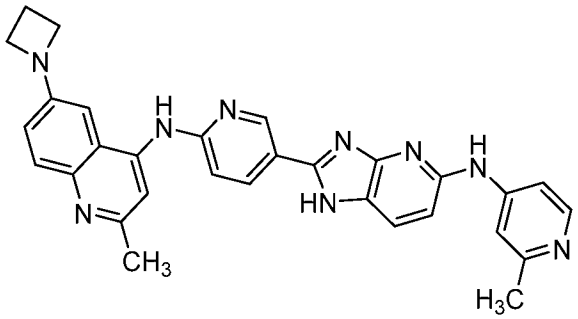


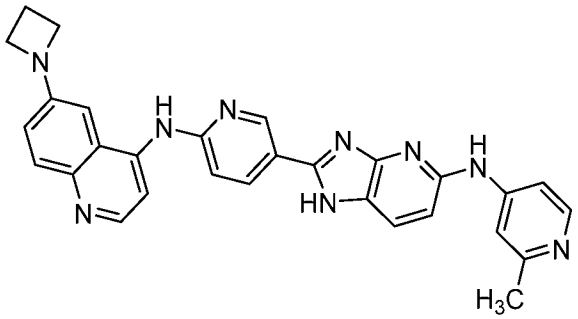


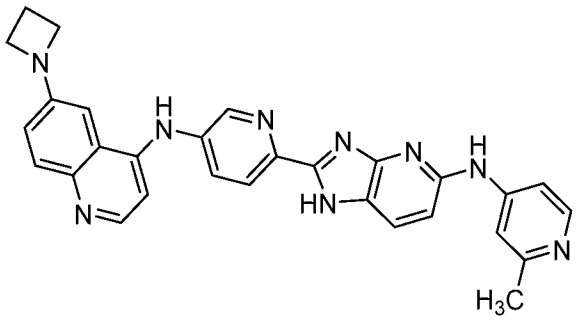


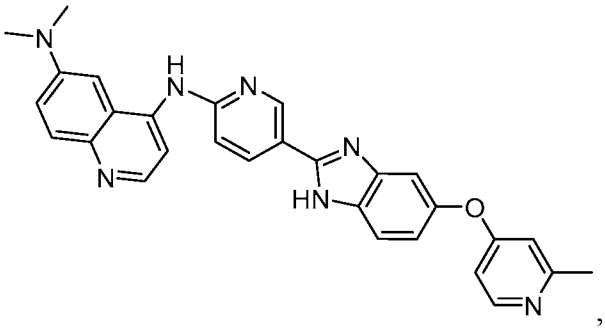
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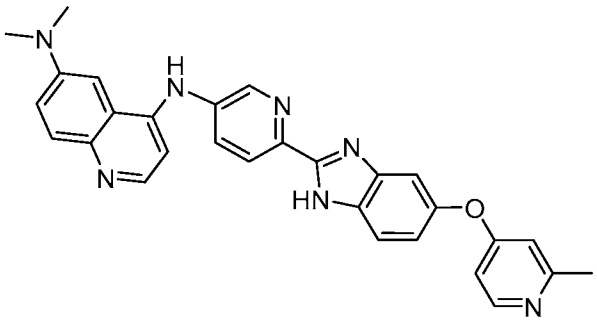

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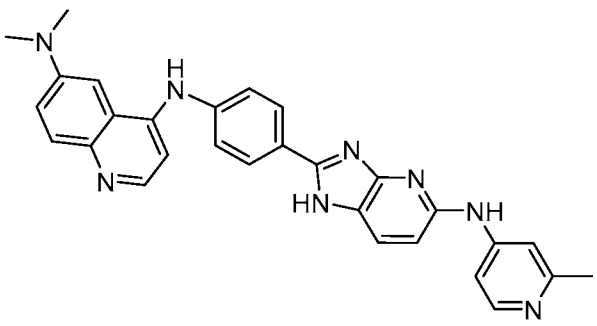

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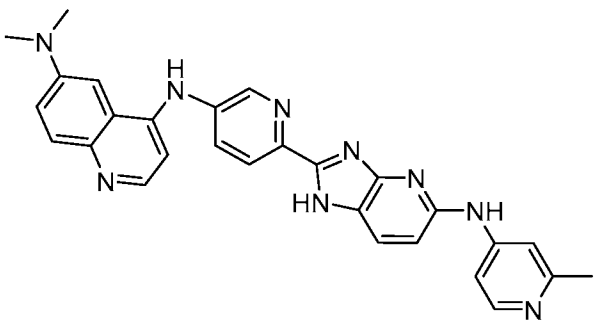

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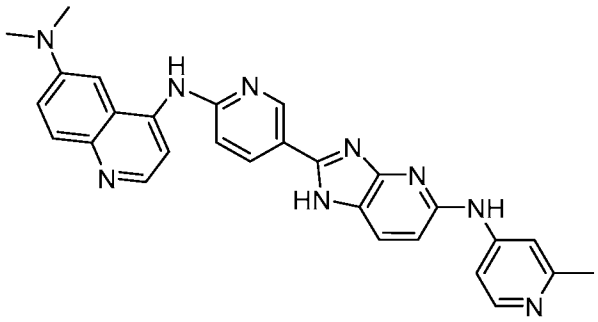

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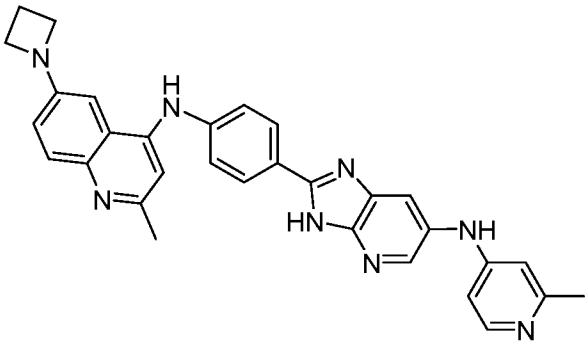

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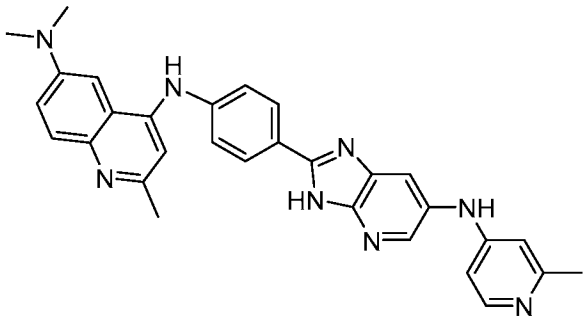

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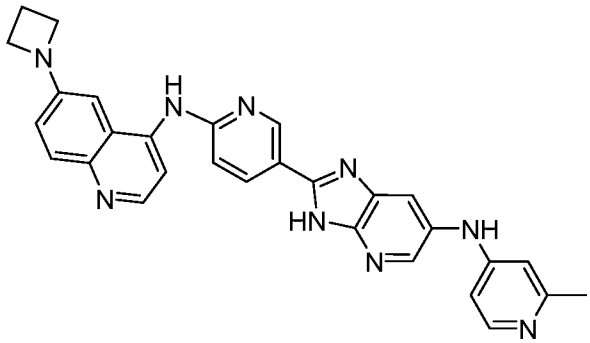
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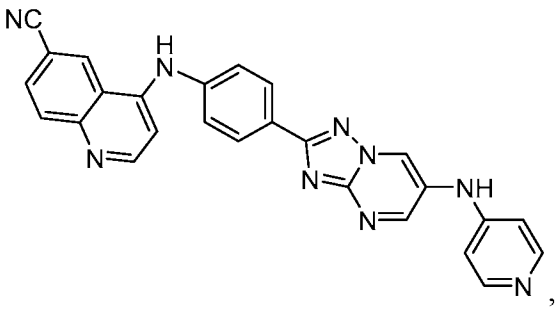


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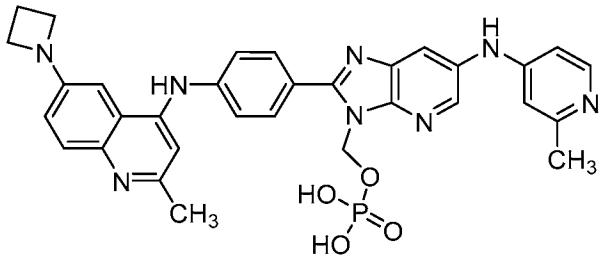
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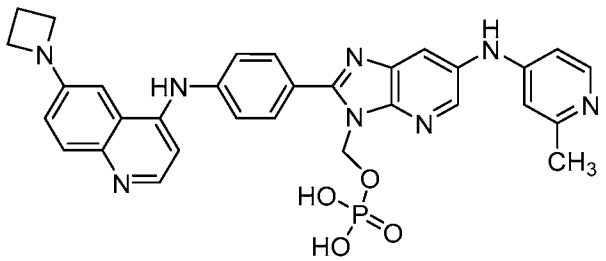
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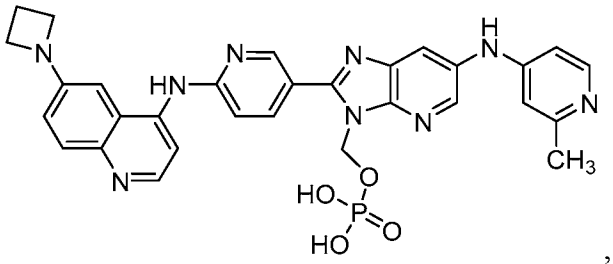
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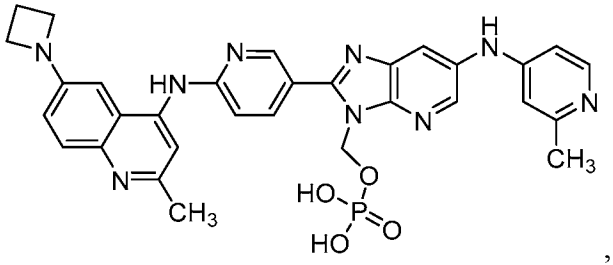
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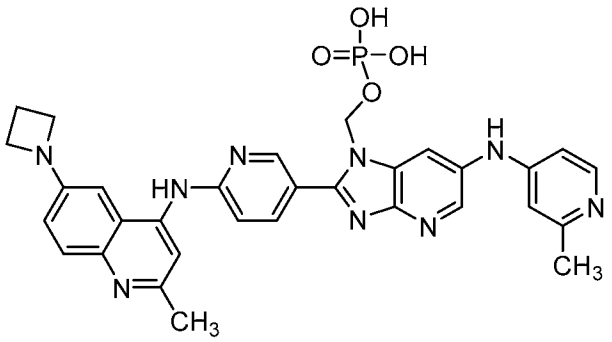
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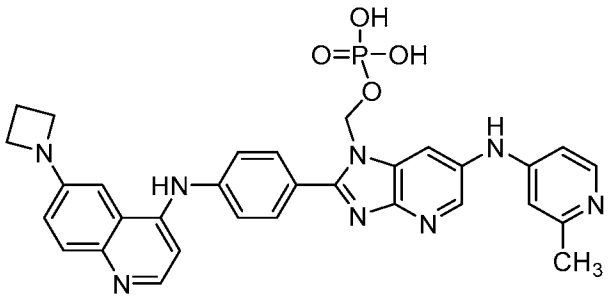
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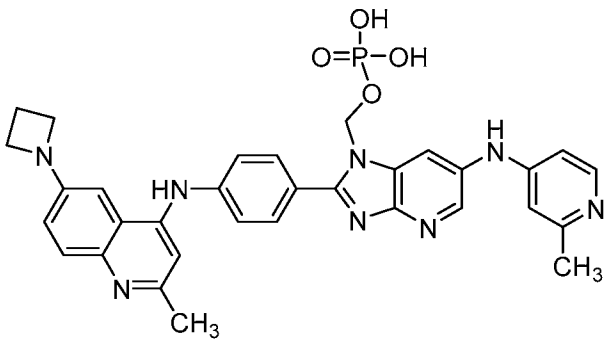
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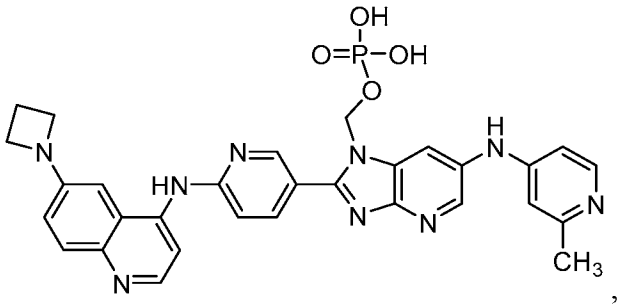
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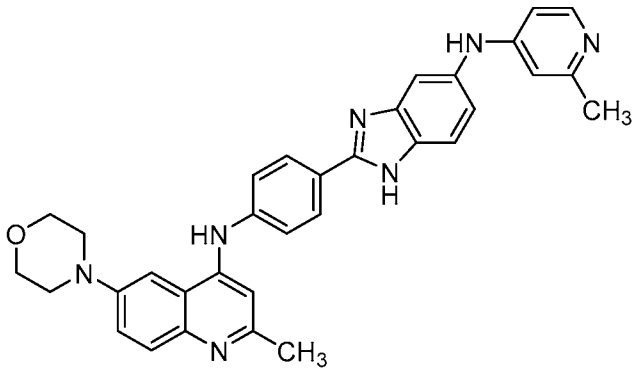
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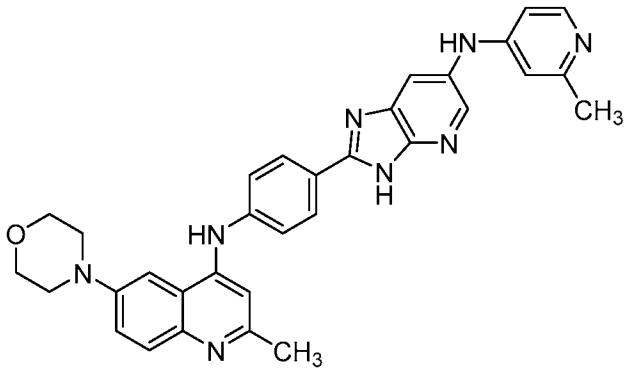
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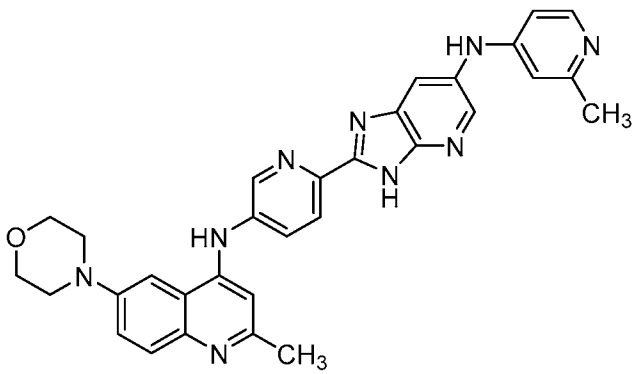
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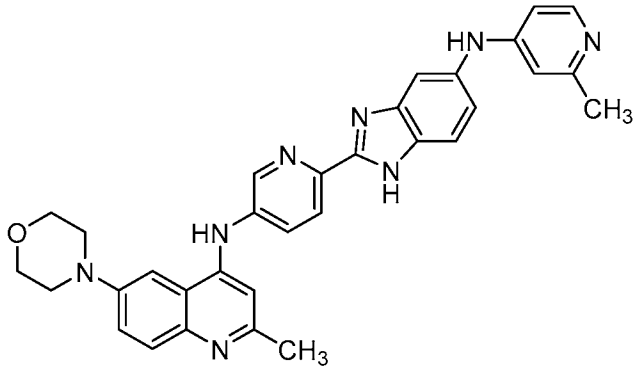
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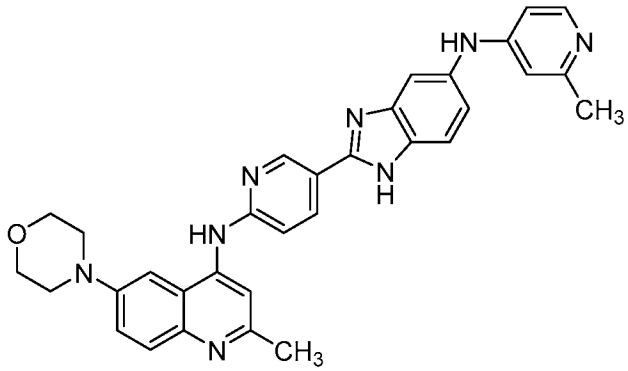
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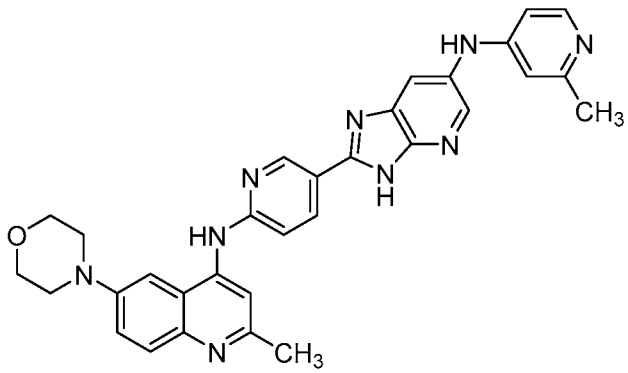
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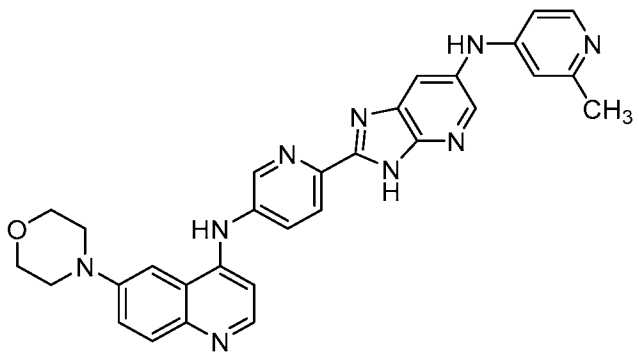
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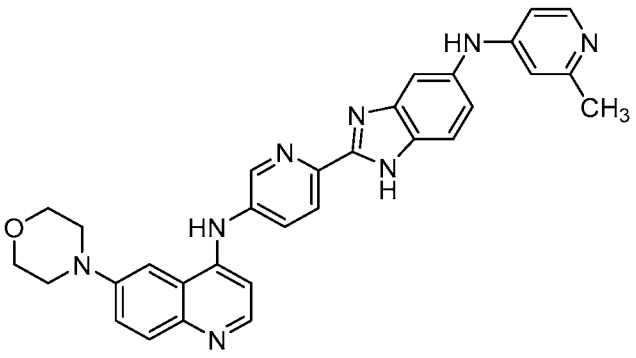
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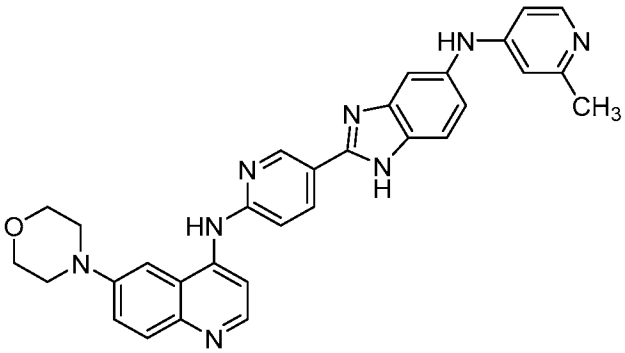
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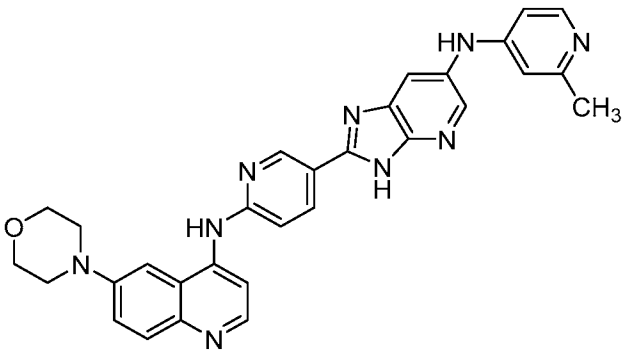
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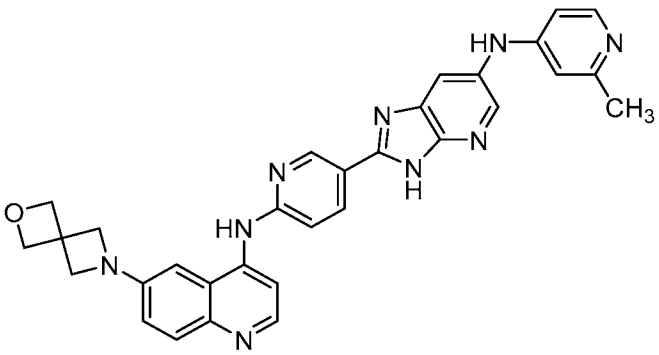
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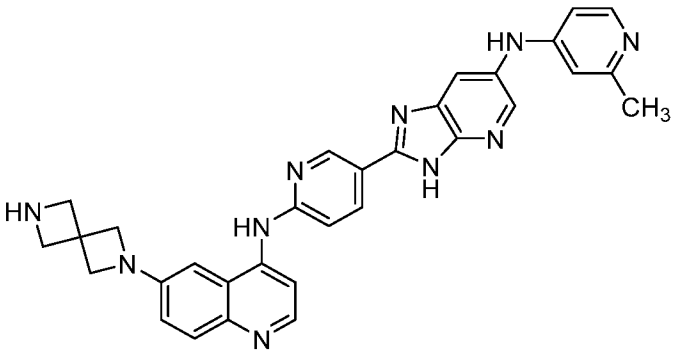
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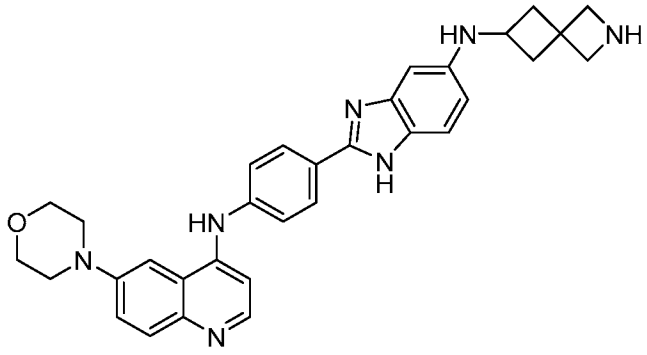
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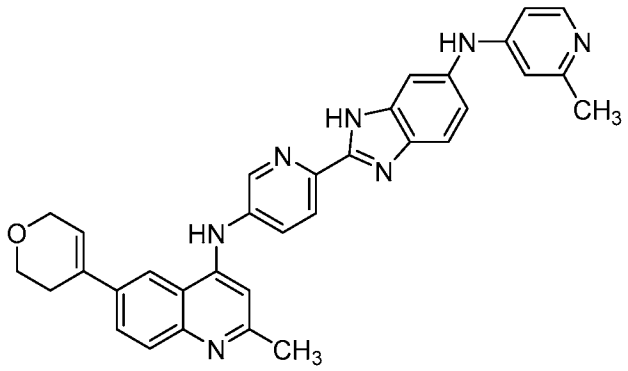
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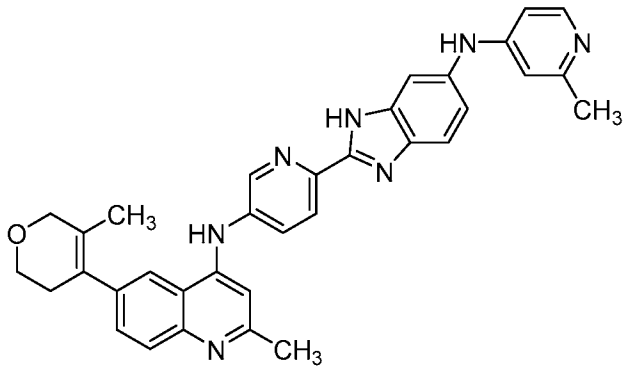
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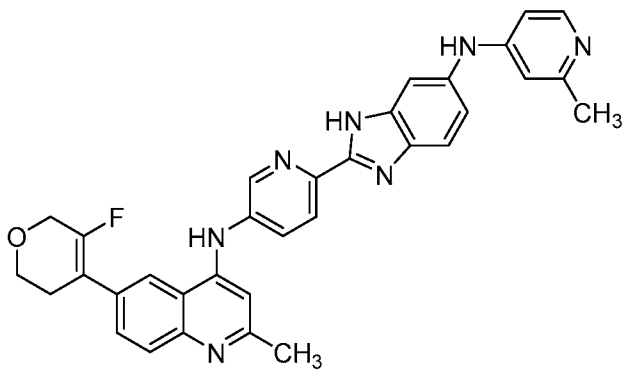
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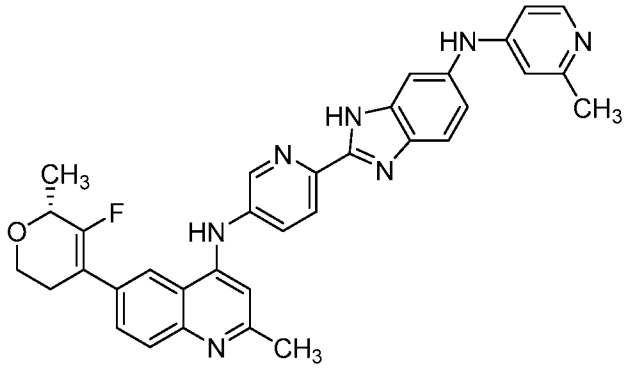
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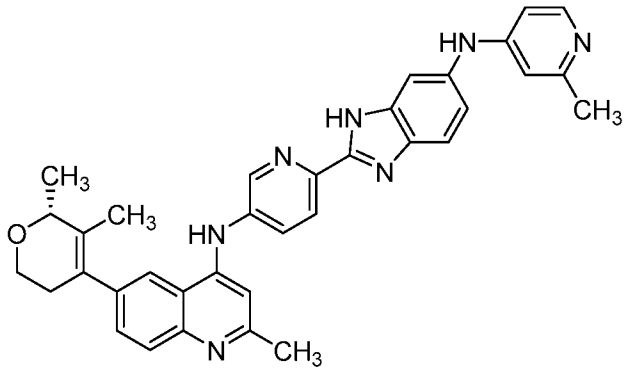
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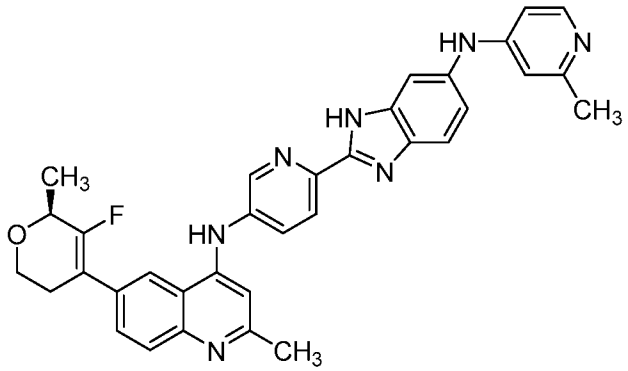
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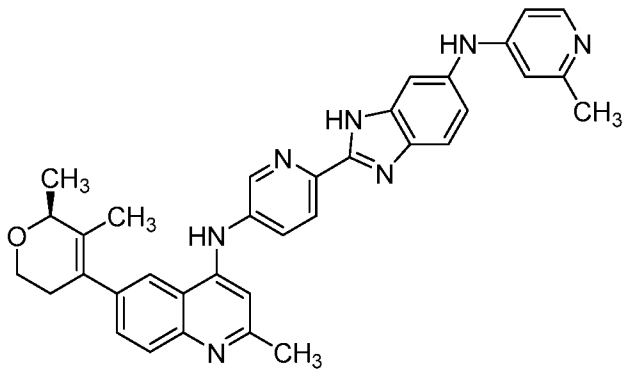
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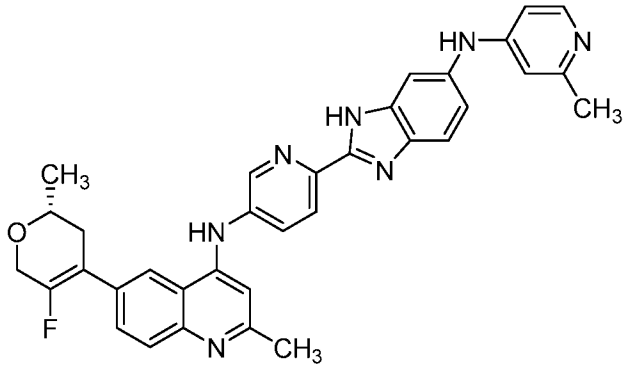
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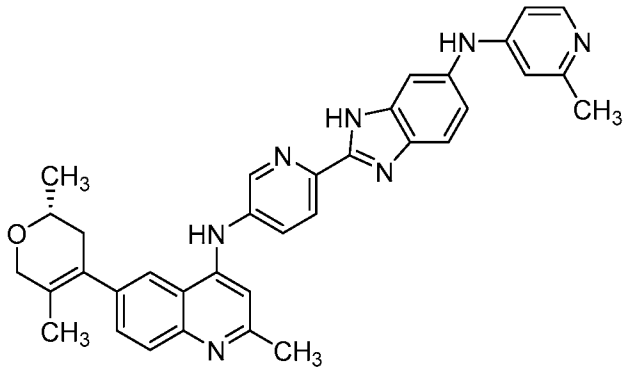
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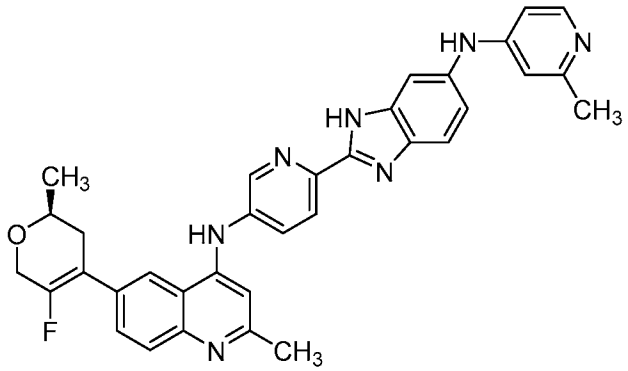
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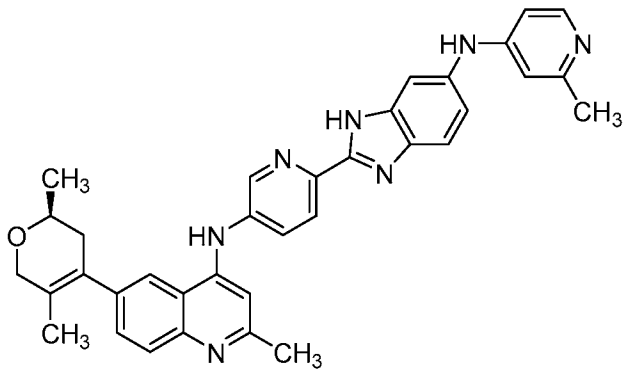
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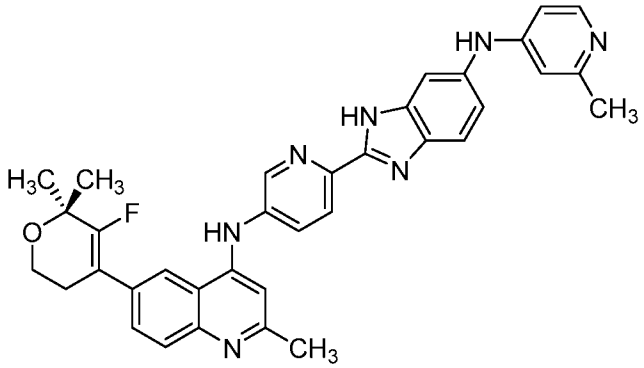
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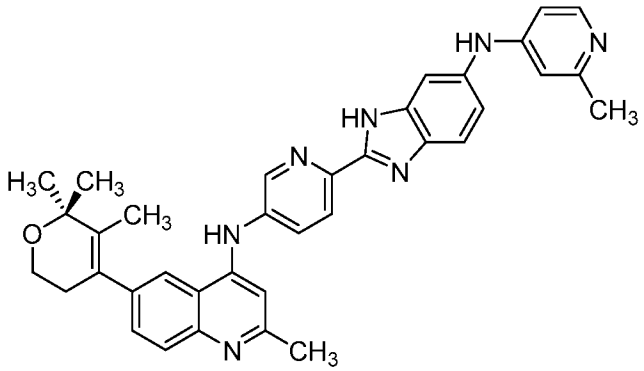
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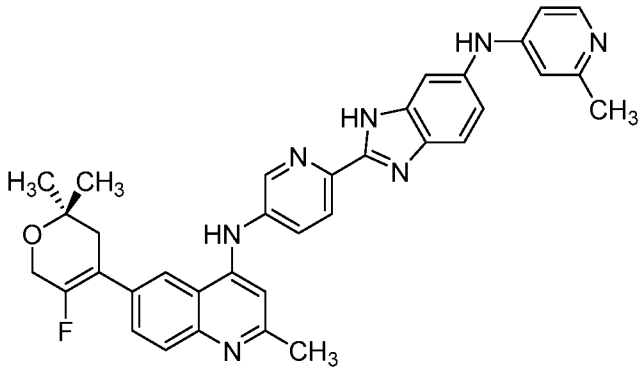
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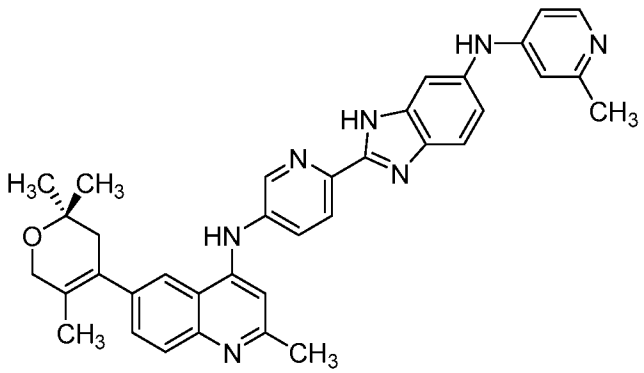
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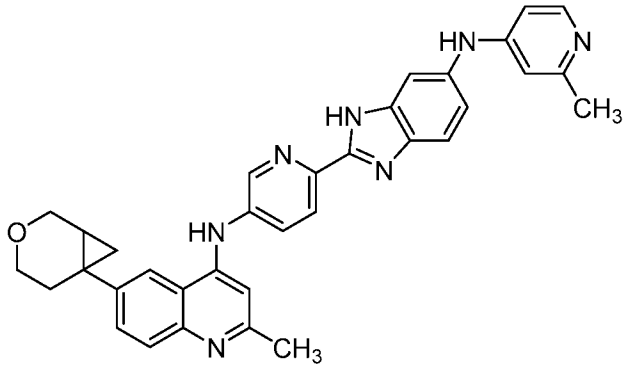
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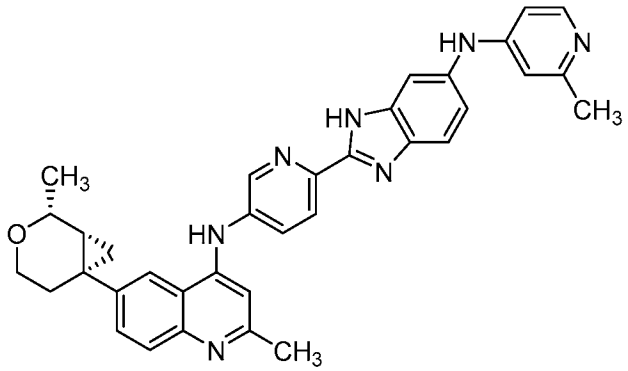
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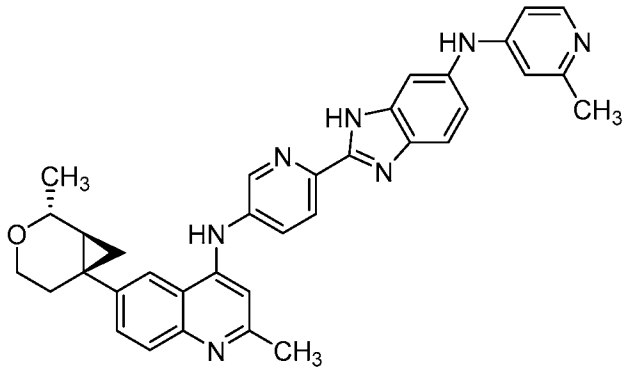
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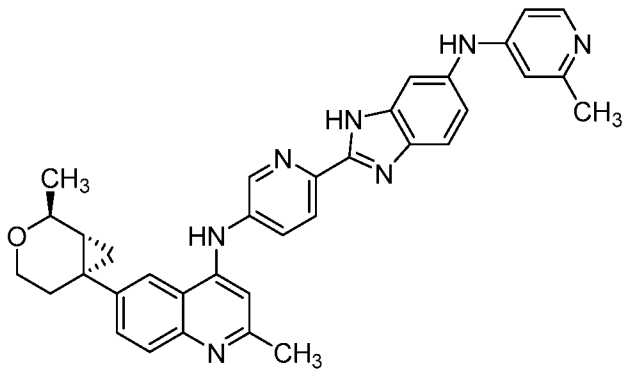
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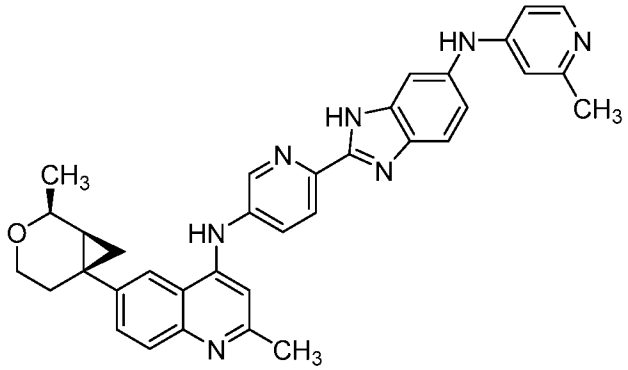
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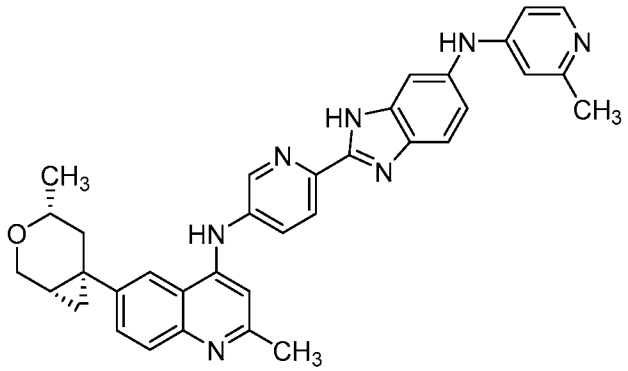


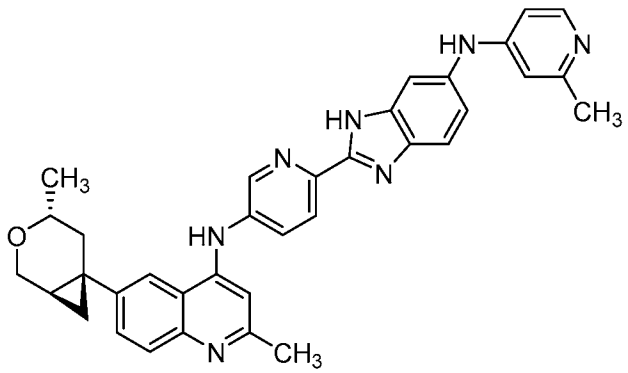
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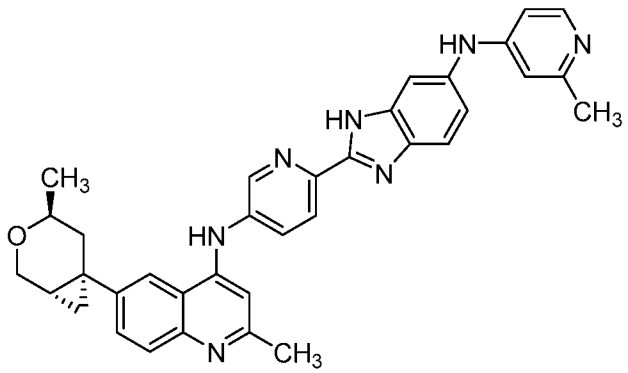


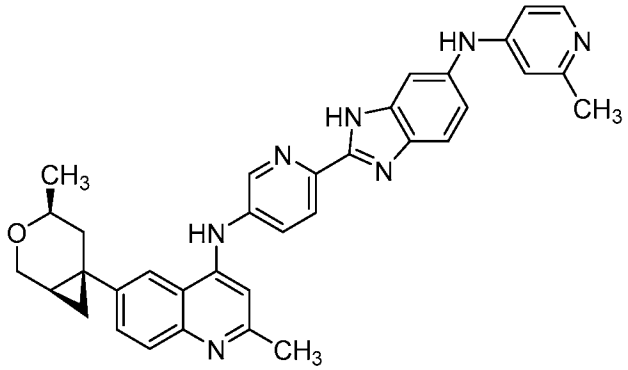
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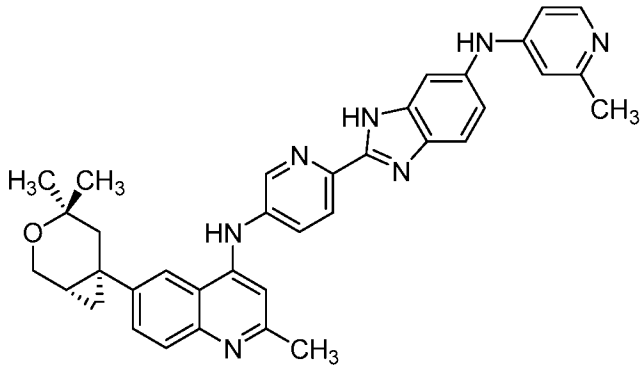

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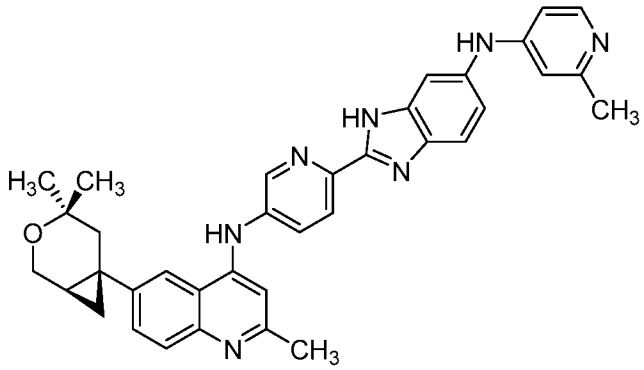

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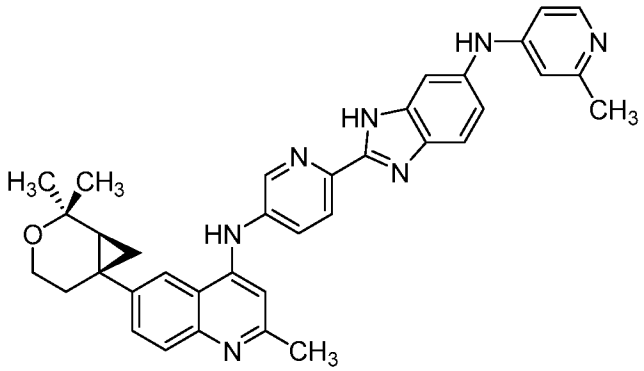
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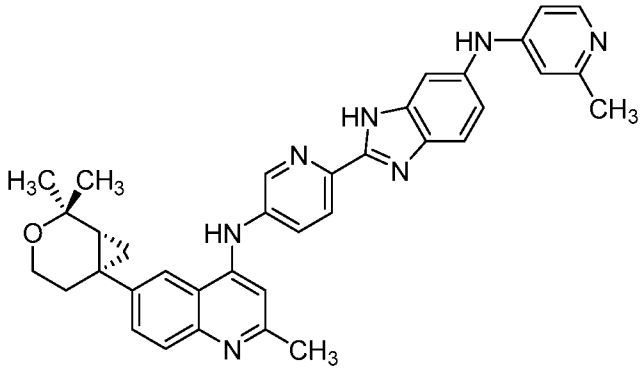
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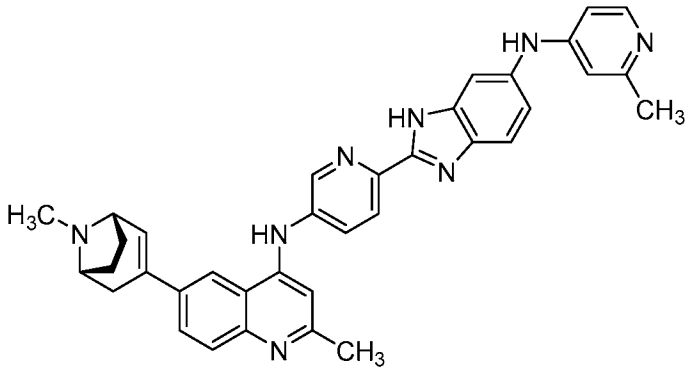
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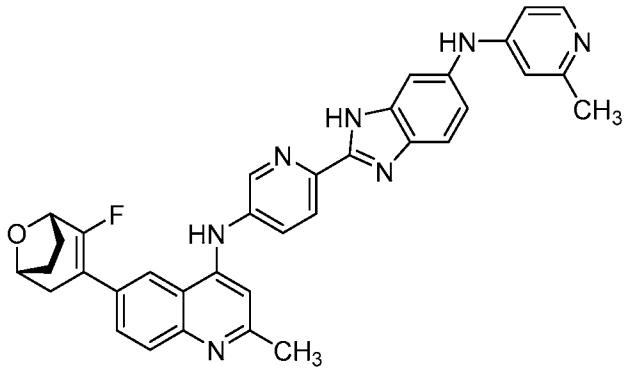
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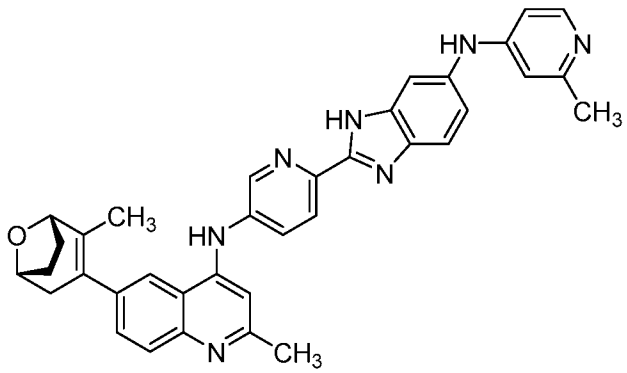
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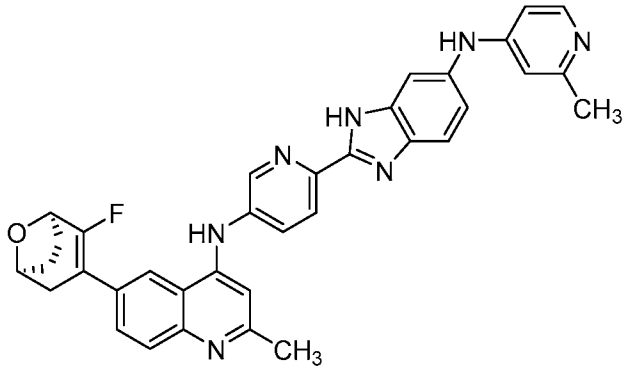
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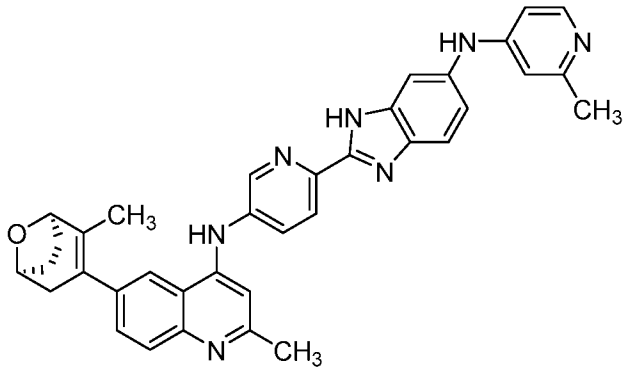


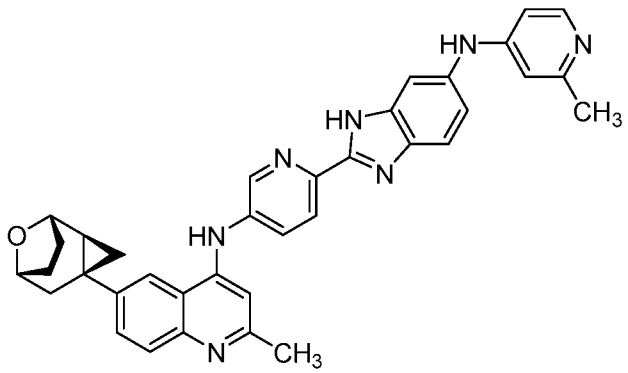
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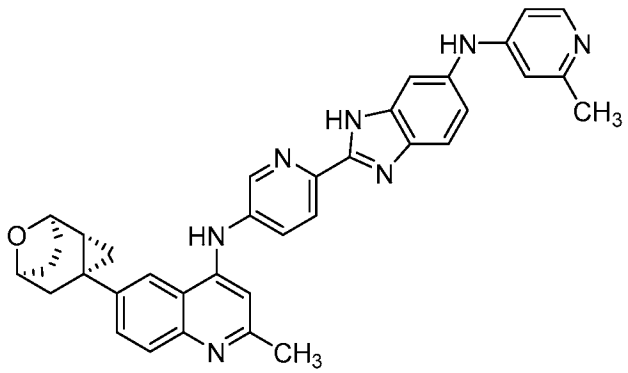


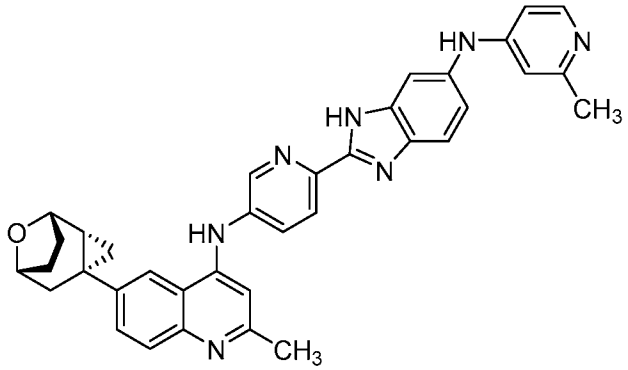
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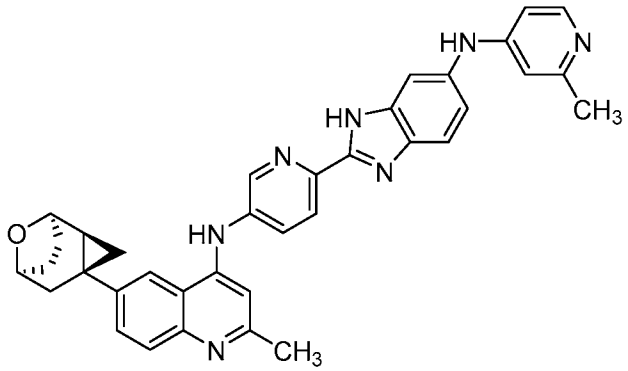

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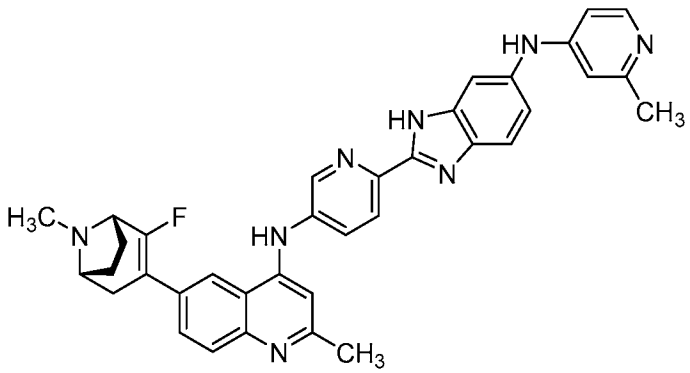

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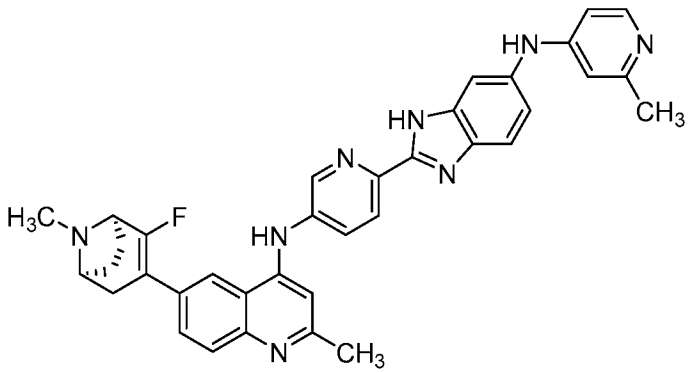
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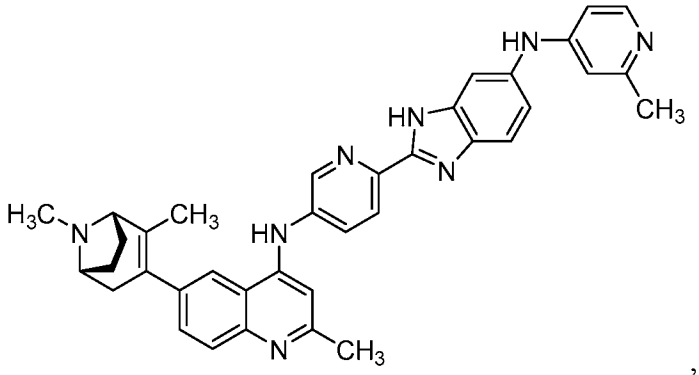
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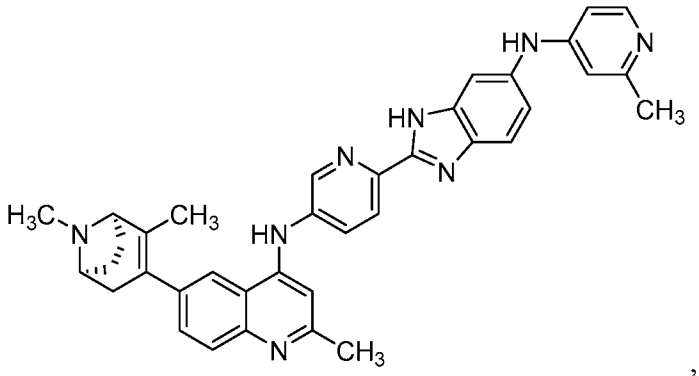


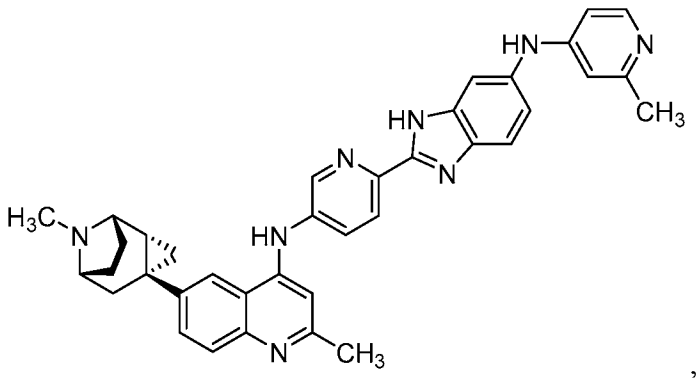
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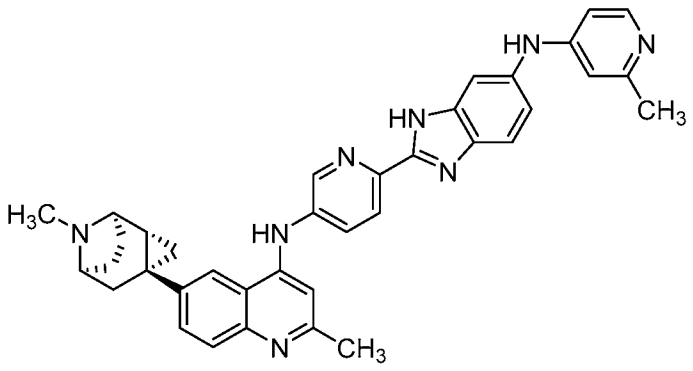


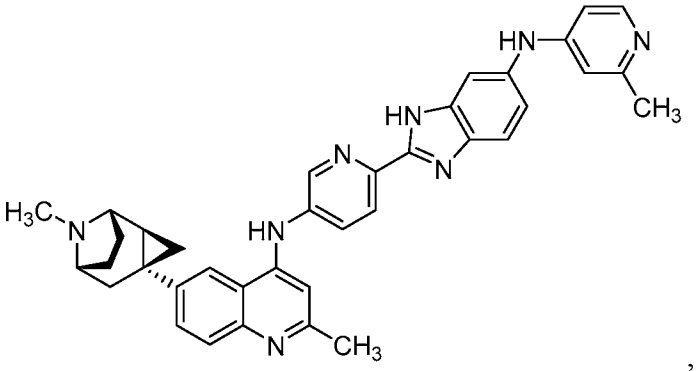
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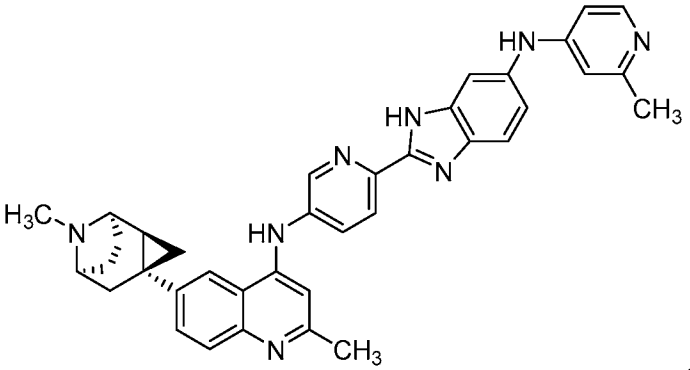

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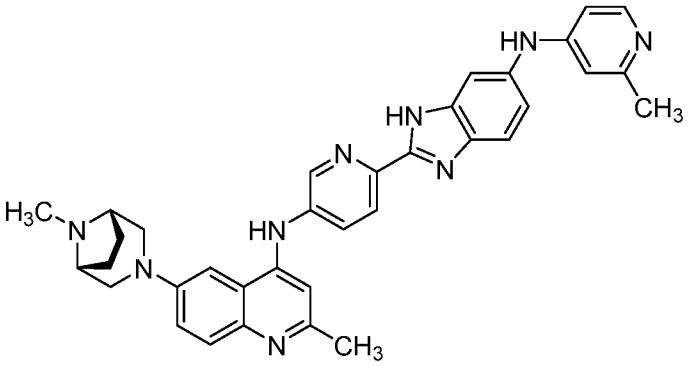

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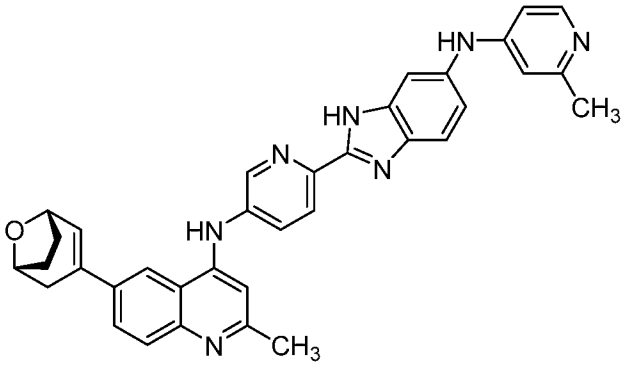

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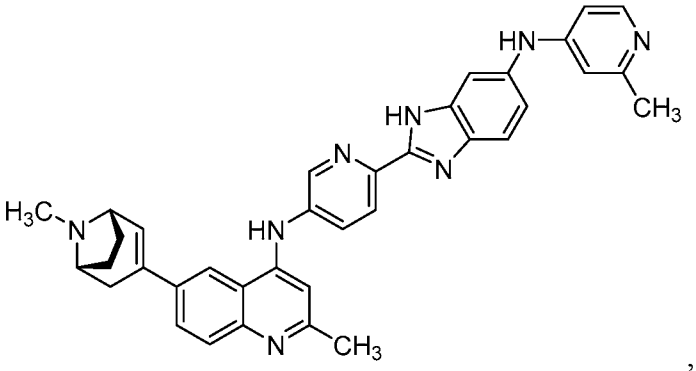

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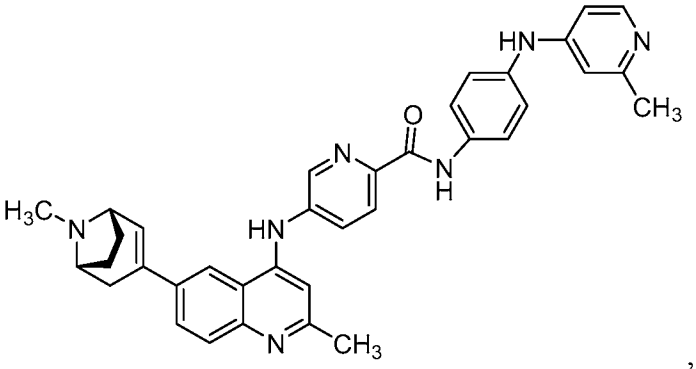

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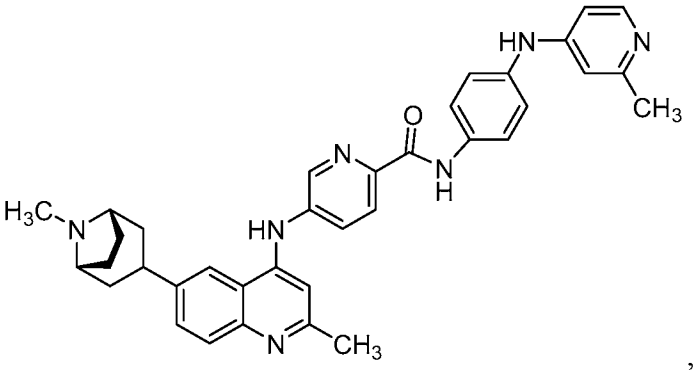

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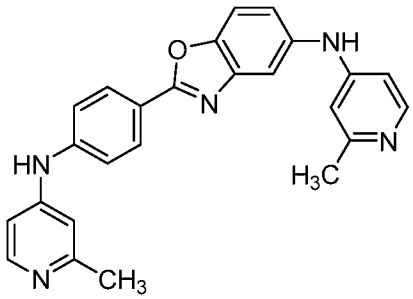
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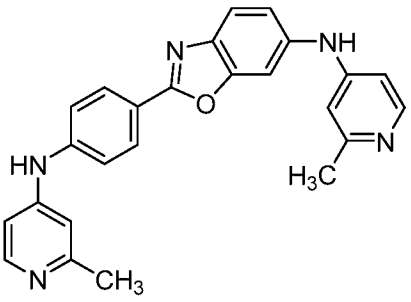
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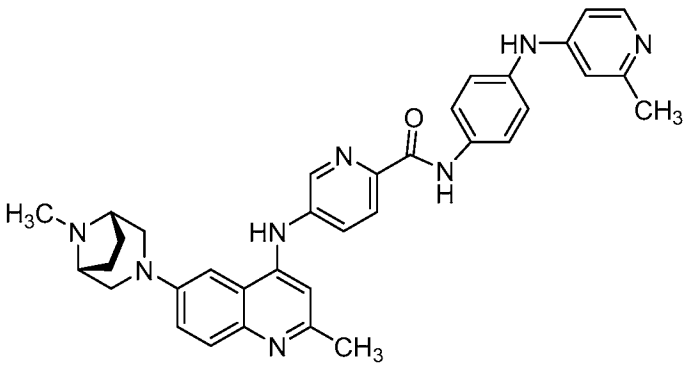
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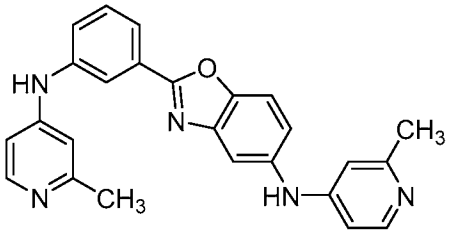
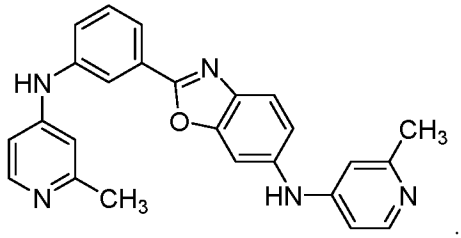


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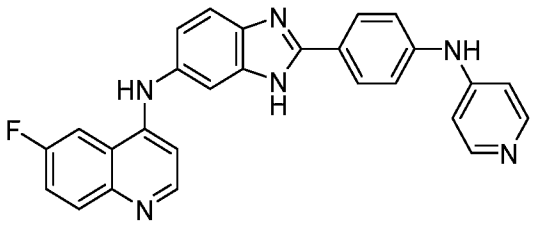
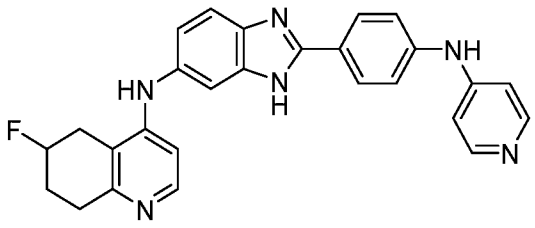
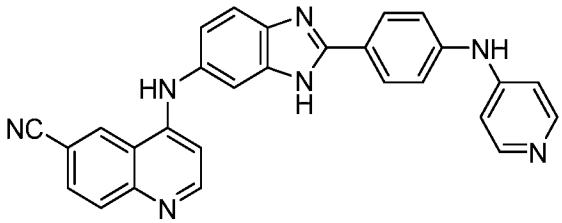
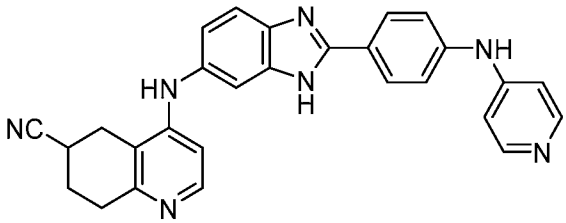
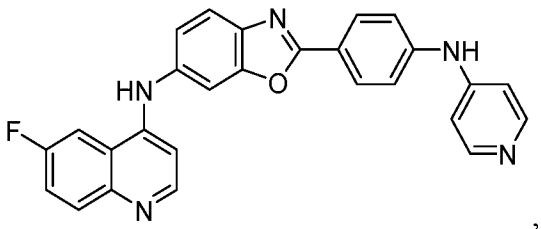
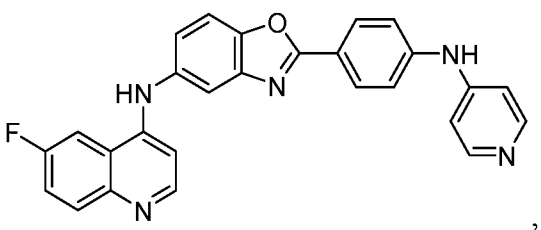
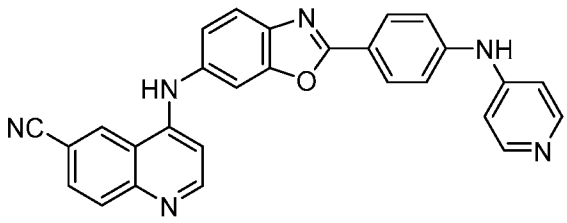
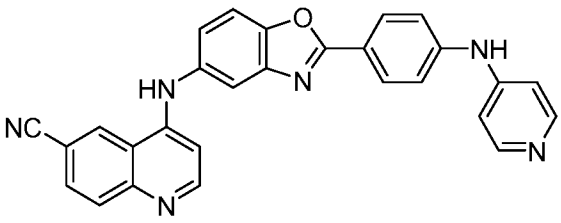


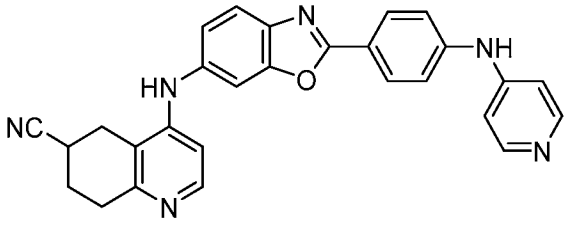
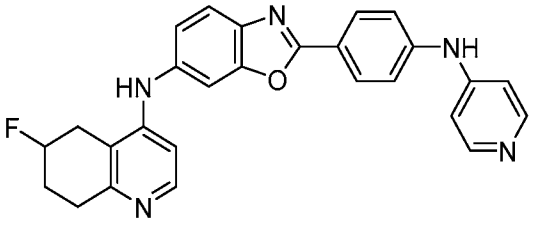
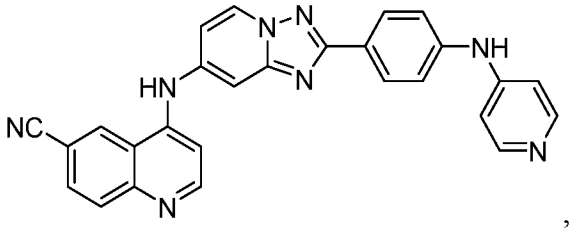
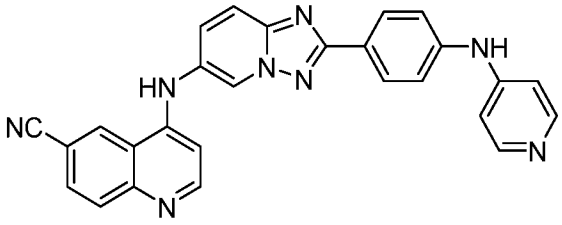
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129. The compound of claim 1, wherein the compound of Formula IIb is

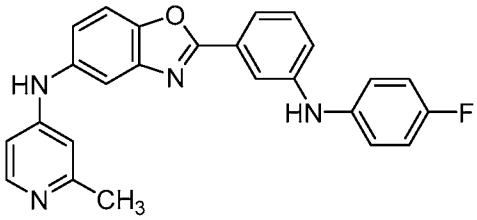

or

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130. The compound of claim 1, wherein the compound of Formula Ic is

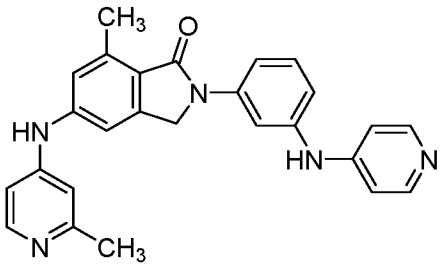
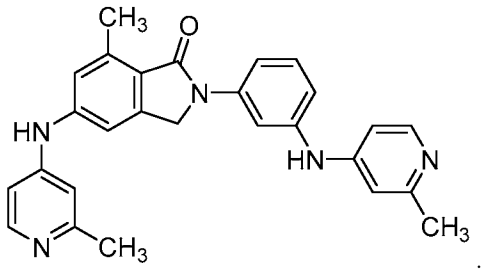

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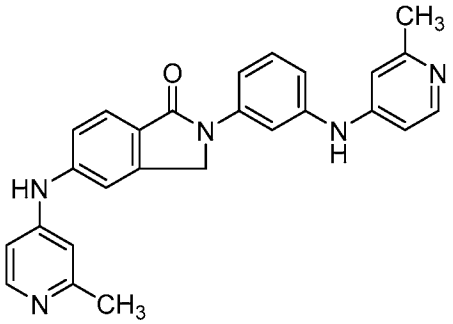
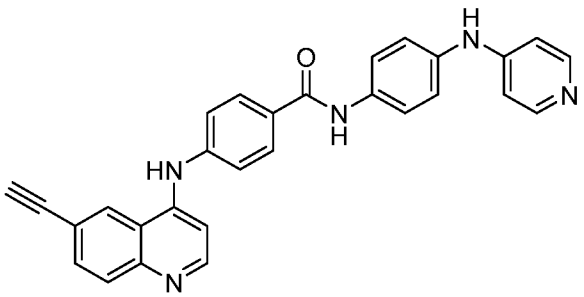
131. The compound of claim 1, wherein the compound of Formula IIc is

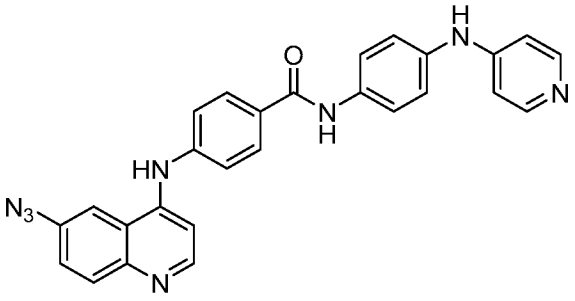
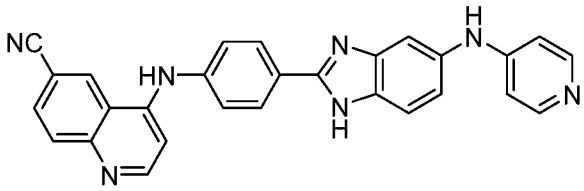
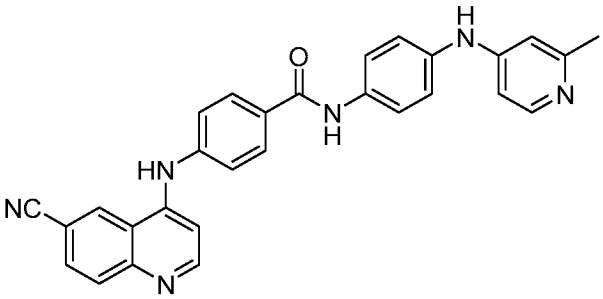
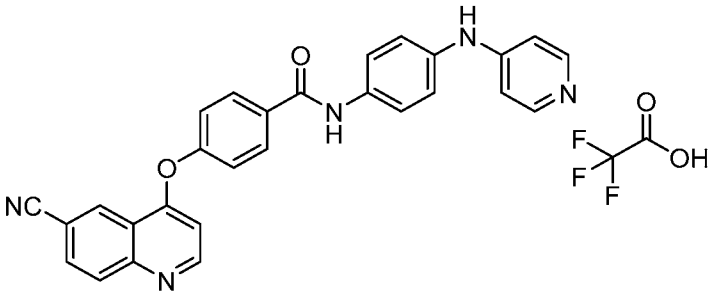
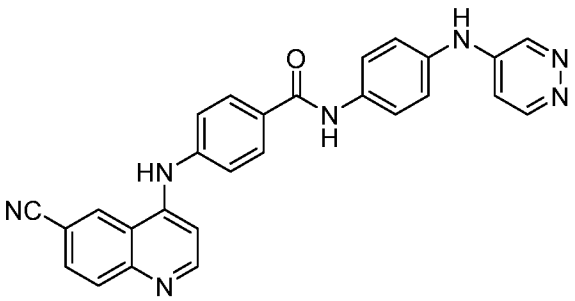
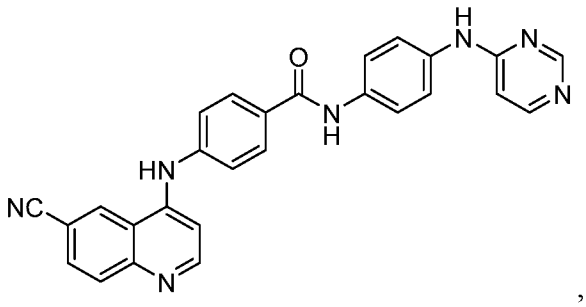
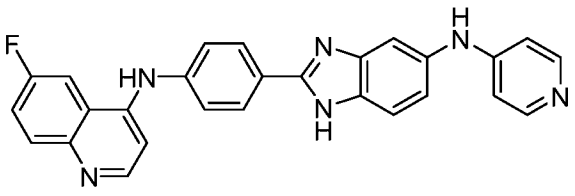
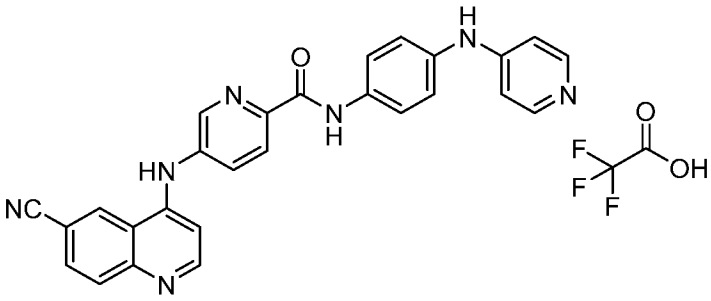

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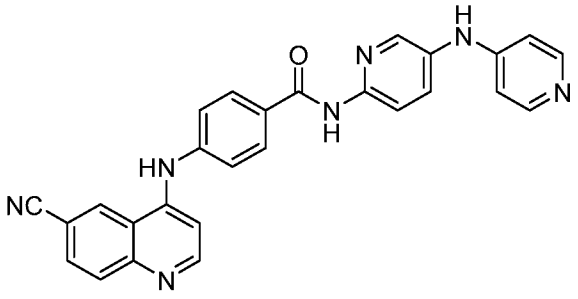
132. The compound of claim 1, wherein the compound of Formula IVa is


or

.

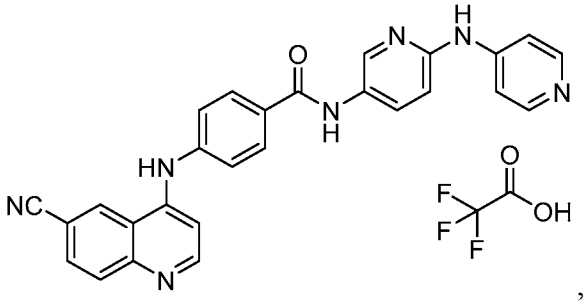
133. The compound of claim 1, wherein the compound is


,

,

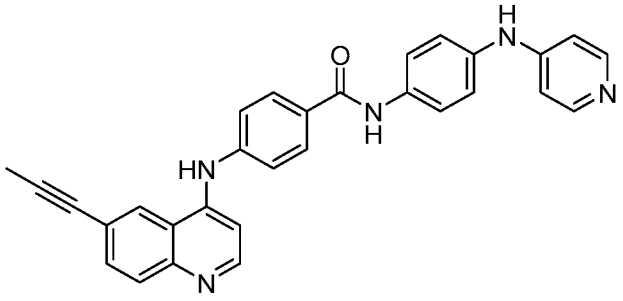

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,



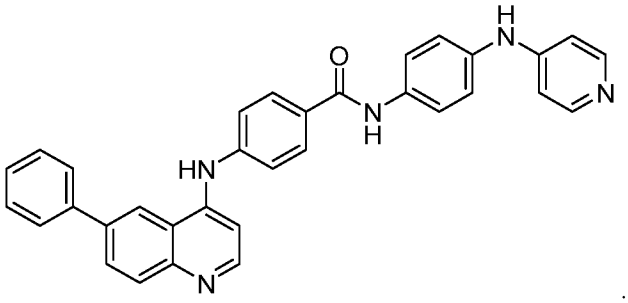
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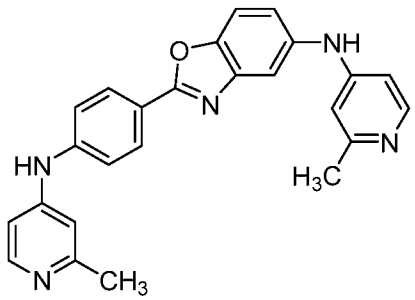
,

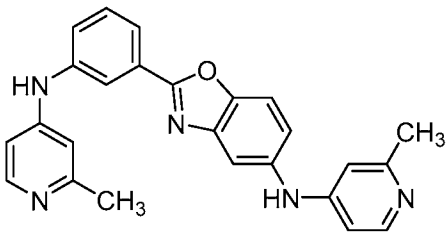


, or

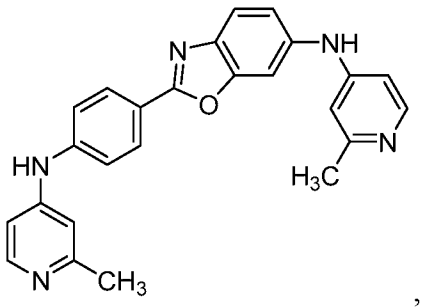


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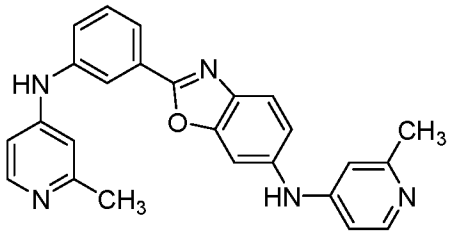
134. The compound of claim 1, wherein the compound is ,



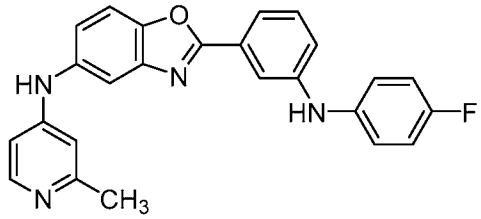
,



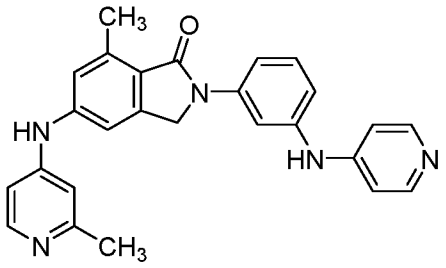
,



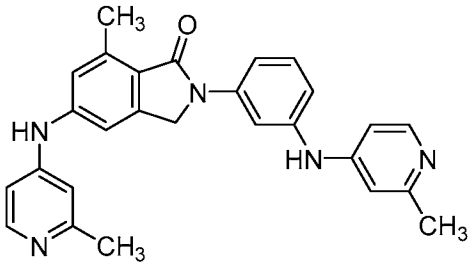
,



,



, or



.

135. The compound of claim 1, wherein the compound is selected from the group consisting of Compounds 2-9, 11-14, 30, and 32-145 in Examples 2-9, 11-14, 30, and 32-145, respectively.

136. A method of treating a disease in a subject in need thereof comprising administering to the subject an effective amount of the compound of any one of the preceding claims.

137. The method of claim 136, wherein 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.

138. The method of claim 137, wherein the disease is neurodegenerative disease.

139. The method of claim 138, wherein 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.

140. The method of claim 137, wherein the disease is cachexia or anorexia.

141. The method of claim 137, wherein the disease is obesity or obesity's complication.

142. The method of claim 141, wherein the obesity's complication is selected from the group consisting of glucose intolerance, hepatic steatosis, dyslipidemia, and a combination thereof.

143. The method of claim 137, wherein the disease is inflammatory disease.

144. The method of claim 143, wherein the inflammatory disease is selected from the group consisting of atopic dermatitis, allergy, asthma, and a combination thereof.

145. The method of claim 137, wherein the disease is viral-induced inflammatory reaction.

146. The method of claim 145, wherein the viral-induced inflammatory reaction is SARS-induced inflammatory pneumonitis, coronavirus disease 2019, or a combination thereof.

147. The method of claim 137, wherein the disease is Gulf War Syndrome or tuberous sclerosis.

148. The method of claim 137, wherein the disease is retinitis pigmentosa or transplant rejection.

149. The method of claim 137, wherein the disease is ischemic tissue injury or traumatic tissue injury.

150. The method of claim 137, wherein the disease is cancer.

151. The method of claim 150, wherein 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.

152. The method of claim 150, wherein the cancer is leukemia.

153. The method of claim 152, wherein the leukemia is adult T-cell leukemia/lymphoma.

154. The method of claim 153, wherein the adult T-cell leukemia/lymphoma is caused by human T-cell lymphotropic virus.

155. The method of claim 137, wherein the disease is autoimmune disease.

156. The method of claim 155, wherein 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.

157. The method of any one of claims 136-156, wherein the compound modulates Akt3 in immune cells.

158. The method of claim 157, wherein the immune cells are selected from the group consisting of T cells, B cells, macrophages, and glial cells.

159. The method of claim 158, wherein the glial cells are astrocytes, microglia, or oligodendrocytes.

160. The method of claim 158, wherein the T cells are T regulatory cells.

161. The method of claim 136 or 137, wherein the compound activates Akt3 signaling.

162. The method of claim 136 or 137, wherein the compound inhibits Akt3 signaling.

163. The method of claim 136 or 137, wherein the compound increases T regulatory cell activity or production.

164. The method of claim 136 or 137, wherein the compound decreases T regulatory cell activity or production.

165. The method of any one of claims 136-164, further comprising administering a second therapeutic agent to the subject.

166. The method of claim 165, wherein 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.

167. The method of any one of claims 136-164, wherein the method further comprises treating the subject with an immune therapeutic agent, an immune modulator, a 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.

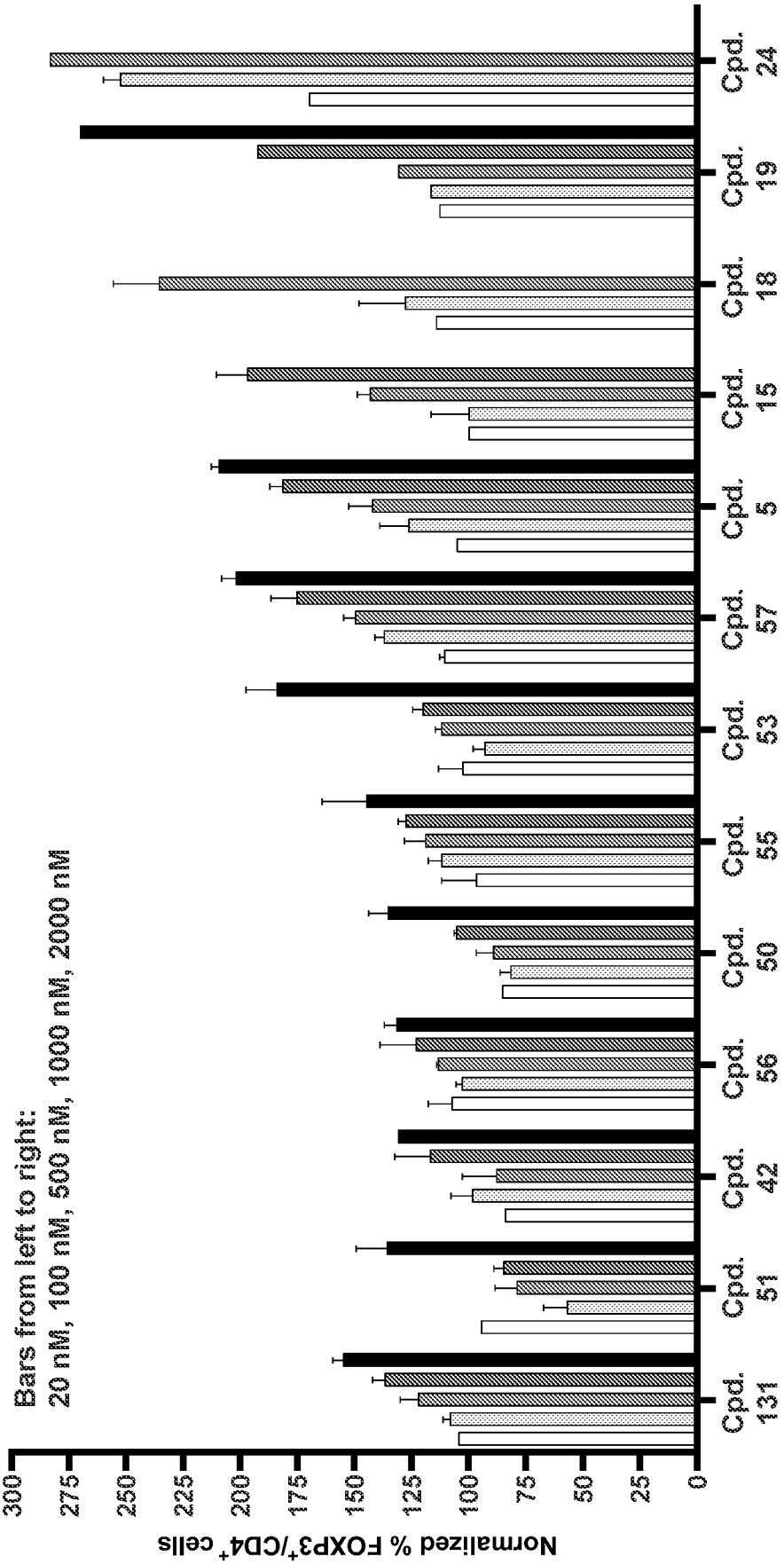

Normalized % FOXP3+/CD4+ cells
300
275
250
225
200
175
150
125
100
75
50
25
0
Bars from left to right:
20 nM, 100 nM, 500 nM, 1000 nM, 2000 nM
Cpd. 131
Cpd. 51
Cpd. 42
Cpd. 56
Cpd. 50
Cpd. 55
Cpd. 53
Cpd. 57
Cpd. 5
Cpd. 15
Cpd. 18
Cpd. 19
Cpd. 24

Figure 1

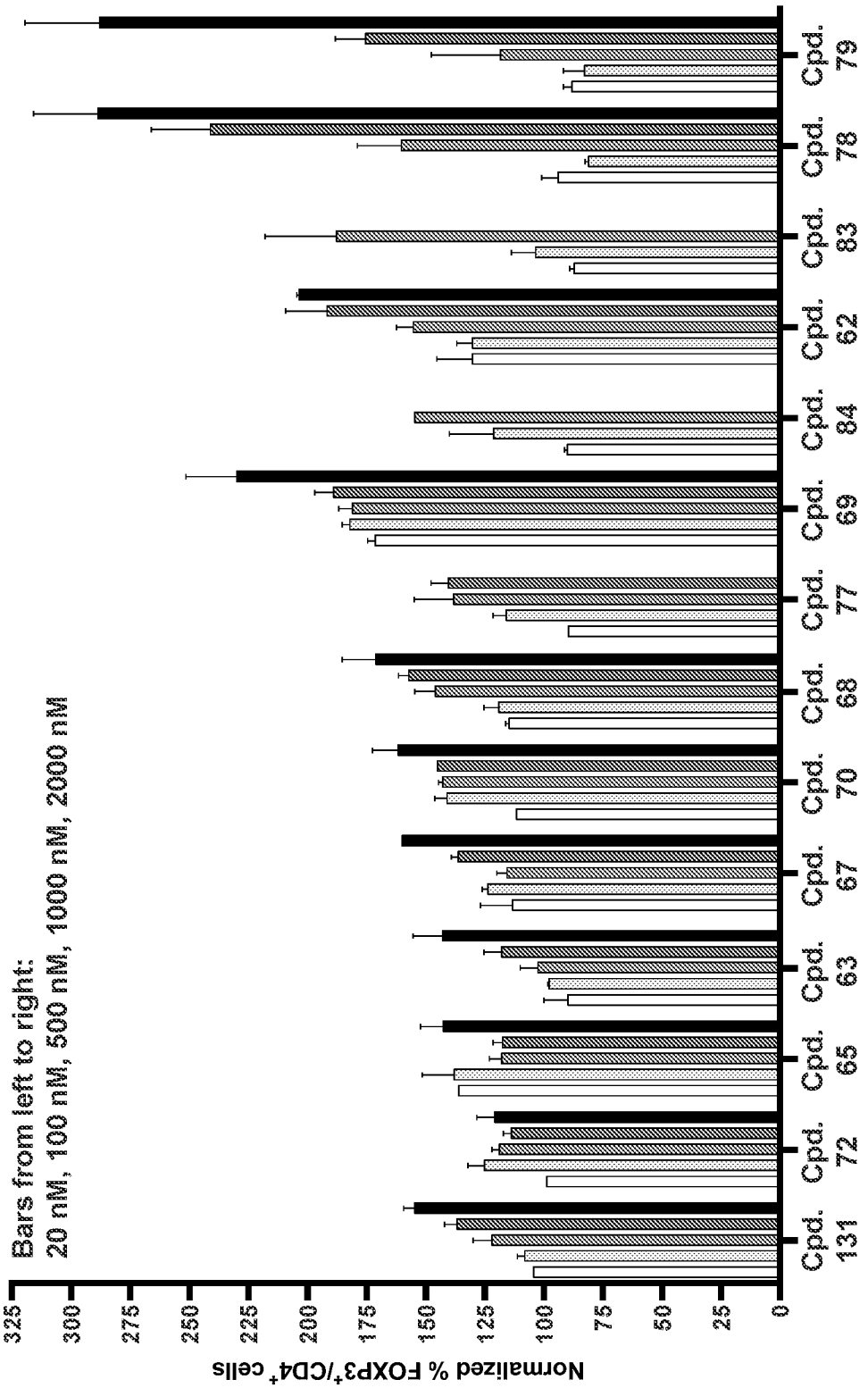

Normalized % FOXP3+/CD4+ cells
0
25
50
75
100
125
150
175
200
225
250
275
300
325
Bars from left to right:
20 nM, 100 nM, 500 nM, 1000 nM, 2000 nM
Cpd. 131
Cpd. 72
Cpd. 65
Cpd. 63
Cpd. 67
Cpd. 70
Cpd. 68
Cpd. 77
Cpd. 69
Cpd. 84
Cpd. 62
Cpd. 83
Cpd. 78
Cpd. 79

Figure 2

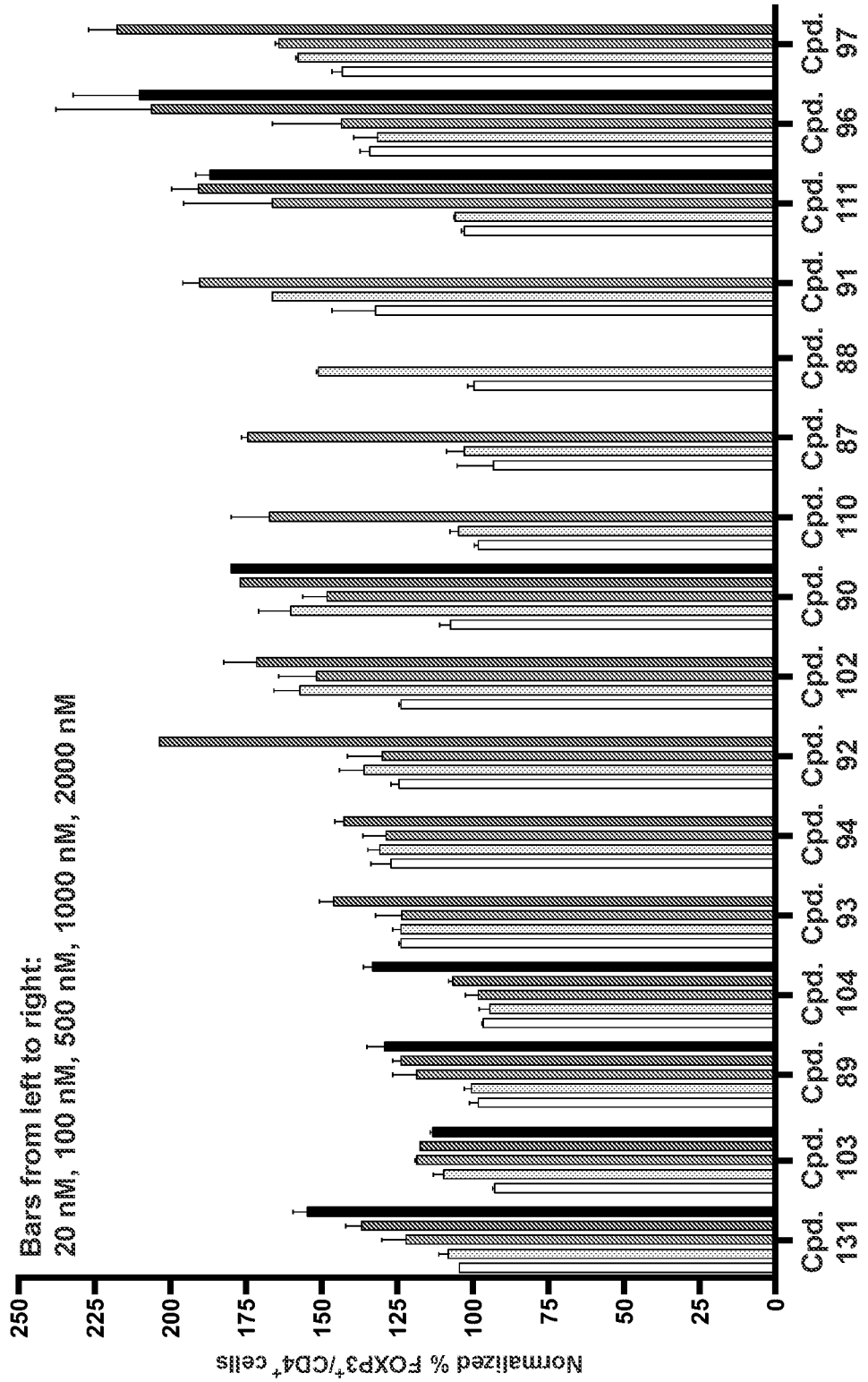

Normalized % FOXP3+/CD4+ cells
250
225
200
175
150
125
100
75
50
25
0
Bars from left to right:
20 nM, 100 nM, 500 nM, 1000 nM, 2000 nM
Cpd. 131
Cpd. 103
Cpd. 89
Cpd. 104
Cpd. 93
Cpd. 94
Cpd. 92
Cpd. 102
Cpd. 90
Cpd. 110
Cpd. 87
Cpd. 88
Cpd. 91
Cpd. 111
Cpd. 96
Cpd. 97

Figure 3

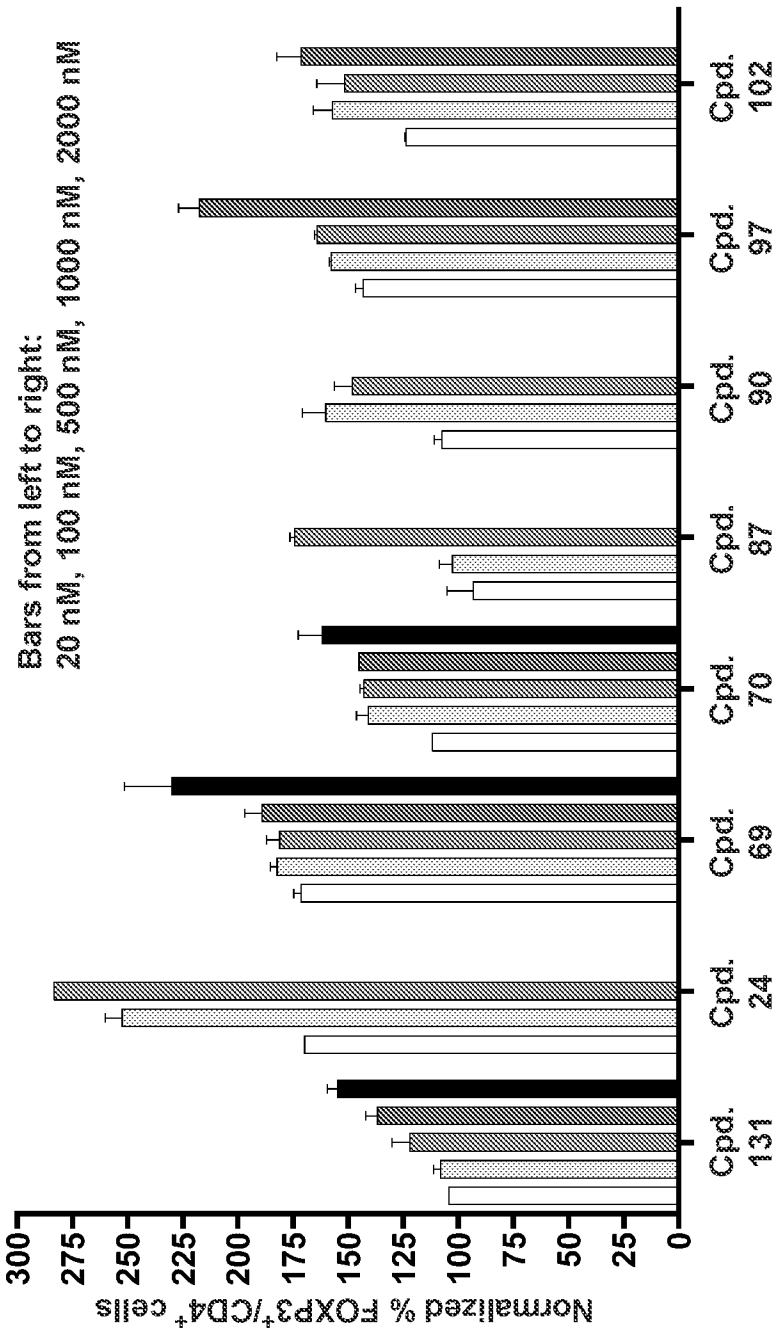

Bars from left to right:
20 nM, 100 nM, 500 nM, 1000 nM, 2000 nM
Normalized % FOXP3+/CD4+ cells
300
275
250
225
200
175
150
125
100
75
50
25
0
Cpd. 131
Cpd. 24
Cpd. 69
Cpd. 70
Cpd. 87
Cpd. 90
Cpd. 97
Cpd. 102

Figure 4

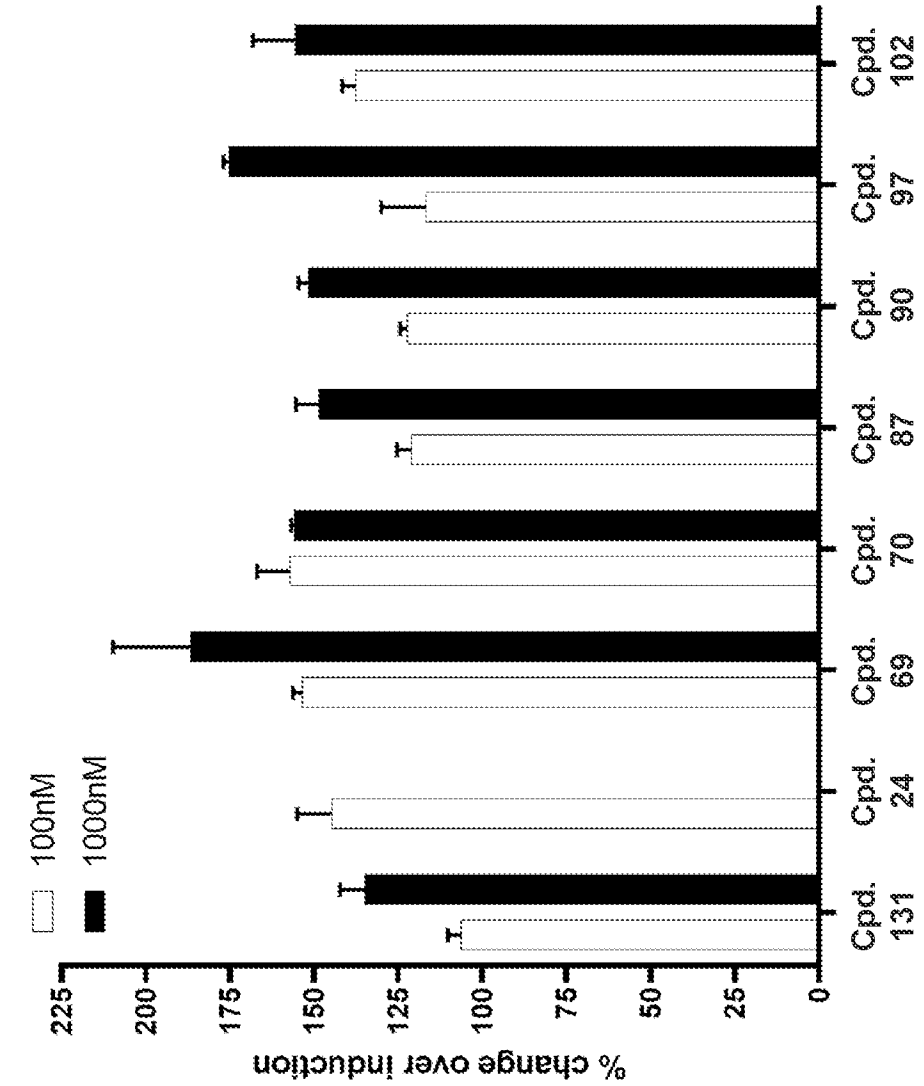

% change over induction
225
200
175
150
125
100
75
50
25
0
100nM
1000nM
Cpd. 131
Cpd. 24
Cpd. 69
Cpd. 70
Cpd. 87
Cpd. 90
Cpd. 97
Cpd. 102

Figure 5

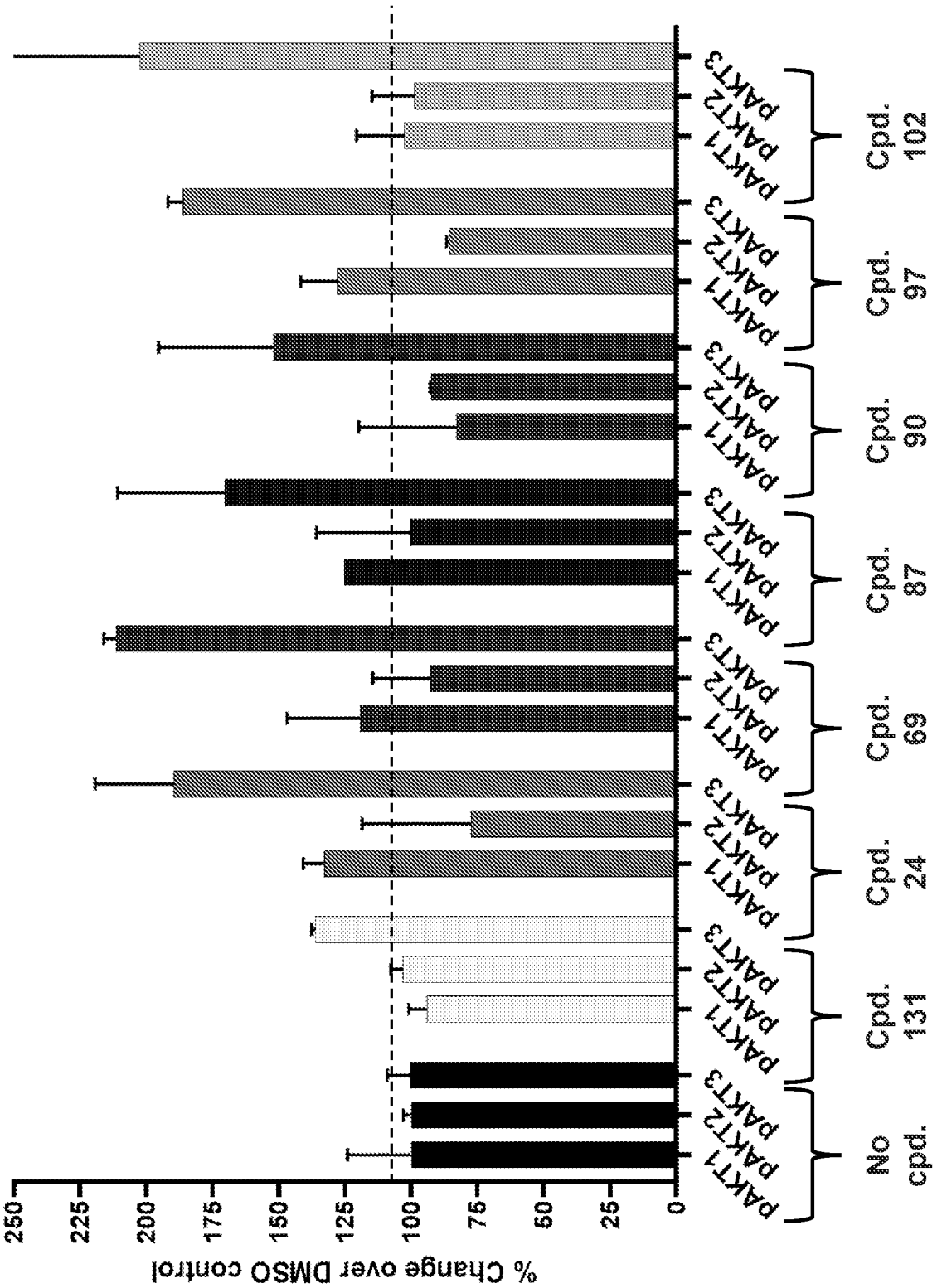

% Change over DMSO control
250
225
200
175
150
125
100
75
50
25
0
PAKT1
PAKT2
PAKT3
No cpd.
Cpd. 131
Cpd. 24
Cpd. 69
Cpd. 87
Cpd. 90
Cpd. 97
Cpd. 102

Figure 6

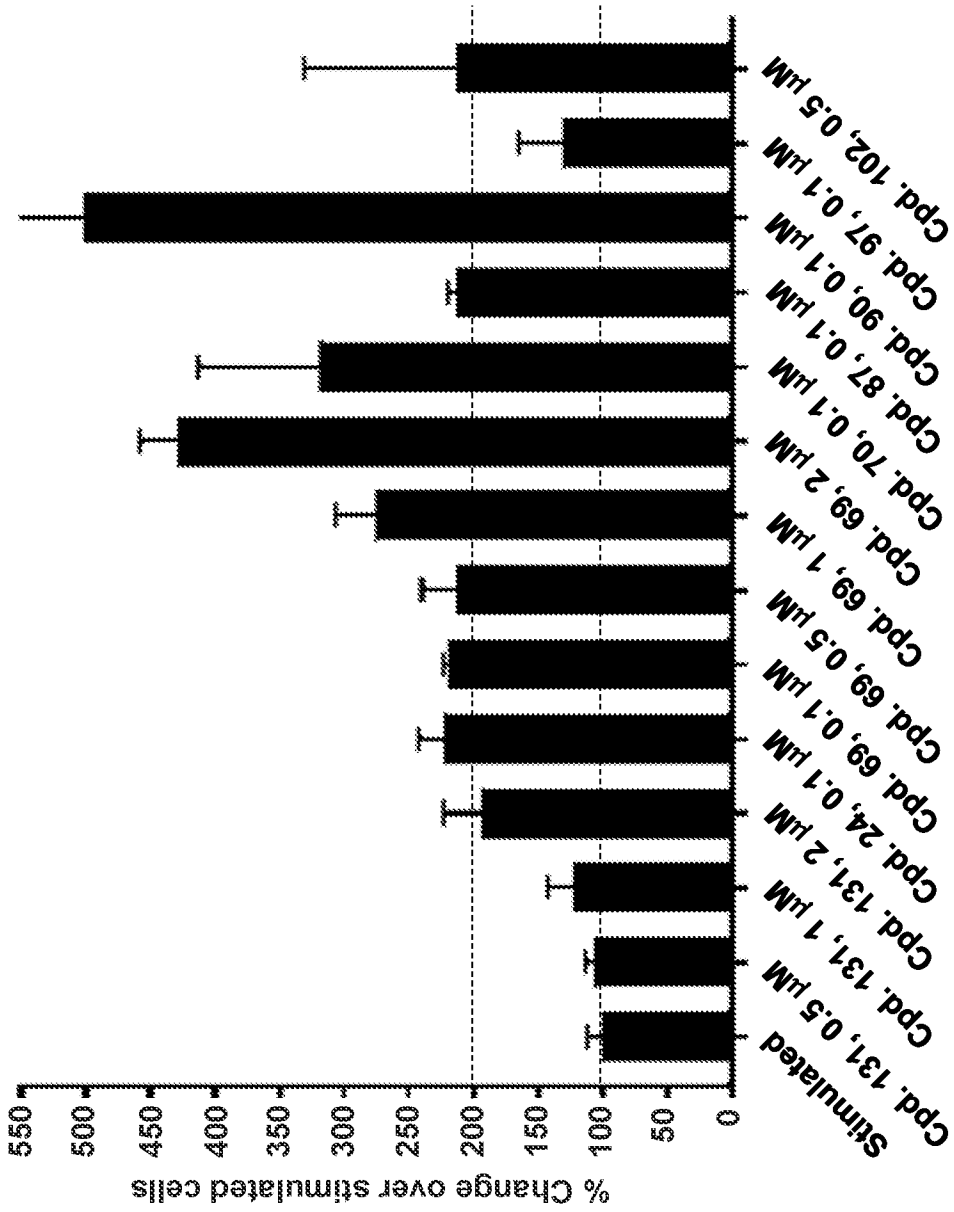

% Change over stimulated cells
550
500
450
400
350
300
250
200
150
100
50
0
Stimulated
Cpd. 131, 0.5 µM
Cpd. 131, 1 µM
Cpd. 131, 2 µM
Cpd. 24, 0.1 µM
Cpd. 69, 0.1 µM
Cpd. 69, 0.5 µM
Cpd. 69, 1 µM
Cpd. 69, 2 µM
Cpd. 70, 0.1 µM
Cpd. 87, 0.1 µM
Cpd. 90, 0.1 µM
Cpd. 97, 0.1 µM
Cpd. 102, 0.5 µM

Figure 7

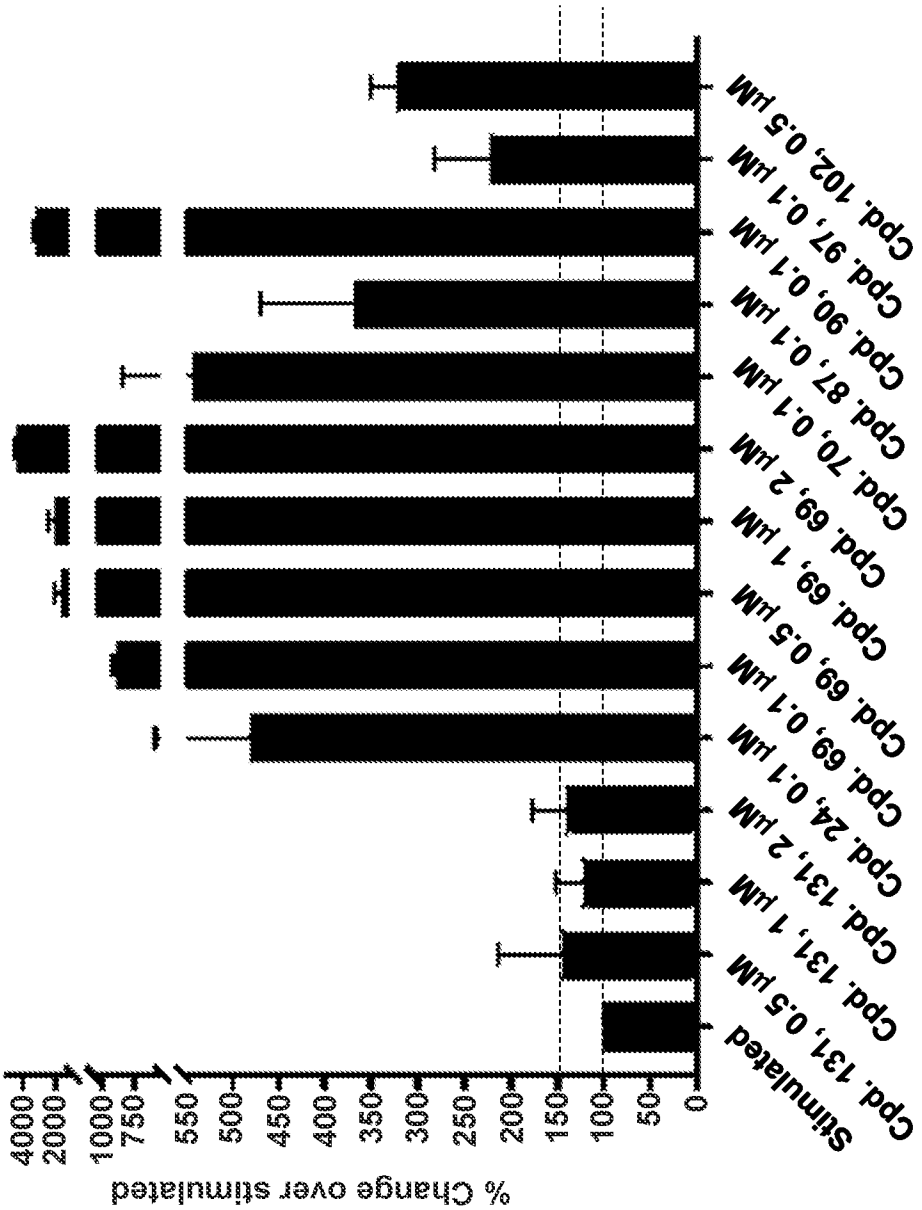

% Change over stimulated
4000
2000
1000
750
550
500
450
400
350
300
250
200
150
100
50
0
Stimulated
Cpd. 131, 0.5 µM
Cpd. 131, 1 µM
Cpd. 131, 2 µM
Cpd. 24, 0.1 µM
Cpd. 69, 0.1 µM
Cpd. 69, 0.5 µM
Cpd. 69, 1 µM
Cpd. 69, 2 µM
Cpd. 70, 0.1 µM
Cpd. 87, 0.1 µM
Cpd. 90, 0.1 µM
Cpd. 97, 0.1 µM
Cpd. 102, 0.5 µM

Figure 8

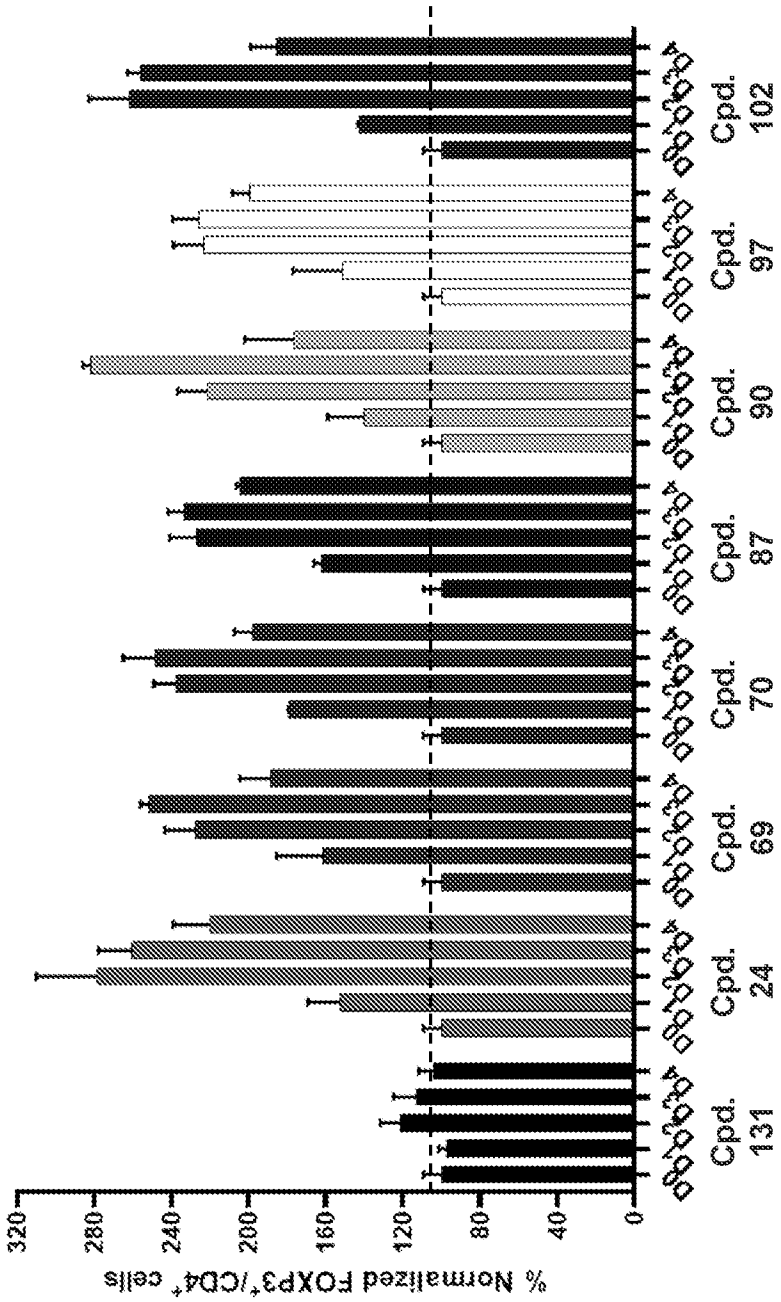

% Normalized FOXP3+/CD4+ cells
320
280
240
200
160
120
80
40
0
Cpd. 131
Cpd. 24
Cpd. 69
Cpd. 70
Cpd. 87
Cpd. 90
Cpd. 97
Cpd. 102

Figure 9

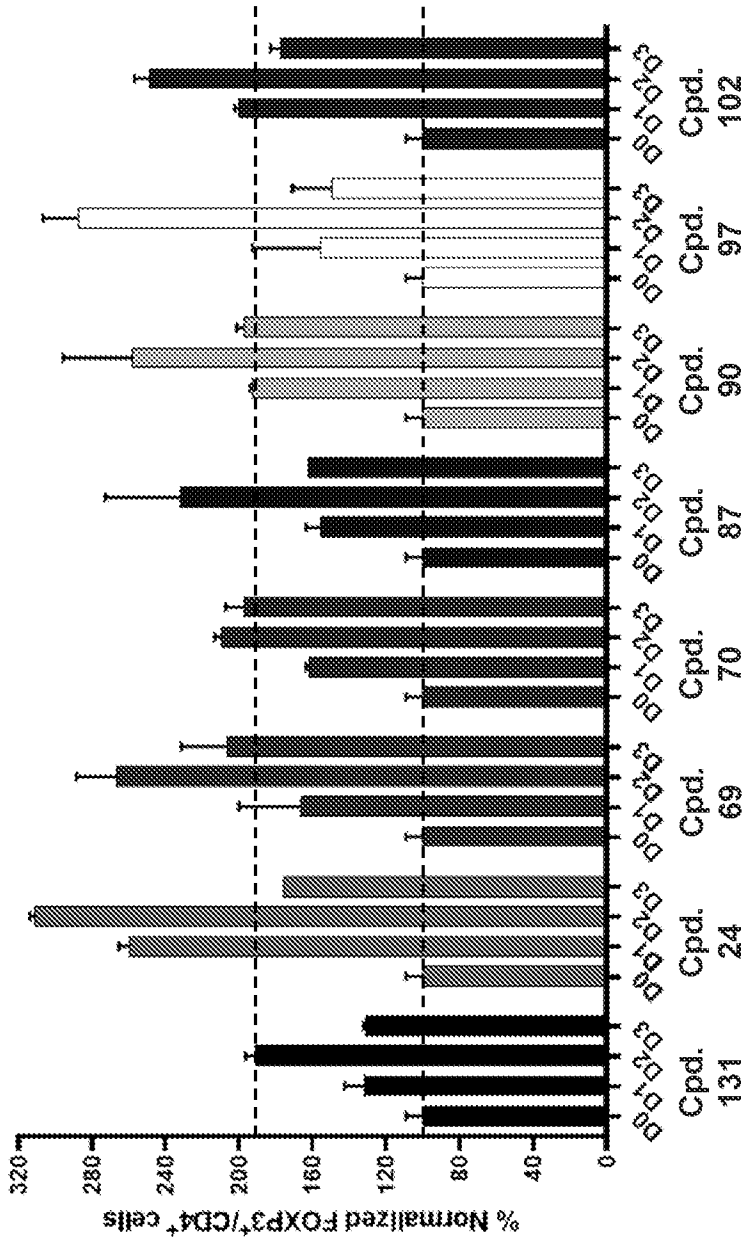

% Normalized FOXP3+/CD4+ cells
320
280
240
200
160
120
80
40
0
DO
D1
D3
D4
Cpd. 131
Cpd. 24
Cpd. 69
Cpd. 70
Cpd. 87
Cpd. 90
Cpd. 97
Cpd. 102

Figure 10

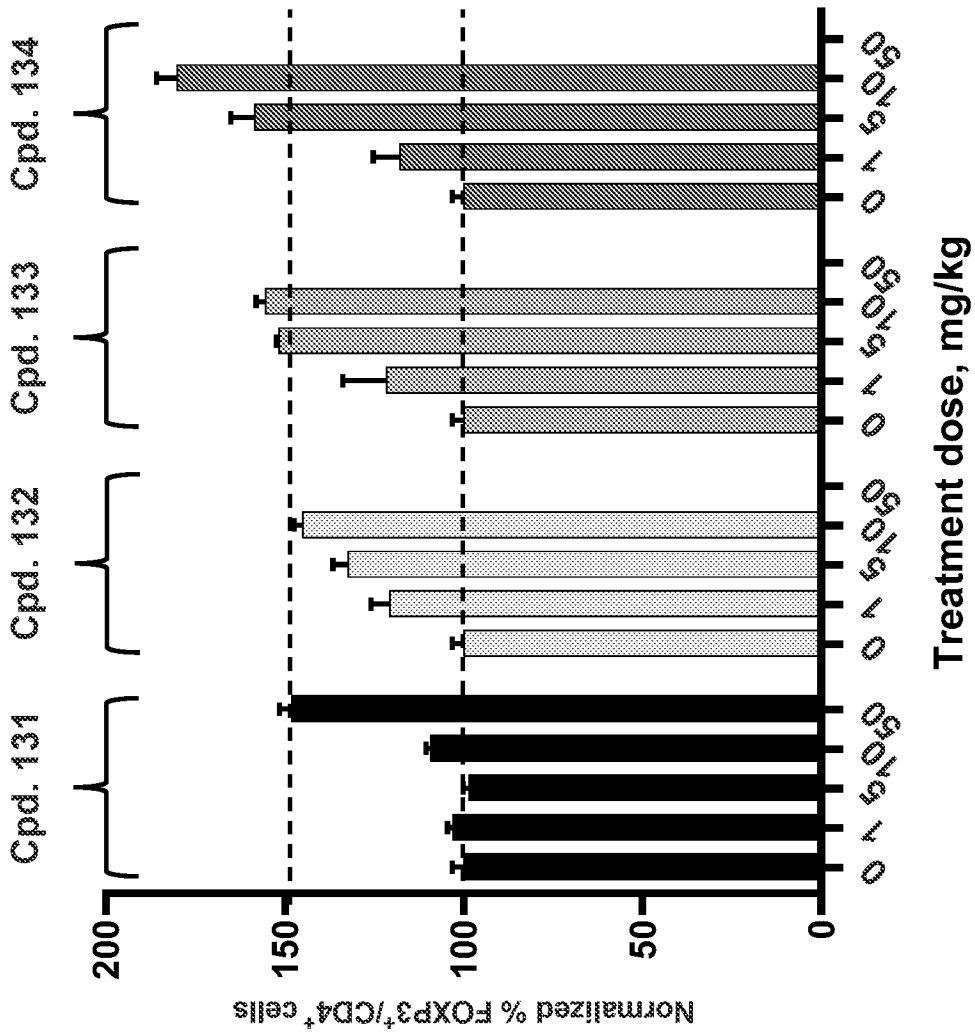

Normalized % FOXP3+/CD4+ cells
200
150
100
50
0
Cpd. 131
Cpd. 132
Cpd. 133
Cpd. 134
0
1.5625
3.125
6.25
12.5
25
50
100
Treatment dose, mg/kg

Figure 11

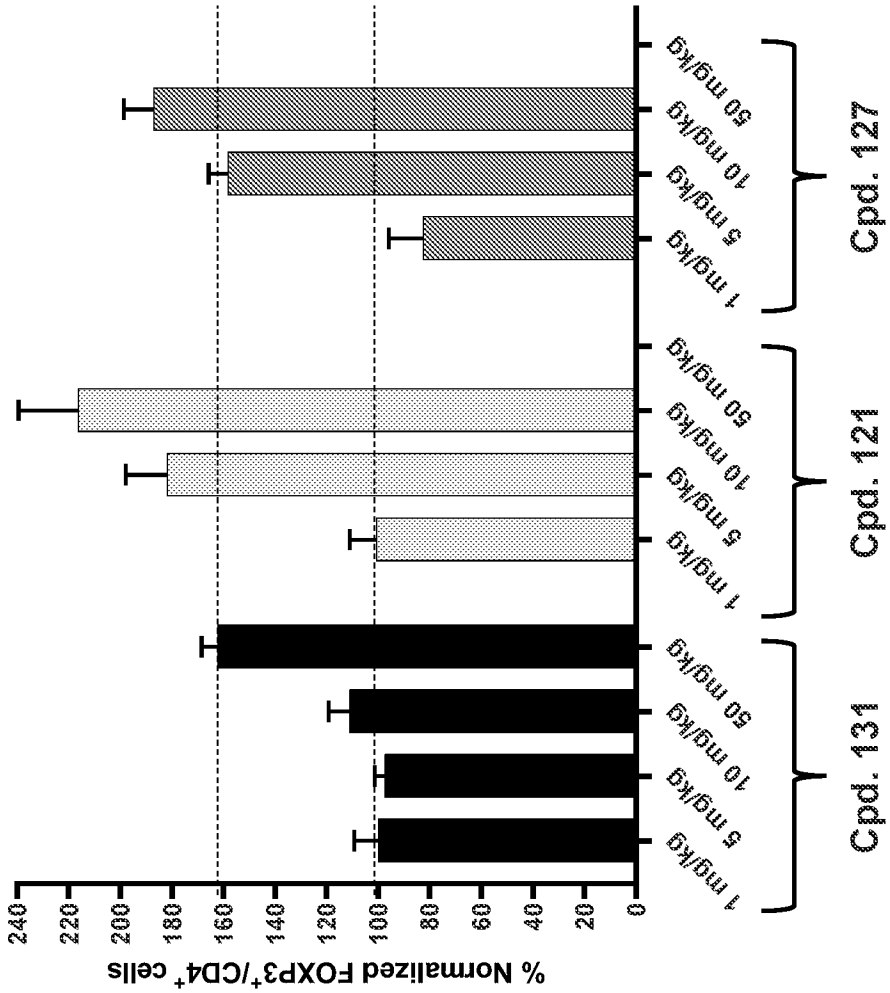

% Normalized FOXP3+/CD4+ cells
0
20
40
60
80
100
120
140
160
180
200
220
240
1 mg/kg
5 mg/kg
10 mg/kg
50 mg/kg
Cpd. 131
1 mg/kg
5 mg/kg
10 mg/kg
50 mg/kg
Cpd. 121
1 mg/kg
5 mg/kg
10 mg/kg
50 mg/kg
Cpd. 127

Figure 12

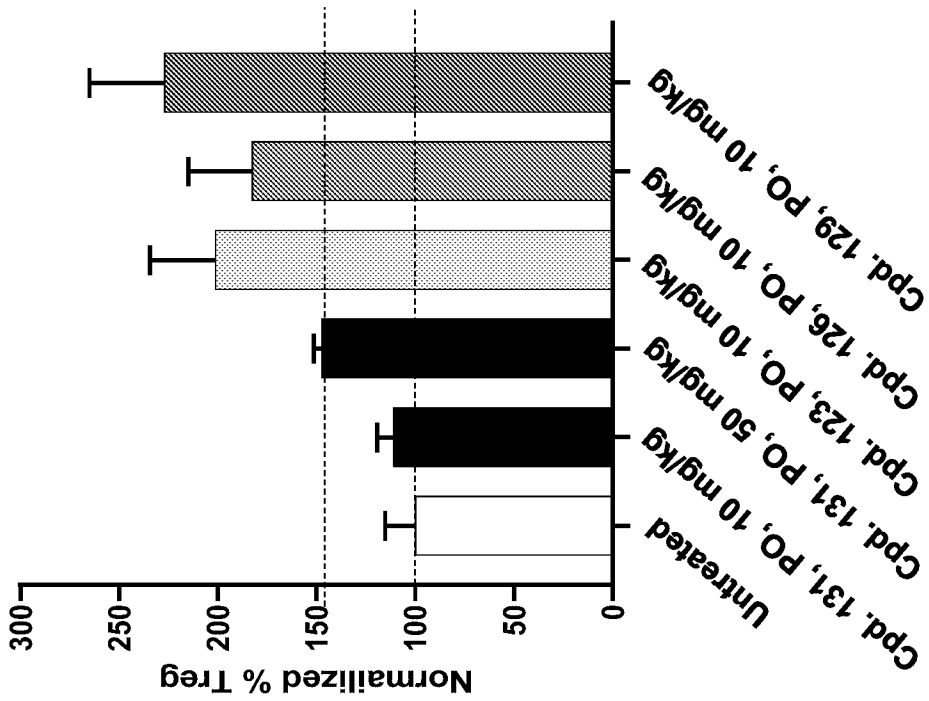

Normalized % Treg
300
250
200
150
100
50
0
Untreated
Cpd. 131, PO, 10 mg/kg
Cpd. 131, PO, 50 mg/kg
Cpd. 123, PO, 10 mg/kg
Cpd. 126, PO, 10 mg/kg
Cpd. 129, PO, 10 mg/kg

Figure 13

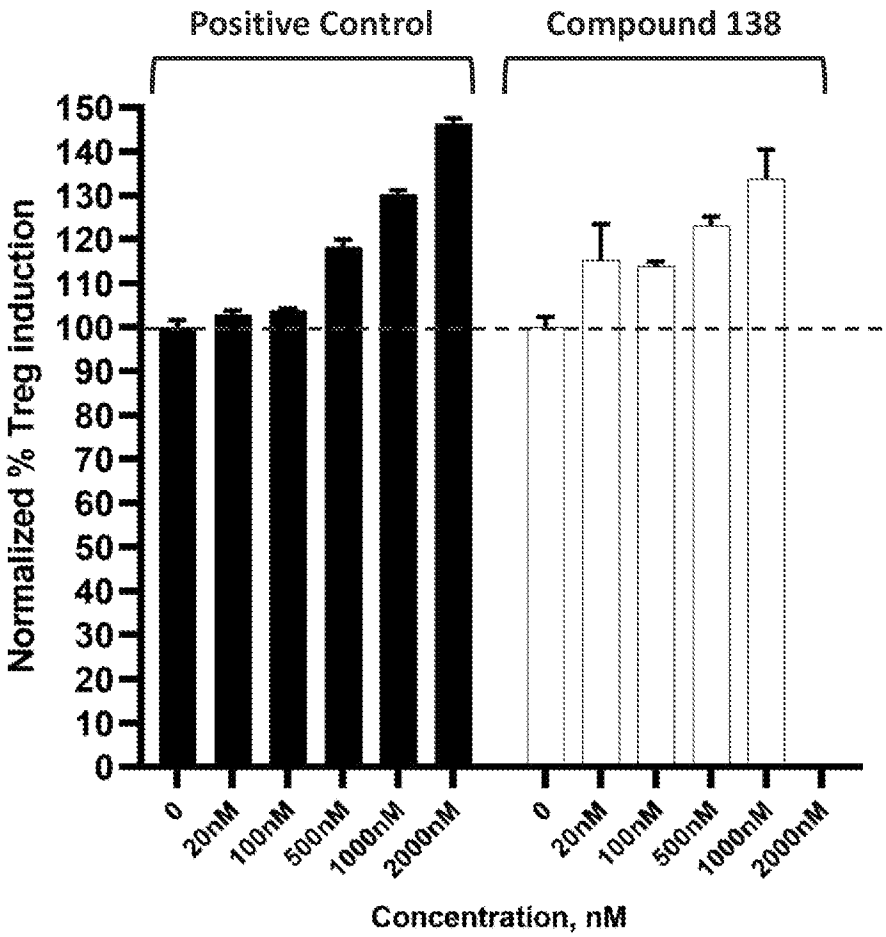

Positive Control
Compound 138
Normalized % Treg induction
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
0
20nM
100nM
500nM
1000nM
2000nM
0
20nM
100nM
500nM
1000nM
2000nM
Concentration, nM

Figure 14

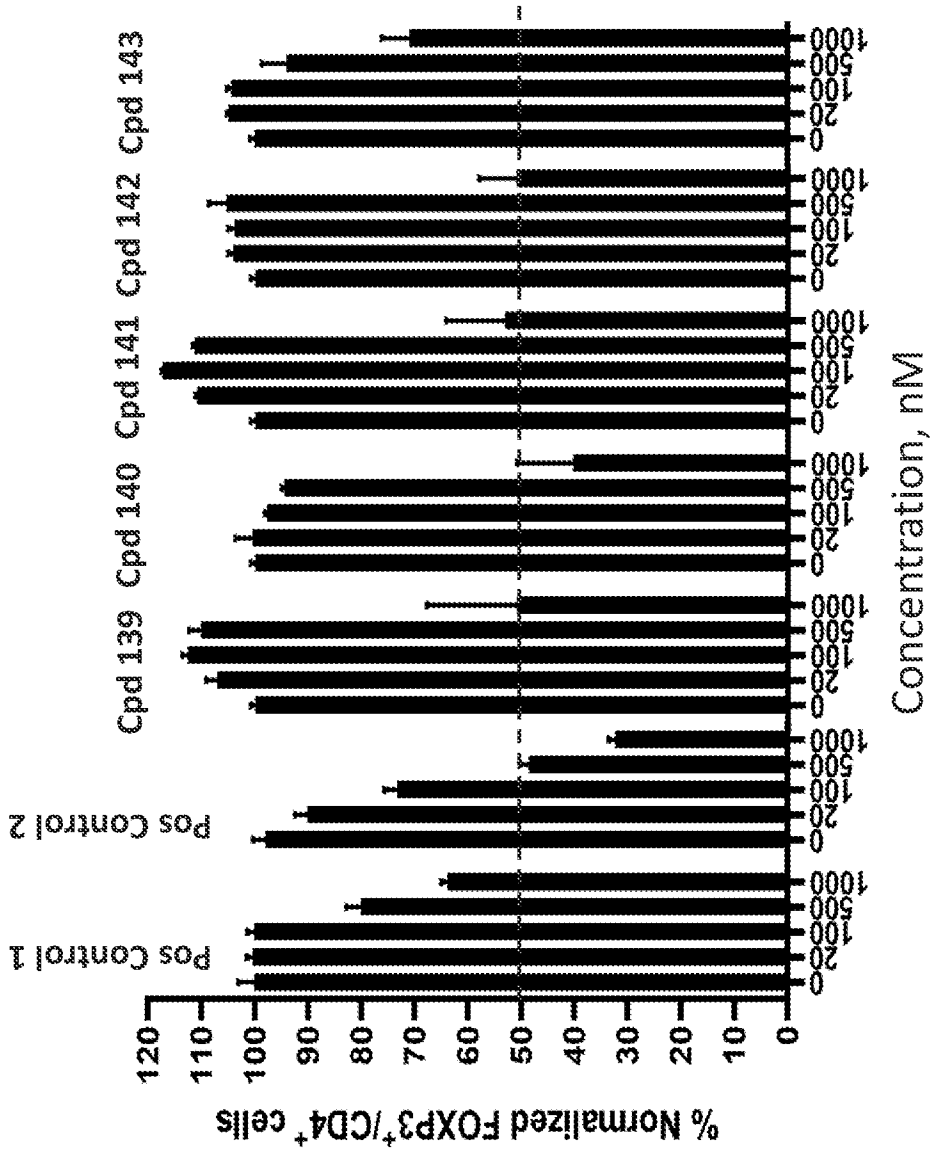

% Normalized FOXP3+/CD4+ cells
120
110
100
90
80
70
60
50
40
30
20
10
0
Pos Control 1
Pos Control 2
Cpd 139
Cpd 140
Cpd 141
Cpd 142
Cpd 143
0
20
100
500
1000
Concentration, nM

Figure 15

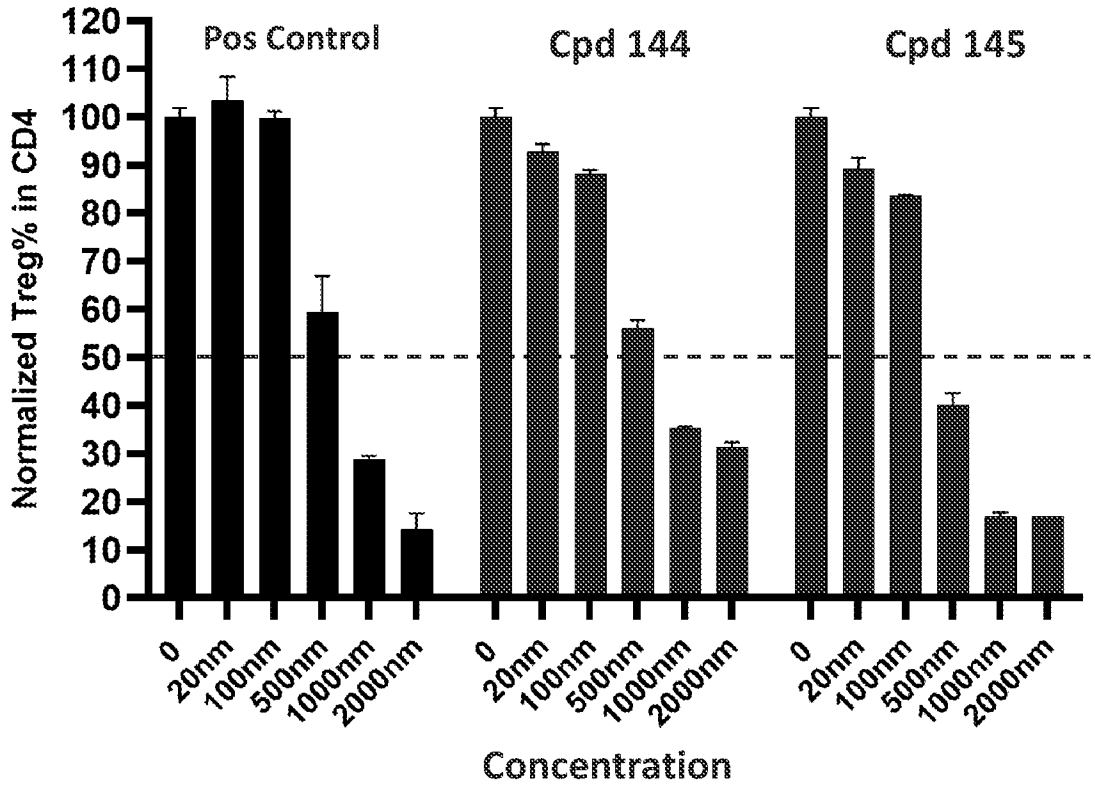

Pos Control
Cpd 144
Cpd 145
Normalized Treg% in CD4
120
110
100
90
80
70
60
50
40
30
20
10
0
0
20nm
100nm
500nm
1000nm
2000nm
Concentration

Figure 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/79344

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/167, C07D 213/74, C07D 401/12 (2022.01)
ADD. C07D 401/14 (2022.01)

CPC - INV. A61K 31/167, C07D 213/74, C07D 401/12
ADD. C07D 401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/049132 A1 (SUPERGEN, INC.) 16 April 2009 (16.04.2009) abstract; pg 150, ln 1-4	1, 3/1, 49, 109, 110/(1,109)
A	US 2017/0202829 A1 (AUGUSTA UNIVERSITY RESEARCH INSTITUTE, INC.) 20 July 2017 (20.07.2017) para [0057]	1, 3/1, 49, 109, 110/(1,109)
A	PUBCHEM-SID:244652007 Deposit Date: 17 March 2015 (17.03.2015) pages 1-7; pg 2	1, 3/1, 49, 109, 110/(1,109)
A	US 2011/0201602 A1 (GEUNS-MEYER et al.) 18 August 2011 (18.08.2011) para [0033], pg 70, compound 138	1, 3/1, 49, 109, 110/(1,109)

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 2022	MAR 03 2023
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/79344

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-48, 54-56, 58-71, 75, 77, 79, 85, 86, 88-91, 97, 98, 100-104, 111-117 and 136-167
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--Please see attached sheet----

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 3/1, 49, 109 and 110/(1,109)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/79344

Attachment to Box No. III:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-3, 49-53, 57, 72-74, 76, 78, 80-84, 87, 92-96, 99, 105-110 and 118-135, directed to a compound of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc, or a pharmaceutically acceptable salt thereof, as described n the claims and selected from the compounds specified in claims 127-135.
The compound will be searched to the extent that the compound encompasses the first species of claim 1, represented by Formula Ia, wherein A is the first moiety specified in claim 1, wherein each occurrence of Xi, X2, X3, X4, X5, X6, X7 is CR1, wherein each R1 is H; Q is C(Ra)2, wherein each occurrence of Ra is H;
Y1, Y2, Y3, Y4 are each N;
-E-G- is -C(=O)NRx-, wherein Rx is H;
Z1, Z2, Z3, Z4 are each N;
V is absent; and R4 is C1-alkyl, which is unsubstituted.
It is believed that claims 1, 3/1, 49, 109, 110/(1,109), read on this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1, described above. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines.€
Applicant is invited to elect additional compound(s) wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the first -listed compound of claim 127, represented by Formula Ia, wherein
A is the first moiety specified in claim 1, wherein each occurrence of X1, X3, X4, X5, X6, X7 is CR1, wherein each R1 is independently H or halo; X2 is N; Q is NRa, wherein Ra is H;
Y1, Y2, Y3, Y4 are each CR2, wherein each R2 is H;
-E-G- is -C(=O)NRx-, wherein Rx is H;
Z1, Z2, Z3, Z4 are each CR3, wherein each R3 is H; V is NRa, wherein Ra is H; and R4 is heteroaryl, substituted with one R5, wherein R5 is C1-alkyl, which is unsubstituted (i.e., claims 1-3, 49, 53/(1,49), 72/(1,49), 106, 110/(1,106), 118-119, and 127).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ share the technical features of a compound having the core structure of Formula Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, or IVc, or a pharmaceutically acceptable salt thereof.
This shared technical feature, however, does not provide a contribution over the prior art, as being anticipated by US 2017/0202829 A1 to Augusta University Research Institute, Inc. (hereinafter Augusta), which discloses a compound of formula IIa, wherein
A is the first moiety specified in claim 1, wherein each occurrence of X1, X3, X4, X5, X6, X7 is CR1, wherein each R1 is independently H or NO2; and X2 is N;
Q is NRa, wherein Ra is H;
Y1, Y2, Y3, Y4 are each CR2, wherein each R2 is H;
-E-G- is -C(=O)NRx-, wherein Rx is H;
Z1, Z2, Z3, Z4 are each CR3, wherein each R3 is H;
V is NRa, wherein Ra is H; and R4 is heteroaryl, which is unsubstituted, such that the compound s other than the excluded compounds of claim 1 (para [0057], compound (5)).
As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature, that would otherwise unify the inventions of Group I+.

The inventions of Groups I+, thus lack unity under PCT Rule 13.

item 4(contd): Claims 4-48, 54-56, 58-71, 75, 77, 79, 85, 86, 88-91, 97, 98, 100-104, 111-117 and 136-167 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are, therefore, not included in the above analysis.