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(54) Title: 1,4-PYRIDONE BICYCLIC HETEROARYL COMPOUNDS

(57) Abstract: The present invention relates to 1,4-pyridone bicyclic heteroaryl compounds. The present invention also relates to pharmaceutical compositions containing these compounds and methods of treating cancer by administering these compounds and pharmaceutical compositions to subjects in need thereof. The present invention also relates to the use of such compounds for research or other non-therapeutic purposes.

1,4-PYRIDONE BICYCLIC HETEROARYL COMPOUNDS

RELATED APPLICATIONS

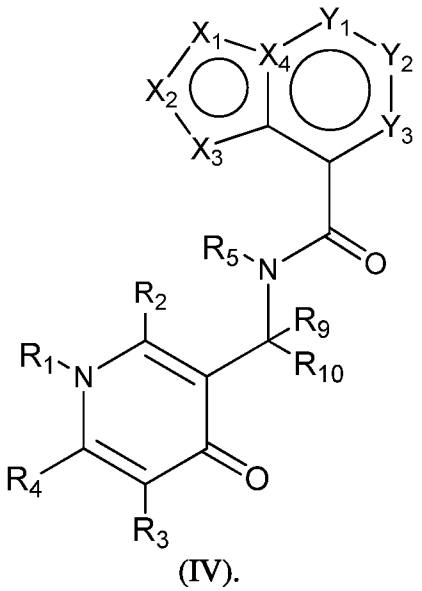
[001] This application claims priority to, and the benefit of, U.S. provisional application No. 61/745,194, filed December 21, 2012 and U.S. provisional application No. 61/785,042, filed March 14, 2013. The entire contents of each of these applications are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

[002] There is an ongoing need for new agents as inhibitors of EZH2 mutants, which can be used for treating an EZH2-mediated disorder (e.g., cancer).

SUMMARY OF THE INVENTION

[003] In one aspect, the present invention features an azole bicyclic heteroaryl compound of Formula (IV) below or a pharmaceutically acceptable salt thereof.



(IV).

In this Formula,

X_1 is NR_7 or CR_7;

X_2 is N, NR_8, CR_8, O, or S;

X_3 is NR_8, CR_8, O, or S;

X_4 is C or N;

Y_1 is N or CH;

Y_2 is N or CR_6;

Y_3 is N, or CR_{11}, and at least one of X_1, X_2, X_3, X_4, Y_1, Y_2, and Y_3 is N or NR_7;

each of R_1, R_5, R_9, and R_{10}, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_1 is H, halo, hydroxyl, COOH, cyano, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C_1-C_6 thioalkyl, C(O)O-C_1-C_6 alkyl, $CONH_2$, SO_2NH_2, -CO-NH(C_1-C_6 alkyl), -CO-N(C_1-C_6 alkyl)$_2$, -SO_2-NH(C_1-C_6 alkyl), - SO_2-N(C_1-C_6 alkyl)$_2$, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_6-C_{10} aryloxy,amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, and 5 to 6-membered heteroaryl; or R_1 and R_2, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R_1 and R_4, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R_3 and R_4, together with the C atoms to which they are attached, form C_5-C_8 cycloalkyl, C_6-C_{10} aryl, or a 5- or 6-membered heteroaryl having 1 to 3 heteroatoms, or a 5 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms; in which each of the ring structures formed by R_1 and R_2, by R_1 and R_4, or by R_3 and R_4, independently is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, C_1-C_6 alkyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each R_6 independently is H, halo, OR_a, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_2R_a$, $-S(O)_2NR_aR_b$, or R_{S2}, in which each of R_a and R_b, independently is H or R_{S3} and each of R_{S2} and R_{S3}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom; and each of R_{S2}, R_{S3}, and the 4 to 7-membered heterocycloalkyl ring containing R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano, $-OR_c$, $-NR_cR_d$, $-(NR_cR_dR_{d'})^+A^-$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c R_d, and $R_{d'}$, independently is H or R_{S5}, A^- is a pharmaceutically acceptable anion, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom, and each of R_{S4}, R_{S5}, and the 4 to 7-membered heterocycloalkyl ring containing R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of H, halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, 5 to 6-membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl optionally substituted with OH, O-C_1-C_6 alkyl, or NH-C_1-C_6 alkyl; or $-Q_3$-T_3 is oxo; or $-Q_2$-T_2 is oxo; or any two neighboring $-Q_2$-T_2, together with the atoms to which they are attached form a 5- or 6-membered ring optionally containing 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, and 5 to 6-membered heteroaryl; provided that $-Q_2$-T_2 is not H;

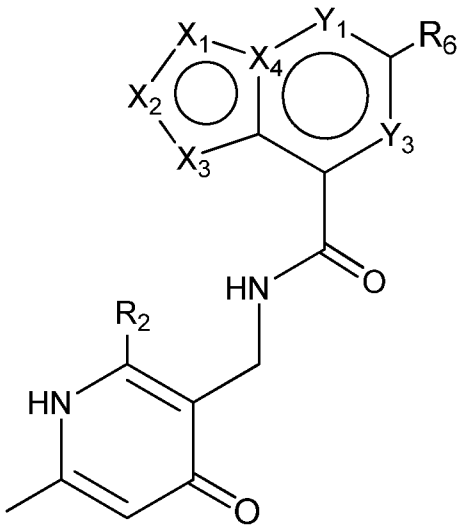
each R_7 independently is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl

or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, -OR_g, -$C(O)R_g$, -$C(O)OR_g$, -$C(O)NR_gR_h$, -$C(O)NR_gOR_h$, -$NR_gC(O)R_h$, -$S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more –Q_5-T_5, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, NR_k, $S(O)_2$, $NR_kS(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_1-C_6 alkylene-C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_1-C_6 alkylene-C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, C_1-C_6 alkylene-4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or C_1-C_6 alkylene-5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, O-C_1-C_4 alkylene-C_1-C_4 alkoxy, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, and 5 to 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or –Q_5-T_5 is oxo; provided that –Q_4-T_4 is not H; and

each of R_8 and R_{11}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino.

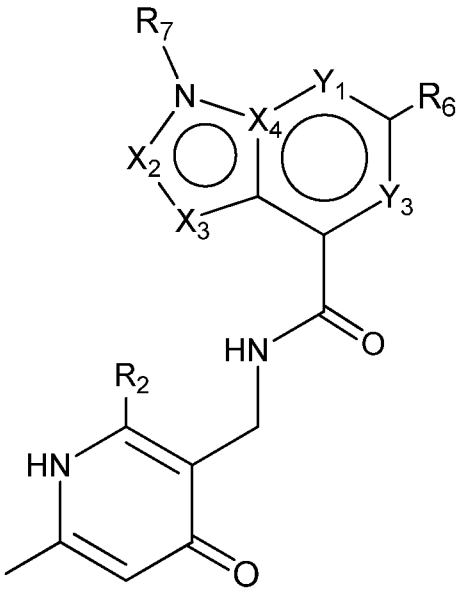
[004] In one subset of the compounds of Formula (IV), at least one of Y_1, Y_3, and X_4 is N and when X_4 is C, Y_1 is N, Y_2 is CR_6, and Y_3 is CR_{11}, then X_2 is CR_8.

[005] One subset of the compounds of Formula (IV) includes those of Formula (IVa):



(IVa).

[006] Another subset of the compounds of Formula (IV) includes those of Formula (IVb).



(IVb).

[007] The compounds of Formulae (IV), (IVa), and (IVb) can include one or more of the following features when applicable:

[008] X_4 is C.

[009] X_2 is N or CH.

[010] X_3 is CR_8.

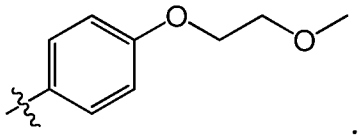
[011] Y_3 is CR_{11}.

[012] R_6 is phenyl substituted with one or more $-Q_2$-T_2.

[013] R_6 is 5 to 6-membered heteroaryl containing 1-3 additional heteroatoms selected from N, O, and S and optionally substituted with one or more $-Q_2$-T_2, provided that the heteroaryl is not thiophenyl.

[014] R_6 is pyridinyl, pyrazolyl, pyrimidinyl, or furyl, each of which is optionally substituted with one or more $-Q_2-T_2$.

[015] R_6 is phenyl or 5- or 6-membered heteroaryl substituted with O-C_{1-6} alkyl or NH-C_{1-6} alkyl, each of which is optionally substituted with hydroxyl, O-C_{1-3} alkyl or NH-C_{1-3} alkyl, each of the O-C_{1-3} alkyl and NH-C_{1-3} alkyl being optionally further substituted with O-C_{1-3} alkyl or NH-C_{1-3} alkyl.

[016] R_6 is  .

[017] R_6 is halo, C_1-C_3 alkyl substituted with one or more $-Q_2-T_2$, C_2-C_6 alkenyl, C_4-C_6 cycloalkyl, C(O)H, OR_a, or $-C(O)R_a$, in which R_a is C_1-C_6 alkyl or 4 to 7-membered heterocycloalkyl.

[018] R_6 is 4 to 7-membered heterocycloalkyl optionally substituted with one or more $-Q_2-T_2$, in which $-Q_2-T_2$ is oxo or Q_2 is a bond and T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-S(O)_2R_c$, C_1-C_6 alkyl, or 4 to 7-membered heterocycloalkyl, each of which is optionally substituted with one or more $-Q_3-T_3$ when R_c or R_d is not H.

[019] R_6 is piperidinyl, 2,2,6,6-tetramethyl-piperidinyl, 1,2,3,6-tetrahydropyridinyl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, or pyrrolidinyl, each of which is optionally substituted with one or more $-Q_2-T_2$.

[020] Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, halo, OR_e, $-S(O)_2R_e$, $-NR_eR_f$, and-$C(O)NR_eR_f$.

[021] R_7 is C_1-C_6 alkyl, C_2-C_4 alkenyl, C_4-C_6 cycloalkyl, 4 to 7-membered heterocycloalkyl, or C_6-C_{10} aryl, each optionally substituted with one or more $-Q_5-T_5$.

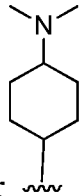
[022] R_7 is cyclopentyl.

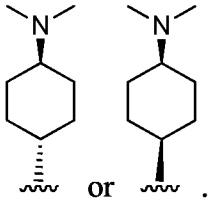
[023] R_7 is unsubstituted C_1-C_6 alkyl.

[024] R_7 is isopropyl or sec-butyl.

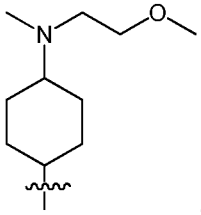
[025] R_7 is 5 to 6-membered heterocycloalkyl optionally substituted with one or more $-Q_5-T_5$.

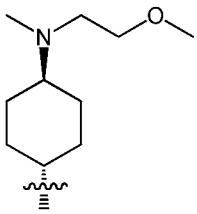
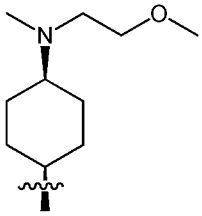
[026] R_7 is piperidinyl optionally substituted with one $-Q_5-T_5$.

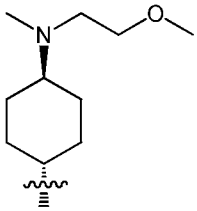
[027] R_7 is tetrahydropyran or  .

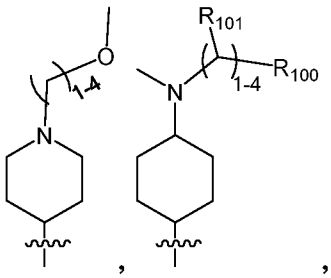
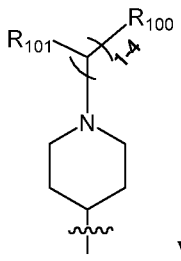
[028] R_7 is  or .

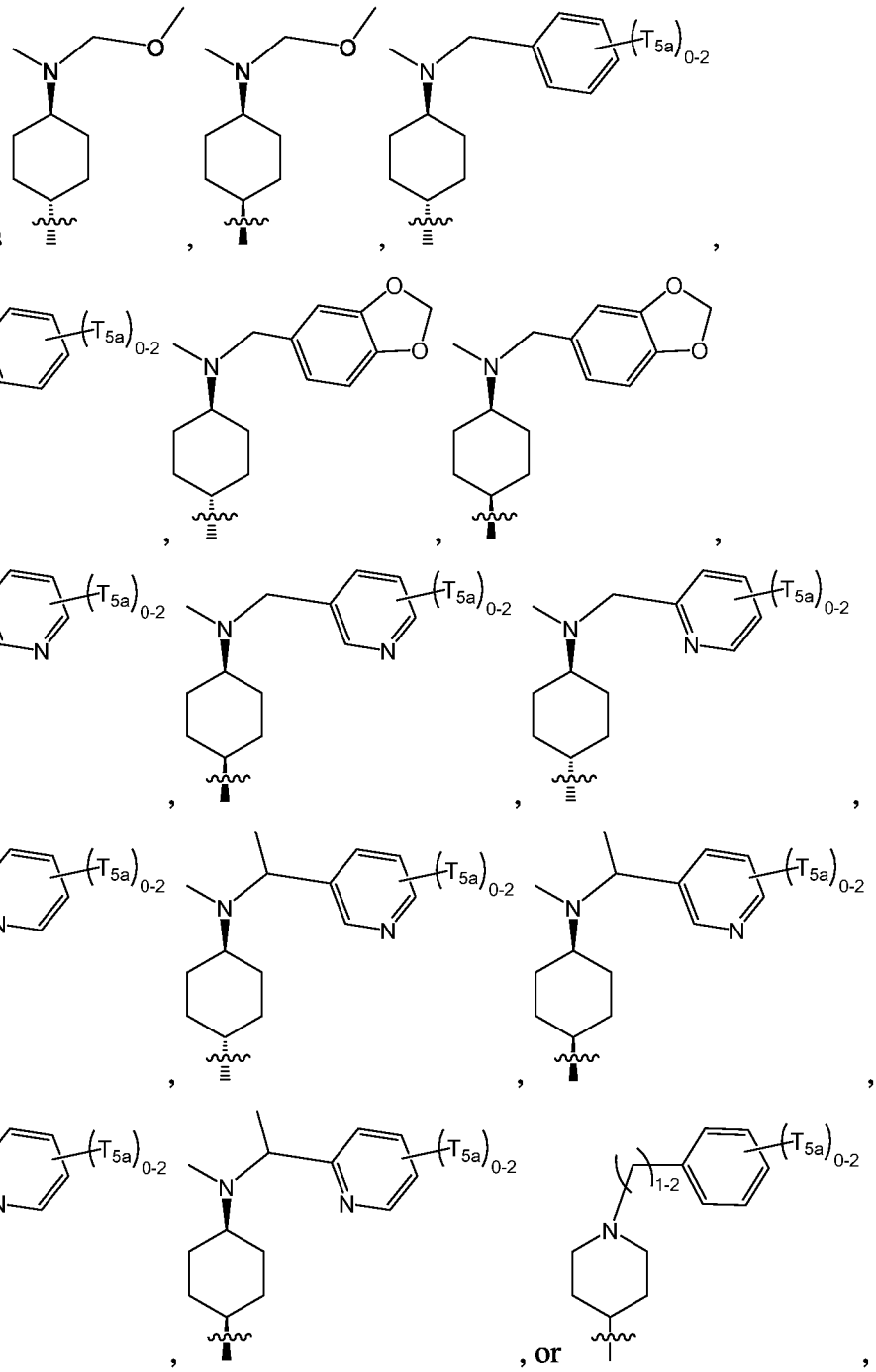
[029] R_7 is  .

[030] R_7 is  .

[031] R_7 is  or  .

[032] R_7 is  .

[033] R_7 is  ,  , or wherein R_{100} is phenyl, 5- or 6-membered heteroaryl, or 4 to 12-membered heterocycloalkyl, each optionally substituted with one or more T_{5a} in which each T_{5a} is independently C_1-C_6 alkoxyl or O-C_1-C_4 alkylene-C_1-C_4 alkoxy, and R_{101} is H or C_1-C_4 alkyl.

[034] R_7 is  , wherein each T_{5a} is independently C_1-C_3 alkoxyl or O-C_1-C_3 alkylene-C_1-C_2 alkoxy.

[035] T_5 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 7-membered heterocycloalkyl.

[036] Q_5 is a bond and T_5 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[037] Q_5 is CO and T_5 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[038] Q_5 is C_1-C_3 alkyl linker and T_5 is H or C_6-C_{10} aryl.

[039] R_{11} is H.

[040] Each of R_2 and R_4, independently is H or C_1-C_6 alkyl optionally substituted with amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_6-C_{10} aryl.

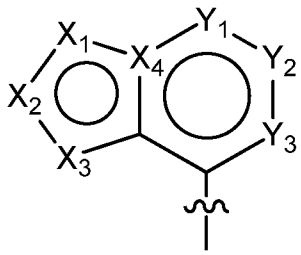
[041] Each of R_2 and R_4, independently is C_1-C_3 alkyl optionally substituted withC_1-C_6 alkoxyl.

[042] Each of R_2 and R_4 is methyl.

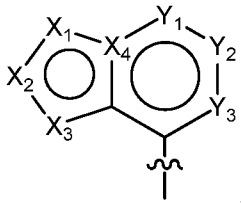
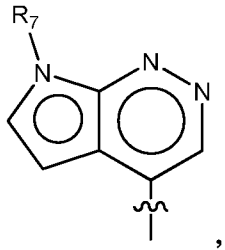
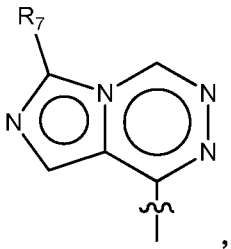
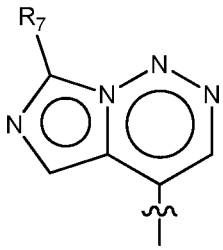
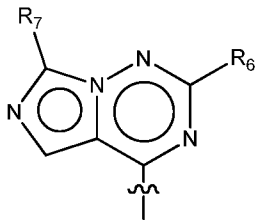
[043] R_1 is H.

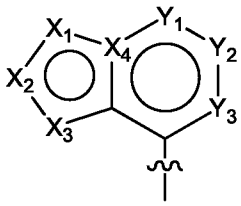
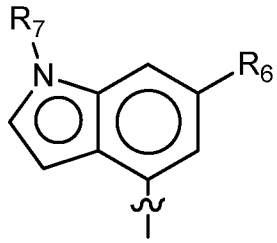
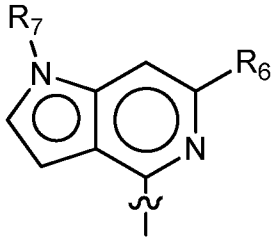
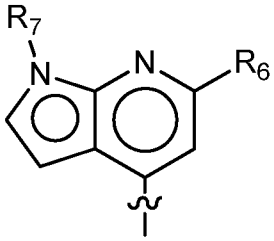
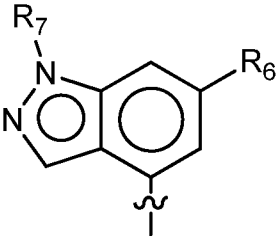
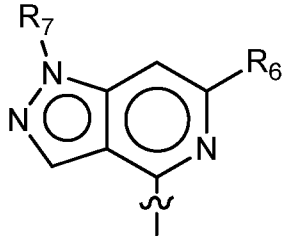
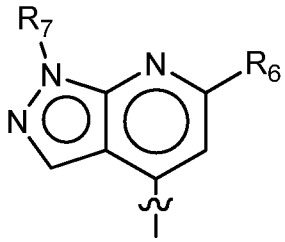
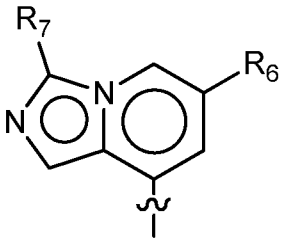
[044] R_8 is H, methyl, or ethyl.

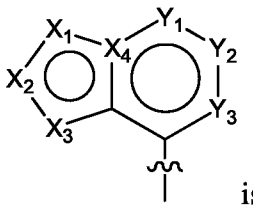
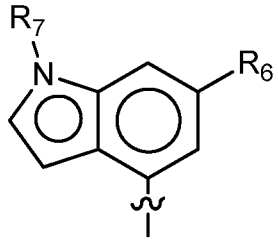
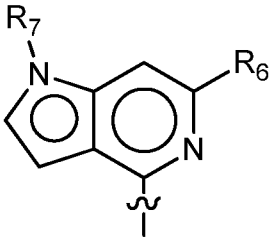
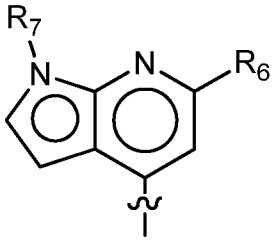
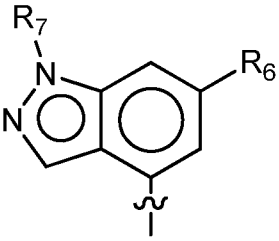
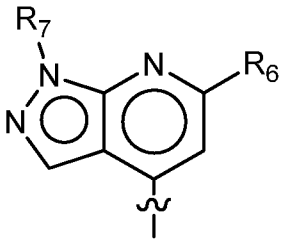
[045] R_3 is H.

[046] 

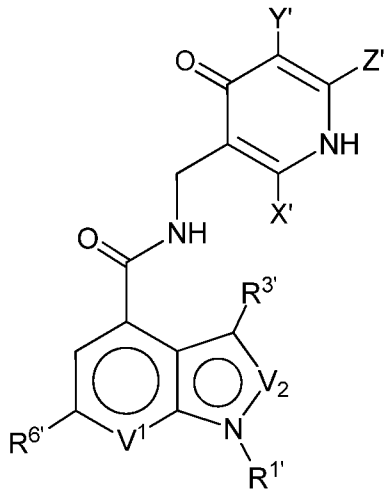
is selected from the group consisting of indolyl, isoindolyl, indolizinyl, benzofuryl, isobenzofuryl, benzo[b]thienyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, purinyl, indazolyl, pyrrolopyridinyl, imidazopyridinyl, pyrazolopyridinyl, pyrrolopyrazinyl, imidazopyrazinyl, pyrazolopyrazinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, pyrrolopyridazinyl, imidazopyridazinyl, pyrazolopyridazinyl, furopyridinyl, thienopyridinyl, furopyrazinyl, thienopyrazinyl, oxazolopyridinyl, isoxazolopyridinyl, thiazolopyridinyl, isothiazolopyridinyl, oxadiazolopyridinyl, thiadiazolopyridinyl, triazolopyridinyl, oxazolopyrazinyl, isoxazolopyrazinyl, thiazolopyrazinyl, isothiazolopyrazinyl, oxadiazolopyrazinyl, thiadiazolopyrazinyl, triazolopyrazinyl, furopyrimidinyl, thienopyrimidinyl, furopyridazinyl, thienopyridazinyl, oxazolopyrimidinyl, isoxazolopyrimidinyl, thiazolopyrimidinyl, isothiazolopyrimidinyl, oxadiazolopyrimidinyl, thiadiazolopyrimidinyl, triazolopyrimidinyl, oxazolopyridazinyl, isoxazolopyridazinyl, thiazolopyridazinyl, isothiazolopyridazinyl, oxadiazolopyridazinyl, thiadiazolopyridazinyl, triazolopyridazinyl, and imidazotriazinyl.

[047]  is selected from the group consisting of  ,  ,  , and  .

[048]  is selected from the group consisting of  ,  ,  ,  ,  ,  , and  .

[049]  is selected from the group consisting of  ,  ,  ,  , and  .

[050] In another aspect, the present invention features a compound of Formula (V) or a pharmaceutically acceptable salt thereof:



(V),

wherein,

V^1 is N or $CR^{7'}$,

V^2 is N or $CR^{2'}$, provided when V^1 is N, V^2 is N,

X' and Z' are selected independently from the group consisting of hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, unsubstituted or substituted $(C_3\text{-}C_8)$cycloalkyl, unsubstituted or substituted $(C_3\text{-}C_8)$cycloalkyl-$(C_1\text{-}C_8)$alkyl or -$(C_2\text{-}C_8)$alkenyl, unsubstituted or substituted $(C_5\text{-}C_8)$cycloalkenyl, unsubstituted or

substituted (C_5-C_8)cycloalkenyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, (C_6-C_{10})bicycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted heterocycloalkyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, halo, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$, $-SR^{a'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)R^{b'}$, $-NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)OR^{a'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, and $-OC(O)NR^{a'}R^{b'}$;

Y' is H or halo;

$R^{1'}$ is (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, unsubstituted or substituted (C_3-C_8)cycloalkyl, unsubstituted or substituted (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted (C_6-C_{10})bicycloalkyl, unsubstituted or substituted heterocycloalkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted heterocycloalkyl-(C_1-C_8)alkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$;

$R^{2'}$ is hydrogen, (C_1-C_8)alkyl, trifluoromethyl, alkoxy, or halo, in which said (C_1-C_8)alkyl is optionally substituted with one to two groups selected from amino and (C_1-C_3)alkylamino;

$R^{7'}$ is hydrogen, (C_1-C_3)alkyl, or alkoxy;

$R^{3'}$ is hydrogen, (C_1-C_8)alkyl, cyano, trifluoromethyl, $-NR^{a'}R^{b'}$, or halo;

$R^{6'}$ is selected from the group consisting of hydrogen, halo, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, unsubstituted or substituted (C_3-C_8)cycloalkyl, unsubstituted or substituted (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl-(C_1-C_8)alkyl, (C_6-C_{10})bicycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted heterocycloalkyl-(C_1-C_8)alkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-(C_1-C_8)alkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-(C_1-C_8)alkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$, $-SR^{a'}$,

-$SOR^{a'}$, -$SO_2R^{a'}$, -$SO_2NR^{a'}R^{b'}$, nitro, -$NR^{a'}R^{b'}$, -$NR^{a'}C(O)R^{b'}$, -$NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}C(O)OR^{a'}$, -$NR^{a'}SO_2R^{b'}$, -$NR^{a'}SO_2NR^{a'}R^{b'}$, -$NR^{a'}NR^{a'}R^{b'}$, -$NR^{a'}NR^{a'}C(O)R^{b'}$, -$NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}NR^{a'}C(O)OR^{a'}$, -$OR^{a'}$, -$OC(O)R^{a'}$, -$OC(O)NR^{a'}R^{b'}$;

wherein any (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, heterocycloalkyl, aryl, or heteroaryl group is optionally substituted by 1, 2 or 3 groups independently selected from the group consisting of -$O(C_1-C_6)$alkyl$(R^{c'})_{1-2}$, -$S(C_1-C_6)$alkyl$(R^{c'})_{1-2}$, -(C_1-C_6)alkyl$(R^{c'})_{1-2}$, -(C_1-C_8)alkyl-heterocycloalkyl, (C_3-C_8)cycloalkyl-heterocycloalkyl, halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_1-C_6)haloalkyl, cyano, -$COR^{a'}$, -$CO_2R^{a'}$,-$CONR^{a'}R^{b'}$, -$SR^{a'}$, -$SOR^{a'}$, -$SO_2R^{a'}$, -$SO_2NR^{a'}R^{b'}$, nitro, -$NR^{a'}R^{b'}$, -$NR^{a'}C(O)R^{b'}$, -$NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}C(O)OR^{a'}$, -$NR^{a'}SO_2R^{b'}$, -$NR^{a'}SO_2NR^{a'}R^{b'}$, -$OR^{a'}$, -$OC(O)R^{a'}$, $OC(O)NR^{a'}R^{b'}$, heterocycloalkyl, aryl, heteroaryl, aryl(C_1-C_4)alkyl, and heteroaryl(C_1-C_4)alkyl;

wherein any aryl or heteroaryl moiety of said aryl, heteroaryl, aryl(C_1-C_4)alkyl, or heteroaryl(C_1-C_4)alkyl is optionally substituted by 1, 2 or 3 groups independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_1-C_6)haloalkyl, cyano, -$COR^{a'}$, -$CO_2R^{a'}$, -$CONR^{a}R^{b'}$,-$SR^{a'}$, -$SOR^{a'}$, -$SO_2R^{a'}$, -$SO_2NR^{a'}R^{b'}$, nitro, -$NR^{a'}R^{b'}$, -$NR^{a'}C(O)R^{b'}$,-$NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}C(O)OR^{a'}$, -$NR^{a'}SO_2R^{b'}$, -$NR^{a'}SO_2NR^{a'}R^{b'}$, -$OR^{a'}$, -$OC(O)R^{a'}$, and -$OC(O)NR^{a'}R^{b'}$;

$R^{a'}$ and $R^{b'}$ are each independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_6-C_{10})bicycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein said (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl,heterocycloalkyl ,aryl or heteroaryl group is optionally substituted by 1, 2 or 3 groups independently selected from halo, hydroxyl, (C_1-C_4)alkoxy, amino, (C_1-C_4)alkylamino, $((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl)amino, -CO_2H, -$CO_2(C_1-C_4)$alkyl, -$CONH_2$,-$CONH(C_1-C_4)$alkyl, -$CON((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl), -$SO_2(C_1-C_4)$alkyl, -SO_2NH_2,-$SO_2NH(C_1-C_4)$alkyl, and $SO_2N((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl);

or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 5-8 membered saturated or unsaturated ring, optionally containing an additional heteroatom selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted by 1, 2 or 3 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, amino, (C_1-C_4)alkylamino, $((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl)amino, hydroxyl,

oxo, (C_1-C_4)alkoxy, and (C_1-C_4)alkoxy(C_1-C_4)alkyl, wherein said ring is optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring;

or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 6- to 10-membered bridged bicyclic ring system optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring; and

each $R^{c'}$ is independently (C_1-C_4)alkylamino, $-NR^{a'}SO2R^{b'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}R^{b'}$, or $-CO_2R^{a'}$.

[051] The present invention also provides pharmaceutical compositions comprising one or more pharmaceutically acceptable carriers and one or more compounds selected from those of any of the Formulae described herein.

[052] Another aspect of this invention is a method of treating or preventing an EZH2-mediated disorder. The method includes administering to a subject in need thereof a therapeutically effective amount of one or more compounds selected from those of any of the Formulae described herein. The EZH2-mediated disorder is a disease, disorder, or condition that is mediated at least in part by the activity of EZH2. In one embodiment, the EZH2-mediated disorder is related to an increased EZH2 activity. In one embodiment, the EZH2-mediated disorder is a cancer. The EZH2-mediated cancer may be lymphoma, leukemia or melanoma, for example, diffuse large B-cell lymphoma (DLBCL), non-Hodgkin's lymphoma (NHL), follicular lymphoma, chronic myelogenous leukemia (CML), acute myeloid leukemia, acute lymphocytic leukemia, mixed lineage leukemia, or myelodysplastic syndromes (MDS). In one embodiment the EZH2-mediated cancer may be a malignant rhabdoid tumor or INI1-defecient tumor. The histologic diagnosis of malignant rhabdoid tumor depends on identification of characteristic rhabdoid cells (large cells with eccentrically located nuclei and abundant, eosinophilic cytoplasm) and immunohistochemistry with antibodies to vimentin, keratin and epithelial membrane antigen. In most malignant rhabdoid tumors, the SMARCB1/INI1 gene, located in chromosome band 22q11.2, is inactivated by deletions and/or mutations. In one embodiment, the malignant rhabdoid tumors may be INI1-defecient tumor.

[053] Unless otherwise stated, any description of a method of treatment includes uses of the compounds to provide such treatment or prophylaxis as is described in the specification, as well as uses of the compounds to prepare a medicament to treat or prevent such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models. Methods described herein may be used to identify suitable candidates for treating or preventing EZH2-mediated disorders. For example, the

invention also provides methods of identifying an inhibitor of a wild-type EZH2, a mutant EZH2 (e.g., a Y641, A677, and/or A687 mutant EZH2), or both.

[054] For example, the method comprises the step of administering to a subject having a cancer with aberrant H3-K27 methylation an effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer. Examples of aberrant H3-K27 methylation may include a global increase in and/or altered distribution of H3-K27 di or tri-methylation within the cancer cell chromatin.

[055] For example, the cancer is selected from the group consisting of cancers that overexpress EZH2 or other PRC2 subunits, contain loss-of-function mutations in H3-K27 demethylases such as UTX, or overexpress accessory proteins such as PHF19/PCL3 capable of increasing and or mislocalizing EZH2 activity (see references in Sneeringer *et al. Proc Natl Acad Sci USA* 107(49):20980-5, 2010).

[056] For example, the method comprises the step of administering to a subject having a cancer overexpressing EZH2 a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer.

[057] For example, the method comprises the step of administering to a subject having a cancer with a loss-of-function mutation in the H3-K27 demethylase UTX a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer

[058] For example, the method comprises the step of administering to a subject having a cancer overexpressing an accessory component(s) of the PRC2, such as PHF19/PCL3, a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer

[059] In still another aspect, this invention relates to a method of modulating the activity of the wild-type EZH2, the catalytic subunit of the PRC2 complex which catalyzes the mono- through tri-methylation of lysine 27 on histone H3 (H3-K27). For example, the present invention relates to a method of inhibiting the activity of EZH2 in a cell. This method can be conducted either *in vitro* or *in vivo*.

[060] In yet another aspect, this invention features to a method of inhibiting in a subject conversion of H3-K27 to trimethylated H3-K27. The method comprises administering to a

subject a therapeutically effective amount of one or more of the compounds of Formulae described herein to inhibit histone methyltransferase activity of EZH2, thereby inhibiting conversion of H3-K27 to trimethylated H3-K27 in the subject.

[061] For example, the method comprises the step of administering to a subject having a cancer expressing a mutant EZH2 a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer.

[062] For example, the cancer is selected from the group consisting of follicular lymphoma and diffuse large B-cell lymphoma (DLBCL) of germinal center B cell-like (GCB) subtype. For example, the cancer is lymphoma, leukemia or melanoma. Preferably, the lymphoma is non-Hodgkin's lymphoma (NHL), follicular lymphoma or diffuse large B-cell lymphoma. Alternatively, the leukemia is chronic myelogenous leukemia (CML), acute myeloid leukemia, acute lymphocytic leukemia or mixed lineage leukemia.

[063] For example, the precancerous condition is myelodysplastic syndromes (MDS, formerly known as preleukemia).

[064] For example, the cancer is a hematological cancer.

[065] For example, the cancer is selected from the group consisting of brain and central nervous system (CNS) cancer, head and neck cancer, kidney cancer, ovarian cancer, pancreatic cancer, leukemia, lung cancer, lymphoma, myeloma, sarcoma, breast cancer, and prostate cancer. Preferably, a subject in need thereof is one who had, is having or is predisposed to developing brain and CNS cancer, kidney cancer, ovarian cancer, pancreatic cancer, leukemia, lymphoma, myeloma, and/or sarcoma. Exemplary brain and central CNS cancer includes medulloblastoma, oligodendroglioma, atypical teratoid/rhabdoid tumor, choroid plexus carcinoma, choroid plexus papilloma, ependymoma, glioblastoma, meningioma, neuroglial tumor, oligoastrocytoma, oligodendroglioma, and pineoblastoma. Exemplary ovarian cancer includes ovarian clear cell adenocarcinoma, ovarian endomethrioid adenocarcinoma, and ovarian serous adenocarcinoma. Exemplary pancreatic cancer includes pancreatic ductal adenocarcinoma and pancreatic endocrine tumor. Exemplary sarcoma includes chondrosarcoma, clear cell sarcoma of soft tissue, ewing sarcoma, gastrointestinal stromal tumor, osteosarcoma, rhabdomyosarcoma, and not otherwise specified (NOS) sarcoma. Alternatively, cancers to be treated by the compounds of the present invention are non NHL cancers.

[066] For example, the cancer is selected from the group consisting of medulloblastoma, oligodendroglioma, ovarian clear cell adenocarcinoma, ovarian endomethrioid

adenocarcinoma, ovarian serous adenocarcinoma, pancreatic ductal adenocarcinoma, pancreatic endocrine tumor, malignant rhabdoid tumor, astrocytoma, atypical teratoid/rhabdoid tumor, choroid plexus carcinoma, choroid plexus papilloma, ependymoma, glioblastoma, meningioma, neuroglial tumor, oligoastrocytoma, oligodendroglioma, pineoblastoma, carcinosarcoma, chordoma, extragonadal germ cell tumor, extrarenal rhabdoid tumor, schwannoma, skin squamous cell carcinoma, chondrosarcoma, clear cell sarcoma of soft tissue, ewing sarcoma, gastrointestinal stromal tumor, osteosarcoma, rhabdomyosarcoma, and not otherwise specified (NOS) sarcoma. Preferably, the cancer is medulloblastoma, ovarian clear cell adenocarcinoma, ovarian endomethrioid adenocarcinoma, pancreatic ductal adenocarcinoma, malignant rhabdoid tumor, atypical teratoid/rhabdoid tumor, choroid plexus carcinoma, choroid plexus papilloma, glioblastoma, meningioma, pineoblastoma, carcinosarcoma, extrarenal rhabdoid tumor, schwannoma, skin squamous cell carcinoma, chondrosarcoma, ewing sarcoma, epithelioid sarcoma, renal medullary carcinoma, diffuse large B-cell lymphoma, follicular lymphoma and/or NOS sarcoma. More preferably, the cancer is malignant rhabdoid tumor, medulloblastoma and/or atypical teratoid/rhabdoid tumor.

[067] For example, the method comprises the step of administering to a subject having a cancer expressing a mutant EZH2 a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits activity (e.g., histone methyltransferase activity) of the mutant EZH2, the wild-type EZH2, or both, thereby treating the cancer.

[068] For example, the method further comprises the steps of performing an assay to detect a mutant EZH2 in a sample comprising cancer cells from a subject in need thereof.

[069] In another aspect, the invention features a method of selecting a therapy for a patient having a disease associated with EZH2-mediated protein methylation. The method includes the steps of determining the presence of gene mutation in the EZH2 gene of the subject; and selecting, based on the presence of a gene mutation in the EZH2 gene a therapy for treating the disease. In one embodiment, the therapy includes the administration of one or more of the compounds of the invention. In one embodiment, the method further includes administrating one or more of the compounds of the invention to the subject. In one embodiment, the disease is cancer and the mutation is a Y641 mutation.

[070] In yet another aspect, a method of treatment is provided for a patient in need thereof, the method comprising the steps of determining the presence of gene mutation in the EZH2 gene and treating the patient in need thereof, based on the presence of a gene

mutation in the EZH2 gene, with a therapy that includes the administration of the compounds of the invention. In one embodiment, the patient is a cancer patient and the mutation is a Y641 mutation.

[071] In still another aspect, this invention relates to a method of modulating the activity of the wild-type and mutant histone methyltransferase EZH2, the catalytic subunit of the PRC2 complex which catalyzes the mono- through tri-methylation of lysine 27 on histone H3 (H3-K27). For example, the present invention relates to a method of inhibiting the activity of certain mutant forms of EZH2 in a cell. The mutant forms of EZH2 include a substitution of another amino acid residue for tyrosine 641 (Y641, also Tyr641) of wild-type EZH2. The method includes contacting the cell with an effective amount of one or more of the compounds of any Formula described herein. This method can be conducted either *in vitro* or *in vivo*.

[072] In yet another aspect, this invention features to a method of inhibiting in a subject conversion of H3-K27 to trimethylated H3-K27. The method comprises administering to a subject expressing a mutant EZH2 a therapeutically effective amount of one or more of the compounds of any Formula described herein to inhibit histone methyltransferase activity of EZH2, thereby inhibiting conversion of H3-K27 to trimethylated H3-K27 in the subject. For example, the histone methyltransferase activity inhibited is that of the Y641 mutant of EZH2. For example, the compound of this invention selectively inhibits histone methyltransferase activity of the Y641 mutant of EZH2. For example, the Y641 mutant of EZH2 is selected from the group consisting of Y641C, Y641F, Y641H, Y641N, and Y641S.

[073] The method of inhibiting in a subject conversion of H3-K27 to trimethylated H3-K27 may also comprise performing an assay to detect a mutant EZH2 in a sample from a subject before administering to the subject expressing a mutant EZH2 a therapeutically effective amount of one or more of the compounds of any Formula described herein. For example, performing the assay to detect the mutant EZH2 includes whole-genome resequencing or target region resequencing that detects a nucleic acid encoding the mutant EZH2. For example, performing the assay to detect the mutant EZH2 includes contacting the sample with an antibody that binds specifically to a polypeptide or fragment thereof characteristic of the mutant EZH2. For example, performing the assay to detect the mutant EZH2 includes contacting the sample under highly stringent conditions with a nucleic acid probe that hybridizes to a nucleic acid encoding a polypeptide or fragment thereof characteristic of the mutant EZH2.

[074] Further, the invention also relates to a method of identifying an inhibitor of a mutant EZH2, wild-type EZH2, or both. The method comprises the steps of combining an isolated EZH2 with a histone substrate, a methyl group donor, and a test compound, wherein the histone substrate comprises a form of H3-K27 selected from the group consisting of unmethylated H3-K27, monomethylated H3-K27, dimethylated H3-K27, and any combination thereof; and performing an assay to detect methylation of H3-K27 (e.g., formation of trimethylated H3-K27) in the histone substrate, thereby identifying the test compound as an inhibitor of the EZH2 when methylation of H3-K27 (e.g., formation of trimethylated H3-K27) in the presence of the test compound is less than methylation of H3-K27 (e.g., formation of trimethylated H3-K27) in the absence of the test compound.

[075] In one embodiment, performing the assay to detect methylation of H3-K27 in the histone substrate comprises measuring incorporation of labeled methyl groups.

[076] In one embodiment, the labeled methyl groups are isotopically labeled methyl groups.

[077] In one embodiment, performing the assay to detect methylation of H3-K27 in the histone substrate comprises contacting the histone substrate with an antibody that binds specifically to trimethylated H3-K27.

[078] Also within the scope of the invention is a method of identifying a selective inhibitor of a mutant EZH2. The method comprises the steps of combining an isolated mutant EZH2 with a histone substrate, a methyl group donor, and a test compound, wherein the histone substrate comprises a form of H3-K27 selected from the group consisting of monomethylated H3-K27, dimethylated H3-K27, and a combination of monomethylated H3-K27 and dimethylated H3-K27, thereby forming a test mixture; combining an isolated wild-type EZH2 with a histone substrate, a methyl group donor, and a test compound, wherein the histone substrate comprises a form of H3-K27 selected from the group consisting of monomethylated H3-K27, dimethylated H3-K27, and a combination of monomethylated H3-K27 and dimethylated H3-K27, thereby forming a control mixture; performing an assay to detect trimethylation of the histone substrate in each of the test mixture and the control mixture; calculating the ratio of (a) trimethylation with the mutant EZH2 and the test compound (M+) to (b) trimethylation with the mutant EZH2 without the test compound (M-); calculating the ratio of (c) trimethylation with wild-type EZH2 and the test compound (WT+) to (d) trimethylation with wild-type EZH2 without the test compound (WT-); comparing the ratio (a)/(b) with the ratio (c)/(d); and identifying the test compound

as a selective inhibitor of the mutant EZH2 when the ratio (a)/(b) is less than the ratio (c)/(d).

[079] The present invention further provides a method of identifying a subject as a candidate for treatment with one or more compounds of the invention. The method comprises the steps of performing an assay to detect a mutant EZH2 in a sample from a subject; and identifying a subject expressing a mutant EZH2 as a candidate for treatment with one or more compounds of the invention, wherein the compound(s) inhibits histone methyltransferase activity of EZH2.

[080] Still another aspect of the invention is a method of inhibiting conversion of H3-K27 to trimethylated H3-K27. The method comprises the step of contacting wild-type EZH2, a mutant EZH2, or both with a histone substrate comprising H3-K27 and an effective amount of a compound of the present invention, wherein the compound inhibits histone methyltransferase activity of EZH2, thereby inhibiting conversion of H3-K27 to trimethylated H3-K27.

[081] Further, the compounds or methods described herein can be used for research (e.g., studying epigenetic enzymes) and other non-therapeutic purposes.

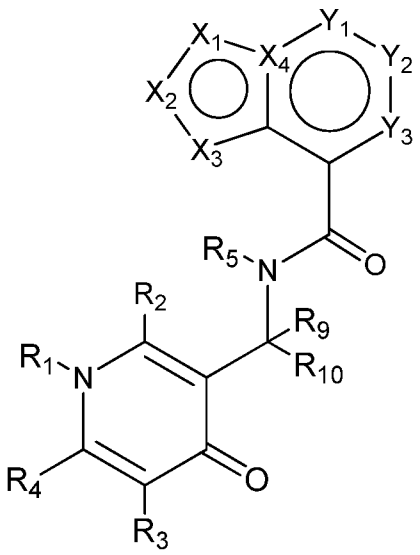
[082] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

[083] Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

[084] The present invention provides novel 1,4-pyridone bicyclic heteroaryl compounds, synthetic methods for making the compounds, pharmaceutical compositions containing them and various uses of the compounds.

[085] The present invention provides the compounds of Formula (IV) or pharmaceutically acceptable salts thereof:



(IV),

wherein:

X_1 is NR_7 or CR_7;

X_2 is N, NR_8, CR_8, O, or S;

X_3 is NR_8, CR_8, O, or S;

X_4 is C or N;

Y_1 is N or CH;

Y_2 is N or CR_6;

Y_3 is N, or CR_{11}, and at least one of X_1, X_2, X_3, X_4, Y_1, Y_2, and Y_3 is N or NR_7;

each of R_1, R_5, R_9, and R_{10}, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy,

and T_1 is H, halo, hydroxyl, COOH, cyano, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C_1-C_6 thioalkyl, C(O)O-C_1-C_6 alkyl, $CONH_2$, SO_2NH_2, -CO-NH(C_1-C_6 alkyl), -CO-N(C_1-C_6 alkyl)$_2$, -SO_2-NH(C_1-C_6 alkyl), - SO_2-N(C_1-C_6 alkyl)$_2$, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_6-C_{10} aryloxy,amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, and 5 to 6-membered heteroaryl; or R_1 and R_2, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R_1 and R_4, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R_3 and R_4, together with the C atoms to which they are attached, form C_5-C_8 cycloalkyl, C_6-C_{10} aryl, or a 5- or 6-membered heteroaryl having 1 to 3 heteroatoms, or a 5 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms; in which each of the ring structures formed by R_1 and R_2, by R_1 and R_4, or by R_3 and R_4, independently is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, C_1-C_6 alkyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each R_6 independently is H, halo, OR_a, -NR_aR_b, -C(O)R_a, -C(O)OR_a, -C(O)NR_aR_b, -$NR_bC(O)R_a$, -$S(O)_2R_a$, -$S(O)_2NR_aR_b$, or R_{S2}, in which each of R_a and R_b, independently is H or R_{S3} and each of R_{S2} and R_{S3}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom; and each of R_{S2}, R_{S3}, and the 4 to 7-membered heterocycloalkyl ring containing R_a and R_b, is optionally substituted with one or more –Q_2-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano,

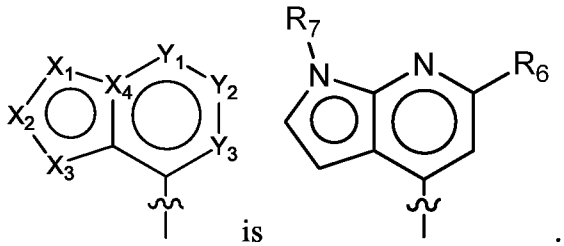
$-OR_c$, $-NR_cR_d$, $-(NR_cR_dR_{d'})^+A^-$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c R_d, and $R_{d'}$, independently is H or R_{S5}, A^- is a pharmaceutically acceptable anion, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom, and each of R_{S4}, R_{S5}, and the 4 to 7-membered heterocycloalkyl ring containing R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of H, halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, 5 to 6-membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl optionally substituted with OH, O-C_1-C_6 alkyl, or NH-C_1-C_6 alkyl; or $-Q_3$-T_3 is oxo; or $-Q_2$-T_2 is oxo; or any two neighboring $-Q_2$-T_2, together with the atoms to which they are attached form a 5- or 6-membered ring optionally containing 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, and 5 to 6-membered heteroaryl; provided that $-Q_2$-T_2 is not H;

each R_7 independently is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5$-T_5, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, NR_k, $S(O)_2$, $NR_kS(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_1-C_6 alkylene-C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_1-C_6 alkylene-C_6-C_{10} aryl, 4 to 12-membered

heterocycloalkyl, C_1-C_6 alkylene-4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or C_1-C_6 alkylene-5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, O-C_1-C_4 alkylene-C_1-C_4 alkoxy, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, and 5 to 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo; provided that $-Q_4$-T_4 is not H; and

each of R_8 and R_{11}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino.

[086] For example, at least one of Y_1, Y_3, and X_4 is N and when X_4 is C, Y_1 is N, Y_2 is CR_6, and Y_3 is CR_{11} then X_2 is CR_8.

[087] For example,  is .

[088] For example, X_4 is C.

[089] For example, X_2 is N or CH.

[090] For example, X_3 is CR_8.

[091] For example, Y_3 is CR_{11}.

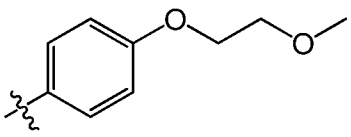
[092] For example, R_6 is phenyl substituted with one or more $-Q_2$-T_2.

[093] For example, R_6 is 5 to 6-membered heteroaryl containing 1-3 additional heteroatoms selected from N, O, and S and optionally substituted with one or more $-Q_2$-T_2, provided that the heteroaryl is not thiophenyl.

[094] For example, R_6 is pyridinyl, pyrazolyl, pyrimidinyl, or furyl, each of which is optionally substituted with one or more $-Q_2$-T_2.

[095] For example, R_6 is phenyl or 5- or 6-membered heteroaryl substituted with O-C_{1-6} alkyl or NH-C_{1-6} alkyl, each of which is optionally substituted with hydroxyl, O-C_{1-3} alkyl

or NH-C_{1-3} alkyl, each of the O-C_{1-3} alkyl and NH-C_{1-3} alkyl being optionally further substituted with O-C_{1-3} alkyl or NH-C_{1-3} alkyl.

[096] For example, R_6 is  .

[097] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine).

[098] For example, R_6 is C_1-C_3 alkyl substituted with one or more $-Q_2$-T_2.

[099] For example, R_6 is C_2-C_6 alkenyl or C_4-C_6 cycloalkyl each optionally substituted with one or more $-Q_2$-T_2.

[0100] For example, R_6 is C(O)H.

[0101] For example, R_6 is OR_a or -$C(O)R_a$.

[0102] For example, R_a is C_1-C_6 alkyl or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, and morpholinyl, and the like), which is optionally substituted with one or more $-Q_2$-T_2.

[0103] For example, R_6 is -NR_aR_b, -$C(O)R_a$, -$C(O)OR_a$, -$C(O)NR_aR_b$, -$NR_bC(O)R_a$, -$S(O)_2R_a$, or -$S(O)_2NR_aR_b$.

[0104] For example, each of R_a and R_b, independently is H or C_1-C_6 alkyl optionally substituted with one or more $-Q_2$-T_2.

[0105] For example, one of R_a and R_b is H.

[0106] For example, R_a and R_b, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom (e.g., azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, and morpholinyl, and the like) and the ring is optionally substituted with one or more $-Q_2$-T_2.

[0107] For example, R_6 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_2$-T_2.

[0108] For example, R_6 is piperidinyl, 2,2,6,6-tetramethyl-piperidinyl, 1,2,3,6-tetrahydropyridinyl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl, piperazinyl,

morpholinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, or pyrrolidinyl, each of which is optionally substituted with one or more $-Q_2-T_2$.

[0109] For example, R_6 is 4 to 7-membered heterocycloalkyl optionally substituted with one or more $-Q_2-T_2$, and $-Q_2-T_2$ is oxo or Q_2 is a bond and T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-S(O)_2R_c$, C_1-C_6 alkyl, or 4 to 7-membered heterocycloalkyl, each of which is optionally substituted with one or more $-Q_3-T_3$ when R_c or R_d is not H.

[0110] For example, $-Q_2-T_2$ is oxo.

[0111] For example, Q_2 is a bond.

[0112] For example, Q_2 is an unsubstituted C_1-C_3 alkyl linker.

[0113] For example, T_2 is C_1-C_6 alkyl or C_6-C_{10} aryl, each optionally substituted with one or more $-Q_3-T_3$.

[0114] For example, T_2 is an unsubstituted substituted straight chain C_1-C_6 or branched C_3-C_6 alkyl, including but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl.

[0115] For example, T_2 is phenyl.

[0116] For example, T_2 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine).

[0117] For example, T_2 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_3-T_3$.

[0118] For example, T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, or $-S(O)_2R_c$.

[0119] For example, T_2 is $-(NR_cR_dR_{d'})^+A^-$,--$C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, or $-S(O)_2NR_cR_d$.

[0120] For example, Q_2 is a bond or methyl linker and T_2 is H, halo, $-OR_c$, $-NR_cR_d$, $-(NR_cR_dR_{d'})^+A^-$, or $-S(O)_2NR_cR_d$.

[0121] For example, R_c is C_1-C_6 alkyl or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, and morpholinyl, and the like), which is optionally substituted with one or more $-Q_3-T_3$.

[0122] For example, each of R_c and R_d, independently is H or C_1-C_6 alkyl optionally substituted with one or more $-Q_3-T_3$.

[0123] For example, R_c is H.

[0124] For example, R_d is H.

[0125] For example, R_c and R_d, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom (e.g., azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, and morpholinyl, and the like) and the ring is optionally substituted with one or more $-Q_3$-T_3.

[0126] For example, Q_2 is a bond and T_2 is -OR_c, -NR_cR_d, -$C(O)R_c$, -$C(O)OR_c$, -$S(O)_2R_c$, C_1-C_6 alkyl, or 4 to 7-membered heterocycloalkyl, each of which is optionally substituted with one or more $-Q_3$-T_3 when R_c or R_d is not H.

[0127] For example,$-Q_3$-T_3 is oxo.

[0128] For example, T_2 is 4 to 7-membered heterocycloalkyl or C_3-C_8 cycloalkyl and one or more $-Q_3$-T_3 are oxo.

[0129] For example, Q_3 is a bond or unsubstituted or substituted C_1-C_3 alkyl linker.

[0130] For example, T_3 is H, halo, 4 to 7-membered heterocycloalkyl, C_1-C_3 alkyl, OR_e, $COOR_e$,-$S(O)_2R_e$,$-NR_eR_f$, or -$C(O)NR_eR_f$.

[0131] For example, one of R_d and R_e is H.

[0132] For example, Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, halo, OR_e, -$S(O)_2R_e$, -NR_eR_f, and-$C(O)NR_eR_f$.

[0133] For example, R_e is H.

[0134] For example, R_f is H.

[0135] For example, R_7 is C_1-C_6 alkyl optionally substituted with one or more $-Q_5$-T_5.

[0136] For example, R_7 is C_3-C_8 cycloalkyl optionally substituted with one or more $-Q_5$-T_5.

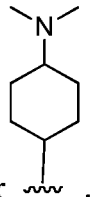
[0137] For example, R_7 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_5$-T_5.

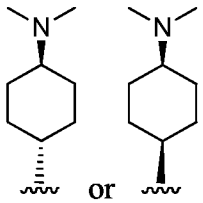
[0138] For example, R_7 is cyclopentyl.

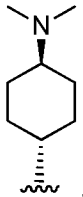
[0139] For example, R_7 is isopropyl or sec-butyl.

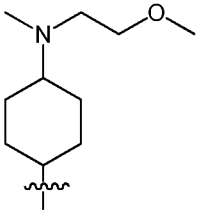
[0140] For example, R_7 is 5 to 6-membered heterocycloalkyl optionally substituted with one or more $-Q_5$-T_5.

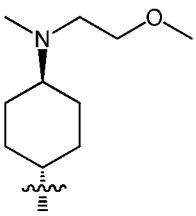
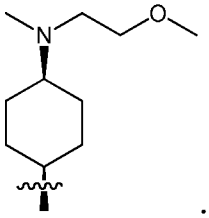
[0141] For example, R_7 is piperidinyl optionally substituted with one $-Q_5$-T_5.

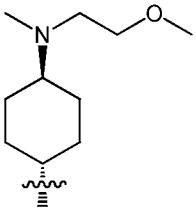
[0142] For example, R_7 is tetrahydropyran or  .

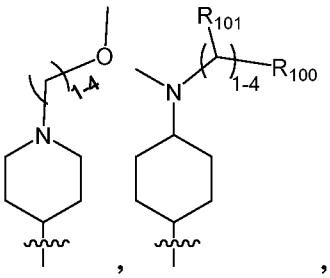
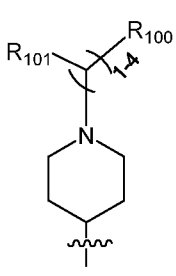
[0143] For example, R_7 is  or .

[0144] For example, R_7 is  .

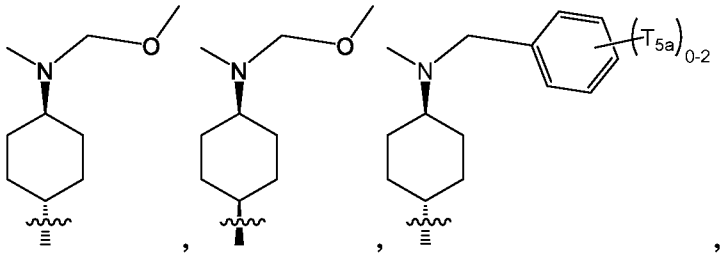
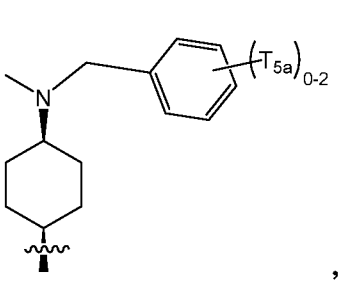
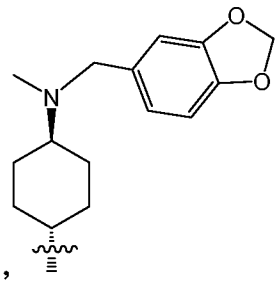
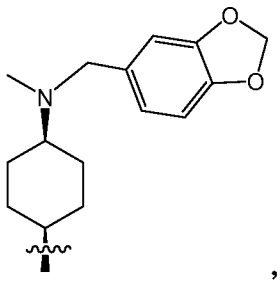
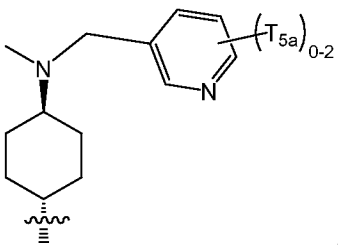
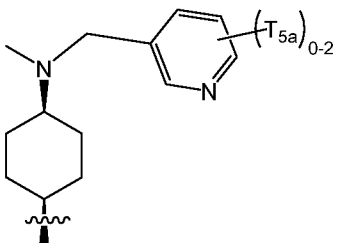
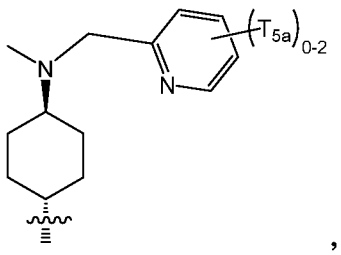
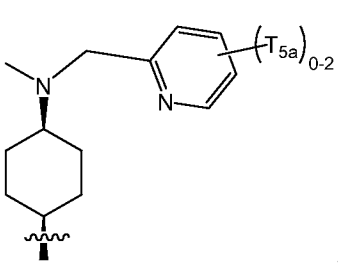
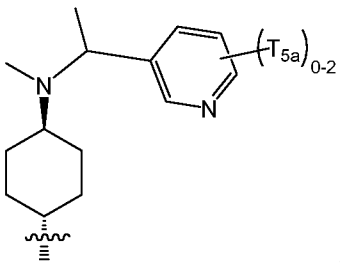
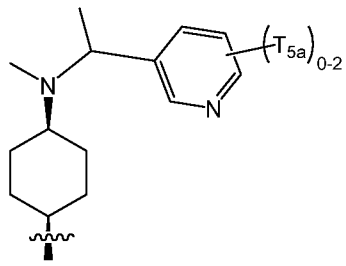
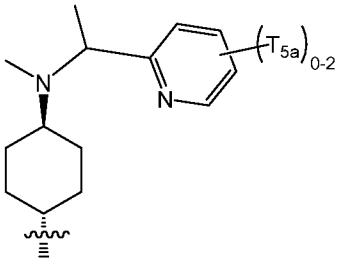
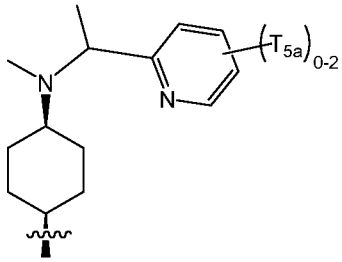
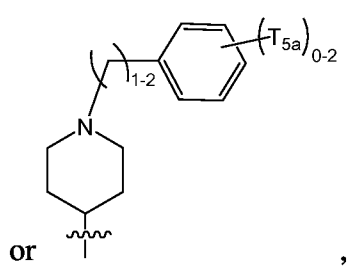
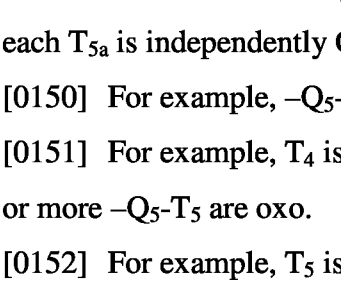
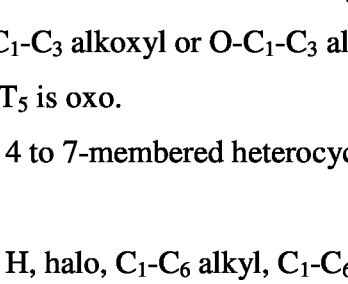
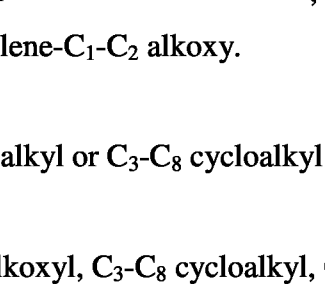
[0145] For example, R_7 is  .

[0146] For example, R_7 is  or  .

[0147] For example, R_7 is  .

[0148] For example, R_7 is  , , or  wherein R_{100} is phenyl, 5- or 6-membered heteroaryl, or 4 to 12-membered heterocycloalkyl, each

optionally substituted with one or more T_{5a} in which each T_{5a} is independently C_1-C_6 alkoxyl or O-C_1-C_4 alkylene-C_1-C_4 alkoxy, and R_{101} is H or C_1-C_4 alkyl.

[0149] For example, R_7 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  , wherein each T_{5a} is independently C_1-C_3 alkoxyl or O-C_1-C_3 alkylene-C_1-C_2 alkoxy.

[0150] For example, $-Q_5$-T_5 is oxo.

[0151] For example, T_4 is 4 to 7-membered heterocycloalkyl or C_3-C_8 cycloalkyl and one or more $-Q_5$-T_5 are oxo.

[0152] For example, T_5 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 7-membered heterocycloalkyl.

[0153] For example, Q_5 is a bond and T_5 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0154] For example, Q_5 is CO and T_5 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0155] For example, T_5 is C_1-C_6 alkyl optionally substituted with halo, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_3-C_8 cycloalkyl.

[0156] For example, Q_5 is C_1-C_3 alkyl linker and T_5 is H or C_6-C_{10} aryl.

[0157] For example, R_{11} is H.

[0158] For example, each of R_2 and R_4, independently, is H or C_1-C_6 alkyl optionally substituted with amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_6-C_{10} aryl.

[0159] For example, each of R_2 and R_4, independently is C_1-C_3 alkyl optionally substituted withC_1-C_6 alkoxyl.

[0160] For example, each of R_2 and R_4 is methyl.

[0161] For example, each of R_2 and R_4, independently is halo, e.g., F, Cl, or Br.

[0162] For example, each of R_2 and R_4, independently, is CN, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino.

[0163] For example, each of R_2 and R_4, independently, is optionally substituted phenyl.

[0164] For example, each of R_2 and R_4, independently, is optionally substituted 5- or 6-membered heteroaryl (e.g., pyrrolyl, pyrazolyl, imidazoly, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, and the like).

[0165] For example, each of R_2 and R_4, independently, is optionally substituted 4 to 12-membered heterocycloalkyl (e.g., pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, and morpholinyl, and the like).

[0166] For example, each of R_2 and R_4, independently, is $C_{1\text{-}6}$ alkoxyl or C_6-C_{10} aryloxy, each optionally substituted with one or more halo.

[0167] For example, R_2 is $C_{1\text{-}6}$ alkoxyl or C_6-C_{10} aryloxy, each optionally substituted with one or more halo.

[0168] For example, R_4 is halo, or $C_{1\text{-}4}$ alkyl or $C_{1\text{-}6}$ alkoxyl, each optionally substituted with one or more halo.

[0169] For example, R_3 is H, halo, or $C_{1\text{-}4}$ alkyl;

[0170] For example, R_1 is H or $C_{1\text{-}4}$ alkyl.

[0171] For example, R_1 and R_2, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms (e.g.,

pyrrolyl, pyrazolyl, imidazoly, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, and the like), or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms (e.g., pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, and morpholinyl, and the like). Further,each of the ring structures formed by R_1 and R_2 mentioned above, independently, is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, C_1-C_6 alkyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl.

[0172] For example, R_1 and R_4, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms (e.g., pyrrolyl, pyrazolyl, imidazoly, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, and the like), or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms (e.g., pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, and morpholinyl, and the like). Further,each of the ring structures formed by R_1 and R_4 mentioned above, independently, is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, C_1-C_6 alkyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl.

[0173] For example, R_3 and R_4, together with the C atoms to which they are attached, form C_5-C_8 cycloalkyl (e.g., C_5-C_6 cycloalkyl), C_6-C_{10} aryl (e.g., phenyl), or a 5- or 6-membered heteroaryl having 1 to 3 heteroatoms (e.g., pyrrolyl, pyrazolyl, imidazoly, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, and the like), or a 5 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms(e.g., pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, and morpholinyl, and the like). Further, each of the above-mentioned ring structures formed by R_3 and R_4, independently, is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, C_1-C_6 alkyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8

cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl.

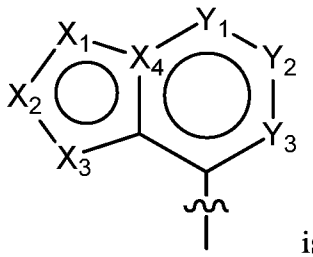
[0174] For example, R_1 is H.

[0175] For example, R_8 is H, methyl, or ethyl.

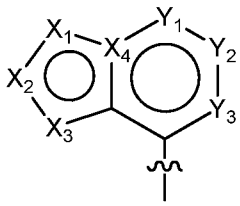
[0176] For example, R_3 is H.

[0177] For example, each of R_5, R_9, and R_{10} is H.

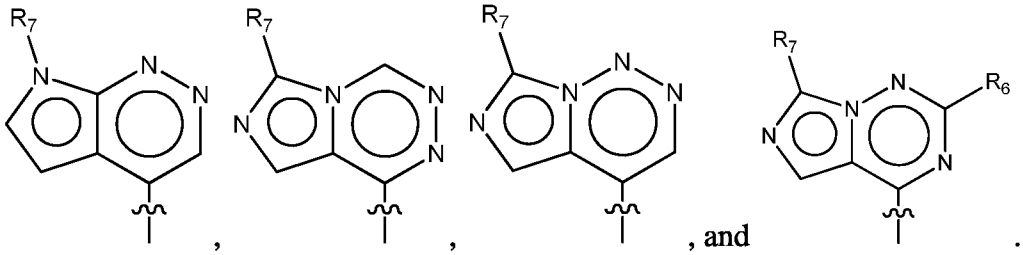
[0178] For example, A^- is Br^-.



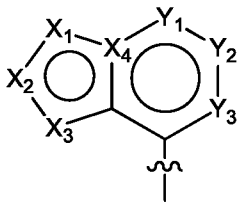
[0179] For example, is selected from the group consisting of indolyl, isoindolyl, indolizinyl, benzofuryl, isobenzofuryl, benzo[b]thienyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, purinyl, indazolyl, pyrrolopyridinyl, imidazopyridinyl, pyrazolopyridinyl, pyrrolopyrazinyl, imidazopyrazinyl, pyrazolopyrazinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, pyrrolopyridazinyl, imidazopyridazinyl, pyrazolopyridazinyl, furopyridinyl, thienopyridinyl, furopyrazinyl, thienopyrazinyl, oxazolopyridinyl, isoxazolopyridinyl, thiazolopyridinyl, isothiazolopyridinyl, oxadiazolopyridinyl, thiadiazolopyridinyl, triazolopyridinyl, oxazolopyrazinyl, isoxazolopyrazinyl, thiazolopyrazinyl, isothiazolopyrazinyl, oxadiazolopyrazinyl, thiadiazolopyrazinyl, triazolopyrazinyl, furopyrimidinyl, thienopyrimidinyl, furopyridazinyl, thienopyridazinyl, oxazolopyrimidinyl, isoxazolopyrimidinyl, thiazolopyrimidinyl, isothiazolopyrimidinyl, oxadiazolopyrimidinyl, thiadiazolopyrimidinyl, triazolopyrimidinyl, oxazolopyridazinyl, isoxazolopyridazinyl, thiazolopyridazinyl, isothiazolopyridazinyl, oxadiazolopyridazinyl, thiadiazolopyridazinyl, triazolopyridazinyl, and imidazotriazinyl.



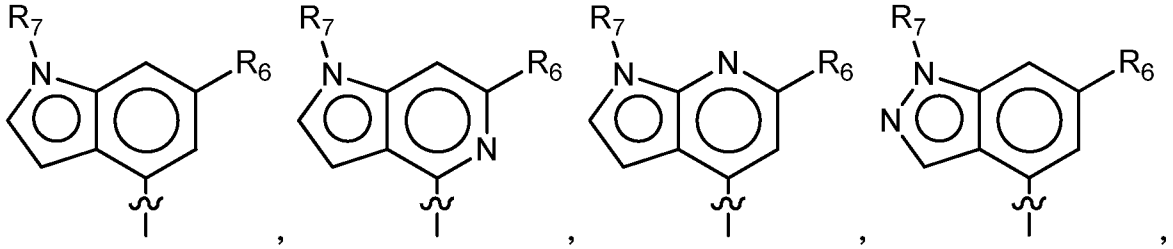
[0180] For example, is selected from the group consisting of



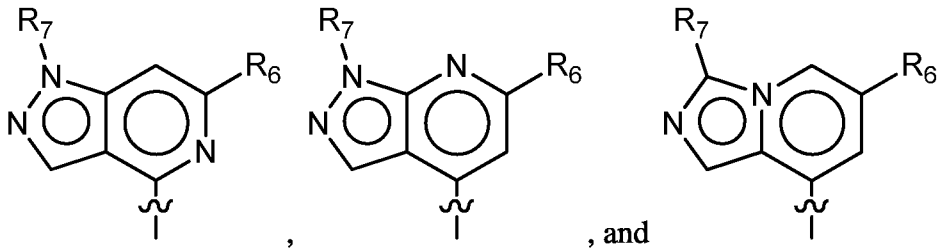
, , , and .



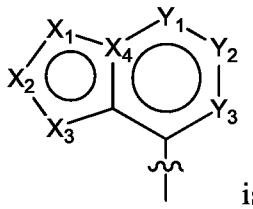
[0181] For example, is selected from the group consisting of



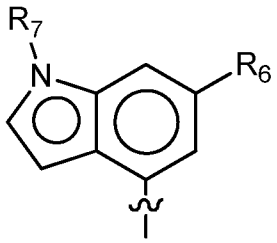
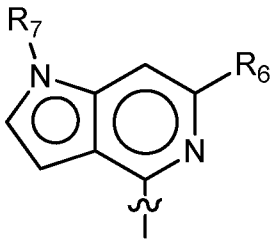
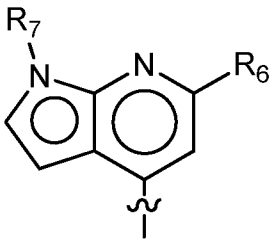
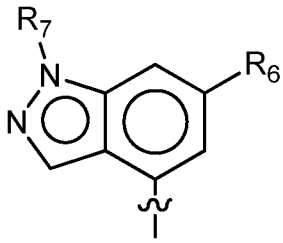
, , , , ,



, , and



[0182] For example, is selected from the group consisting of


,

,

,

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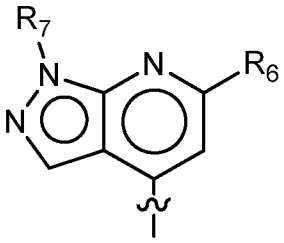
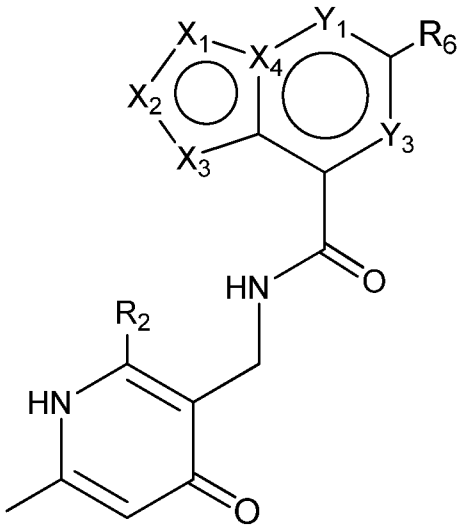
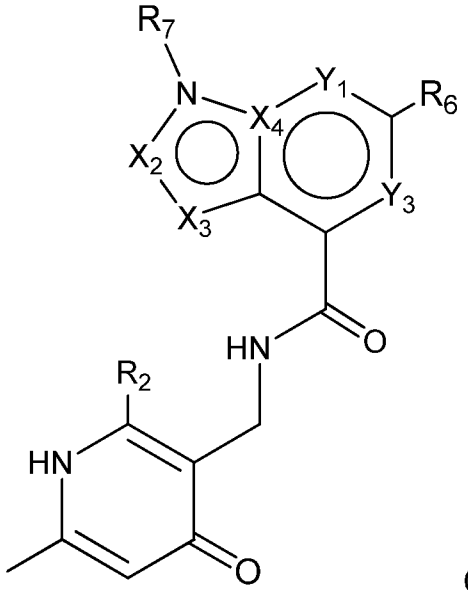

and .

[0183] One subset of the compounds of Formula (IV) includes those of Formula (IVa):

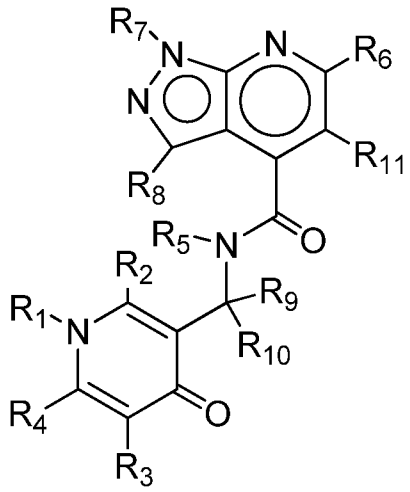

(IVa).

[0184] Another subset of the compounds of Formula (IV) includes those of Formula (IVb).

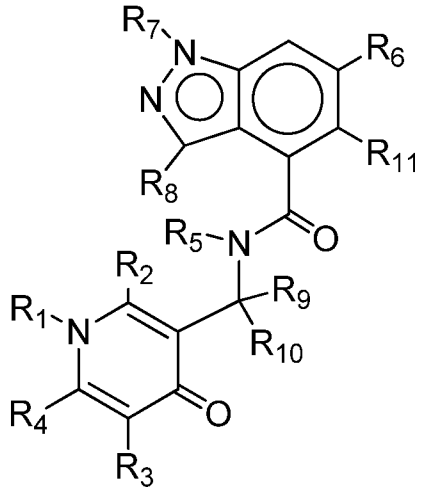


(IVb).

[0185] The present invention provides the compounds of Formulae (II) and (III):



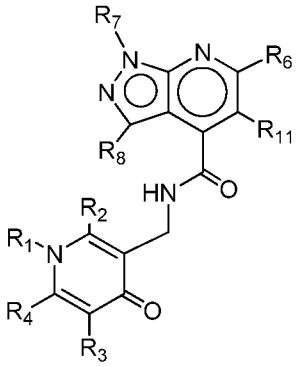
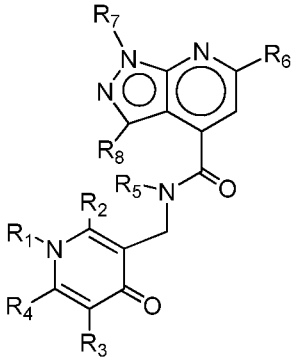
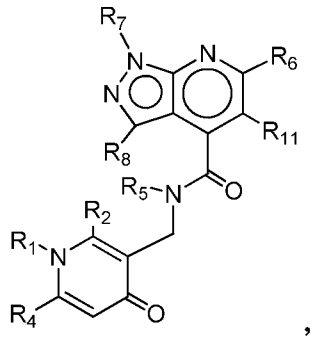
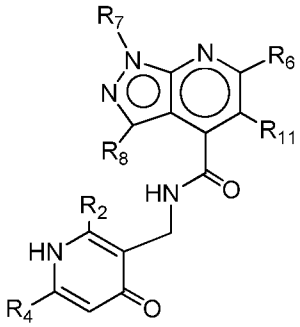
or



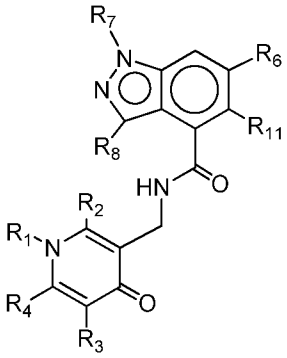
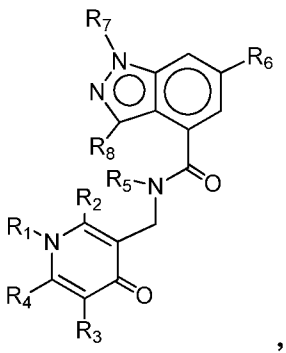
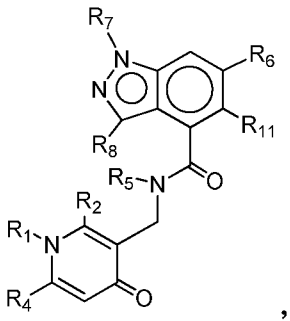
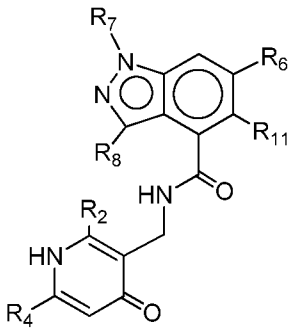
(II) (III)

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, and R_{11} are defined herein.

[0186] The present invention provides the compounds of Formulae (IIa)-(IId) and (IIIa)-(IIId):

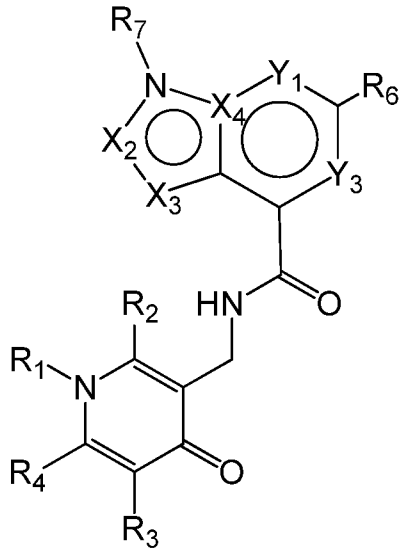
(IIa) (IIb) (IIc) (IId)

(IIIa) (IIIb) (IIIc) (IIId)

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_{11} are defined herein.

[0187] Still another subset of the compounds of Formula (IV) includes those of Formula (VI):

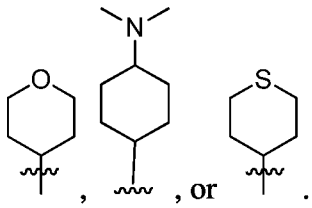


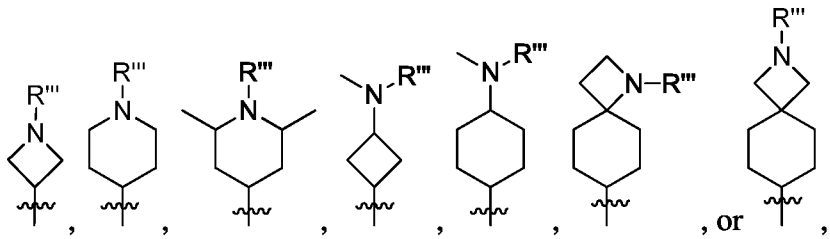
(VI),

or pharmaceutically acceptable salts thereof, wherein R_7 is $-Q_4$-T_4, wherein Q_4 is a bond or methyl linker, T_4 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl or optionally substituted 4- to 14-membered heterocycloalkyl, and R_1, R_2, R_3, R_4, R_6, X_2, X_3, X_4, Y_1, and Y_3, are as defined herein for Formula (IV).

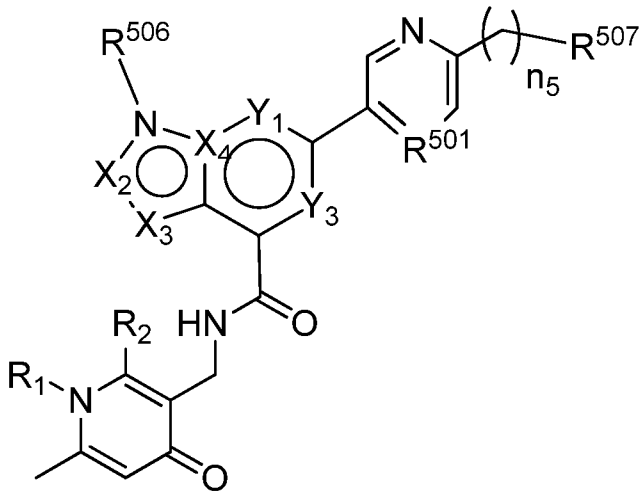
[0188] In addition to the above-described features of the compounds of this invention where applicable, the compounds of Formula (VI) can include one or more of the following features:

[0189] For example, T_4 is alkyl such as i-propyl.

[0190] For example, T_4 is  .

[0191] For example, T_4 is  , in which R''' is T_5, $-C(O)T_5$, or $S(O)_2T_5$, T_5 being as defined herein for Formula (IV).

[0192] For example, the compounds of Formula (VI) include those of Formula (VIa):



(VIa)

or a pharmaceutically acceptable salt thereof; wherein

n_5 is 0, 1, or 2;

R^{501} is C(H) or N;

R^{506} is C_1-C_6 alkyl, piperidine substituted by 1, 2, or 3 C_{1-4} alkyl groups, or cyclohexyl substituted by $N(C_{1-4}$ alkyl$)_2$ wherein one or both of the C_{1-4} alkyl is optionally substituted with C_{1-6} alkoxyl;

R^{507} is morpholine, piperazine, piperidine, diazepane, pyrrolidine, azetidine, O-C_{1-6} alkyl, NH-C_{1-6} alkyl, or O-heterocycle, wherein the heterocycle is a 4-7 membered heterocycle containing an oxygen or nitrogen, or both, and wherein the nitrogen can optionally be substituted with C_{1-3} alkyl; wherein the piperazine, piperidine, diazepane, pyrrolidine or azetidine groups can be optionally further substituted with OH, C_{1-6} alkyl, or O-C_{1-3} alkyl; and wherein each of the O-C_{1-6} alkyl and NH-C_{1-6} alkyl is optionally substituted with hydroxyl, O-C_{1-3} alkyl or NH-C_{1-3} alkyl, each of the O-C_{1-3} alkyl and NH-C_{1-3} alkyl being optionally further substituted with O-C_{1-3} alkyl or NH-C_{1-3} alkyl; and

each of R_1, R_2, X_2, X_3, X_4, Y_1, and Y_3, is as defined herein for Formula (IV).

[0193] In addition to the above-described features of the compounds of this invention where applicable, the compounds of Formula (VIa) can include one or more of the following features.

[0194] For example, R^{501} is C(H), and R^{507} is piperidine; diazepane; pyrrolidine; azetidine; O-C_{1-6} alkyl; or O-heterocycle, wherein the heterocycle is a 4-7 membered heterocycle containing an oxygen or nitrogen, or both, and wherein the nitrogen can optionally be

substituted with C_{1-3} alkyl; wherein the piperidine, diazepane, pyrrolidine or azetidine groups can be optionally further substituted with OH, C_{1-6} alkyl, or O-C_{1-3} alkyl.

[0195] For example, R^{501} is C(H) and R^{507} is piperidine, diazepane, pyrrolidine, azetidine or O-C_{1-6} alkyl, wherein the piperidine, diazepane, pyrrolidine or azetidine groups can be optionally further substituted with OH or C_{1-6} alkyl.

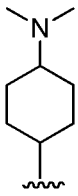
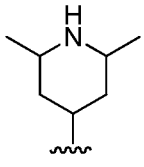
[0196] For example, R^{501} is C(H), R^{507} is piperazine optionally further substituted with C_{1-6} alkyl, and R^{506} is piperidine substituted by 1, 2, or 3 C_{1-4} alkyl groups.

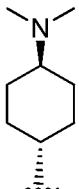
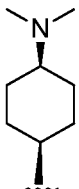
[0197] For example, R^{501} is N, and R^{507} is morpholine, piperidine, piperazine, diazepane, pyrrolidine, azetidine or O-C_{1-6} alkyl, wherein the piperidine, piperazine, diazepane, pyrrolidine or azetidine groups can be optionally further substituted with OH or C_{1-6} alkyl.

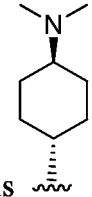
[0198] For example, R_1 is H, methyl, or ethyl, and R_2 is halo, cyano, C_1-C_6 alkoxyl optionally substituted with C_1-C_6 alkoxyl, C_1-C_3 alkyl optionally substituted with C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, optionally substituted 4 to 6-membered heterocycloalkyl (e.g., pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl), optionally substituted phenyl, or optionally substituted 5- or 6-membered heteroaryl (e.g., pyridinyl, pyrazolyl, pyrimidinyl, quinolinyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, or thienyl).

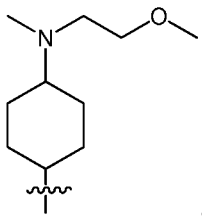
[0199] For example, R_1 and R_2, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms (e.g., pyrazolyl) or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms (pyrrolidinyl).

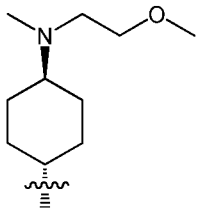
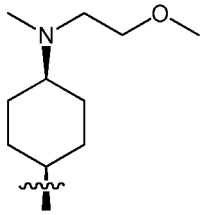
[0200] For example, R^{506} is C_1-C_6 alkyl such as i-propyl.

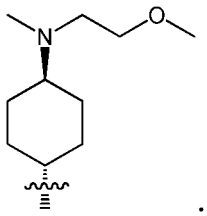
[0201] For example, R^{506} is  or  .

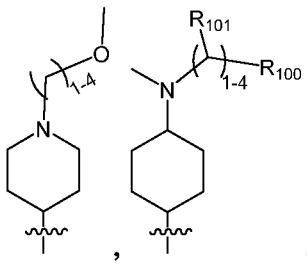
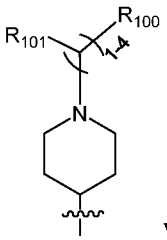
[0202] For example, R^{506} is  or  .

[0203] For example, R^{506} is  .

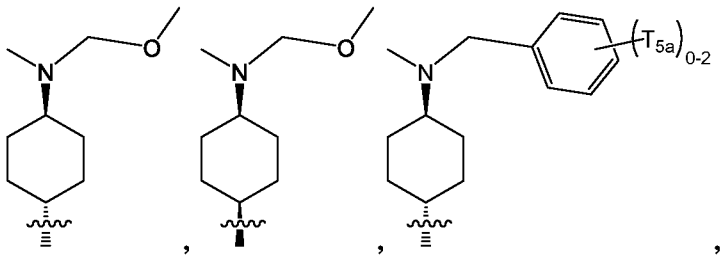
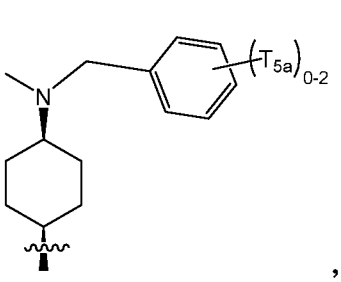
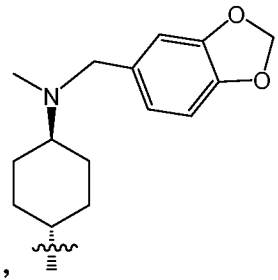
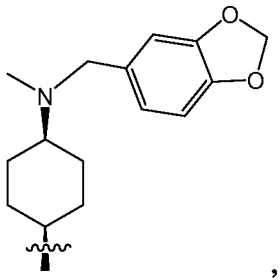
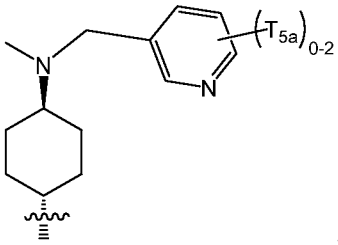
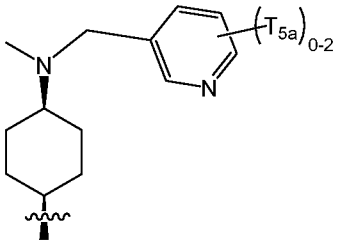
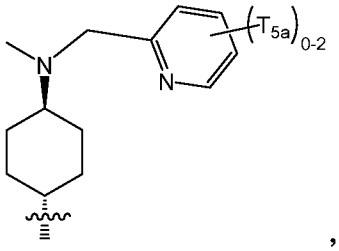
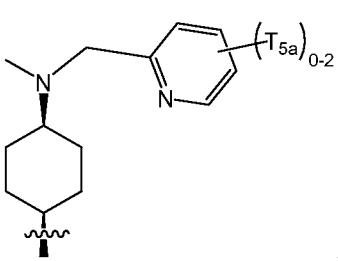
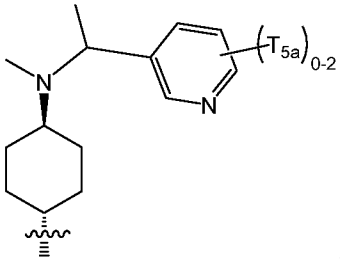
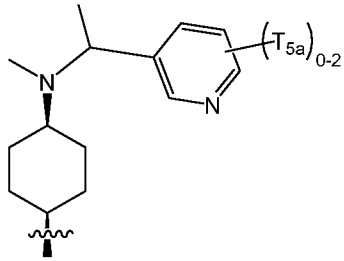
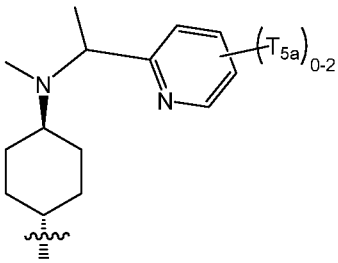
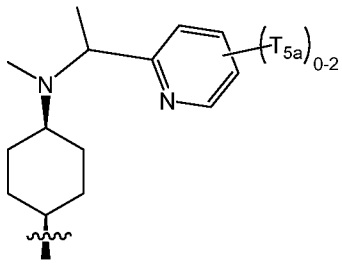
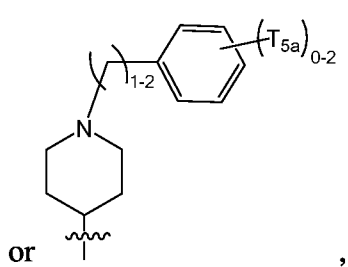
[0204] For example, R^{506} is  .

[0205] For example, R^{506} is  or  .

[0206] For example, R^{506} is  .

[0207] For example, R^{506} is  , , or 

wherein R_{100} is phenyl, 5- or 6-membered heteroaryl, or 4 to 12-membered heterocycloalkyl, each optionally substituted with one or more T_{5a} in which each T_{5a} is independently C_1-C_6 alkoxyl or O-C_1-C_4 alkylene-C_1-C_4 alkoxy, and R_{101} is H or C_1-C_4 alkyl.

[0208] For example, R^{506} is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , or , wherein each T_{5a} is independently C_1-C_3 alkoxyl or O-C_1-C_3 alkylene-C_1-C_2 alkoxy.

[0209] For example, when R^{501} is C(H), R^{507} is piperidine or diazepane, which are substituted with OH or C_{1-6} alkyl, or when R^{501} is N, R^{507} is piperidine, piperazine, or diazepane, which are optionally further substituted with OH or C_{1-6} alkyl.

[0210] For example, when R^{501} is C(H), R^{507} is piperidine substituted with C_{1-6} alkyl, or when R^{501} is N, R^{507} is piperidine substituted with OH or piperazine substituted with C_{1-6} alkyl.

[0211] For example, when R^{501} is N, R^{507} is unsubstituted piperazine.

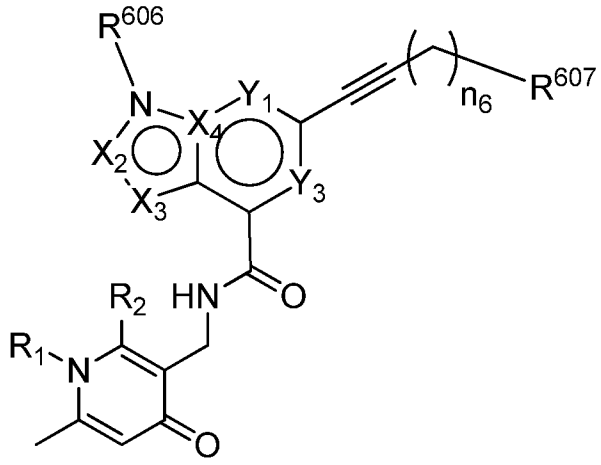
[0212] For example, n_5 is 0 or 1.

[0213] For example, when R^{501} is C(H) or N, R^{507} is O-C_{1-6} alkyl or O-heterocycle, and n_5 is 1.

[0214] For example, when R^{501} is C(H), R^{507} is unsubstituted piperazine and R^{506} is piperidine substituted by 1, 2, or 3 C_{1-4} alkyl groups.

[0215] For example, R^{507} is O-C_{2-3} alkyl substituted with O-C_{1-2} alkyl, e.g., -$OCH_2CH_2OCH_3$.

[0216] For example, the compounds of Formula (VI) include those of Formula (VIb):



(VIb)

or a pharmaceutically acceptable salt thereof; wherein

n_6 is 0, 1 or 2;

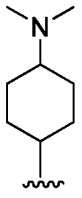
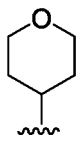
R^{606} is C_1-C_6 alkyl, tetrahydropyranyl, piperidine substituted by 1, 2, or 3 C_{1-4} alkyl groups, or cyclohexyl substituted by N(C_{1-4} alkyl)$_2$ wherein one or both of the C_{1-4} alkyl is optionally substituted with C_{1-6} alkoxyl;

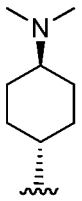
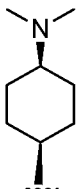
R^{607} is morpholine, piperidine, piperazine, pyrrolidine, diazepane, oxetane, azetidine or O-C_{1-6} alkyl, wherein the piperidine, diazepane, oxetane or azetidine groups can be optionally further substituted with one or more C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

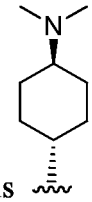
each of R_1, R_2, X_2, X_3, X_4, Y_1, and Y_3, is as defined herein for Formula (IV).

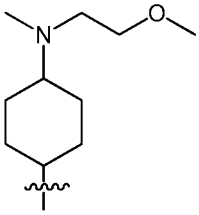
[0217] In addition to the above-described features of the compounds of this invention where applicable, the compounds of Formula (VIb) can include one or more of the following features:

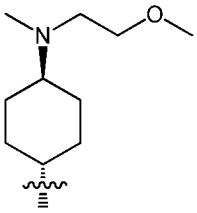
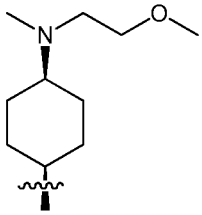
[0218] For example, R^{606} is C_1-C_6 alkyl such as i-propyl.

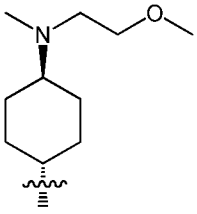
[0219] For example, R^{606} is  or  .

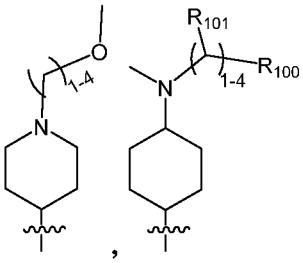
[0220] For example, R^{606} is  or  .

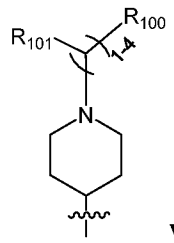
[0221] For example, R^{606} is  .

[0222] For example, R^{606} is  .

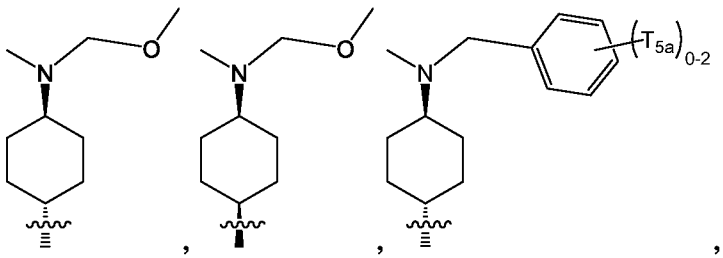
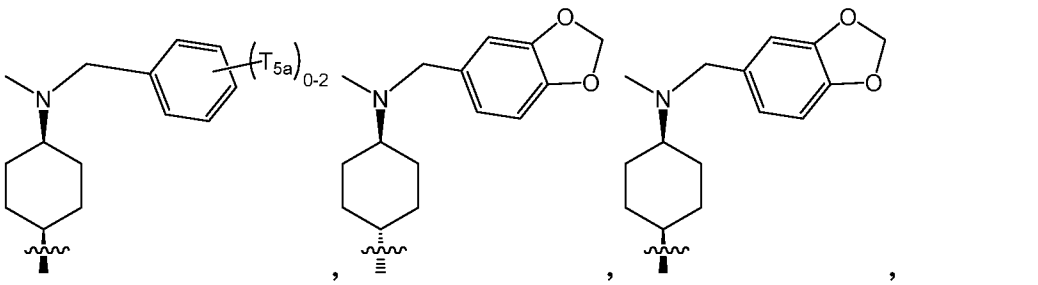
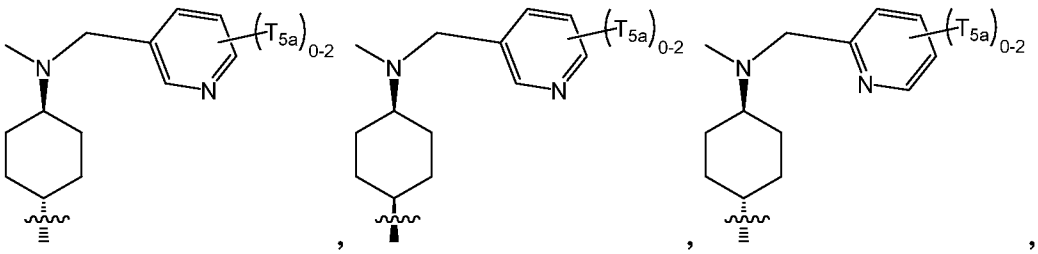
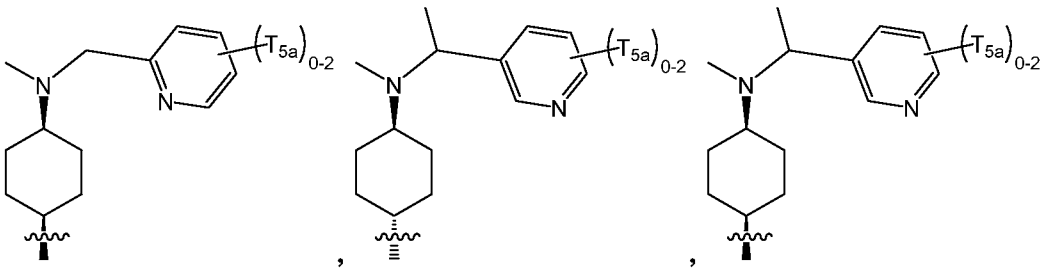
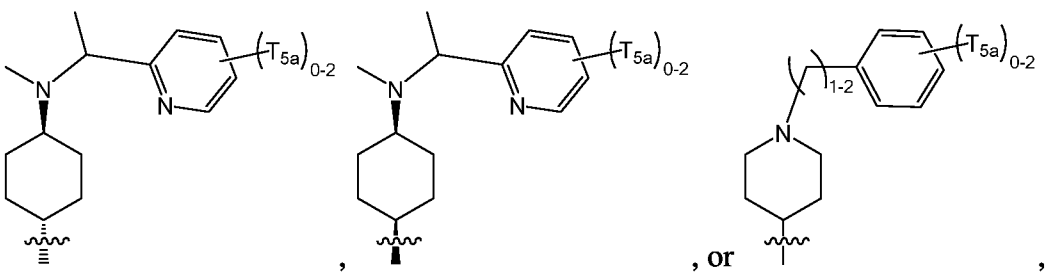
[0223] For example, R^{606} is  or  .

[0224] For example, R^{606} is  .

[0225] For example, R^{606} is  , , or



wherein R_{100} is phenyl, 5- or 6-membered heteroaryl, or 4 to 12-membered heterocycloalkyl, each optionally substituted with one or more T_{5a} in which each T_{5a} is independently C_1-C_6 alkoxyl or O-C_1-C_4 alkylene-C_1-C_4 alkoxy, and R_{101} is H or C_1-C_4 alkyl.

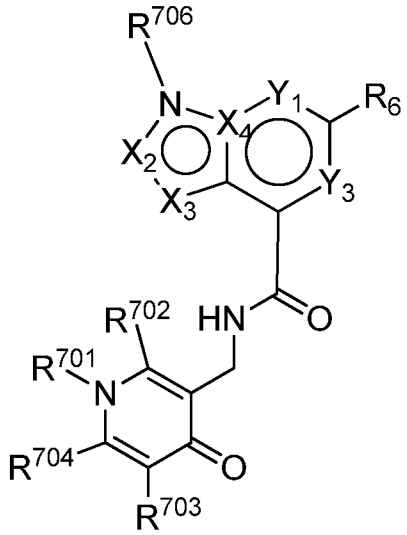
[0226] For example, R^{606}  ,  ,  ,  ,  , , or , wherein each T_{5a} is independently C_1-C_3 alkoxyl or O-C_1-C_3 alkylene-C_1-C_2 alkoxy.

[0227] For example, R^{607} is piperidine or oxetane, each of which is substituted with C_{1-6} alkyl.

[0228] For example, R^{607} is piperidine substituted with CH_2CF_3, cyclopropyl, cyclobutyl, or oxetane.

[0229] For example, n_6 is 0 or 1.

[0230] For example, the compounds of Formula (VI) include those of Formula (VIc):



(VIc),

or a pharmaceutically acceptable salt thereof; wherein

R^{701} is H or C_{1-4} alkyl;

R^{702} is C_{1-6} alkoxyl or C_6-C_{10} aryloxy, each optionally substituted with one or more halo;

R^{703} is H, halo, or C_{1-4} alkyl;

R^{704} is halo, or C_{1-4} alkyl or C_{1-6} alkoxyl, each optionally substituted with one or more halo;

or R^{701} and R^{702}, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R^{701} and R^{704}, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R^{703} and R^{704}, together with the C atoms to which they are attached, form C_5-C_8 cycloalkyl, C_{6-10} aryl, or a 5- or 6-membered heteroaryl having 1 to 3 heteroatoms, or a 5 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms; in which each of the ring structures formed by R^{701} and R^{702}, by R^{701} and R^{704}, or by R^{703} and R^{704},

independently is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, C_1-C_6 alkyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

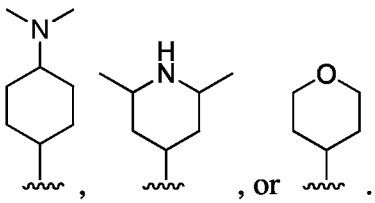
R^{706} is C_{1-6} alkyl, C_{3-8} cycloalkyl, tetrahydropyranyl, piperidine substituted by 1, 2, or 3 R^{707} groups, or cyclohexyl substituted by $N(R^{707})_2$, wherein each R^{707} is independently C_{1-4} alkyl that is optionally substituted with C_{1-6} alkoxyl, 4 to 12-membered heterocycloalkyl, C_6-C_{10} aryl that is optionally further substituted with C_1-C_6 alkoxyl or O-C_1-C_4 alkylene-C_1-C_4 alkoxy, or 5- or 6-membered heteroaryl that is optionally further substituted with C_1-C_6 alkoxyl or O-C_1-C_4 alkylene-C_1-C_4 alkoxy; and

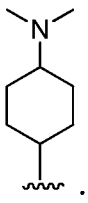
each of R_6, X_2, X_3, X_4, Y_1, and Y_3, is as defined herein for Formula (IV).

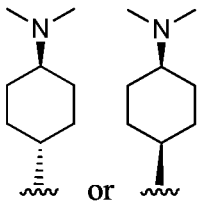
[0231] In addition to the above-described features of the compounds of this invention where applicable, the compounds of Formula (IVc) can include one or more of the following features:

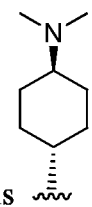
[0232] For example, R^{706} is alkyl such as sec-butyl or iso-propyl.

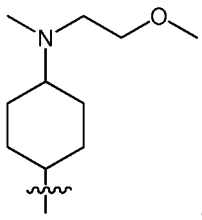
[0233] For example, R^{706} is cyclopentyl.

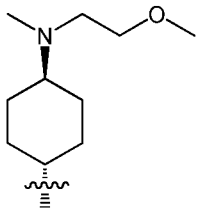
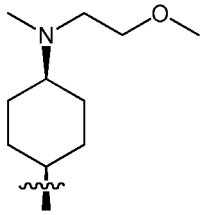
[0234] For example, R^{706} is  .

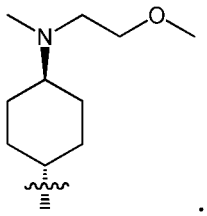
[0235] For example, R^{706} is  .

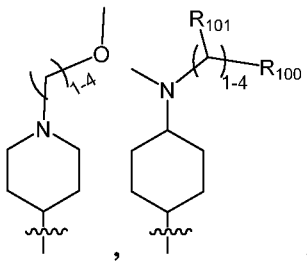
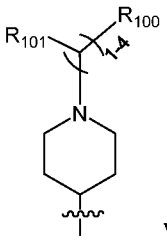
[0236] For example, R^{706} is  .

[0237] For example, R^{706} is  .

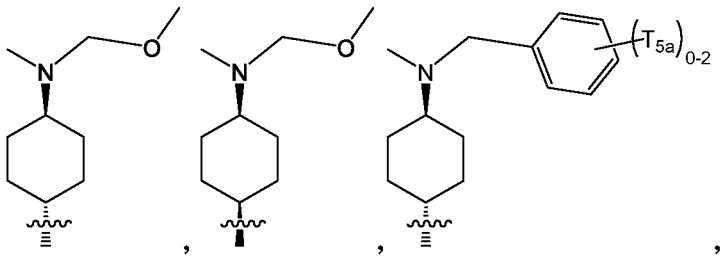
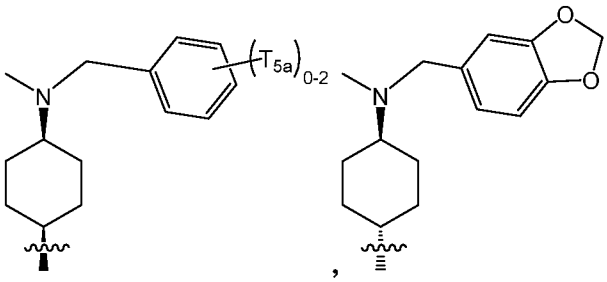
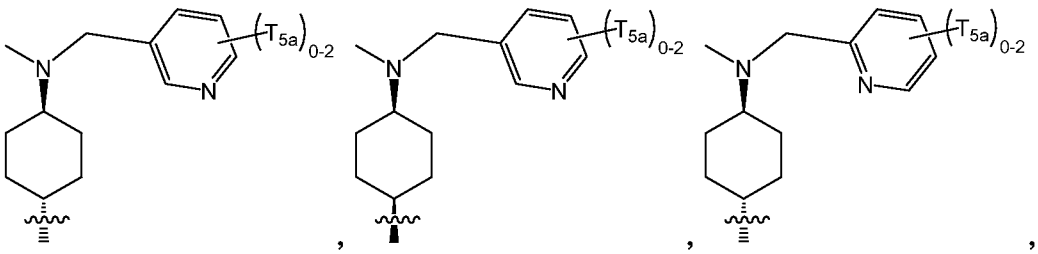
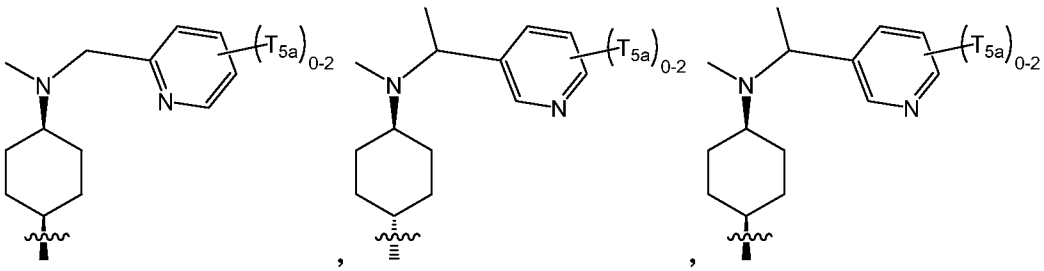
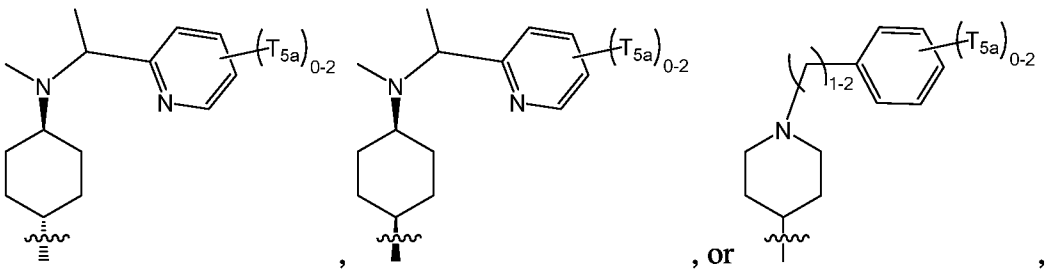
[0238] For example, R^{706} is  .

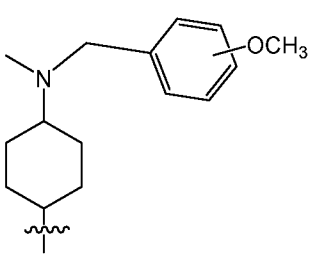
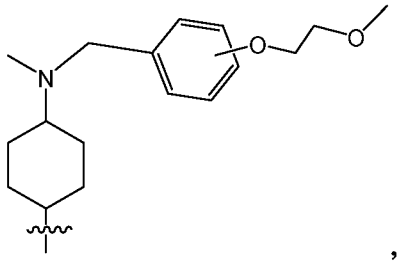
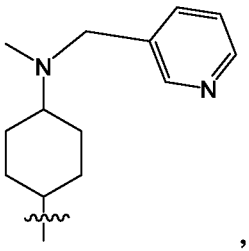
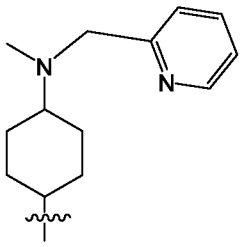
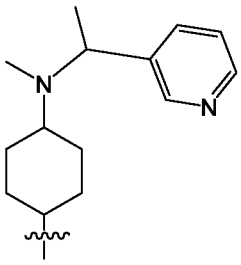
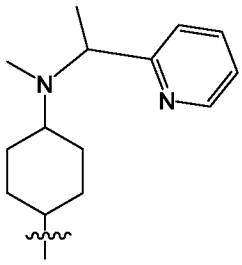
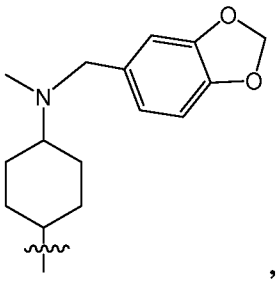
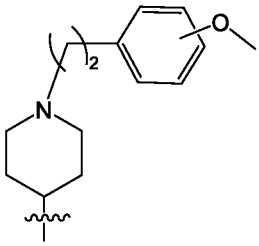
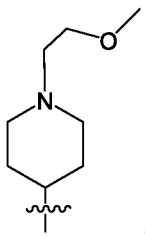
[0239] For example, R^{706} is  or  .

[0240] For example, R^{706} is  .

[0241] For example, R^{706} is  , , or 

wherein R_{100} is phenyl, 5- or 6-membered heteroaryl, or 4 to 12-membered heterocycloalkyl, each optionally substituted with one or more T_{5a} in which each T_{5a} is independently C_1-C_6 alkoxyl or O-C_1-C_4 alkylene-C_1-C_4 alkoxy, and R_{101} is H or C_1-C_4 alkyl.

[0242] For example, R^{706} is  ,  ,  ,  ,  , wherein each T_{5a} is independently C_1-C_3 alkoxyl or O-C_1-C_3 alkylene-C_1-C_2 alkoxy.

[0243] For example, R^{706} is  ,  ,  ,  ,  ,  ,  ,  , or  .

[0244] For example, R^{701} is H.

[0245] For example, R^{702} is methoxy, ethoxy, $-OCF_3$, or phenoxy.

[0246] For example, R^{703} is H.

[0247] For example, R^{703} is F.

[0248] For example, R^{704} is methyl, ethyl or CF_3.

[0249] For example, R^{704} is methoxy or ethoxy.

[0250] For example, R^{704} is F or Cl.

[0251] For example, R^{701} and R^{702}, together with the N and C atoms to which they are attached, form a 5 to 6-membered heterocycloalkyl ring having an oxygen atom.

[0252] For example, R^{703} and R^{704}, together with the C atoms to which they are attached, form C_5-C_6 cycloalkyl.

[0253] For example, R^{703} and R^{704}, together with the C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 1 to 3 heteroatoms, and the heteroaryl is optionally substituted with C_{1-4} alkyl.

[0254] For example, R^{703} and R^{704}, together with the C atoms to which they are attached, form a 5 to 7-membered heterocycloalkyl ring having 1 to 3 heteroatoms, and the heterocycloalkyl ring is optionally substituted with C_{1-4} alkyl.

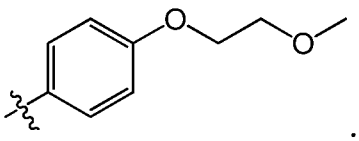
[0255] For example, R^{701} and R^{702}, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl or a 5 to 6-membered heterocycloalkyl, and R^{703} and R^{704}, together with the C atoms to which they are attached, form C_5-C_6 cycloalkyl, a 5- or 6-membered heteroaryl, or a 5 to 12-membered heterocycloalkyl ring.

[0256] For example, R_6 is halo, e.g., F, Cl, or Br.

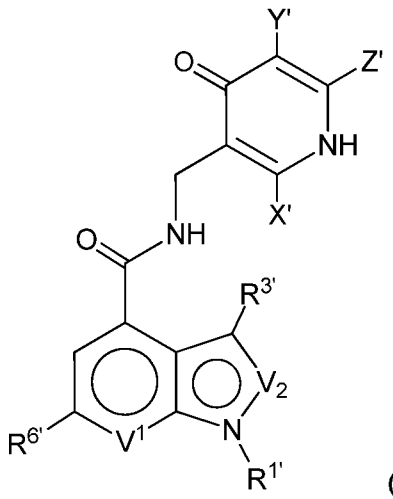
[0257] For example, R_6 is Cl.

[0258] For example, R_6 is unsubstituted or substituted phenyl or 5- or 6-membered heteroaryl.

[0259] For example, R_6 is phenyl or 5- or 6-membered heteroaryl substituted with O-C_{1-6} alkyl or NH-C_{1-6} alkyl, each of which is optionally substituted with hydroxyl, O-C_{1-3} alkyl or NH-C_{1-3} alkyl, each of the O-C_{1-3} alkyl and NH-C_{1-3} alkyl being optionally further substituted with O-C_{1-3} alkyl or NH-C_{1-3} alkyl.

[0260] For example, R_6 is  .

[0261] The compounds of this invention also include those of Formula (V) or pharmaceutically acceptable salts thereof:



(V),

wherein,

V^1 is N or $CR^{7'}$,

V^2 is N or $CR^{2'}$, provided when V^1 is N, V^2 is N,

X' and Z' are selected independently from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, unsubstituted or substituted (C_3-C_8)cycloalkyl, unsubstituted or substituted (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl, unsubstituted or

substituted (C_5-C_8)cycloalkenyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, (C_6-C_{10})bicycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted heterocycloalkyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, halo, cyano, -$COR^{a'}$, -$CO_2R^{a'}$, -$CONR^{a'}R^{b'}$, -$CONR^{a'}NR^{a'}R^{b'}$, -$SR^{a'}$, -$SOR^{a'}$, -$SO_2R^{a'}$, -$SO_2NR^{a'}R^{b'}$, nitro, -$NR^{a'}R^{b'}$, -$NR^{a'}C(O)R^{b'}$, -$NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}C(O)OR^{a'}$, -$NR^{a'}SO_2R^{b'}$, -$NR^{a'}SO_2NR^{a'}R^{b'}$, -$NR^{a'}NR^{a'}R^{b'}$, -$NR^{a'}NR^{a'}C(O)R^{b'}$, -$NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}NR^{a'}C(O)OR^{a'}$, -$OR^{a'}$, -$OC(O)R^{a'}$, and -$OC(O)NR^{a'}R^{b'}$;

Y' is H or halo;

$R^{1'}$ is (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, unsubstituted or substituted (C_3-C_8)cycloalkyl, unsubstituted or substituted (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted (C_6-C_{10})bicycloalkyl, unsubstituted or substituted heterocycloalkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted heterocycloalkyl-(C_1-C_8)alkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, -$COR^{a'}$, -$CO_2R^{a'}$, -$CONR^{a'}R^{b'}$, -$CONR^{a'}NR^{a'}R^{b'}$;

$R^{2'}$ is hydrogen, (C_1-C_8)alkyl, trifluoromethyl, alkoxy, or halo, in which said (C_1-C_8)alkyl is optionally substituted with one to two groups selected from amino and (C_1-C_3)alkylamino;

$R^{7'}$ is hydrogen, (C_1-C_3)alkyl, or alkoxy;

$R^{3'}$ is hydrogen, (C_1-C_8)alkyl, cyano, trifluoromethyl, -$NR^{a'}R^{b'}$, or halo;

$R^{6'}$ is selected from the group consisting of hydrogen, halo, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, unsubstituted or substituted (C_3-C_8)cycloalkyl, unsubstituted or substituted (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl-(C_1-C_8)alkyl, (C_6-C_{10})bicycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted heterocycloalkyl-(C_1-C_8)alkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-(C_1-C_8)alkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-(C_1-C_8)alkyl, cyano, -$COR^{a'}$, -$CO_2R^{a'}$, -$CONR^{a'}R^{b'}$, -$CONR^{a'}NR^{a'}R^{b'}$, -$SR^{a'}$,

-$SOR^{a'}$, -$SO_2R^{a'}$, -$SO_2NR^{a'}R^{b'}$, nitro, -$NR^{a'}R^{b'}$, -$NR^{a'}C(O)R^{b'}$, -$NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}C(O)OR^{a'}$, -$NR^{a'}SO_2R^{b'}$, -$NR^{a'}SO_2NR^{a'}R^{b'}$, -$NR^{a'}NR^{a'}R^{b'}$, -$NR^{a'}NR^{a'}C(O)R^{b'}$, -$NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}NR^{a'}C(O)OR^{a'}$, -$OR^{a'}$, -$OC(O)R^{a'}$, -$OC(O)NR^{a'}R^{b'}$;

wherein any (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, heterocycloalkyl, aryl, or heteroaryl group is optionally substituted by 1, 2 or 3 groups independently selected from the group consisting of -$O(C_1$-$C_6)alkyl(R^{c'})_{1-2}$, -$S(C_1$-$C_6)alkyl(R^{c'})_{1-2}$, -(C_1-C_6)alkyl($R^{c'})_{1-2}$, -(C_1-C_8)alkyl-heterocycloalkyl, (C_3-C_8)cycloalkyl-heterocycloalkyl, halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_1-C_6)haloalkyl, cyano, -$COR^{a'}$, -$CO_2R^{a'}$,-$CONR^{a'}R^{b'}$, -$SR^{a'}$, -$SOR^{a'}$, -$SO_2R^{a'}$, -$SO_2NR^{a'}R^{b'}$, nitro, -$NR^{a'}R^{b'}$, -$NR^{a'}C(O)R^{b'}$, -$NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}C(O)OR^{a'}$, -$NR^{a'}SO_2R^{b'}$, -$NR^{a'}SO_2NR^{a'}R^{b'}$, -$OR^{a'}$, -$OC(O)R^{a'}$, $OC(O)NR^{a'}R^{b'}$, heterocycloalkyl, aryl, heteroaryl, aryl(C_1-C_4)alkyl, and heteroaryl(C_1-C_4)alkyl;

wherein any aryl or heteroaryl moiety of said aryl, heteroaryl, aryl(C_1-C_4)alkyl, or heteroaryl(C_1-C_4)alkyl is optionally substituted by 1, 2 or 3 groups independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_1-C_6)haloalkyl, cyano, -$COR^{a'}$, -$CO_2R^{a'}$, -$CONR^{a}R^{b'}$,-$SR^{a'}$, -$SOR^{a'}$, -$SO_2R^{a'}$, -$SO_2NR^{a'}R^{b'}$, nitro, -$NR^{a'}R^{b'}$, -$NR^{a'}C(O)R^{b'}$,-$NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}C(O)OR^{a'}$, -$NR^{a'}SO_2R^{b'}$, -$NR^{a'}SO_2NR^{a'}R^{b'}$, -$OR^{a'}$, -$OC(O)R^{a'}$, and -$OC(O)NR^{a'}R^{b'}$;

$R^{a'}$ and $R^{b'}$ are each independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_6-C_{10})bicycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein said (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl,heterocycloalkyl ,aryl or heteroaryl group is optionally substituted by 1, 2 or 3 groups independently selected from halo, hydroxyl, (C_1-C_4)alkoxy, amino, (C_1-C_4)alkylamino, ((C_1-C_4)alkyl)((C_1-C_4)alkyl)amino, -CO_2H, -CO_2(C_1-C_4)alkyl, -$CONH_2$,-CONH(C_1-C_4)alkyl, -CON((C_1-C_4)alkyl)((C_1-C_4)alkyl), -SO_2(C_1-C_4)alkyl, -SO_2NH_2,-SO_2NH(C_1-C_4)alkyl, and SO_2N((C_1-C_4)alkyl)((C_1-C_4)alkyl);

or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 5-8 membered saturated or unsaturated ring, optionally containing an additional heteroatom selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted by 1, 2 or 3 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, amino, (C_1-C_4)alkylamino, ((C_1-C_4)alkyl)((C_1-C_4)alkyl)amino, hydroxyl,

oxo, (C_1-C_4)alkoxy, and (C_1-C_4)alkoxy(C_1-C_4)alkyl, wherein said ring is optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring;

or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 6- to 10-membered bridged bicyclic ring system optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring; and

each $R^{c'}$ is independently (C_1-C_4)alkylamino, -$NR^{a'}SO2R^{b'}$, -$SOR^{a'}$, -$SO_2R^{a'}$, -$NR^{a'}C(O)OR^{a'}$, -$NR^{a'}R^{b'}$, or -$CO_2R^{a'}$.

[0262] Subgroups of the compounds encompassed by the general structure of Formula (IV) are represented as follows:

Subgroup A of Formula (V)

[0263] X' and Z' are selected from the group consisting of (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -$NR^{a'}R^{b'}$, and -$OR^{a'}$;

[0264] Y is H or F;

[0265] $R^{1'}$ is selected from the group consisting of (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

[0266] $R^{2'}$ is hydrogen, (C_1-C_8)alkyl, trifluoromethyl, alkoxy, or halo, in which said (C_1-C_8)alkyl is optionally substituted with one to two groups selected from amino and (C_1-C_3)alkylamino;

[0267] $R^{7'}$ is hydrogen, (C_1-C_3)alkyl, or alkoxy;

[0268] $R^{3'}$ is selected from the group consisting of hydrogen, (C_1-C_8)alkyl, cyano, trifluoromethyl,-$NR^{a'}R^{b'}$, and halo;

[0269] $R^{6'}$ is selected from the group consisting of hydrogen, halo, cyano, trifluoromethyl, amino, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl;, aryl, heteroaryl, acylamino; (C_2-C_8)alkynyl, arylalkynyl, heteroarylalkynyl; -$SO_2R^{a'}$; -$SO_2NR^{a'}R^{b'}$ and -$NR^{a'}SO_2R^{b'}$;

wherein any (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_8)alkynyl, arylalkynyl, heteroarylalkynyl group is optionally substituted by 1, 2 or 3 groups independently selected from -O(C_1-C_6)alkyl($R^{c'}$)$_{1-2}$, -S(C_1-C_6)alkyl($R^{c'}$)$_{1-2}$, -(C_1-C_6)alkyl($R^{c'}$)$_{1-2}$, -(C_1-C_8)alkyl-heterocycloalkyl, (C_3-C_8)cycloalkyl-heterocycloalkyl, halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_1-C_6)haloalkyl, cyano, -$COR^{a'}$, -$CO_2R^{a'}$, -$CONR^{a'}R^{b'}$, -$SR^{a'}$, -$SOR^{a'}$, -$SO_2R^{a'}$, -$SO_2NR^{a'}R^{b'}$, nitro, -$NR^{a'}R^{b'}$, -$NR^{a'}C(O)R^{b'}$, -$NR^{a'}C(O)NR^{a'}R^{b'}$, -$NR^{a'}C(O)OR^{a'}$, -$NR^{a'}SO_2R^{b'}$, - $NR^{a'}SO_2NR^{a'}R^{b'}$, -$OR^{a'}$, -$OC(O)R^{a'}$, -$OC(O)NR^{a'}R^{b'}$, heterocycloalkyl, aryl, heteroaryl, aryl(C_1-C_4)alkyl, and heteroaryl(C_1-C_4)alkyl;

[0270] $R^{a'}$ and $R^{b'}$ are each independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_6-C_{10})bicycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein said (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, heterocycloalkyl ,aryl or heteroaryl group is optionally substituted by 1, 2 or 3 groups independently selected from halo, hydroxyl, (C_1-C_4)alkoxy, amino, (C_1-C_4)alkylamino, $((C_1-C_4)alkyl)((C_1-C_4)alkyl)amino$, $-CO_2H$, $-CO_2(C_1-C_4)$alkyl, $-CONH_2$, $-CONH(C_1-C_4)$alkyl, $-CON((C_1-C_4)alkyl)((C_1-C_4)alkyl)$, $-SO_2(C_1-C_4)$alkyl, $-SO_2NH_2$,$-SO_2NH(C_1-C_4)$alkyl, and $-SO_2N((C_1-C_4)alkyl)((C_1-C_4)alkyl)$;

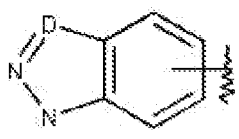
or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 5-8 membered saturated or unsaturated ring, optionally containing an additional heteroatom selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted by 1, 2 or 3 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, amino, (C_1-C_4)alkylamino, $((C_1-C_4)alkyl)((C_1-C_4)alkyl)amino$, hydroxyl, oxo, (C_1-C_4)alkoxy, and $(C_1-C_4)alkoxy(C_1-C_4)$alkyl, wherein said ring is optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring;

or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 6- to 10-membered bridged bicyclic ring system optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring. An aryl or heteroaryl group in this particular subgroup A is selected independently from the group consisting of furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole, tetrazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, phenyl, pyridine, pyridazine, pyrimidine, pyrazine, triazine, tetrazine, quinoline, cinnoline, quinazoline, quinoxaline, and naphthyridine or another aryl or heteroaryl group as follows:

(1)

wherein in (1),

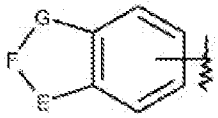
A is O, NH, or S; B is CH or N, and C is hydrogen or C_1-C_8 alkyl; or



(2)

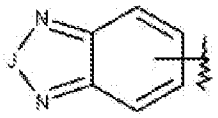
wherein in (2),

D is N or C optionally substituted by hydrogen or C_1-C_8 alkyl; or


(3)

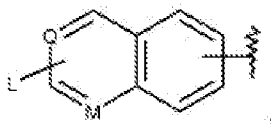
wherein in (3),

E is NH or CH_2; F is O or CO; and G is NH or CH_2; or


(4)

wherein in (4),

J is O, S or CO; or


(5)

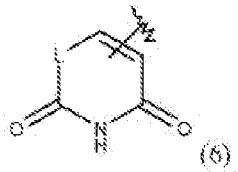
wherein in (5),

Q is CH or N;

M is CH or N; and

L/(5) is hydrogen, halo, amino, cyano, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)R^{b'}$, $-NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, or $-OR^{a'}$,

wherein any $(C_1\text{-}C_8)$alkyl or $(C_3\text{-}C_8)$cycloalkyl group is optionally substituted by 1, 2 or 3 groups independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_5\text{-}C_8)$cycloalkenyl, $(C_1\text{-}C_6)$haloalkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-SR^{a'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, and $-OC(O)NR^{a'}R^{b'}$; wherein $R^{a'}$ and $R^{b'}$ are defined as above; or


(6)

wherein in (6),

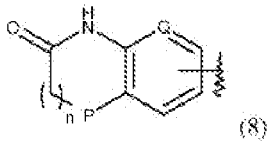
L/(6)is NH or CH_2; or

(7)

wherein in (7),

M/(7) is hydrogen, halo, amino, cyano, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, heterocycloalkyl, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$,$-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)R^{b'}$, $-NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, or $-OR^{a'}$,

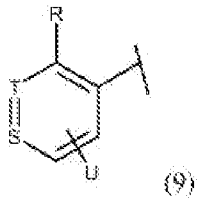
wherein any $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, or heterocycloalkyl group is optionally substituted by 1, 2 or 3 groups independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_5\text{-}C_8)$cycloalkenyl, $(C_1\text{-}C_6)$haloalkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-SR^{a'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, and $-OC(O)NR^{a'}R^{b'}$; wherein $R^{a'}$ and $R^{b'}$ are defined as above; or



(8)

wherein in (8),

P is CH_2, NH, O, or S; Q/(8) is CH or N; and n is 0-2; or



(9)

wherein in (9),

S/(9) and T/(9) is C, or S/(9) is C and T/(9) is N, or S/(9) is N and T/(9) is C;

R is hydrogen, amino, methyl, trifluoromethyl, or halo;

U is hydrogen, halo, amino, cyano, nitro, trifluoromethyl, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$,$-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)R^{b'}$, $-OR^{a'}$, or 4-(1H-pyrazol-4-yl),

wherein any $(C_1\text{-}C_8)$alkyl or $(C_3\text{-}C_8)$cycloalkyl group is optionally substituted by 1, 2 or 3 groups independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_5\text{-}C_8)$cycloalkenyl, $(C_1\text{-}C_6)$haloalkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$,$-CONR^{a'}R^{b'}$, $-SR^{a'}$, $SOR^{a'}$,

$-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, and $-OC(O)NR^{a'}R^{b'}$; wherein $R^{a'}$ and $R^{b'}$ are defined as above.

Subgroup B of Formula (V)

[0271] X' and Z' are selected independently from the group consisting of (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NR^{a'}R^{b'}$, and $-OR^{a'}$;

[0272] Y' is H;

[0273] $R^{1'}$ is (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, or heterocycloalkyl;

[0274] $R^{2'}$ is hydrogen, (C_1-C_3)alkyl, or halo, in which said (C_1-C_3)alkyl is optionally substituted with one to two groups selected from amino and (C_1-C_3)alkylamino;

[0275] $R^{7'}$ is hydrogen, (C_1-C_3)alkyl, or alkoxy;

[0276] $R^{3'}$ is hydrogen, (C_1-C_8)alkyl or halo;

[0277] $R^{6'}$ is hydrogen, halo, cyano, trifluoromethyl, amino, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, aryl, heteroaryl, acylamino; (C_2-C_8)alkynyl, arylalkynyl, heteroarylalkynyl, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, or $-NR^{a'}SO_2R^{b'}$;

wherein any (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_8)alkynyl, arylalkynyl, or heteroarylalkynyl group is optionally substituted by 1, 2 or 3 groups independently selected from halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_1-C_6)haloalkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-SR^{a'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, $-OC(O)NR^{a'}R^{b'}$, heterocycloalkyl, aryl, heteroaryl, aryl(C_1-C_4)alkyl, and heteroaryl(C_1-C_4)alkyl;

[0278] $R^{a'}$ and $R^{b'}$ are each independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_6-C_{10})bicycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein said (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, heterocycloalkyl ,aryl or heteroaryl group is optionally substituted by 1, 2 or 3 groups independently selected from halo, hydroxyl, (C_1-C_4)alkoxy, amino, (C_1-C_4)alkylamino, $((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl)amino, $-CO_2H$, $-CO_2(C_1-C_4)$alkyl, $-CONH_2$,$-CONH(C_1-C_4)$alkyl, $-CON((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl), $-SO_2(C_1-C_4)$alkyl, $-SO_2NH_2$, $-SO_2NH(C_1-C_4)$alkyl, and $-SO_2N((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl);

or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 5-8 membered saturated or unsaturated ring, optionally containing an additional heteroatom selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted by 1,

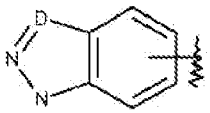
2 or 3 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, amino, (C_1-C_4)alkylamino, ((C_1-C_4)alkyl)((C_1-C_4)alkyl)amino, hydroxyl, oxo, (C_1-C_4)alkoxy, and (C_1-C_4)alkoxy(C_1-C_4)alkyl, wherein said ring is optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring;

or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 6- to 10-membered bridged bicyclic ring system optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring. Aryl and heteroaryl in this definition are selected from the group consisting of furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole, tetrazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, phenyl, pyridine, pyridazine, pyrimidine, pyrazine, triazine, tetrazine, quinoline, cinnoline, quinazoline, quinoxaline, and naphthyridine or a compound of another aryl or heteroaryl group as follows:

(1)

wherein in (1),

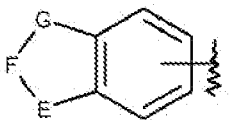
A is O, NH, or S; B is CH or N, and C is hydrogen or C_1-C_8 alkyl; or



(2)

wherein in (2),

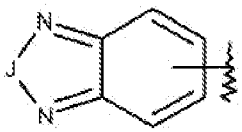
D is N or C optionally substituted by hydrogen or C_1-C_8 alkyl; or



(3)

wherein in (3),

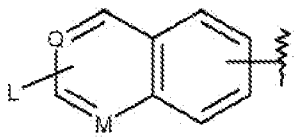
E is NH or CH_2; F is O or CO; and G is NH or CH_2; or



(4)

wherein in (4),

J is O, S or CO; or



(5)

wherein in (5),

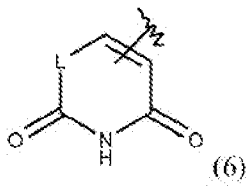
Q is CH or N;

M is CH or N; and

L/(5) is hydrogen, halo, amino, cyano, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)R^{b'}$, $-NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, or $-OR^{a'}$,

wherein any $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, group is optionally substituted by 1,2 or 3 groups independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_5\text{-}C_8)$cycloalkenyl, $(C_1\text{-}C_6)$haloalkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-SR^{a'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, and $-OC(O)NR^{a'}R^{b'}$,

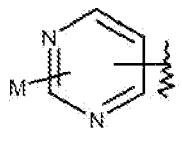
wherein $R^{a'}$ and $R^{b'}$ are defined as above; or



(6)

wherein in (6),

L/(6) is NH or CH_2; or



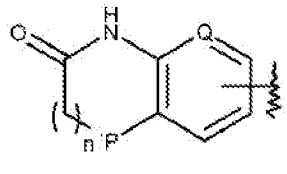
(7)

wherein in (7),

M/(7) is hydrogen, halo, amino, cyano, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, heterocycloalkyl, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)R^{b'}$, $-NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, or $-OR^{a'}$,

wherein any $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, heterocycloalkyl group is optionally substituted by 1, 2 or 3 groups independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_5\text{-}C_8)$cycloalkenyl, $(C_1\text{-}C_6)$haloalkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, - $CONR^{a'}R^{b'}$, $-SR^{a'}$, -

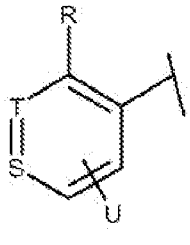
$SOR^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, and-$OC(O)NR^{a'}R^{b'}$; wherein $R^{a'}$ and $R^{b'}$ are defined as above; or



(8)

wherein in (8),

P is CH_2, NH, O, or S; Q/(8) is CH or N; and n is 0-2; or



(9)

wherein in (9),

S/(9) and T/(9) is C, or S/(9) is C and T/(9) is N, or S/(9) is N and T/(9) is C;

R is hydrogen, amino, methyl, trifluoromethyl, halo;

U is hydrogen, halo, amino, cyano, nitro, trifluoromethyl, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, $-COR^a$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$,$-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)R^{b'}$, $-OR^{a'}$,or 4-(1H-pyrazol-4-yl),

wherein any (C_1-C_8)alkyl, or (C_3-C_8)cycloalkyl group is optionally substituted by 1, 2 or 3 groups independently selected from (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_1-C_6)haloalkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$,$-CONR^{a'}R^{b'}$,$-SOR^{a'}$,$-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$,

$-NR^{a'}SO2NR^{a'}R^{b'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, and $-OC(O)NR^{a'}R^{b'}$, wherein $R^{a'}$ and $R^{b'}$ are defined as above.

Subgroup C of Formula (V)

[0279] X' is methyl, ethyl, n-propyl, isopropyl , cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, trifluoromethyl, tetrahydropyran, hydroxymethyl, methoxymethyl, or benzyl;

[0280] Y' is H;

[0281] Z' is methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, or benzyl;

[0282] $R^{1'}$ is isopropyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, (1-methylethyl)cyclopropyl, 1,1-dioxo-tetrahydrothiophene-3-yl, 1-Me-piperidin-4-yl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, *N,N*-dimethyl-1-propanaminyl, benzyl, or 4-pyridyl;

[0283] $R^{2'}$ is hydrogen, $(C_1\text{-}C_3)$alkyl, or halo, in which said $(C_1\text{-}C_3)$alkyl is optionally substituted with one to two groups selected from amino and $(C_1\text{-}C_3)$alkylamino;

[0284] $R^{7'}$ is hydrogen, $(C_1\text{-}C_3)$alkyl, or alkoxy;

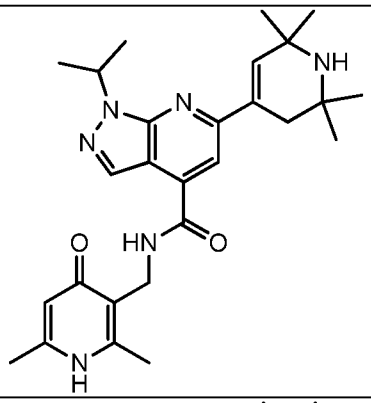
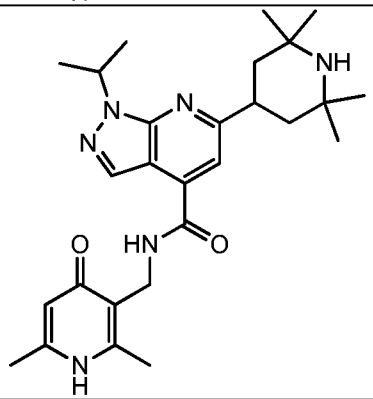
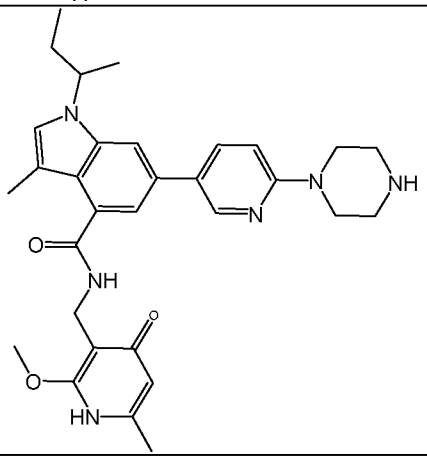
[0285] $R^{3'}$ is H, methyl, or Br; and

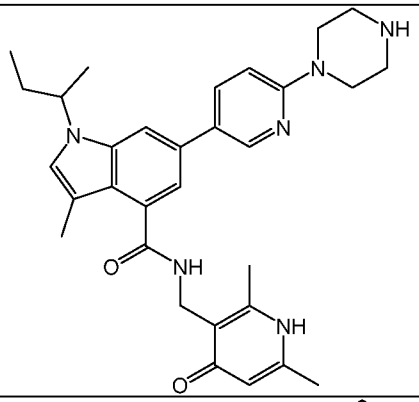
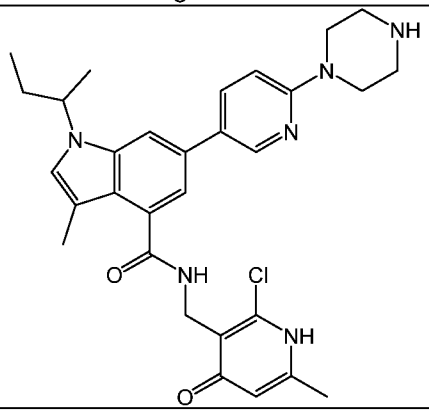
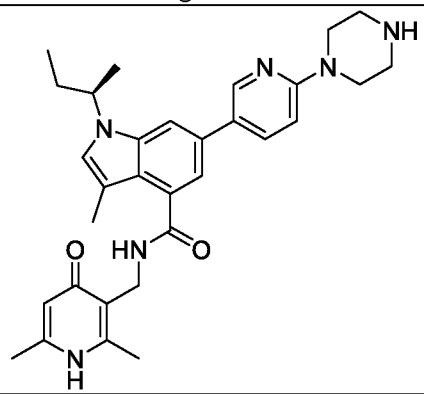
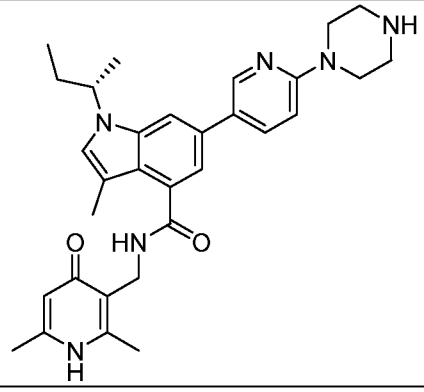
[0286] $R^{6'}$ is methyl, bis(1,1-dimethylethyl), bis(1-methylethyl), cyclopropyl, propyl, dimethylamino, ethylamino, (2-hydroxyethyl)amino, 2-propen-l-ylamino, 1-piperazinyl, 1-piperidinyl, 4-morpholinyl, 4-piperidinylamino, tetrahydro-2H-pyran-4-ylamino, phenylamino, (phenylmethyl)amino, (4-pyridinylmethyl)amino, [2-(2-pyridinylamino)ethyl]amino, 2-(dimethylamino)ethyl]amino, 4-pyridinylamino , 4-(aminocarbonyl)phenyl]amino, 3-hydroxy-3-methyl-l-butyn-l-yl, 4-pyridinylethynyl, phenylethynyl, 2-furanyl, 3-thienyl; 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-indazol-6-yl, 3-methyl-1H-indazol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2-oxo-2,3- dihydro-1H-benzimidazol-5-yl, 2-oxo-2,3-dihydro-1H-indo1-5-yl, 2-oxo-2,3-dihydro-1H-indo1-6-yl, 2,1,3-benzoxadiazol-5-yl, 2-amino-6-quinazolinyl, 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl, 2-amino-5-pyrimidinyl, 7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridin-3-yl, phenyl, 2-methylphenyl, 2-nitrophenyl, 2-phenylethyl, 3-aminophenyl, 4-aminophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-(methyloxy)phenyl, 3-(acetylamino)phenyl, 4-(acetylamino)phenyl, 4-(aminocarbonyl)phenyl, 4-(1H-pyrazol-4-yl)phenyl, 4-(aminosulfonyl)phenyl, 4-(methylsulfonyl)phenyl, 4-[(dimethylamino)sulfonyl]phenyl, 4-[(methylamino)carbonyl]phenyl, 4-[(methylamino)sulfonyl]phenyl, 4-[(methylsulfonyl)amino]phenyl, 3-pyridinyl, 4-pyridinyl, 2-(4-morpholinyl)-4-pyridinyl, 2-amino-4-pyridinyl, 5-(methyloxy)-3-pyridinyl, 5-(methylsulfony1)-3-pyridinyl, 5-[(cyclopropylsulfonyl)amino]-6-(methyloxy)-3-pyridinyl, 5-[(phenylsulfonyl)amino]-3-pyridinyl, 6-(4-methyl-l-piperaziny1)-3-pyridinyl, 6-(4-morpholinyl)-3-pyridinyl, 6-(acetylamino)-3-pyridinyl, 6-(dimethylamino)-3-pyridinyl, 6-(methyloxy)-3-pyridinyl, 6-[(methylamino)carbony1]-3-pyridinyl, 6-[(methylamino)sulfony1]-3-pyridinyl, 6-methyl-3-pyridinyl, or 4-pyridinyloxy.

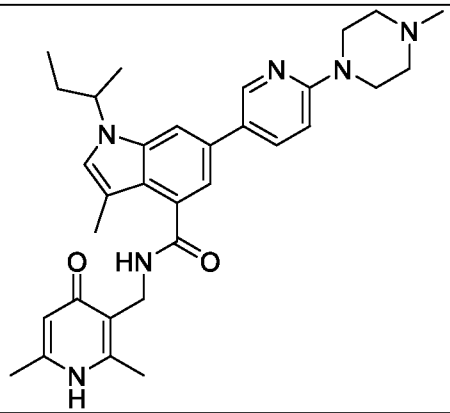
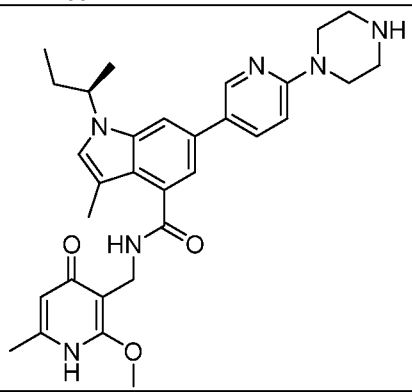
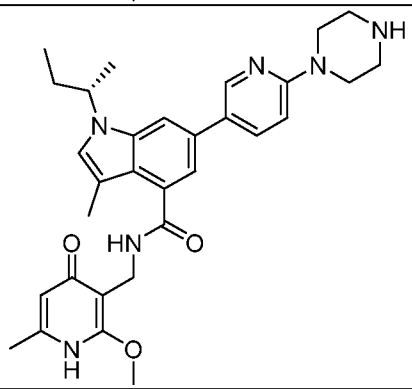
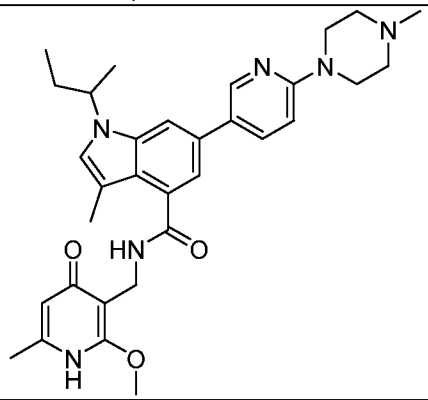
[0287] Representative compounds of the present invention include compounds listed in Tables 1-4. In Table 2, X_1 through X_4 and Y_1 through Y_3 are as defined herein for Formula

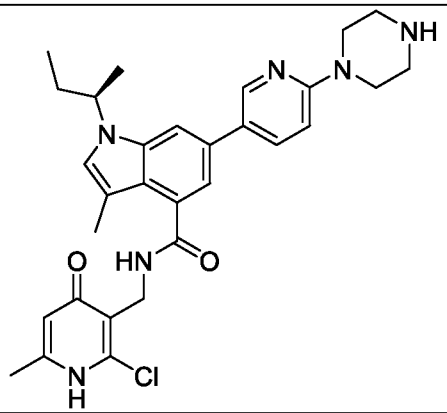
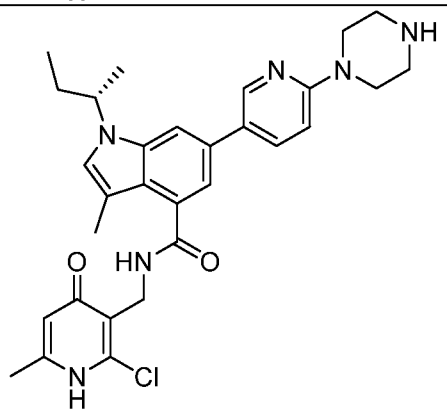
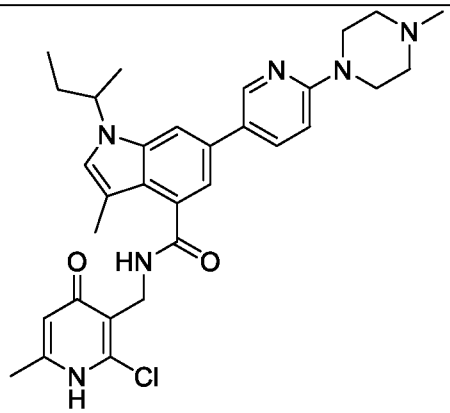
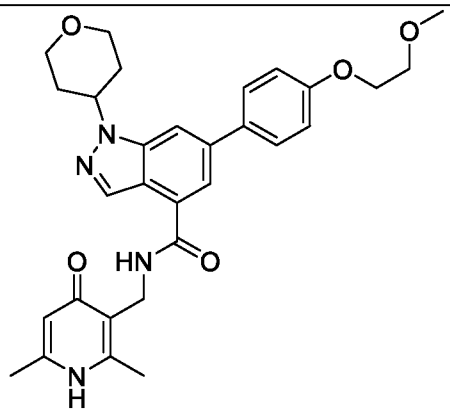
(IV). In Table 3, except for R_6 and R_7, variables such as X_2 through X_4, Y_1, Y_3 R_1, and R_2 are as defined herein for Formula (IV). In Table 3 or 4, R''' is T_5, $-C(O)T_5$, or $S(O)_2T_5$, and the other variables such as X_2 through X_4, Y_1, Y_3, R_1, R_2, R_6, T_5 and T_{5a} are as defined herein for Formula (IV).

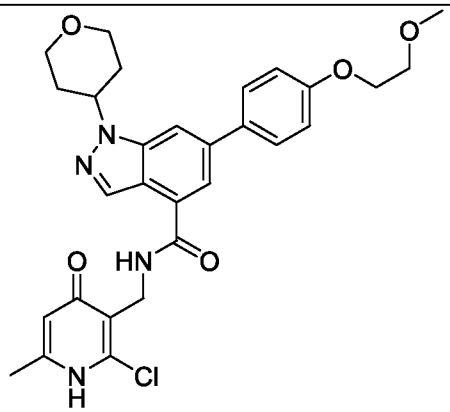
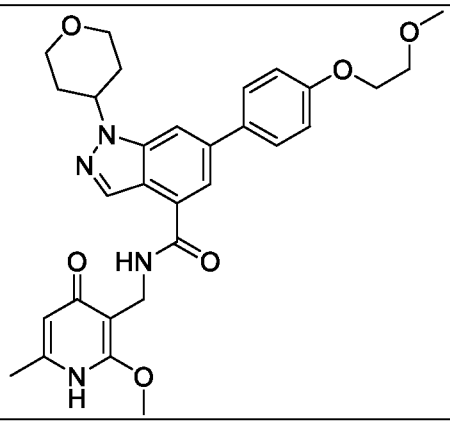
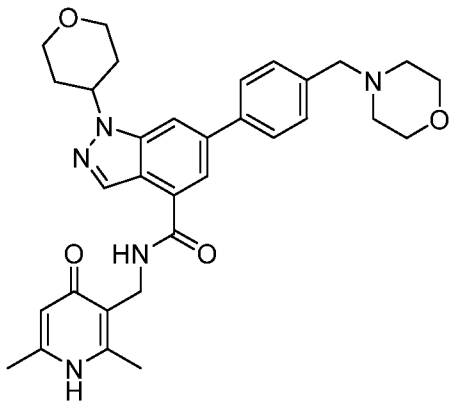
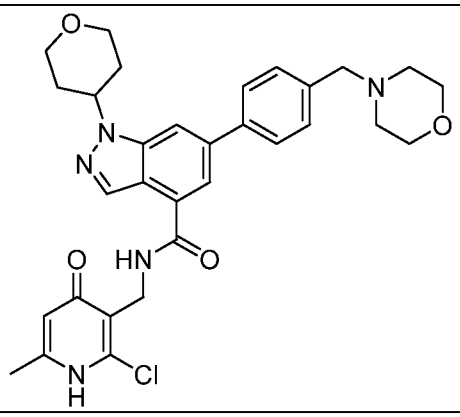
Table 1

Compound Number	Structure	MS $(M+1)^+$
1		477.30
2		479.4
3		

Compound Number	Structure	MS $(M+1)^+$
4		527.50
5		
6		
7		

Compound Number	Structure	MS $(M+1)^+$
8		
9		
10		
11		

Compound Number	Structure	MS (M+1)$^+$
12		
13		
14		
15		

Compound Number	Structure	MS $(M+1)^+$
16		
17		
18		
19		

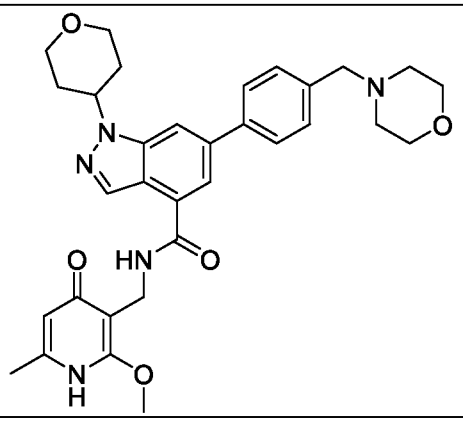
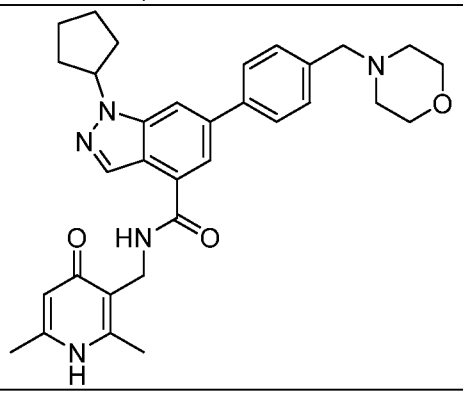
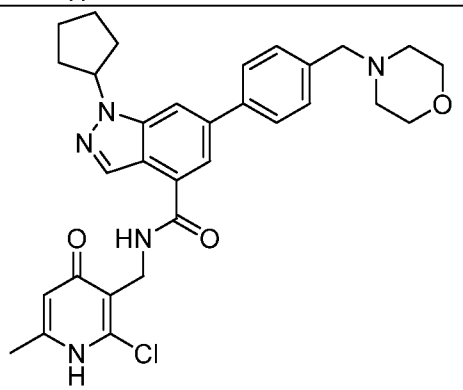
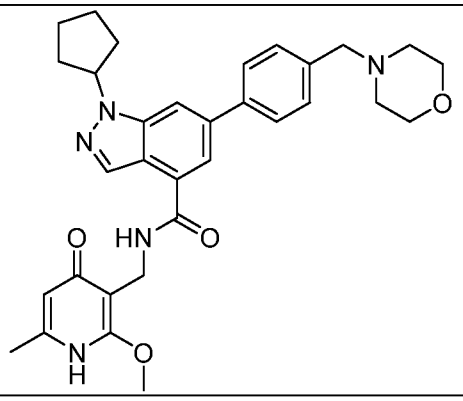
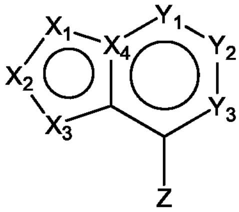
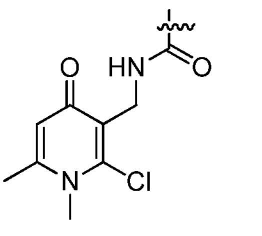
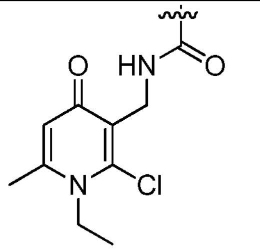
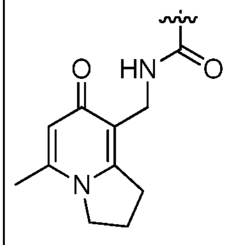
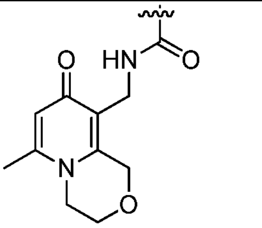
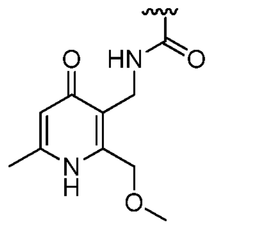
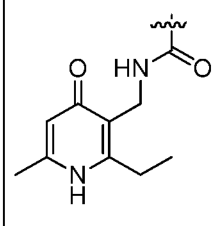
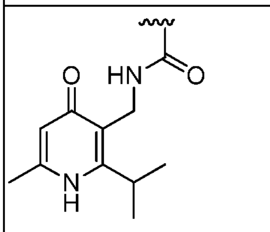
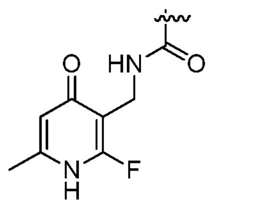
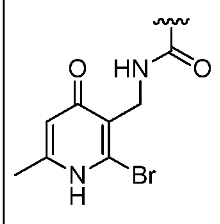
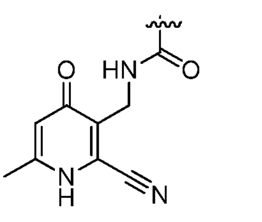
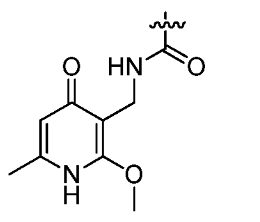
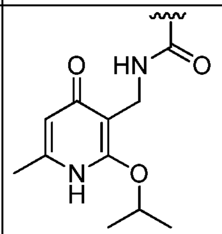
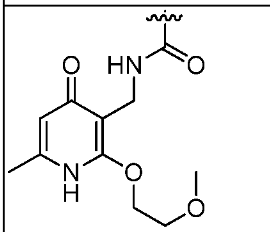
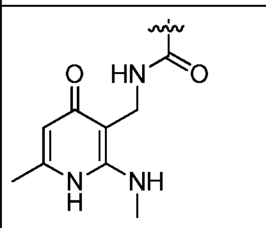
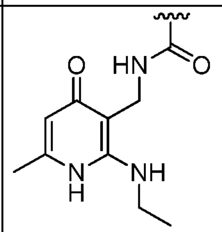
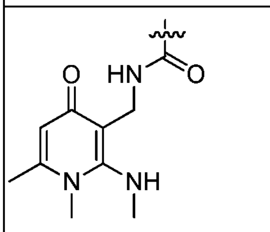
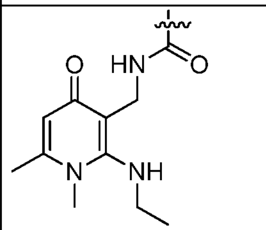
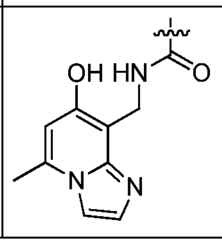
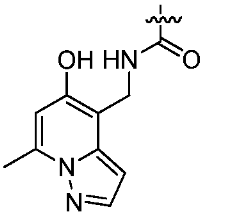
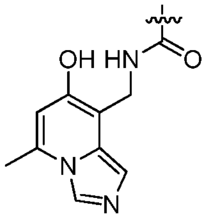
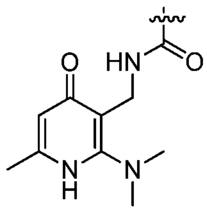
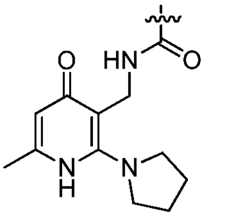
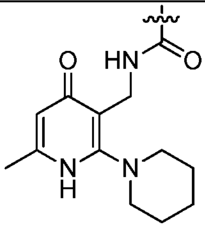
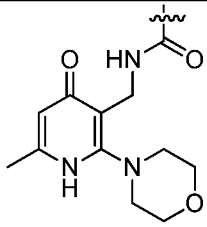
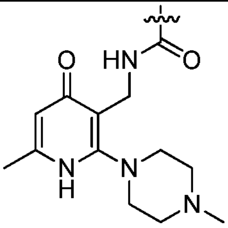
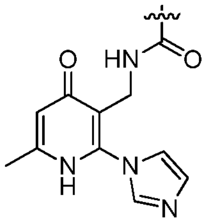
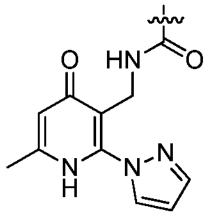
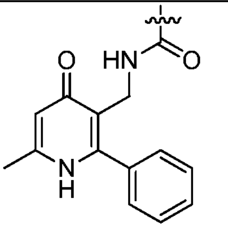
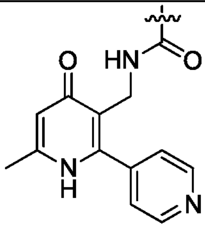
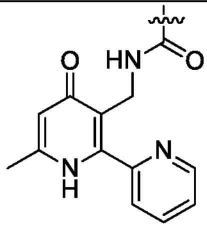
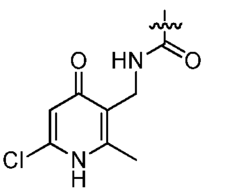
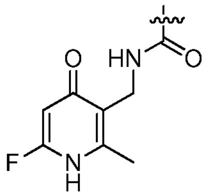
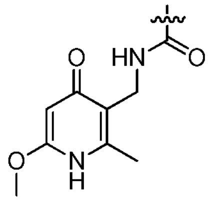
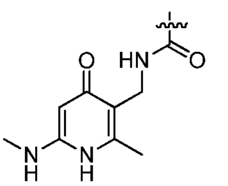
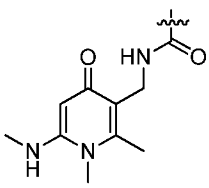
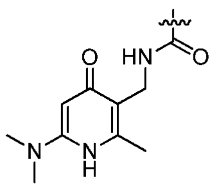
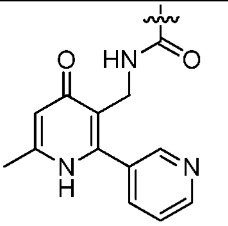
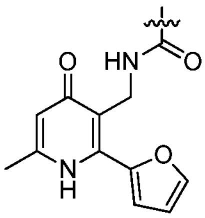
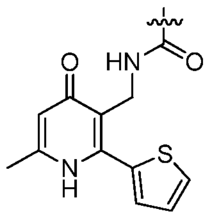
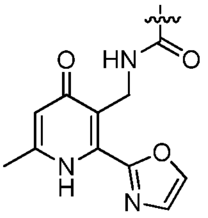
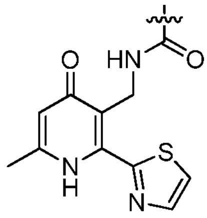
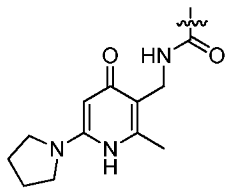
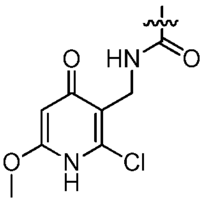
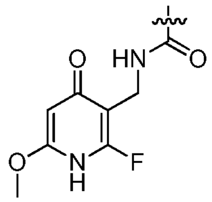
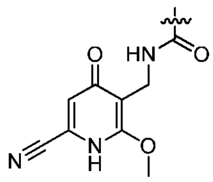
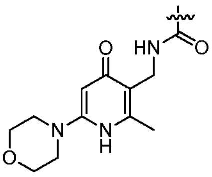
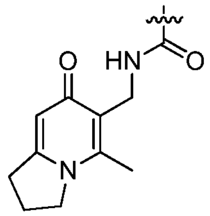
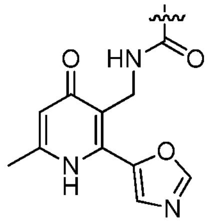
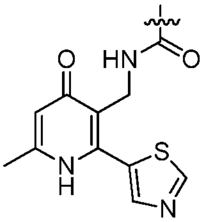
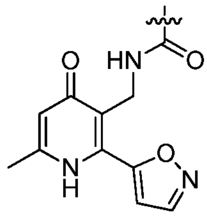
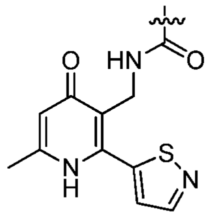
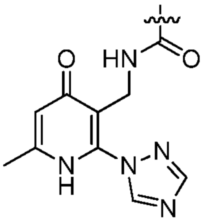
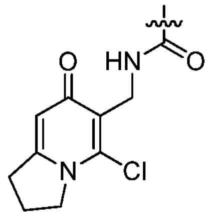
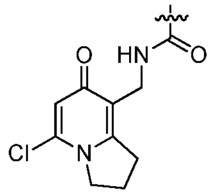
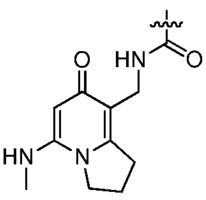
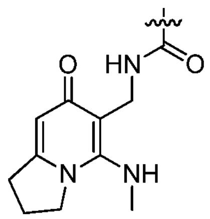
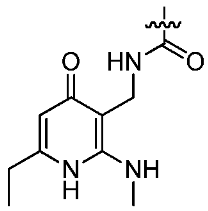
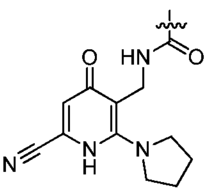
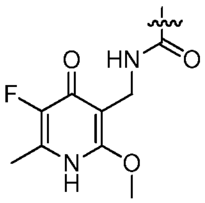
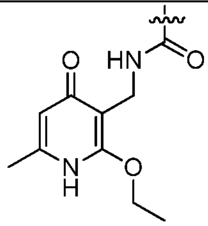
Compound Number	Structure	MS $(M+1)^+$
20		
21		
22		
23		

Table 2



Structure of Z	Structure of Z	Structure of Z
		
		
		
		
		
		

Structure of Z	**Structure of Z**	**Structure of Z**
		
		
		
		
		
		
		

Structure of Z	**Structure of Z**	**Structure of Z**
		
		
		
		
		
		
		

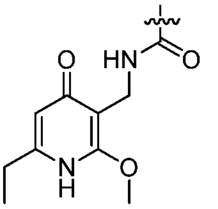
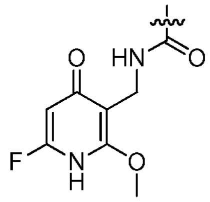
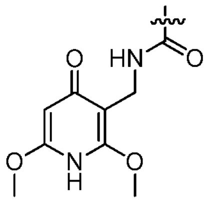
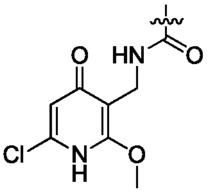
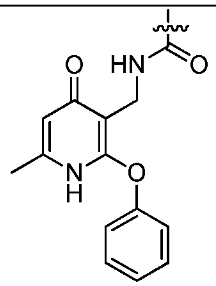
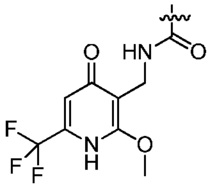
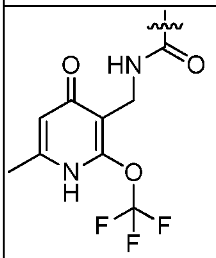
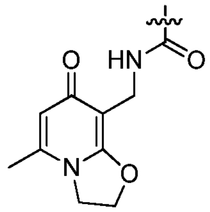
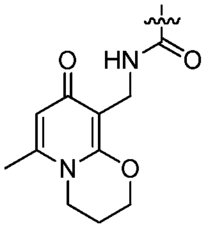
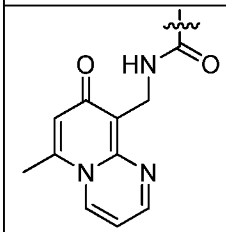
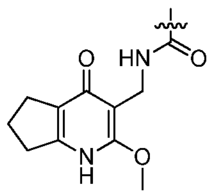
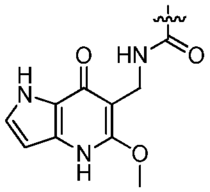
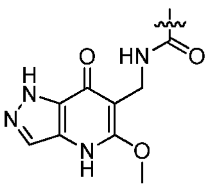
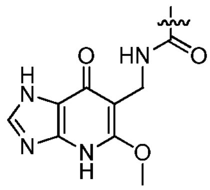
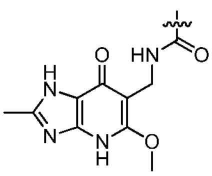
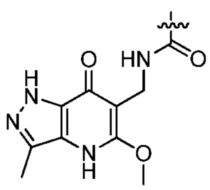
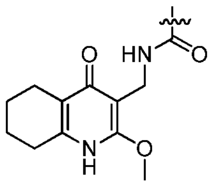
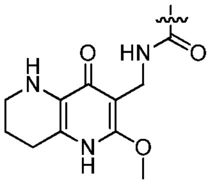
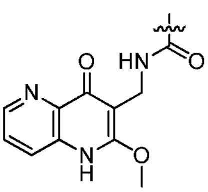
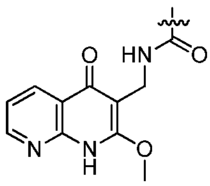
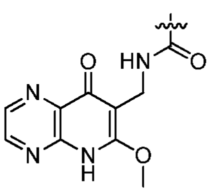
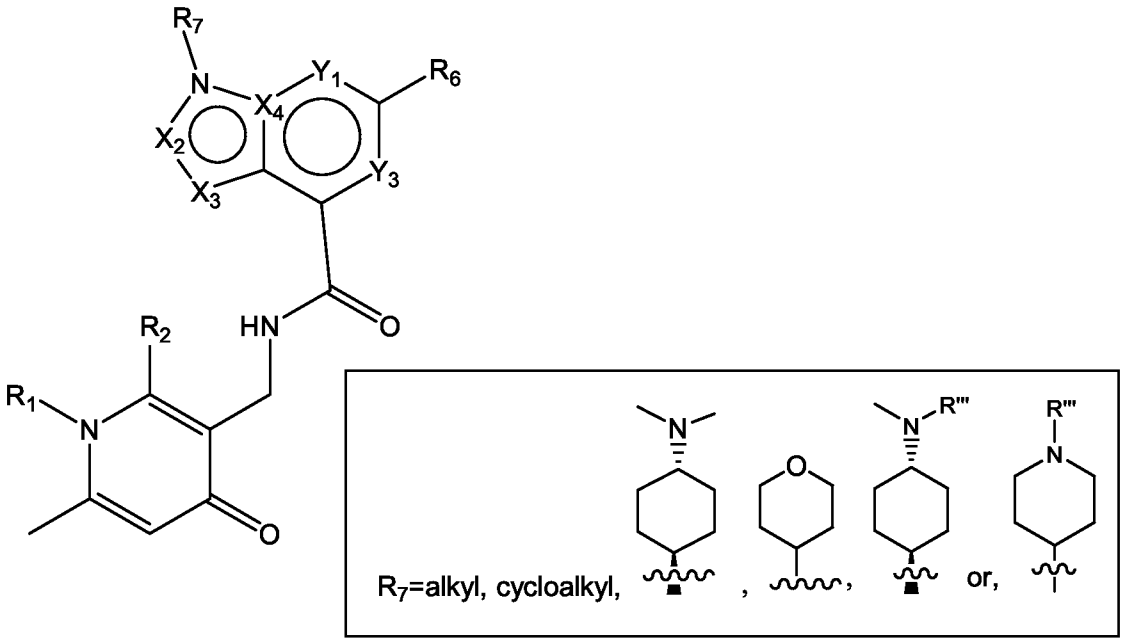
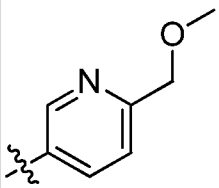
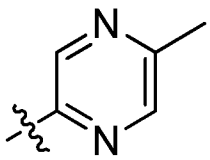
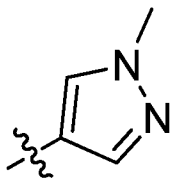
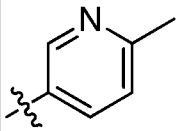
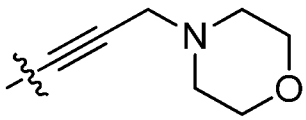
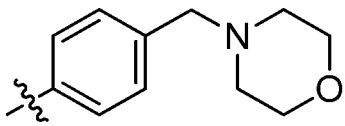
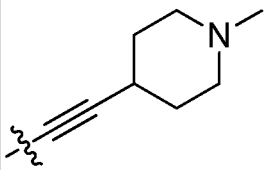
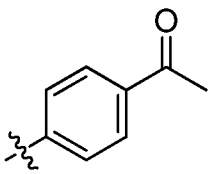
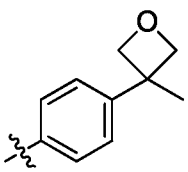
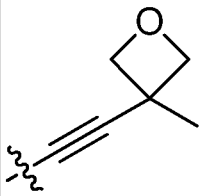
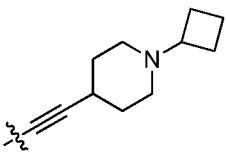
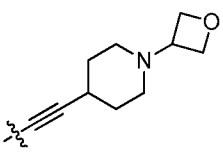
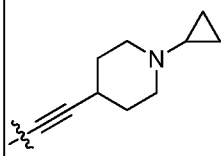
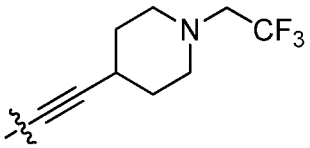
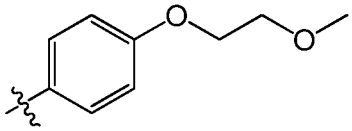
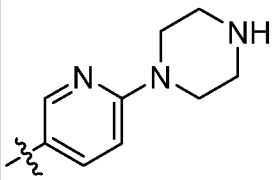
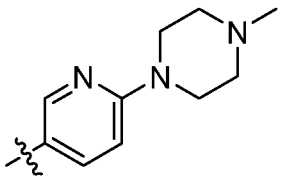
Structure of Z	**Structure of Z**	**Structure of Z**
		
		
		
		
		
		
		

Table 3



Structure of R_6	Structure of R_6	Structure of R_6
		
		
		
		

Structure of R_6	Structure of R_6	Structure of R_6
		
		

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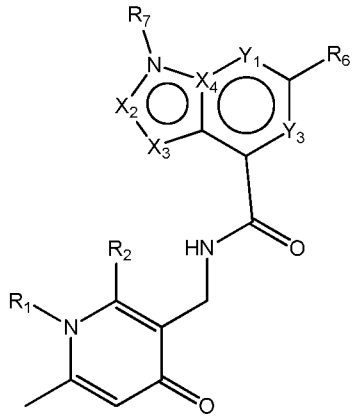
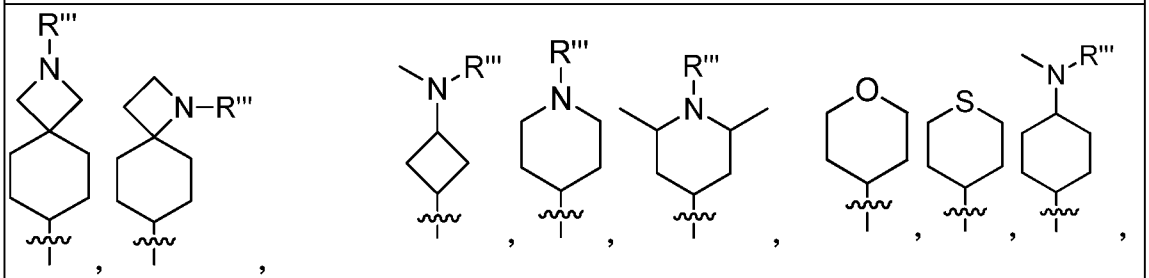
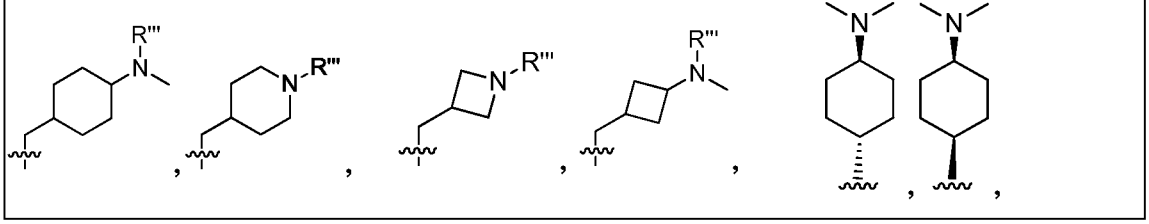
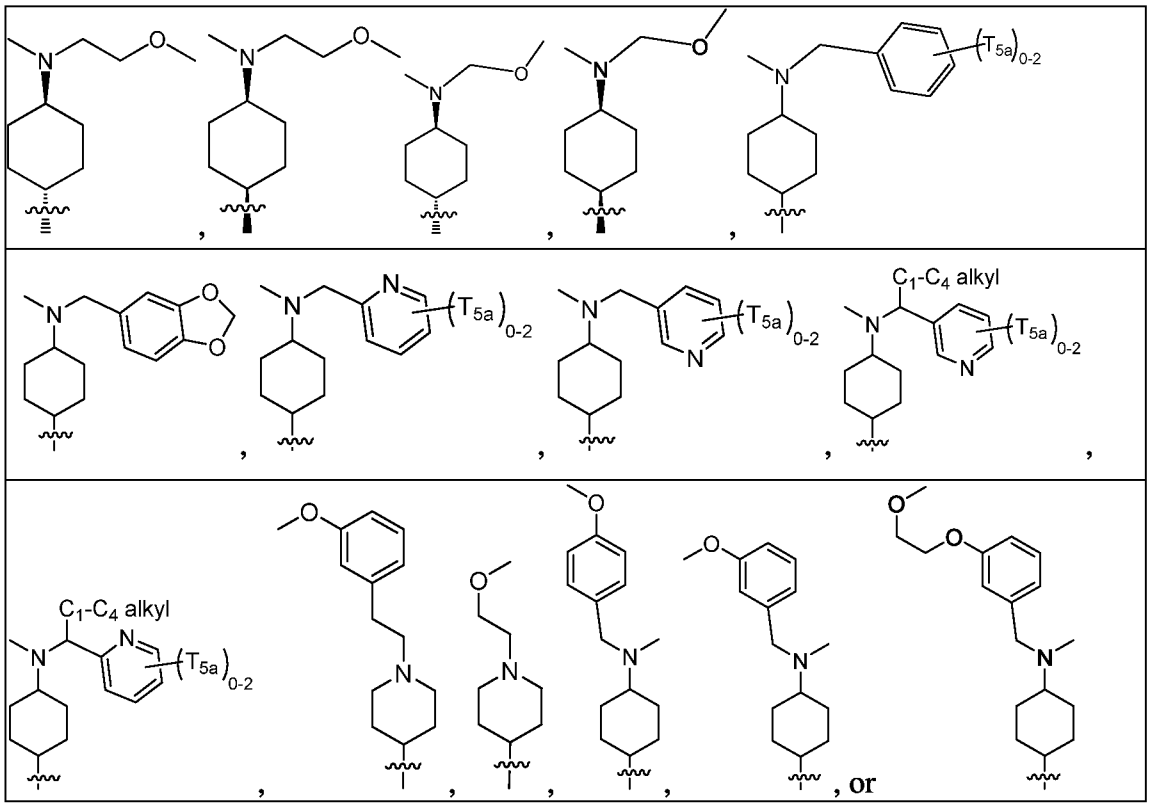


Structure of R_7





[0288] In certain embodiments, compounds listed in Table 2 have the R_6 and R_7 as listed in Table 3 and/or the R_7 as listed in Table 4 above.

[0289] As used herein, "alkyl", "C_1, C_2, C_3, C_4, C_5 or C_6 alkyl" or "C_1-C_6 alkyl" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl or n-hexyl.

[0290] In certain embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[0291] As used herein, the term "cycloalkyl" refers to a saturated or unsaturated nonaromatic hydrocarbon mono-or multi-ring (e.g., fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (e.g., C_3-C_{10}). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and adamantyl. The term "heterocycloalkyl" refers to a saturated or unsaturated nonaromatic 3-8 membered monocyclic, 7-12 membered

bicyclic (fused, bridged, or spiro rings), or 11-14 membered tricyclic ring system (fused, bridged, or spiro rings) having one or more heteroatoms (such as O, N, S, or Se), unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, tetrahydrofuranyl, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, oxiranyl, azetidinyl, oxetanyl, thietanyl, 1,2,3,6-tetrahydropyridinyl, tetrahydropyranyl, dihydropyranyl, pyranyl, morpholinyl, tetrahydrothiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,4-dioxaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like.

[0292] The term "optionally substituted alkyl" refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0293] An "arylalkyl" or an "aralkyl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (benzyl)). An "alkylaryl" moiety is an aryl substituted with an alkyl (*e.g.*, methylphenyl).

[0294] As used herein, "alkyl linker" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated divalent aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl linker is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl linker groups. Examples of alkyl linker include, moieties having from one to six carbon atoms, such as, but not limited to, methyl (-CH_2-), ethyl (-CH_2CH_2-), n-propyl (-$CH_2CH_2CH_2$-), i-propyl (-$CHCH_3CH_2$-), n-butyl (-

$CH_2CH_2CH_2CH_2$-), s-butyl (-$CHCH_3CH_2CH_2$-), i-butyl (-$C(CH_3)_2CH_2$-), n-pentyl (-$CH_2CH_2CH_2CH_2CH_2$-), s-pentyl (-$CHCH_3CH_2CH_2CH_2$-) or n-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_2$-).

[0295] "Alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkenyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkenyl groups containing three to six carbon atoms.

[0296] The term "optionally substituted alkenyl" refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0297] "Alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, "alkynyl" includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkynyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkynyl groups containing three to six carbon atoms.

[0298] The term "optionally substituted alkynyl" refers to unsubstituted alkynyl or alkynyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl,

alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0299] Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidinyl and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl.

[0300] "Aryl" includes groups with aromaticity, including "conjugated," or multicyclic systems with at least one aromatic ring and do not contain any heteroatom in the ring structure. Examples include phenyl, benzyl, 1,2,3,4-tetrahydronaphthalenyl, etc.

[0301] "Heteroaryl" groups are aryl groups, as defined above, except having from one to four heteroatoms in the ring structure, and may also be referred to as "aryl heterocycles" or "heteroaromatics." As used herein, the term "heteroaryl" is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*, 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or other substituents, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

[0302] Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

[0303] Furthermore, the terms "aryl" and "heteroaryl" include multicyclic aryl and heteroaryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole,

benzothiazole, benzoimidazole, benzothiophene, quinoline, isoquinoline, naphthrydine, indole, benzofuran, purine, benzofuran, deazapurine, indolizine.

[0304] In the case of multicyclic aromatic rings, only one of the rings needs to be aromatic (*e.g.*, 2,3-dihydroindole), although all of the rings may be aromatic (*e.g.*, quinoline). The second ring can also be fused or bridged.

[0305] The cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring can be substituted at one or more ring positions (e.g., the ring-forming carbon or heteroatom such as N) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl and heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, tetralin, methylenedioxyphenyl such as benzo[*d*][1,3]dioxole-5-yl).

[0306] As used herein, "carbocycle" or "carbocyclic ring" is intended to include any stable monocyclic, bicyclic or tricyclic ring having the specified number of carbons, any of which may be saturated, unsaturated, or aromatic. Carbocycle includes cycloalkyl and aryl. For example, a C_3-C_{14} carbocycle is intended to include a monocyclic, bicyclic or tricyclic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. Examples of carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, fluorenyl, phenyl, naphthyl, indanyl, adamantyl and tetrahydronaphthyl. Bridged rings are also included in the definition of carbocycle, including, for example, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, and [4.4.0] bicyclodecane and [2.2.2] bicyclooctane. A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. In one embodiment, bridge rings are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (*e.g.*, naphthyl, tetrahydronaphthyl) and spiro rings are also included.

[0307] As used herein, "heterocycle" or "heterocyclic group" includes any ring structure (saturated, unsaturated, or aromatic) which contains at least one ring heteroatom (*e.g.*, N, O or S). Heterocycle includes heterocycloalkyl and heteroaryl. Examples of heterocycles include, but are not limited to, morpholine, pyrrolidine, tetrahydrothiophene, piperidine, piperazine, oxetane, pyran, tetrahydropyran, azetidine, and tetrahydrofuran.

[0308] Examples of heterocyclic groups include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl (e.g., benzo[*d*][1,3]dioxole-5-yl), morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazol5(4H)-one, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

[0309] The term "substituted," as used herein, means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N). "Stable compound" and "stable structure" are meant to indicate

a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0310] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0311] When any variable (*e.g.*, R) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R moieties, then the group may optionally be substituted with up to two R moieties and R at each occurrence is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0312] The term "hydroxy" or "hydroxyl" includes groups with an -OH or $-O^-$.

[0313] As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo and iodo. The term "perhalogenated" generally refers to a moiety wherein all hydrogen atoms are replaced by halogen atoms. The term "haloalkyl" or "haloalkoxyl" refers to an alkyl or alkoxyl substituted with one or more halogen atoms.

[0314] The term "carbonyl" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. Examples of moieties containing a carbonyl include, but are not limited to, aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

[0315] The term "carboxyl" refers to –COOH or its C_1-C_6 alkyl ester.

[0316] "Acyl" includes moieties that contain the acyl radical (R-C(O)-) or a carbonyl group. "Substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by, for example, alkyl groups, alkynyl groups, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl,

sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0317] "Aroyl" includes moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

[0318] "Alkoxyalkyl," "alkylaminoalkyl," and "thioalkoxyalkyl" include alkyl groups, as described above, wherein oxygen, nitrogen, or sulfur atoms replace one or more hydrocarbon backbone carbon atoms.

[0319] The term "alkoxy" or "alkoxyl" includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropyloxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[0320] The term "ether" or "alkoxy" includes compounds or moieties which contain an oxygen bonded to two carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl," which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to an alkyl group.

[0321] The term "ester" includes compounds or moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, etc.

[0322] The term "thioalkyl" includes compounds or moieties which contain an alkyl group connected with a sulfur atom. The thioalkyl groups can be substituted with groups such as alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy,

alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, carboxyacid, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties.

[0323] The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom.

[0324] The term "thioether" includes moieties which contain a sulfur atom bonded to two carbon atoms or heteroatoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include moieties with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" refers to moieties wherein an alkyl, alkenyl or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkenyl group; and alkthioalkynyls" refers to moieties wherein an alkyl, alkenyl or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

[0325] As used herein, "amine" or "amino" refers to unsubstituted or substituted -NH_2. "Alkylamino" includes groups of compounds wherein nitrogen of -NH_2 is bound to at least one alkyl group. Examples of alkylamino groups include benzylamino, methylamino, ethylamino, phenethylamino, etc. "Dialkylamino" includes groups wherein the nitrogen of -NH_2 is bound to at least two additional alkyl groups. Examples of dialkylamino groups include, but are not limited to, dimethylamino and diethylamino. "Arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. "Aminoaryl" and "aminoaryloxy" refer to aryl and aryloxy substituted with amino. "Alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. "Alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group. "Acylamino" includes groups wherein nitrogen is bound to an acyl group. Examples of acylamino include, but are not limited to, alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

[0326] The term "amide" or "aminocarboxy" includes compounds or moieties that contain a nitrogen atom that is bound to the carbon of a carbonyl or a thiocarbonyl group. The term

includes "alkaminocarboxy" groups that include alkyl, alkenyl or alkynyl groups bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. It also includes "arylaminocarboxy" groups that include aryl or heteroaryl moieties bound to an amino group that is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarboxy", "alkenylaminocarboxy", "alkynylaminocarboxy" and "arylaminocarboxy" include moieties wherein alkyl, alkenyl, alkynyl and aryl moieties, respectively, are bound to a nitrogen atom which is in turn bound to the carbon of a carbonyl group. Amides can be substituted with substituents such as straight chain alkyl, branched alkyl, cycloalkyl, aryl, heteroaryl or heterocycle. Substituents on amide groups may be further substituted.

[0327] Compounds of the present invention that contain nitrogens can be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, 3-chloroperoxybenzoic acid (*m*CPBA) and/or hydrogen peroxides) to afford other compounds of the present invention. Thus, all shown and claimed nitrogen-containing compounds are considered, when allowed by valency and structure, to include both the compound as shown and its N-oxide derivative (which can be designated as $N \rightarrow O$ or $N^{+}\text{-}O^{-}$). Furthermore, in other instances, the nitrogens in the compounds of the present invention can be converted to N-hydroxy or N-alkoxy compounds. For example, N-hydroxy compounds can be prepared by oxidation of the parent amine by an oxidizing agent such as *m*-CPBA. All shown and claimed nitrogen-containing compounds are also considered, when allowed by valency and structure, to cover both the compound as shown and its N-hydroxy (*i.e.*, N-OH) and N-alkoxy (*i.e.*, N-OR, wherein R is substituted or unsubstituted C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, 3-14-membered carbocycle or 3-14-membered heterocycle) derivatives.

[0328] In the present specification, the structural formula of the compound represents a certain isomer for convenience in some cases, but the present invention includes all isomers, such as geometrical isomers, optical isomers based on an asymmetrical carbon, stereoisomers, tautomers, and the like, it being understood that not all isomers may have the same level of activity. In addition, a crystal polymorphism may be present for the compounds represented by the formula. It is noted that any crystal form, crystal form mixture, or anhydride or hydrate thereof is included in the scope of the present invention.

[0329] "Isomerism" means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers."

Stereoisomers that are not mirror images of one another are termed "diastereoisomers," and stereoisomers that are non-superimposable mirror images of each other are termed "enantiomers" or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture."

[0330] A carbon atom bonded to four nonidentical substituents is termed a "chiral center."

[0331] "Chiral isomer" means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed "diastereomeric mixture." When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0332] "Geometric isomer" means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cylcobutyl). These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

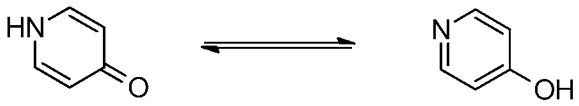
[0333] It is to be understood that the compounds of the present invention may be depicted as different chiral isomers or geometric isomers. It should also be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present invention, and the naming of the compounds does not exclude any isomeric forms, it being understood that not all isomers may have the same level of activity.

[0334] Furthermore, the structures and other compounds discussed in this invention include all atropic isomers thereof, it being understood that not all atropic isomers may have the same level of activity. "Atropic isomers" are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[0335] "Tautomer" is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertable by tautomerizations is called tautomerism.

[0336] Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0337] Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (*e.g.*, in nucleobases such as guanine, thymine and cytosine), imine-enamine and enamine-enamine. An example of keto-enol equilibria is between pyridin-4(1H)-ones and the corresponding pyridin-4-ols, as shown below.



pyridin-4(1*H*)-one pyridin-4-ol

[0338] It is to be understood that the compounds of the present invention may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present invention, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[0339] The term "crystal polymorphs", "polymorphs" or "crystal forms" means crystal structures in which a compound (or a salt or solvate thereof) can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectral, melting points, density hardness, crystal shape, optical and electrical properties, stability and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other

factors may cause one crystal form to dominate. Crystal polymorphs of the compounds can be prepared by crystallization under different conditions.

[0340] The compounds of any Formula described herein include the compounds themselves, as well as their salts, and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a 1,4-pyridone bicyclic heteroaryl compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (e.g., trifluoroacetate). The term "pharmaceutically acceptable anion" refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a 1,4-pyridone bicyclic heteroaryl compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The 1,4-pyridone bicyclic heteroaryl compounds also include those salts containing quaternary nitrogen atoms.

[0341] Additionally, the compounds of the present invention, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0342] "Solvate" means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H_2O.

[0343] As used herein, the term "analog" refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0344] As defined herein, the term "derivative" refers to compounds that have a common core structure, and are substituted with various groups as described herein. For example, all of the compounds represented by Formula (IV) or (V) are 1,4-pyridone bicyclic heteroaryl compounds, and have Formula (IV) or (V) as a common core.

[0345] The term "bioisostere" refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulfonimides, tetrazoles, sulfonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0346] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include C-13 and C-14.

[0347] The present invention provides methods for the synthesis of the compounds of any of the Formulae described herein. The present invention also provides detailed methods for the synthesis of various disclosed compounds of the present invention according to the following schemes as shown in the Examples.

[0348] Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0349] The synthetic processes of the invention can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt thereof.

[0350] Compounds of the present invention can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from

readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present invention.

[0351] Compounds of the present invention can be conveniently prepared by a variety of methods familiar to those skilled in the art or those described in WO 2012/142504, WO 2012/142513 and WO 2012/118812, which are incorporated herein by reference. The compounds of this invention with any of the Formulae described herein may be prepared according to the procedures illustrated in Schemes 1-6 below, from commercially available starting materials or starting materials which can be prepared using literature procedures. The Y and R groups (such as R_1, R_2, R_3, R_4, R_6, R_7, R_{11}, and Y_1) in Schemes 1-6 are as defined in any Formula described herein, unless otherwise specified.

[0352] One of ordinary skill in the art will note that, during the reaction sequences and synthetic schemes described herein, the order of certain steps may be changed, such as the introduction and removal of protecting groups.

[0353] One of ordinary skill in the art will recognize that certain groups may require protection from the reaction conditions via the use of protecting groups. Protecting groups may also be used to differentiate similar functional groups in molecules. A list of protecting groups and how to introduce and remove these groups can be found in Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999.

[0354] Preferred protecting groups include, but are not limited to:

[0355] For a hydroxyl moiety: TBS, benzyl, THP, Ac

[0356] For carboxylic acids: benzyl ester, methyl ester, ethyl ester, allyl ester

[0357] For amines: Cbz, BOC, DMB

[0358] For diols: Ac (x2) TBS (x2), or when taken together acetonides

[0359] For thiols: Ac

[0360] For benzimidazoles: SEM, benzyl, PMB, DMB

[0361] For aldehydes: di-alkyl acetals such as dimethoxy acetal or diethyl acetyl.

[0362] In the reaction schemes described herein, multiple stereoisomers may be produced. When no particular stereoisomer is indicated, it is understood to mean all possible stereoisomers that could be produced from the reaction. A person of ordinary skill in the art will recognize that the reactions can be optimized to give one isomer preferentially, or new schemes may be devised to produce a single isomer. If mixtures are produced, techniques such as preparative thin layer chromatography, preparative HPLC, preparative chiral HPLC, or preparative SFC may be used to separate the isomers.

[0363] The following abbreviations are used throughout the specification and are defined below:

[0364] AA ammonium acetate

[0365] ACN acetonitrile

[0366] Ac acetyl

[0367] AcOH acetic acid

[0368] atm atmosphere

[0369] aq. Aqueous

[0370] BID or b.i.d. bis in die (twice a day)

[0371] tBuOK potassium t-butoxide

[0372] Bn benzyl

[0373] BOC tert-butoxy carbonyl

[0374] BOP (benzotriazol-1-yloxy)tris(dimethylamino)-phosphoniumhexafluorophosphate

[0375] Cbz benzyloxy carbonyl

[0376] $CDCl_3$ deuterated chloroform

[0377] CH_2Cl_2 dichloromethane

[0378] COMU (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethyl-amino-morpholino-carbenium hexafluorophosphate

[0379] d days

[0380] DBU 1,8-diazabicyclo[5.4.0]undec-7-ene

[0381] DCE 1,2 dichloroethane

[0382] DCM dichloromethane

[0383] DEAD Diethyl azodicarboxylate

[0384] DIAD Diisopropyl azodicarboxylate

[0385] DiBAL-H diisobutyl aluminium hydride

[0386] DIPEA N,N-diisopropylethylamine (Hunig's base)

[0387] DMA Dimethylacetamide

[0388] DMAP N, N dimethyl-4-aminopyridine

[0389] DMB 2,4 dimethoxy benzyl

[0390] DMF N,N-Dimethylformamide

[0391] DMSO Dimethyl sulfoxide

[0392] DPPA Diphenylphosphonic azide

[0393] EA or EtOAc Ethyl acetate

[0394] EDC or EDCI N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide

[0395] Et_2O diethyl ether

[0396] ELS Evaporative Light Scattering

[0397] ESI- Electrospray negative mode

[0398] ESI+ Electrospray positive mode

[0399] Et_3N or TEA triethylamine

[0400] EtOH ethanol

[0401] FA formic acid

[0402] FC or FCC Flash chromatogrpahy

[0403] h hours

[0404] H_2O water

[0405] HATU O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate

[0406] HOAT 1-Hydroxy-7-azabenzotriazole

[0407] HOBt 1-Hydroxybenzotriazole

[0408] HO-Su N-Hydroxysuccinimide

[0409] HCl hydrogen chloride or hydrochloric acid

[0410] HPLC High performance liquid chromatography

[0411] K_2CO_3 potassium carbonate

[0412] KHMDs Potassium hexamethyldisilazide

[0413] LC/MS or LC-MS Liquid chromatography mass spectrum

[0414] LDA Lithium diisopropylamide

[0415] LiHMDs Lithium hexamethyldisilazide

[0416] LG leaving group

[0417] M Molar

[0418] m/z mass/charge ratio

[0419] m-CPBA meta-chloroperbenzoic acid

[0420] MeCN Acetonitrile

[0421] MeOD d4-methanol

[0422] MeI Methyl iodide

[0423] MS3Å3Å molecular sieves

[0424] $MgSO_4$ Magnesium Sulfate

[0425] min minutes

[0426] Ms Mesyl

[0427] MsCl Mesyl chloride

[0428] MsO Mesylate

[0429] MS Mass Spectrum

[0430] MWI microwave irradiation

[0431] Na_2CO_3 sodium carbonate

[0432] Na_2SO_4 sodium sulfate

[0433] $NaHCO_3$ sodium bicarbonate

[0434] NaHMDs Sodium hexamethyldisilazide

[0435] NaOH sodium hydroxide

[0436] $NaHCO_3$ sodium bicarbonate

[0437] Na_2SO_4 sodium sulfate

[0438] NIS N-iodosuccinimide

[0439] NMR Nuclear Magnetic Resonance

[0440] o/n or O/N overnight

[0441] Pd/C Palladium on carbon

[0442] $Pd(dppf)Cl_2.DCM$ [1,1′-Bis(diphenylphosphino)ferrocene] dichloropalladium(II),complex with dichloromethane

[0443] PPAA 1-Propanephosphonic acid cyclic anhydride

[0444] $Pd(OH)_2$ Palladium dihydroxide

[0445] PE Petroleum Ether

[0446] PG protecting group

[0447] PMB para methoxybenzyl

[0448] ppm parts per million

[0449] p.o. per os (oral adinsitration)

[0450] prep HPLC preparative High Performance Liquid Chromatography

[0451] prep TLC preparative thin layer chromatography

[0452] p-TsOH para-toluenesulfonic acid

[0453] PYBOP (Benzotriazol-1-yloxy)tripyrrolidinophosphonium Hexafluorophosphate

[0454] QD or q.d. quaque die (once a day)

[0455] RBF round bottom flask

[0456] RP-HPLC Reverse phase High Perfomance liquid chromatography

[0457] Rt or RT Room temperature

[0458] SEM (Trimethylsilyl)ethoxymethyl

[0459] SEMCl (Trimethylsilyl)ethoxymethyl chloride

[0460] SFC Super critical chromatography

[0461] SGC silica gel chromatography

[0462] STAB Sodium triacetoxy borohydride

[0463] TBAF tetra-n-butylammonium fluoride

[0464] TBME *tert*-Butyl methyl ether

[0465] TEA Triethylamine

[0466] TFA trifluoroacetic acid

[0467] TfO triflate

[0468] THF tetrahydrofuran

[0469] THP tetrahydropyran

[0470] TID or t.i.d ter in die (three times a day)

[0471] TLC thin layer chromatography

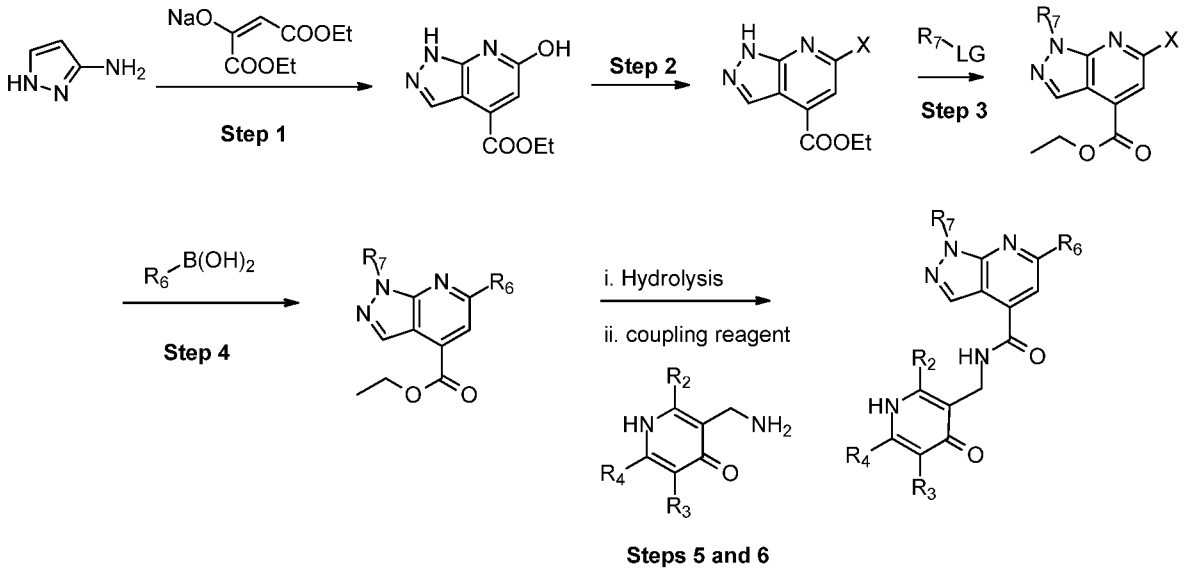
[0472] TMSCl Trimethylsilyl chloride

[0473] Ts tosyl

[0474] TsOH tosic acid

[0475] UV ultraviolet

Scheme 1

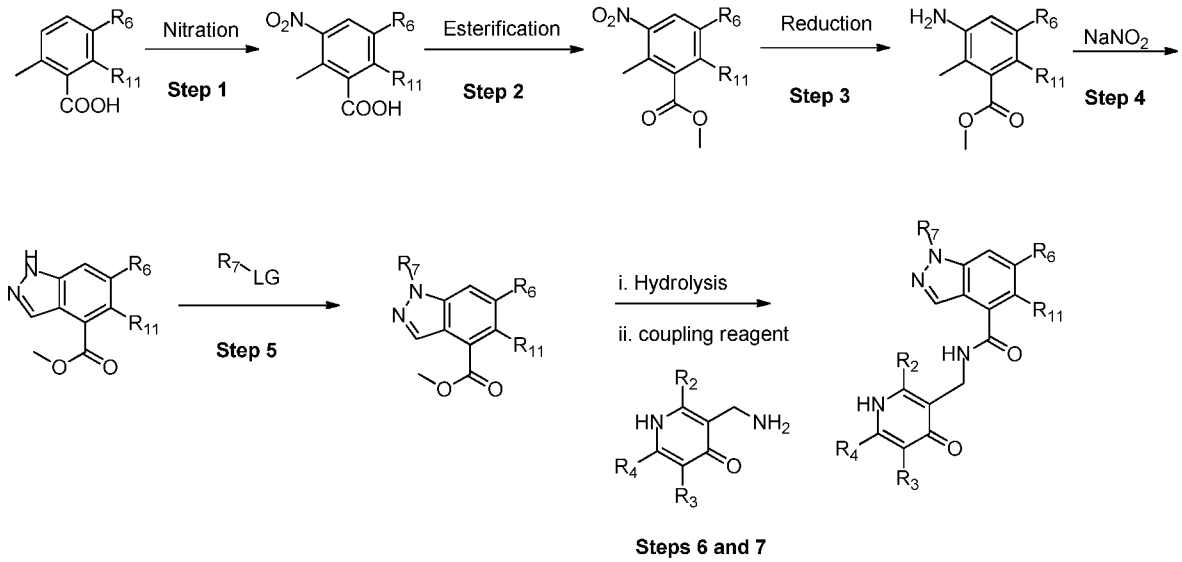


Steps 5 and 6

[0476] Scheme 1 shows the synthesis of modified pyrazolopyridine analogs following a general route that utilizes well-established chemistry. Condensation of 1H-pyrazol-3-amine with sodium (E)-1,4-diethoxy-1,4-dioxobut-2-en-2-olate in a polar solvent such as water using a mild acid catalyst such as acetic acid can provide the hydroxyl-pyrazolopyridine (Step 1). The hydroxyl group can then be converted to a leaving group "X" such as bromide using phosphoryl tribromide at elevated temperatures in an appropriate polar solvent such as acetonitrile to give the bromide (Step 2). Introduction of the R_7 can be done using an appropriate R_7-LG where LG is a leaving group such as OTs or Br. Subjecting the intermediate to R_7-LG in the presence of a mild base such as potassium carbonate in an appropriate polar solvent such as acetonitrile gives the desired substituted pyrazolopyridine (Step 3). A variety of R_6 substituents can then be introduced using standard transition metal-based protocols that rely upon a leaving group such as a bromide as a connection point or through direct SN_{Ar} displacement of the bromide with a nucleophile. The bromide can be combined with an appropriate boronic ester derivative, in the presence of a mild base and a palladium catalyst in a polar solvent such as dioxane/water, at elevated temperature to give the desired pyrazolopyridine ester (Step 4). Alternatively, the bromide can be combined with a nucleophile such as an amine in the presence of a mild base such as potassium carbonate in a polar solvent such as acetone to give the desired pyrazolopyridine ester. The ester moiety can be converted to an amide using a standard two step protocol. The ester can be hydrolyzed to the corresponding acid using a suitable base such as sodium hydroxide in a polar solvent such as ethanol (Step 5). The acid is then subjected to a standard amide coupling reaction whereupon the appropriate amine is added along with a

suitable amide coupling reagent such as PYBOP in a suitable solvent such as DMSO to give the desired amide (Step 6).

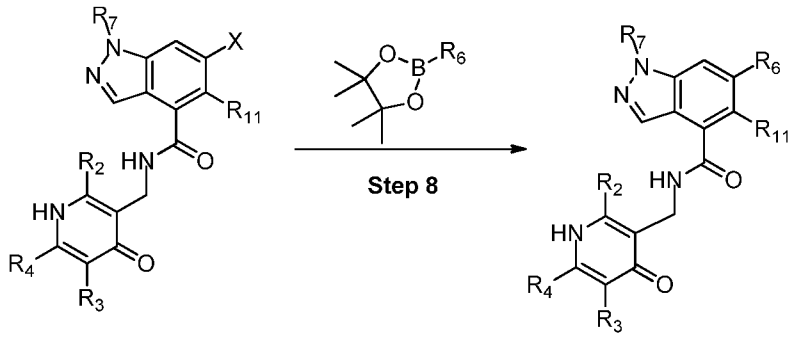
Scheme 2



[0477] Scheme 2 shows the synthesis of modified indazole analogs following a general route that utilizes well-established chemistry. Introduction of a nitro group to a tolyl compound can be achieved using standard nitration conditions such as nitric acid in sulfuric acid (Step 1). The acid can be esterified by treatment with an alkylating agent such as methyliodide in the presence of a base such as sodium carbonate in an appropriate polar solvent such as DMF (Step 2). Reduction of the nitro group using an appropriate reducing agent such as iron with an acid such as ammonium chloride in a protic solvent such as ethanol can provide an aniline (Step 3). Diazotization with an appropriate reagent such as sodium nitrite in a polar solvent such as acetic acid can lead to cyclization to provide an indazole (Step 4). It will be apparent to one skilled in the art that there are multiple ways to synthesize indazoles (*J. Org. Chem.* **2006**, *71*, 8166-8172). Introduction of the R_7 to the indazole can be done using an appropriate R_7-LG where LG is a leaving group such as OTs or Br. Subjecting the intermediate to R_7-LG in the presence of a mild base such as cesium carbonate in an appropriate polar solvent such as DMF can give the desired R_7-substituted indazole ester (Step 5). The ester moiety can be converted to an amide using a standard two step protocol. The ester can be hydrolyzed to the corresponding acid using a suitable base such as sodium hydroxide in a polar solvent such as ethanol (Step 6). The acid can then be subjecting to a standard amide coupling reaction whereupon the appropriate amine can be

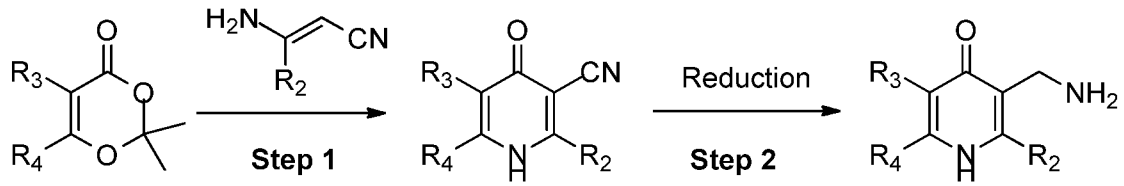
added along with a suitable amide coupling reagent such as PYBOP in a suitable solvent such as DMSO to give the desired amide (Step 7).

Scheme 3



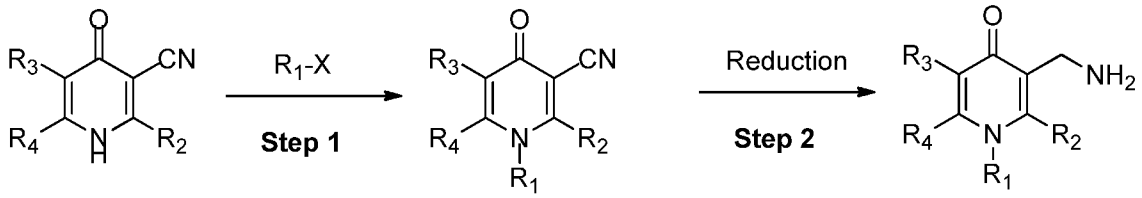
[0478] When R_6 is an appropriate group such as bromide or triflate, a variety of substituents could then be introduced using standard transition metal-based protocols. For example, the bromide can be combined with an appropriate boronic ester derivative, in the presence of a mild base and a palladium catalyst in a polar solvent such as dioxane/ water, at elevated temperature to give the desired indazole (Step 8).

Scheme 4



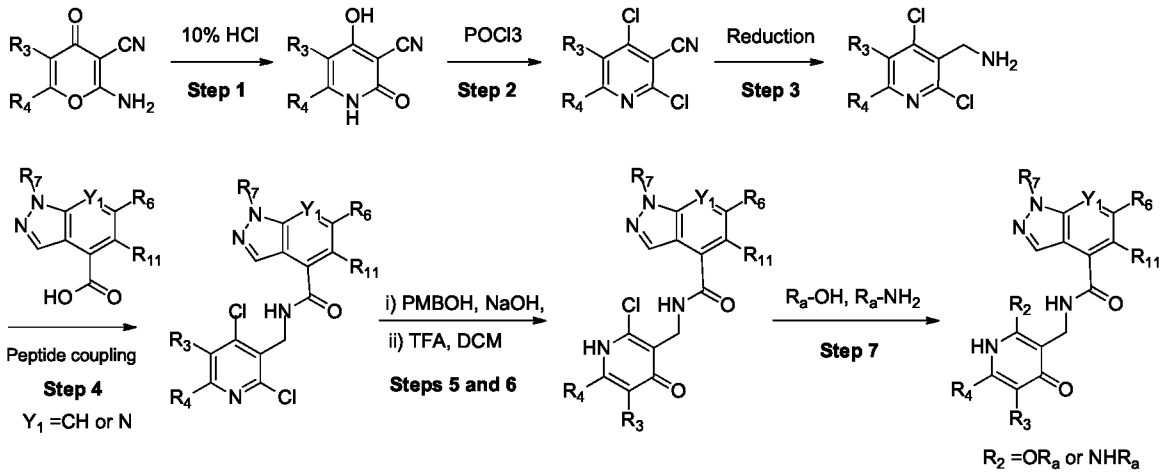
[0479] Scheme 4 shows the synthesis of modified pyridone analogs following a general route that utilizes well-established chemistry. Substituted 1,3-dioxin-4-ones, many of which are commercially available or can be made via rearrangement of acylated Meldrum's acid or via halogenation of 1,3-dioxin-4-one followed by aliphatic, aromatic or heteroaromatic coupling reactions, or other chemistry known to ones skilled in the art, can be converted to the substituted 1,4-pyridones by reaction under heating with appropriately substituted (E)-3-aminoacrylonitriles (Step 1). The resulting nitrile group can be reduced to an amine using an appropriate reducing agent such as Raney-Nickel in the presence of hydrogen in a protic solvent such as methanol containing ammonia at an appropriate temperature such as 22 °C (Step 2).

Scheme 5



[0480] In certain embodiments the 1,4-pyridone can be modified via alkylation or acylation protocols known to ones skilled in the art, prior to condensation with the elaborated acid coupling partner. A variety of R_1 groups can be introduced by alkylation using R_1-LG, where LG is a leaving group such as iodine, in the presence of a strong base such as NaH in an appropriate polar aprotic solvent such as DMF at an appropriate temperature such as 80 °C (Step 2).

Scheme 6



[0481] In another protocol as depicted in Scheme 4, substituted 2,4-dichloronicotinonitriles can be synthesized in two steps from substituted 2-amino-4H-pyran-4-ones. Rearrangement to the 4-hydroxypyridin-2(1H)-one is affected by the addition of aqueous inorganic acid and the resulting pyridone is converted into the 2,4-dichloronicotinonitrile by dehydrative chlorination using an appropriate reagent such as $POCl_3$ in an aprotic solvent such as DMF (Steps 1-2). The nitrile group can then be reduced to an amine using an appropriate reducing agent such as Raney-Nickel in the presence of hydrogen in a protic solvent such as methanol containing ammonia at an appropriate temperature such as 22 °C (Step 3). The resulting amine would then be subjected to a standard amide coupling reaction whereupon the appropriate acid (see, e.g., Scheme 1, WO 2012/142504 and WO 2012/142513, which are incorporated herein by reference) would be added along with a suitable amide coupling reagent such as PYBOP in a suitable solvent such as DMSO to give the desired amide (Step 4). In Steps 5 and 6, the 2,4-dichloropyridine can be converted into a mixture of 1,2 and

1,4-pyridones by heating in the presence of NaOH in p-methoxy benzyl alcohol as solvent followed by deprotection of the resulting PMB ethers with an appropriate reagent such as TFA in an appropriate solvent such as dichloromethane. Purification of the resulting pyridone mixture can be accomplished using standard protocols known to ones skilled in the art including, but not limited to, RP-HPLC and preparative TLC. In Step 7, the remaining chlorine is replaced with R_2 by reacting the purified 1,4-pyridonewith an alcohol or amine.

[0482] A person of ordinary skill in the art will recognize that in the above schemes the order of many of the steps are interchangeable.

[0483] Compounds of the present invention inhibit the histone methyltransferase activity of EZH2 or a mutant thereof and, accordingly, in one aspect of the invention certain compounds disclosed herein are candidates for treating, or preventing, certain conditions and diseases in which EZH2 plays a role. The present invention provides methods for treating conditions and diseases the course of which can be influenced by modulating the methylation status of histones or other proteins, wherein said methylation status is mediated at least in part by the activity of EZH2. Modulation of the methylation status of histones can in turn influence the level of expression of target genes activated by methylation, and/or target genes suppressed by methylation. The method includes administering to a subject in need of such treatment, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, polymorph, solvate, or stereoisomeror thereof.

[0484] Unless otherwise stated, any description of a method of treatment includes uses of the compounds to provide such treatment or prophylaxis as is described in the specification, as well as uses of the compounds to prepare a medicament to treat or prevent such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[0485] In still another aspect, this invention relates to a method of modulating the activity of the EZH2, the catalytic subunit of the PRC2 complex which catalyzes the mono- through tri-methylation of lysine 27 on histone H3 (H3-K27) in a subject in need thereof. For example, the method comprises the step of administering to a subject having a cancer expressing a mutant EZH2 a therapeutically effective amount of a compound described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer.

[0486] For example, the EZH2-mediated cancer is selected from the group consisting of follicular lymphoma and diffuse large B-cell lymphoma (DLBCL) of germinal center B cell-like (GCB) subtype. For example, the cancer is lymphoma, leukemia or melanoma. Preferably, the lymphoma is non-Hodgkin's lymphoma (NHL), follicular lymphoma or diffuse large B-cell lymphoma. Alternatively, the leukemia is chronic myelogenous leukemia (CML), acute myeloid leukemia, acute lymphocytic leukemia or mixed lineage leukemia.

[0487] For example, the EZH2-mediated precancerous condition is myelodysplastic syndromes (MDS, formerly known as preleukemia).

[0488] For example, the EZH2-mediated cancer is a hematological cancer.

[0489] The compound(s) of the present invention inhibit the histone methyltransferase activity of EZH2 or a mutant thereof and, accordingly, the present invention also provides methods for treating conditions and diseases the course of which can be influenced by modulating the methylation status of histones or other proteins, wherein said methylation status is mediated at least in part by the activity of EZH2. In one aspect of the invention, certain compounds disclosed herein are candidates for treating, or preventing certain conditions and diseases. Modulation of the methylation status of histones can in turn influence the level of expression of target genes activated by methylation, and/or target genes suppressed by methylation. The method includes administering to a subject in need of such treatment, a therapeutically effective amount of a compound of the present invention.

[0490] As used herein, a "subject" is interchangeable with a "subject in need thereof", both of which refer to a subject having a disorder in which EZH2-mediated protein methylation plays a part, or a subject having an increased risk of developing such disorder relative to the population at large. A "subject" includes a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In one embodiment, the mammal is a human. A subject in need thereof can be one who has been previously diagnosed or identified as having cancer or a precancerous condition. A subject in need thereof can also be one who has (e.g., is suffering from) cancer or a precancerous condition. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disorder relative to the population at large (*i.e.*, a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a precancerous condition. A subject in need thereof can have

refractory or resistant cancer (i.e., cancer that doesn't respond or hasn't yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof has cancer recurrence following remission on most recent therapy. In some embodiments, the subject in need thereof received and failed all known effective therapies for cancer treatment. In some embodiments, the subject in need thereof received at least one prior therapy. In a preferred embodiment, the subject has cancer or a cancerous condition. For example, the cancer is lymphoma, leukemia, melanoma, or rhabdomyosarcoma. Preferably, the lymphoma is non-Hodgkin's lymphoma, follicular lymphoma or diffuse large B-cell lymphoma. Alternatively, the leukemia is chronic myelogenous leukemia (CML). The precancerous condition is myelodysplastic syndromes (MDS, formerly known as preleukemia).

[0491] As used herein, "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present invention, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term "treat" can also include treatment of a cell *in vitro* or an animal model.

[0492] A compound of the present invention, or a pharmaceutically acceptable salt, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes. As used herein, "preventing," "prevent," or "protecting against" describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0493] Point mutations of the EZH2 gene at a single amino acid residue (e.g., Y641, A677, and A687) of EZH2 have been reported to be linked to lymphoma. More examples of EZH2 mutants and methods of detection of mutation and methods treatment of mutation-associated disorders are described in, e.g., U.S. Patent Application Publication No. US 20130040906, the entire content of which is incorporated herein by reference in its entirety.

[0494] One skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al., Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al., Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al., Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna *et al., Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al., The Pharmacological Basis of Therapeutics* (1975),

Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the invention.

[0495] As used herein, "combination therapy" or "co-therapy" includes the administration of a compound of the present invention, or a pharmaceutically acceptable salt, polymorph or solvate thereof, and at least a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents.

[0496] The present invention also provides pharmaceutical compositions comprising a compound of any of the Formulae described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0497] A "pharmaceutical composition" is a formulation containing the compounds of the present invention in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0498] As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0499] "Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[0500] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.,* intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0501] A compound or pharmaceutical composition of the invention can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, for treatment of cancers, a compound of the invention may be injected directly into tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, cancer, precancer, and the like) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0502] The term "therapeutically effective amount", as used herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is

within the skill and judgment of the clinician. In a preferred aspect, the disease or condition to be treated is cancer. In another aspect, the disease or condition to be treated is a cell proliferative disorder.

[0503] For any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50}. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0504] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0505] The pharmaceutical compositions containing active compounds of the present invention may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0506] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF,

Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0507] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0508] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating

agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0509] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0510] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0511] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0512] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0513] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the invention vary depending on the agent, the age, weight, and clinical

condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. In preferred aspects, dosages can range from about 1 mg/kg per day to about 1000 mg/kg per day. In an aspect, the dose will be in the range of about 0.1 mg/day to about 50 g/day; about 0.1 mg/day to about 25 g/day; about 0.1 mg/day to about 10 g/day; about 0.1 mg to about 3 g/day; or about 0.1 mg to about 1 g/day, in single, divided, or continuous doses (which dose may be adjusted for the patient's weight in kg, body surface area in m^2, and age in years). An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. For example, regression of a tumor in a patient may be measured with reference to the diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Regression is also indicated by failure of tumors to reoccur after treatment has stopped. As used herein, the term "dosage effective manner" refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[0514] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0515] The compounds of the present invention are capable of further forming salts. All of these forms are also contemplated within the scope of the claimed invention.

[0516] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present invention wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic,

malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0517] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present invention also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ration other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

[0518] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0519] The compounds of the present invention can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.*, a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.*, acetate, propionate or other ester.

[0520] The compounds, or pharmaceutically acceptable salts thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperintoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0521] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

[0522] Techniques for formulation and administration of the disclosed compounds of the invention can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0523] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present invention are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present invention. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present invention.

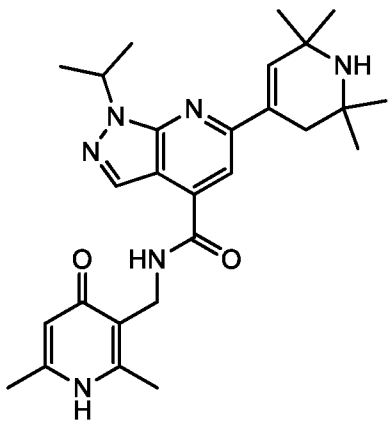
[0524] In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the invention to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

[0525] Compounds designed, selected and/or optimized by methods described above, once produced, can be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules can be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

[0526] Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described herein for activity, using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

[0527] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

[0528] **Example 1:** Synthesis of Compound 1: N-((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-1-isopropyl-6-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrazolo[3,4-b]pyridine-4-carboxamide



Compound 1

[0529] Step 1: Synthesis of 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carbonitrile.

[0530] A mixture of 2,2,6-trimethyl-4H-1,3-dioxin-4-one (40 mmol) and 3-amino crotononitrile (20 mmol) was heated at 120-130 °C for 1 h, under anhydrous conditions. After 1 h, the reaction mixture was cooled to rt and diluted with ethyl acetate. Precipitated solids were filtered and dried under vacuum to afford the title product (40% yield).

[0531] Step 2: Synthesis of 3-(aminomethyl)-2,6-dimethylpyridin-4(1H)-one.

[0532] To a solution of 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carbonitrile (1 mmol) in methanol (10 mL), Raney Ni and ammonia (0.4 mL, 1 mmol) were added and reaction was stirred under H_2 atmosphere for 3 h. Upon completion, the reaction mixture was filtered through celite and the filtrate was concentrated to obtain the title product.

[0533] .

[0534] Step 3: Synthesis of ethyl 6-hydroxy-1H-pyrazolo [3,4-b]pyridine-4-carboxylate.

[0535] A stirred solution of 1H-pyrazol-3-amine (45 g, 542.16 mmol) in acetic acid (297 mL) and water (900 mL) was cooled to 0 °C and diethyl oxaloacetate sodium salt (113.85 g, 542.16 mmol) was added. The resulting solution was heated at 100 °C for 16 h. After which time the solids were filtered and dried to obtain the title compound (22% yield).

[0536] Step 4: Synthesis of ethyl 6-bromo-1H-pyrazolo [3,4-b]pyridine-4-carboxylate.

[0537] Ethyl 6-hydroxy-1H-pyrazolo [3,4-b]pyridine-4-carboxylate (25 g, 120.77 mmol) was suspended in acetonitrile (250 mL) and $POBr_3$ (69.56 g, 241.54 mmol) was added. The reaction mixture was refluxed for 6 h. On completion of the reaction, acetonitrile was removed under reduced pressure and residue was neutralized with saturated $NaHCO_3$ solution. After extraction with EtOAc, the combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to provide the title compound (77% yield).

[0538] Step 5: Synthesis of ethyl 6-bromo-1-isopropyl-1H-pyrazolo-[3,4-b]-pyridine-4-carboxylate.

[0539] Intermediate ethyl 6-bromo-1H-pyrazolo-[3,4-b]-pyridine-4-carboxylate (20 g, 74.34 mmol) was suspended in acetonitrile (200 mL) and K_2CO_3 (15.39 g, 111.52 mmol) and 2-bromopropane (18.13 g, 148.64 mmol) were added. The reaction mixture was refluxed for 8 h. On completion, the solvent was removed under reduced pressure and the residue was diluted with water. The solution was extacted with ethyl acetate and the combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and residue was purified by silica gel column chromatography to obtain the title compound (58% yield).

[0540] Step 6: Synthesis of 6-bromo-1-isopropyl-1H-pyrazolo-[3,4-b]-pyridine-4-carboxylic acid.

[0541] Aqueous NaOH (3.85 g, 96.46 mmol) was added to a solution of ethyl 6-bromo-1H-pyrazolo-[3,4-b]pyridine-4-carboxylate (20 g, 64.30 mmol) in EtOH (200 mL) and the resulting solution was stirred at 60 °C for 1 h. After completion, the solvent was removed under reduced pressure and residue was acidified using 10% citric acid solution. The solution was extracted with ethyl acetate and the combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide the title compound (83% yield).

[0542] Step 7: Synthesis of 6-bromo-N-((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-pyrazolo[3,4-b]pyridine-4-carboxamide.

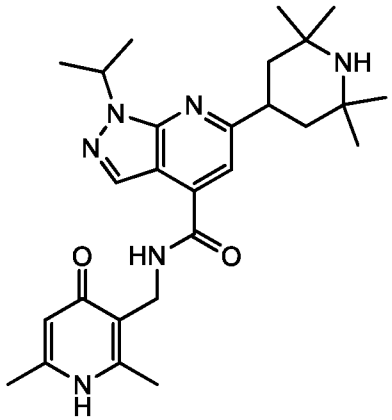
[0543] 6-bromo-1-isopropyl-1H-pyrazolo-[3,4-b]-pyridine-4-carboxylic acid (0.25 g, 0.88 mmol) was dissolved in DMSO (3 mL) and 3-(aminomethyl)-2,6-dimethylpyridin-4(1H)-one (0.265 g, 1.76 mmol) was added. The reaction mixture was stirred at room temperature for 15 min then PYBOP (0.686 g, 1.32 mmol) was added and was stirring was continued for 16 h. After completion of the reaction, the reaction mass was poured onto ice, the resulting solids were filtered and washed with acetonitrile followed by ether to provide the title compound (49% yield).

[0544] Step 8: Synthesis of N-((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-1-isopropyl-6-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrazolo[3,4-b]pyridine-4-carboxamide (Compound 1).

[0545] A solution of 6-bromo-N-((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-pyrazolo[3,4-b]pyridine-4-carboxamide (0.16 g, 0.383 mmol), 2,2,6,6-tetramethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (0.12 g, 0.46 mmol) and $Pd(PPh_3)_4$ (0.045 g, 0.0383 mmol) in 1,4-dioxane (3 mL) was purged with argon for 10 min. Then, 2 M Na_2CO_3 (0.146 g, 1.38 mmol) in water was added and the mixture was purged with argon for 10 min. The reaction mixture was stirred at 100 °C for 1h. After completion of the reaction, the mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography to afford the title compound (55% yield).

[0546] LCMS: 477.30 (M+1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.06 (s, 1H), 8.90 (m, 1H), 8.26 (s, 1H), 7.80 (s, 1H), 6.81 (s, 1H), 5.91 (s, 1H), 5.23-5.19 (m, 1H), 4.33 (d, J=4.8 Hz, 2H), 2.43 (s, 2H), 2.37 (s, 3H), 2.16 (s, 3H), 1.49 (d, J=6.8 Hz, 6H), 1.24 (s, 6H), 1.14 (s, 6H). 1H merged in solvent peaks.

[0547] **Example 2:** Synthesis of Compound 2: N-((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-1-isopropyl-6-(2,2,6,6-tetramethylpiperidin-4-yl)-1H-pyrazolo[3,4-b]pyridine-4-carboxamide



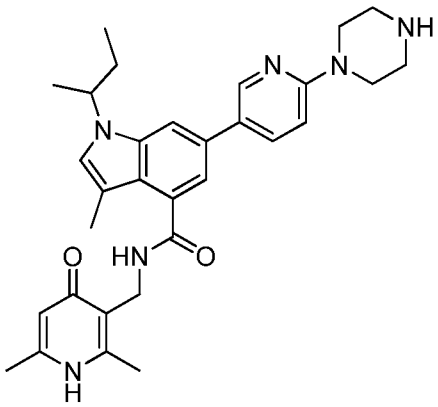
Compound 2

[0548] Step 1: Synthesis of N-((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-1-isopropyl-6-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrazolo[3,4-b]pyridine-4-carboxamide.

[0549] A solution of 6-bromo-N-((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-pyrazolo[3,4-b]pyridine-4-carboxamide (0.16 g, 0.38 mmol), 2,2,6,6-tetramethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine (0.12 g, 0.46 mmol) and $Pd(PPh_3)_4$ (0.045 g, 0.038 mmol) in 1,4-dioxane (3 mL) was purged with argon for 10 min. 2 M Na_2CO_3 (0.146 g, 1.38 mmol) in water was added to it and the reaction was purged with argo for 10 min. The reaction mixture was stirred at 100 °C for 1 h. After completion of the reaction, water was added and the combined solution was extraction with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the title compound (55% yield).

[0550] LCMS: 479.4 (M+1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.09 (brs, 1H), 8.80 (m, 1H), 8.26 (s, 1H), 7.51 (s, 1H), 5.91 (s, 1H), 5.22-5.19 (m, 1H), 4.32 (d, J=3.6 Hz, 2H), 2.36 (s, 3H), 2.35 (m, 1H), 2.16 (s, 3H), 1.73-1.70 (m, 2H), 1.49-1.47 (m, 8H), 1.24 (s, 6H), 1.09 (s, 6H). 1H merged in solvent peaks.

Example 3: Synthesis of 1-(sec-butyl)-N-((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-3-methyl-6-(6-(piperazin-1-yl)pyridin-3-yl)-1H-indole-4-carboxamide:



Compound 4

[0551] Step 1: Synthesis of 5-bromo-2-methyl-3-nitrobenzoic acid:

To stirred solution of 2-methyl-3-nitrobenzoic acid (25 g, 138.1 mmol) in conc. H_2SO_4 (100 mL) at 0 °C, 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (23.7 g, 82.87 mmol) was added portion wise and the reaction mass was stirred at rt for 6 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mass was poured on ice cold water, the solid precipitated was filtered, washed with water and dried under reduced pressure to afford the title compound (29 g, 81%).

[0552] Step 2: Synthesis of methyl 5-bromo-2-methyl-3-nitrobenzoate:

[0553] To a stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (29 g, 111.9 mmol) in DMF (300 mL), sodium carbonate (48 g, 447.8 mmol) and MeI (63.59 g, 447.8 mmol) were added. The resulting reaction mass was heated at 60 °C for 12 h.The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was filtered and washed with diethyl ether. The filtrate was diluted with water and extracted with diethyl ether. The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford the title compound (30 g, 98%)

[0554] Step 3: Synthesis of methyl 6-bromo-1H-indole-4-carboxylate:

[0555] To a stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzoate (25 g, 91.24 mmol) in DMF (250 mL), DMF-DMA (65.14 g, 547.44 mmol) was added and the reaction was stirred at 100 °C for 12 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated to dryness under reduced pressure. The residue obtained was dissolved in acetic acid (250 mL). Iron powder (50 g, 892.8) was added and the reaction mixture was stirred at 80 °C for 4 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated to dryness under reduced pressure. The residue obtained was diluted with ethanol and filtered. The

filtrate was concentrated under reduced pressure to afford the crude material; which was purified by column chromatography to give title compound (20 g, 86%).

[0556] Step 4: Synthesis of methyl 6-bromo-1-(sec-butyl)-1H-indole-4-carboxylate:

[0557] To a stirred solution of NaH (60%, 0.755 g, 18.89 mmol) in dry DMF (10 mL) at 0 °C, methyl 6-bromo-1H-indole-4-carboxylate (4 g, 15.74 mmol) was added and the solution was stirred at 0 °C for 20 min. Then 2-bromobutane (5.39 g, 39.34 mmol) was added at 0 °C and the reaction was stirred at rt for 16 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford the title compound (2 g, 41%).

[0558] Step 5: Synthesis of methyl 6-bromo-1-(sec-butyl)-3-formyl-1H-indole-4-carboxylate:

[0559] To a mixture of methyl 6-bromo-1-(sec-butyl)-1H-indole-4-carboxylate (3 g, 9.67 mmol) and $POCl_3$ (2.70 mL, 29.03) at 0 °C, DMF (1.48 mL, 19.35 mmol) was added slowly. The resulting reaction mixture was stirred at 80 °C for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated to dryness under reduced pressure. The residue obtained was basified with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford the title compound (1.5 g, 50%).

[0560] Step 6: Synthesis of methyl 6-bromo-1-(sec-butyl)-3-methyl-1H-indole-4-carboxylate:

[0561] To a stirred solution of methyl 6-bromo-1-(sec-butyl)-3-formyl-1H-indole-4-carboxylate (1.5 g, 4.43 mmol) in DMF (15 mL), PTSA (0.11 g, 0.576 mmol), p-toluene sulfonyl hydrazide (1.07 g, 5.76 mmol) and sulfolane (15 mL) were added and the solution was stirred at 100 °C for 1 h. After 1 h, the reaction mixture was cooled to rt and sodium cyanoborohydride (1.1 g, 17.74 mmol) was added at 0 °C. The resulting reaction mixture was stirred at 100 °C for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford the title compound (1 g, 69%).

[0562] Step 7: Synthesis of methyl 6-(6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)-1-(sec-butyl)-3-methyl-1H-indole-4-carboxylate:

[0563] To a stirred solution of methyl 6-bromo-1-(sec-butyl)-3-methyl-1H-indole-4-carboxylate (1 g, 3.09 mmol) and tert-butyl 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate (1.32 g, 3.39 mmol) in dioxane/water mixture (8 mL + 2 mL), K_3PO_4 (1.96 g, 9.25 mmol) was added and the solution was purged with argon for 20 min. Then $Pd(dppf)Cl_2$ (0.252 g, 0.309 mmol) was added and argon was purged again for 15 min. The reaction mass was heated at 80 °C for 5 h. The progress of the reaction was monitored by TLC. Upon completion the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford the title compound (0.8 g, 51%).

[0564] Step 8: Synthesis of 6-(6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)-1-(sec-butyl)-3-methyl-1H-indole-4-carboxylic acid:

[0565] To a stirred solution of methyl 6-(6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)-1-(sec-butyl)-3-methyl-1H-indole-4-carboxylate (0.8 g, 1.58 mmol) in EtOH (10 mL), aq. NaOH (0.252 g, 6.32 mmol) was added and the reaction was stirred at 60 °C for 1 h. The progress of the reaction was monitored by TLC. Upon completion, the ethanol was removed under reduced pressure and the reaction mass was acidified using dil. HCl to pH 6 and extracted with 10%MeOH/DCM. The combined organic layers were dried, concentrated giving the respective acid (0.65 g) which was used in the subsequent step without further purification.

[0566] Step 9: Synthesis of tert-butyl 4-(5-(1-(sec-butyl)-4-(((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)carbamoyl)-3-methyl-1H-indol-6-yl)pyridin-2-yl)piperazine-1-carboxylate:

[0567] To a stirred solution of 6-(6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)-1-(sec-butyl)-3-methyl-1H-indole-4-carboxylic acid (0.3 g, 0.609 mmol) in DMSO (3 mL), 3-(aminomethyl)-2,6-dimethylpyridin-4(1H)-one (0.111 g, 0.73 mmol) and triethylamine (0.25 mL, 1.82 mmol) were added. The reaction mixture was stirred at rt for 15 min before PyBOP (0.476 g, 0.91 mmol) was added to it and stirring was continued at rt for 16 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mass was diluted with water and extracted with 10%MeOH/DCM. The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford the title compound (0.1 g, 26%).

[0568] Step 10: Synthesis of 1-(sec-butyl)-N-((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-3-methyl-6-(6-(piperazin-1-yl)pyridin-3-yl)-1H-indole-4-carboxamide:

[0569] To a stirred solution of tert-butyl 4-(5-(1-(sec-butyl)-4-(((2,6-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)carbamoyl)-3-methyl-1H-indol-6-yl)pyridin-2-yl)piperazine-1-carboxylate (0.1 g, 0.159 mmol) in methanolic HCl (2 mL), conc. HCl (2-3 drops) was added and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated to dryness under reduced pressure. The residue obtained was basified with aqueous sodium bicarbonate solution and extracted with 10% MeOH/DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by acetonitirle and pentane washing to afford the title compound (0.018 g, 21%).

[0570] LCMS: 527.50 (M+1); ^{1}H NMR (400 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.49 (s, 1H), 8.09 (t, *J* = 4.9 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.72 (s, 1H), 7.25 (s, 1H), 7.15 (s, 1H), 6.87 (d, *J* = 8.9 Hz, 1H), 5.86 (s, 1H), 4.60 (q, *J* = 6.9 Hz, 1H), 4.29 (d, *J* = 5.0 Hz, 2H), 3.43 (t, *J* = 5.0 Hz, 4H), 2.79 (t, *J* = 5.0 Hz, 4H), 2.37 (s, 3H), 2.15 (s, 6H), 1.80-1.78 (m, 2H), 1.40 (d, *J* = 6.6 Hz, 3H), 0.73 (t, *J* = 7.3 Hz, 3H). 1H merged in solvent peak.

[0571] **Example 4:** Bioassay protocol and General Methods

Protocol for Wild-Type and Mutant PRC2 Enzyme Assays

[0572] **General Materials.** *S*-adenosylmethionine (SAM), *S*-adenosylhomocyteine (SAH), bicine, KCl, Tween20, dimethylsulfoxide (DMSO) and bovine skin gelatin (BSG) were purchased from Sigma-Aldrich at the highest level of purity possible. Dithiothreitol (DTT) was purchased from EMD. ^{3}H-SAM was purchased from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

[0573] **Substrates.** Peptides representative of human histone H3 residues 21 – 44 containing either an unmodified lysine 27 (H3K27me0) or dimethylated lysine 27 (H3K27me2) were synthesized with a C-terminal G(K-biotin) linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptides were high-performance liquid chromatography (HPLC) purified to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequences are listed below.

H3K27me0: ATKAARKSAPATGGVKKPHRYRPGGK(biotin)-amide (SEQ ID NO: 101)

H3K27me2: ATKAARK(me2)SAPATGGVKKPHRYRPGGK(biotin)-amide (SEQ ID NO: 102)

[0574] Chicken erythrocyte oligonucleosomes were purified from chicken blood according to established procedures.

[0575] **Recombinant PRC2 Enzymes.** Human PRC2 enzymes were purified as 4-component enzyme complexes co-expressed in *Spodoptera frugiperda* (sf9) cells using a baculovirus expression system. The subunits expressed were wild-type EZH2 (NM_004456) or EZH2 Y641F, N, H, S or C mutants generated from the wild-type EZH2 construct, EED (NM_003797), Suz12 (NM_015355) and RbAp48 (NM_005610). The EED subunit contained an N-terminal FLAG tag that was used to purify the entire 4-component complex from sf9 cell lysates. The purity of the complexes met or exceeded 95% as determined by SDS-PAGE and Agilent Bioanalyzer analysis. Concentrations of enzyme stock concentrations (generally 0.3 – 1.0 mg/mL) was determined using a Bradford assay against a bovine serum albumin (BSA) standard.

[0576] **General Procedure for PRC2 Enzyme Assays on Peptide Substrates.** The assays were all performed in a buffer consisting of 20 mM bicine (pH = 7.6), 0.5 mM DTT, 0.005% BSG and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1 μL) were spotted into polypropylene 384-well V-bottom plates (Greiner) using a Platemate 2 X 3 outfitted with a 384-channel pipet head (Thermo). DMSO (1 μL) was added to columns 11, 12, 23, 24, rows A – H for the maximum signal control, and SAH, a known product and inhibitor of PRC2 (1 μL) was added to columns 11,12, 23, 24, rows I – P for the minimum signal control. A cocktail (40 μL) containing the wild-type PRC2 enzyme and H3K27me0 peptide or any of the Y641 mutant enzymes and H3K27me2 peptide was added by Multidrop Combi (Thermo). The compounds were allowed to incubate with PRC2 for 30 min at 25 °C, then a cocktail (10 μL) containing a mixture of non-radioactive and ^{3}H-SAM was added to initiate the reaction (final volume = 51 μL). In all cases, the final concentrations were as follows: wild-type or mutant PRC2 enzyme was 4 nM, SAH in the minimum signal control wells was 1 mM and the DMSO concentration was 1%. The final concentrations of the rest of the components are indicated in Table 5, below. The assays were stopped by the addition of non-radioactive SAM (10 μL) to a final concentration of 600 μM, which dilutes the ^{3}H-SAM to a level where its incorporation into the peptide substrate is no longer detectable. 50 μL of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1h before being washed

three times with 0.1% Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount platereader to measure the quantity of ^{3}H-labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

Table 5: Final concentrations of components for each assay variation based upon EZH2 identity (wild-type or Y641 mutant EZH2)

PRC2 Enzyme (denoted by EZH2 identity)	Peptide (nM)	Non-radioactive SAM (nM)	^{3}H-SAM (nM)
Wild-type	185	1800	150
Y641F	200	850	150
Y641N	200	850	150
Y641H	200	1750	250
Y641S	200	1300	200
Y641C	200	3750	250

[0577] **General Procedure for Wild-Type PRC2 Enzyme Assay on Oligonucleosome Substrate.** The assays was performed in a buffer consisting of 20 mM bicine (pH = 7.6), 0.5 mM DTT, 0.005% BSG, 100 mM KCl and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1 μL) were spotted into polypropylene 384-well V-bottom plates (Greiner) using a Platemate 2 X 3 outfitted with a 384-channel pipet head (Thermo). DMSO (1 μL) was added to columns 11, 12, 23, 24, rows A – H for the maximum signal control, and SAH, a known product and inhibitor of PRC2 (1 μL) was added to columns 11,12, 23, 24, rows I – P for the minimum signal control. A cocktail (40 μL) containing the wild-type PRC2 enzyme and chicken erythrocyte oligonucleosome was added by Multidrop Combi (Thermo). The compounds were allowed to incubate with PRC2 for 30 min at 25 °C, then a cocktail (10 μL) containing a mixture of non-radioactive and ^{3}H-SAM was added to initiate the reaction (final volume = 51 μL). The final concentrations were as follows: wild-type PRC2 enzyme was 4 nM, non-radioactive SAM was 430 nM, ^{3}H-SAM was 120 nM, chicken erythrocyte olignonucleosome was 120 nM, SAH in the minimum signal control wells was 1 mM and the DMSO concentration was 1%. The assay was stopped by the addition of non-radioactive SAM (10 μL) to a final concentration of 600 μM, which dilutes the ^{3}H-SAM to a level where its incorporation into the chicken erythrocyte olignonucleosome substrate is no longer detectable. 50 μL of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the chicken erythrocyte nucleosomes were immobilized to the surface of the plate,

which was then washed three times with 0.1% Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount platereader to measure the quantity of ^{3}H-labeled chicken erythrocyte oligonucleosome bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

[0578] **% Inhibition Calculation**

$$\% \text{ inh} = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}} \right) \text{ x100}$$

[0579] Where dpm = disintegrations per minute, cmpd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

[0580] **Four-parameter IC_{50} fit**

$$Y = Bottom + \frac{(Top - Bottom)}{1 + \left(\frac{X}{IC_{50}}\right)^{\text{Hill Coefficient}}}$$

[0581] Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

[0582] IC_{50} values for the PRC2 enzyme assays on peptide substrates (e.g., EZH2 wild type andY641F) are presented in Table 6 below.

[0583] **WSU-DLCL2 Methylation Assay**

[0584] WSU-DLCL2 suspension cells were purchased from DSMZ (German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany). RPMI/Glutamax Medium, Penicillin-Streptomycin, Heat Inactivated Fetal Bovine Serum, and D-PBS were purchased from Life Technologies, Grand Island, NY, USA. Extraction Buffer and Neutralization Buffer(5X) were purchased from Active Motif, Carlsbad, CA, USA. Rabbit anti-Histone H3 antibody was purchased from Abcam, Cambridge, MA, USA. Rabbit anti-H3K27me3 and HRP-conjugated anti-rabbit-IgG were purchased from Cell Signaling Technology, Danvers, MA, USA. TMB "Super Sensitive" substrate was sourced from BioFX Laboratories, Owings Mills, MD, USA. IgG-free Bovine Serum Albumin was purchased from Jackson ImmunoResearch, West Grove, PA, USA. PBS with Tween (10X PBST) was purchased from KPL, Gaithersburg, MD, USA. Sulfuric Acid was purchased from Ricca Chemical, Arlington, TX, USA. Immulon ELISA plates were purchased from Thermo,

Rochester, NY, USA. V-bottom cell culture plates were purchased from Corning Inc., Corning, NY, USA.V-bottom polypropylene plates were purchased from Greiner Bio-One, Monroe, NC, USA.

[0585] WSU-DLCL2 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) and cultured at 37 °C under 5% CO_2. Under assay conditions, cells were incubated in Assay Medium (RPMI 1640 supplemented with 20% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) at 37 °C under 5% CO_2 on a plate shaker.

[0586] WSU-DLCL2 cells were seeded in assay medium at a concentration of 50,000 cells per mL to a 96-well V-bottom cell culture plate with 200 µL per well. Compound (1µL) from 96 well source plates was added directly to V-bottom cell plate. Plates were incubated on a titer-plate shaker at 37 °C, 5% CO_2 for 96 hours. After four days of incubation, plates were spun at 241 x g for five minutes and medium was aspirated gently from each well of cell plate without disturbing cell pellet. Pellet was resuspended in 200 µL DPBS and plates were spun again at 241 x g for five minutes. The supernatant was aspirated and cold (4 °C) Extraction buffer (100 µL) was added per well. Plates were incubated at 4 °C on orbital shaker for two hours. Plates were spun at 3427 x g x 10 minutes. Supernatant (80 µL per well) was transferred to its respective well in 96 well V-bottom polypropylene plate. Neutralization Buffer 5X (20 µL per well) was added to V-bottom polypropylene plate containing supernatant. V-bottom polypropylene plates containing crude histone preparation (CHP) were incubated on orbital shaker x five minutes. Crude Histone Preparations were added (2µL per well) to each respective well into duplicate 96 well ELISA plates containing 100 µL Coating Buffer (1X PBS + BSA 0.05% w/v). Plates were sealed and incubated overnight at 4 °C. The following day, plates were washed three times with 300 µL per well 1X PBST. Wells were blocked for two hours with 300 µL per well ELISA Diluent ((PBS (1X) BSA (2% w/v) and Tween20 (0.05% v/v)). Plates were washed three times with 1X PBST. For the Histone H3 detection plate, 100 µL per well were added of anti-Histone-H3 antibody (Abcam, ab1791) diluted 1:10,000 in ELISA Diluent. For H3K27 trimethylation detection plate, 100 µL per well were added of anti-H3K27me3 diluted 1:2000 in ELISA diluent. Plates were incubated for 90 minutes at room temperature. Plates were washed three times with 300 µL 1X PBST per well. For Histone H3 detection, 100 µL of HRP-conjugated anti-rabbit IgG antibody diluted to 1:6000 in ELISA diluent was added per well. For H3K27me3 detection, 100 µL of HRP conjugated anti-rabbit IgG antibody diluted to

1:4000 in ELISA diluent was added per well. Plates were incubated at room temperature for 90 minutes. Plates were washed four times with 1X PBST 300 µL per well. TMB substrate100 µL was added per well. Histone H3 plates were incubated for five minutes at room temperature. H3K27me3 plates were incubated for 10 minutes at room temperature. The reaction was stopped with sulfuric acid 1N (100 µL per well). Absorbance for each plate was read at 450 nm.

[0587] First, the ratio for each well was determined by: $\left(\frac{H3K27me3\ OD450\ value}{Histone\ H3\ OD450\ value}\right)$

[0588] Each plate included eight control wells of DMSO only treatment (Minimum Inhibition) as well as eight control wells for maximum inhibition (Background wells).

[0589] The average of the ratio values for each control type was calculated and used to determine the percent inhibition for each test well in the plate. Test compound was serially diluted three-fold in DMSO for a total of ten test concentrations, beginning at 25 µM. Percent inhibition was determined and IC_{50} curves were generated using duplicate wells per concentration of compound. IC_{50} values for this assay are presented in Table 6 below.

[0590] Percent Inhibition = 100-

$$\left(\left(\frac{(\text{Individual Test Sample Ratio})-(\text{Background Avg Ratio})}{(\text{Minimum Inhibition Ratio})-(\text{Background Average Ratio})}\right)*100\right)$$

[0591] **Cell proliferation analysis**

[0592] WSU-DLCL2 suspension cells were purchased from DSMZ (German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany). RPMI/Glutamax Medium, Penicillin-Streptomycin, Heat Inactivated Fetal Bovine Serum were purchased from Life Technologies, Grand Island, NY, USA. V-bottom polypropylene 384-well plates were purchased from Greiner Bio-One, Monroe, NC, USA. Cell culture 384-well white opaque plates were purchased from Perkin Elmer, Waltham, MA, USA. Cell-Titer Glo® was purchased from Promega Corporation, Madison, WI, USA. SpectraMax M5 plate reader was purchased from Molecular Devices LLC, Sunnyvale, CA, USA.

[0593] WSU-DLCL2 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and cultured at 37 °C under 5% CO_2. Under assay conditions, cells were incubated in Assay Medium (RPMI 1640 supplemented with 20% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) at 37 °C under 5% CO_2.

[0594] For the assessment of the effect of compounds on the proliferation of the WSU-DLCL2 cell line, exponentially growing cells were plated in 384-well white opaque plates

at a density of 1250 cell/ml in a final volume of 50 µl of assay medium. A compound source plate was prepared by performing triplicate nine-point 3-fold serial dilutions in DMSO, beginning at 10 mM (final top concentration of compound in the assay was 20 µM and the DMSO was 0.2%). A 100 nL aliquot from the compound stock plate was added to its respective well in the cell plate. The 100% inhibition control consisted of cells treated with 200 nM final concentration of staurosporine and the 0% inhibition control consisted of DMSO treated cells. After addition of compounds, assay plates were incubated for 6 days at 37 ºC, 5% CO_2, relative humidity > 90% for 6 days. Cell viability was measured by quantization of ATP present in the cell cultures, adding 35 µl of Cell Titer Glo® reagent to the cell plates. Luminescence was read in the SpectraMax M5. The concentration inhibiting cell viability by 50% was determined using a 4-parametric fit of the normalized dose response curves. IC_{50} values for this assay are also presented in Table 6 below.

Table 6

Cpd #	WT EZH2 IC_{50} (µM)	Mutant Y641F IC_{50} (µM)	H3K27Me3 ELISA IC_{50} (µM)	WSU proliferation IC_{50} (µM)
1	6.6			
2	7.1			
4	0.028		11.9	

[0595] **Example 5:** Derivation of the Lowest Cytotoxic Concentration (LCC)

[0596] It is well established that cellular proliferation proceeds through cell division that results in a doubling of the number of cells after division, relative to the number of cells prior to division. Under a fixed set of environmental conditions (e.g., pH, ionic strength, temperature, cell density, medium content of proteins and growth factors, and the like) cells will proliferate by consecutive doubling (i.e., division) according to the following equation, provided that sufficient nutrients and other required factors are available.

[0597] $$N_t = N_0 \times 2^{\frac{t}{t_D}} \qquad \text{(A.1)}$$

where N_t is the cell number at a time point (t) after initiation of the observation period, N_0 is the cell number at the initiation of the observation period, t is the time after initiation of the observation period and t_D is the time interval required for cell doubling, also referred to as the doubling time. Equation A.1 can be converted into the more convenient form of an exponential equation in base e, taking advantage of the equality, 0.693 = ln(2).

[0598] $$N_t = N_0 e^{\frac{0.693t}{t_D}} \quad \text{(A.2)}$$

[0599] The rate constant for cell proliferation (k_p) is inversely related to the doubling time as follows.

[0600] $$k_p = \frac{0.693}{t_D} \quad \text{(A.3)}$$

[0601] Combining equation A.2 and A.3 yields,

[0602] $$N_t = N_0 e^{k_p t} \quad \text{(A.4)}$$

[0603] Thus, according to equation A.4 cell number is expected to increase exponentially with time during the early period of cell growth referred to as log-phase growth. Exponential equations like equation A.4 can be linearized by taking the natural logarithm of each side.

[0604] $$\ln(N_t) = \ln(N_0) + k_p t \quad \text{(A.5)}$$

[0605] Thus a plot of $\ln(N_t)$ as a function of time is expected to yield an ascending straight line with slope equal to k_p and y-intercept equal to $\ln(N_0)$.

[0606] Changes in environmental conditions can result in a change in the rate of cellular proliferation that is quantifiable as changes in the proliferation rate constant k_p. Among conditions that may result in a change in proliferation rate is the introduction to the system of an antiproliferative compound at the initiation of the observation period (i.e., at t = 0). When an antiproliferative compound has an immediate impact on cell proliferation, one expects that plots of $\ln(N_t)$ as a function of time will continue to be linear at all compound concentrations, with diminishing values of k_p at increasing concentrations of compound.

[0607] Depending on the mechanistic basis of antiproliferative action, some compounds may not immediately effect a change in proliferation rate. Instead, there may be a period of latency before the impact of the compound is realized. In such cases a plot of $\ln(N_t)$ as a function of time will appear biphasic, and a time point at which the impact of the compound begins can be identified as the breakpoint between phases. Regardless of whether a compound's impact on proliferation is immediate or begins after a latency period, the rate constant for proliferation at each compound concentration is best defined by the slope of the $\ln(N_t)$ vs. time curve from the time point at which compound impact begins to the end of the observation period of the experiment.

[0608] A compound applied to growing cells may affect the observed proliferation in one of two general ways: by inhibiting further cell division (cytostasis) or by cell killing (cytotoxicity). If a compound is cytostatic, increasing concentration of compound will reduce the value of k_p until there is no further cell division. At this point, the rate of cell growth, and therefore the value of k_p, will be zero. If, on the other hand, the compound is cytotoxic, then the value of k_p will be composed of two rate constants: a rate constant for continued cell growth in the presence of the compound (k_g) and a rate constant for cell killing by the compound (k_d). The overall rate constant for proliferation at a fixed concentration of compound will thus be the difference between the absolute values of these opposing rate constants.

[0609] $$k_p = |k_g| - |k_d| \qquad \text{(A.6)}$$

[0610] At compound concentrations for which the rate of cell growth exceeds that of cell killing, the value of k_p will have a positive value (i.e., $k_p > 0$). At compound concentrations for which the rate of cell growth is less than that for cell killing, the value of k_p will have a negative value (i.e., $k_p < 0$) and the cell number will decrease with time, indicative of robust cytotoxicity. When k_g exactly matches k_d then the overall proliferation rate constant, k_p, will have a value of zero. We can thus define the lowest cytotoxic concentration (LCC) as that concentration of compound that results in a value of k_p equal to zero, because any concentration greater than this will result in clearly observable cytotoxicity. *Nota bene*: at concentrations below the LCC there is likely to be cell killing occurring, but at a rate that is less than that of residual cell proliferation. The treatment here is not intended to define the biological details of compound action. Rather, the goal here is to merely define a practical parameter with which to objectively quantify the concentration of compound at which the rate of cell killing exceeds new cell growth. Indeed, the LCC represents a breakpoint or critical concentration above which frank cytotoxicity is observed, rather than a cytotoxic concentration per se. In this regard, the LCC can be viewed similar to other physical breakpoint metrics, such as the critical micelle concentration (CMC) used to define the concentration of lipid, detergent or other surfactant species above which all molecules incorporate into micellar structures.

[0611] Traditionally, the impact of antiproliferative compounds on cell growth has been most commonly quantified by the IC_{50} value, which is defined as that concentration of compound that reduces the rate of cell proliferation to one half that observed in the absence

of compound (i.e., for the vehicle or solvent control sample). The IC_{50}, however, does not allow the investigator to differentiate between cytostatic and cytotoxic compounds. The LCC, in contrast, readily allows one to make such a differentiation and to further quantify the concentration at which the transition to robust cytotoxic behavior occurs.

[0612] If one limits the observation time window to between the start of impact and the end of the experiment, then the data will generally fit well to a linear equation when plotted as $\ln(N_t)$ as a function of time (*vide supra*). From fits of this type, the value of k_p can be determined at each concentration of compound tested. A replot of the value of k_p as a function of compound concentration ([I]) will have the form of a descending isotherm, with a maximum value at [I] = 0 of k_{max} (defined by the vehicle or solvent control sample) and a minimum value at infinite compound concentration of k_{min}.

[0613] $$k_p = \frac{(k_{max} - k_{min})}{1 + \frac{[I]}{I_{mid}}} + k_{min} \qquad (A.7)$$

where I_{mid} is the concentration of compound yielding a value of k_p that is midway between the values of k_{max} and k_{min} (note that the value of I_{mid} is not the same as the IC_{50}, except in the case of a complete and purely cytostatic compound). Thus, fitting the replot data to equation A.7 provides estimates of k_{max}, k_{min} and I_{mid}. If a compound is cytostatic (as defined here), the value of k_{min} cannot be less than zero. For cytotoxic compounds, k_{min} will be less than zero and the absolute value of k_{min} will relate directly to the effectiveness of the compound in killing cells.

[0614] The fitted values derived from equation A.7 can also be used to determine the value of the LCC. By definition, when [I] = LCC, $k_p = 0$. Thus, under these conditions equation A.7 becomes.

[0615] $$0 = \frac{(k_{max} - k_{min})}{1 + \frac{LCC}{I_{mid}}} + k_{min} \qquad (A.8)$$

[0616] Algebraic rearrangement of equation A.8 yields an equation for the LCC.

[0617] $$LCC = I_{mid}\left[\left(\frac{k_{max} - k_{min}}{-k_{min}}\right) - 1\right] \qquad (A.9)$$

[0618] This analysis is simple to implement with nonlinear curve fitting software and may be applied during cellular assays of compound activity throughout the drug discovery and development process. In this manner, the LCC may provide a valuable metric for the assessment of compound SAR (structure-activity relationship).

[0619] **Example 6:** *In vivo* Assays

Mice

[0620] Female Fox Chase SCID® Mice (CB17/Icr-*Prkdc*$_{scid}$/IcrIcoCrl, Charles River Laboratories) or athymic nude mice (Crl:NU(Ncr)-*Foxn1*$_{nu}$, Charles River Laboratories) are 8 weeks old and had a body-weight (BW) range of 16.0–21.1 g on D1 of the study. The animals are fed *ad libitum* water (reverse osmosis 1 ppm Cl) and NIH 31 Modified and Irradiated Lab Diet® consisting of 18.0% crude protein, 5.0% crude fat, and 5.0% crude fiber. The mice are housed on irradiated Enrich-o'cobs™ bedding in static microisolators on a 12-hour light cycle at 20–22 °C (68–72 °F) and 40–60% humidity. All procedures comply with the recommendations of the *Guide for Care and Use of Laboratory Animals* with respect to restraint, husbandry, surgical procedures, feed and fluid regulation, and veterinary care.

Tumor Cell Culture

[0621] Human lymphoma cell lines line are obtained from different sources (ATCC, DSMZ), e.g., WSU-DLCL2 obtained from DSMZ. The cell lines are maintained at Piedmont as suspension cultures in RPMI-1640 medium containing 100 units/mL penicillin G sodium salt, 100 g/mL streptomycin, and 25 g/mL gentamicin. The medium is supplemented with 10% fetal bovine serum and 2 mM glutamine. The cells are cultured in tissue culture flasks in a humidified incubator at 37 °C, in an atmosphere of 5% CO_2 and 95% air.

***In Vivo* Tumor Implantation**

[0622] Human lymphoma cell lines, e.g., WSU-DLCL2 cells, are harvested during mid-log phase growth, and re-suspended in PBS with 50% Matrigel™ (BD Biosciences). Each mouse receives 1 x 10^7 cells (0.2 mL cell suspension) subcutaneously in the right flank. Tumors are calipered in two dimensions to monitor growth as the mean volume approached the desired 80–120 mm^3 range. Tumor size, in mm^3, is calculated from:

$$Tumor\ volume = \frac{w^2 \times l}{2}$$

where w = width and l = length, in mm, of the tumor. Tumor weight can be estimated with the assumption that 1 mg is equivalent to 1 mm3 of tumor volume. After 10-30 days mice with 108–126 mm^3 tumors are sorted into treatment groups with mean tumor volumes of 117–119 mm^3.

Test Articles

[0623] Test compounds are stored at room temperature and protected from light. On each treatment day, fresh compound formulations are prepared by suspending the powders in 0.5% sodium carboxymethylcellulose (NaCMC) and 0.1% Tween® 80 in deionized water. Compound 141 (free base) is dissolved in sterile saline and the pH is adjusted to 4.5 with HCl fresh every day. The vehicles, 0.5% NaCMC and 0.1% Tween® 80 in deionized water or sterile saline pH 4.5, are used to treat the control groups at the same schedules. Formulations are stored away from light at 4 °C prior to administration. Unless otherwise specified, compounds referered to and tested in this experiment are in their specific salt forms mentioned in this paragraph.

Treatment Plan

[0624] Mice are treated at compound doses ranging from 12.5 – 600 mg/kg and at TID (three time a day every 8h), BID (2 times a day every 12 h) or QD (once a day) schedules for various amounts of days by oral gavage or injections via the intraperitoneal route. Each dose is delivered in a volume of 0.2 mL/20 g mouse (10 mL/kg), and adjusted for the last recorded weight of individual animals. The maximal treatment length is 28 days.

Median Tumor Volume (MTV) and Tumor Growth Inhibition (TGI) Analysis

[0625] Treatment efficacy is determined on the last treatment day. MTV(n), the median tumor volume for the number of animals, n, evaluable on the last day, is determined for each group. Percent tumor growth inhibition (%TGI) can be defined several ways. First, the difference between the MTV(n) of the designated control group and the MTV(n) of the drug-treated group is expressed as a percentage of the MTV(n) of the control group:

$$\%TGI = \left(\frac{MTV(n)_{control} - MTV(n)_{treated}}{MTV(n)_{control}}\right) \times 100$$

[0626] Another way of calculating %TGI is taking the change of the tumor size from day 1 to day n into account with n being the last treatment day.

$$\%TGI = \left(\frac{\Delta MTV_{control} - \Delta MTV_{treated}}{\Delta MTV_{control}}\right) \times 100$$

$$\Delta MTV_{control} = MTV(n)_{control} - MTV(1)_{control}$$

$$\Delta MTV_{treated} = MTV(n)_{treated} - MTV(1)_{treated}$$

Toxicity

[0627] Animals are weighed daily on Days 1–5, and then twice weekly until the completion of the study. The mice are examined frequently for overt signs of any adverse, treatment related side effects, which are documented. Acceptable toxicity for the maximum tolerated dose (MTD) is defined as a group mean BW loss of less than 20% during the test, and not more than 10% mortality due to TR deaths. A death is to be classified as TR if it is attributable to treatment side effects as evidenced by clinical signs and/or necropsy, or due to unknown causes during the dosing period. A death is to be classified as NTR if there is evidence that the death is unrelated to treatment side effects. NTR deaths during the dosing interval would typically be categorized as NTRa (due to an accident or human error) or NTRm (due to necropsy-confirmed tumor dissemination by invasion and/or metastasis). Orally treated animals that die from unknown causes during the dosing period may be classified as NTRu when group performance does not support a TR classification and necropsy, to rule out a dosing error, is not feasible.

Sampling

[0628] On days 7 or 28 during the studies mice are sampled in a pre-specified fashion to assess target inhibition in tumors. Tumors are harvested from specified mice under RNAse free conditions and bisected. Frozen tumor tissue from each animal is snap frozen in liquid N_2 and pulverized with a mortar and pestle.

Statistical and Graphical Analyses

[0629] All statistical and graphical analyses are performed with Prism 3.03 (GraphPad) for Windows. To test statistical significance between the control and treated groups over the whole treatment time course a repeated measures ANOVA test followed by Dunnets multiple comparison post test or a 2 way ANOVA test are employed. Prism reports results

as non-significant (ns) at $P > 0.05$, significant (symbolized by "*") at $0.01 < P < 0.05$, very significant ("**") at $0.001 < P < 0.01$ and extremely significant ("***") at $P < 0.001$.

Histone Extraction

[0630] For isolation of histones, 60-90 mg tumor tissue is homogenized in 1.5 ml nuclear extraction buffer (10 mM Tris-HCl, 10 mM $MgCl_2$, 25 mM KCl, 1% Triton X-100, 8.6% Sucrose, plus a Roche protease inhibitor tablet 1836145) and incubated on ice for 5 minutes. Nuclei are collected by centrifugation at 600 g for 5 minutes at 4 °C and washed once in PBS. Supernatant is removed and histones extracted for one hour, with vortexing every 15 minutes, with 0.4 N cold sulfuric acid. Extracts are clarified by centrifugation at 10,000 g for 10 minutes at 4 °C and transferred to a fresh microcentrifuge tube containing 10x volume of ice cold acetone. Histones are precipitated at -20 °C for 2 hours-overnight, pelleted by centrifugation at 10,000 g for 10 minutes, and resuspended in water.

ELISA

[0631] Histones are prepared in equivalent concentrations in coating buffer (PBS+0.05%BSA) yielding 0.5 ng/ul of sample, and 100 ul of sample or standard is added in duplicate to 2 96-well ELISA plates (Thermo Labsystems, Immulon 4HBX #3885). The plates are sealed and incubated overnight at 4 °C. The following day, plates are washed 3x with 300 ul/well PBST (PBS+0.05% Tween 20; 10X PBST, KPL #51-14-02) on a Bio Tek plate washer. Plates are blocked with 300 ul/well of diluent (PBS+2%BSA+0.05% Tween 20), incubated at RT for 2 hours, and washed 3x with PBST. All antibodies are diluted in diluent. 100 ul/well of anti-H3K27me3 (CST #9733, 50% glycerol stock 1:1,000) or anti-total H3 (Abcam ab1791, 50% glycerol 1:10,000) is added to each plate. Plates are incubated for 90 min at RT and washed 3x with PBST. 100 ul/well of anti-Rb-IgG-HRP (Cell Signaling Technology, 7074) is added 1:2,000 to the H3K27Me3 plate and 1:6,000 to the H3 plate and incubated for 90 min at RT. Plates are washed 4X with PBST. For detection, 100 ul/well of TMB substrate (BioFx Laboratories, #TMBS) is added and plates incubated in the dark at RT for 5 min. Reaction is stopped with 100 ul/well 1N H_2SO_4. Absorbance at 450 nm is read on SpectaMax M5 Microplate reader.

7 day PD study

[0632] In order to test whether a compound can modulate the H3K27me3 histone mark in tumors *in vivo*, WSU-DLCL2 xenograft tumor bearing mice are treated with the compound at either 200 mg/kg BID or 400 mg/kg QD or vehicle (BID schedule) for 7 days. There are 4 animals per group. Animals are euthanized 3 h after the last dose and tumor is preserved

in a frozen state as described above. Following histone extraction the samples are applied to ELISA assays using antibodies directed against the trimethylated state of histone H3K27 (H3K27me3) or total histone H3. Based on these data the ratio of globally methylated to total H3K27 is calculated. The mean global methylation ratios for all groups as measured by ELISA indicate target inhibition range compared to vehicle.

28 day efficacy study in WSU-DLCL2 xenograft model

[0633] In order to test whether a compound could induce a tumor growth inhibition *in vivo* WSU-DLCL2 xenograft tumor bearing mice are treated with the compound at 12.5, 25 or 50 mg/kg QD for 28 days via intraperitoneal injection. Tumor volume and body weights are determined twice a week. A parallel cohort of mice (n=4 per group) is treated at the same doses for 7 days, and mice are euthanized on day 7, 3 h after the last dose for tumor sampling and assessment of target inhibition. The result of the ELISA measuring global methylation of H3K27me3 normalized to total H3 is determined.

Efficacy study with increasing doses in WSU-DLCL2 xenograft model

[0634] In order to test whether a compound could induce an anti-tumor effect *in vivo,* WSU-DLCL2 xenograft tumor bearing mice are treated with a compound at, e.g., 37.5, 75 or 150 mg/kg TID for 28 days. There are 12 mice per group for the efficacy arm of the experiment. A parallel cohort is dosed for 7 days at the same doses and schedules for assessment of target inhibition after 7 days (n=6 per group). The tumor growth over the treatment course of 28 days for vehicle and compound treated groups is measured.

[0635] Histones are extracted from tumors collected after 7 days of dosing (parallel PD cohort) and at the end of the study on day 28 for the efficacy cohort (3h after the last dose for both cohorts). The H3K27me3 methyl mark is assessed for modulation with treatment in a dose dependent matter.

Efficacy study at different dose schedules

[0636] To assess whether a compound would lead to tumor growth inhibition at other dosing schedules but TID a WSU-DLCL2 xenograft efficacy study is performed where TID, BID and QD schedules are compared side by side. There are 12 animals per group, and mice are treated for 28 days. The tumor growth over the treatment course of 28 days for vehicle and compound treated groups is measured.

[0637] On day 28 mice are euthanized and tumors were collected 3h after the last dose for assessment of target inhibition.

[0638] **Example 7:** Anti-cancer effect on the KARPAS-422 human diffused large B-Cell lymphoma mouse xenograft model

[0639] A test compound is analyzed for its anti-cancer activity in KARPAS-422 mouse xenograft model, which is a human diffused large B-Cell lymphoma xenograft model. 45 female of CAnN.Cg-Foxn1nu/CrlCrlj mice (Charles River Laboratories Japan) with KARPAS-422 tumors whose mean tumor volume (TV) reaches approximately 150 mm^3 are selected based on their TVs, and are randomly divided into five groups. The oral administration of compound (e.g., 80.5, 161, 322, and 644 mg/kg) or vehicle is started on day 1. Compound is given once daily on day 1 and day 29 and twice daily everyday from day 2 to day 28. The administration volume (0.1 mL/10 g body weight) is calculated from the body weight before administration. The TV and body weight are measured twice a week. The design for this experiment is shown in Table 7.

Table 7 Dosing Scheme

Group	No. of Animals	Treatment (twice a day)	Route and Schedule
1	9	Vehicle (0.5% Methyl Cellulose, 0.1% Tween-80)	PO; BID x 28 days
2	9	80.5 mg/kg Compound	PO; BID x 28 days
3	9	161 mg/kg Compound	PO; BID x 28 days
4	9	322 mg/kg Compound	PO; BID x 28 days
5	9	644 mg/kg Compound	PO; bid x 28 days

[0640] TV is calculated from caliper measurements by the formula for the volume of a prolate ellipsoid $(LxW^2)/2$ where L and W are the respective orthogonal length and width measurements (mm).

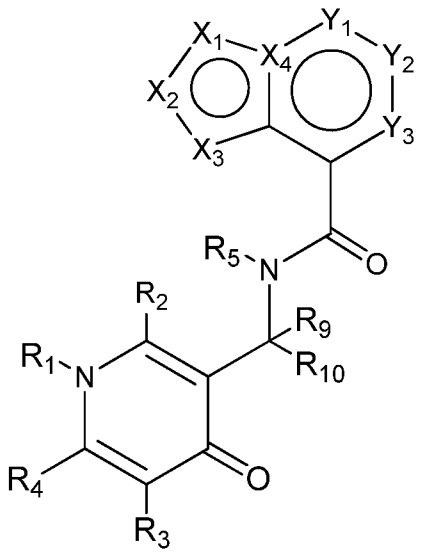
[0641] Data are expressed as the mean ± standard deviation (SD). The differences in TV between the vehicle-treated and compound -treated groups are analyzed by a repeated measures analysis of variance (ANOVA) followed by the Dunnett-type multiple comparison test. A value of $P < 0.05$ (two sided) is considered statistically significant. Statistical analyses are performed using the Prism 5 software package version 5.04 (GraphPad Software, Inc., CA, USA).

[0642] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

[0643] The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

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



(IV),

wherein,

X_1 is NR_7 or CR_7;

X_2 is N, NR_8, CR_8, O, or S;

X_3 is NR_8, CR_8, O, or S;

X_4 is C or N;

Y_1 is N or CH;

Y_2 is N or CR_6;

Y_3 is N, or CR_{11}, and at least one of X_1, X_2, X_3, X_4, Y_1, Y_2, and Y_3 is N or NR_7;

each of R_1, R_5, R_9, and R_{10}, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_1 is H, halo, hydroxyl, COOH, cyano, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C_1-C_6 thioalkyl, C(O)O-C_1-C_6 alkyl, $CONH_2$, SO_2NH_2, -CO-NH(C_1-C_6 alkyl), -CO-N(C_1-C_6 alkyl)$_2$, -SO_2-NH(C_1-C_6 alkyl), - SO_2-N(C_1-C_6 alkyl)$_2$, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_6-C_{10} aryloxy, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of

halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, and 5 to 6-membered heteroaryl; or R_1 and R_2, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R_1 and R_4, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R_3 and R_4, together with the C atoms to which they are attached, form C_5-C_8 cycloalkyl, C_6-C_{10} aryl, or a 5- or 6-membered heteroaryl having 1 to 3 heteroatoms, or a 5 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms; in which each of the ring structures formed by R_1 and R_2, by R_1 and R_4, or by R_3 and R_4, independently is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, C_1-C_6 alkyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

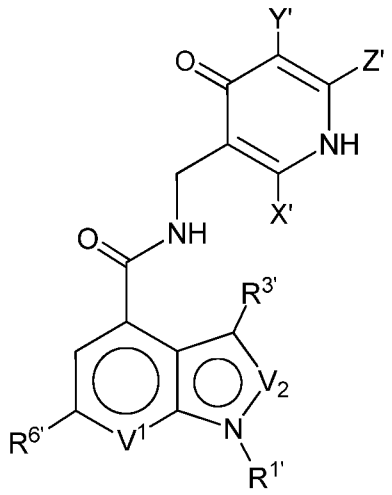
each R_6 independently is H, halo, OR_a, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_2R_a$, $-S(O)_2NR_aR_b$, or R_{S2}, in which each of R_a and R_b, independently is H or R_{S3} and each of R_{S2} and R_{S3}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom; and each of R_{S2}, R_{S3}, and the 4 to 7-membered heterocycloalkyl ring containing R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano,
$-OR_c$, $-NR_cR_d$, $-(NR_cR_dR_{d'})^+A^-$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c, R_d, and $R_{d'}$, independently is H or R_{S5}, A^- is a pharmaceutically acceptable anion, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom, and each of R_{S4}, R_{S5}, and the 4 to 7-membered heterocycloalkyl ring containing R_c and R_d, is optionally substituted with one or more $-Q_3$-

T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of H, halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, 5 to 6-membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl optionally substituted with OH, O-C_1-C_6 alkyl, or NH-C_1-C_6 alkyl; or $-Q_3$-T_3 is oxo; or $-Q_2$-T_2 is oxo; or any two neighboring $-Q_2$-T_2, together with the atoms to which they are attached form a 5- or 6-membered ring optionally containing 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, and 5 to 6-membered heteroaryl; provided that $-Q_2$-T_2 is not H;

each R_7 independently is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5$-T_5, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, NR_k, $S(O)_2$, $NR_kS(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, or 5 to 6-membered heteroaryl and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered heterocycloalkyl, and 5 to 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo; provided that $-Q_4$-T_4 is not H; and

each of R_8 and R_{11}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino.

2. A compound of Formula (V) or a pharmaceutically acceptable salt or ester thereof:



(V),

wherein,

V^1 is N or $CR^{7'}$,

V^2 is N or $CR^{2'}$, provided when V^1 is N, V^2 is N,

X' and Z' are selected independently from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, unsubstituted or substituted (C_3-C_8)cycloalkyl, unsubstituted or substituted (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, (C_6-C_{10})bicycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted heterocycloalkyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, halo, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$, $-SR^{a'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)R^{b'}$, $-NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)OR^{a'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, and $-OC(O)NR^{a'}R^{b'}$;

Y' is H or halo;

$R^{1'}$ is (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, unsubstituted or substituted (C_3-C_8)cycloalkyl, unsubstituted or substituted (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted (C_6-C_{10})bicycloalkyl, unsubstituted or substituted heterocycloalkyl or -(C_2-C_8)alkenyl,

unsubstituted or substituted heterocycloalkyl-(C_1-C_8)alkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-(C_1-C_8)alkyl or -(C_2-C_8)alkenyl, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$;

$R^{2'}$ is hydrogen, (C_1-C_8)alkyl, trifluoromethyl, alkoxy, or halo, in which said (C_1-C_8)alkyl is optionally substituted with one to two groups selected from amino and (C_1-C_3)alkylamino;

$R^{7'}$ is hydrogen, (C_1-C_3)alkyl, or alkoxy;

$R^{3'}$ is hydrogen, (C_1-C_8)alkyl, cyano, trifluoromethyl, $-NR^{a'}R^{b'}$, or halo;

$R^{6'}$ is selected from the group consisting of hydrogen, halo, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, unsubstituted or substituted (C_3-C_8)cycloalkyl, unsubstituted or substituted (C_3-C_8)cycloalkyl-(C_1-C_8)alkyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl, unsubstituted or substituted (C_5-C_8)cycloalkenyl-(C_1-C_8)alkyl, (C_6-C_{10})bicycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted heterocycloalkyl-(C_1-C_8)alkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-(C_1-C_8)alkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-(C_1-C_8)alkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a'}R^{b'}$, $-CONR^{a'}NR^{a'}R^{b'}$, $-SR^{a'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)R^{b'}$, $-NR^{a'}NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}NR^{a'}C(O)OR^{a'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, $-OC(O)NR^{a'}R^{b'}$;

wherein any (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, heterocycloalkyl, aryl, or heteroaryl group is optionally substituted by 1, 2 or 3 groups independently selected from the group consisting of $-O(C_1$-$C_6)alkyl(R^{c'})_{1-2}$, $-S(C_1$-$C_6)alkyl(R^{c'})_{1-2}$, $-(C_1$-$C_6)alkyl(R^{c'})_{1-2}$, -(C_1-C_8)alkyl-heterocycloalkyl, (C_3-C_8)cycloalkyl-heterocycloalkyl, halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_1-C_6)haloalkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$,- $CONR^{a'}R^{b'}$, $-SR^{a'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, $OC(O)NR^{a'}R^{b'}$, heterocycloalkyl, aryl, heteroaryl, aryl(C_1-C_4)alkyl, and heteroaryl(C_1-C_4)alkyl;

wherein any aryl or heteroaryl moiety of said aryl, heteroaryl, aryl(C_1-C_4)alkyl, or heteroaryl(C_1-C_4)alkyl is optionally substituted by 1, 2 or 3 groups independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_1-C_6)haloalkyl, cyano, $-COR^{a'}$, $-CO_2R^{a'}$, $-CONR^{a}R^{b'}$,$-SR^{a'}$, $-SOR^{a'}$, $-SO_2R^{a'}$,

$-SO_2NR^{a'}R^{b'}$, nitro, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$,$-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}SO_2R^{b'}$, $-NR^{a'}SO_2NR^{a'}R^{b'}$, $-OR^{a'}$, $-OC(O)R^{a'}$, and $-OC(O)NR^{a'}R^{b'}$;

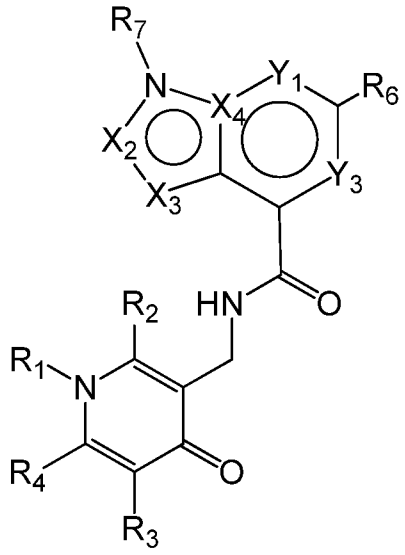
$R^{a'}$ and $R^{b'}$ are each independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (C_6-C_{10})bicycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein said (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl,heterocycloalkyl ,aryl or heteroaryl group is optionally substituted by 1, 2 or 3 groups independently selected from halo, hydroxyl, (C_1-C_4)alkoxy, amino, (C_1-C_4)alkylamino, $((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl)amino, $-CO_2H$, $-CO_2(C_1-C_4)$alkyl, $-CONH_2$,$-CONH(C_1-C_4)$alkyl, $-CON((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl), $-SO_2(C_1-C_4)$alkyl, $-SO_2NH_2$,$-SO_2NH(C_1-C_4)$alkyl, and $SO_2N((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl);

or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 5-8 membered saturated or unsaturated ring, optionally containing an additional heteroatom selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted by 1, 2 or 3 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, amino, (C_1-C_4)alkylamino, $((C_1-C_4)$alkyl$)((C_1-C_4)$alkyl)amino, hydroxyl, oxo, (C_1-C_4)alkoxy, and (C_1-C_4)alkoxy(C_1-C_4)alkyl, wherein said ring is optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring;

or $R^{a'}$ and $R^{b'}$ taken together with the nitrogen to which they are attached represent a 6- to 10-membered bridged bicyclic ring system optionally fused to a (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring; and

each $R^{c'}$ is independently (C_1-C_4)alkylamino, $-NR^{a'}SO2R^{b'}$, $-SOR^{a'}$, $-SO_2R^{a'}$, $-NR^{a'}C(O)OR^{a'}$, $-NR^{a'}R^{b'}$, or $-CO_2R^{a'}$.

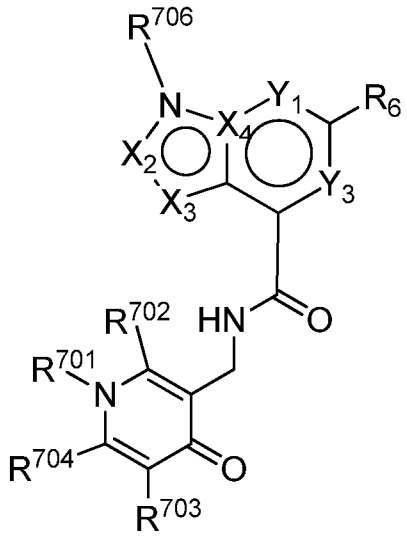
3. The compound of claim 1, wherein the compound is of Formula (VI):



(VI),

wherein R_7 is $-Q_4$-T_4, wherein Q_4 is a bond or methyl linker, T_4 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl or optionally substituted 4- to 14-membered heterocycloalkyl.

4. The compound of claim 1, wherein the compound is of Formula (VIc):



(VIc),

wherein

R^{701} is H or C_{1-4} alkyl;

R^{702} is C_{1-6} alkoxyl or C_6-C_{10} aryloxy, each optionally substituted with one or more halo;

R^{703} is H, halo, or C_{1-4} alkyl;

R^{704} is halo, or C_{1-4} alkyl or C_{1-6} alkoxyl, each optionally substituted with one or more halo;

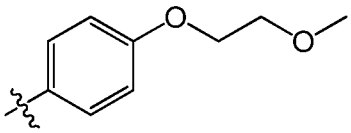
or R^{701} and R^{702}, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R^{701} and R^{704}, together with the N and C atoms to which they are attached, form a 5- or 6-membered heteroaryl having 0 to 2 additional heteroatoms or a 5 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms; or R^{703} and R^{704}, together with the C atoms to which they are attached, form C_5-C_8 cycloalkyl, C_{6-10} aryl, or a 5- or 6-membered heteroaryl having 1 to 3 heteroatoms, or a 5 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms; in which each of the ring structures formed by R^{701} and R^{702}, by R^{701} and R^{704}, or by R^{703} and R^{704}, independently is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, C_1-C_6 alkyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl; and

R^{706} is C_{1-6} alkyl, C_{3-8} cycloalkyl, tetrahydropyranyl, piperidine substituted by 1, 2, or 3 C_{1-4} alkyl groups, or cyclohexyl substituted by $N(C_{1-4}$ alkyl$)_2$ wherein one or both of the C_{1-4} alkyl is optionally substituted with C_{1-6} alkoxyl.

5. The compound of claim 4, wherein R^{706} is sec-butyl, cyclopentyl, or iso-propyl.

6. The compound of claim 1 or 3, wherein R_7 is is sec-butyl, cyclopentyl, or iso-propyl.

7. The compound of any of claims 1 and 3-6, wherein R_6 is



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8. The compound of any of claims 1 and 3-6, wherein the compound is Compound 1 or 2, or a pharmaceutically acceptable salt or ester thereof.

9. A pharmaceutical composition comprising a compound of any of claims 1-8 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

10. A method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of claims 1-8 or a pharmaceutically acceptable salt thereof.

11. The method of claim 10, wherein the cancer is lymphoma, leukemia or melanoma.

12. The method of claim 10, wherein the cancer is diffuse large B-cell lymphoma (DLBCL), non-Hodgkin's lymphoma (NHL), follicular lymphoma or diffuse large B-cell lymphoma, chronic myelogenous leukemia (CML), acute myeloid leukemia, acute lymphocytic leukemia or mixed lineage leukemia, or myelodysplastic syndromes (MDS).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/077086

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04 (2006.01) C07D 401/14 (2006.01) C07D 401/12 (2006.01) A61K 31/395 (2006.01) A61K 31/444 (2006.01) A61K 31/4545 (2006.01) A61K 31/495 (2006.01) A61K 31/5377 (2006.01) A61P 35/00 (2006.01)

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)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Applicant and Inventor name search.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN Registry and CAPlus: Substructure search based on compounds of Formula (IV).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] 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
"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
3 March 2014	03 March 2014
Name and mailing address of the ISA/AU	**Authorised officer**
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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	**PCT/US2013/077086**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/118812 A2 (EPIZYME, INC.) 07 September 2012 Paragraphs [010], [048] & [049]	1 - 7, 9 - 12
A	WO 2012/075080 A1 (GLAXOSMITHKLINE LLC) 07 June 2012 Page 2 line 20 to page 4 line 33	1 - 7, 9 - 12
A	WO 2012/005805 A1 (GLAXOSMITHKLINE LLC) 12 January 2012 Page 2 line 20 to page 4 line 30	1 - 7, 9 - 12
A	WO 2011/140325 A1 (GLAXOSMITHKLINE LLC) 10 November 2011 Page 3 line 1 to page 5 line 15	1 - 7, 9 - 12
A	WO 2011/140324 A1 (GLAXOSMITHKLINE LLC) 10 November 2011 Page 2 line 20 to page 5 line 2	1 - 7, 9 - 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/077086

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:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☒ Claims Nos.: **8**
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:
See Supplemental Box

3. ☐ Claims Nos:
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:

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.:

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/US2013/077086

Supplemental Box

Continuation of **Box II**
Claim 8 does not comply with Rule 6.2(a) because it relies on references to the description.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2013/077086**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2012/118812 A2	07 Sep 2012	EP 2681216 A2	08 Jan 2014
		US 2013317026 A1	28 Nov 2013
		US 8598167 B1	03 Dec 2013
		US 2014057891 A1	27 Feb 2014
		WO 2012118812 A2	07 Sep 2012
WO 2012/075080 A1	07 Jun 2012	JP 2013544840 A	19 Dec 2013
		US 2013245016 A1	19 Sep 2013
		WO 2012075080 A1	07 Jun 2012
WO 2012/005805 A1	12 Jan 2012	JP 2013527173 A	27 Jun 2013
		US 2013059849 A1	07 Mar 2013
		US 8637509 B2	28 Jan 2014
		WO 2012005805 A1	12 Jan 2012
WO 2011/140325 A1	10 Nov 2011	JP 2013528591 A	11 Jul 2013
		US 2013053383 A1	28 Feb 2013
		WO 2011140325 A1	10 Nov 2011
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		CN 102970869 A	13 Mar 2013
		CR 20120565 A	20 Feb 2013
		DO P2012000282 A	28 Feb 2013
		EA 201291194 A1	30 Apr 2013
		EP 2566327 A1	13 Mar 2013
		JP 2013525498 A	20 Jun 2013
		KR 20130062290 A	12 Jun 2013
		MA 34284 B1	01 Jun 2013
		MX 2012012966 A	22 Jan 2013
		PE 06472013 A1	26 Jun 2013
		SG 185431 A1	28 Dec 2012
		US 2013053397 A1	28 Feb 2013
		US 8536179 B2	17 Sep 2013
		US 2013345200 A1	26 Dec 2013
		WO 2011140324 A1	10 Nov 2011

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.