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(54) **Title:** AMINE-SUBSTITUTED HETEROCYCLIC COMPOUNDS AS EHMT2 INHIBITORS AND METHODS OF USE THEREOF

(57) **Abstract:** The present disclosure relates to amine-substituted heterocyclic compounds. The present disclosure also relates to pharmaceutical compositions containing these compounds and methods of treating a disorder (e.g., cancer) via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2, by administering an amine-substituted heterocyclic heterocyclic compound disclosed herein or a pharmaceutical composition thereof to subjects in need thereof. The present disclosure also relates to the use of such compounds for research or other non-therapeutic purposes.

AMINE-SUBSTITUTED HETEROCYCLIC COMPOUNDS AS EHMT2 INHIBITORS AND METHODS OF USE THEREOF

RELATED APPLICATION

[001] This application claims priority to U.S. Application Nos. 62/517,840, filed June 9, 2017, and 62/436,139, filed December 19, 2016, the entire contents of each of which are incorporated herein by reference.

BACKGROUND

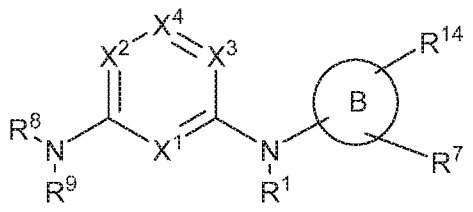
[002] Methylation of protein lysine residues is an important signaling mechanism in eukaryotic cells, and the methylation state of histone lysines encodes signals that are recognized by a multitude of proteins and protein complexes in the context of epigenetic gene regulation.

[003] Histone methylation is catalyzed by histone methyltransferases (HMTs), and HMTs have been implicated in various human diseases. HMTs can play a role in either activating or repressing gene expression, and certain HMTs (*e.g.*, euchromatic histone-lysine N-methyltransferase 2 or EHMT2, also called G9a) may methylate many nonhistone proteins, such as tumor suppressor proteins (*see, e.g.*, Liu *et al., Journal of Medicinal Chemistry* 56:8931-8942, 2013 and Krivega *et al., Blood* 126(5):665-672, 2015).

[004] Two related HMTs, EHMT1 and EHMT2, are overexpressed or play a role in diseases and disorders such as sickle cell anemia (*see, e.g.*, Renneville *et al., Blood* 126(16): 1930–1939, 2015) and proliferative disorders (*e.g.*, cancers), and other blood disorders.

SUMMARY

[005] In one aspect, the present disclosure features an amine-substituted heterocyclic compound of any of Formulae (I0)-(IV0) below:



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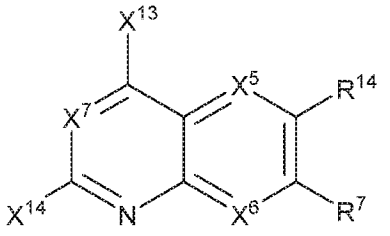
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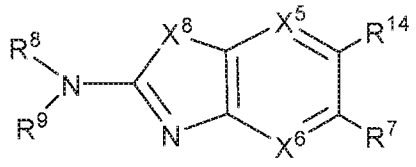
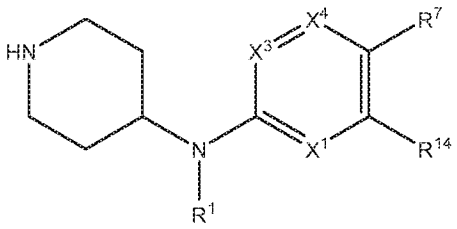

(III0), or


(IV0),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein

X^1 is N or CR^2;

X^2 is N or CR^3;

X^3 is N or CR^4;

X^4 is N or CR^5;

X^5 is N or CH;

X^6 is N or CR^{15};

X^7 is N or CH;

X^8 is NR^{13} or $CR^{11}R^{12}$;

one of X^{13} and X^{14} independently is NR^8R^9, and the other is R^{10};

B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl optionally substituted with one or more R^{15};

R^1 is H or C_1-C_4 alkyl;

each of R^2, R^3, R^4, and R^5, independently is selected from the group consisting of H, halo, cyano, C_1-C_6 alkoxyl, C_6-C_{10} aryl, OH, NR^aR^b, $C(O)NR^aR^b$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^b$, $NR^aC(O)OR^b$, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein the C_6-C_{10} aryl, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, C_1-C_6 alkoxyl,

C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, are each optionally substituted with one or more of halo, OR^a, or NR^aR^b, in which each of R^a and R^b independently is H or C_1-C_6 alkyl;

R^6 is $-Q^1$-T^1, in which Q^1 is a bond, or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, oxo, or C_1-C_6 alkoxyl, and T^1 is H, halo, cyano, or R^{S1}, in which R^{S1} is C_3-C_8 cycloalkyl, phenyl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- or 6-membered heteroaryl and R^{S1} is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, $-C(O)R^c$, $-C(O)OR^c$, $-SO_2R^c$, $-SO_2N(R^c)_2$, $-NR^cC(O)R^d$, $-C(O)NR^cR^d$, $-NR^cC(O)OR^d$, $-OC(O)NR^cR^d$, NR^cR^d, or C_1-C_6 alkoxyl, in which each of R^c and R^d independently is H or C_1-C_6 alkyl;

R^7 is $-Q^2$-T^2, in which Q^2 is a bond, $C(O)NR^e$, or $NR^eC(O)$, R^e being H or C_1-C_6 alkyl and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, and wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $-Q^3$-T^3, wherein each Q^3 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^3 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^f, $C(O)R^f$, $C(O)OR^f$, $OC(O)R^f$, $S(O)_2R^f$, NR^fR^g, $OC(O)NR^fR^g$, $NR^fC(O)OR^g$, $C(O)NR^fR^g$, and $NR^fC(O)R^g$, each of R^f and R^g independently being H, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl, in which the C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy; or $-Q^3$-T^3 is oxo;

R^8 is H or C_1-C_6 alkyl;

R^9 is $-Q^4$-T^4, in which Q^4 is a bond or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxyl, and T^4 is H, halo, OR^h, NR^hR^i, $NR^hC(O)R^i$, $C(O)NR^hR^i$, $C(O)R^h$, $C(O)OR^h$, $NR^hC(O)OR^i$, $OC(O)NR^hR^i$, $S(O)_2R^h$, $S(O)_2NR^hR^i$, or R^{S2}, in which each of R^h and R^i independently is H or C_1-C_6 alkyl, and R^{S2} is C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- to 10-membered heteroaryl, and R^{S2} is optionally substituted with one or more $-Q^5$-T^5, wherein each Q^5 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of

halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^5 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^j, $C(O)R^j$, $C(O)OR^j$, $OC(O)R^j$, $S(O)_2R^j$, NR^jR^k, $OC(O)NR^jR^k$, $NR^jC(O)OR^k$, $C(O)NR^jR^k$, and $NR^jC(O)R^k$, each of R^j and R^k independently being H or C_1-C_6 alkyl; or $-Q^5$-T^5 is oxo;

R^{10} is halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein each of the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and 4- to 12-membered heterocycloalkyl is optionally substituted with one or more halo, cyano, hydroxyl, oxo, amino, mono- or di- alkylamino, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, $C(O)NR^jR^k$, or $NR^jC(O)R^k$;

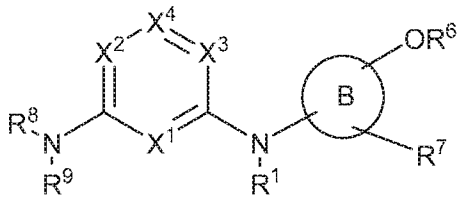
R^{11} and R^{12} together with the carbon atom to which they are attached form a C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein the C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, amino, mono- or di- alkylamino, or C_1-C_6 alkoxyl;

R^{13} is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} cycloalkyl, or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S;

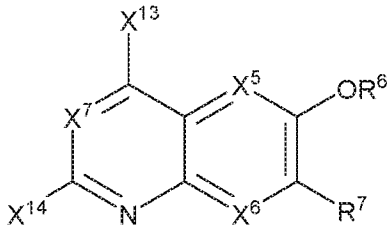
R^{14} is H, halo, cyano, $P(O)R^lR^m$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, or $-OR^6$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is optionally substituted with one or more of halo or OR^6, and each of R^l and R^m independently is C_1-C_6 alkyl; and

R^{15} is H, halo, cyano, or $-OR^6$.

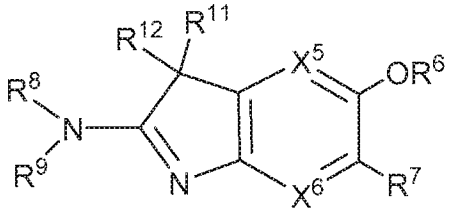
[006] Subsets of the compounds of Formulae (I0)-(IV0) include those of Formulae (I)-(III):



(I),



(II), or



(III),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein

X^1 is N or CR^2;

X^2 is N or CR^3;

X^3 is N or CR^4;

X^4 is N or CR^5;

X^5 is N or CH;

X^6 is N or CR^{15};

X^7 is N or CH;

one of X^{13} and X^{14} independently is NR^8R^9, and the other is R^{10};

B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl optionally substituted with one or more R^{15};

R^1 is H or C_1-C_4 alkyl;

each of R^2, R^3, R^4, and R^5, independently is selected from the group consisting of H, halo, cyano, C_1-C_6 alkoxyl, C_6-C_{10} aryl, OH, NR^aR^b, $C(O)NR^aR^b$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^b$, $NR^aC(O)OR^b$, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein the C_6-C_{10} aryl, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, C_1-C_6 alkoxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, are each optionally substituted with one or more of halo, OR^a, or NR^aR^b, in which each of R^a and R^b independently is H or C_1-C_6 alkyl;

R^6 is $-Q^1$-T^1, in which Q^1 is a bond, or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, oxo, or C_1-C_6 alkoxyl, and T^1 is H, halo, cyano, or R^{S1}, in which R^{S1} is C_3-C_8 cycloalkyl, phenyl, 4- to 12-

membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- or 6-membered heteroaryl and R^{S1} is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, -$C(O)R^c$, -$C(O)OR^c$, -SO_2R^c, -$SO_2N(R^c)_2$, -$NR^cC(O)R^d$, -$C(O)NR^cR^d$, -$NR^cC(O)OR^d$, -$OC(O)NR^cR^d$, NR^cR^d, or C_1-C_6 alkoxyl, in which each of R^c and R^d independently is H or C_1-C_6 alkyl;

R^7 is $–Q^2$-T^2, in which Q^2 is a bond, $C(O)NR^e$, or $NR^eC(O)$, R^e being H or C_1-C_6 alkyl and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, and wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $–Q^3$-T^3, wherein each Q^3 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^3 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^f, $C(O)R^f$, $C(O)OR^f$, $OC(O)R^f$, $S(O)_2R^f$, NR^fR^g, $OC(O)NR^fR^g$, $NR^fC(O)OR^g$, $C(O)NR^fR^g$, and $NR^fC(O)R^g$, each of R^f and R^g independently being H, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl, in which the C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy; or $–Q^3$-T^3 is oxo;

R^8 is H or C_1-C_6 alkyl;

R^9 is $–Q^4$-T^4, in which Q^4 is a bond or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxyl, and T^4 is H, halo, OR^h, NR^hR^i, $NR^hC(O)R^i$, $C(O)NR^hR^i$, $C(O)R^h$, $C(O)OR^h$, $NR^hC(O)OR^i$, $OC(O)NR^hR^i$, $S(O)_2R^h$, $S(O)_2NR^hR^i$, or R^{S2}, in which each of R^h and R^i independently is H or C_1-C_6 alkyl, and R^{S2} is C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- to 10-membered heteroaryl, and R^{S2} is optionally substituted with one or more $–Q^5$-T^5, wherein each Q^5 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^5 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^j, $C(O)R^j$, $C(O)OR^j$, $OC(O)R^j$, $S(O)_2R^j$, NR^jR^k, $OC(O)NR^jR^k$,

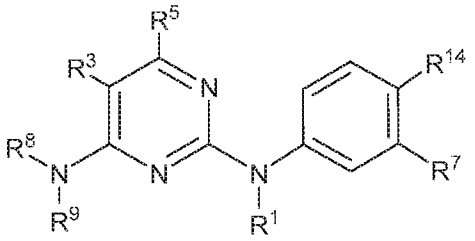
$NR^jC(O)OR^k$, $C(O)NR^jR^k$, and $NR^jC(O)R^k$, each of R^j and R^k independently being H or C_1-C_6 alkyl; or $-Q^5$-T^5 is oxo;

R^{10} is halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein each of the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and 4- to 12-membered heterocycloalkyl is optionally substituted with one or more halo, cyano, hydroxyl, oxo, amino, mono- or di- alkylamino, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, $C(O)NR^jR^k$, or $NR^jC(O)R^k$;

R^{11} and R^{12} together with the carbon atom to which they are attached form a C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein the C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, amino, mono- or di- alkylamino, or C_1-C_6 alkoxyl; and

R^{15} is H, halo, cyano, or $-OR^6$.

[007] Subsets of the compounds of Formula (I0) include those of Formulae (I0a)-(I0l):



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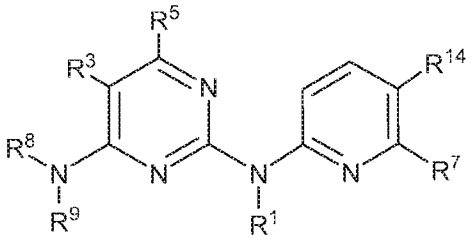

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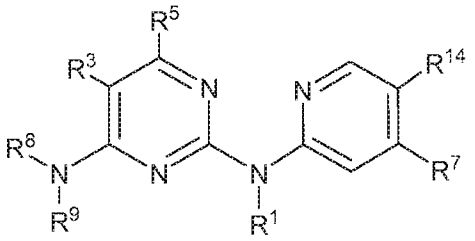
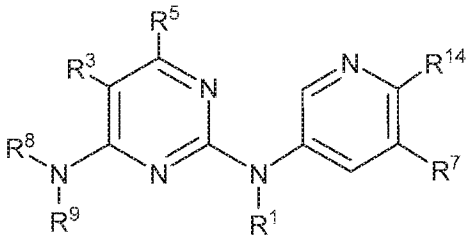
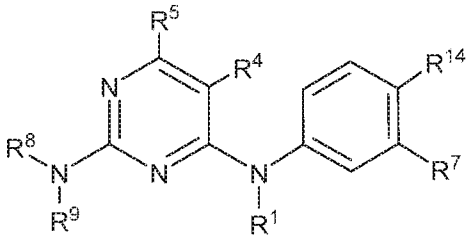
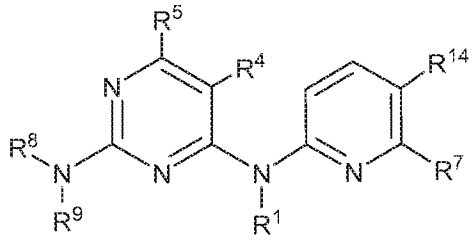


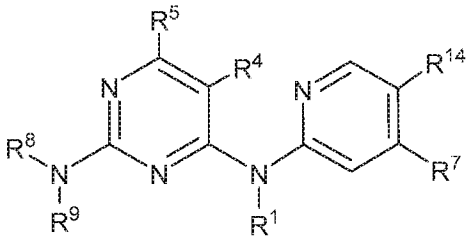
(I0c),

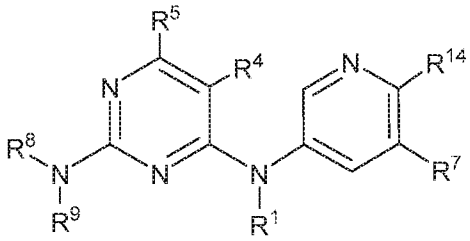


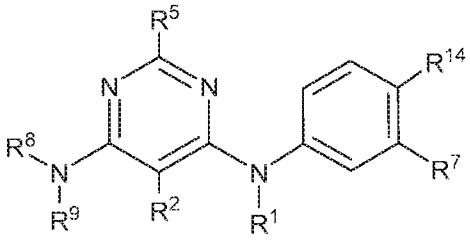
(I0d),

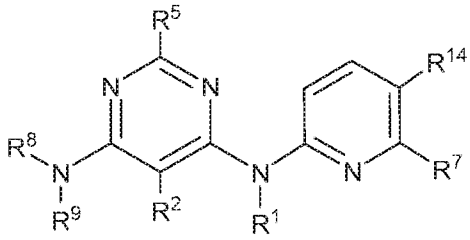

(I0e),

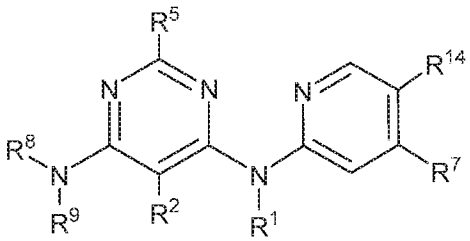

(I0f),

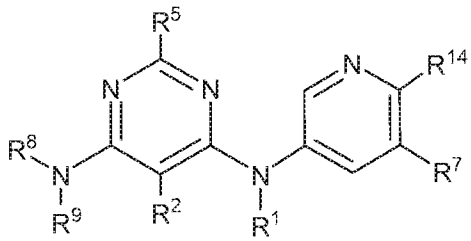

(I0g),


(I0h),


(I0i),

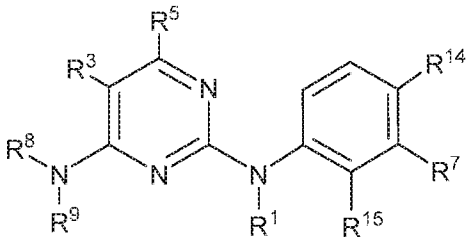

(I0j),

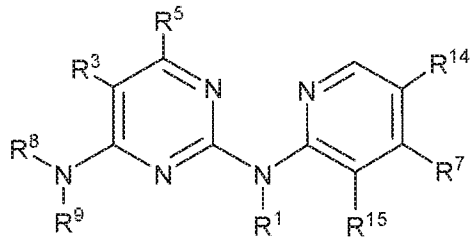

(I0k),

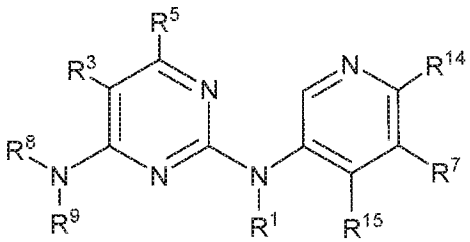

(I0l),

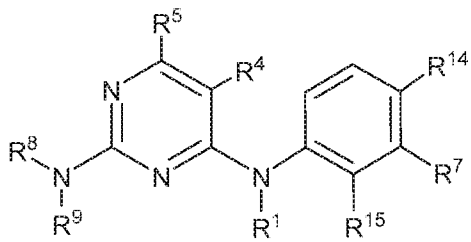
and tautomers thereof, and pharmaceutically acceptable salts of the compounds and the tautomers.

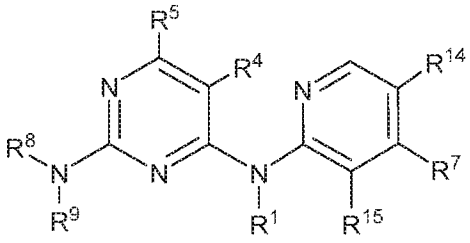
[008] Subsets of the compounds of Formula (I0) include those of Formulae (I0a')-(I0i'):

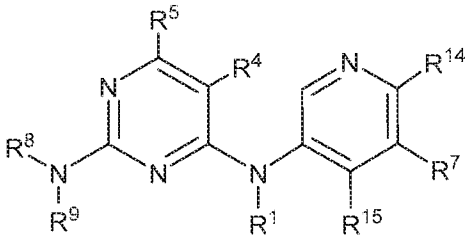

(I0a'),

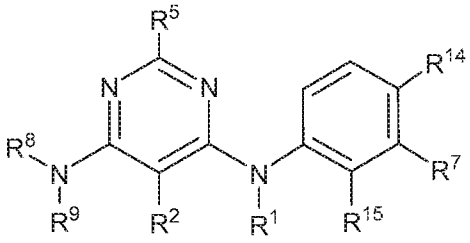

(I0b'),

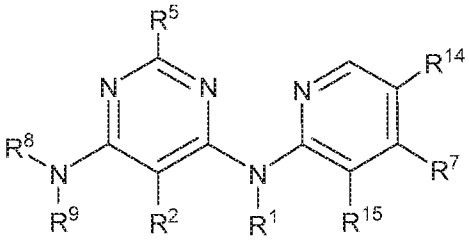

(I0c'),

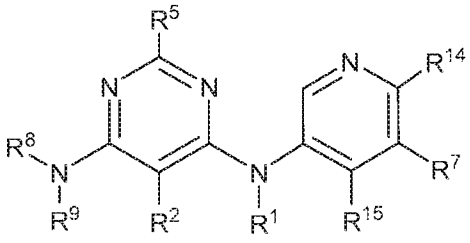

(I0d'),


(I0e'),


(I0f'),

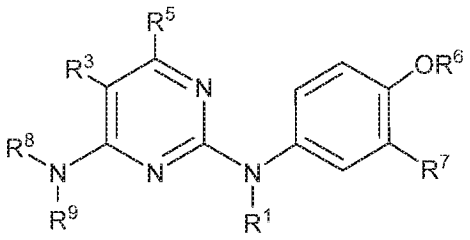

(I0g'),

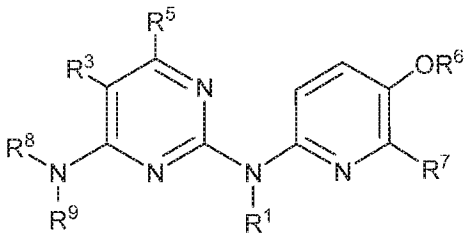

(I0h'),

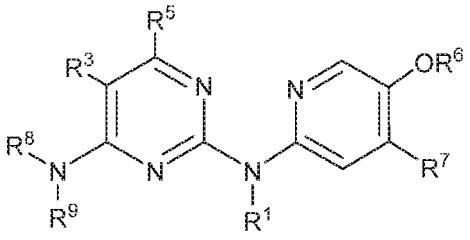

(I0i'),

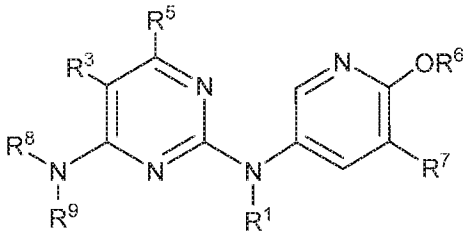
and tautomers thereof, and pharmaceutically acceptable salts of the compounds and the tautomers.

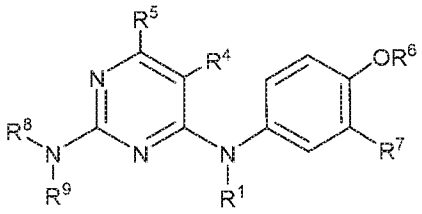
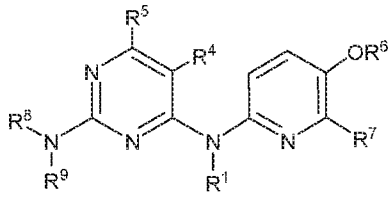
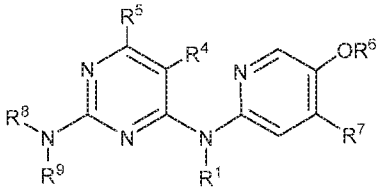
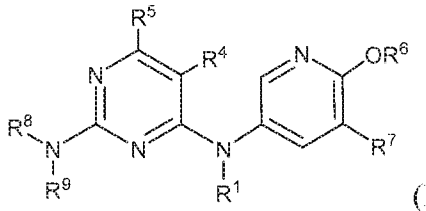
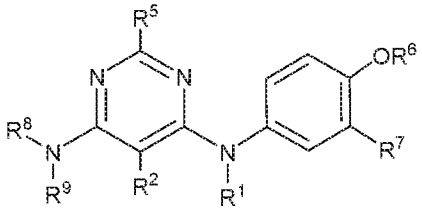
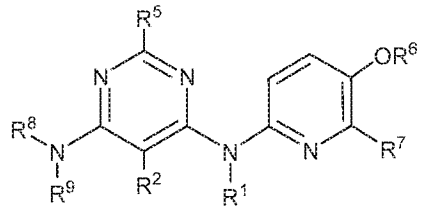
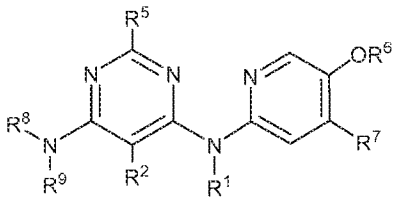
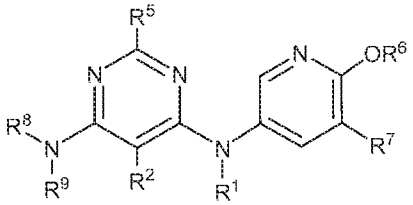
[009] Subsets of the compounds of Formula (I) include those of Formulae (Ia)-(Il):


(Ia),


(Ib),

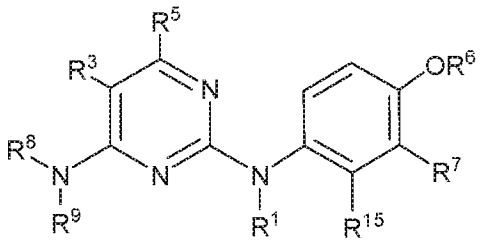
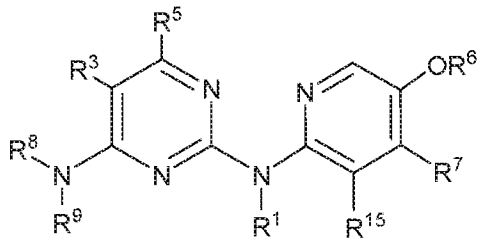
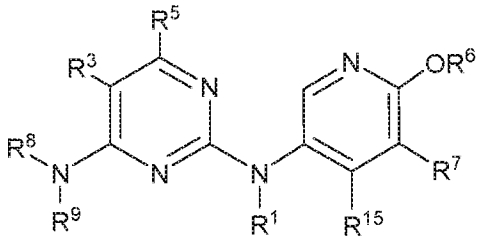
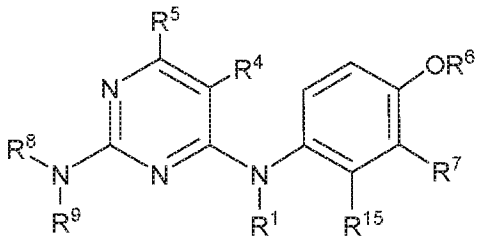

(Ic),

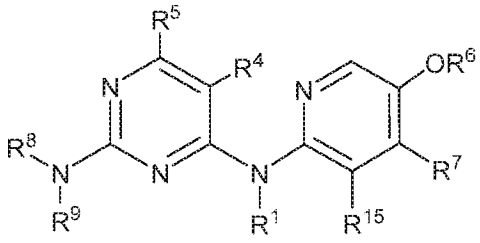
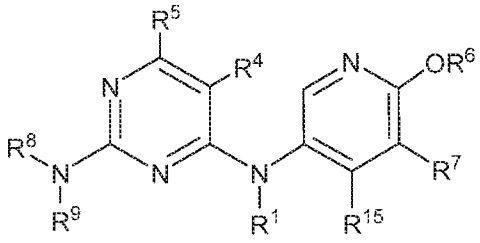
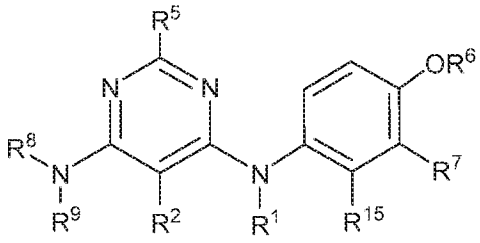
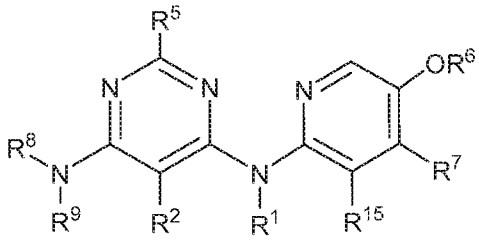
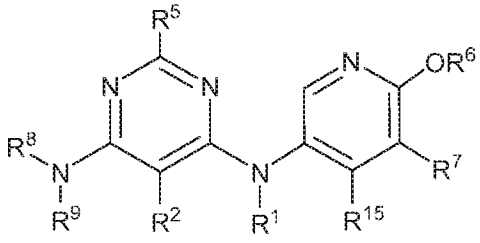

(Id),


(Ie),

(If),

(Ig),

(Ih),

(Ii),

(Ij),

(Ik),

(Il),

and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

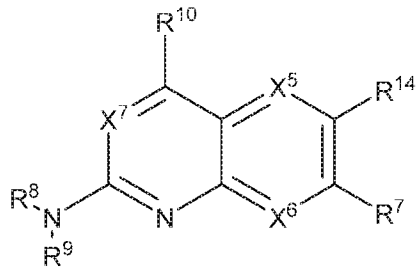
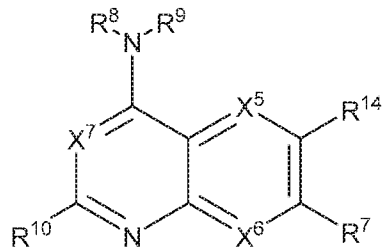
[010] Subsets of the compounds of Formula (I) include those of Formulae (Ia')-(Ii'):


(Ia'),

(Ib'),

(Ic'),

(Id'),


(Ie'),

(If'),

(Ig'),

(Ih'),

(Ii'),

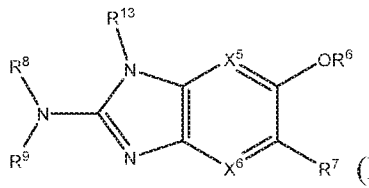
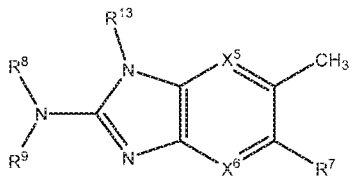
and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[011] Subsets of the compounds of Formula (II0) include those of Formulae (II0a) and (II0b):


(II0a),

(II0b),

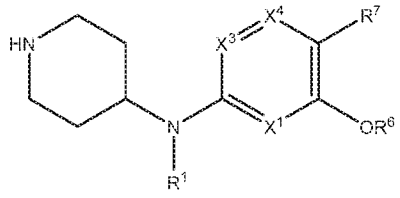
and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[012] Subsets of the compounds of Formula (III0) include those of Formulae (III0a) and (III0b):

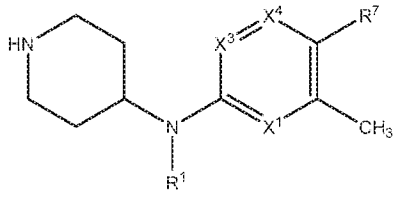

(III0a),

(III0b),

and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[013] Subsets of the compounds of Formula (IV0) include those of Formulae (IV0a) and (IV0b):



(IV0a),



(IV0b),

and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[014] Subsets of the compounds of Formula (II) include those, wherein (i) each of X^5, X^6 and X^7 is CH; (ii) at least one of X^5, X^6 and X^7 is N; or (iii) at most one of X^5, X^6 and X^7 is N, and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[015] Subsets of the compounds of Formula (III) include those, wherein (i) each of X^5 and X^6 is CH; (ii) each of X^5 and X^6 is N; or (iii) one of X^5 and X^6 is CH and the other is CH, and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[016] In some embodiments, one or more of the compounds disclosed herein are selective inhibitors of EHMT2. In some embodiments, one or more of the compounds disclosed herein inhibit EHMT2 with an enzyme inhibition IC_{50} value of about 1 μM or less, about 500 nM or less, about 200 nM or less, about 100 nM or less, or about 50 nM or less.

[017] In some embodiments, one or more of the compounds disclosed herein inhibit a kinase with an enzyme inhibition IC_{50} value of about 100 nM or greater, 1 μM or greater, 10 μM or greater, 100 μM or greater, or 1000 μM or greater.

[018] In some embodiments, one or more of the compounds disclosed herein inhibit a kinase with an enzyme inhibition IC_{50} value of about 1 mM or greater.

[019] In some embodiments, one or more of the compounds disclosed herein inhibit a kinase with an enzyme inhibition IC_{50} value of 1 μM or greater, 2 μM or greater, 5 μM or greater, or 10 μM or greater, wherein the kinase is one or more of the following: Abl, AurA, CHK1, MAP4K, IRAK4, JAK3, EphA2, FGFR3, KDR, Lck, MARK1, MNK2, PKCb2, SIK, and Src.

[020] Also provided herein are pharmaceutical compositions comprising one or more pharmaceutically acceptable carriers and one or more compounds of any of the Formulae disclosed herein, such as Formulae (I0)-(IV0) and Formulae (I)-(III) described herein.

[021] Another aspect of this disclosure is a method of preventing or treating an EHMT-mediated disorder. The method includes administering to a subject in need thereof a therapeutically effective amount of a compound of any of the Formulae disclosed herein, such as Formulae (I0)-(IV0) and Formulae (I)-(III), or a tautomer thereof, or a pharmaceutically acceptable salt of the

compound or the tautomer. The EHMT-mediated disorder is a disease, disorder, or condition that is mediated at least in part by the activity of EHMT1 or EHMT2 or both. In one embodiment, the EHMT-mediated disorder is a blood disease or disorder. In certain embodiments, the EHMT-mediated disorder is selected from proliferative disorders (*e.g.*, cancers such as leukemia, hepatocellular carcinoma, prostate carcinoma, and lung cancer), addiction (*e.g.*, cocaine addiction), and mental retardation.

[022] Unless otherwise stated, any description of a method of treatment includes use of the compounds to provide such treatment or prophylaxis as is described herein, as well as use 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 EHMT-mediated disorders. For example, the disclosure also provides methods of identifying an inhibitor of EHMT1 or EHMT2 or both.

[023] For example, the EHMT-mediated disease or disorder comprises a disorder that is associated with gene silencing by EHMT1 or EHMT2, e.g., blood diseases or disorders associated with gene silencing by EHMT2.

[024] For example, the method comprises the step of administering to a subject having a disease or disorder associated with gene silencing by EHMT1 or EHMT2 a therapeutically effective amount of one or more compounds of the Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EHMT1 or EHMT2, thereby treating the disease or disorder.

[025] For example, the blood disease or disorder is selected from the group consisting of sickle cell anemia and beta-thalassemia.

[026] For example, the blood disease or disorder is hematological cancer.

[027] For example, the hematological cancer is acute myeloid leukemia (AML) or chronic lymphocytic leukemia (CLL).

[028] For example, the method further comprises the steps of performing an assay to detect the degree of histone methylation by EHMT1 or EHMT2 in a sample comprising blood cells from a subject in need thereof.

[029] In one embodiment, performing the assay to detect methylation of H3-K9 in the histone substrate comprises measuring incorporation of labeled methyl groups.

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

[031] In one embodiment, performing the assay to detect methylation of H3-K9 in the histone substrate comprises contacting the histone substrate with an antibody that binds specifically to dimethylated H3-K9.

[032] Still another aspect of the disclosure is a method of inhibiting conversion of H3-K9 to dimethylated H3-K9. The method comprises the step of contacting a mutant EHMT, the wild-type EHMT, or both, with a histone substrate comprising H3-K9 and an effective amount of a compound of the present disclosure, wherein the compound inhibits histone methyltransferase activity of EHMT, thereby inhibiting conversion of H3-K9 to dimethylated H3-K9.

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

[034] In some aspects, the present disclosure provides a compound disclosed herein for use in preventing or treating a blood disorder via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2.

[035] In some aspects, the present disclosure provides a compound disclosed herein for use in preventing or treating a cancer via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2.

[036] In some aspects, the present disclosure provides use of a compound disclosed herein in manufacture of a medicament for preventing or treating a blood disorder via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2.

[037] In some aspects, the present disclosure provides use of a compound disclosed herein in manufacture of a medicament for preventing or treating a cancer via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2.

[038] 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 disclosure 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 disclosure, 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.

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

DETAILED DESCRIPTION

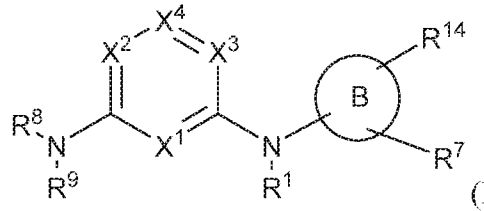
[040] The present disclosure provides novel amine-substituted heterocyclic compounds, synthetic methods for making the compounds, pharmaceutical compositions containing them and various uses of the compounds.

[041] In one aspect, the compounds disclosed herein may be used to treat a blood disorder, e.g., sickle-cell anemia (i.e., sickle-cell disease). Non-limiting examples of sickle-cell anemia forms that may be treated using the contemplated compounds include hemoglobin SS disease, hemoglobin SC disease, hemoglobin $S\beta^0$ thalassemia disease, hemoglobin $S\beta^+$ thalassemia disease, hemoglobin SD disease, and hemoglobin SE disease.

[042] Without wishing to be bound by any theory, it is believed that sickle-cell anemia describes a group of inherited red blood cell disorders in which at least some of the red blood cells of a subject having sickle-cell anemia contain hemoglobin S ("HbS"). Hemoglobin S is a mutated, abnormal form of adult hemoglobin. Without wishing to be bound by any theory, it is believed that the contemplated compounds may treat sickle cell anemia by inducing fetal hemoglobin ("HbF") expression. *See, e.g.*, Renneville *et al.*, *Blood* 126(16): 1930–1939, 2015, the content of which is incorporated herein by reference in its entirety.

[043] In some embodiments, one or more complications of sickle-cell anemia may be treated or prevented using the contemplated compounds disclosed herein. Non-limiting examples of complications that may be treated or prevented using the contemplated compounds include anemia (e.g., severe anemia), hand-foot syndrome, splenic sequestration, delayed developmental growth, eye disorders (e.g., vision loss caused by, e.g., blockages in blood vessels supplying the eyes), skin ulcers (e.g., leg ulcers), heart disease, chest syndrome (e.g., acute chest syndrome), priapism, and pain.

[044] The present disclosure provides compounds of any of Formulae (I0)-(IV0) below: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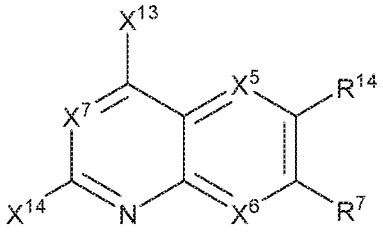
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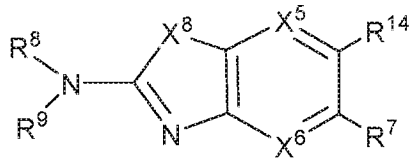
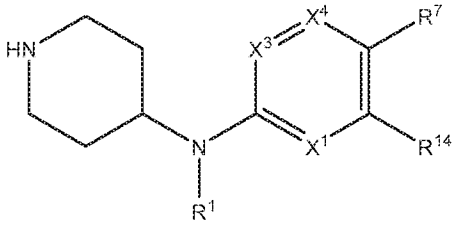

(III0), or


(IV0),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein

X^1 is N or CR^2;

X^2 is N or CR^3;

X^3 is N or CR^4;

X^4 is N or CR^5;

X^5 is N or CH;

X^6 is N or CR^{15};

X^7 is N or CH;

X^8 is NR^{13} or $CR^{11}R^{12}$;

one of X^{13} and X^{14} independently is NR^8R^9, and the other is R^{10};

B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl optionally substituted with one or more R^{15};

R^1 is H or C_1-C_4 alkyl;

each of R^2, R^3, R^4, and R^5, independently is selected from the group consisting of H, halo, cyano, C_1-C_6 alkoxyl, C_6-C_{10} aryl, OH, NR^aR^b, $C(O)NR^aR^b$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^b$, $NR^aC(O)OR^b$, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein the C_6-C_{10} aryl, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, C_1-C_6 alkoxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, are each optionally substituted with one or more of halo, OR^a, or NR^aR^b, in which each of R^a and R^b independently is H or C_1-C_6 alkyl;

R^6 is $-Q^1$-T^1, in which Q^1 is a bond, or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, oxo, or C_1-C_6 alkoxyl, and T^1 is H, halo, cyano, or R^{S1}, in which R^{S1} is C_3-C_8 cycloalkyl, phenyl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- or 6-membered heteroaryl and R^{S1} is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, $-C(O)R^c$, $-C(O)OR^c$, $-SO_2R^c$, $-SO_2N(R^c)_2$, $-NR^cC(O)R^d$, $-C(O)NR^cR^d$, $-NR^cC(O)OR^d$, $-OC(O)NR^cR^d$, NR^cR^d, or C_1-C_6 alkoxyl, in which each of R^c and R^d independently is H or C_1-C_6 alkyl;

R^7 is $-Q^2$-T^2, in which Q^2 is a bond, $C(O)NR^e$, or $NR^eC(O)$, R^e being H or C_1-C_6 alkyl and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, and wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $-Q^3$-T^3, wherein each Q^3 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^3 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^f, $C(O)R^f$, $C(O)OR^f$, $OC(O)R^f$, $S(O)_2R^f$, NR^fR^g, $OC(O)NR^fR^g$, $NR^fC(O)OR^g$, $C(O)NR^fR^g$, and $NR^fC(O)R^g$, each of R^f and R^g independently being H, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl, in which the C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy; or $-Q^3$-T^3 is oxo;

R^8 is H or C_1-C_6 alkyl;

R^9 is $-Q^4$-T^4, in which Q^4 is a bond or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxyl, and T^4 is H, halo, OR^h, NR^hR^i, $NR^hC(O)R^i$, $C(O)NR^hR^i$, $C(O)R^h$, $C(O)OR^h$,

$NR^hC(O)OR^i$, $OC(O)NR^hR^i$, $S(O)_2R^h$, $S(O)_2NR^hR^i$, or R^{S2}, in which each of R^h and R^i independently is H or C_1-C_6 alkyl, and R^{S2} is C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- to 10-membered heteroaryl, and R^{S2} is optionally substituted with one or more $-Q^5$-T^5, wherein each Q^5 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^5 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^j, $C(O)R^j$, $C(O)OR^j$, $OC(O)R^j$, $S(O)_2R^j$, NR^jR^k, $OC(O)NR^jR^k$, $NR^jC(O)OR^k$, $C(O)NR^jR^k$, and $NR^jC(O)R^k$, each of R^j and R^k independently being H or C_1-C_6 alkyl; or $-Q^5$-T^5 is oxo;

R^{10} is halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein each of the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and 4- to 12-membered heterocycloalkyl is optionally substituted with one or more halo, cyano, hydroxyl, oxo, amino, mono- or di- alkylamino, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, $C(O)NR^jR^k$, or $NR^jC(O)R^k$;

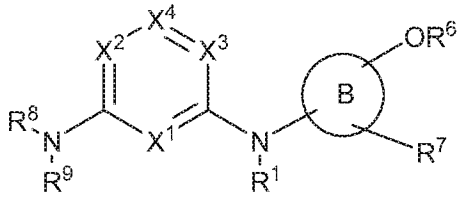
R^{11} and R^{12} together with the carbon atom to which they are attached form a C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein the C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, amino, mono- or di- alkylamino, or C_1-C_6 alkoxyl;

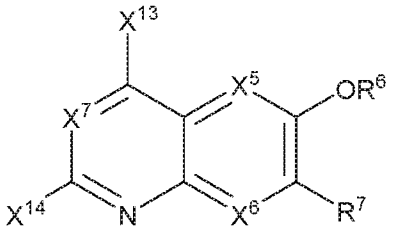
R^{13} is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} cycloalkyl, or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S; and

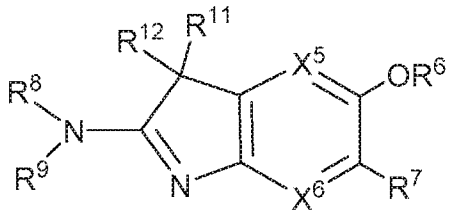
R^{14} is H, halo, cyano, $P(O)R^lR^m$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, or $-OR^6$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is optionally substituted with one or more of halo or OR^6, and each of R^l and R^m independently is C_1-C_6 alkyl; and

R^{15} is H, halo, cyano, or $-OR^6$.

[045] The present disclosure also provides compounds of any of Formulae (I)-(III) below:


(I),


(II), or


(III),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

[046] The compounds of the Formulae disclosed herein, such as Formulae (I0)-(IV0) and Formulae (I)-(III) may include one or more of the following features when applicable.

[047] In some embodiments, the compound is of Formula (III0), in which X^8 is NR^{13}.

[048] In some embodiments, R^{13} is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl (e.g., C_3-C_8 cycloalkyl), or 4- to 12-membered heterocycloalkyl (e.g., 4- to 7-membered heterocycloalkyl) containing 1-4 heteroatoms selected from N, O, and S (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, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, morpholinyl, etc.)

[049] In some embodiments, R^{13} is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

[050] In some embodiments, the compound is of Formula (III0), in which X^8 is $CR^{11}R^{12}$.

[051] In some embodiments, the compound is of Formula (I0), (II0), or (IV0), in which R^{14} is H, halo, or C_1-C_6 alkyl.

[052] In some embodiments, the compound is of Formula (I0), (II0), or (IV0), in which R^{14} is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

[053] In some embodiments, the compound is of Formula (I0), (II0), or (IV0), in which R^{14} is $-OR^6$.

[054] In some embodiments, R^{14} is H.

[055] In some embodiments, R^{14} is halo (*e.g.*, F, Cl, Br, or I). In some embodiments, R^{14} is F. In some embodiments, R^{14} is Cl. In some embodiments, R^{14} is Br. In some embodiments, R^{14} is I.

[056] In some embodiments, R^{14} is cyano.

[057] In some embodiments, R^{14} is $P(O)R^lR^m$, wherein each of R^l and R^m independently is C_1-C_6 alkyl (e.g., each of R^l and R^m is CH_3).

[058] In some embodiments, R^{14} is C_1-C_6 alkyl optionally substituted with one or more of halo or OR^6. In some embodiments, R^{14} is C_1-C_6 alkyl (e.g., CH_3). In some embodiments, R^{14} is C_1-C_6 alkyl substituted with one or more halo (e.g., CF_3). In some embodiments, R^{14} is C_1-C_6 alkyl substituted with one or more OR^6. In some embodiments, R^{14} is C_1-C_6 alkyl substituted with one or more OCH_3.

[059] In some embodiments, R^{14} is C_3-C_{12} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl).

[060] In some embodiments, R^{14} is 4- to 7- membered heterocycloalkyl (e.g., oxetanyl, or tetrahydrofuranyl).

[061] In some embodiments, R^{14} is 5- to 6-membered heteroaryl (e.g., isoxazolyl).

[062] In some embodiments, R^{14} is $-OR^6$ (e.g., OCH_3).

[063] In some embodiments, R^{15} is H.

[064] In some embodiments, R^{15} is halo (*e.g.*, F, Cl, Br, or I). In some embodiments, R^{15} is F. In some embodiments, R^{15} is Cl. In some embodiments, R^{15} is Br. In some embodiments, R^{15} is I.

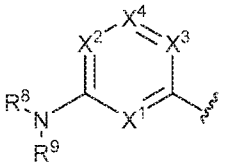
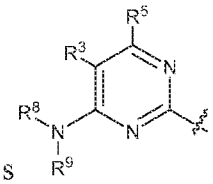
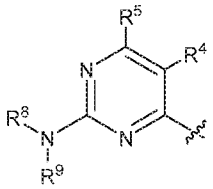
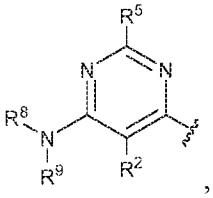
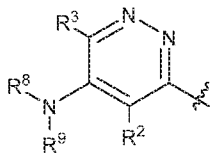
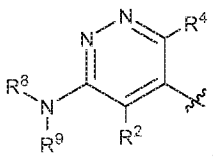
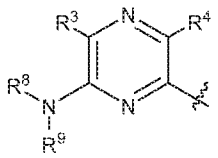
[065] In some embodiments, R^{15} is cyano.

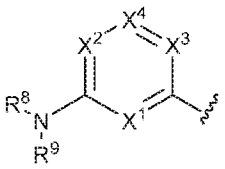
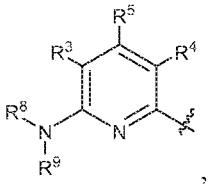
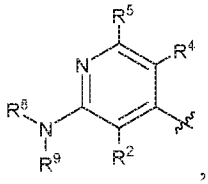
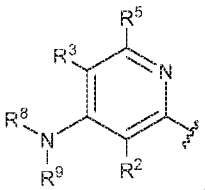
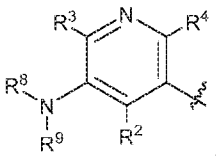
[066] In some embodiments, R^{15} is $-OR^6$ (e.g., OCH_3).

[067] In some embodiments, the compound is of Formula (I0) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

[068] In some embodiments, at least one of X^1, X^2, X^3 and X^4 is N.

[069] In some embodiments, X^1 and X^3 are N. In some embodiments, X^2 is CR^3 and X^4 is CR^5.

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

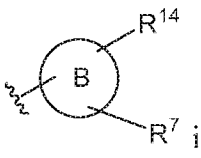
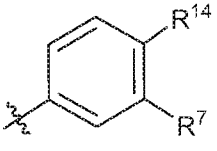
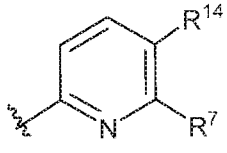
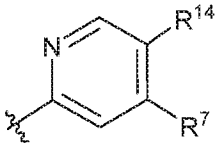
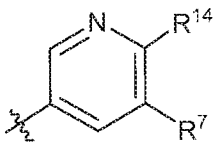
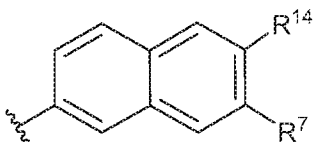
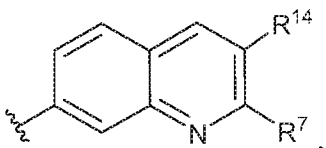
[071] In some embodiments,  is  ,  ,  , or  .

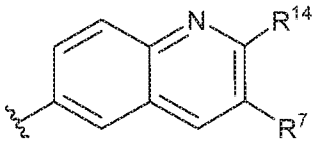
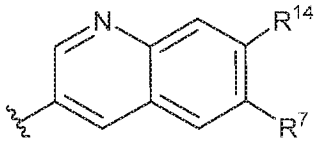
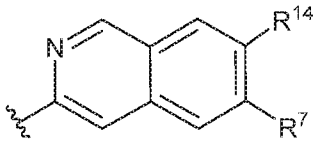
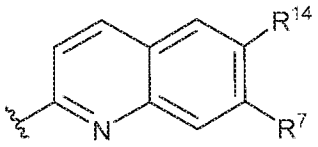
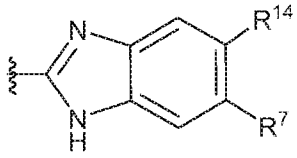
[072] In some embodiments, ring B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl.

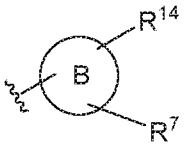
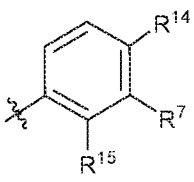
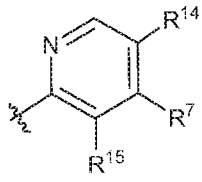
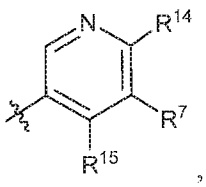
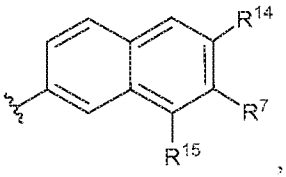
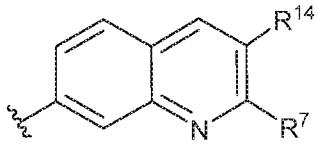
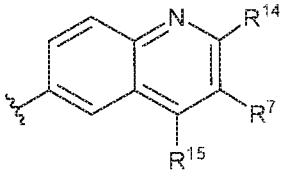
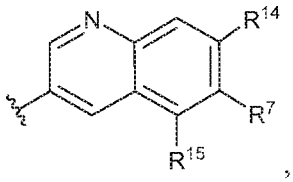
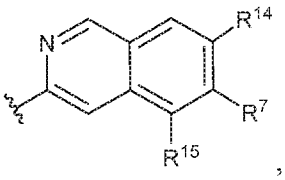
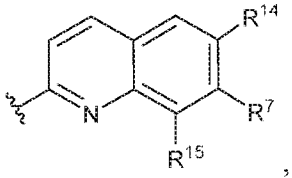
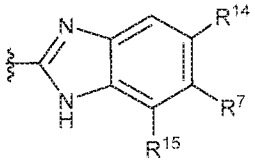
[073] In some embodiments, ring B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl substituted with one or more R^{15}.

[074] In some embodiments, ring B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl substituted with one R^{15}.

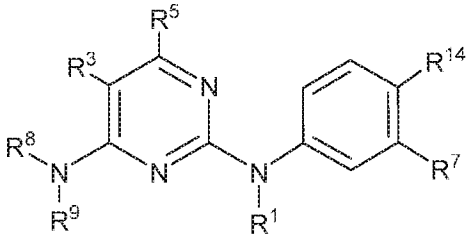
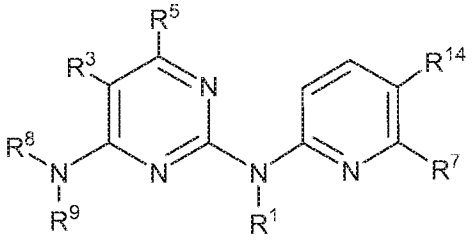
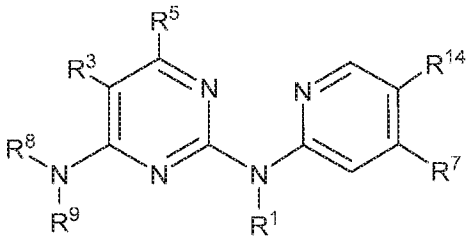
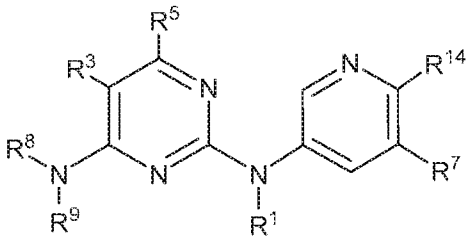
[075] In some embodiments, ring B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl substituted with two or more R^{15}.

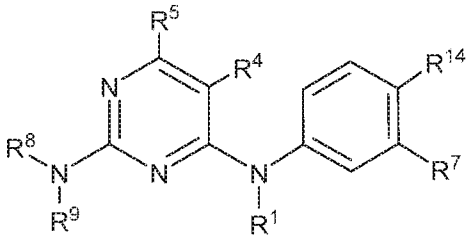
[076] In some embodiments,  is  ,  ,  ,  ,  ,  .

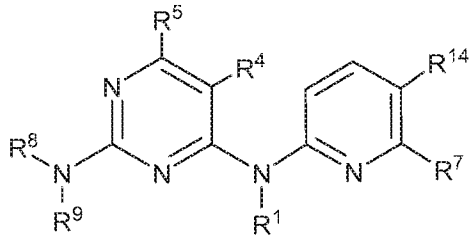






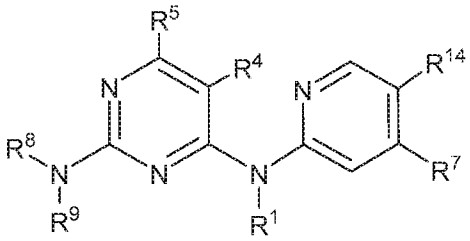
[077] In some embodiments,  is 










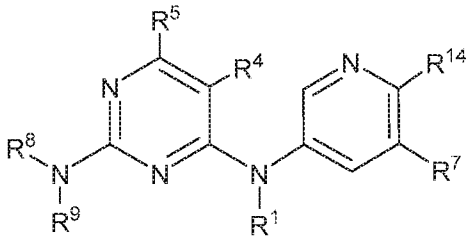
[078] In some embodiments, the compounds of Formula (I0) include those of any of Formulae (I0a)-(I0l):

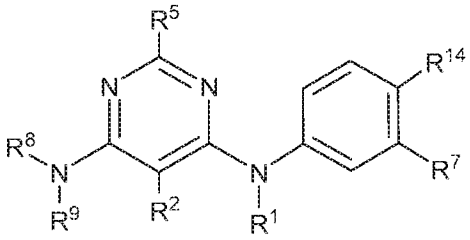

(I0a),

(I0b),

(I0c),

(I0d),

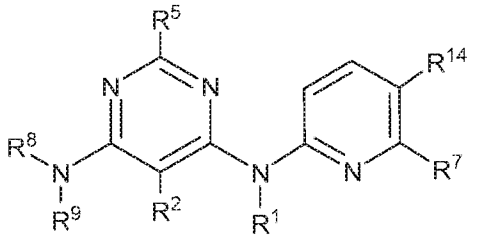

(I0e),

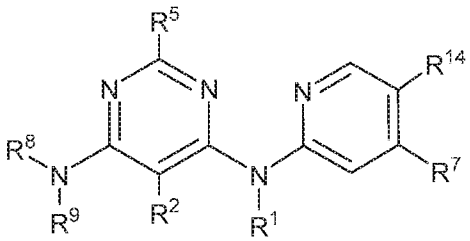

(I0f),

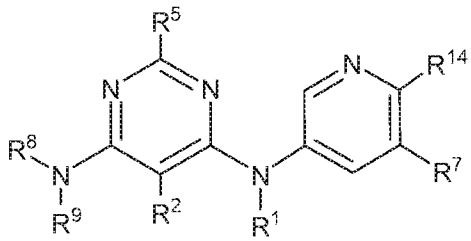

(I0g),


(I0h),


(I0i),

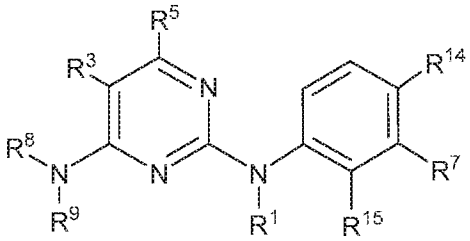

(I0j),

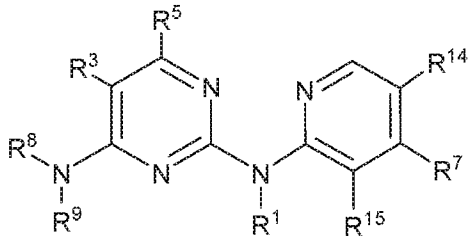

(I0k),

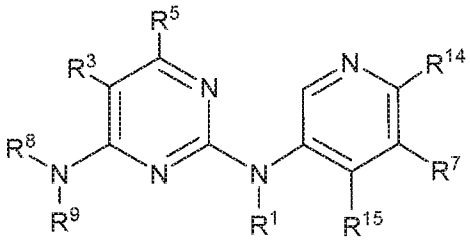

(I0l),

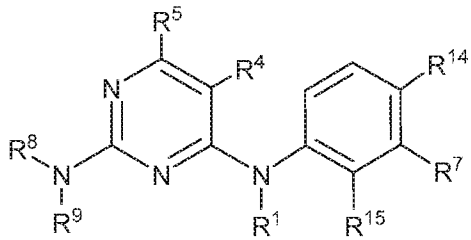
and tautomers thereof, and pharmaceutically acceptable salts of the compounds and the tautomers.

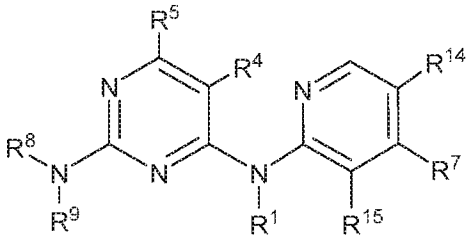
[079] In some embodiments, the compounds of Formula (I0) include those of any of Formulae (I0a')-(I0i'):

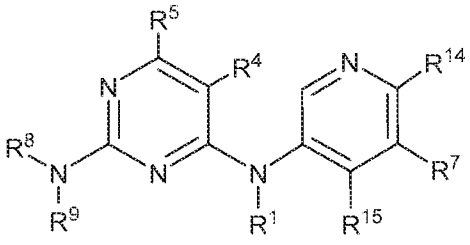

(I0a'),

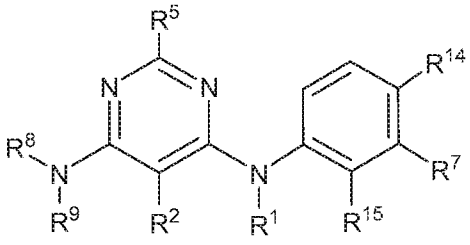

(I0b'),

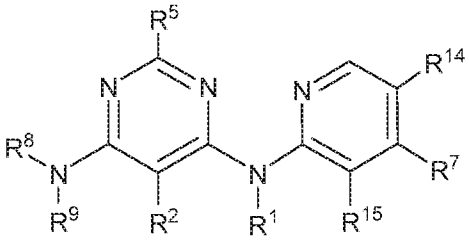

(I0c'),

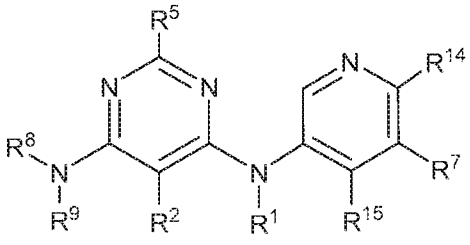

(I0d'),


(I0e'),


(I0f'),


(I0g'),


(I0h'),


(I0i'),

and tautomers thereof, and pharmaceutically acceptable salts of the compounds and the tautomers.

[080] In some embodiments, R^1 is C_1-C_4 alkyl. In some embodiments, R^1 is methyl. In some embodiments, R^1 is H.

[081] In some embodiments, R^3 is C_1-C_6 alkyl. In some embodiments, R^3 is methyl. In some embodiments, R^3 is H.

[082] In some embodiments, R^5 is C_1-C_6 alkyl. In some embodiments, R^5 is methyl.

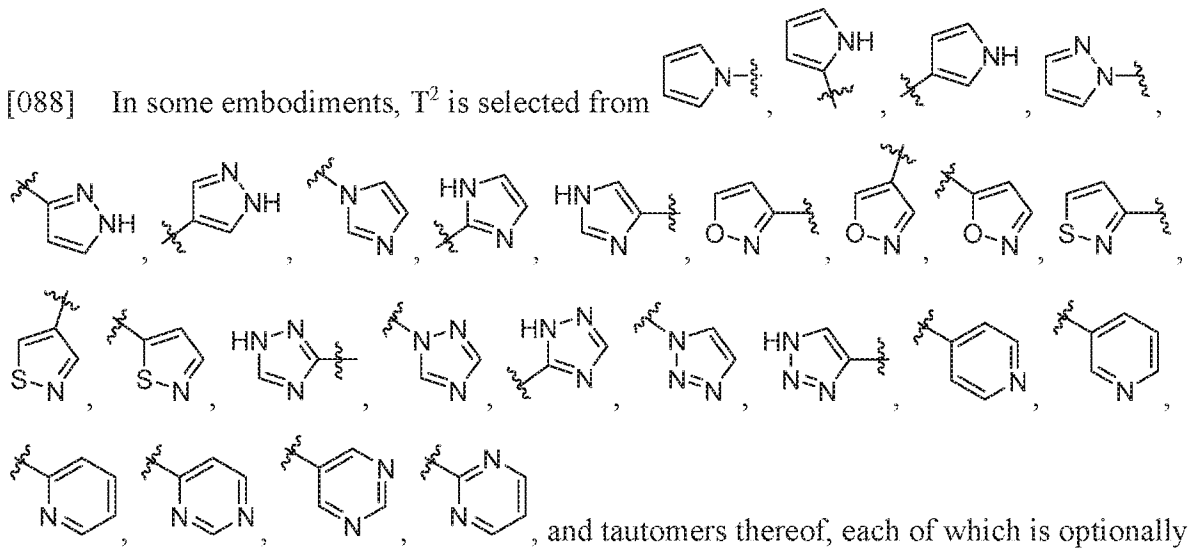
[083] In some embodiments, R^8 is C_1-C_6 alkyl. In some embodiments, R^8 is methyl. In some embodiments, R^8 is H.

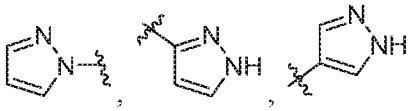
[084] In some embodiments, R^9 is $-Q^4$-T^4, in which Q^4 is C_1-C_6 alkylene, and T^4 is H. In some time, R^9 is methyl.

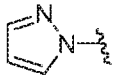
[085] In some embodiments, R^7 is $-Q^2$-T^2, in which Q^2 is a bond or $C(O)NR^e$, and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $-Q^3$-T^3.

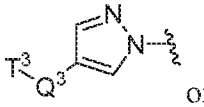
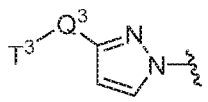
[086] In some embodiments, R^7 is $-Q^2$-T^2, in which Q^2 is a bond, and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $-Q^3$-T^3.

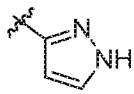
[087] In some embodiments, R^7 is $-Q^2-T^2$, in which Q^2 is a bond, and T^2 is 5- to 10-membered heteroaryl, wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more $-Q^3-T^3$.

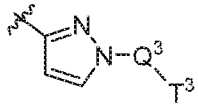
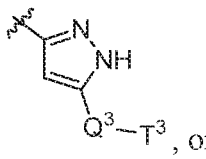
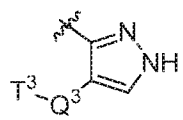
[088] In some embodiments, T^2 is selected from  , and tautomers thereof, each of which is optionally substituted with one or more $-Q^3-T^3$.

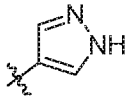
[089] In some embodiments, T^2 is selected from  , and tautomers thereof, each of which is optionally substituted with one or more $-Q^3-T^3$.

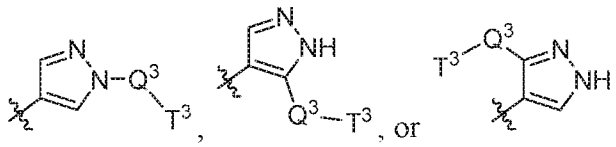
[090] In some embodiments, T^2 is  optionally substituted with one or more $-Q^3-T^3$.

[091] In some embodiments, T^2 is  or  .

[092] In some embodiments, T^2 is  optionally substituted with one or more $-Q^3-T^3$.

[093] In some embodiments, T^2 is  ,  , or  .

[094] In some embodiments, T^2 is  optionally substituted with one or more $-Q^3-T^3$.

[095] In some embodiments, T^2 is  .

[096] In some embodiments, each Q^3 independently is a C_1-C_3 alkylene linker, and each T^3 independently is selected from the group consisting of OR^f, $C(O)R^f$, $C(O)OR^f$, $OC(O)R^f$, $S(O)_2R^f$, NR^fR^g, $OC(O)NR^fR^g$, $NR^fC(O)OR^g$, $C(O)NR^fR^g$, and $NR^fC(O)R^g$, each of R^f and R^g independently being H, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl, in which the C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy.

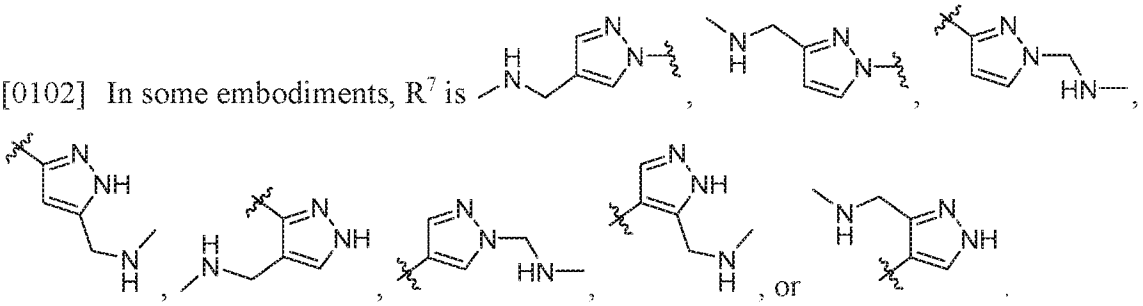
[097] In some embodiments, each Q^3 independently is a C_1-C_3 alkylene linker, and each T^3 independently is NR^fR^g, each of R^f and R^g independently being H, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl, in which the C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy.

[098] In some embodiments, each Q^3 independently is a C_1-C_3 alkylene linker, and each T^3 independently is NR^fR^g, each of R^f and R^g independently being H or C_1-C_6 alkyl.

[099] In some embodiments, each Q^3 independently is a C_1-C_3 alkylene linker, and each T^3 independently is NR^fR^g, each of R^f and R^g independently being H or methyl.

[0100] In some embodiments, each Q^3 independently is a C_1-C_3 alkylene linker, and each T^3 independently is $NHCH_3$.

[0101] In some embodiments, each Q^3 independently is methylene, and each T^3 independently is $NHCH_3$.

[0102] In some embodiments, R^7 is  .

[0103] In some embodiments, R^{14} is H, halo, or $-OR^6$.

[0104] In some embodiments, R^{14} is halo or $-OR^6$.

[0105] In some embodiments, R^{14} is H.

[0106] In some embodiments, R^{14} is halo. In some embodiments, R^{14} is F. In some embodiments, R^{14} is Cl. In some embodiments, R^{14} is Br. In some embodiments, R^{14} is I.

[0107] In some embodiments, R^{14} is $-OR^6$. In some embodiments, R^6 is $-Q^1$-T^1, in which Q^1 is a C_1-C_6 alkylene linker, and T^1 is H. In some embodiments, R^6 is $-Q^1$-T^1, in which Q^1 is methylene, and T^1 is H. In some embodiments, R^{14} is -OCH_3.

[0108] In some embodiments, R^{15} is H or halo.

[0109] In some embodiments, R^{15} is H.

[0110] In some embodiments, R^{15} is halo. In some embodiments, R^{15} is F. In some embodiments, R^{15} is Cl. In some embodiments, R^{15} is Br. In some embodiments, R^{15} is I.

[0111] In some embodiments, R^{14} is halo or $-OR^6$, and R^{15} is H or halo.

[0112] In some embodiments, R^{14} is halo, and R^{15} is H. In some embodiments, R^{14} is F, and R^{15} is H. In some embodiments, R^{14} is Cl, and R^{15} is H. In some embodiments, R^{14} is Br, and R^{15} is H. In some embodiments, R^{14} is I, and R^{15} is H.

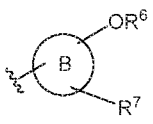
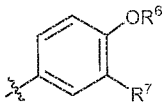
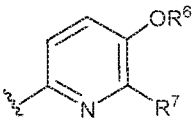
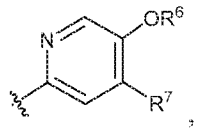
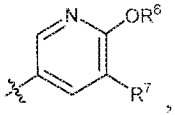
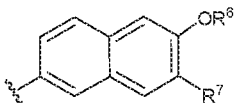
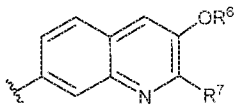
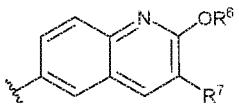
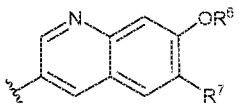
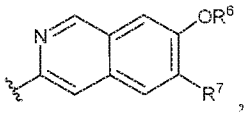
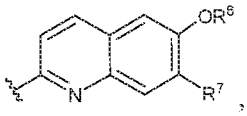
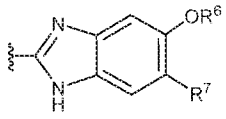
[0113] In some embodiments, R^{14} is–OR^6, and R^{15} is H. In some embodiments, R^{14} is -OCH_3, and R^{15} is H.

[0114] In some embodiments, R^{14} is halo, and R^{15} is halo. In some embodiments, R^{14} is F, and R^{15} is F. In some embodiments, R^{14} is Cl, and R^{15} is F. In some embodiments, R^{14} is Br, and R^{15} is F. In some embodiments, R^{14} is I, and R^{15} is F. In some embodiments, R^{14} is F, and R^{15} is Cl. In some embodiments, R^{14} is Cl, and R^{15} is Cl. In some embodiments, R^{14} is Br, and R^{15} is Cl. In some embodiments, R^{14} is I, and R^{15} is Cl. In some embodiments, R^{14} is F, and R^{15} is Br. In some embodiments, R^{14} is Cl, and R^{15} is Br. In some embodiments, R^{14} is Br, and R^{15} is Br. In some embodiments, R^{14} is I, and R^{15} is Br. In some embodiments, R^{14} is F, and R^{15} is I. In some embodiments, R^{14} is Cl, and R^{15} is I. In some embodiments, R^{14} is Br, and R^{15} is I. In some embodiments, R^{14} is I, and R^{15} is I.

[0115] In some embodiments, R^{14} is $-OR^6$, and R^{15} is halo. In some embodiments, R^{14} is -OCH_3, and R^{15} is halo. In some embodiments, R^{14} is -OCH_3, and R^{15} is F. In some embodiments, R^{14} is -OCH_3, and R^{15} is Cl. In some embodiments, R^{14} is -OCH_3, and R^{15} is Br. In some embodiments, R^{14} is -OCH_3, and R^{15} is I.

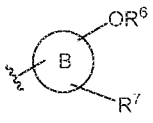
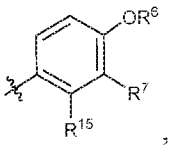
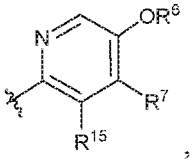
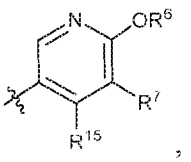
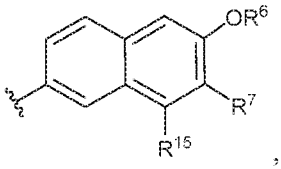
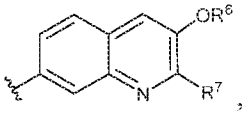
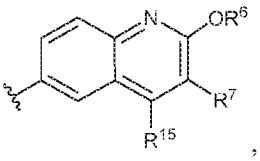
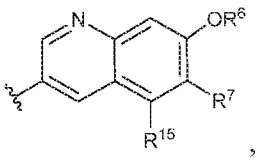
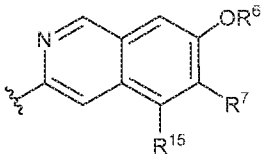
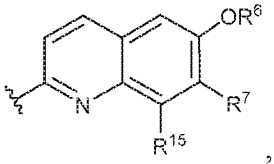
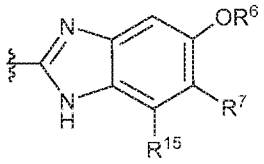
[0116] In some embodiments, the compound is of Formula (I), or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

[0117] In some embodiments, ring B is phenyl or 6-membered heteroaryl (e.g., pyridyl or pyrimidyl).

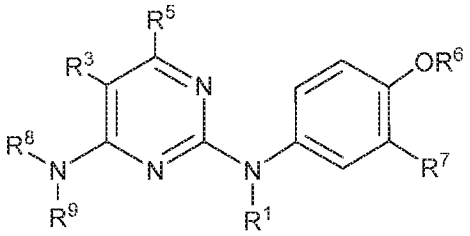
[0118] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[0119] In some embodiments, ring B is phenyl or 6-membered heteroaryl (e.g., pyridyl or pyrimidyl) optionally substituted with one or more R^{15}.

[0120] In some embodiments, ring B is phenyl or 6-membered heteroaryl (e.g., pyridyl or pyrimidyl) optionally substituted with one R^{15}.

[0121] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[0122] In some embodiments, the compounds of Formula (I) include those of any of Formulae (Ia)-(II):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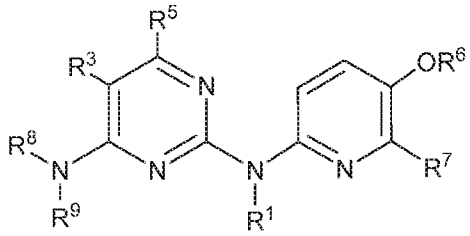
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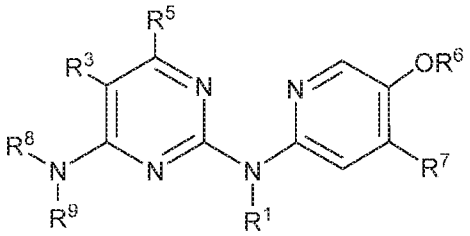
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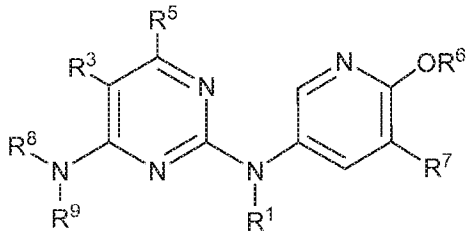
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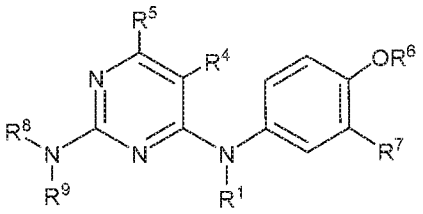
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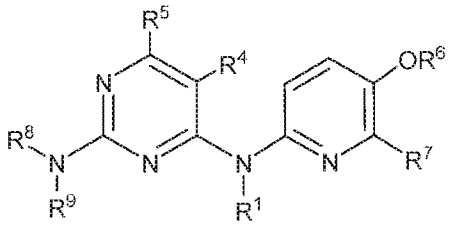
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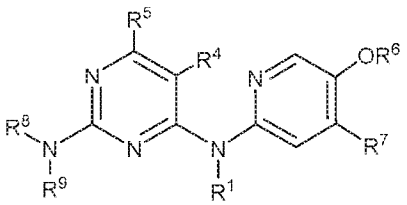
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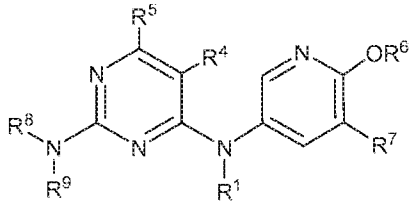
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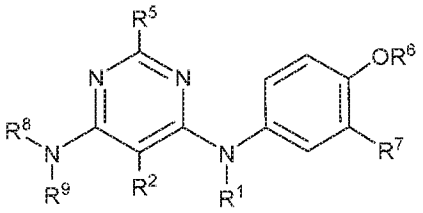
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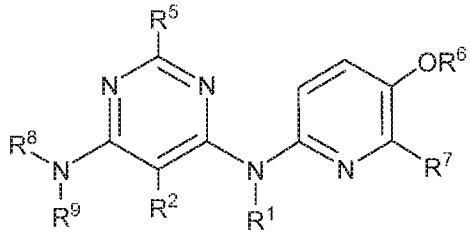
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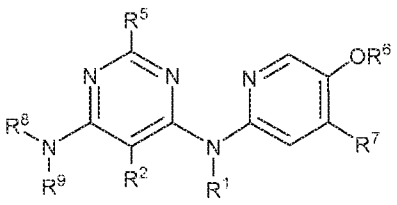
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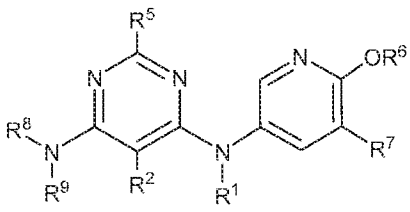
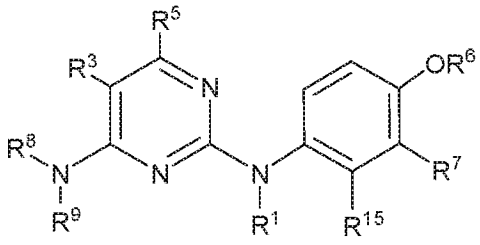

(Il),

and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[0123] In some embodiments, the compounds of Formula (I) include those of any of Formulae (Ia')-(Ii'):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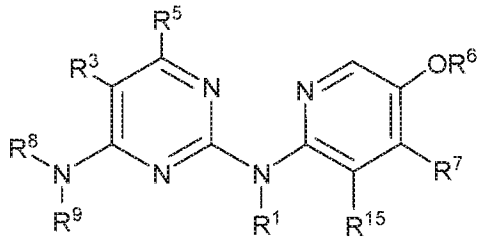
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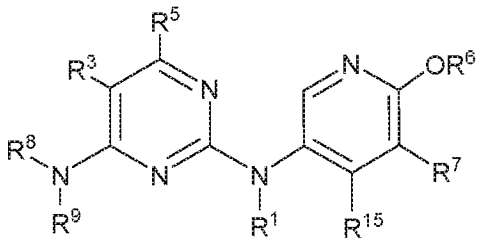
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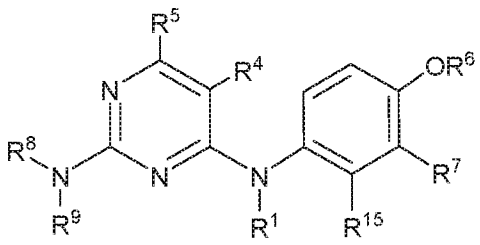
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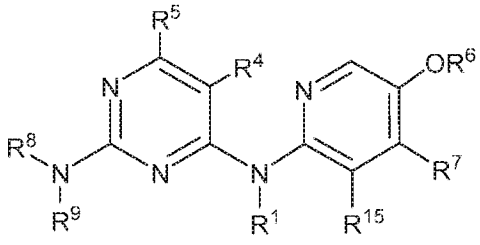
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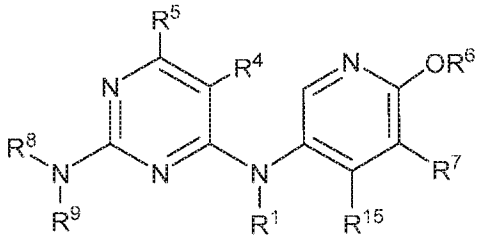
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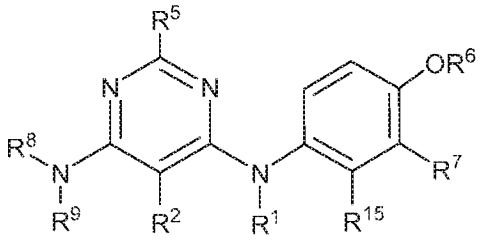
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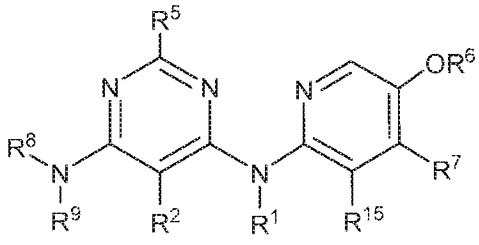
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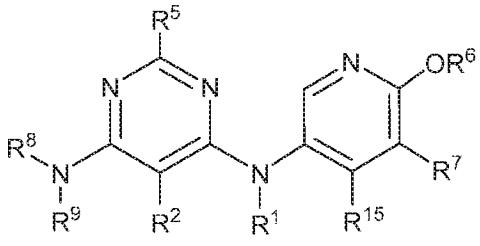
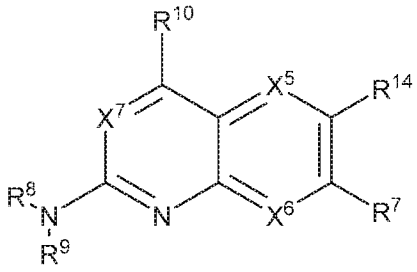
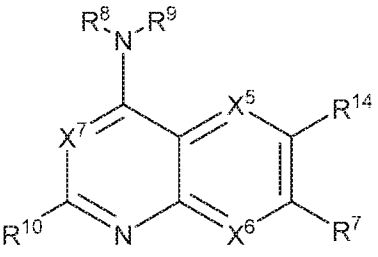

(Ii'),

and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[0124] In some embodiments, the compound is of Formula (II0) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

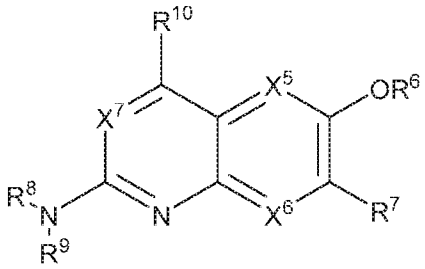
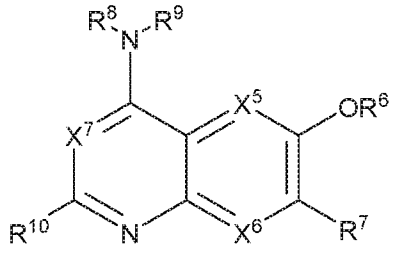
[0125] In some embodiments, the compounds of Formula (II0) include those of any of Formulae (II0a) and (II0b):


(II0a),

(II0b),

and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[0126] In some embodiments, the compound is of Formula (II) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

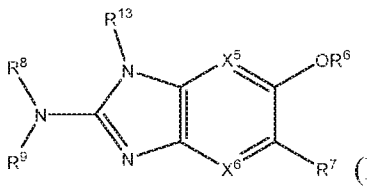
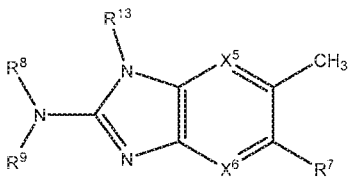
[0127] In some embodiments, the compound is of Formula (II) include those of any of Formulae (IIa) and (IIb):


(II0a),

(II0b),

and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[0128] In some embodiments, the compound is of Formula (III0) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

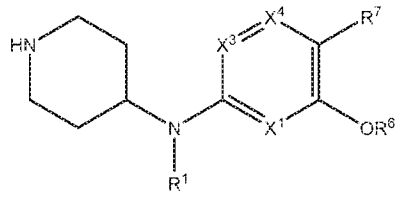
[0129] In some embodiments, the compounds of Formula (III0) include those of any of Formulae (III0a) and (III0b):


(III0a),

(III0b), and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

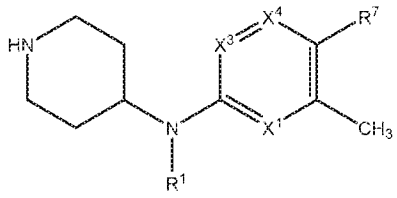
[0130] In some embodiments, the compound is of Formula (III) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

[0131] In some embodiments, the compound is of Formula (IV0) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

[0132] In some embodiments, the compounds of Formula (IV0) include those of Formulae (IV0a) and (IV0b):



(IV0a),



(IV0b), and tautomers thereof, and pharmaceutically acceptable salts of the compounds or the tautomers.

[0133] In some embodiments, at most one of R^3 and R^5 is not H.

[0134] In some embodiments, at least one of R^3 and R^5 is not H.

[0135] In some embodiments, R^3 is H or halo.

[0136] In some embodiments, at most one of R^4 and R^5 is not H.

[0137] In some embodiments, at least one of R^4 and R^5 is not H.

[0138] In some embodiments, R^4 is H, C_1-C_6 alkyl, or halo.

[0139] In some embodiments, at most one of R^2 and R^5 is not H.

[0140] In some embodiments, at least one of R^2 and R^5 is not H.

[0141] In some embodiments, R^2 is H, C_1-C_6 alkyl, or halo.

[0142] In some embodiments, R^5 is C_1-C_6 alkyl optionally substituted with one or more of halo, hydroxyl, or C_1-C_6 alkoxyl. In some embodiments, R^5 is unsubstituted C_1-C_6 alkyl (e.g., methyl or ethyl).

[0143] In some embodiments, each of X^5, X^6 and X^7 is CH.

[0144] In some embodiments, at least one of X^5, X^6 and X^7 is N.

[0145] In some embodiments, at most one of X^5, X^6 and X^7 is N.

[0146] In some embodiments, R^{10} is optionally substituted 4- to 7-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S (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, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, morpholinyl, etc.). In some embodiments, R^{10} is optionally substituted with one or more halo, cyano, hydroxyl, oxo, amino, mono- or di- alkylamino, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, $C(O)NR^jR^k$, or $NR^jC(O)R^k$.

[0147] In some embodiments, R^{10} is connected to the bicyclic group of Formula (II) via a carbon-carbon bond. In some embodiments, R^{10} is connected to the bicyclic group of Formula (II) via a carbon-nitrogen bond.

[0148] In some embodiments, R^{10} is halo.

[0149] In some embodiments, R^{10} is optionally substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, e.g., optionally substituted with one or more halo, cyano, hydroxyl, oxo, amino, mono- or di- alkylamino, C_1-C_6 alkoxy, $C(O)NR^jR^k$, or $NR^jC(O)R^k$.

[0150] In some embodiments, R^{10} is C_3-C_8 cycloalkyl optionally substituted with one or more halo, cyano, hydroxyl, oxo, amino, mono- or di- alkylamino, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, $C(O)NR^jR^k$, or $NR^jC(O)R^k$.

[0151] In some embodiments, R^{10} is C_3-C_8 cycloalkyl optionally substituted with $C(O)NR^jR^k$ or $NR^jC(O)R^k$.

[0152] In some embodiments, R^{11} and R^{12} together with the carbon atom to which they are attached form a 4- to 7-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S (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, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, morpholinyl, etc.), wherein the 4- to 7-membered heterocycloalkyl is optionally substituted with one or more of halo, C_1-C_6 alkyl, hydroxyl, oxo, amino, mono- or di- alkylamino, or C_1-C_6 alkoxyl.

[0153] In some embodiments, R^{11} and R^{12} together with the carbon atom to which they are attached form an unsubstituted 4- to 7-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S (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, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, morpholinyl, etc.).

[0154] In some embodiments, R^{11} and R^{12} together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl which is optionally substituted with one or more of halo, C_1-C_6 alkyl, hydroxyl, oxo, amino, mono- or di- alkylamino, or C_1-C_6 alkoxyl.

[0155] In some embodiments, R^{11} and R^{12} together with the carbon atom to which they are attached form an unsubstituted C_4-C_8 cycloalkyl.

[0156] In some embodiments, each of X^5 and X^6 is CH.

[0157] In some embodiments, each of X^5 and X^6 is N.

[0158] In some embodiments, one of X^5 and X^6 is CH and the other is CH.

[0159] In some embodiments, R^6 is $-Q^1$-T^1, in which Q^1 is a bond or C_1-C_6 alkylene linker optionally substituted with one or more of halo, and T^1 is H, halo, cyano, or R^{S1}, in which R^{S1} is C_3-C_8 cycloalkyl, phenyl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- or 6-membered heteroaryl and R^{S1} is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, NR^cR^d, or C_1-C_6 alkoxyl.

[0160] In some embodiments, R^6 is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxyl.

[0161] In some embodiments, R^6 is unsubstituted C_1-C_6 alkyl (e.g., methyl).

[0162] In some embodiments, R^7 is $-Q^2$-T^2, in which Q^2 is a bond or $C(O)NR^e$, and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $-Q^3$-T^3.

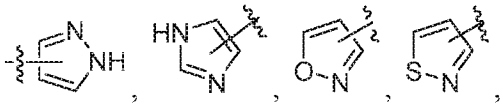
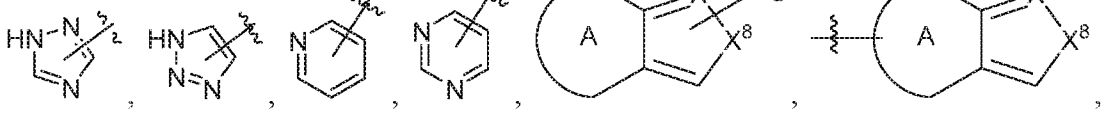
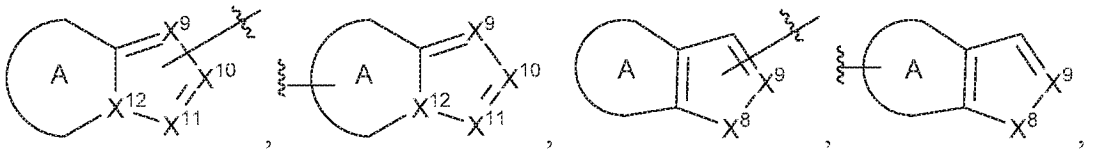
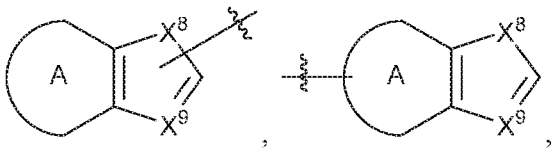
[0163] In some embodiments, Q^2 is a bond.

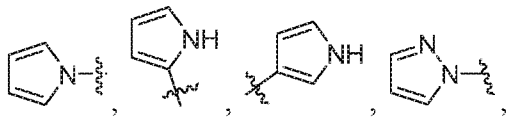
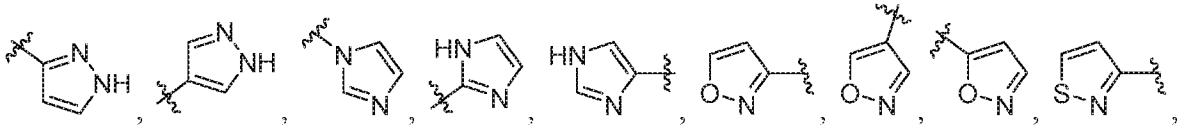
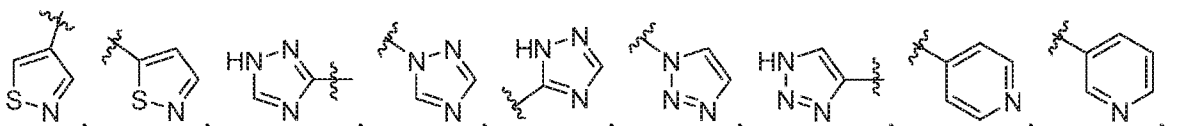
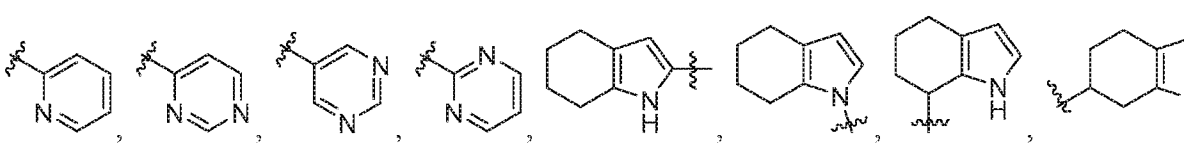
[0164] In some embodiments, Q^2 is CONH or NHCO.

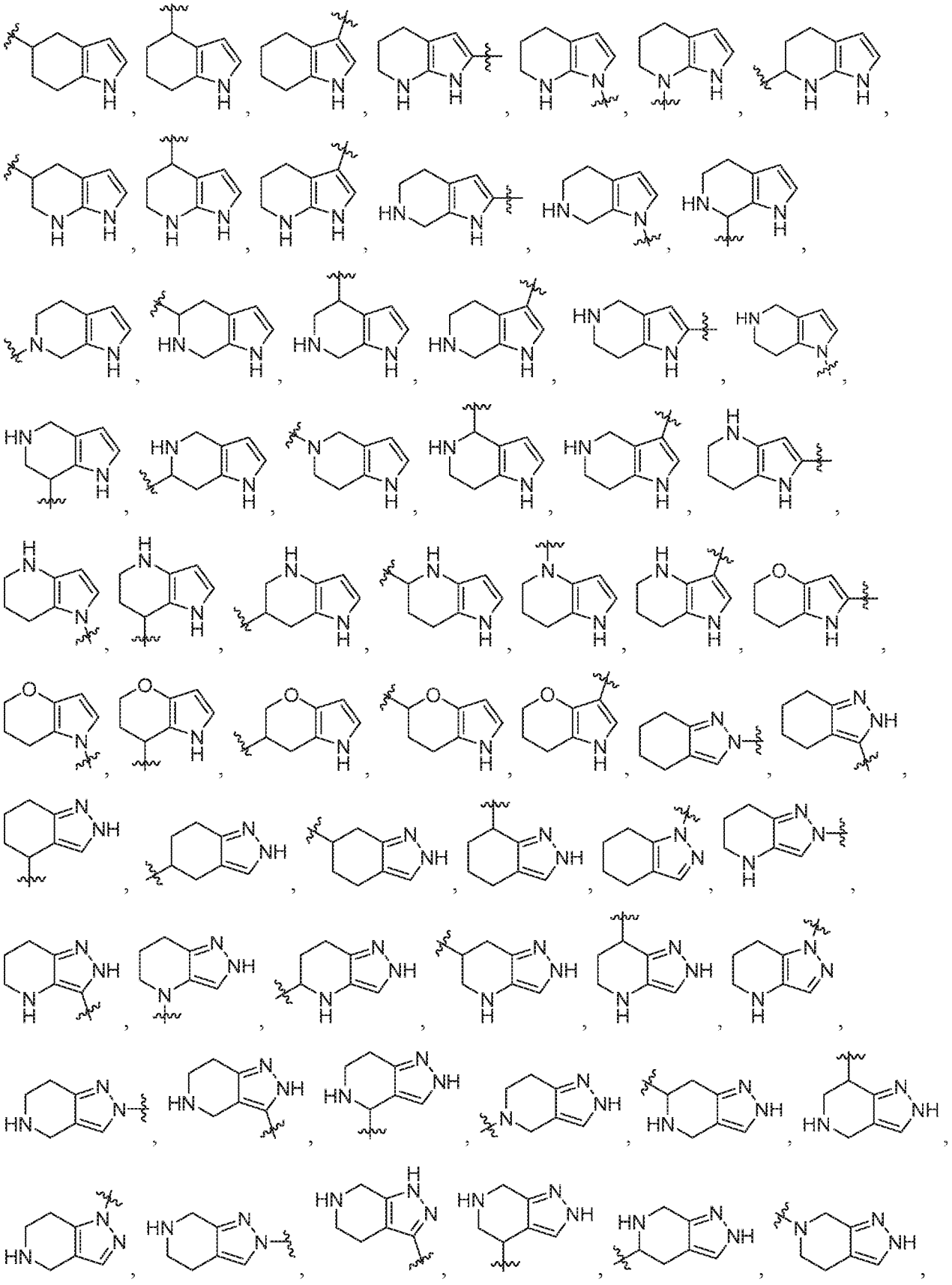
[0165] In some embodiments, T^2 is 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S (e.g., a 4 to 7-membered monocyclic heterocycloalkyl or 7 to 12-membered bicyclic heterocycloalkyl such as azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 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, morpholinyl, 3-azabicyclo[3.1.0]hexan-3-yl, 3-azabicyclo[3.1.0]hexanyl, 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazolyl, 3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridinyl, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 2-azaspiro[3.3]heptanyl, 2-methyl-2-azaspiro[3.3]heptanyl, 2-azaspiro[3.5]nonanyl, 2-methyl-2-azaspiro[3.5]nonanyl, 2-azaspiro[4.5]decanyl, 2-methyl-2-azaspiro[4.5]decanyl, 2-oxa-azaspiro[3.4]octanyl, 2-oxa-azaspiro[3.4]octan-6-yl, and the like), which is optionally substituted with one or more $-Q^3$-T^3.

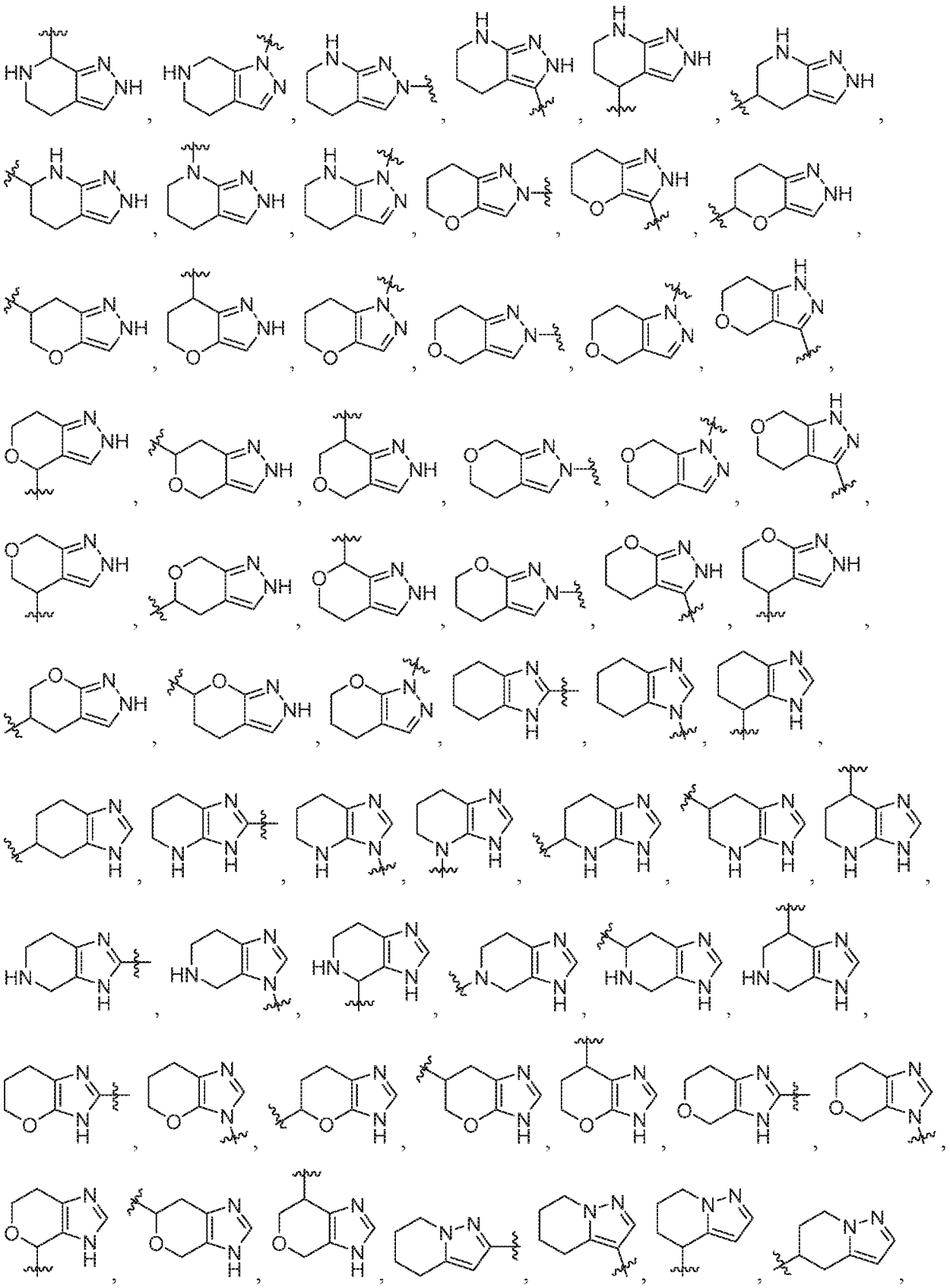
[0166] In some embodiments, T^2 is 8- to 12-membered bicyclic heterocycloalkyl that comprises a 5- or 6-membered aryl or heteroaryl ring fused with a non-aromatic ring. In some embodiments, the 5- or 6-membered aryl or heteroaryl ring is connected to Q^2.

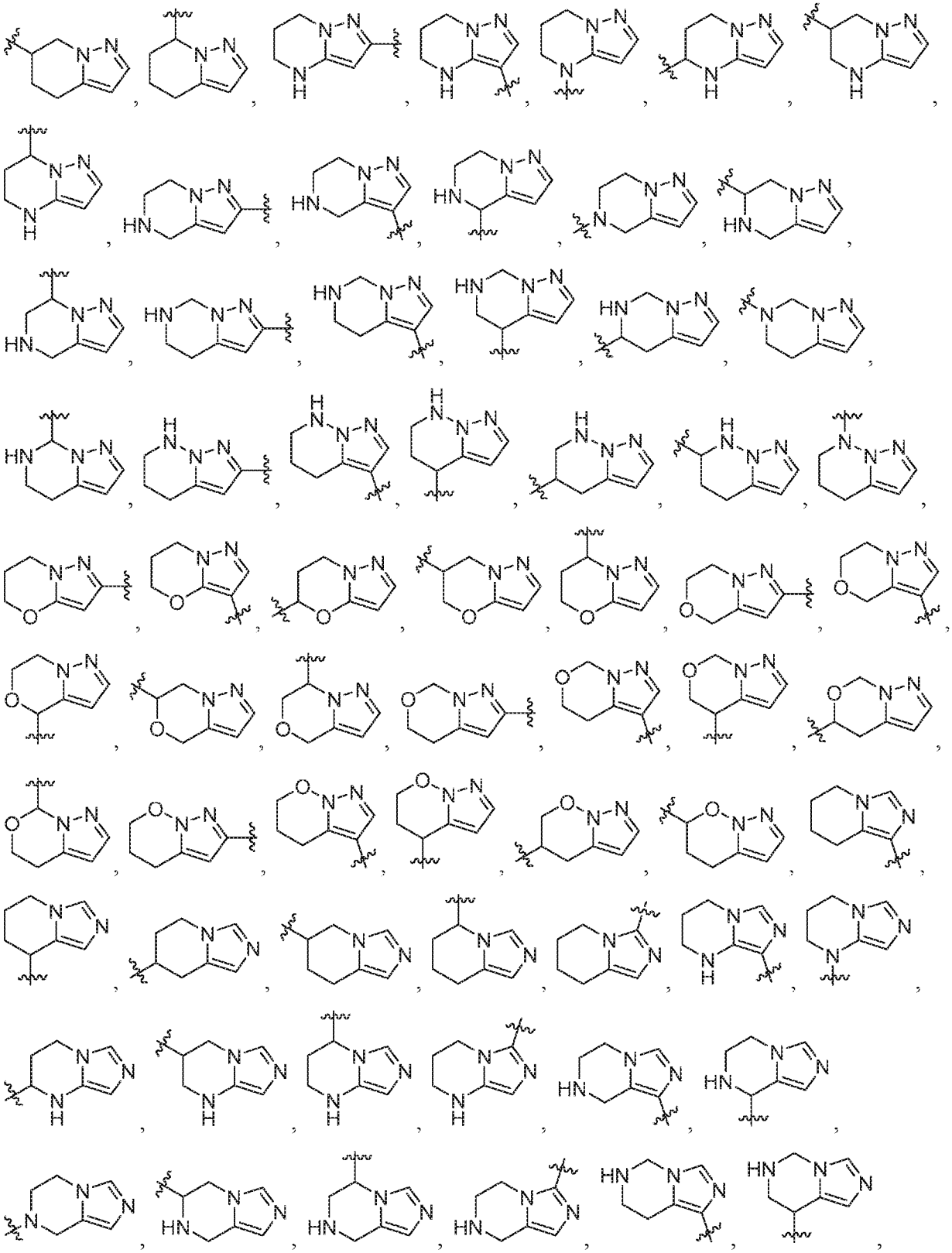
[0167] In some embodiments, T^2 is 5- to 10-membered heteroaryl.

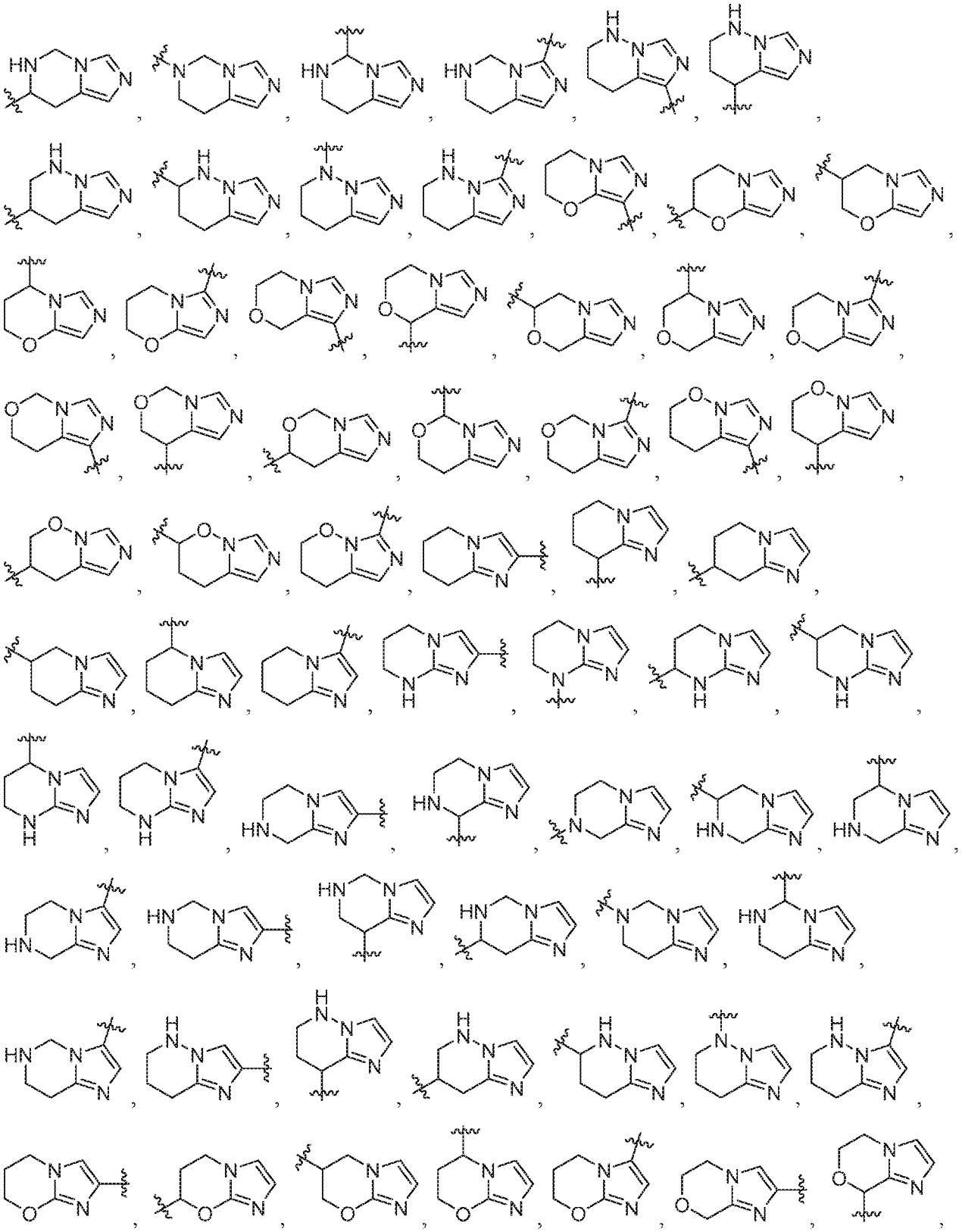
[0168] In some embodiments, T^2 is selected from  ,  ,  ,  , and tautomers thereof, each of which is optionally substituted with one or more $-Q^3$-T^3, wherein X^8 is NH, O, or S, each of X^9, X^{10}, X^{11}, and X^{12} is independently CH or N, and at least one of X^9, X^{10}, X^{11}, and X^{12} is N, and ring A is a C_5-C_8 cycloalkyl, phenyl, 6-membered heteroaryl, or 4- to 8-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S.

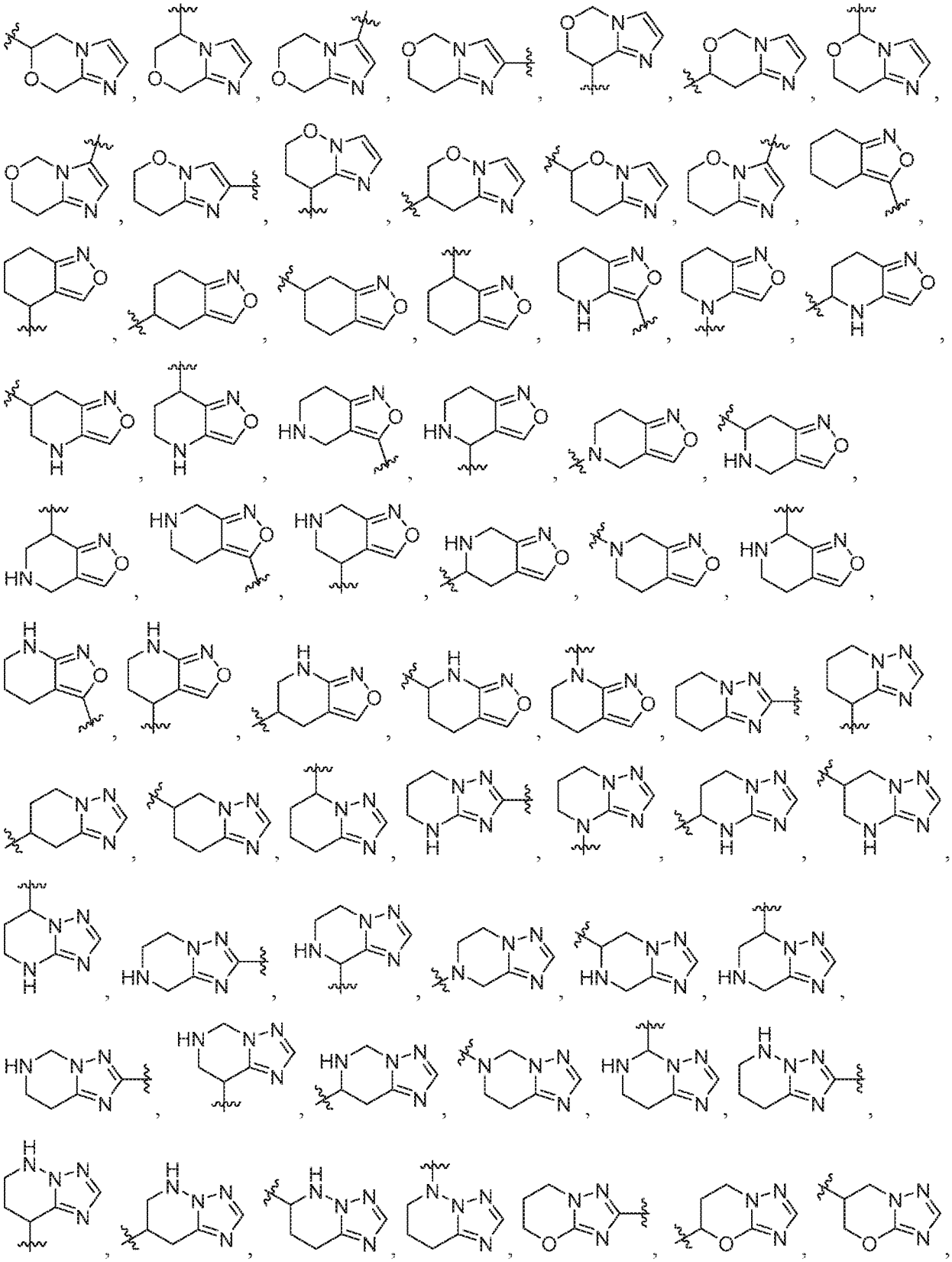
[0169] In some embodiments, T^2 is selected from  ,  ,  ,  ,

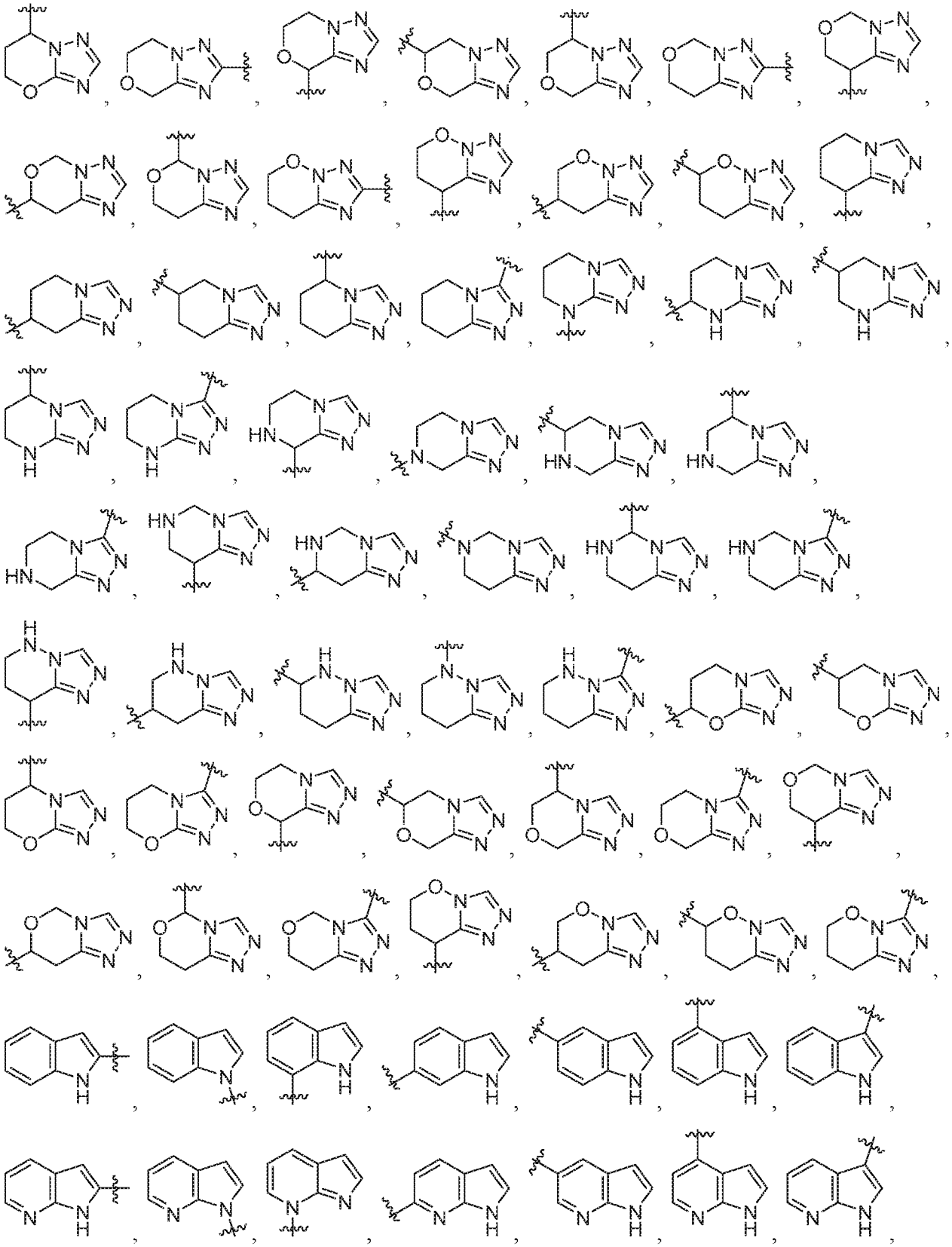


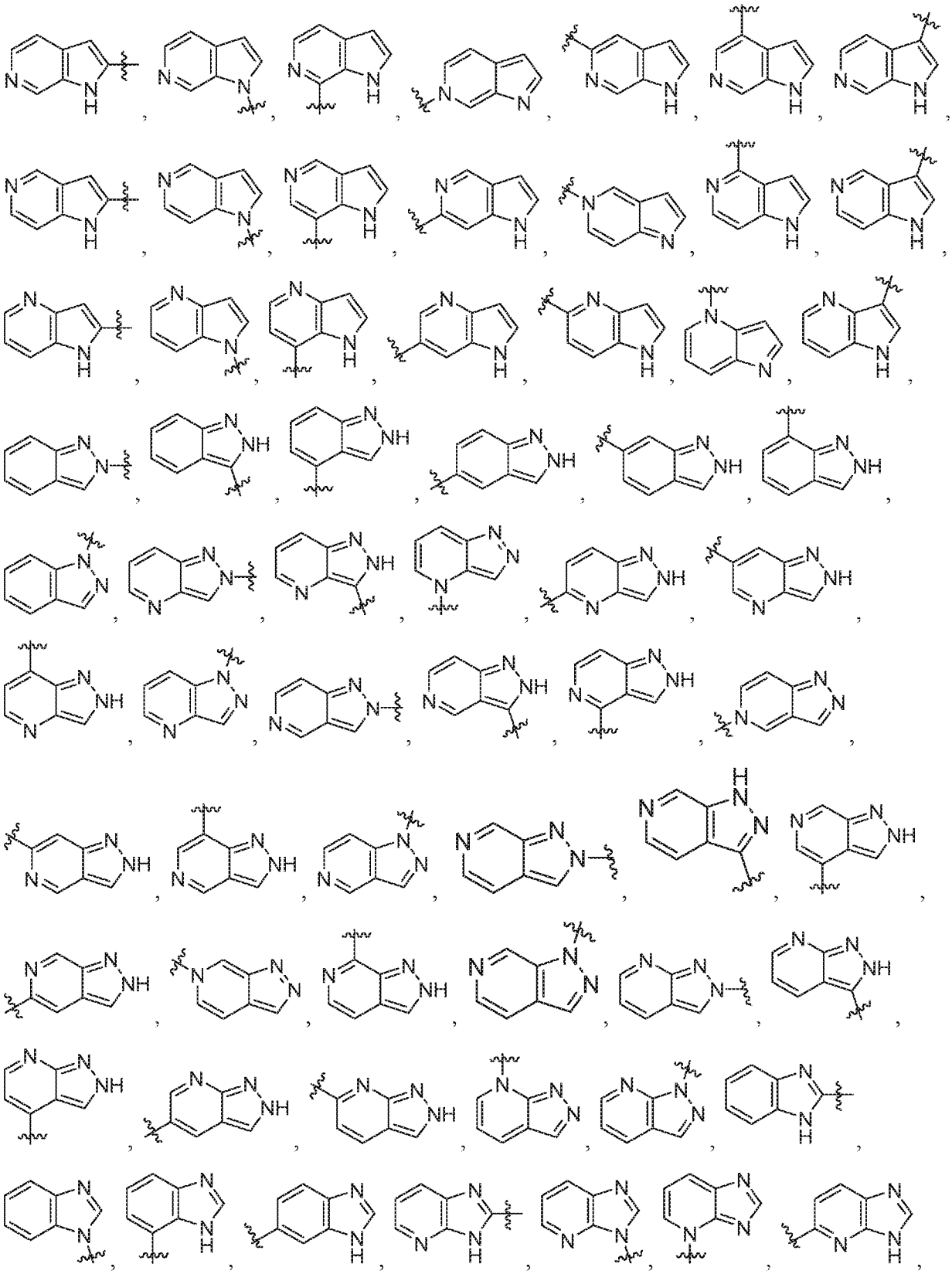


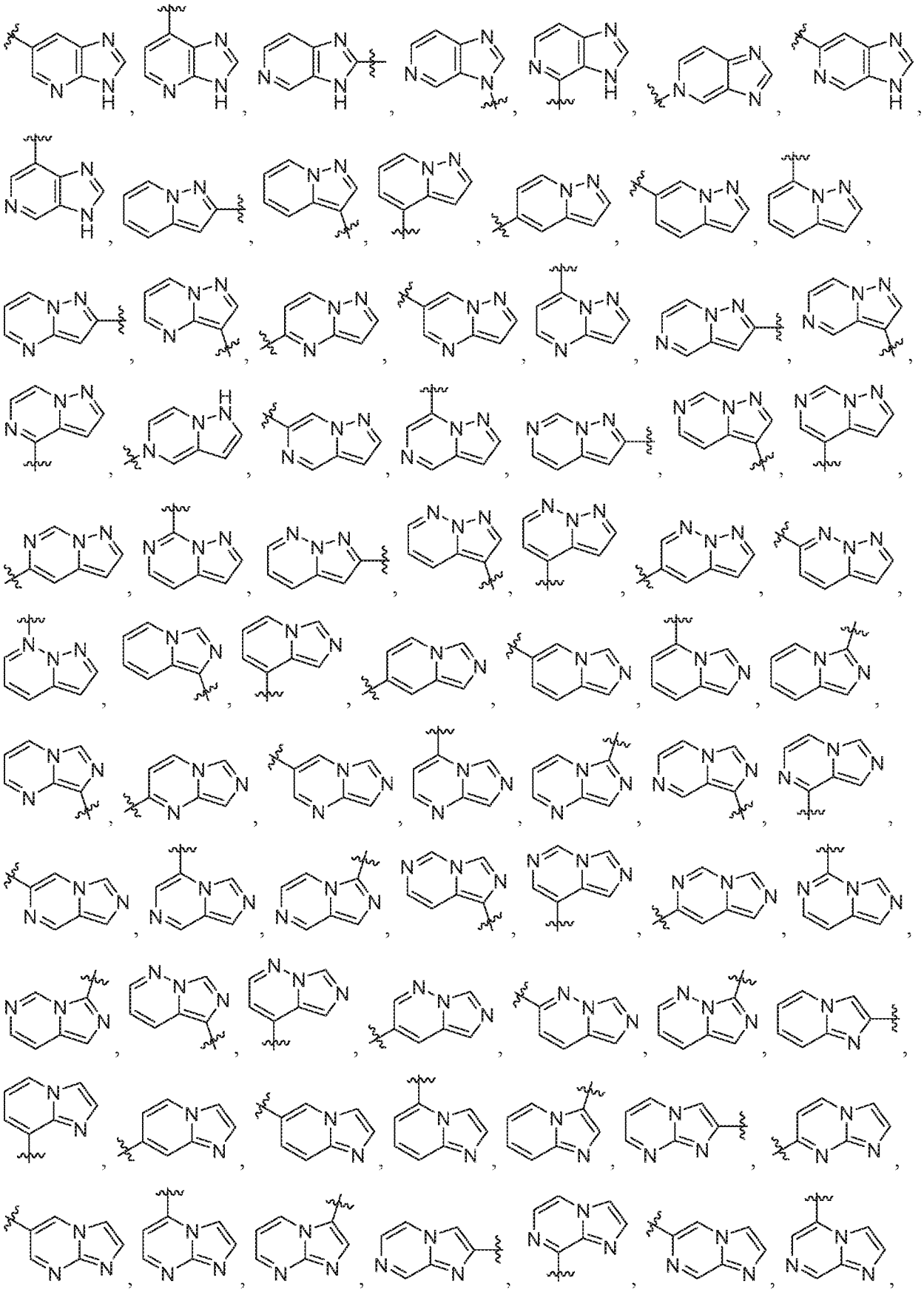


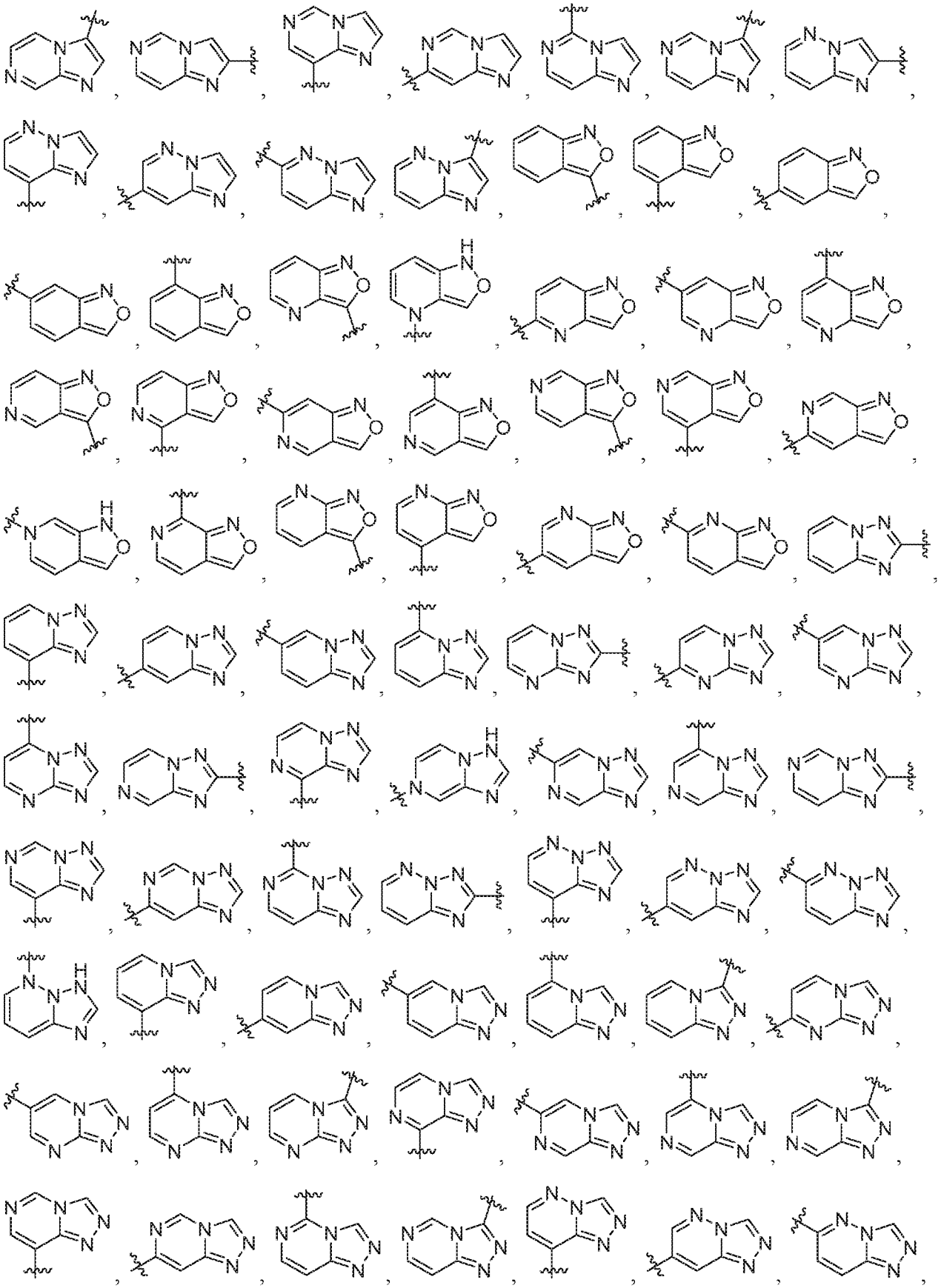


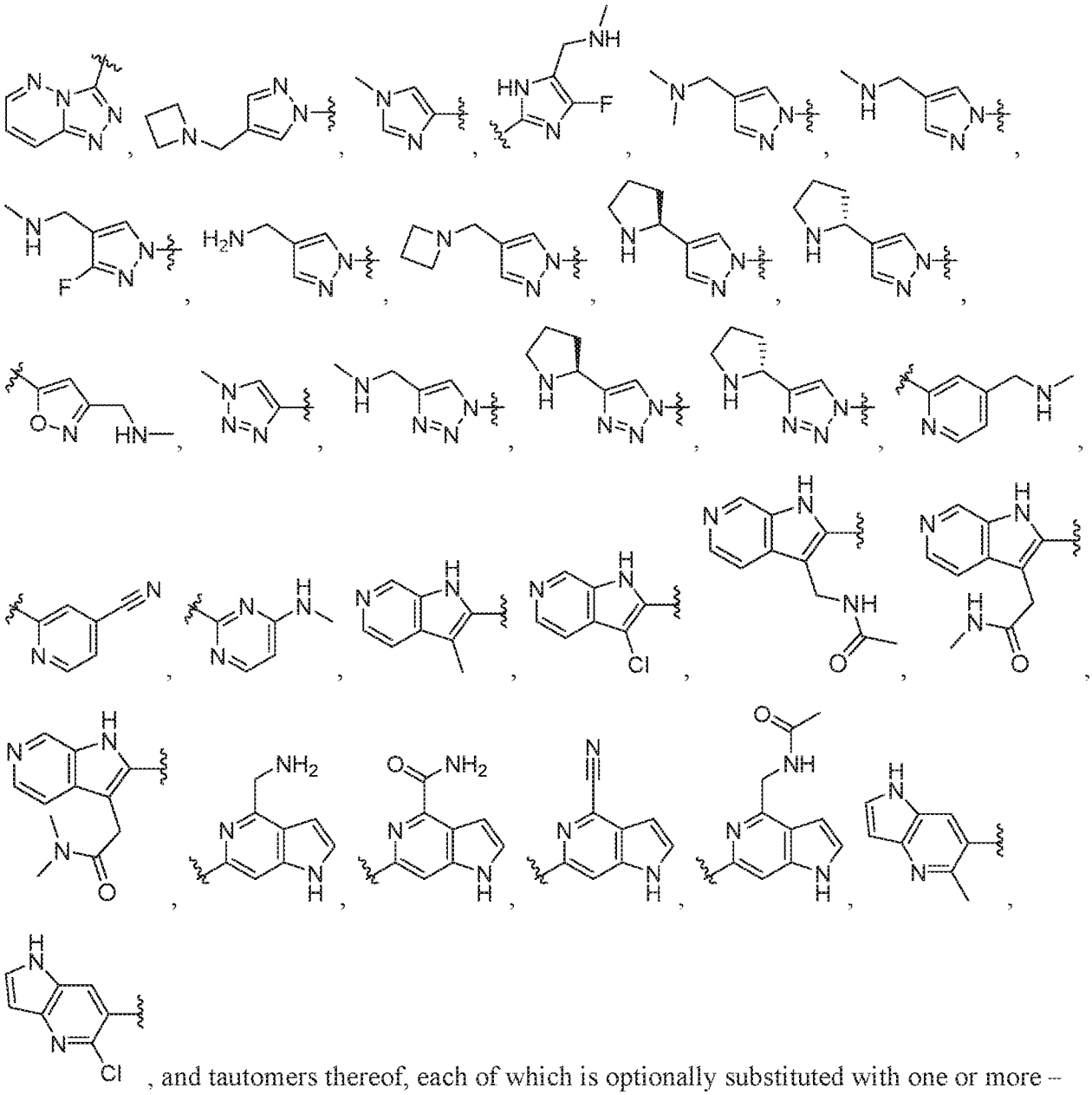




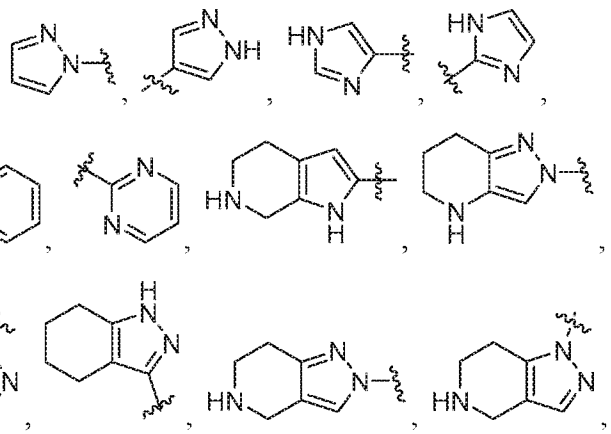


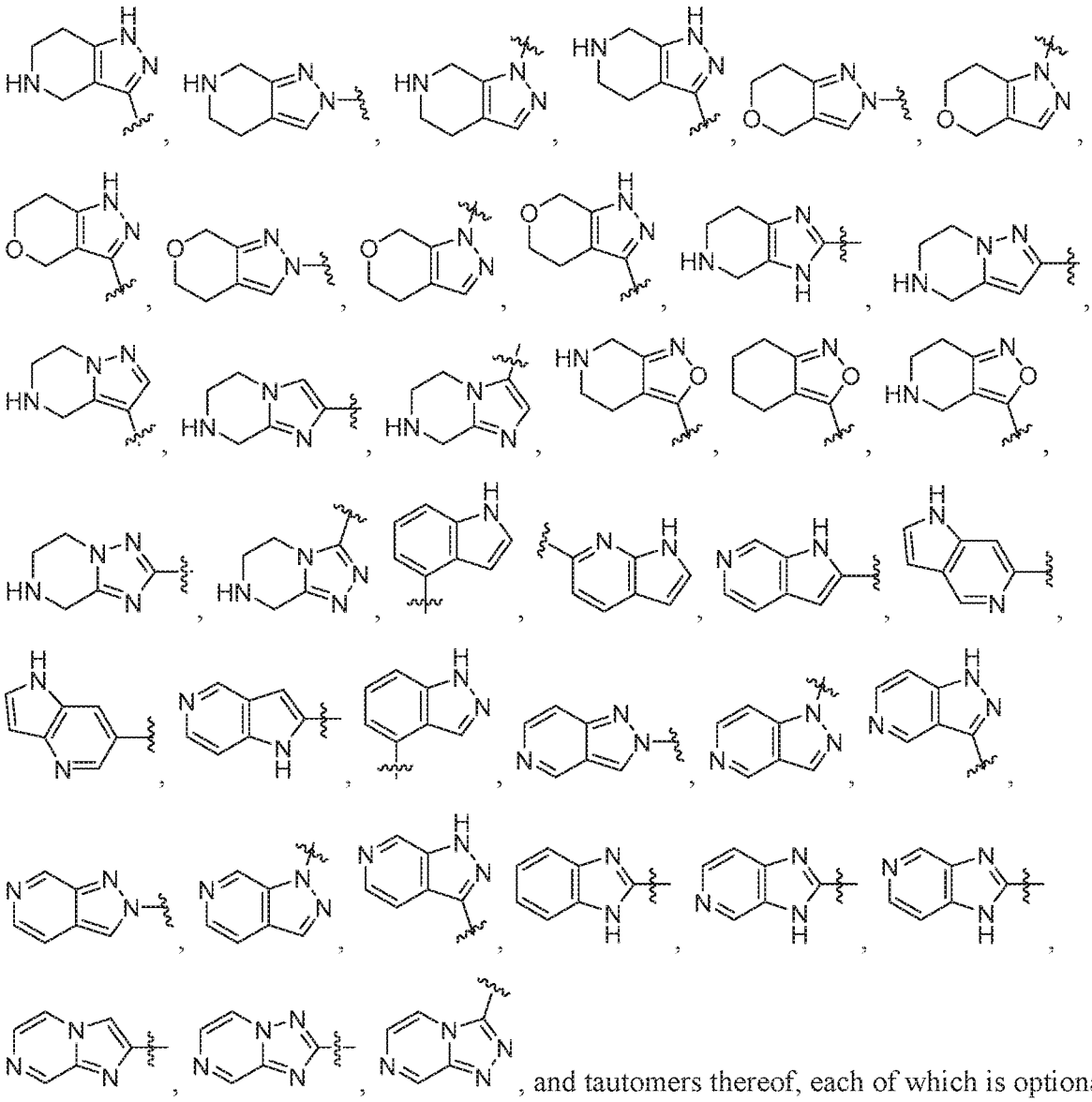






, and tautomers thereof, each of which is optionally substituted with one or more –Q^3-T^3.

[0170] In some embodiments, T^2 is selected from 



, and tautomers thereof, each of which is optionally substituted with one or more $-Q^3-T^3$.

[0171] In some embodiments, each Q^3 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy.

[0172] In some embodiments, each T^3 independently is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocycloalkyl, OR^f, $C(O)R^f$, $C(O)OR^f$, NR^fR^g, $C(O)NR^fR^g$, and $NR^fC(O)R^g$, in which the C_3-C_8 cycloalkyl or 4- to 7-membered heterocycloalkyl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl or C_1-C_6 alkoxy.

[0173] In some embodiments, $-Q^3-T^3$ is oxo.

[0174] In some embodiments, each T^3 independently is NR^fR^g, $C(O)NR^fR^g$, or $NR^fC(O)R^g$. In some embodiments, each of R^f and R^g is H. In some embodiments, each of R^f and R^g

independently is H, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl. In some embodiments, one of R^f and R^g is H and the other is C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl. In some embodiments, one of R^f and R^g is H and the other is C_3-C_8 cycloalkyl. In some embodiments, one of R^f and R^g is C_1-C_6 alkyl and the other is C_3-C_8 cycloalkyl.

[0175] In some embodiments, at least one of R^8 and R^9 is H.

[0176] In some embodiments, each of R^8 and R^9 is H.

[0177] In some embodiments, R^8 is H.

[0178] In some embodiments, R^9 is $-Q^4$-T^4, in which Q^4 is a bond or C_1-C_6 alkylene linker optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxyl, and T^4 is H, halo, OR^h, NR^hR^i, $NR^hC(O)R^i$, $C(O)NR^hR^i$, $C(O)R^h$, $C(O)OR^h$, or R^{S2}, in which R^{S2} is C_3-C_8 cycloalkyl or 4- to 7-membered heterocycloalkyl, and R^{S2} is optionally substituted with one or more $-Q^5$-T^5.

[0179] In some embodiments, each Q^5 independently is a bond or C_1-C_3 alkylene linker.

[0180] In some embodiments, each T^5 independently is selected from the group consisting of H, halo, cyano, C_1-C_6 alkyl, OR^j, $C(O)R^j$, $C(O)OR^j$, NR^jR^k, $C(O)NR^jR^k$, and $NR^jC(O)R^k$.

[0181] In some embodiments, R^9 is C_1-C_3 alkyl.

[0182] For a compound of any one of formulae (I0)-(IV0), (I)-(III), (I0a)-(I0l), (I0a')-(I0i'), (Ia)-(Il), (Ia')-(Ii'), (II0a)-(II0b), (III0a)-(III0b), and (IV0a)-(IV0b), X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, ring B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^l, and R^m can each be, where applicable, selected from any of the groups described herein, and any group described herein for any of X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, ring B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^l, and R^m can be combined, where applicable, with any group described herein for one or more of the remainder of X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, ring B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^l, and R^m.

[0183] In some embodiments, the compound is selected from those in Table 1, tautomers thereof, and pharmaceutically acceptable salts of the compounds and tautomers.

[0184] In some embodiments, one or more of the compounds disclosed herein (e.g., a compound of any of Formulae (I0)-(IV0) and Formula (I)-(III)) inhibit a kinase with an enzyme

inhibition IC_{50} value of about 100 nM or greater, 1 μM or greater, 10 μM or greater, 100 μM or greater, or 1000 μM or greater.

[0185] In some embodiments, one or more of the compounds disclosed herein (e.g., a compound of any of Formulae (I0)-(IV0) and Formula (I)-(III)) inhibit a kinase with an enzyme inhibition IC_{50} value of about 1 mM or greater.

[0186] In some embodiments, one or more of the compounds disclosed herein (e.g., a compound of any of Formulae (I0)-(IV0) and Formula (I)-(III)) inhibit a kinase with an enzyme inhibition IC_{50} value of 1 μM or greater, 2 μM or greater, 5 μM or greater, or 10 μM or greater, wherein the kinase is one or more of the following: AbI, AurA, CHK1, MAP4K, IRAK4, JAK3, EphA2, FGFR3, KDR, Lck, MARK1, MNK2, PKCb2, SIK, and Src.

[0187] The present disclosure provides a pharmaceutical composition comprising a compound of any one of the Formulae described herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0188] The present disclosure provides a method of preventing or treating a blood disorder via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, e.g., any of Formulae (I0)-(IV0) and Formulae (I)-(III).

[0189] The present disclosure provides a method of preventing or treating cancer (e.g., via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2), the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, e.g., any of Formulae (I0)-(IV0) and Formulae (I)-(III).

[0190] In some embodiments, the blood disorder is sickle cell anemia or β-thalassemia.

[0191] In some embodiments, the blood disorder is a hematological cancer.

[0192] In some embodiments, the cancer is lymphoma, leukemia, melanoma, breast cancer, ovarian cancer, hepatocellular carcinoma, prostate carcinoma, lung cancer, brain cancer, or hematological cancer.

[0193] In some embodiments, the hematological cancer is acute myeloid leukemia (AML) or chronic lymphocytic leukemia (CLL).

[0194] In some embodiments, one or more of the compounds disclosed herein (e.g., a compound of any of Formulae (I0)-(IV0) and Formula (I)-(III)) are selective inhibitors of EHMT2.

[0195] Representative compounds of the present disclosure include compounds listed in Table 1 or tautomers and salts thereof.

Table 1

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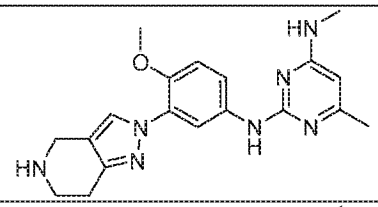
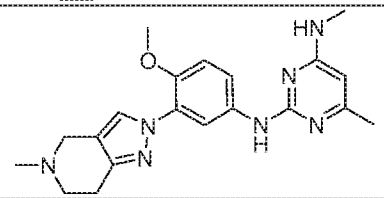
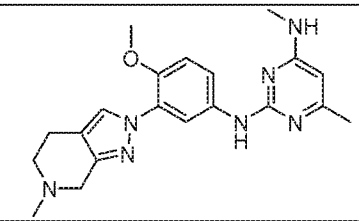
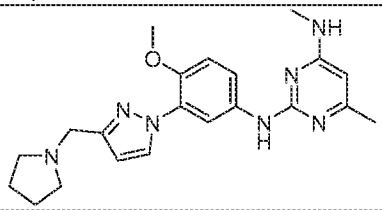
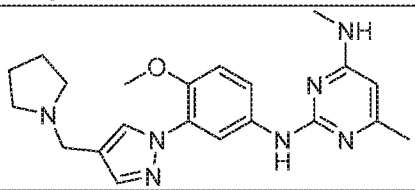
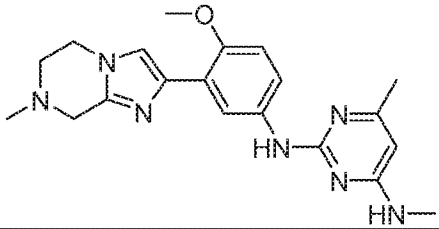
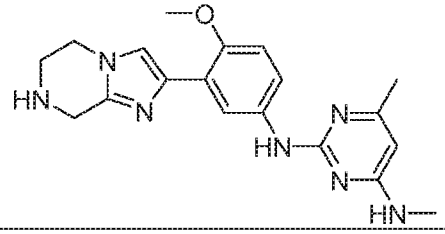
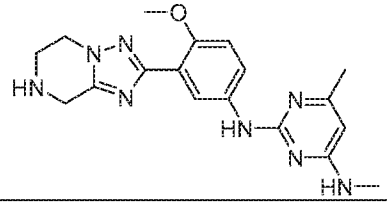
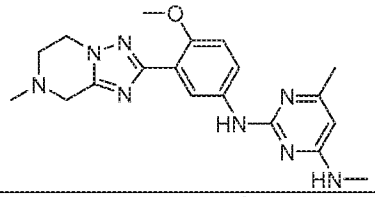
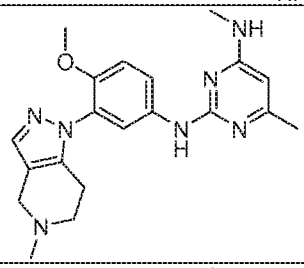
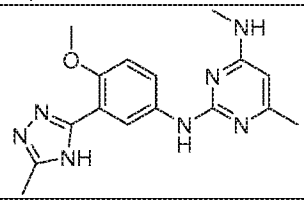
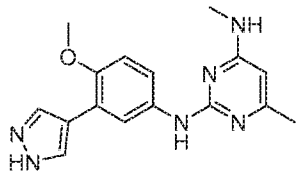
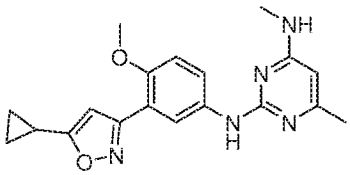
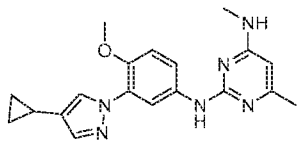
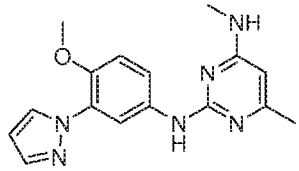
1	
2	
3	
4	
5	
6	
7	

Compound No.	Structure
8	
9	
10	
11	
12	
13	
14	
15	

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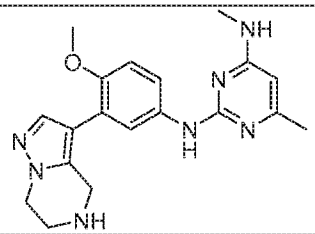
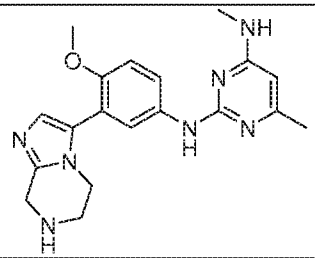
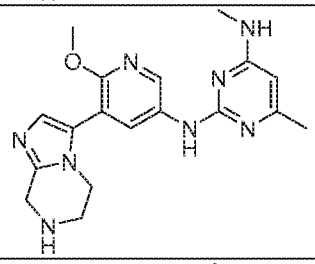
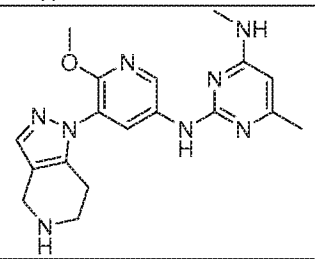
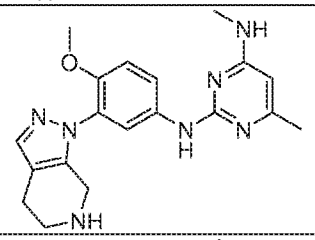
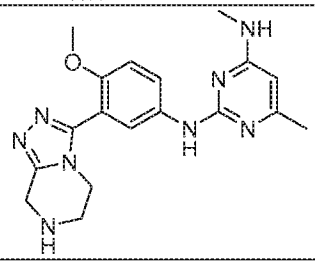
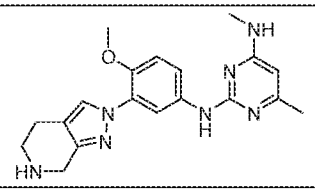
16	
17	
18	
19	
20	
21	
22	

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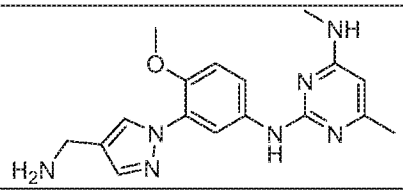
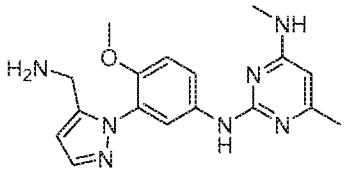
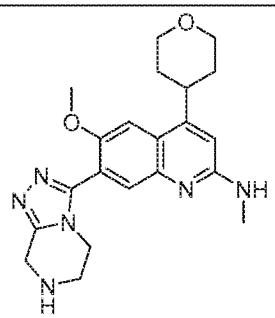
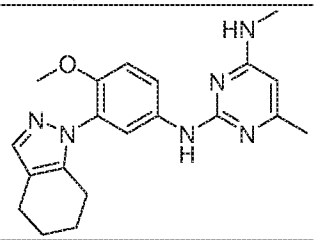
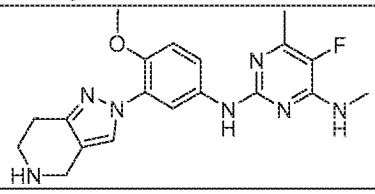
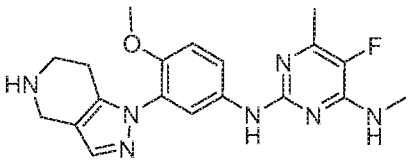
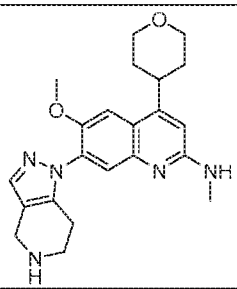
23	
24	
25	
26	
27	
28	
29	

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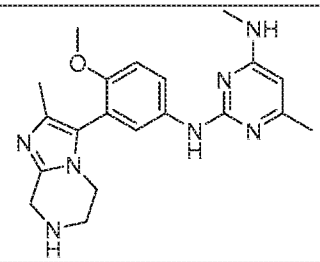
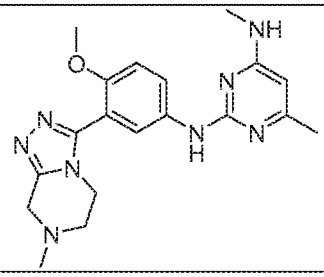
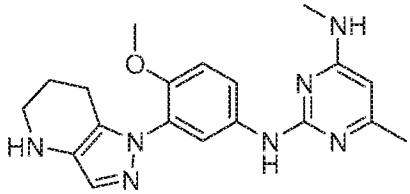
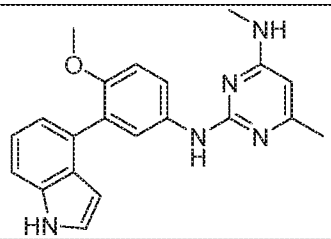
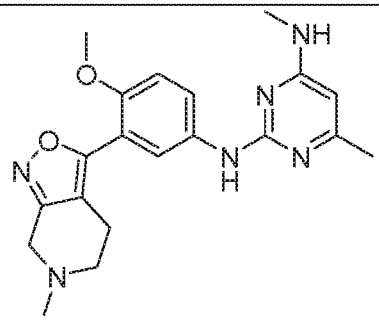
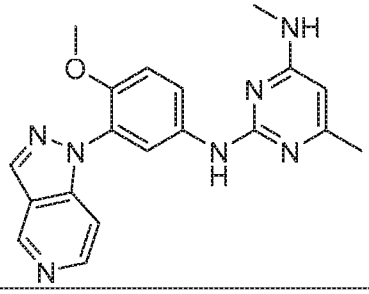
30	
31	
32	
33	
34	
35	

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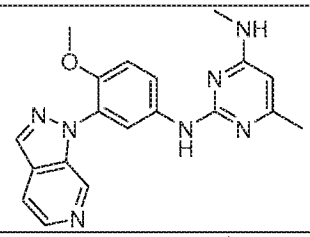
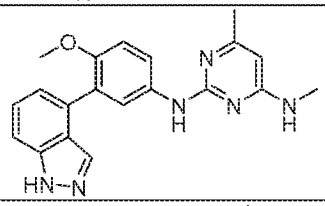
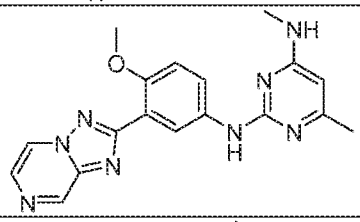
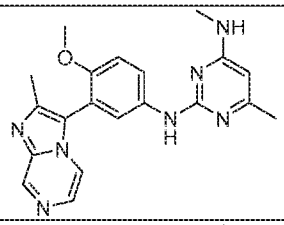
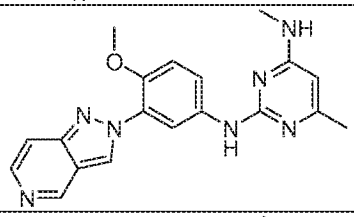
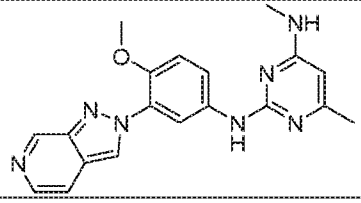
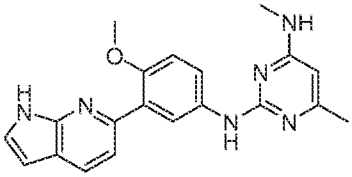
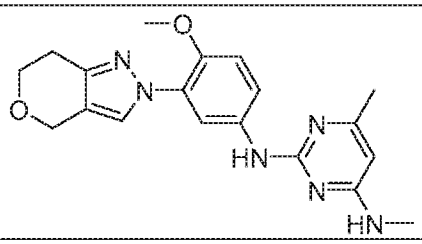
36	
37	
38	
39	
40	
41	
42	
43	

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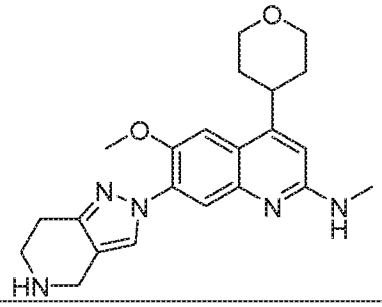
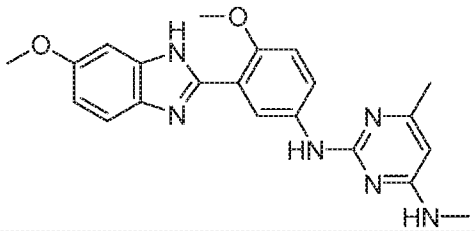
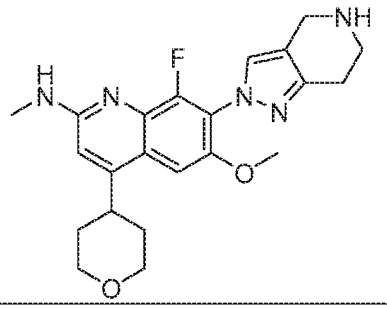
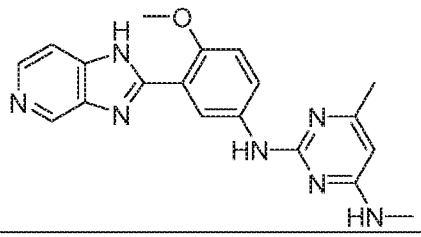
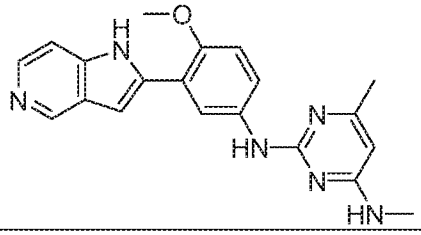
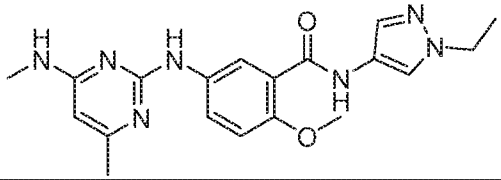
44	
45	
46	
47	
48	
49	

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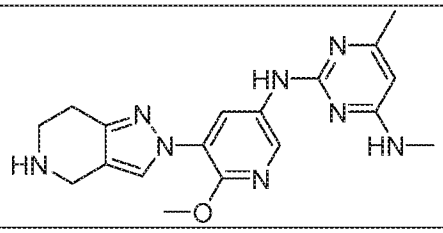
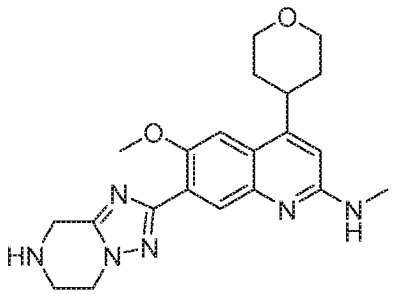
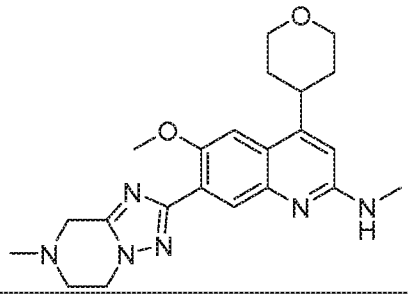
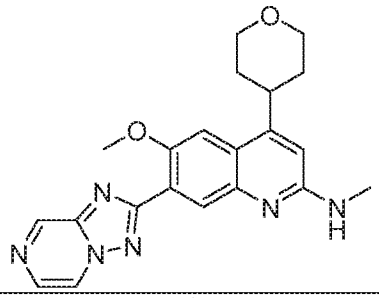
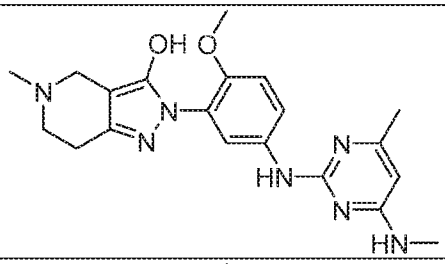
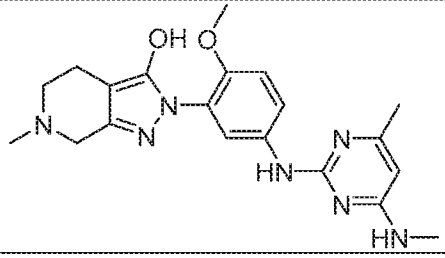
50	
51	
52	
53	
54	
55	

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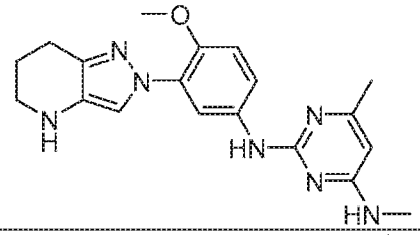
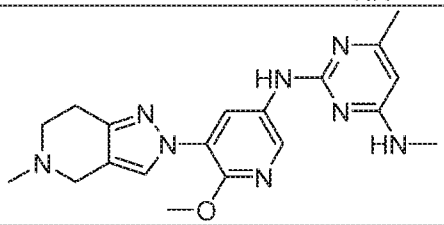
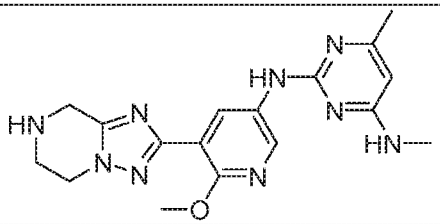
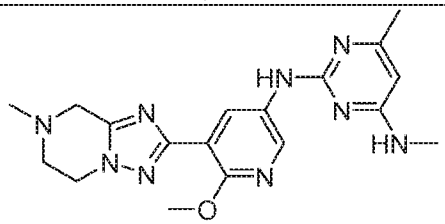
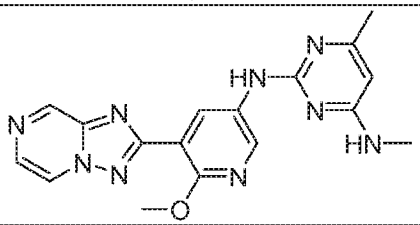
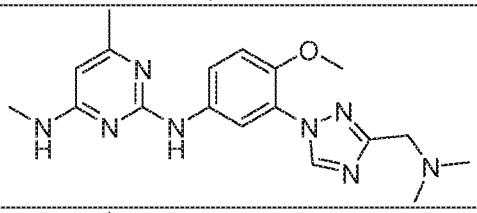
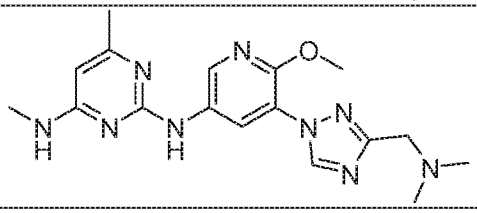
56	
57	
58	
59	
60	
61	
62	

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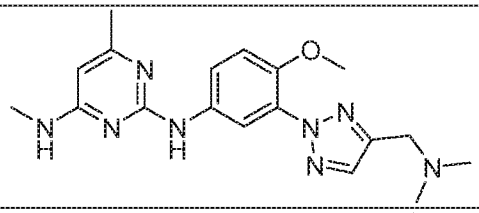
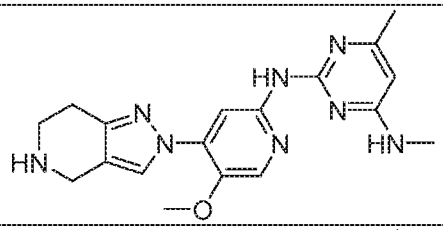
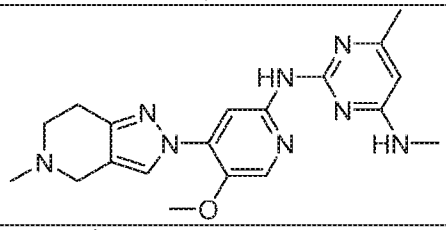
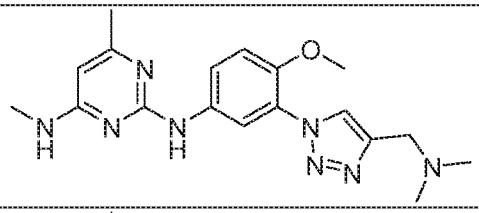
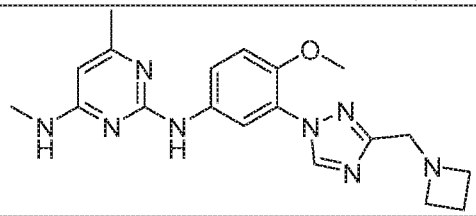
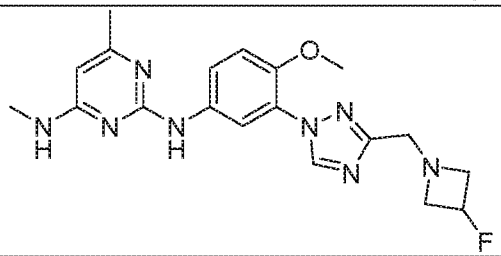
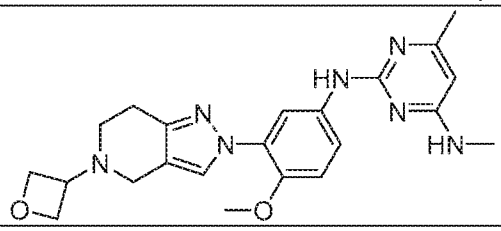
63	
64	
65	
66	
67	
68	
69	

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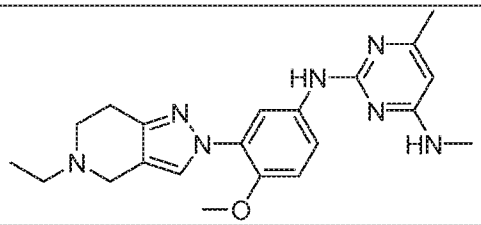
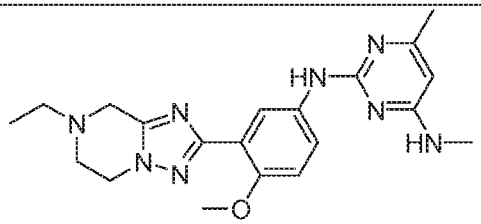
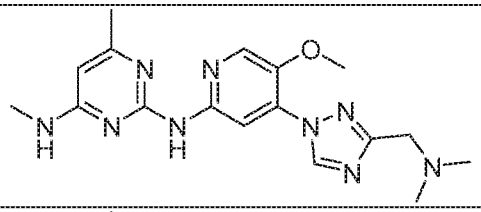
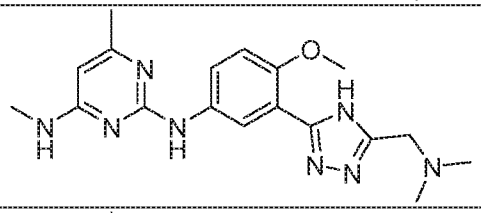
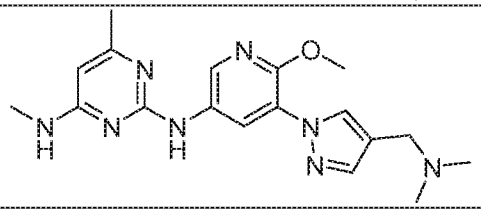
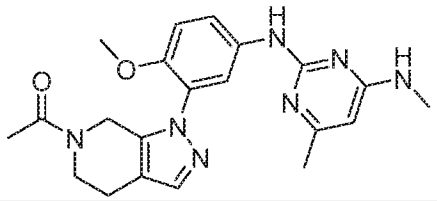
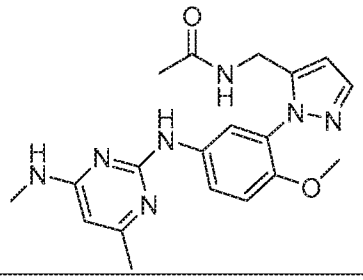
70	
71	
72	
73	
74	
75	
76	

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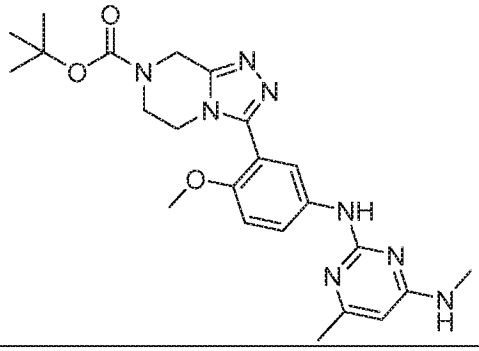
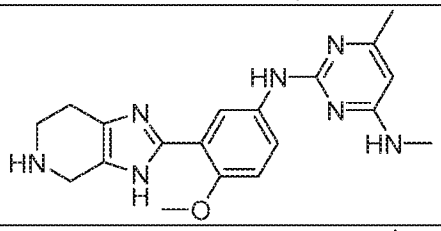
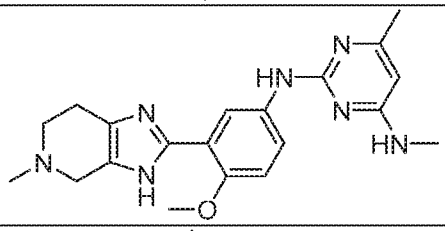
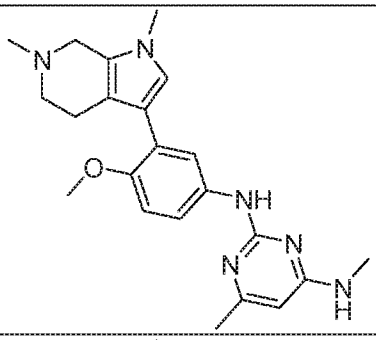
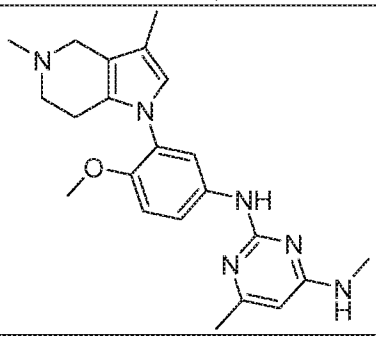
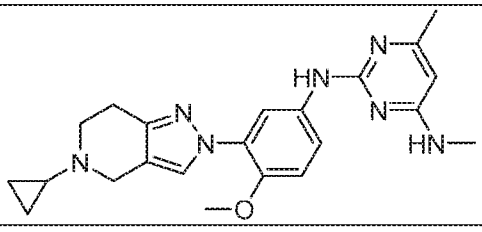
77	
78	
79	
80	
81	
82	

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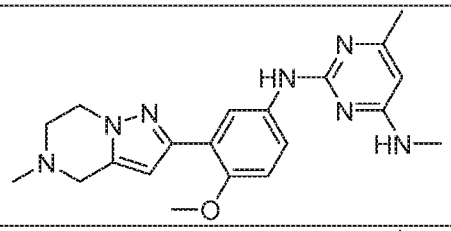
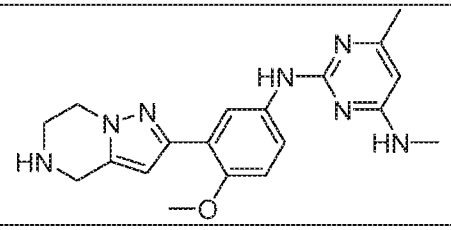
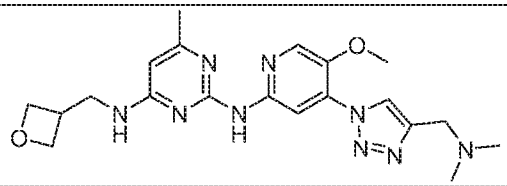
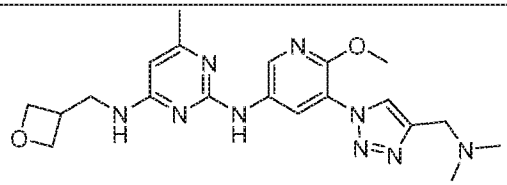
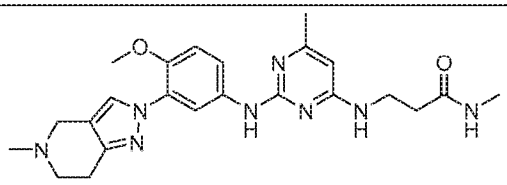
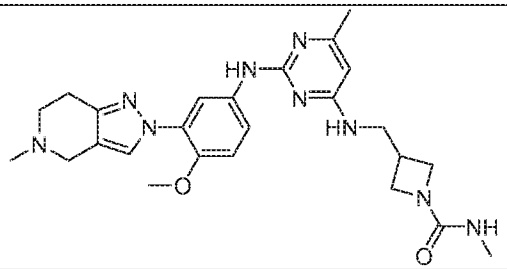
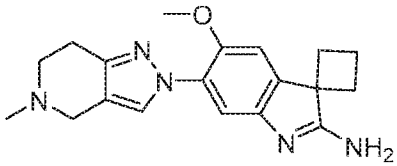
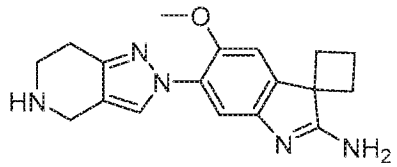
83	
84	
85	
86	
87	
88	
89	
90	

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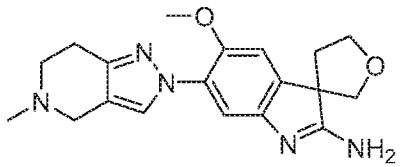
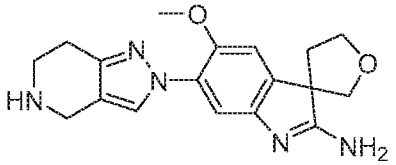
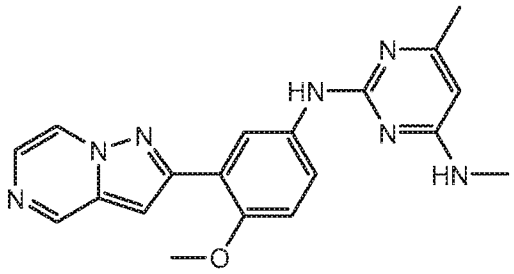
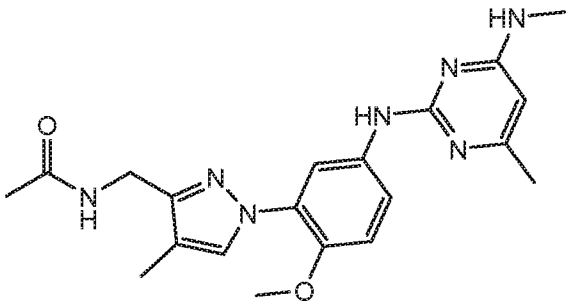
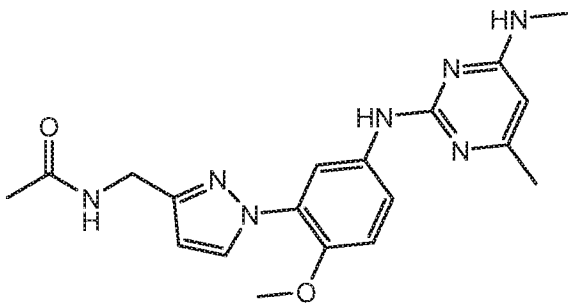
91	
92	
93	
94	
95	

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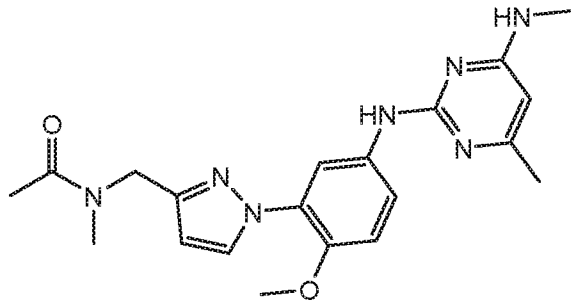
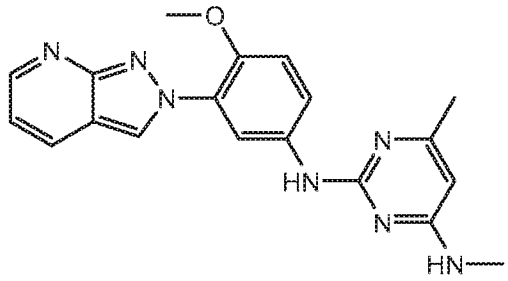
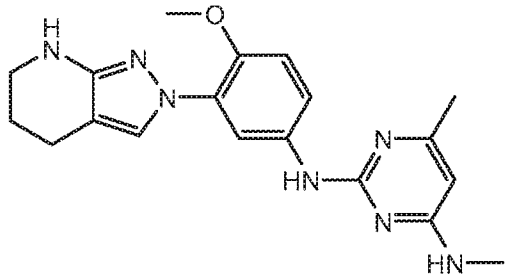
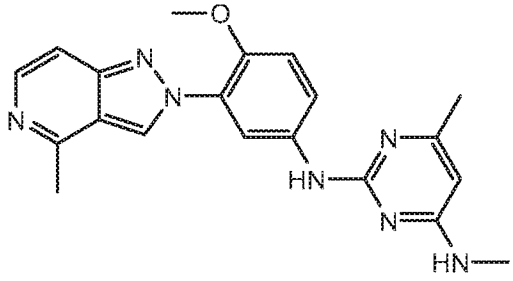
96	
97	
98	
99	

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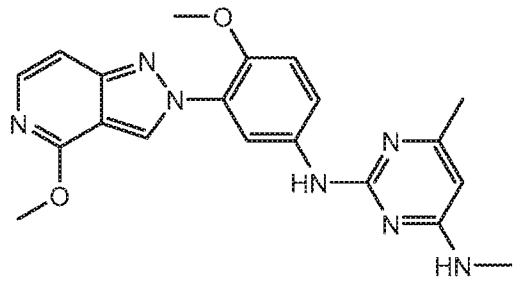
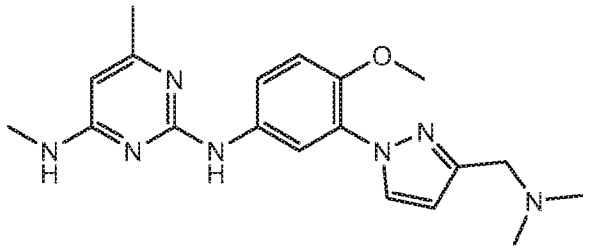
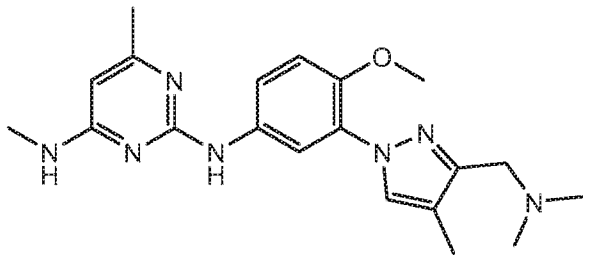
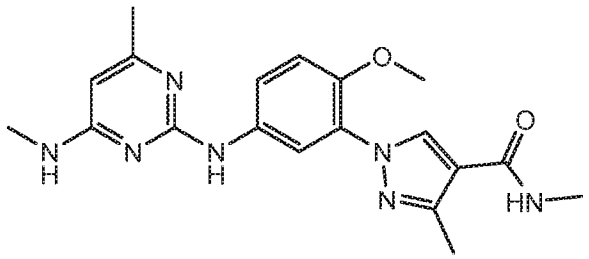
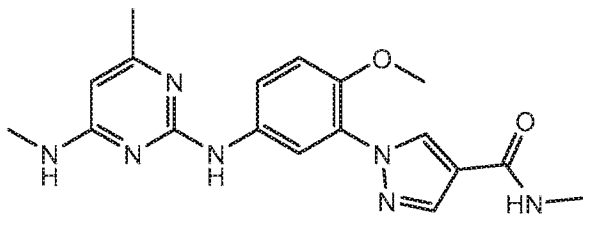
100	
101	
102	
103	
104	

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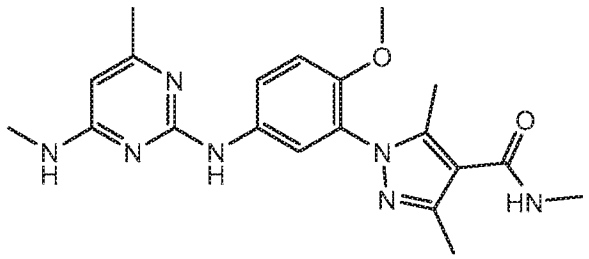
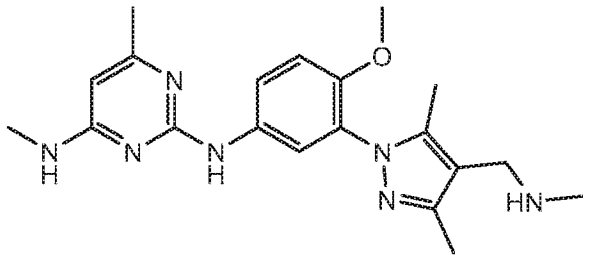
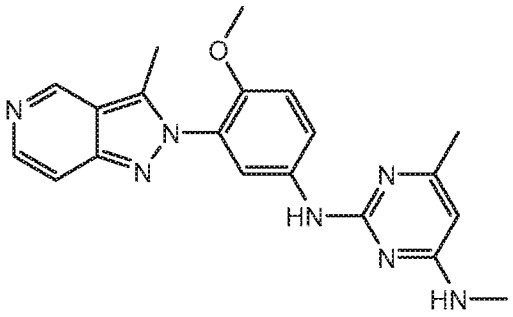
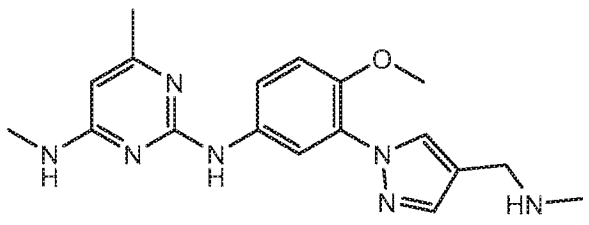
105	
106	
107	
108	

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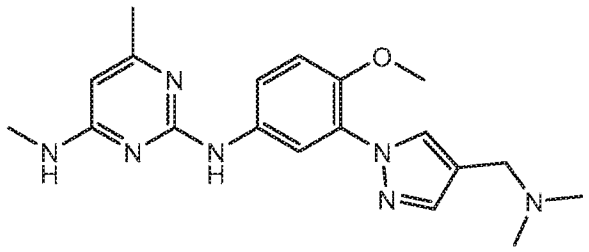
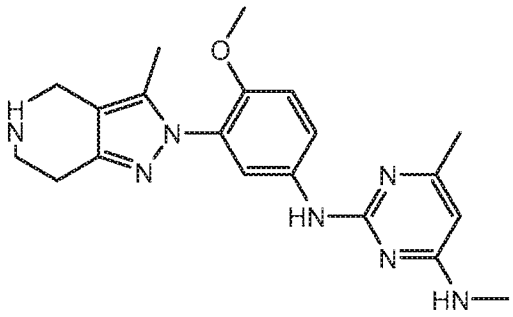
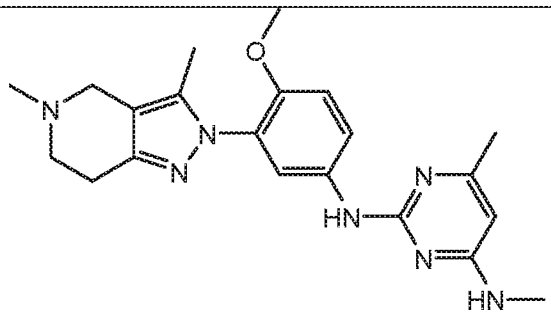
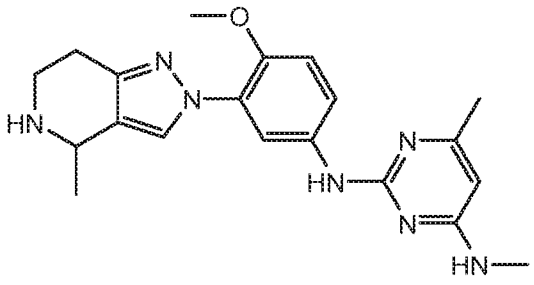
109	
110	
111	
112	

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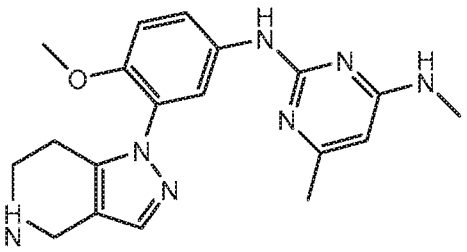
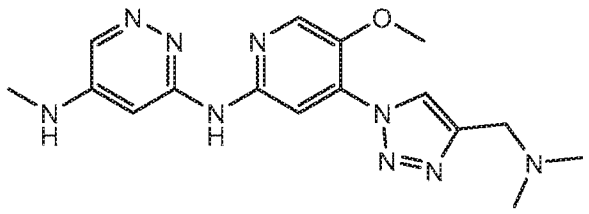
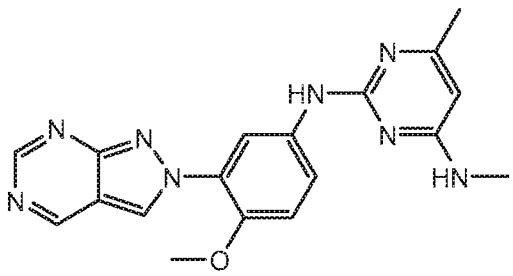
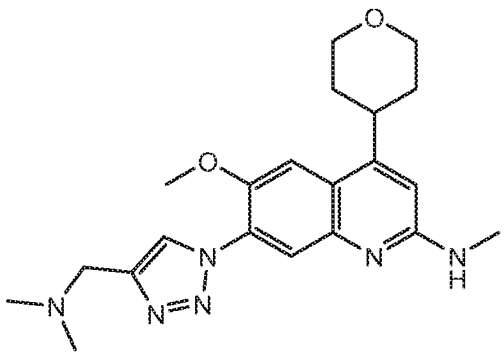
113	
114	
115	
116	

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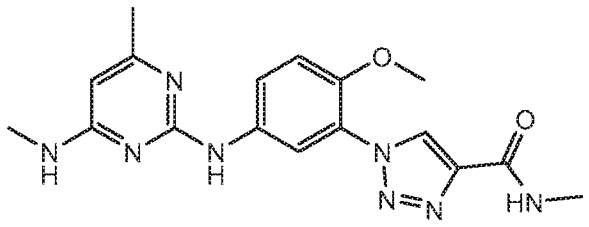
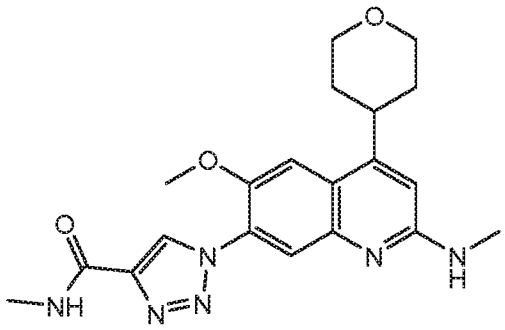
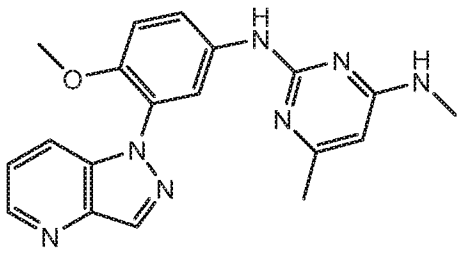
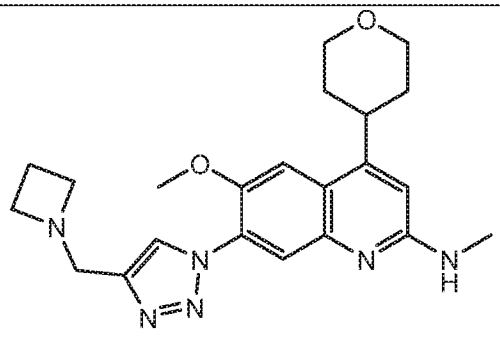
117	
118	
119	
120	

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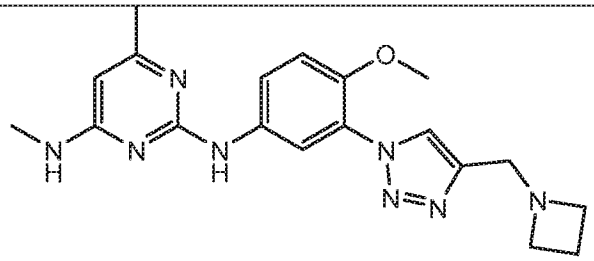
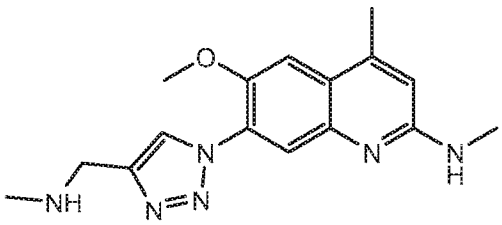
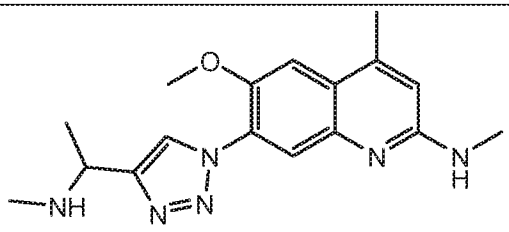
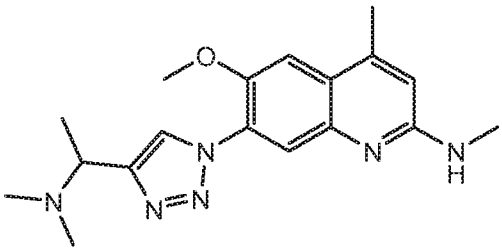
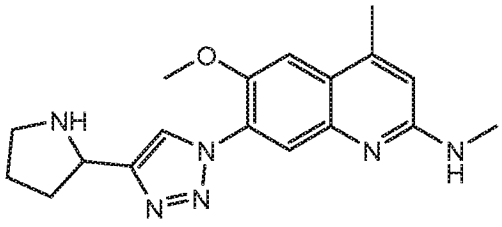
121	
122	
123	
124	
125	

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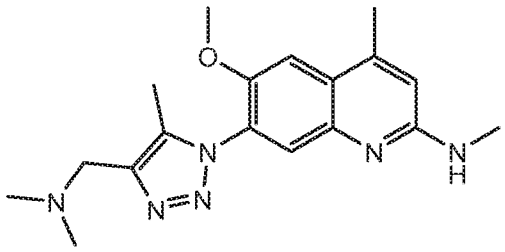
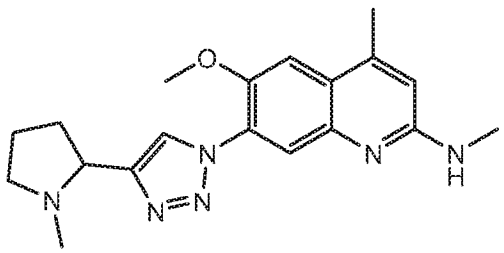
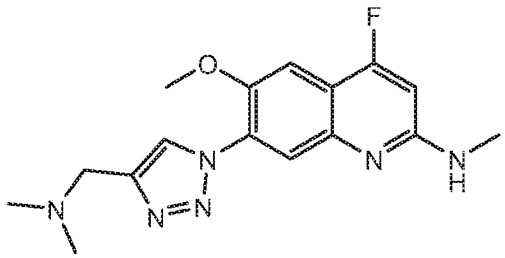
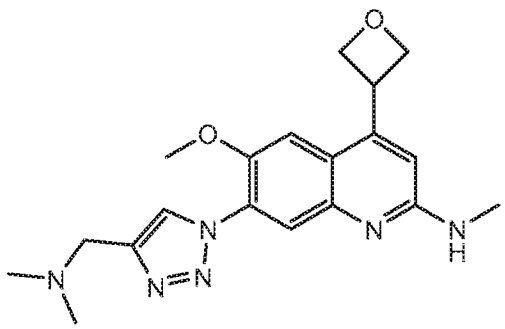
126	
127	
128	
129	

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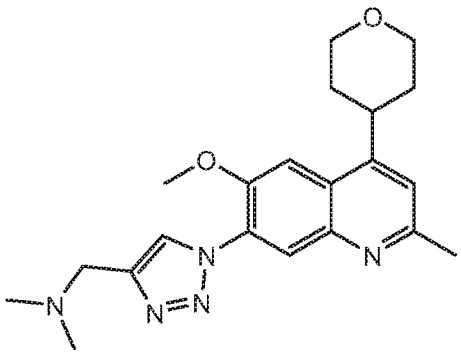
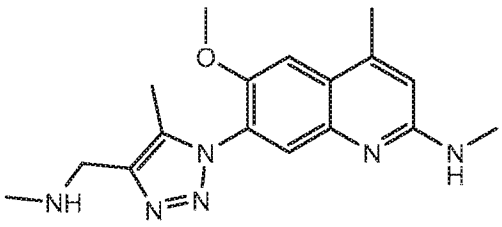
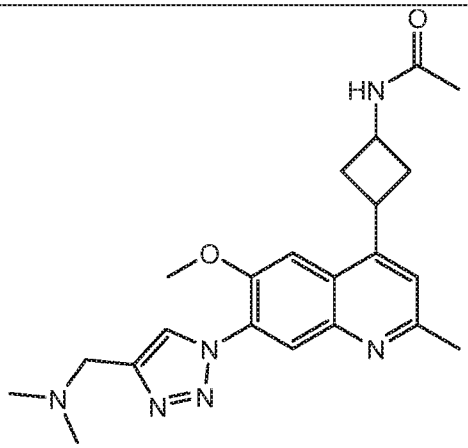
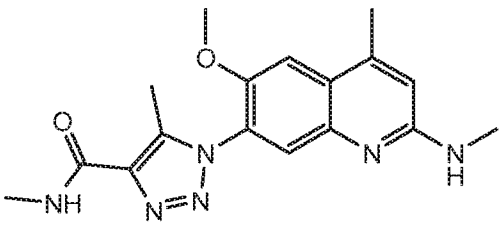
130	
131	
132	
133	

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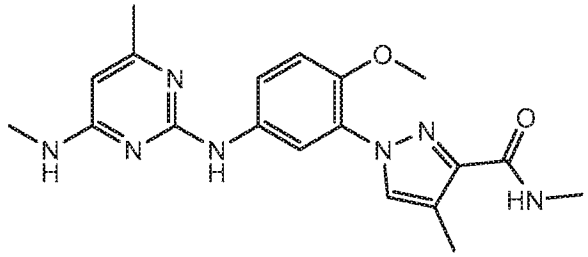
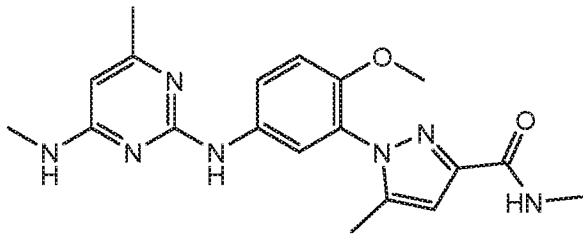
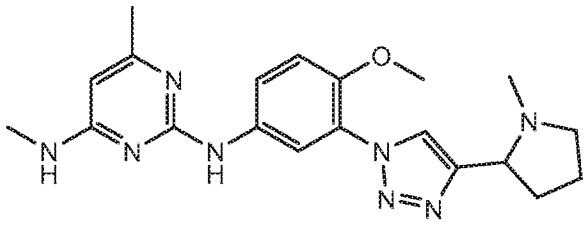
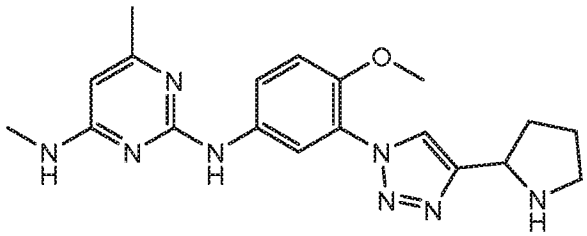
134	
135	
136	
137	

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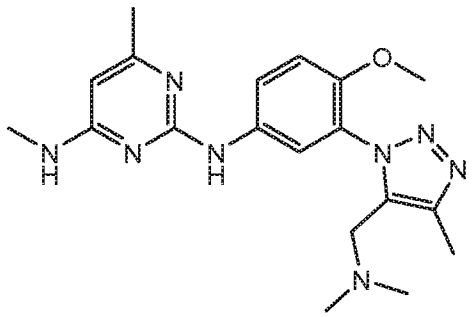
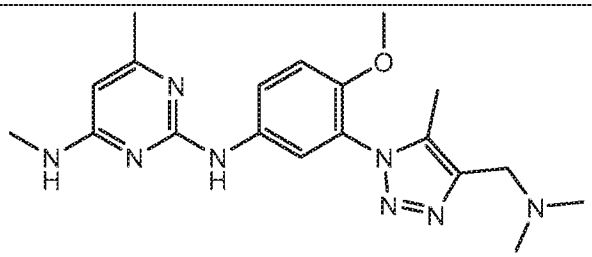
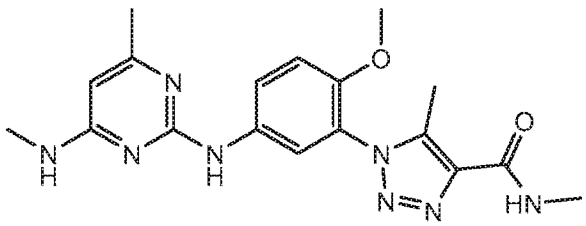
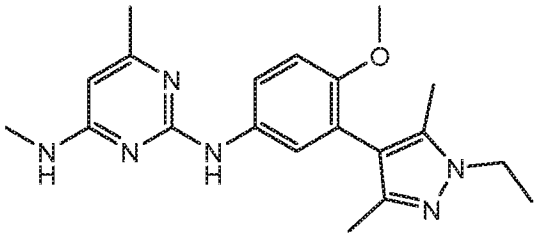
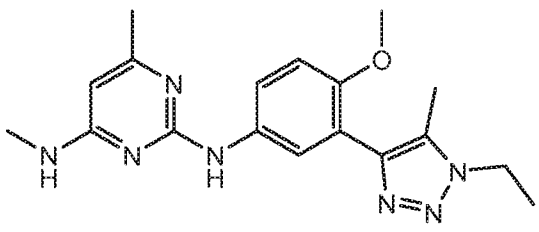
138	
139	
140	
141	
142	

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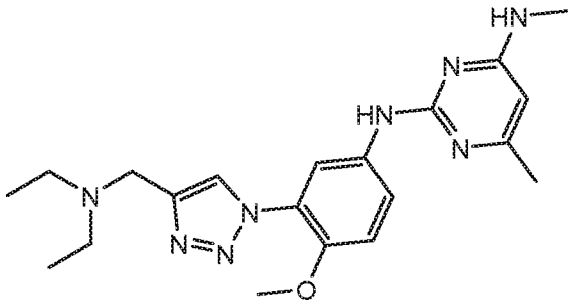
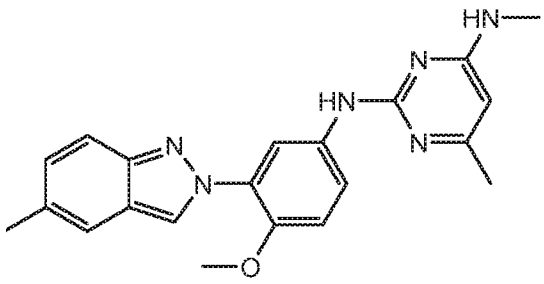
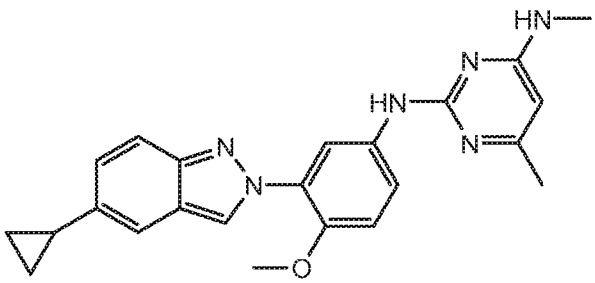
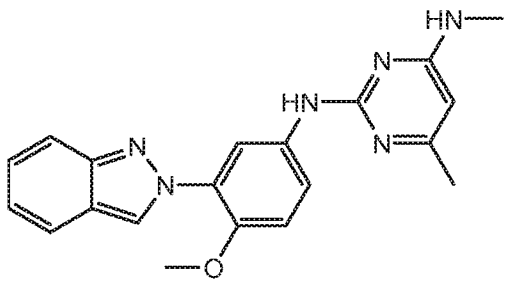
143	
144	
145	
146	

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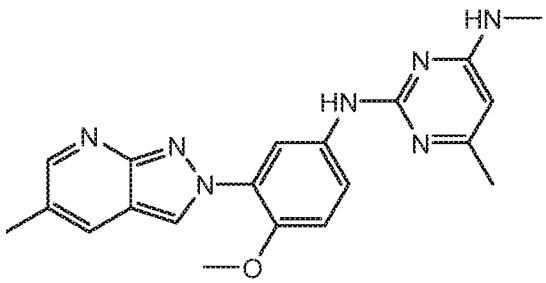
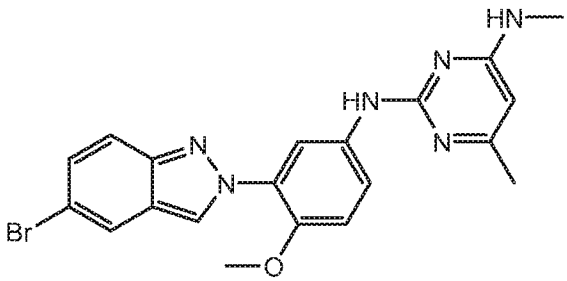
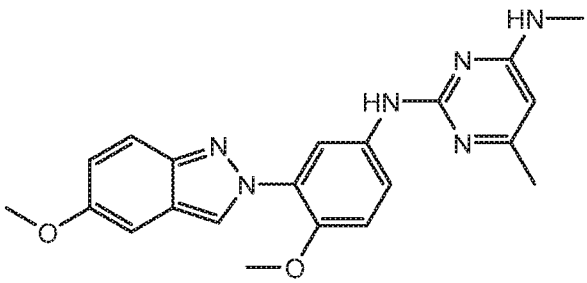
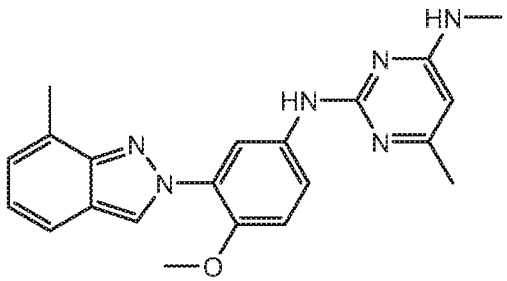
147	
148	
149	
150	

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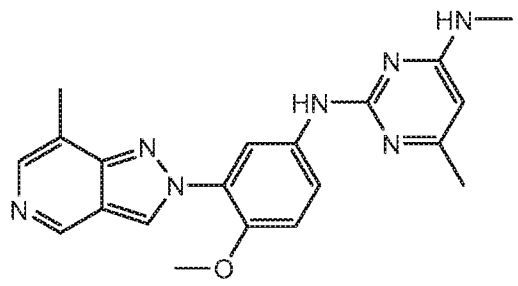
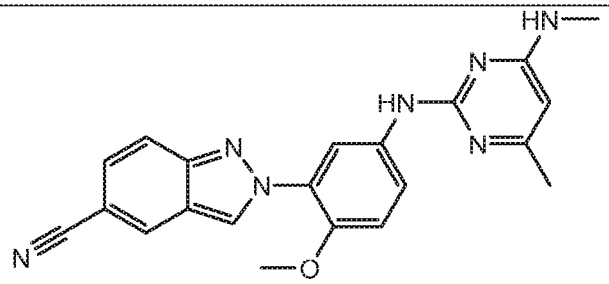
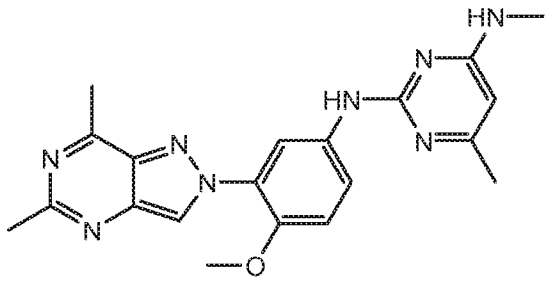
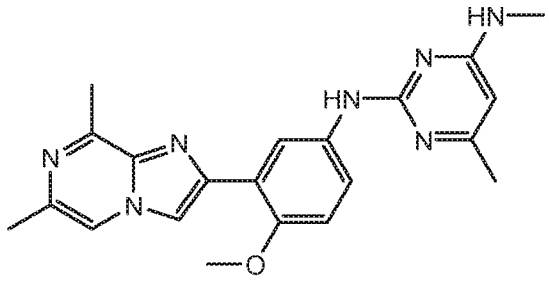
151	
152	
153	
154	

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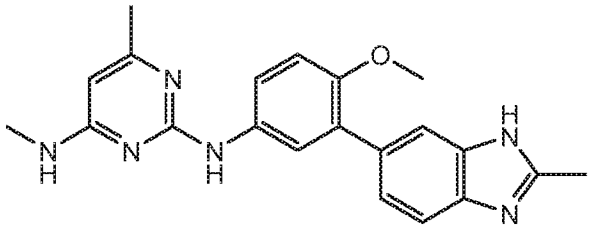
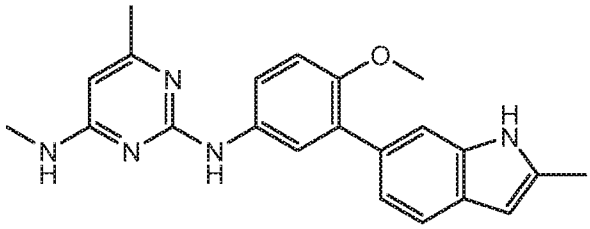
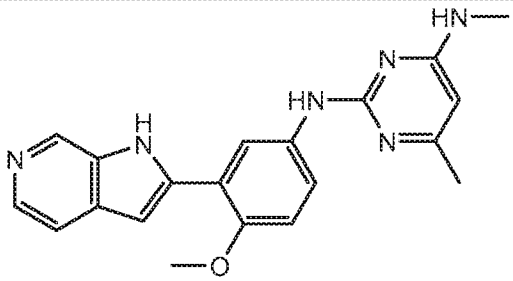
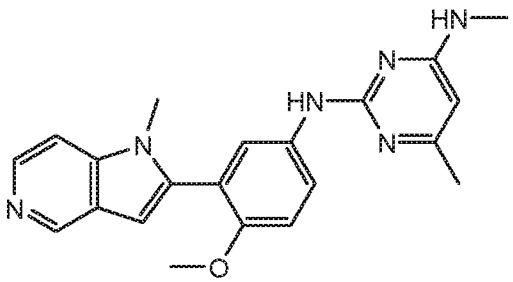
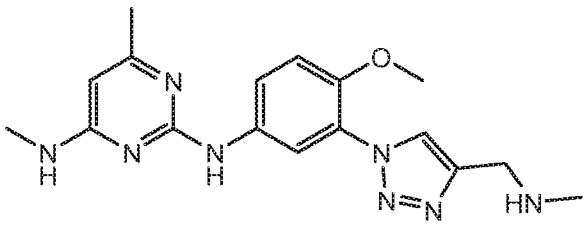
155	
156	
157	
158	
159	

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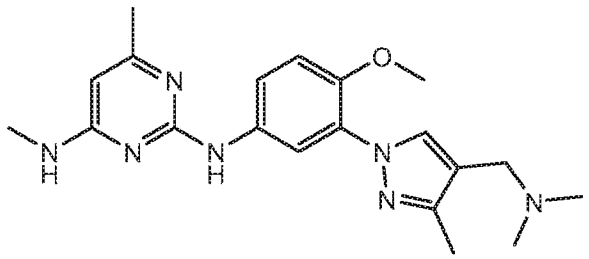
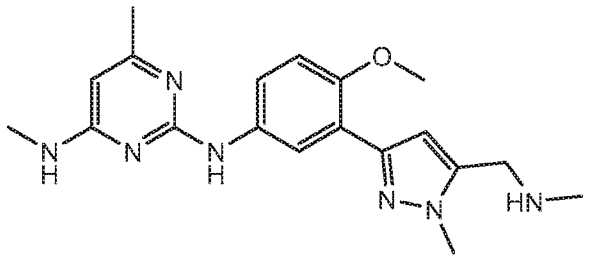
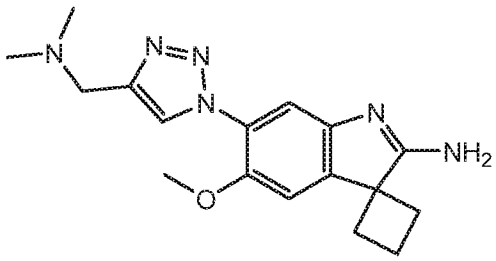
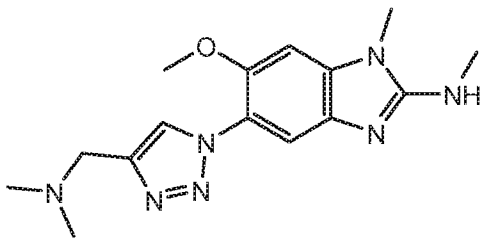
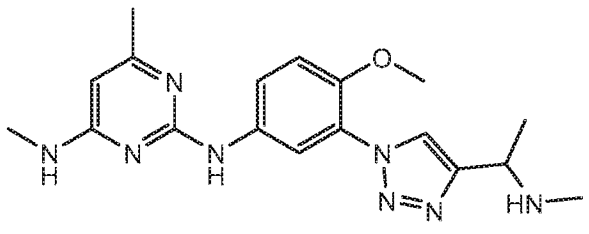
160	
161	
162	
163	
164	

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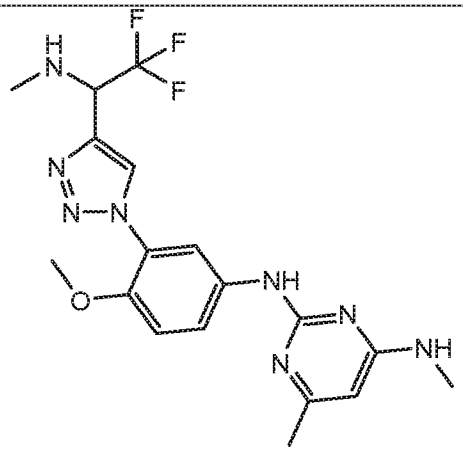
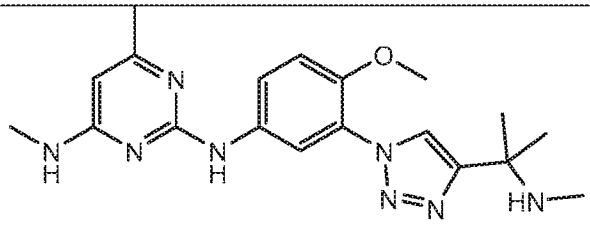
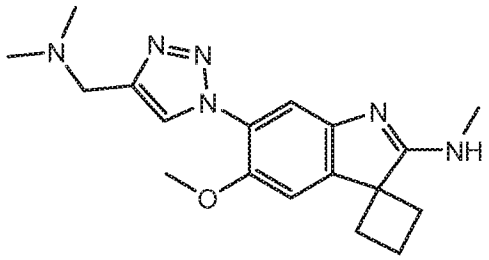
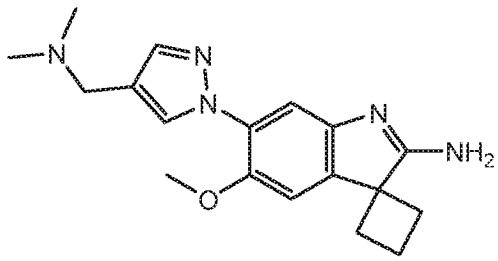
165	
166	
167	
168	

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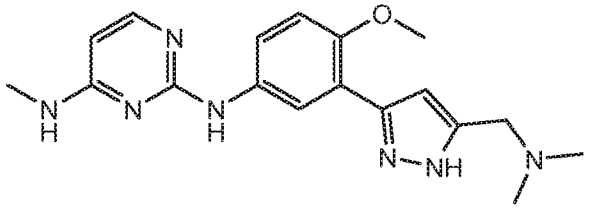
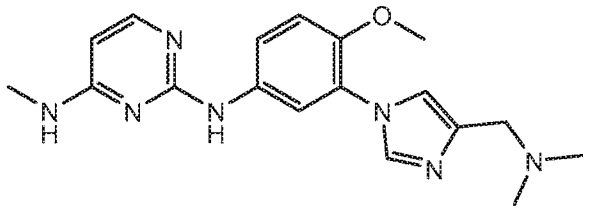
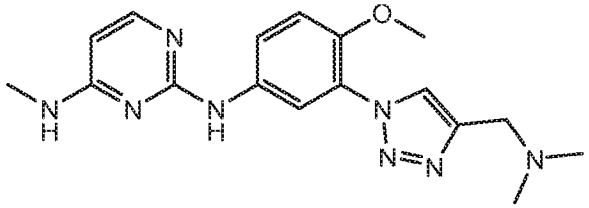
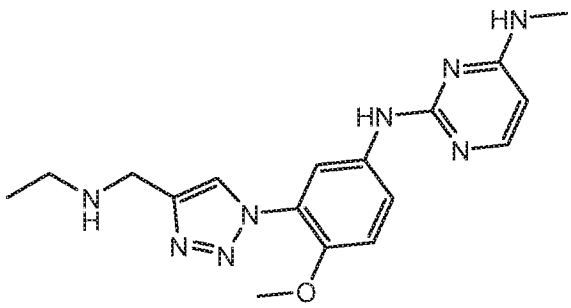
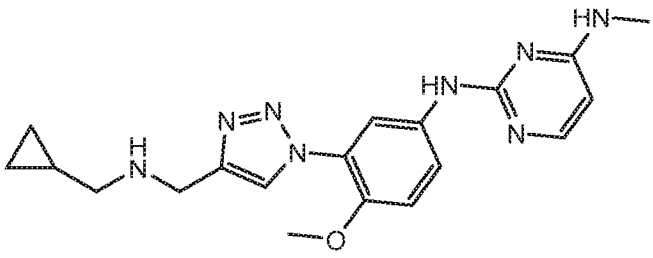
169	
170	
171	
172	
173	

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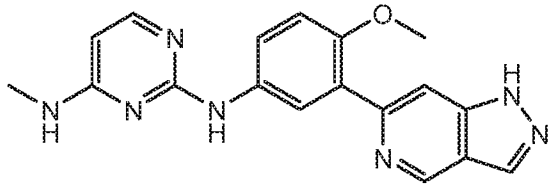
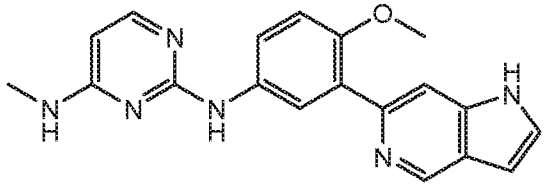
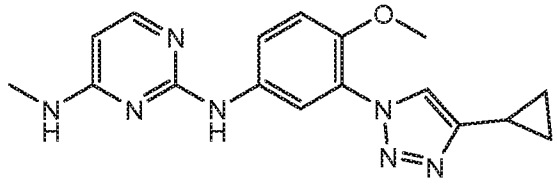
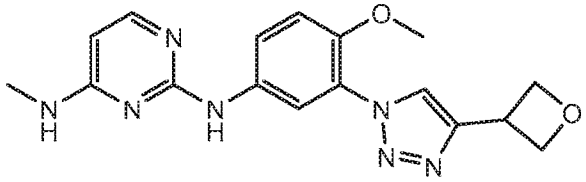
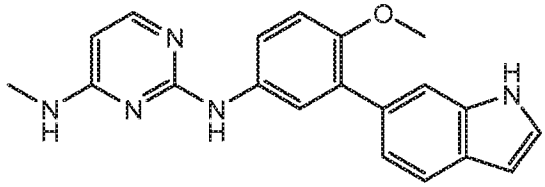
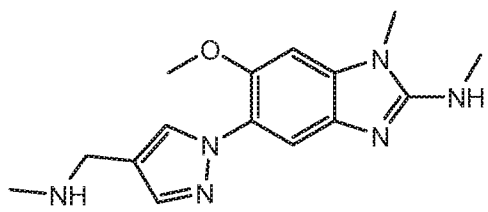
174	
175	
176	
177	
178	
179	

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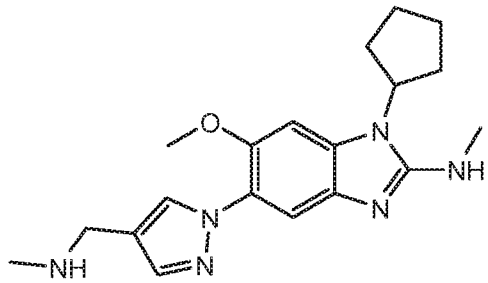
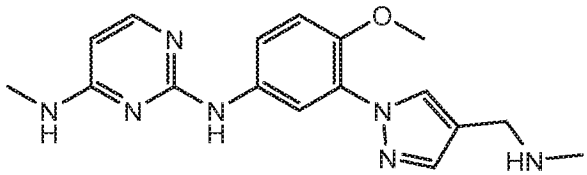
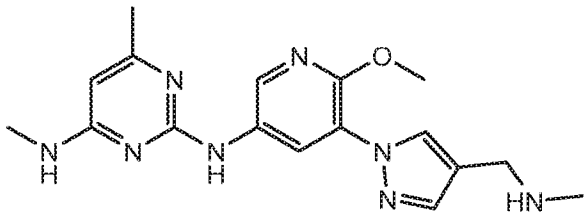
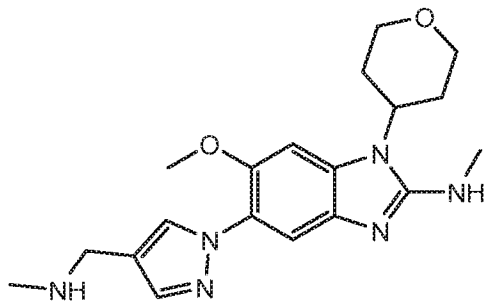
180	
181	
182	
183	

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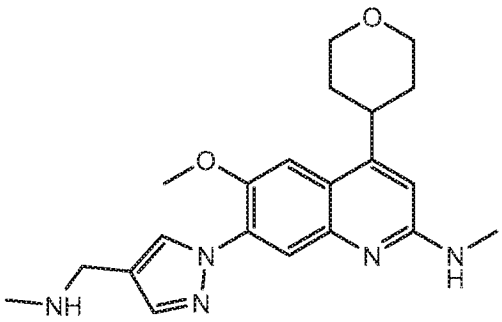
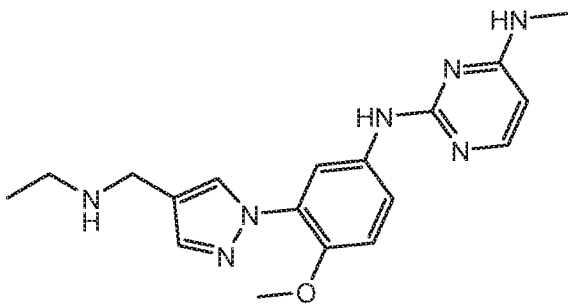
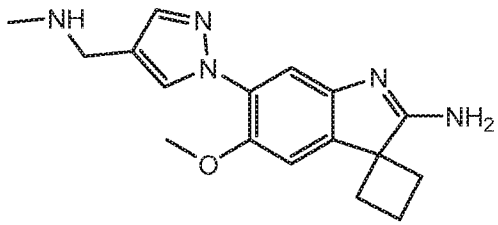
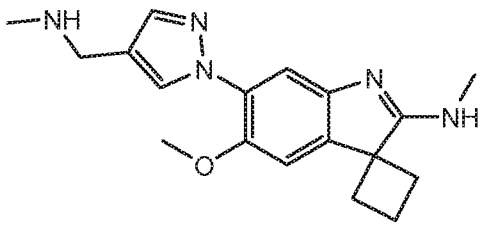
184	
185	
186	
187	

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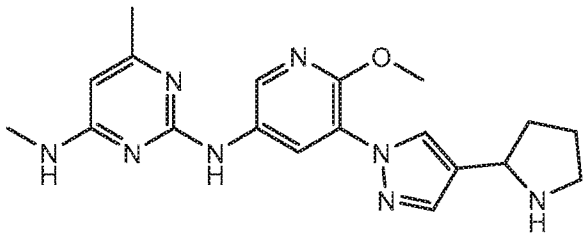
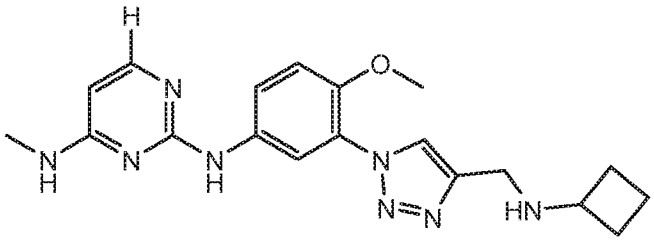
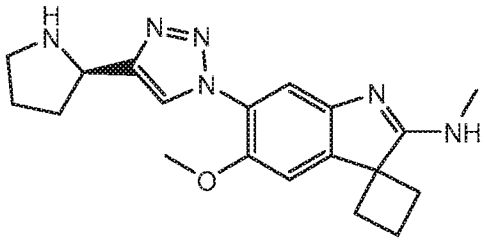
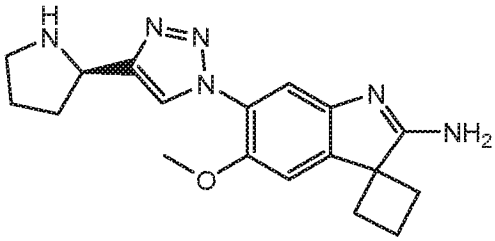
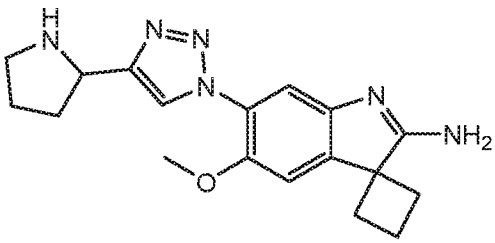
188	
191	
192	
193	
194	

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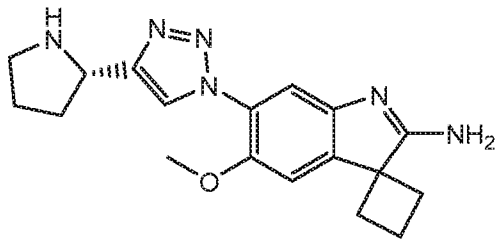
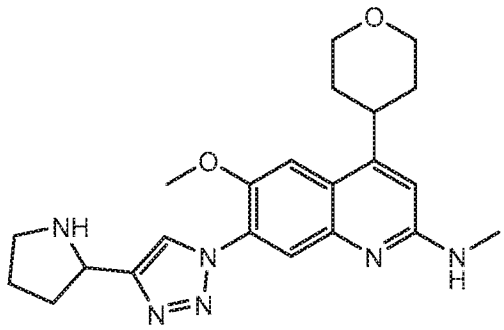
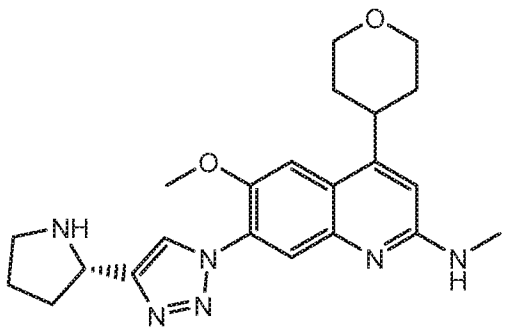
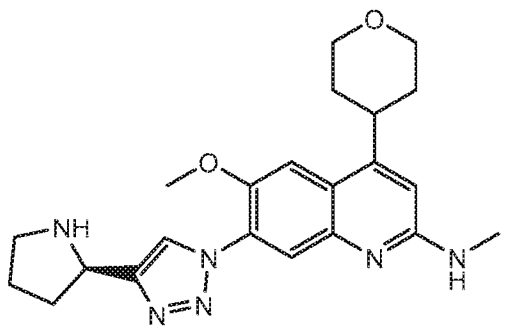
195	
196	
197	
198	

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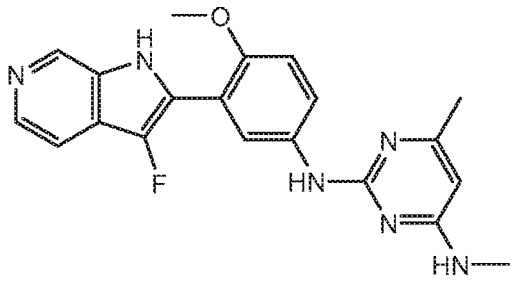
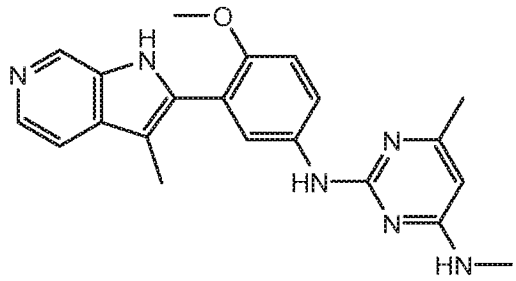
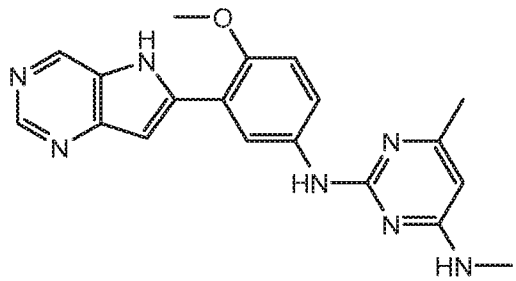
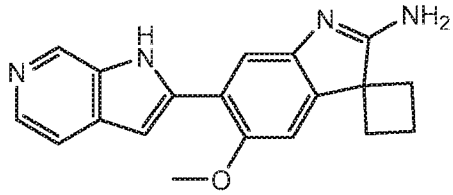
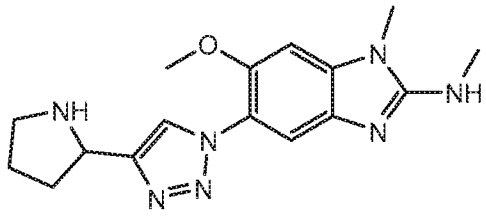
199	
200	
201	
202	
203	

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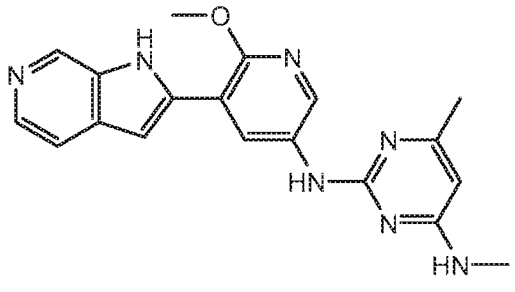
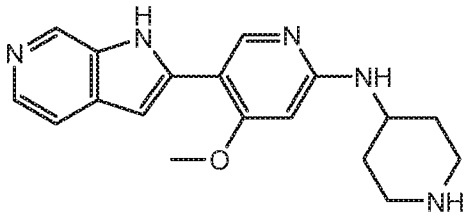
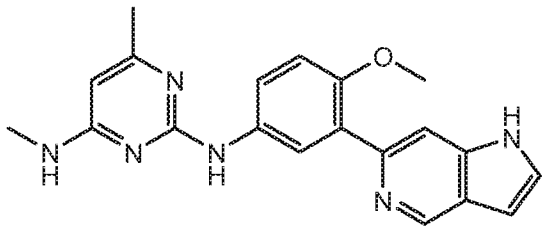
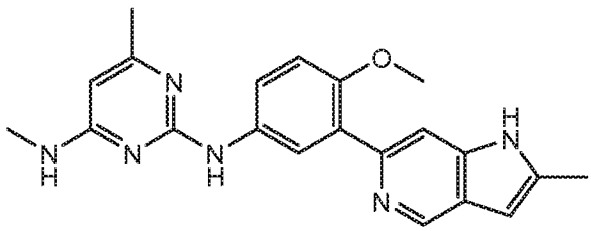
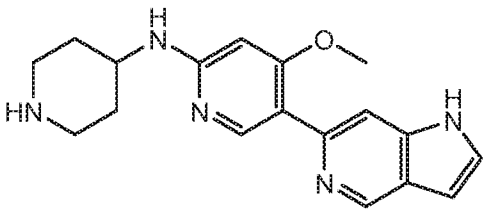
204	
205	
206	
207	
208	

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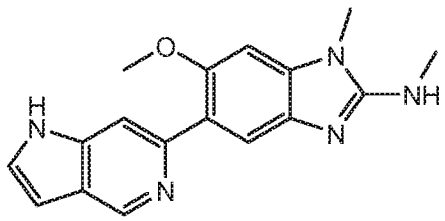
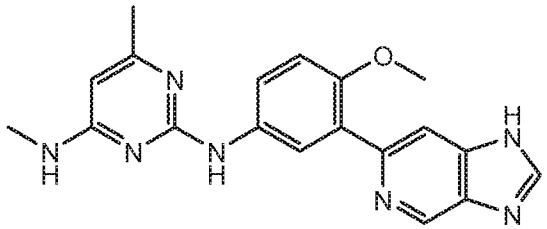
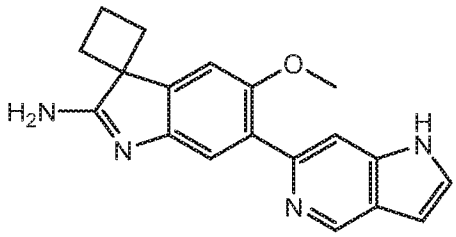
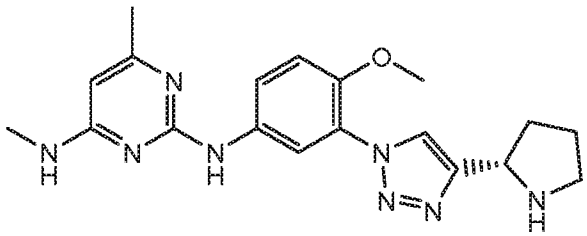
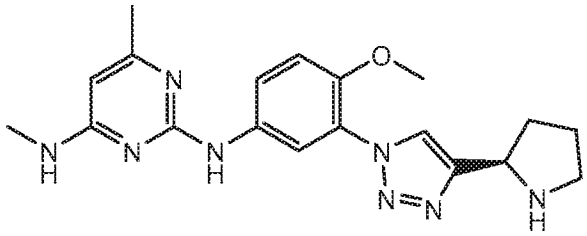
209	
210	
211	
212	
213	

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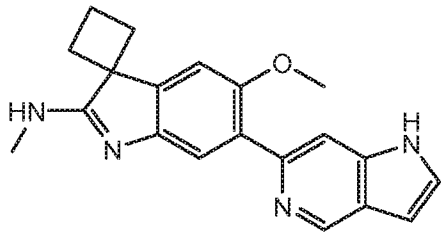
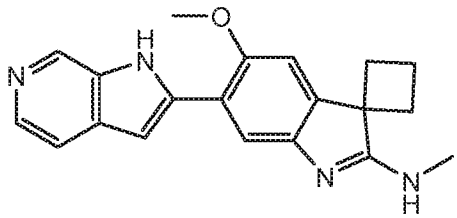
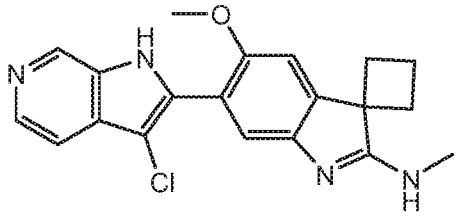
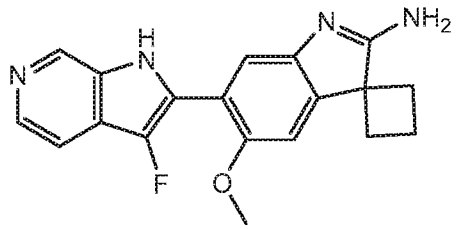
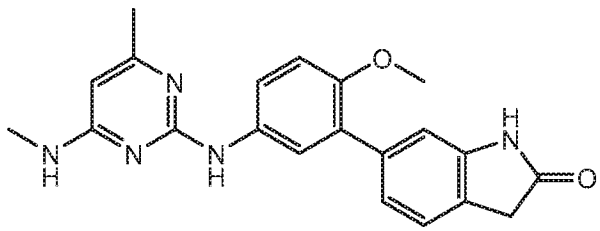
214	
215	
216	
217	
218	

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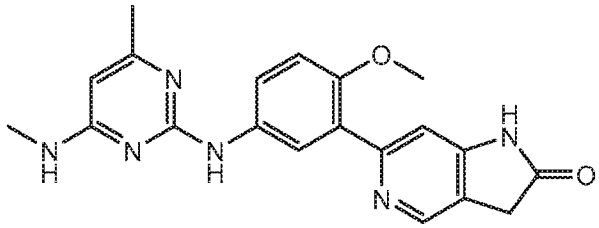
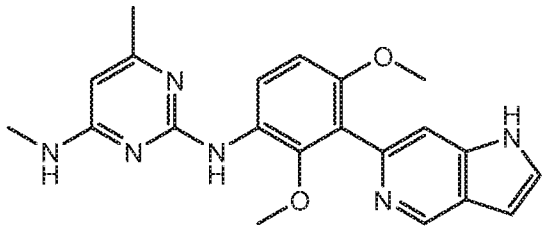
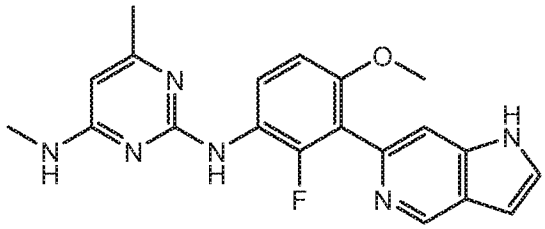
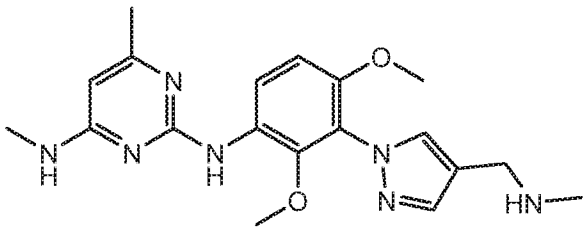
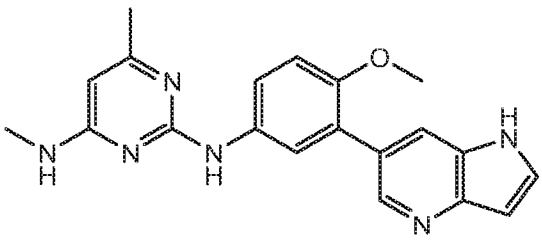
219	
220	
221	
222	
223	

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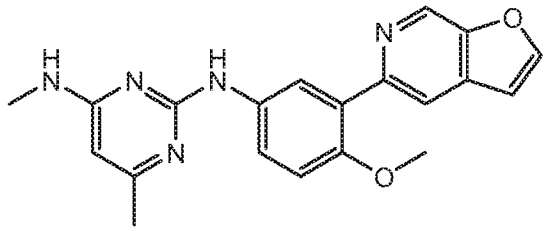
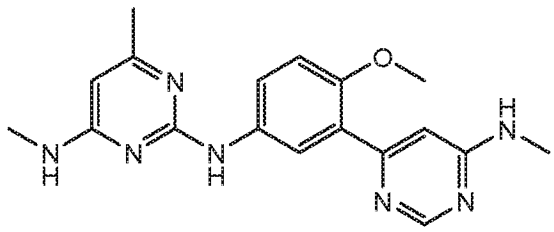
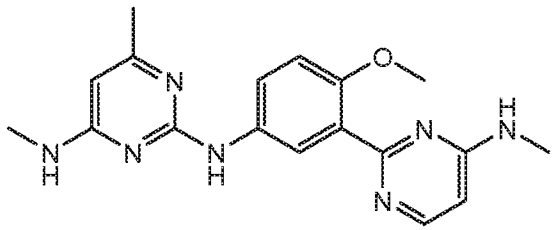
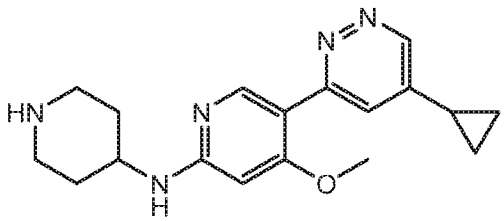
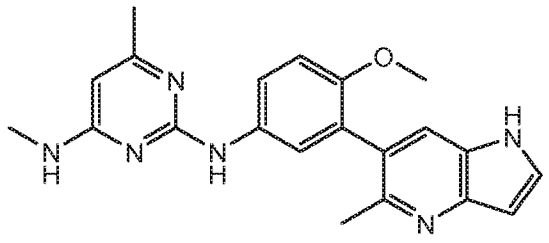
224	
225	
226	
227	
228	

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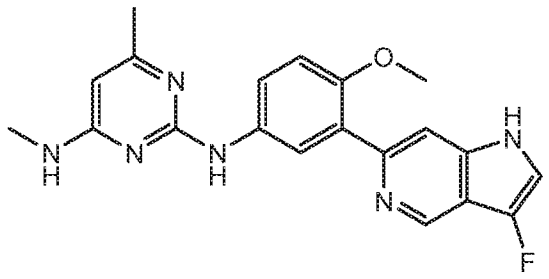
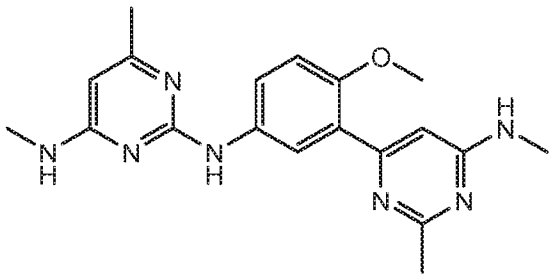
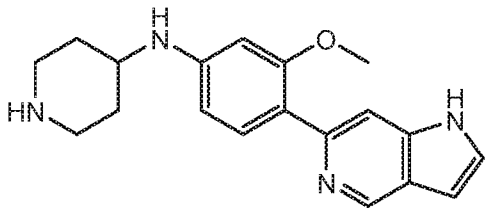
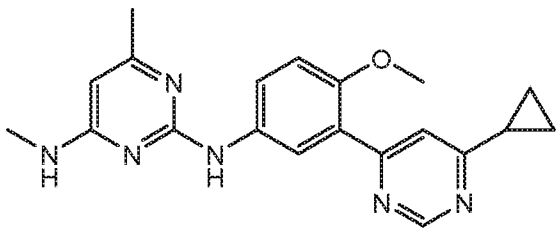
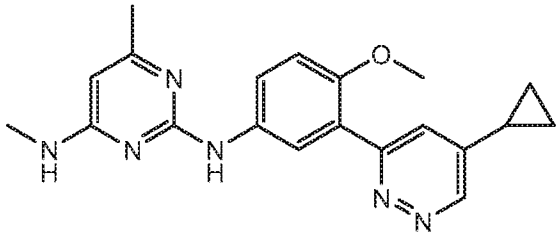
229	
230	
231	
232	
233	

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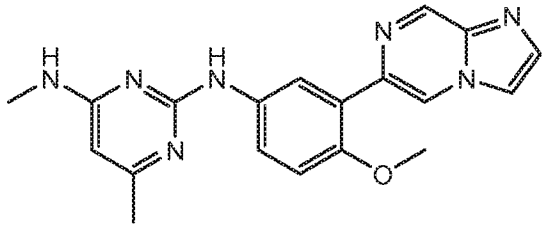
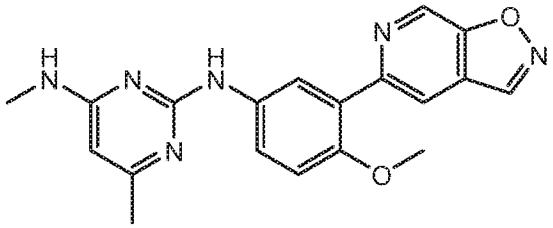
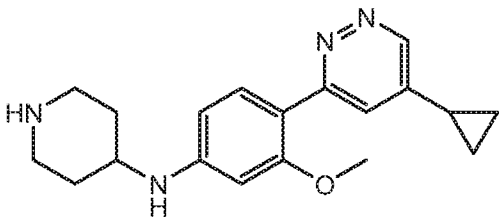
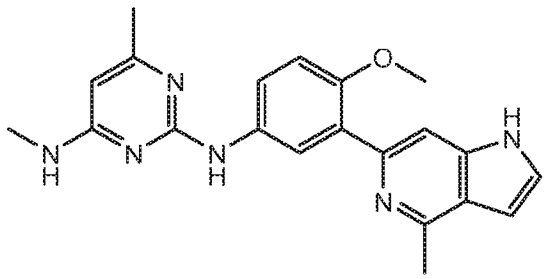
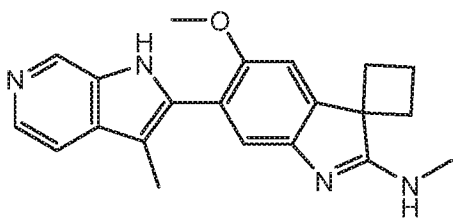
234	
235	
236	
237	
238	

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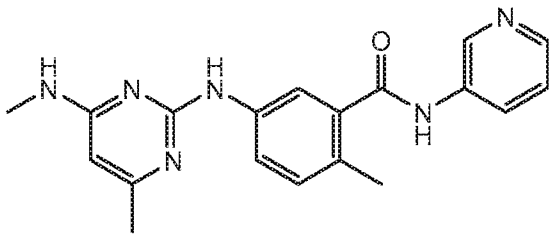
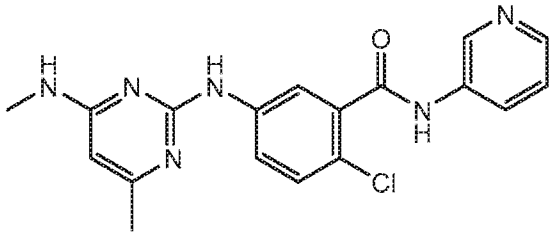
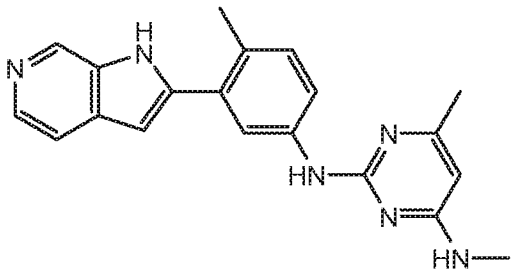
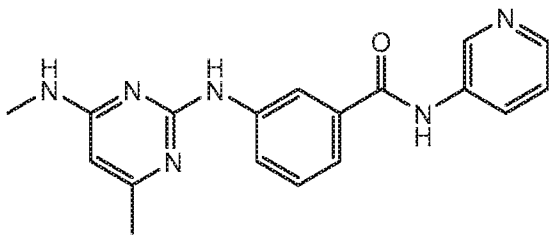
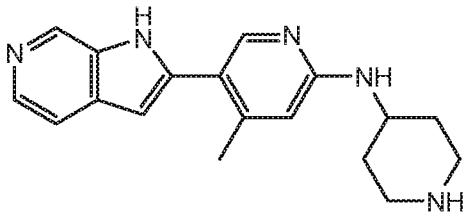
239	
240	
241	
242	
243	

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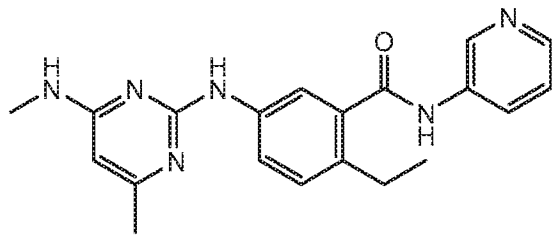
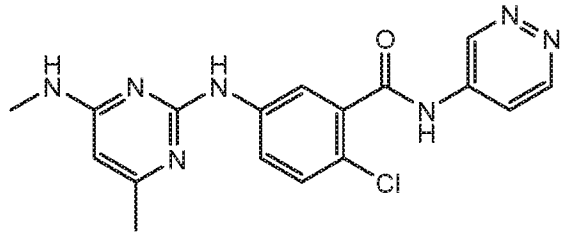
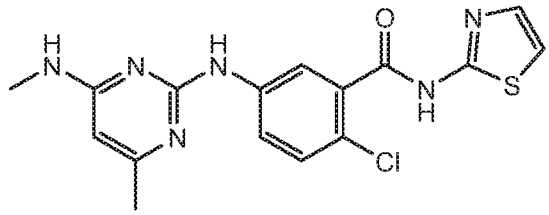
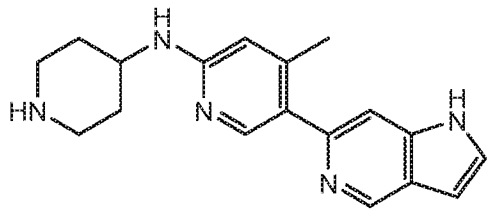
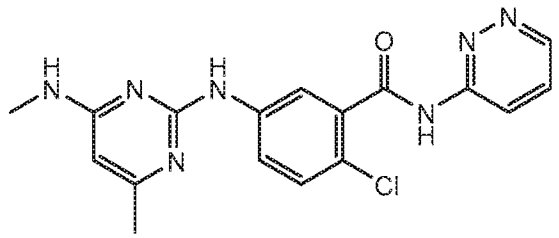
244	
245	
246	
247	
248	

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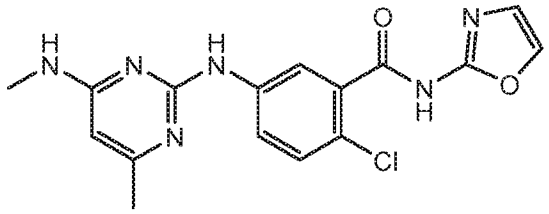
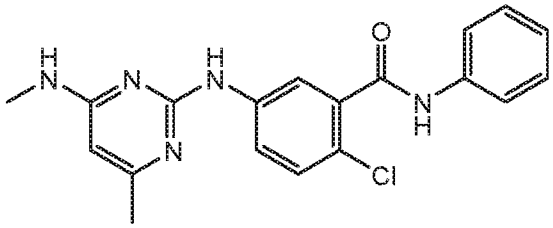
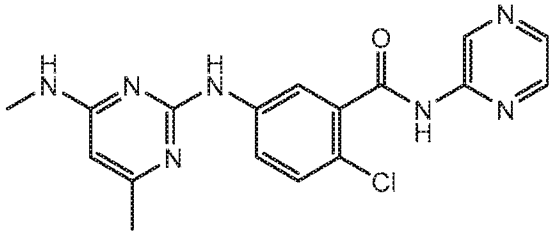
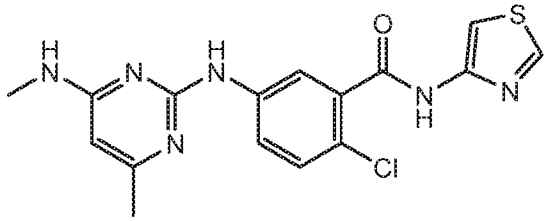
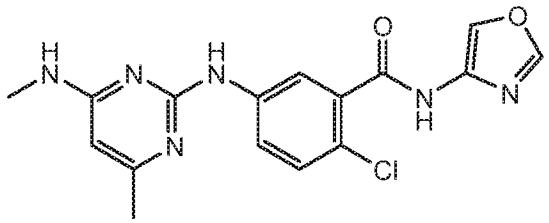
249	
250	
251	
252	
253	

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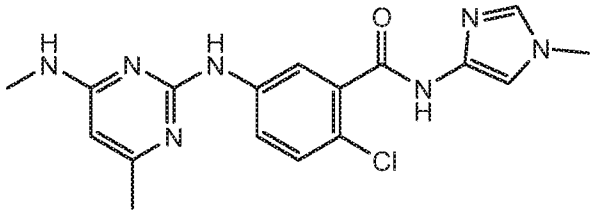
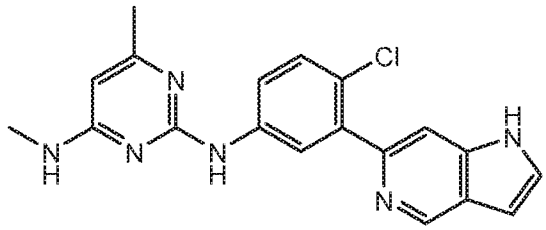
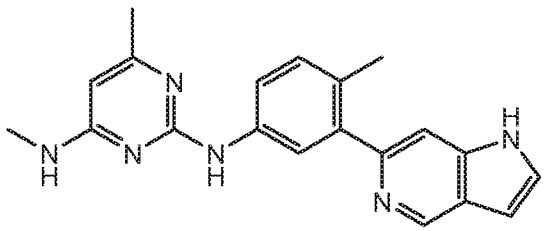
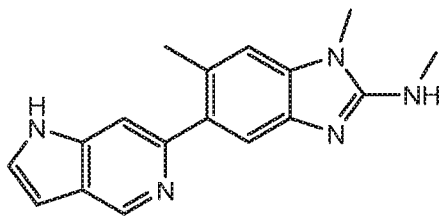
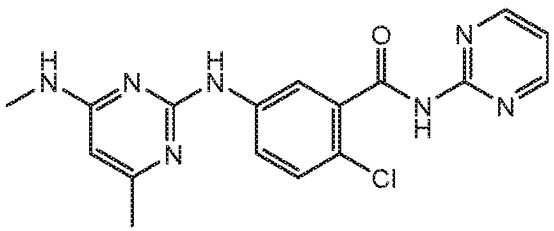
254	
255	
256	
257	
258	

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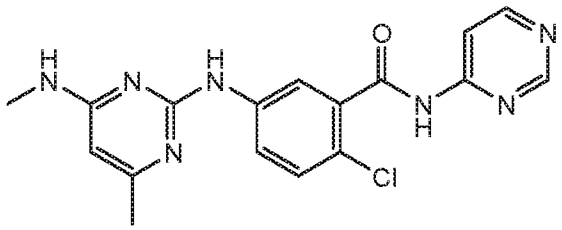
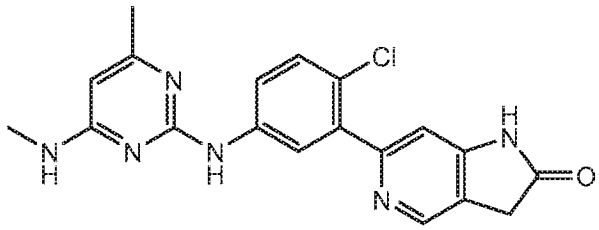
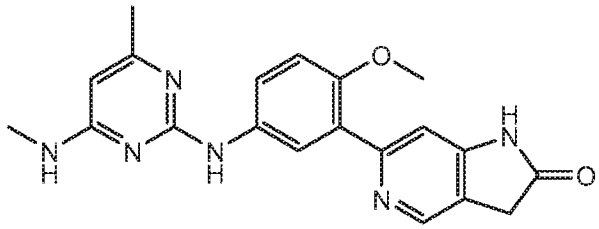
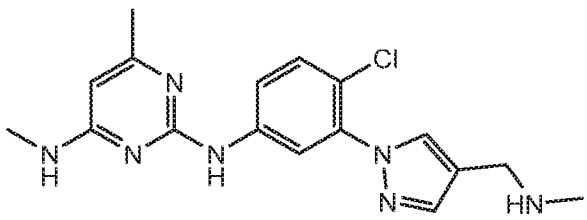
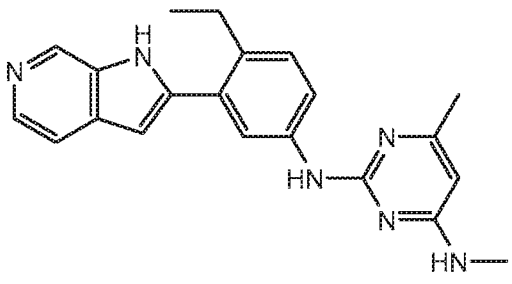
259	
260	
261	
262	
269	

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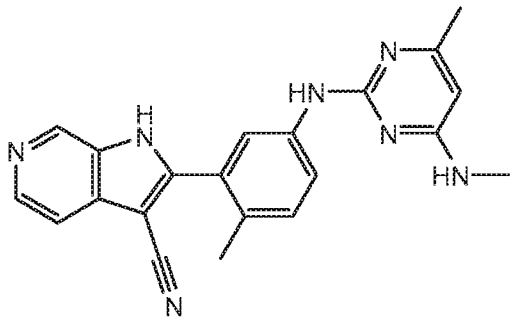
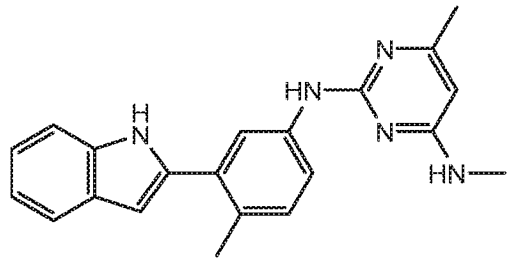
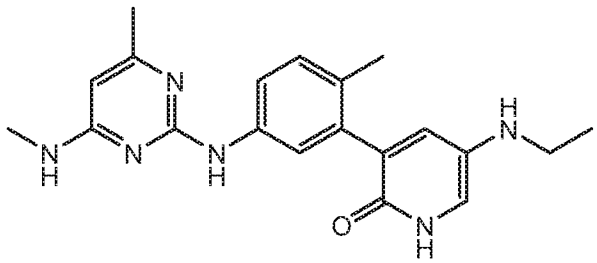
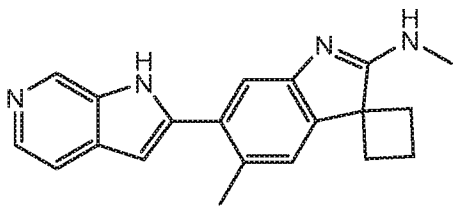
271	
274	
276	
277	

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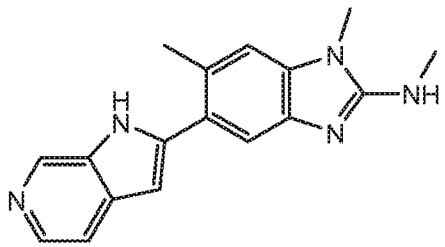
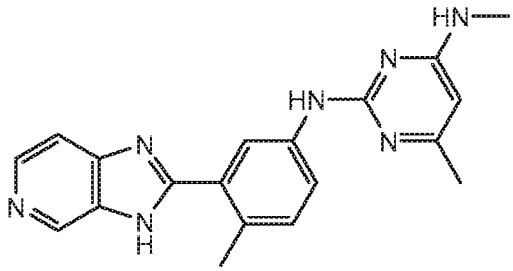
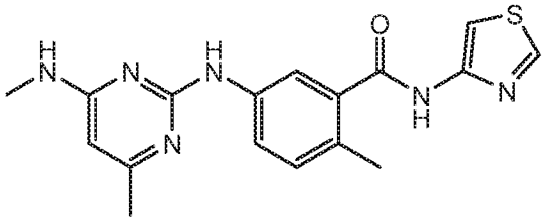
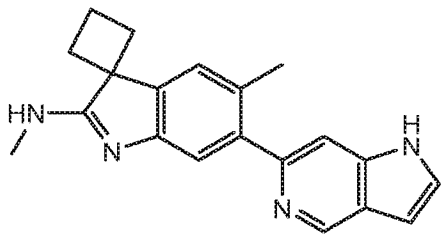
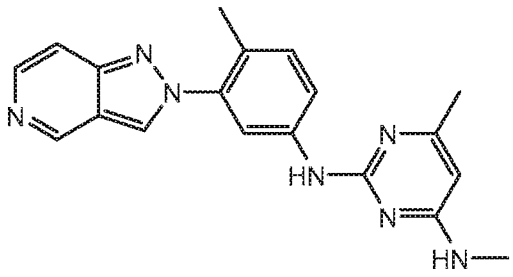
278	
279	
280	
281	
282	

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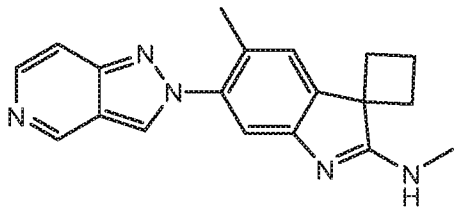
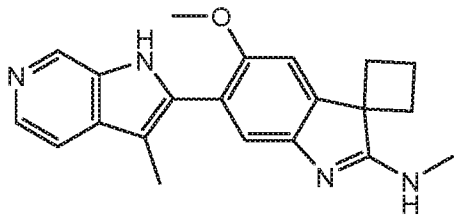
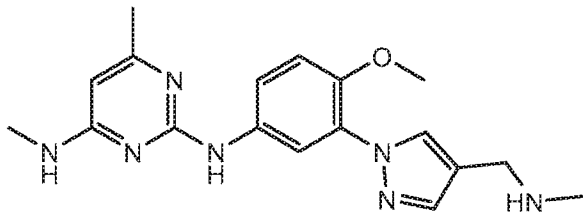
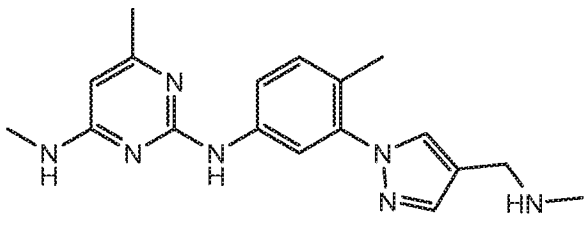
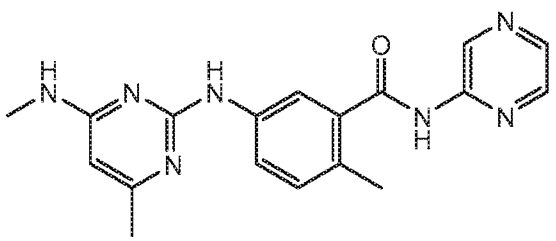
283	
284	
285	
286	
287	

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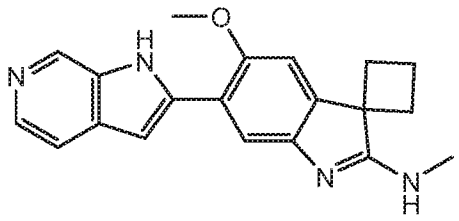
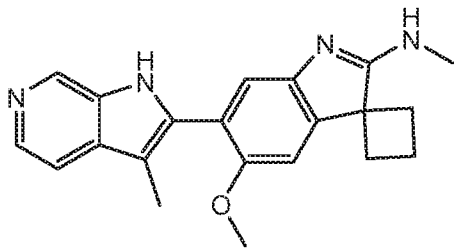
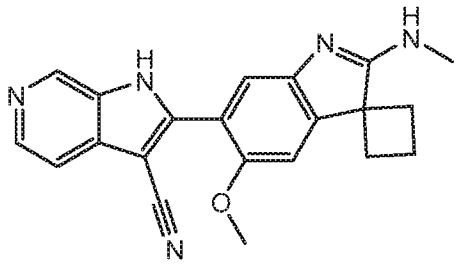
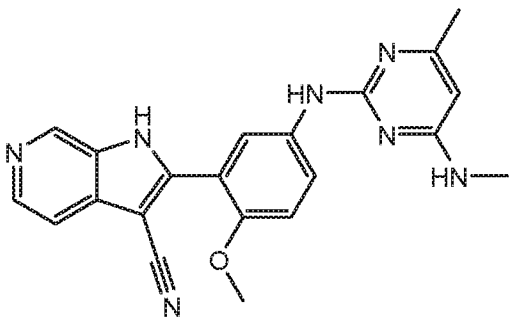
288	
289	
290	
291	

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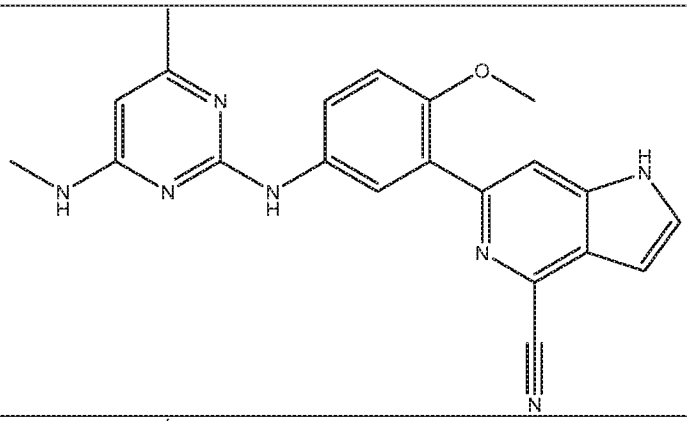
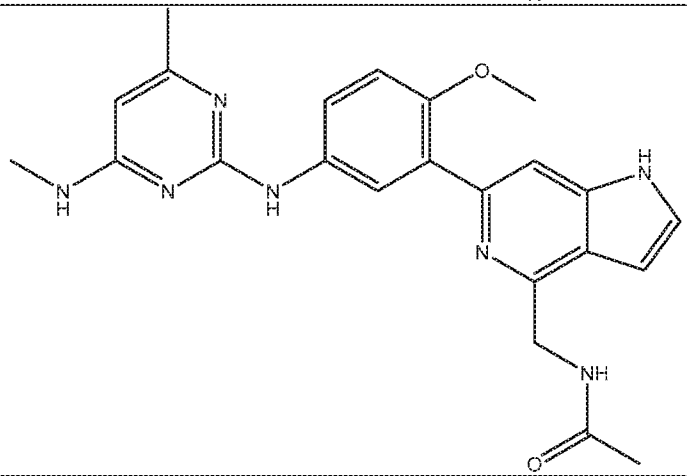
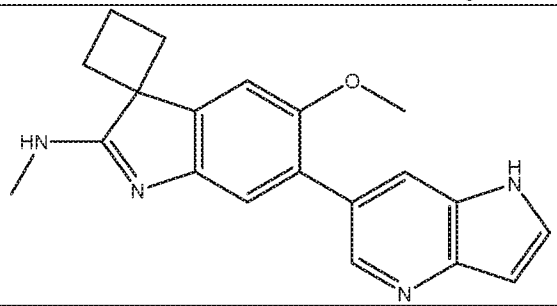
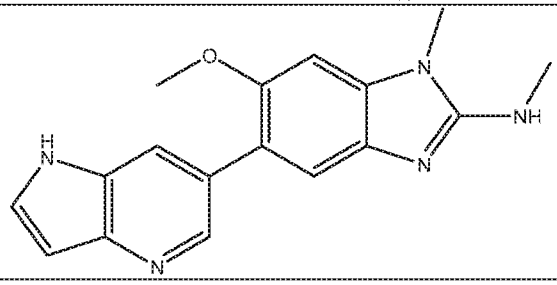
292	
293	
294	
295	

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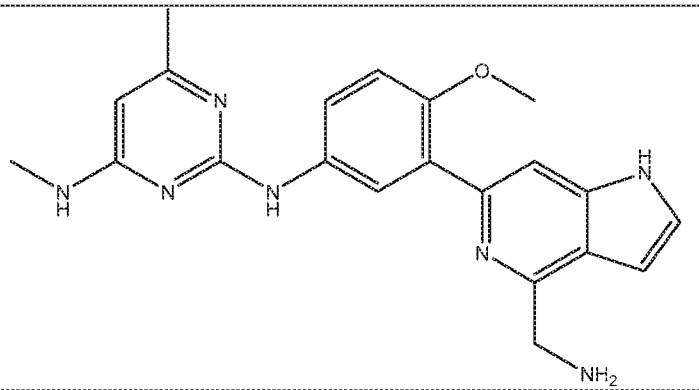
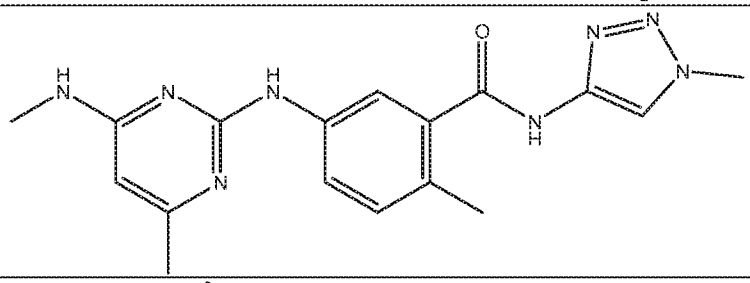
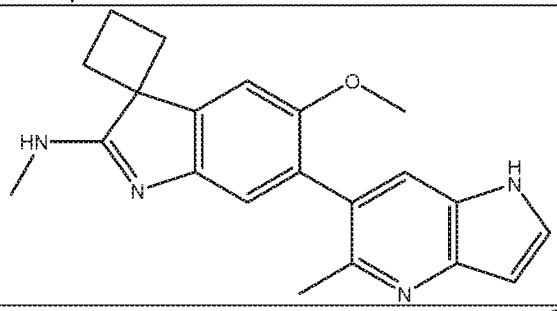
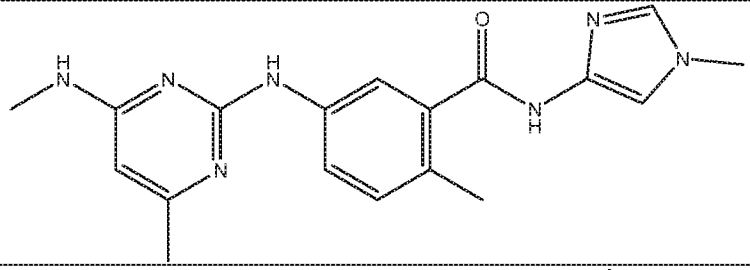
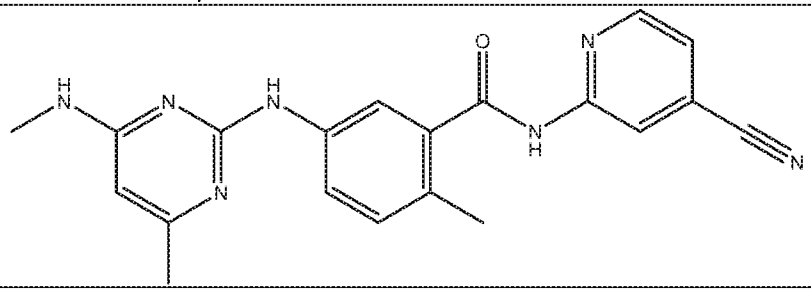
296	
299	
300	
302	
303	

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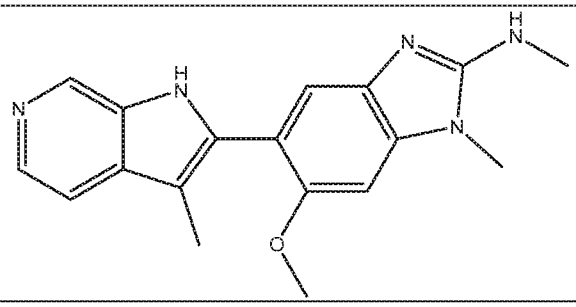
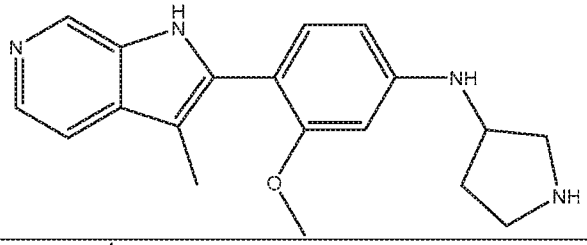
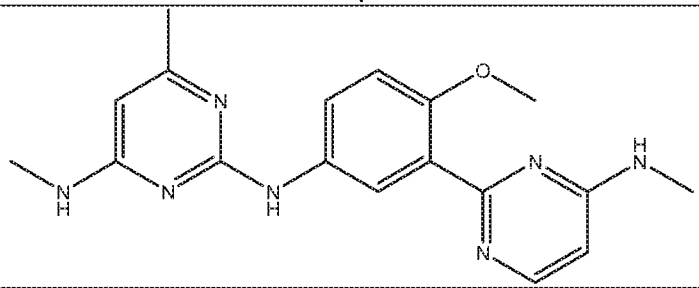
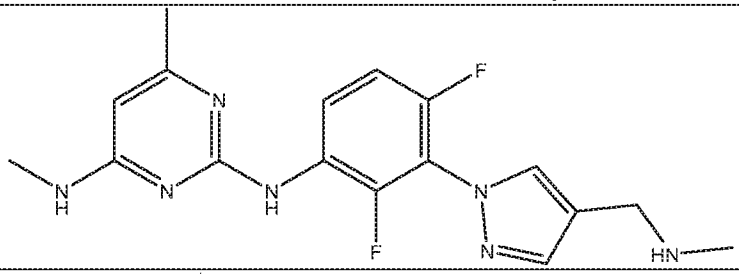
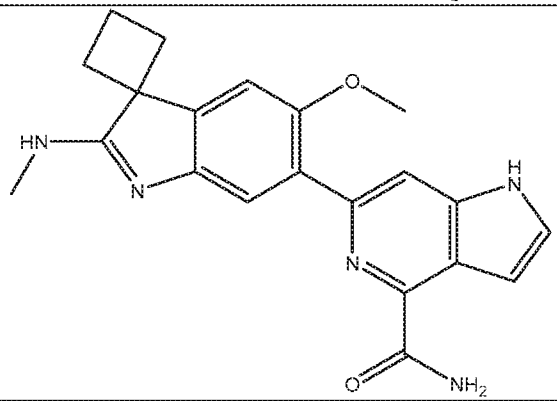
304	
305	
306	
307	
308	

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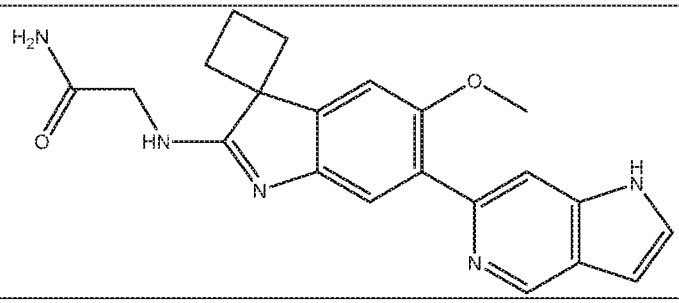
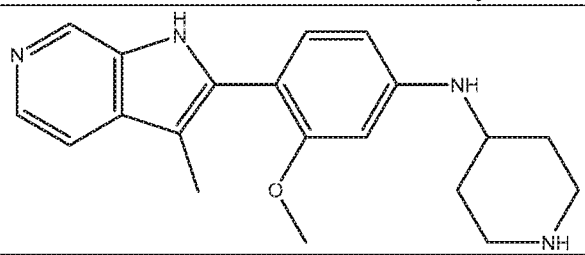
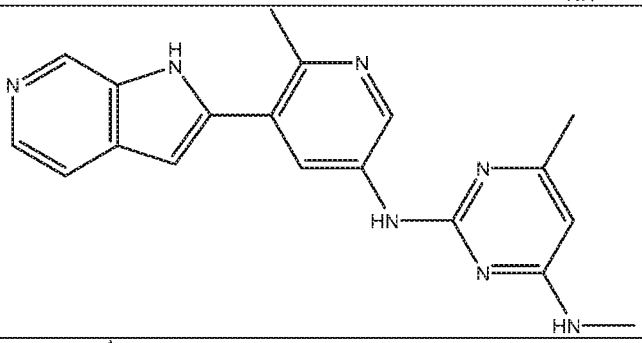
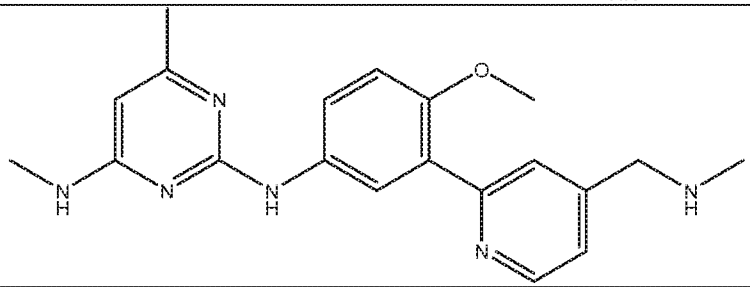
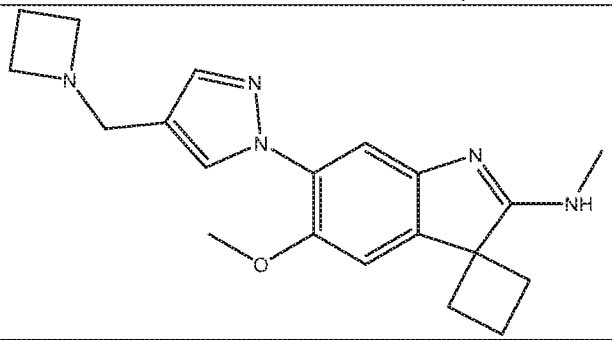
309	
310	
311	
313	
314	

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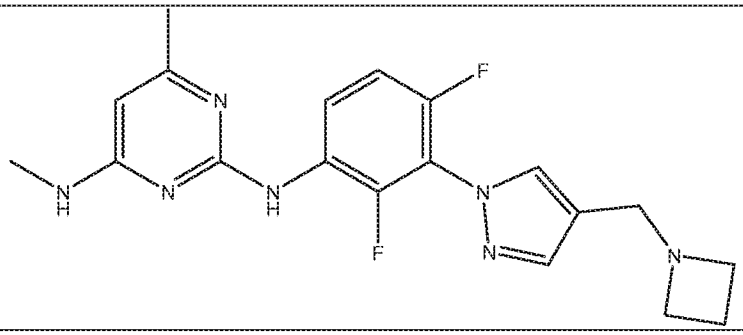
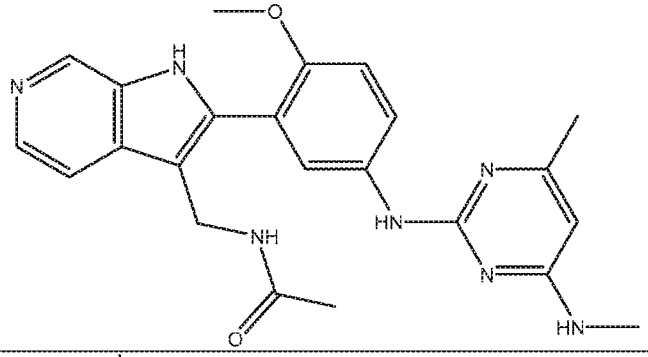
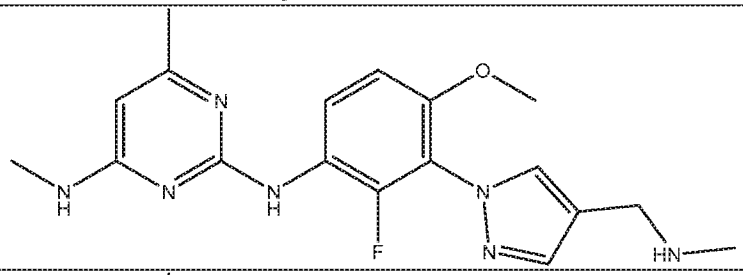
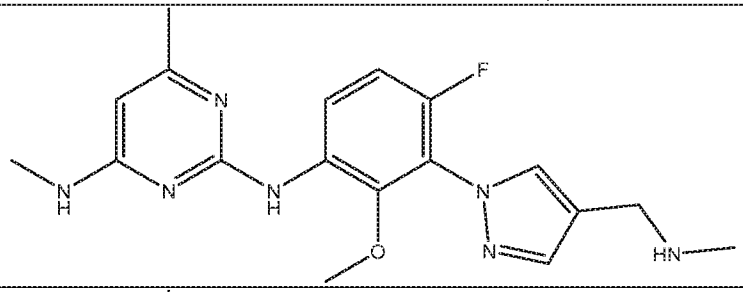
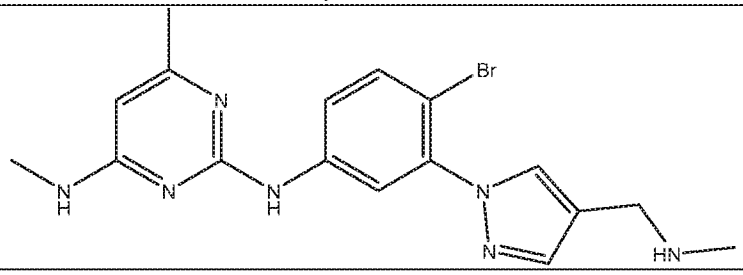
315	
316	
317	
318	
319	

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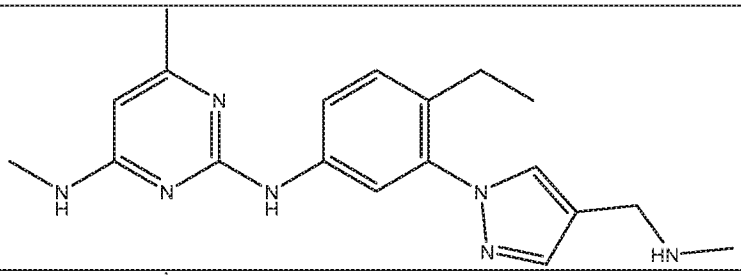
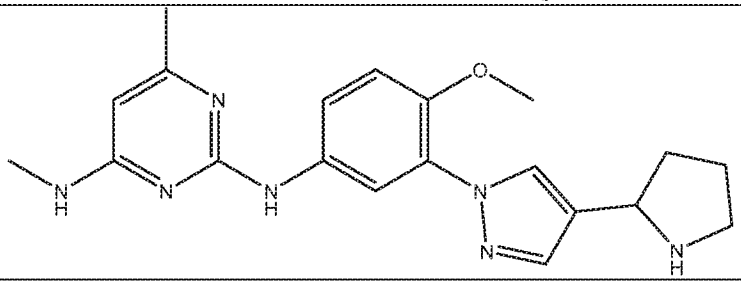
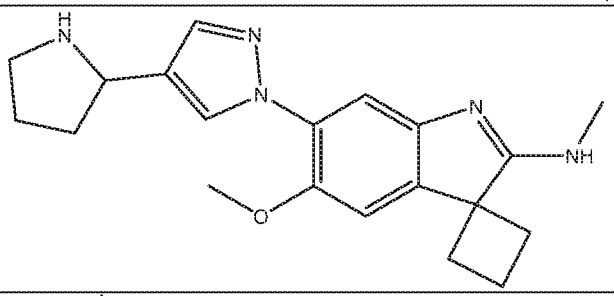
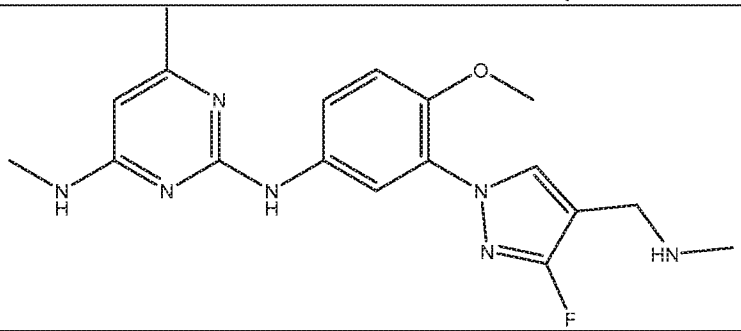
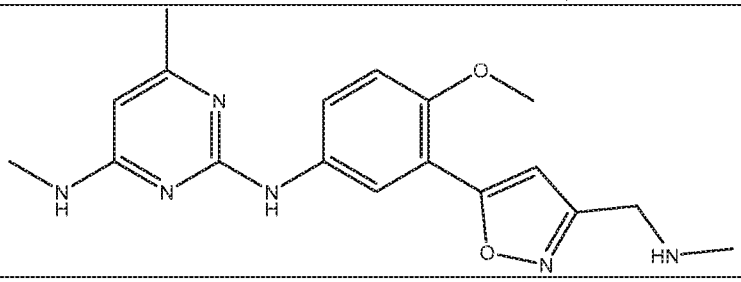
320	
321	
322	
323	
324	

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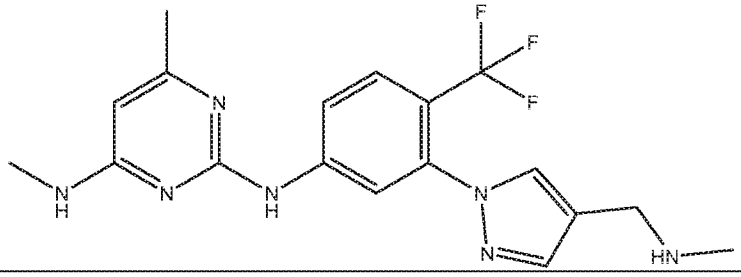
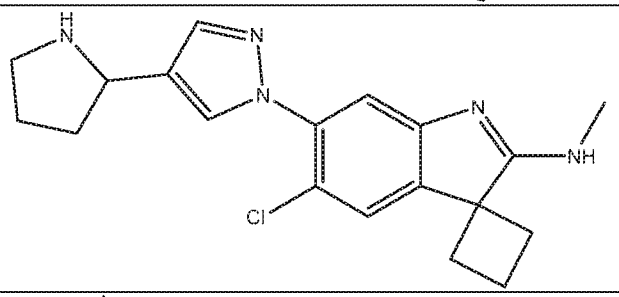
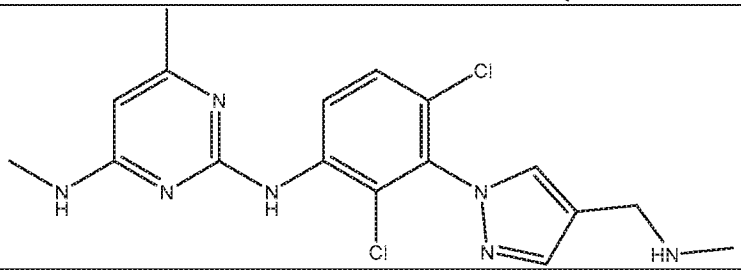
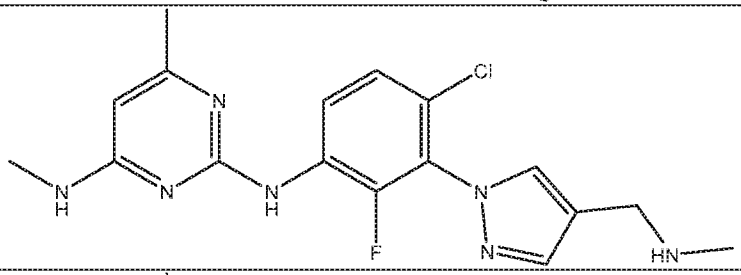
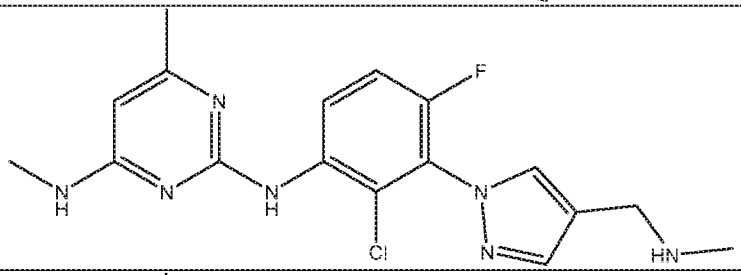
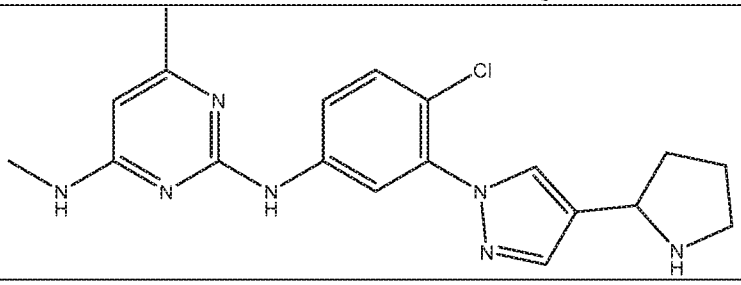
325	
326	
327	
328	
329	
330	

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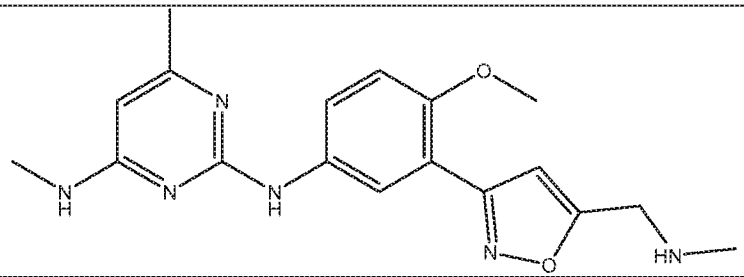
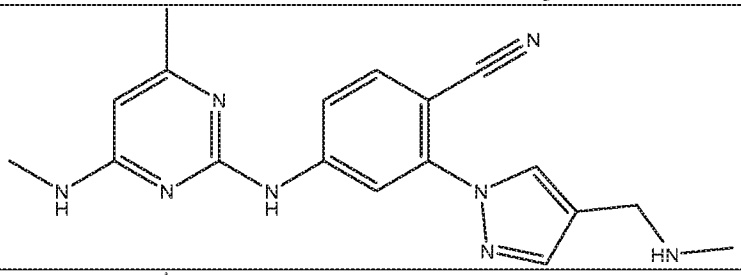
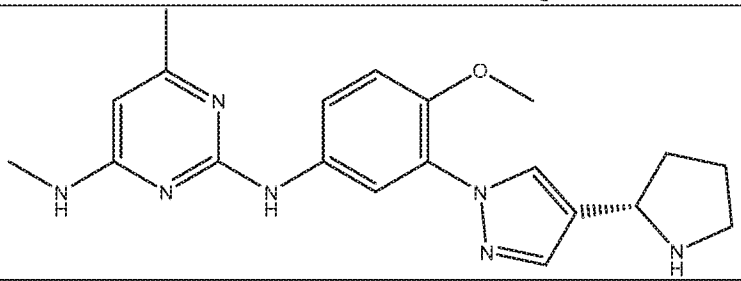
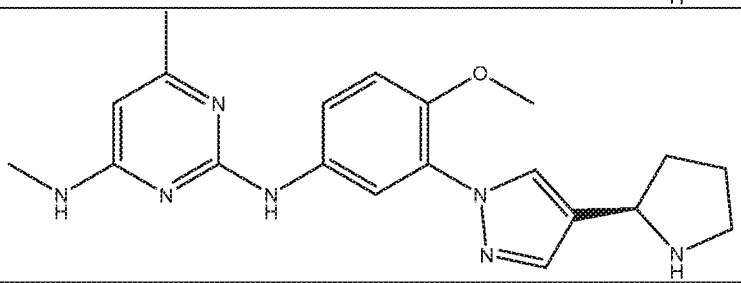
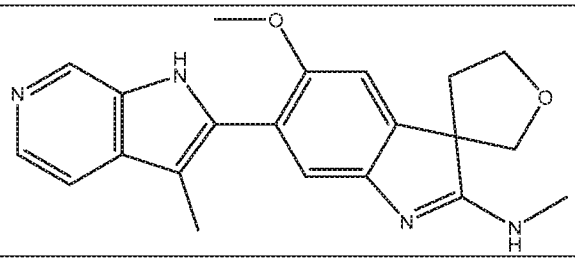
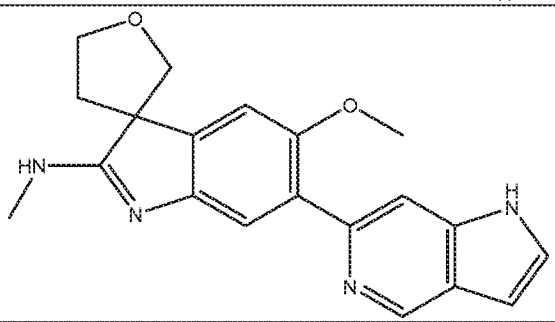
331	
332	
333	
334	
335	
336	

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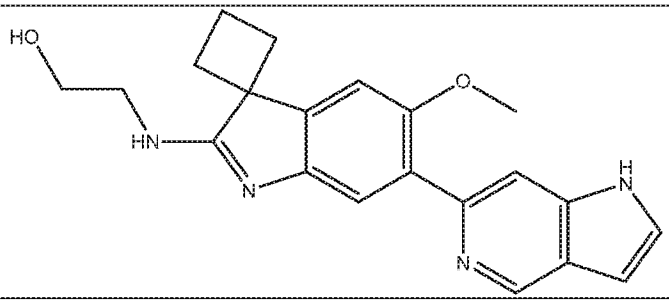
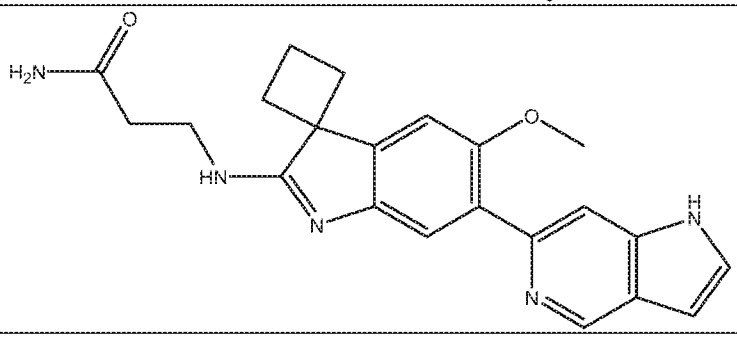
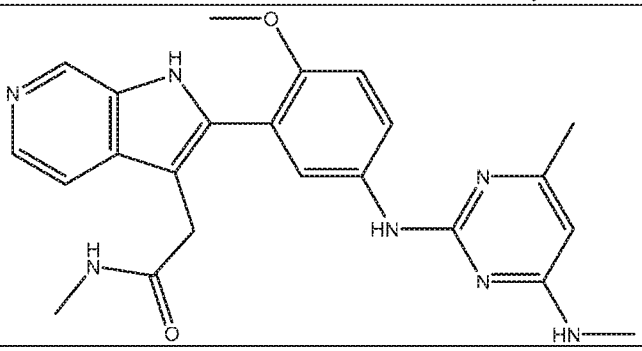
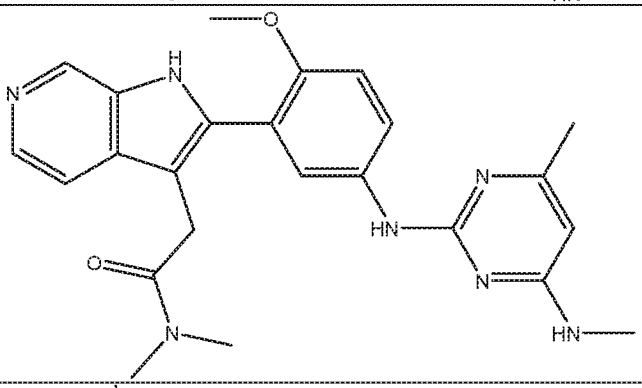
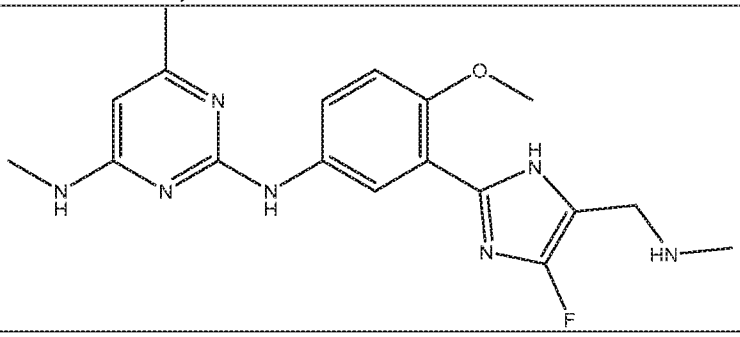
337	
338	
339	
340	
341	

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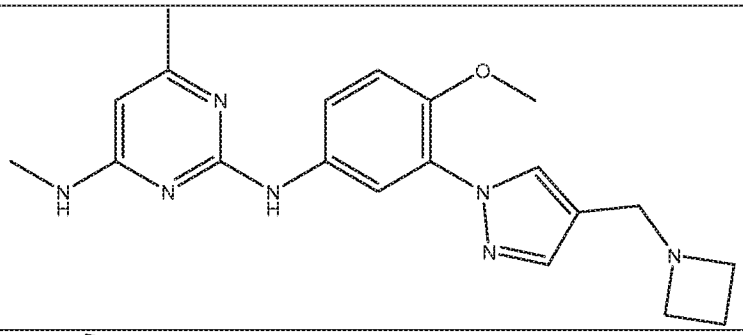
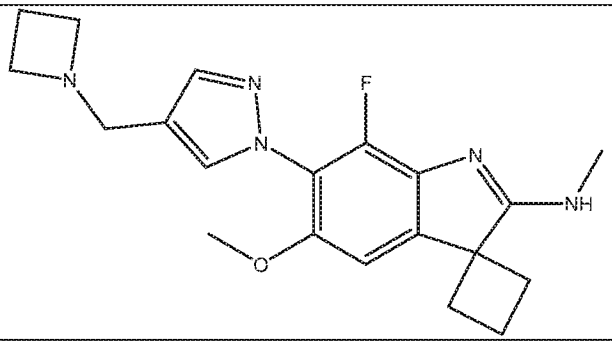
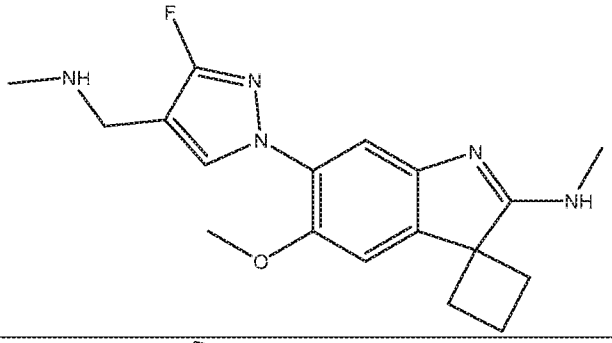
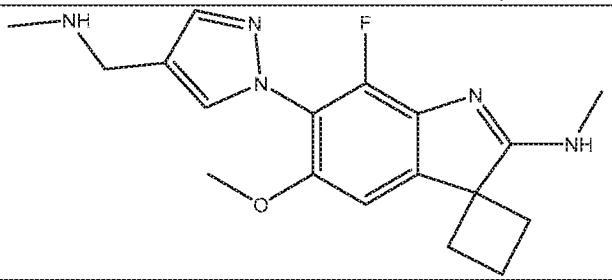
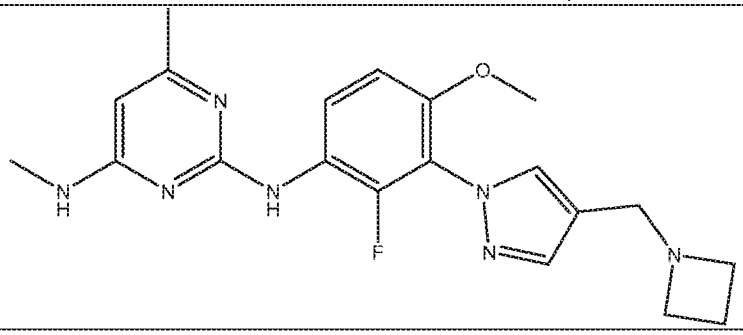
342	
343	
344	
345	
346	

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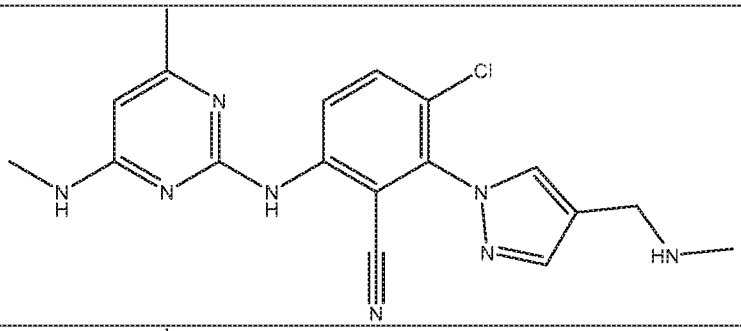
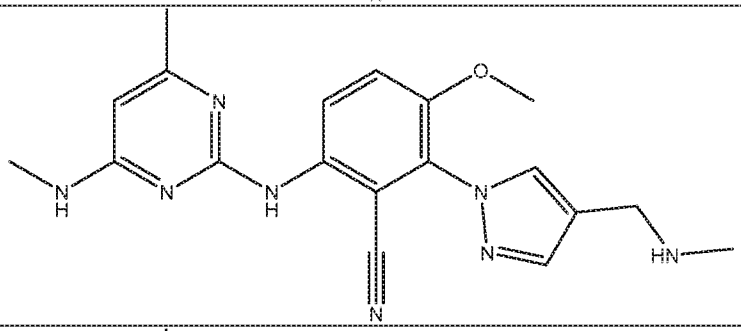
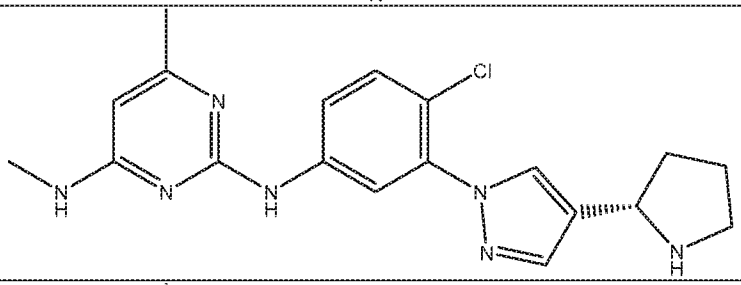
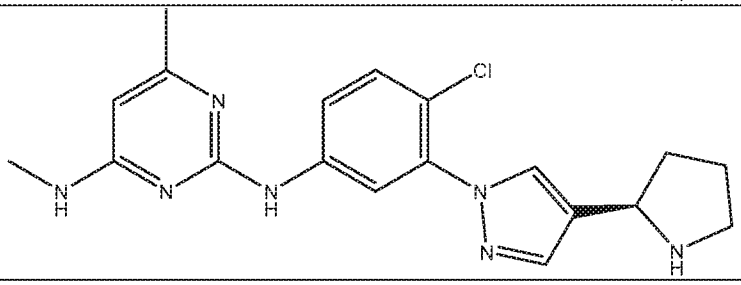
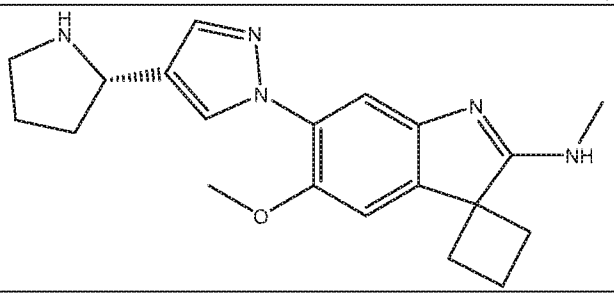
347	
348	
349	
350	
351	

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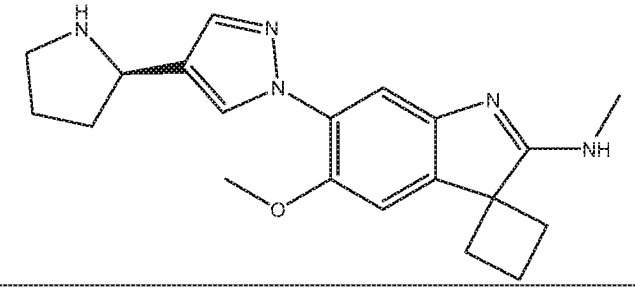
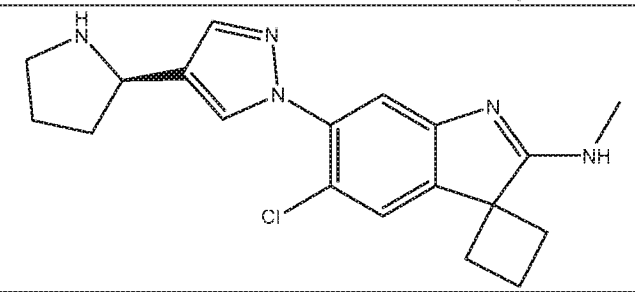
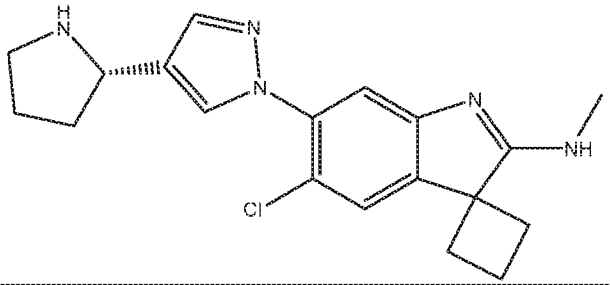
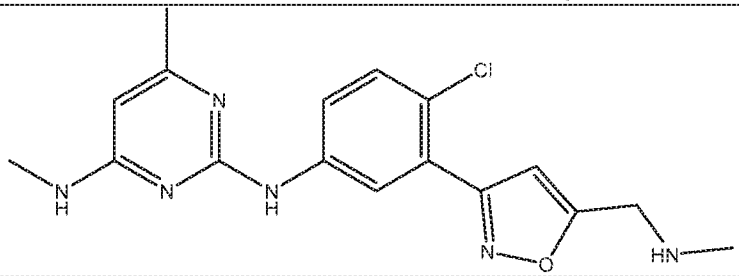
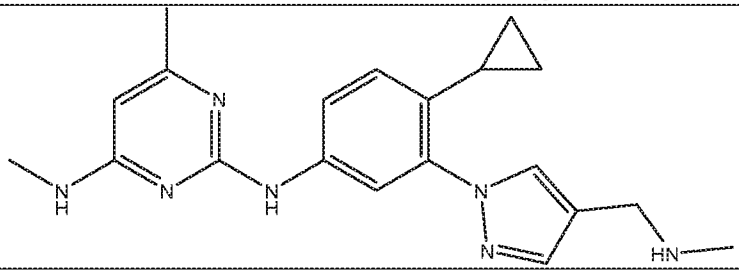
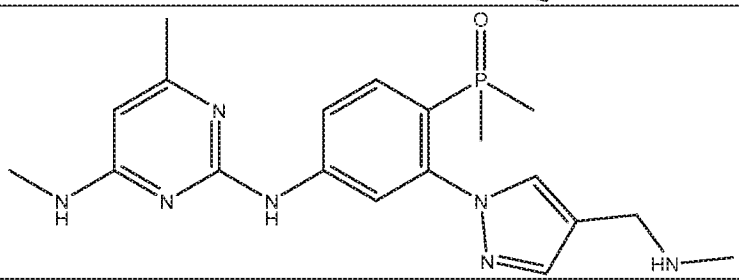
352	
353	
354	
355	
356	
357	

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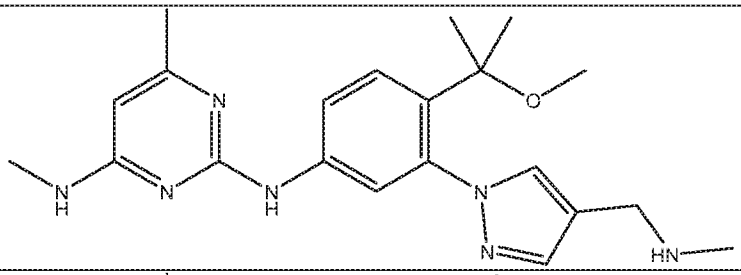
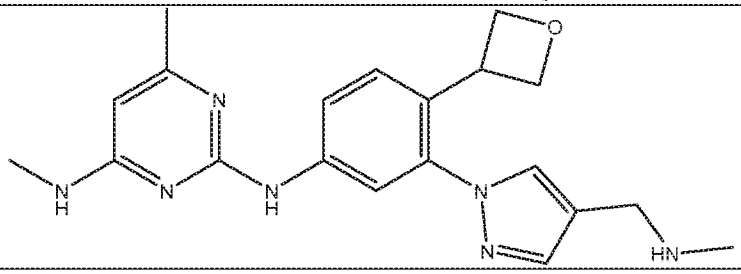
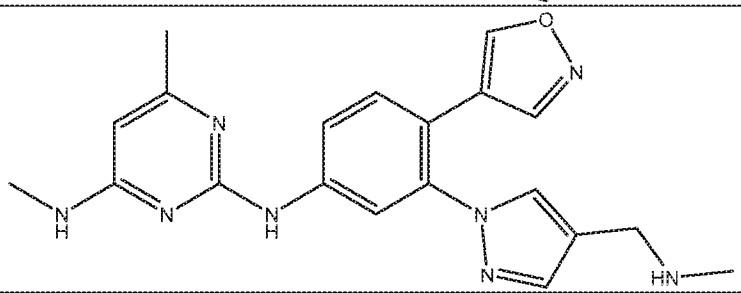
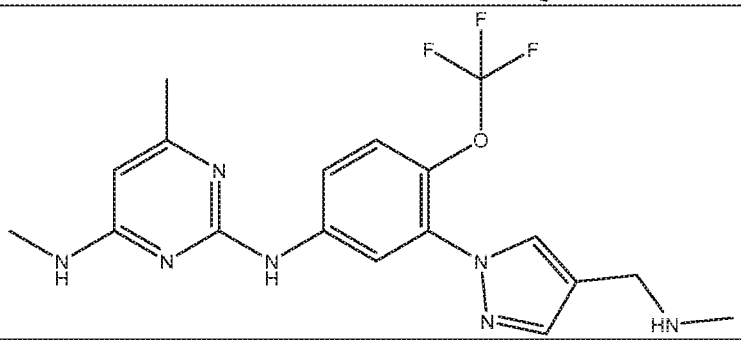
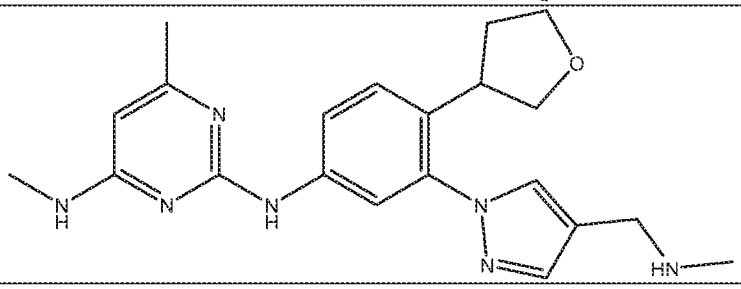
358	
359	
360	
361	
362	

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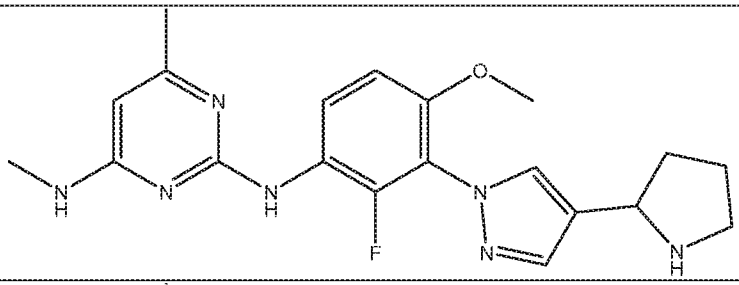
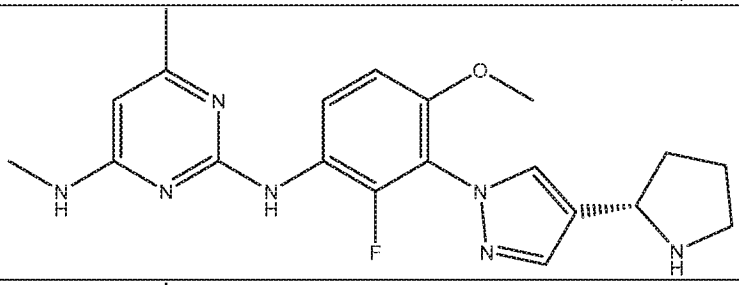
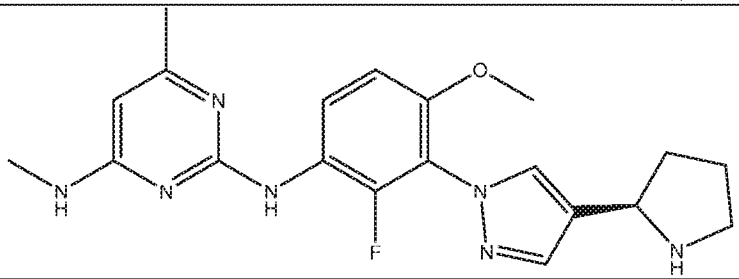
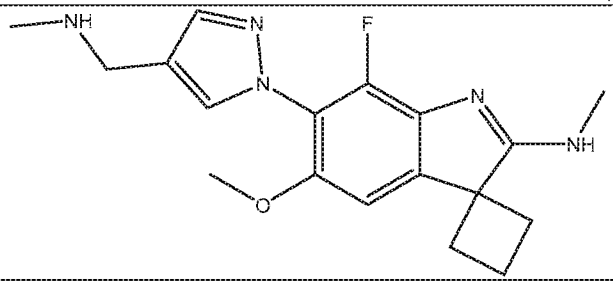
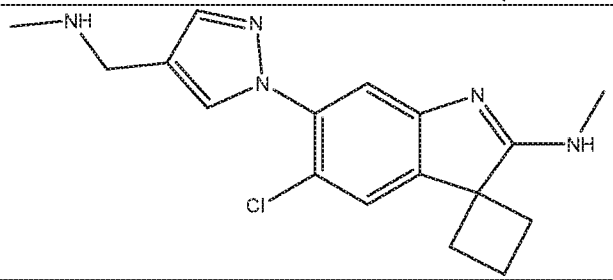
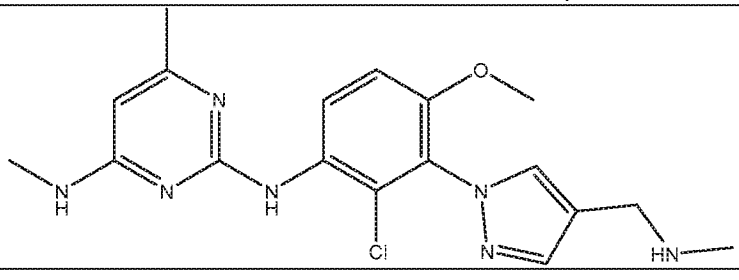
363	
364	
365	
366	
367	
368	

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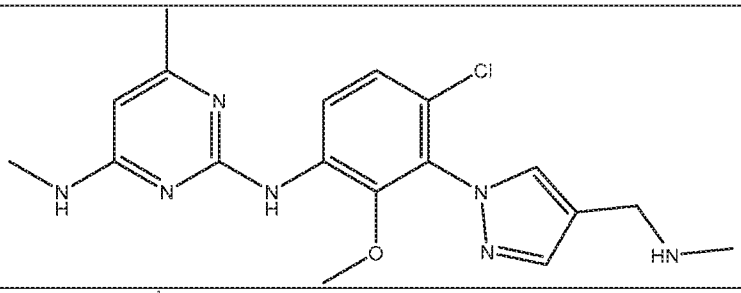
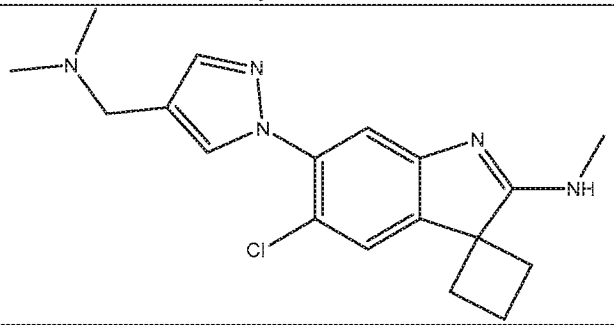
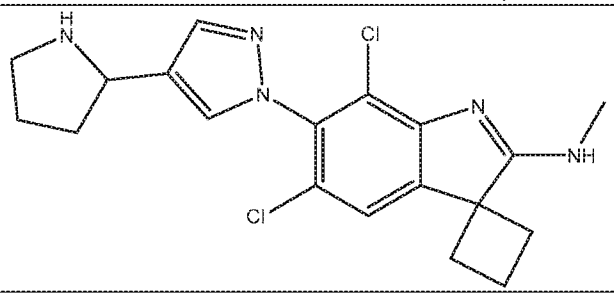
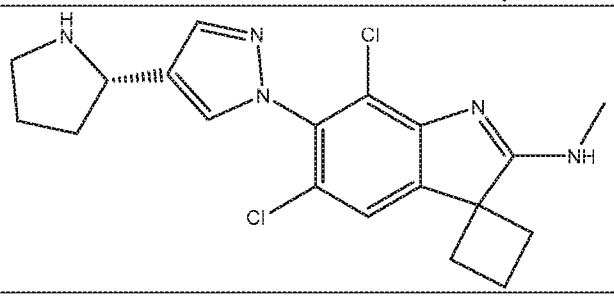
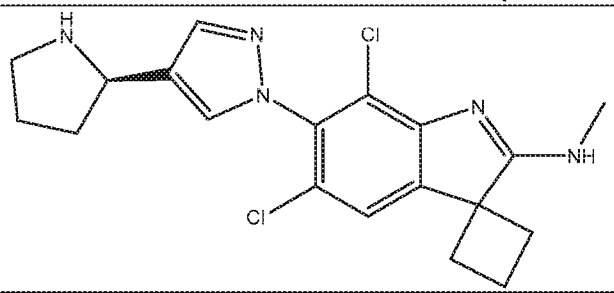
369	
370	
371	
372	
373	

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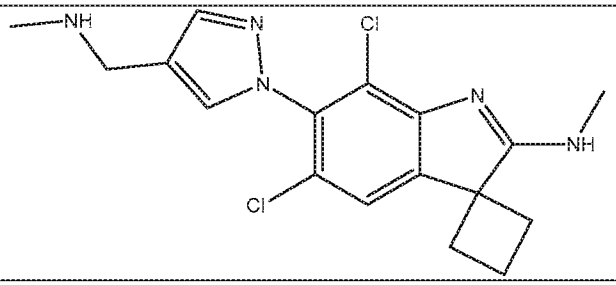
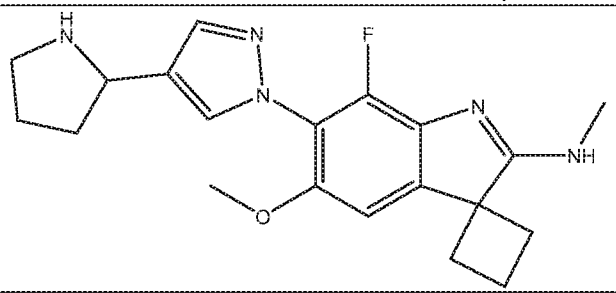
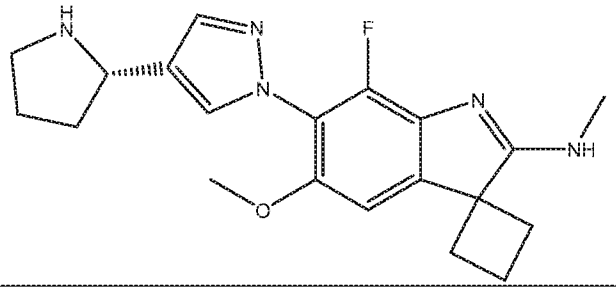
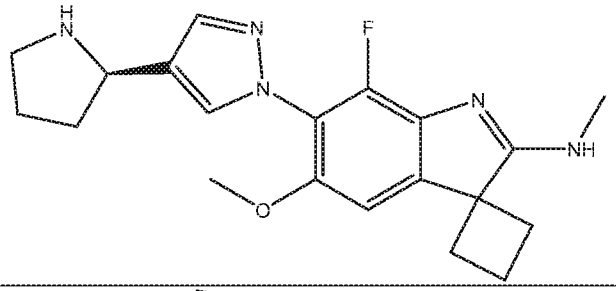
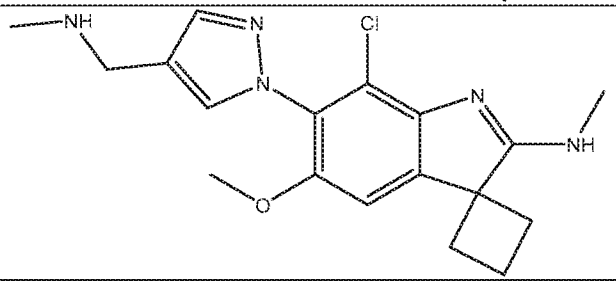
374	
375	
376	
377	
381	

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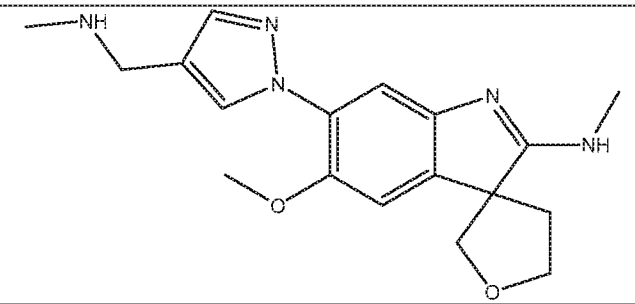
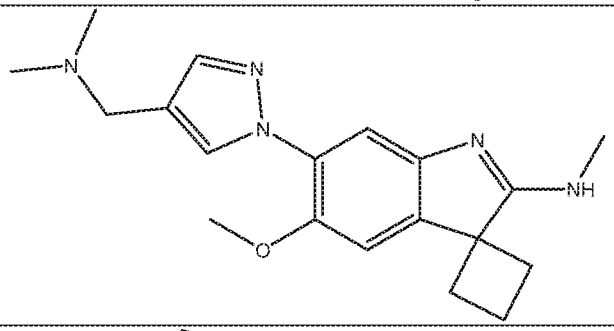
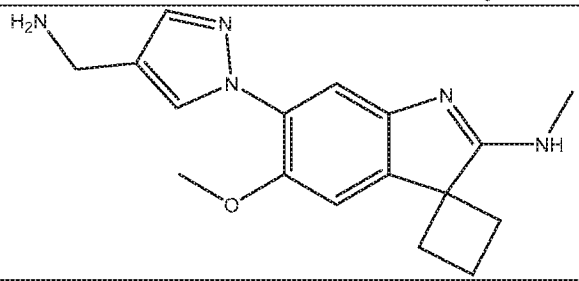
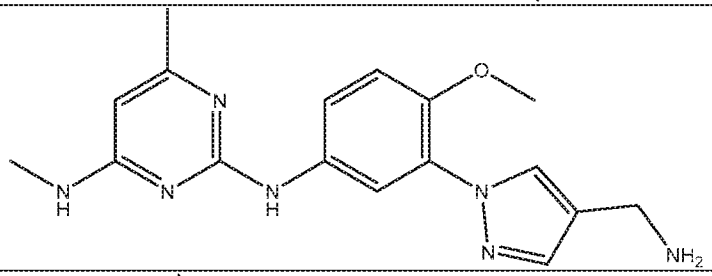
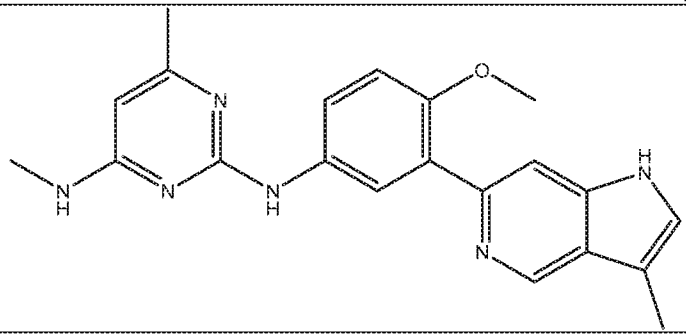
382	
383	
384	
385	
386	

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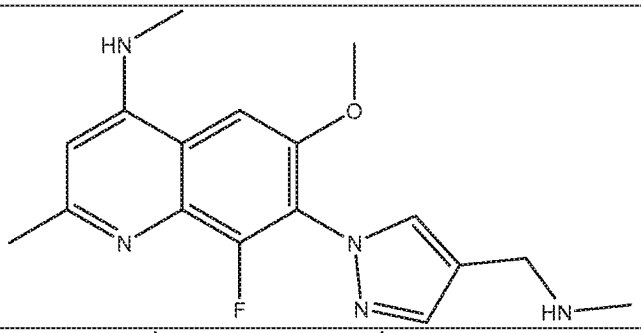
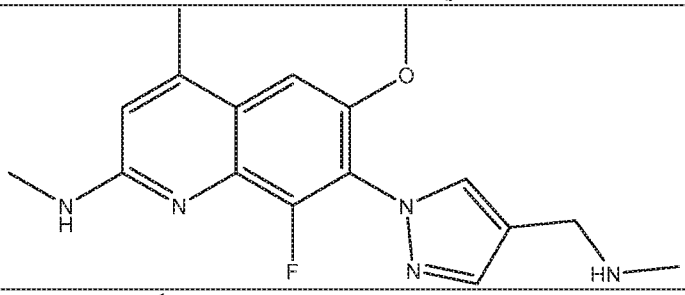
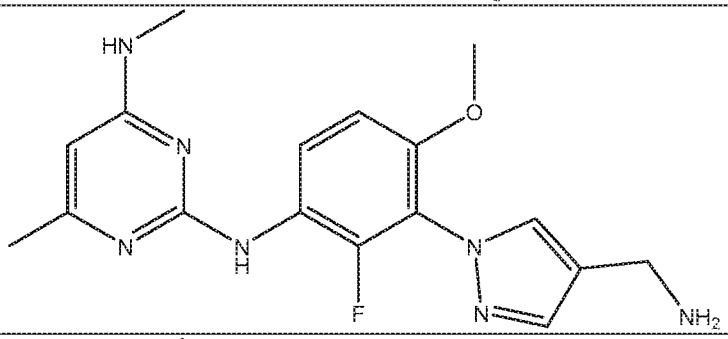
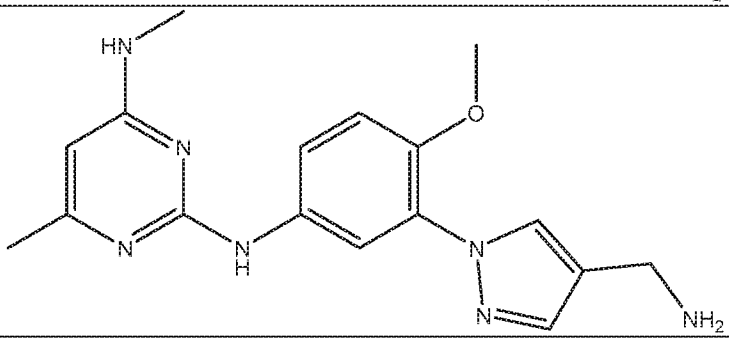
387	
388	
389	
390	

[0196] 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. In some embodiments, 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.

[0197] 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.

[0198] 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_{12}, C_3-C_{10}, or C_3-C_8). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,2,3,4-tetrahydronaphthalenyl, 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, P, or Se), 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, 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, 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, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexan-3-yl, 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazolyl, 3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridinyl, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 2-azaspiro[3.3]heptanyl, 2-methyl-2-azaspiro[3.3]heptanyl, 2-azaspiro[3.5]nonanyl, 2-methyl-2-azaspiro[3.5]nonanyl, 2-azaspiro[4.5]decanyl, 2-methyl-2-azaspiro[4.5]decanyl, 2-oxa-azaspiro[3.4]octanyl, 2-oxa-azaspiro[3.4]octan-6-yl, and the like. In the case of multicyclic non-aromatic rings, only one of the rings needs to be non-aromatic (*e.g.*, 1,2,3,4-tetrahydronaphthalenyl or 2,3-dihydroindole).

[0199] 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.

[0200] As used herein, "alkyl linker" or "alkylene 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. In some embodiments, C_1-C_6 alkylene linker is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkylene linker groups. Examples of alkylene 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 (-$CH_2CH_2CH_2CH_2CH_2CH_2$-).

[0201] "Alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. In some embodiments, the term "alkenyl" includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups.

[0202] 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.

[0203] 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.

[0204] "Alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. In some embodiments, "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. As used herein, "C_2-C_6 alkenylene linker" or "C_2-C_6 alkynylene linker" is intended to include C_2, C_3, C_4, C_5 or C_6 chain (linear or branched) divalent unsaturated aliphatic hydrocarbon groups. In some embodiments, C_2-C_6 alkenylene linker is intended to include C_2, C_3, C_4, C_5 and C_6 alkenylene linker groups.

[0205] 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.

[0206] 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. In some embodiments, 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.

[0207] "Aryl" includes groups with aromaticity, including "conjugated," or multicyclic systems with one or more aromatic rings and do not contain any heteroatom in the ring structure. Examples include phenyl, naphthalenyl, etc.

[0208] "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.

[0209] Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

[0210] 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.

[0211] 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).

[0212] 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. In some embodiments, 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.

[0213] As used herein, "heterocycle" or "heterocyclic group" includes any ring structure (saturated, unsaturated, or aromatic) which contains at least one ring heteroatom (*e.g.*, 1-4 heteroatoms selected from N, O and 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.

[0214] 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.

[0215] 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.

[0216] The term "optionally substituted," as used herein, means not being substituted (e.g., none of the one or more hydrogen atoms on the designated variable is replaced with any other group) or being substituted (e.g., any one or more hydrogen atoms on the designated variable 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).

[0217] 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.

[0218] 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, in some embodiments, 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.

[0219] The term "hydroxy" or "hydroxyl" includes groups with an -OH or -O⁻.

[0220] 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.

[0221] 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.

[0222] The term "carboxyl" refers to –COOH or its C_1-C_6 alkyl ester.

[0223] "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.

[0224] "Aroyl" includes moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

[0225] "Alkoxyalkyl," "alkylaminoalkyl," and "thioalkoxyalkyl" include alkyl groups, as described above, wherein oxygen, nitrogen, or sulfur atoms replace one or more hydrocarbon backbone carbon atoms.

[0226] 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.

[0227] The term "ether" or "alkoxy" includes compounds or moieties which contain an oxygen bonded to two carbon atoms or heteroatoms. In some embodiments, 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.

[0228] 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.

[0229] 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.

[0230] The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom.

[0231] 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.

[0232] As used herein, "amine" or "amino" refers to $-NH_2$. "Alkylamino" includes groups of compounds wherein the 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 two 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.

[0233] 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.

[0234] Compounds of the present disclosure 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 disclosure. 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→O or N^+-O^-). Furthermore, in other instances, the nitrogens in the compounds of the present disclosure can be converted to N-hydroxy or N-alkoxy compounds. In some embodiments, 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.

[0235] In the present specification, the structural formula of the compound represents a certain isomer for convenience in some cases, but the present disclosure 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 disclosure.

[0236] "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."

[0237] A carbon atom bonded to four nonidentical substituents is termed a "chiral center."

[0238] "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).

[0239] "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.

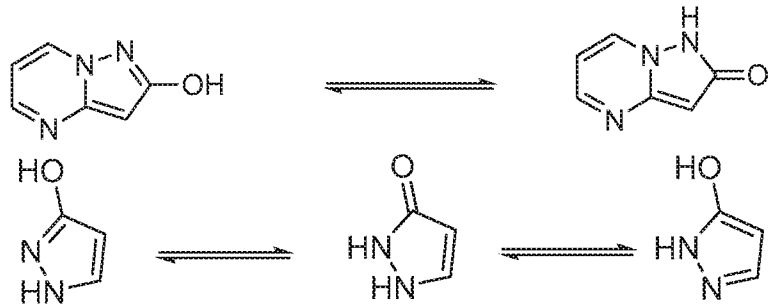
[0240] It is to be understood that the compounds of the present disclosure may be depicted as different chiral isomers or geometric isomers. It should also be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present disclosure, 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.

[0241] Furthermore, the structures and other compounds discussed in this disclosure 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.

[0242] "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.

[0243] 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.

[0244] 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. Examples of lactam-lactim tautomerism are as shown below.



[0245] It is to be understood that the compounds of the present disclosure 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 disclosure, 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.

[0246] 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.

[0247] 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 substituted benzene 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 substituted benzene compound. Suitable

cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The substituted benzene compounds also include those salts containing quaternary nitrogen atoms.

[0248] Additionally, the compounds of the present disclosure, 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.

[0249] "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.

[0250] 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.

[0251] As defined herein, the term "derivative" refers to compounds that have a common core structure, and are substituted with various groups as described herein. In some embodiments, all of the compounds represented by Formula (II) are substituted bi-heterocyclic compounds, and have Formula (II) as a common core.

[0252] 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.

[0253] The present disclosure 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.

[0254] As used herein, the expressions "one or more of A, B, or C," "one or more A, B, or C," "one or more of A, B, and C," "one or more A, B, and C," "selected from the group consisting of A, B, and C", "selected from A, B, and C", and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, i.e., one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[0255] The present disclosure provides methods for the synthesis of the compounds of any of the Formulae described herein. The present disclosure also provides detailed methods for the synthesis of various disclosed compounds of the present disclosure according to the following schemes as well as those shown in the Examples.

[0256] 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.

[0257] The synthetic processes of the disclosure 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.

[0258] Compounds of the present disclosure 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 disclosure.

[0259] Compounds of the present disclosure can be conveniently prepared by a variety of methods familiar to those skilled in the art. The compounds of this disclosure having any of the Formulae described herein may be prepared according to the procedures illustrated in Schemes 1-4 below, from commercially available starting materials or starting materials which can be prepared using literature procedures. Certain variables (such as R^6 and R^7) in Schemes 1-4 are as defined in any Formula described herein, unless otherwise specified.

[0260] 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.

[0261] 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.

[0262] Preferred protecting groups include, but are not limited to:

[0263] For a hydroxyl moiety: TBS, benzyl, THP, Ac

[0264] For carboxylic acids: benzyl ester, methyl ester, ethyl ester, allyl ester

[0265] For amines: Cbz, BOC, DMB

[0266] For diols: Ac (x2) TBS (x2), or when taken together acetonides

[0267] For thiols: Ac

[0268] For benzimidazoles: SEM, benzyl, PMB, DMB

[0269] For aldehydes: di-alkyl acetals such as dimethoxy acetal or diethyl acetyl.

[0270] 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.

[0271] The following abbreviations are used throughout the specification and are defined below:

[0272]	ACN	acetonitrile
[0273]	Ac	acetyl
[0274]	AcOH	acetic acid
[0275]	$AlCl_3$	aluminum chloride
[0276]	BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
[0277]	t-BuOK	potassium t-butoxide
[0278]	tBuONa or t-BuONa	sodium t-butoxide
[0279]	br	broad
[0280]	BOC	tert-butoxy carbonyl
[0281]	Cbz	benzyloxy carbonyl
[0282]	$CDCl_3CHCl_3$	chloroform
[0283]	CH_2Cl_2	dichloromethane
[0284]	CH_3CN	acetonitrile
[0285]	$CsCO_3$	cesium carbonate
[0286]	CH_3NO_3	nitromethane
[0287]	d	doublet
[0288]	dd	doublet of doublets
[0289]	dq	doublet of quartets
[0290]	DCE	1,2 dichloroethane
[0291]	DCM	dichloromethane
[0292]	Δ	heat
[0293]	δ	chemical shift
[0294]	DIEA	N,N-diisopropylethylamine (Hunig's base)
[0295]	DMB	2,4 dimethoxy benzyl
[0296]	DMF	N,N-Dimethylformamide
[0297]	DMSO	Dimethyl sulfoxide
[0298]	DMSO-*d6*	deuterated dimethyl sulfoxide

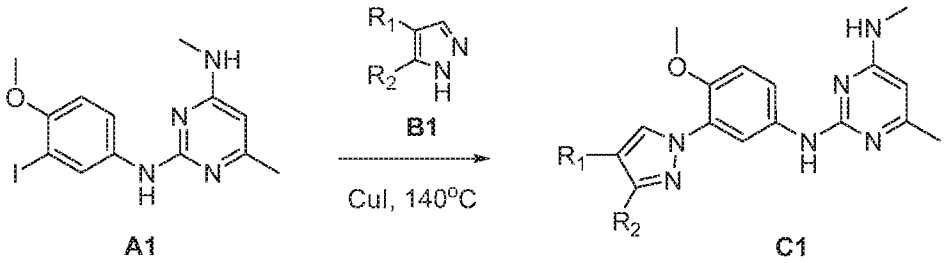
[0299]	EA or EtOAc	Ethyl acetate
[0300]	ES	electrospray
[0301]	Et_3N	triethylamine
[0302]	equiv	equivalents
[0303]	g	grams
[0304]	h	hours
[0305]	H_2O	water
[0306]	HCl	hydrogen chloride or hydrochloric acid
[0307]	HPLC	High performance liquid chromatography
[0308]	Hz	Hertz
[0309]	IPA	isopropyl alcohol
[0310]	i-PrOH	isopropyl alcohol
[0311]	J	NMR coupling constant
[0312]	K_2CO_3	potassium carbonate
[0313]	HI	potassium iodide
[0314]	KCN	potassium cyanide
[0315]	LCMS or LC-MS	Liquid chromatography mass spectrum
[0316]	M	molar
[0317]	m	multiplet
[0318]	mg	milligram
[0319]	MHz	megahertz
[0320]	mL	milliliter
[0321]	mm	millimeter
[0322]	mmol	millimole
[0323]	mol	mole
[0324]	[M+1]	molecular ion plus one mass unit
[0325]	m/z	mass/charge ratio
[0326]	m-CPBA	meta-chloroperbenzoic acid
[0327]	MeCN	Acetonitrile
[0328]	MeOH	methanol
[0329]	MeI	Methyl iodide
[0330]	min	minutes

[0331]	μm	micron
[0332]	MsCl	Mesyl chloride
[0333]	MW	microwave irradiation
[0334]	N	normal
[0335]	Na_2SO_4	sodium sulfate
[0336]	NH_3	ammonia
[0337]	$NaBH(AcO)_3$	sodium triacetoxyborohydride
[0338]	NaI	sodium iodide
[0339]	Na_2SO_4	sodium sulfate
[0340]	NH_4Cl	ammonium chloride
[0341]	NH_4HCO_3	ammonium bicarbonate
[0342]	nm	nanometer
[0343]	NMP	N-methylpyrrolidinone
[0344]	NMR	Nuclear Magnetic Resonance
[0345]	$Pd(OAc)_2$	palladium (II) acetate
[0346]	Pd/C	Palladium on carbon
[0347]	$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
[0348]	PMB	para methoxybenzyl
[0349]	ppm	parts per million
[0350]	$POCl_3$	phosphoryl chloride
[0351]	prep-HPLC	preparative High Performance Liquid Chromatography
[0352]	PTSA	para-toluenesulfonic acid
[0353]	p-TsOH	para-toluenesulfonic acid
[0354]	RT	retention time
[0355]	rt	room temperature
[0356]	s	singlet
[0357]	t	triplet
[0358]	t-BuXPhos	2-Di-*tert*-butylphosphino-2′, 4′, 6′-triisopropylbiphenyl
[0359]	TEA	Triethylamine
[0360]	TFA	trifluoroacetic acid
[0361]	TfO	triflate
[0362]	THP	tetrahydropyran

[0363] TsOH tosic acid

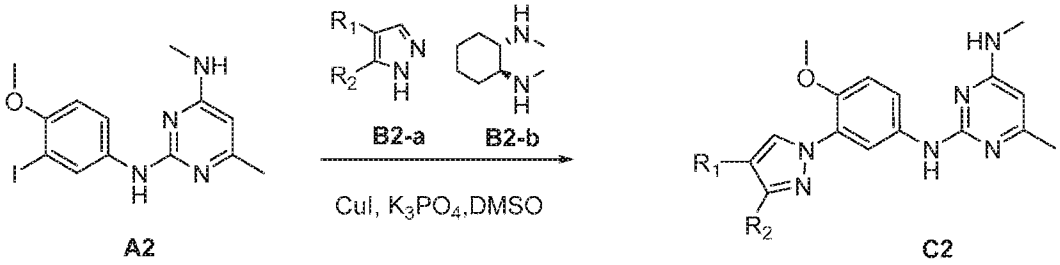
[0364] UV ultraviolet

Scheme 1



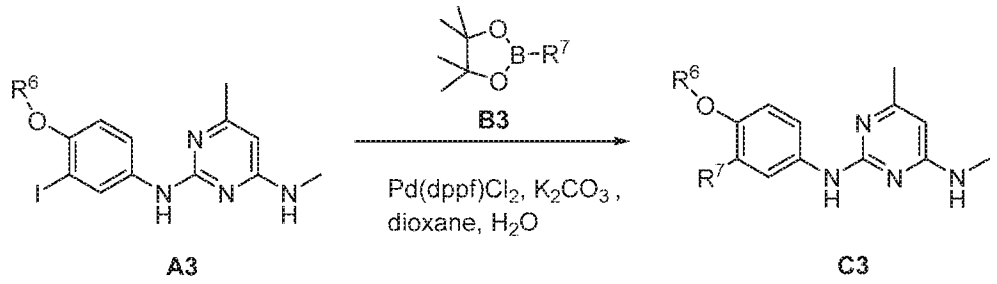
[0365] Scheme 1 shows the synthesis of N2-(4-methoxy-3-(1H-pyrazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine **C1** following a general route. An aryl iodide such as N2-(3-iodo-4-methoxyphenyl)-N4,6-dimethylpyrimidine-2,4-diamine **A1** or a like reagent is heated in an organic solvent (*e.g.*, DMSO) with a copper salt (*e.g.*, CuI) and a nitrogen-containing heterocycle (*e.g.*, disubstituted pyrazole **B1**). The resulting substituted aryl or heteroaryl analog **C1** can be used in further elaboration such as alkylation and salt formation.

Scheme 2



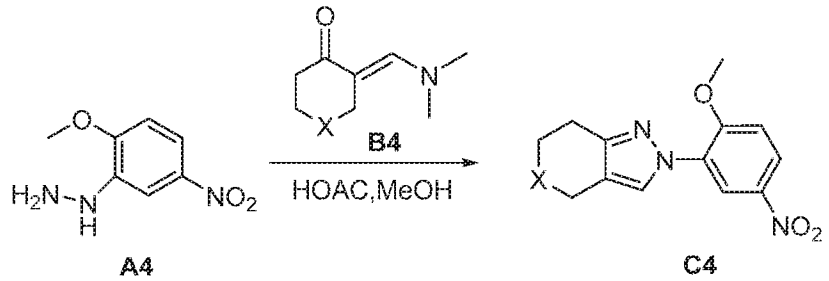
[0366] Scheme 2 shows the synthesis of N2-(4-methoxy-3-(1H-pyrazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine **C2** following an alternate general route. An aryl iodide such as N2-(3-iodo-4-methoxyphenyl)-N4,6-dimethylpyrimidine-2,4-diamine **A2** or a like reagent is combined in an organic solvent (*e.g.*, DMSO) with a copper salt (*e.g.*, CuI), a mild base (*e.g.*, K_3PO_4), a diamine ligand (*e.g.*, (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine **B2-b**) and a nitrogen-containing heterocycle (*e.g.*, disubstituted pyrazole **B2-a**). The resulting substituted aryl or heteroaryl analog **C2** can be used in further elaboration such as alkylation and salt formation.

Scheme 3



[0367] Scheme 3 shows the synthesis of N2-(4-substituted-phenyl)-N4,6-dimethylpyrimidine-2,4-diamine **C3** following a general route. An aryl halide such as N2-(3-iodo-4-methoxyphenyl)-N4,6-dimethylpyrimidine-2,4-diamine **A3** or a like reagent is combined in a mixture of an organic solvent (*e.g.*, dioxane) and water with a palladium (II) compound (*e.g.*, $Pd(dppf)Cl_2$), a mild base (*e.g.*, K_2CO_3), and an aryl or heteroaryl boronate (*e.g.*, **B3**) to yield a substituted aryl or heteroaryl analog **C3**.

Scheme 4



[0368] Scheme 4 depicts the synthesis of 2-(2-methoxy-5-nitrophenyl)-2H-pyrazolo compound **C4** following a general route (X can be CH_2 or NH or O). An aryl hydrazide such as (2-methoxy-5-nitrophenyl)hydrazine **A4** or a like reagent is combined in an organic solvent (*e.g.*, methanol) with an enamineodiketone (*e.g.*, **B4**) in the presence of an acid (*e.g.*, acetic acid) to yield a substituted aryl or heteroaryl intermediate **C4** via a cyclocondensation reaction.

[0369] A person of ordinary skill in the art will recognize that in the above schemes the order of many of the steps are interchangeable.

[0370] Compounds of the present disclosure inhibit the histone methyltransferase activity of G9a, also known as KMT1C (lysine methyltransferase 1C) or EHMT2 (euchromatic histone methyltransferase 2), or a mutant thereof and, accordingly, in one aspect of the disclosure, certain compounds disclosed herein are candidates for treating, or preventing certain conditions, diseases, and disorders in which EHMT2 plays a role. The present disclosure 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 EHMT2. 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 disclosure, or a pharmaceutically acceptable salt, polymorph, solvate, or stereoisomer thereof.

[0371] Unless otherwise stated, any description of a method of treatment includes use of the compounds to provide such treatment or prophylaxis as is described herein, as well as use 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.

[0372] In still another aspect, this disclosure relates to a method of modulating the activity of EHMT2, which catalyzes the dimethylation of lysine 9 on histone H3 (H3K9) in a subject in need thereof. In some embodiments, the method comprises the step of administering to a subject having a cancer expressing a mutant EHMT2 a therapeutically effective amount of a compound described herein, wherein the compound(s) inhibits histone methyltransferase activity of EHMT2, thereby treating the cancer.

[0373] In some embodiments, the EHMT2-mediated cancer is selected from the group consisting of leukemia, prostate carcinoma, hepatocellular carcinoma, and lung cancer.

[0374] In some embodiments, the compounds disclosed herein can be used for treating cancer. In some embodiments, the cancer is a hematological cancer.

[0375] In some embodiments, 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 disclosure are non NHL cancers.

[0376] In some embodiments, the cancer is selected from the group consisting of acute myeloid leukemia (AML) or chronic lymphocytic leukemia (CLL), 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 acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), 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.

[0377] In some embodiments, the cancer is lymphoma, leukemia or melanoma. In some embodiments, the cancer is lymphoma selected from the group consisting of follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), and Burkitt's lymphoma, and Non-Hodgkin's Lymphoma. 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.

[0378] In some embodiments, the EHMT2-mediated disorder is a hematological disorder.

[0379] The compound(s) of the present disclosure inhibit the histone methyltransferase activity of EHMT2 or a mutant thereof and, accordingly, the present disclosure 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 EHMT2. In one aspect of the disclosure, certain compounds

disclosed herein are candidates for treating, or preventing certain conditions, diseases, and disorders. 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 disclosure.

[0380] 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 EHMT2-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 does not respond or has not 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. In some embodiments, the cancer is leukemia, prostate carcinoma, hepatocellular carcinoma, and lung cancer.

[0381] As used herein, "candidate compound" refers to a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, that has been or will be tested in one or more *in vitro* or *in vivo* biological assays, in order to determine if that compound is likely to elicit a desired biological or medical response in a cell, tissue, system, animal or human that is being sought by a researcher or clinician. A candidate compound is a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof. The biological or medical response can be the treatment of cancer. The biological or medical response can be

treatment or prevention of a cell proliferative disorder. The biological response or effect can also include a change in cell proliferation or growth that occurs *in vitro* or in an animal model, as well as other biological changes that are observable *in vitro*. *In vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[0382] In some embodiments, an *in vitro* biological assay that can be used includes the steps of (1) mixing a histone substrate (*e.g.*, an isolated histone sample or an isolated histone peptide representative of human histone H3 residues 1-15) with recombinant EHMT2 enzymes; (2) adding a compound of the disclosure to this mixture; (3) adding non-radioactive and ^{3}H-labeled S-Adenosyl methionine (SAM) to start the reaction; (4) adding excessive amount of non-radioactive SAM to stop the reaction; (4) washing off the free non-incorporated ^{3}H-SAM; and (5) detecting the quantity of ^{3}H-labeled histone substrate by any methods known in the art (*e.g.*, by a PerkinElmer TopCount platereader).

[0383] In some embodiments, an *in vitro* study that can be used includes the steps of (1) treating cancer cells (*e.g.*, breast cancer cells) with a compound of this disclosure; (2) incubating the cells for a set period of time; (3) fixing the cells; (4) treating the cells with primary antibodies that bind to dimethylated histone substrates; (5) treating the cells with a secondary antibody (*e.g.* an antibody conjugated to an infrared dye); (6) detecting the quantity of bound antibody by any methods known in the art (*e.g.*, by a Licor Odyssey Infrared Scanner).

[0384] 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 disclosure, 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.

[0385] A compound of the present disclosure, 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.

[0386] 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 disclosure.

[0387] As used herein, "combination therapy" or "co-therapy" includes the administration of a compound of the present disclosure, 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.

[0388] The present disclosure 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.

[0389] A "pharmaceutical composition" is a formulation containing the compounds of the present disclosure 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 disclosure 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.

[0390] 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.

[0391] "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.

[0392] A pharmaceutical composition of the disclosure 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.

[0393] A compound or pharmaceutical composition of the disclosure can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. In some embodiments, for treatment of cancers, a compound of the disclosure 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.

[0394] 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.

[0395] 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.

[0396] 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.

[0397] The pharmaceutical compositions containing active compounds of the present disclosure 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.

[0398] 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 mannitol 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.

[0399] 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.

[0400] 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.

[0401] 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.

[0402] 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.

[0403] 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.

[0404] 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 disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0405] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure 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. In some embodiments, 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.

[0406] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0407] The compounds of the present disclosure are capable of further forming salts. All of these forms are also contemplated within the scope of the claimed disclosure.

[0408] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present disclosure 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. In some embodiments, 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, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0409] 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 disclosure 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.

[0410] 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.

[0411] The compounds of the present disclosure can also be prepared as esters, for example, pharmaceutically acceptable esters. In some embodiments, 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.

[0412] The compounds, or pharmaceutically acceptable salts thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, 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.

[0413] 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.

[0414] Techniques for formulation and administration of the disclosed compounds of the disclosure 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.

[0415] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0416] 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 disclosure 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.

[0417] 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. In some embodiments, 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.

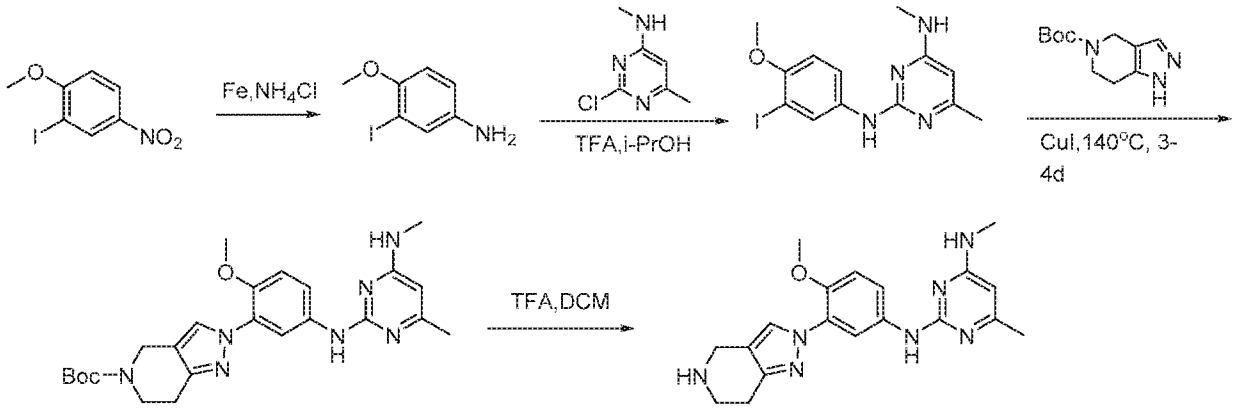
[0418] Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described herein for activity, using techniques known in the art. General methodologies for performing high-throughput screening are described, 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.

[0419] Various *In vitro* or *in vivo* biological assays are may be suitable for detecting the effect of the compounds of the present disclosure. These i*n vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[0420] 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.

Example 1: Synthesis of Compound 1

[0421] **Synthesis of 2-N-(4-methoxy-3-[1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine**



[0422] **Step 1**: Synthesis of 3-iodo-4-methoxyaniline:

[0423] Into a 250-mL round-bottom flask was placed 2-iodo-1-methoxy-4-nitrobenzene (6 g, 21.50 mmol, 1.00 equiv), Fe (3.61 g, 3.00 equiv), NH_4Cl (3.42 g, 63.94 mmol, 3.00 equiv), ethanol (50 mL), and water (10 mL). The resulting solution was stirred for 1 h at 85 °C. The solids were filtered out, and the resulting mixture was concentrated under vacuum. This resulted in 5.35 g (100%) of the title compound as a brown solid.

[0424] LC-MS: (ES, *m/z*): RT = 0.847 min, LCMS 53: *m/z* = 250 [M+1].

[0425] **Step 2:** Synthesis of 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0426] Into a 250-mL round-bottom flask was placed 3-iodo-4-methoxyaniline (5.25 g, 21.08 mmol, 1.00 equiv), 2-chloro-N,6-dimethylpyrimidin-4-amine (3.31 g, 21.00 mmol, 1.00 equiv), trifluoroacetic acid (4.81 g, 42.55 mmol, 2.00 equiv), and iso-propanol (80 mL). The resulting solution was stirred for 3 h at 85 °C. The solids were collected by filtration. This resulted in 7.2 g (92%) of the title compound as a solid.

[0427] LC-MS: (ES, *m/z*): RT =1.041 min, LCMS 15: *m/z* = 371 [M+1]. ^{1}H NMR (300 MHz, DMSO-*d*6) δ 10.23 (s, 1H), 8.95 (s, 1H), 8.14 (d, *J* = 2.6 Hz, 1H), 7.50 (d, *J* = 2.6 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 6.02 (s, 1H), 3.81 (s, 3H), 2.90 (d, *J* = 4.6 Hz,3H), 2.24 (s, 3H).

[0428] **Step 3:** Synthesis of tert-butyl 1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate:

[0429] Into a 25-mL round-bottom flask was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (2.8 g, 7.56 mmol, 1.00 equiv), CuI (580 mg, 3.04 mmol, 0.40 equiv), K_3PO_4 (4.88 g, 22.98 mmol, 3.00 equiv), (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (300 mg, 2.10 mmol, 0.20 equiv), tert-butyl 2H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate (2 g, 8.96 mmol, 1.10 equiv), and DMSO (10 mL). The resulting solution was stirred for 36 h at 140 °C in an oil bath. The crude product was purified by C18 column: ACN:H_2O (0.05%TFA)=1/5. This resulted in 1.4 g (40%) of the title compound as a yellow solid.

[0430] LC-MS: (ES, *m/z*): RT =1.552 min, LCMS33 : *m/z* = 466 [M+1].

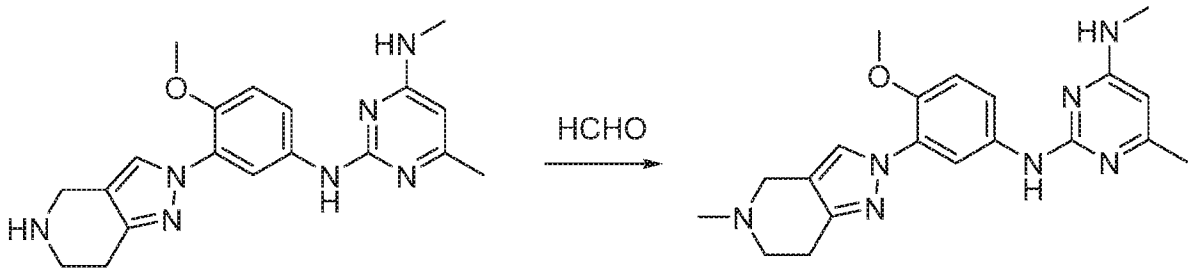
[0431] **Step 4:** Synthesis of 2-N-(4-methoxy-3-[1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0432] Into a 25-mL round-bottom flask was placed tert-butyl 1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate (0.5 g, 1.07 mmol, 1.00 equiv), trifluoroacetic acid (1 mL), and dichloromethane (5 mL). The resulting solution was stirred for 1 h at 25 °C. The resulting mixture was concentrated

under vacuum. The crude product was purified by prep-HPLC; mobile phase, water (10 mmol/L NH_4HCO_3) and ACN (23.0% ACN up to 34.0% in 10 min); detector, UV 254/220nm. This resulted in 55.9 mg (7%) of the title compound as a light yellow solid.

Example 2: Synthesis of Compound 2

[0433] **Synthesis of 2-N-(4-methoxy-3-[1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine**

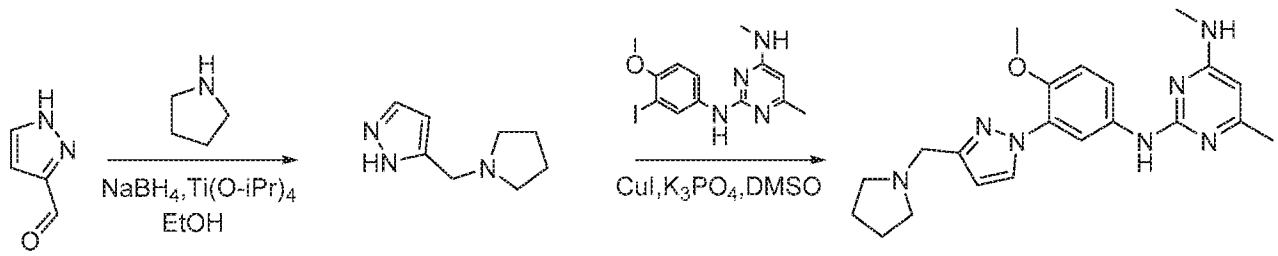


[0434] Synthesis of 2-N-(4-methoxy-3-[1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0435] Into a 100-mL round-bottom flask was placed 2-N-(4-methoxy-3-[1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (500 mg, 1.37 mmol, 1.00 equiv), methanol (6 mL), and formaldehyde (82 mg, 2.56 mmol, 1.00 equiv) and stirred for 30 min at 25 °C. Then $NaBH_3CN$ (345 mg, 5.49 mmol, 4.00 equiv), HOAc (0.02 mL) was added. The resulting solution was stirred for 2 h at 25 °C. The pH value of the solution was adjusted to 8 with sodium bicarbonate. The resulting solution was extracted with 2x50 mL of dichloromethane and the organic layers combined and concentrated under vacuum. The crude product was purified by prep-HPLC; mobile phase, Water(10 mmol/L NH_4HCO_3) and ACN (23.0% ACN up to 34.0% in 10 min); detector, UV 254/220 nm. This resulted in 16.3 mg (2%) of the title compound as a white solid.

Example 3: Synthesis of Compound 4

[0436] **Synthesis of 2-N-[3-[3-(cyclopentylmethyl)-1H-pyrazol-1-yl]-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine; trifluoroacetic acid**



[0437] **Step 1:** Synthesis of 5-(pyrrolidin-1-ylmethyl)-1H-pyrazole:

[0438] Into a 250-mL round-bottom flask was placed 1H-pyrazole-4-carbaldehyde (500 mg, 5.20 mmol, 1.00 equiv), methanol (20 mL), $NaBH_3CN$ (656 mg, 10.44 mmol, 2.01 equiv), and pyrrolidine (370 mg, 5.20 mmol, 1.00 equiv). The resulting solution was stirred for 1 h at 25 °C. The residue was applied onto a silica gel column with H_2O:CH_3CN (89/11). This resulted in 350 mg (44%) the title compound as a yellow oil.

[0439] LC-MS: (ES, *m/z*): RT=0.15 min, LCMS32, m/z=152.1 [M+1].

[0440] **Step 2:** Synthesis of 2-N-[3-[3-(cyclopentylmethyl)-1H-pyrazol-1-yl]-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine, trifluoroacetic acid:

[0441] Into a 30-mL round-bottom flask was placed 5-(pyrrolidin-1-ylmethyl)-1H-pyrazole (190 mg, 1.26 mmol, 1.00 equiv), DMSO (4 mL), 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (230 mg, 0.62 mmol, 0.49 equiv), 1-N,2-N-dimethylcyclohexane-1,2-diamine (73 mg, 0.51 mmol, 0.41 equiv), CuI (47 mg, 0.25 mmol, 0.20 equiv), and K_3PO_4 (400 mg, 1.88 mmol, 1.50 equiv). The resulting solution was stirred for 12 h at 120 °C. The crude product was purified by prep-HPLC; Mobile Phase A:Water/0.05%TFA, Mobile Phase B: ACN. This resulted in 18.2 mg (3%) of the title compound as a white solid.

[0442] LC-MS: (ES, *m/z*): RT=1.06 min, LCMS28, m/z=394.2 [M+1]. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.26 (d, *J* = 2.5 Hz, 1H), 8.12 (d, *J* = 2.7 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 5.99 (d, *J* = 1.1 Hz, 1H), 4.48 (s, 2H), 3.93 (d, *J* = 5.7 Hz, 3H), 3.65 (s, 2H), 3.30 (d, *J* = 7.4 Hz, 2H), 3.02 (s, 3H), 2.34 – 2.29 (m, 3H), 2.21 – 2.11 (m, 2H), 2.10 – 1.99 (m, 2H).

[0443] **Step 3:** Synthesis of 5-(pyrrolidin-1-ylmethyl)-1H-pyrazole:

[0444] Into a 250-mL round-bottom flask was placed 1H-pyrazole-4-carbaldehyde (500 mg, 5.20 mmol, 1.00 equiv), methanol (20 mL), $NaBH_3CN$ (656 mg, 10.44 mmol, 2.01 equiv), and pyrrolidine (370 mg, 5.20 mmol, 1.00 equiv). The resulting solution was stirred for 1 h at 25 °C.

The residue was applied onto a silica gel column with H_2O:CH_3CN (89/11). This resulted in 350 mg (44%) of 5-(pyrrolidin-1-ylmethyl)-1H-pyrazole as a yellow oil.

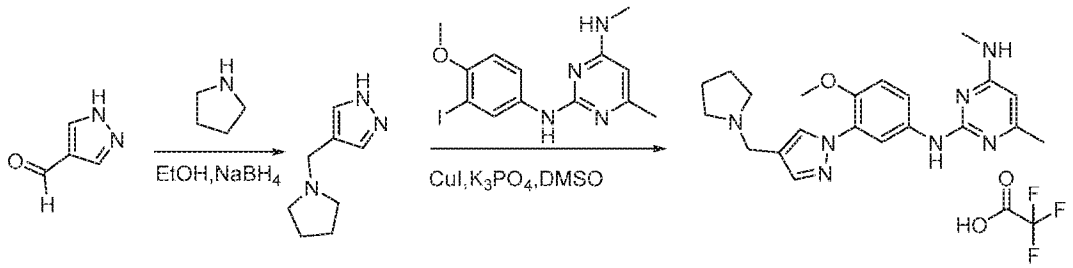
[0445] LC-MS: (ES, *m/z*): RT=0.15min, LCMS32, m/z=152.1[M+1].

[0446] **Step 4:** Synthesis of 2-N-[3-[3-(cyclopentylmethyl)-1H-pyrazol-1-yl]-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine, trifluoroacetic acid:

[0447] Into a 30-mL round-bottom flask was placed 5-(pyrrolidin-1-ylmethyl)-1H-pyrazole (190 mg, 1.26 mmol, 1.00 equiv), DMSO (4 mL), 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (230 mg, 0.62 mmol, 0.49 equiv), 1-N,2-N-dimethylcyclohexane-1,2-diamine (73 mg, 0.51 mmol, 0.41 equiv), CuI (47 mg, 0.25 mmol, 0.20 equiv), and K_3PO_4 (400 mg, 1.88 mmol, 1.50 equiv). The resulting solution was stirred for 12 h at 120 °C. The crude product was purified by prep-HPLC; Mobile Phase A:Water/0.05%TFA, Mobile Phase B: ACN. This resulted in 18.2 mg (3%) of the title compound as a white solid.

Example 4: Synthesis of Compound 5

[0448] **Synthesis of 2-N-[4-methoxy-3-[4-(pyrrolidin-1-ylmethyl)-1H-pyrazol-1-yl]phenyl]-4-N,6-dimethylpyrimidine-2,4-diamine**:



[0449] **Step 1:** Synthesis of 4-(pyrrolidin-1-ylmethyl)-1H-pyrazole:

[0450] Into a 250-mL round-bottom flask was placed 1H-pyrazole-3-carbaldehyde (1 g, 10.41 mmol, 1.00 equiv), $Ti(OiPr)_4$ (10 g), ethanol (20 mL), pyrrolidine (740 mg, 10.40 mmol, 1.00 equiv), and $NaBH_3$ (792 mg). The resulting solution was stirred for 2 h at 25 °C. The residue was applied onto a silica gel column with H_2O:CH_3CN (83/17). This resulted in 570 mg (36%) of the title compound as a white solid.

[0451] LC-MS: (ES, *m/z*): RT = 0.395 min, LCMS31, m/z =152.2 [M+1].

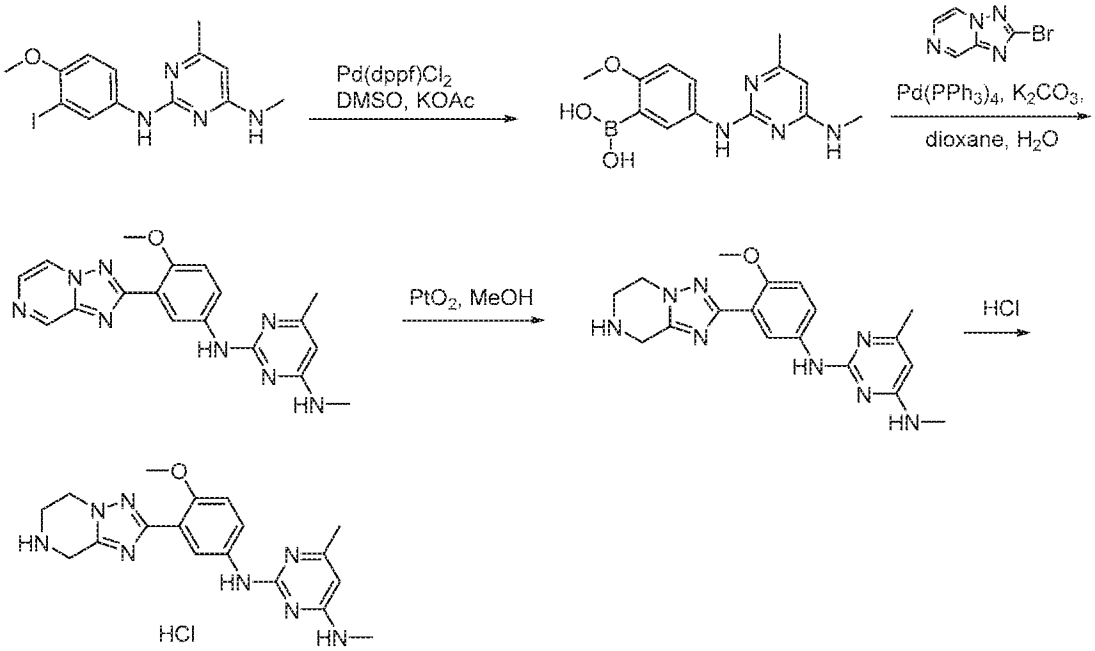
[0452] **Step 2:** Synthesis of 2-N-[4-methoxy-3-[4-(pyrrolidin-1-ylmethyl)-1H-pyrazol-1-yl]phenyl]-4-N,6-dimethylpyrimidine-2,4-diamine, trifluoroacetic acid:

[0453] Into a 30-mL round-bottom flask was placed 4-(pyrrolidin-1-ylmethyl)-1H-pyrazole (80 mg, 0.53 mmol, 1.00 equiv), DMSO (5 mL), K_3PO_4 (171 mg, 0.81 mmol, 1.52 equiv), CuI (21

mg, 0.11 mmol, 0.21 equiv), and 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (100 mg, 0.27 mmol, 0.51 equiv). The resulting solution was stirred for 16 h at 140 °C. The crude product was purified by prep-HPLC; Mobile Phase A:Water/0.05%TFA, Mobile Phase B: ACN. This resulted in 26.6 mg (10%) of the title compound as a light yellow solid.

Example 5: Synthesis of Compound 8

[0454] **Synthesis of 2-N-(4-methoxy-3-[4H,5H,6H,7H-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine hydrochloride:**



[0455] Synthesis of 2-bromo-[1,2,4]triazolo[1,5-a]pyrazine:

[0456] Into a 250-mL round-bottom flask was placed [1,2,4]triazolo[1,5-a]pyrazin-2-amine (5 g, 37.00 mmol, 1.00 equiv), $NaNO_2$ (2 g, 28.99 mmol, 0.78 equiv), CuBr (1.8 g), AcOH (40 mL), and water (15 mL), HBr (25 mL). The resulting solution was stirred for 10 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). This resulted in 1.5 g (20%) of the title compound as a white solid.

[0457] LC-MS: (ES, *m/z*): RT = 1.189 min, LCMS 07: *m/z* = 199 [M+1].

[0458] **Step 1:** Synthesis of (2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)boronic acid:

[0459] Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (2 g,

5.40 mmol, 1.00 equiv), B_2pin_2 (5 g), KOAc (3 g, 30.57 mmol, 5.66 equiv), $Pd(dppf)Cl_2$ (600 mg, 0.82 mmol, 0.15 equiv), and dioxane (200 mL). The resulting solution was stirred for 2 h at 80 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). This resulted in 1.2 g (77%) of the title compound as a yellow solid.

[0460] LC-MS: (ES, *m/z*): RT = 0.981 min, LCMS 07: *m/z* = 289 [M+1].

[0461] **Step 2:** Synthesis of 2-N-(4-methoxy-3-[[1,2,4]triazolo[1,5-a]pyrazin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0462] Into a 125-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed (2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)boronic acid (500 mg, 1.74 mmol, 1.00 equiv), 2-bromo-[1,2,4]triazolo[1,5-a]pyrazine (350 mg, 1.76 mmol, 1.01 equiv), $Pd(PPh_3)_4$ (100 mg, 0.09 mmol, 0.05 equiv), K_2CO_3 (800 mg, 2.46 mmol, 1.41 equiv), dioxane (8 mL), and water(1.5 mL). The resulting solution was stirred for 2 h at 80 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). This resulted in 600 mg (95%) of the title compound as a white solid.

[0463] LC-MS: (ES, *m/z*): RT = 1.003 min, LCMS 07: *m/z* = 363 [M+1].

[0464] **Step 3:** Synthesis of 2-N-(4-methoxy-3-[4H,5H,6H,7H-[1,2,4]triazolo[1,5-a]pyrazine-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0465] Into a 125-mL round-bottom flask was placed 2-N-(4-methoxy-3-[[1,2,4]triazolo[1,5-a]pyrazin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (300 mg, 0.83 mmol, 1.00 equiv), PtO_2 (20 mg), methanol (10 mL), and hydrogen. The resulting solution was stirred for 2 h at room temperature. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 280 mg (92%) of the title compound as a yellow solid.

[0466] LC-MS: (ES, *m/z*): RT = 2.985 min, LCMS 07: *m/z* = 367 [M+1].

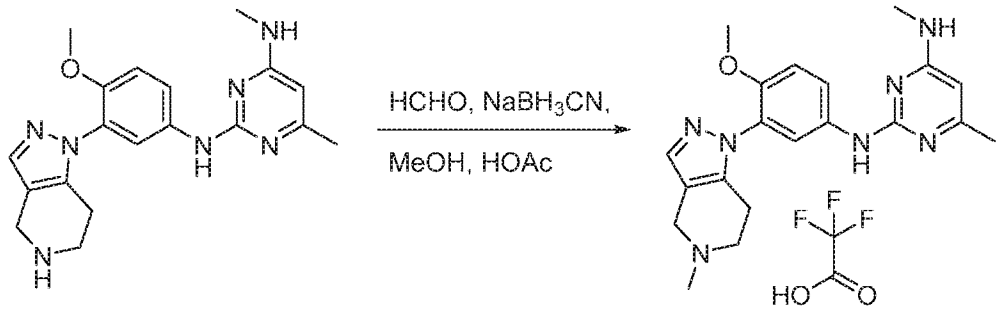
[0467] **Step 4:** Synthesis of 2-N-(4-methoxy-3-[4H,5H,6H,7H-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine hydrochloride:

[0468] Into a 25-mL round-bottom flask was placed 2-N-(4-methoxy-3-[4H,5H,6H,7H-[1,2,4]triazolo[1,5-a]pyrazin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (100 mg, 0.27 mmol, 1.00 equiv), and hydrogen chloride (2 mL). The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product (mL) was purified by Flash-Prep-HPLC; mobile phase, water (0.05%HCl) and ACN (5% ACN up

to 15% in 7 min), detector, 254/220 nm. This resulted in 40.1 mg (97%) of the title compound as a white solid.

Example 6: Synthesis of Compound 10

[0469] **Synthesis of 2-N-(4-methoxy-3-[5-methyl-octahydro-1H-pyrazolidino[4,3-c]pyridin-2-yl]cyclohexyl)-4-N,6-dimethyl-1,3-diazinane-2,4-diamine; trifluoroacetic acid:**

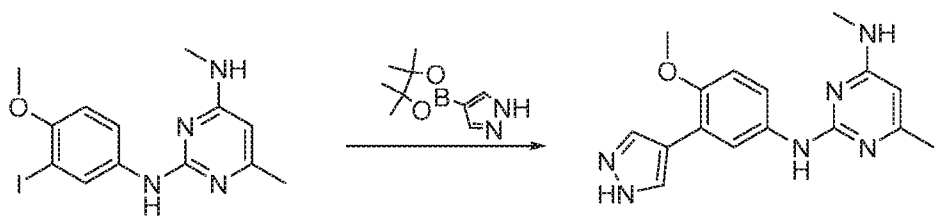


[0470] Synthesis of 2-N-(4-methoxy-3-[5-methyl-octahydro-1H-pyrazolidino[4,3-c]pyridin-2-yl]cyclohexyl)-4-N,6-dimethyl-1,3-diazinane-2,4-diamine:

[0471] Into a 25-mL round-bottom flask was placed 2-N-(4-methoxy-3-[2H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (100 mg, 0.27 mmol, 1.00 equiv), HCHO (16 mg, 2.00 equiv), methanol (2 mL), $NaBH_3CN$ (69 mg, 1.10 mmol, 4.00 equiv), and acetic acid (0.002 mL). The resulting solution was stirred for 30 min at 25 °C. The resulting solution was allowed to react, with stirring, for an additional 2 h at 25 °C. The resulting mixture was concentrated under vacuum. The crude product was purified by Flash-prep-HPLC; mobile phase, H_2O/ACN=38%, detector, UV 254 nm. This resulted in 10 mg (7%) of the title compound as a white solid.

Example 7: Synthesis of Compound 12

[0472] **Synthesis of :2-N-[4-methoxy-3-(1H-pyrazol-4-yl)phenyl]-4-N,6-dimethylpyrimidine-2,4-diamine**:

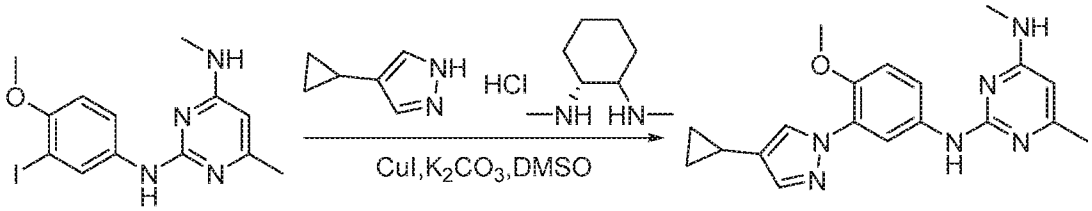


[0473] Synthesis of 2-N-[4-methoxy-3-(1H-pyrazol-4-yl)phenyl]-4-N,6-dimethylpyrimidine-2,4-diamine:

[0474] Into a 100-mL round-bottom flask was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (500 mg, 1.35 mmol, 1.00 equiv), 1,4-dioxane (15 mL), water (5 mL), Cs_2CO_3 (1321.6 mg, 4.06 mmol, 3.00 equiv), Pd(pph3)4 (156.2 mg, 0.14 mmol, 0.10 equiv), and 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (393 mg, 2.03 mmol, 1.50 equiv). The resulting solution was stirred for 6 h at 80 °C. The resulting solution was diluted with 50 mL of water, and the resulting solution was extracted with 3x50 mL of ethyl acetate. The organic layers was washed with 3x50 mL of brine and concentrated under vacuum. The crude product was purified by prep-HPLC; mobile phase, water (10 mmol/L NH_4HCO_3) and ACN (10.0% ACN up to 60.0% in 5 min); detector, UV 254/220 nm. This resulted in 36.9 mg (8.8%) of the title compound as a white solid.

Example 8: Synthesis of Compound 14

[0475] **Synthesis of 2-N-[3-(4-cyclopropyl-1H-pyrazol-1-yl)-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine**:

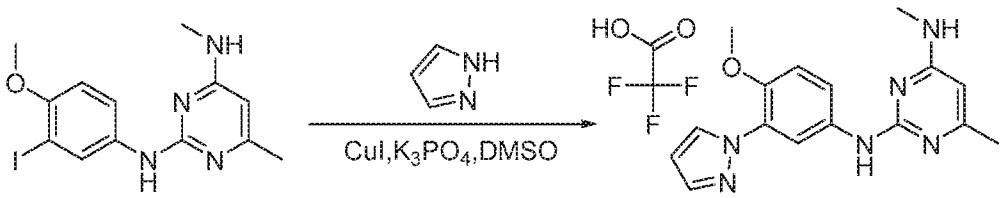


[0476] Synthesis of 2-N-[3-(4-cyclopropyl-1H-pyrazol-1-yl)-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine:

[0477] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (300 mg, 0.81 mmol, 1.00 equiv), 4-cyclopropyl-1H-pyrazole hydrochloride (140 mg, 0.97 mmol, 1.20 equiv), (1R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (80 mg, 0.56 mmol, 0.6 equiv), potassium carbonate (335 mg, 2.42 mmol, 3.00 equiv), DMSO (8 mL), and CuI (123 mg, 0.65 mmol, 0.80 equiv). The resulting solution was stirred for 4 h at 140 °C in an oil bath. The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC; mobile phase, water (10 mmol/L NH_4HCO_3) and ACN (20.0% ACN up to 45.0% in 7 min), detector, UV 254nm. This resulted in 38.9 mg (14%) of the title compound as a white solid.

Example 9: Synthesis of Compound 15

[0478] **Synthesis of 2-N-[4-methoxy-3-(1H-pyrazol-1-yl)phenyl]-4-N,6-dimethylpyrimidine-2,4-diamine; trifluoroacetic acid:**

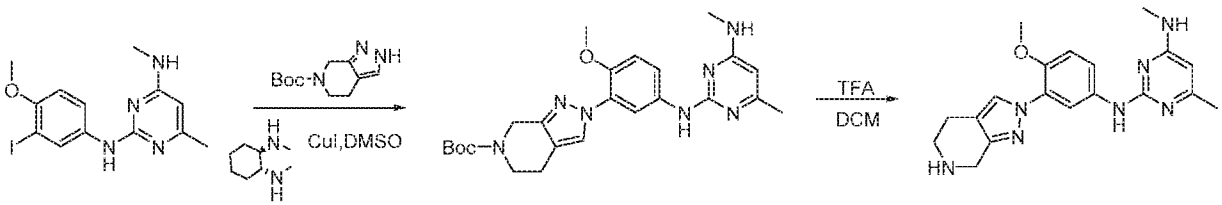


[0479] Synthesis of 2-N-[4-methoxy-3-(1H-pyrazol-1-yl)phenyl]-4-N,6-dimethylpyrimidine-2,4-diamine:

[0480] Into a 100-mL round-bottom flask was placed DMSO (20 mL), 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (300 mg, 0.81 mmol, 1.00 equiv), 1H-pyrazole (165 mg, 2.42 mmol, 2.99 equiv), (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (92 mg, 0.65 mmol, 0.80 equiv), CuI (62 mg, 0.33 mmol, 0.40 equiv), and K_3PO_4 (516 mg, 2.43 mmol, 3.00 equiv). The flask was purged and maintained with N_2. The resulting solution was stirred for 12 h at 120 °C, then concentrated under vacuum. The crude product (102 mg) was purified by prep-HPLC; mobile phase, Water (0.05%TFA) and ACN (3.0% ACN up to 18.0% in 8 min), detector, UV 254/220nm. This resulted in 53.3 mg (15%) of the title compound as a gray solid.

Example 10: Synthesis of Compound 22

[0481] **Synthesis of 2-N-(4-methoxy-3-[2H,4H,5H,6H,7H-pyrazolo[3,4-c]pyridin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine hydrochloride**:



[0482] **Step 1:** Synthesis of tert-butyl 2-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-2H,4H,5H,6H,7H-pyrazolo[3,4-c]pyridine-6-carboxylate:

[0483] Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (1 g, 2.70 mmol, 1.00 equiv), CuI (15 mg, 0.08 mmol, 0.10 equiv), DMSO (10 mL), K_3PO_4 (2.51 g, 8.12 mmol, 3.00 equiv), (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (110 mg, 0.54 mmol, 0.20 equiv), and tert-butyl 2H,4H,5H,6H,7H-pyrazolo[3,4-c]pyridine-6-carboxylate (1.2 g, 5.37

mmol, 2.00 equiv). The resulting solution was stirred for 4 days at 140 °C in an oil bath. The solids were filtered out. The residue was applied onto a silica gel column with H_2O (0.05%TFA):ACN (2:1). This resulted in 200 mg (15%) of the title compound as a white solid.

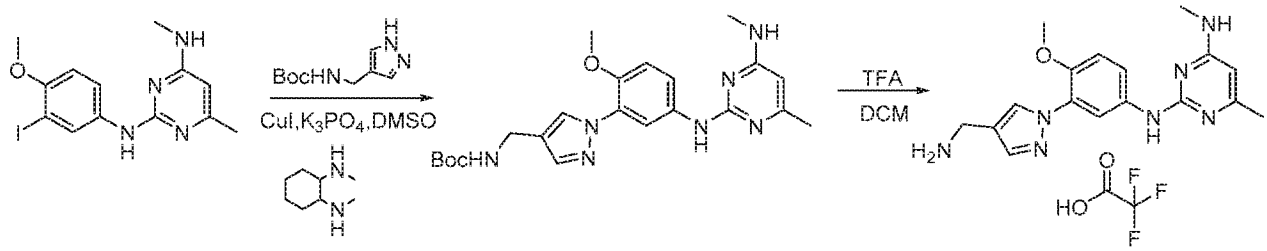
[0484] LC-MS: (ES, *m/z*): RT = 1.142 min; LCMS 33: m/z =466 [M+1]. ^{1}H-NMR: δ8.55 (d, *J* = 2.7 Hz, 1H), 8.27 (d, *J* = 2.7 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 6.06 (d, *J* = 1.2 Hz, 1H), 4.42 (s, 2H), 3.91 (s, 3H), 3.56 (t, *J* = 6.3 Hz, 2H), 3.13 – 2.97 (m, 5H), 2.48 – 2.26 (m, 3H), 1.52 (s, 9H).

[0485] **Step 2:** Synthesis of 2-N-(4-methoxy-3-[2H,4H,5H,6H,7H-pyrazolo[3,4-c]pyridin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine hydrochloride:

[0486] Into a 50-mL round-bottom flask was placed tert-butyl 2-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-2H,4H,5H,6H,7H-pyrazolo[3,4-c]pyridine-6-carboxylate (200 mg, 0.43 mmol, 1.00 equiv), trifluoroacetic acid (147 mg, 1.30 mmol, 3.00 equiv), and dichloromethane (10 mL). The resulting solution was stirred for 14 h at 25 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with H_2O (0.05%TFA):ACN (1:1). This resulted in 9.3 mg (5%) of the title compound as a light yellow solid.

Example 11: Synthesis of Compound 23

[0487] **Synthesis of 2-N-[3-[4-(aminomethyl)-1H-pyrazol-1-yl]-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine; trifluoroacetic acid:**



[0488] **Step 1:** Synthesis of tert-butyl N-[[1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazol-4-yl]methyl]carbamate:

[0489] Into a 30-mL round-bottom flask was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (100 mg, 0.27 mmol, 1.00 equiv), DMSO (4 mL), CuI (21 mg, 0.11 mmol, 0.41 equiv), K_3PO_4 (172 mg, 0.81 mmol, 3.00 equiv), tert-butyl N-(1H-pyrazol-4-ylmethyl)carbamate (212 mg, 1.07 mmol, 3.98 equiv), and 1-N,2-N-dimethylcyclohexane-1,2-diamine (31 mg, 0.22 mmol, 0.81 equiv). The resulting solution was stirred for 12 h at 120 °C. The

crude product was purified by flash-prep-HPLC; mobile phase, H_2O/CH_3CN=1/1; Detector, UV 254 nm. This resulted in 80 mg (67%) of the title compound as white solid.

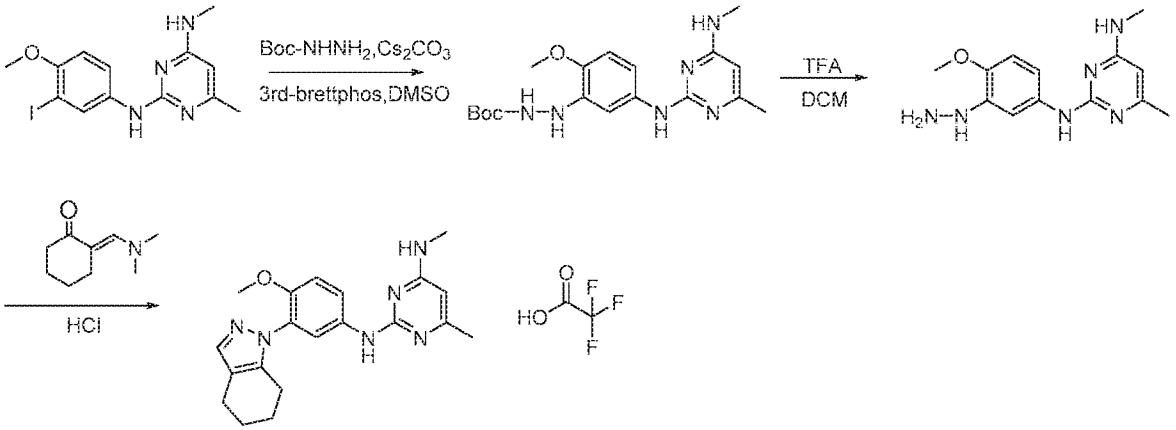
[0490] LC-MS: (ES, *m/z*): RT=1.096 min，LCMS28，m/z=440.2 [M+1].

[0491] **Step 2:** Synthesis of 2-N-[3-[4-(aminomethyl)-1H-pyrazol-1-yl]-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine:

[0492] Into a 50-mL round-bottom flask was placed tert-butyl N-[[1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazol-4-yl]methyl]carbamate (80 mg, 0.18 mmol, 1.00 equiv), dichloromethane (3 mL), and trifluoroacetic acid (1 mL). The resulting solution was stirred for 1 h at 25 °C. The crude product was purified by prep-HPLC; Mobile Phase A:Water/0.05%TFA, Mobile Phase B: ACN. This resulted in 52.4 mg of the title compound as a white solid.

Example 12: Synthesis of Compound 26

[0493] **Synthesis of 2-N-[4-methoxy-3-(4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]-4-N,6-dimethylpyrimidine-2,4-diamine trifluoroacetic acid:**



[0494] **Step 1:** Synthesis of tert-butyl 2-(2-methoxy-5-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)hydrazine-1-carboxylate:

[0495] Into a 100-mL round-bottom flask was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (2 g, 5.40 mmol, 1.00 equiv), DMSO (20 mL), 3rd-brettphos (388 mg), (tert-butoxy)carbohydrazide (566 mg, 4.28 mmol, 0.79 equiv), cesium carbonate (4.2 g, 12.85 mmol, 2.38 equiv). The resulting solution was stirred for 12 h at 80 °C. The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 5x100 mL of water and 1x100 mL of sodium chloride. The

mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 1.5 g (74%) of the title compound as a brown solid.

[0496] LC-MS: (ES, *m/z*): RT=0.699 min, LCMS30, m/z=375.1[M+1].

[0497] **Step 2:** Synthesis of (2E)-2-[(dimethylamino)methylidene]cyclohexan-1-one:

[0498] Into a 30-mL round-bottom flask was placed cyclohexanone (1 g, 10.19 mmol, 1.00 equiv). DMFDMA (1.3 g, 56.46 mmol, 5.54 equiv). The resulting solution was stirred for 12 h at 80 °C. The crude product was purified by Flash-Prep-HPLC; mobile phase, dichloromethane/ CH_3OH = 60/40; Detector, UV 254 nm. This resulted in 150 mg (10%) of the title compound as a yellow oil.

[0499] LC-MS: (ES, *m/z*): RT=4.90 min, GCMS04, m/z=153 [M].

[0500] **Step 3:** Synthesis of 2-N-(3-hydrazinyl-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0501] Into a 100-mL round-bottom flask was placed N-2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)(tert-butoxy)carbohydrazide (600 mg, 1.60 mmol, 1.00 equiv), dichloromethane (5 mL), and trifluoroacetic acid (3 mL). The resulting solution was stirred for 1 h at 25 °C. The resulting mixture was concentrated under vacuum. This resulted in 300 mg (68%) of the title compound as a black solid.

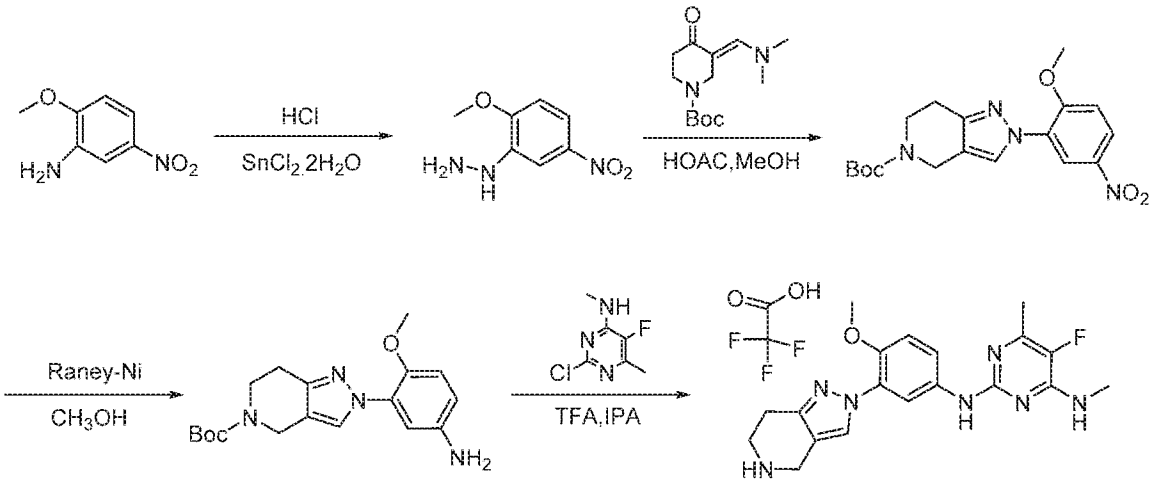
[0502] LC-MS: (ES, *m/z*): RT=0.500 min, LCMS45, m/z=275.2[M+1].

[0503] **Step 4:** Synthesis of 2-N-[4-methoxy-3-(4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]-4-N,6-dimethylpyrimidine-2,4-diamine:

[0504] Into a 50-mL round-bottom flask was placed 2-N-(3-hydrazinyl-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (180 mg, 0.66 mmol, 1.00 equiv), (2E)-2-[(dimethylamino)methylidene]cyclohexan-1-one (100 mg, 0.65 mmol, 0.99 equiv), and hydrogen chloride (0.1 mL). The resulting solution was stirred for 1 h at 70 °C. The crude product was purified by prep-HPLC; Mobile Phase A:Water/0.05%TFA, Mobile Phase B: ACN. This resulted in 22.5 mg (7%) of the title compound as a light yellow solid.

Example 13: Synthesis of Compound 27

[0505] **Synthesis of 5-fluoro-2-N-(4-methoxy-3-[2H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine trifluoroacetic acid:**



[0506] Synthesis of 2,4-dichloro-5-fluoro-6-methylpyrimidine:

[0507] Into a 250-mL 3-necked round-bottom flask was placed bromo(methyl) magnesium (6 mL, 1.50 equiv), oxolane (10 mL), 2,4-dichloro-5-fluoropyrimidine (2 g, 11.98 mmol, 1.00 equiv), ethylene glycol dimethyl ether (10 mL), TEA (2 mL), and diiodane (3 g, 11.82 mmol, 1.00 equiv). The resulting solution was stirred for 1 h at 15 °C. The resulting solution was allowed to react, with stirring, for an additional 1 min while the temperature was maintained at -5 °C in an ice/salt bath. The reaction was then quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). This resulted in 700 mg (32%) of the title compound as a yellow oil.

[0508] LC-MS: (ES, *m/z*): RT = 0.84 min, LCMS15: m/z = 181 [M+1].

[0509] Synthesis of 2-chloro-5-fluoro-N,6-dimethylpyrimidin-4-amine:

[0510] Into a 50-mL round-bottom flask was placed 2,4-dichloro-5-fluoro-6-methylpyrimidine (700 mg, 3.87 mmol, 1.00 equiv), CH_3NH_2.THF (5 mL), TEA (1.2 g, 11.86 mmol, 3.00 equiv), tetrahydrofuran (10 mL). The resulting solution was stirred for 2 h at 20 °C. The resulting mixture was concentrated under vacuum. The crude product (700 mg) was purified by flash-prep-HPLC; mobile phase, CH_3CN/H_2O=30%/70% increasing to CH_3CN/H_2O=40%/60% within 10 min; detector, UV 254 nm. This resulted in 400 mg (59%) of the title compound as an off-white solid.

[0511] LC-MS: (ES, *m/z*): RT = 1.01 min, LCMS15: m/z = 176.03 [M+1]. ^{1}H NMR (400 MHz, Methanol-d4) δ 2.97 (s, 3H), 2.27 (d, *J* = 3.0 Hz, 3H).

[0512] Synthesis of tert-butyl (3E)-3-[(dimethylamino)methylidene]-4-oxopiperidine-1-carboxylate (for use in **Step 2**):

[0513] Into a 20-mL round-bottom flask was placed tert-butyl 4-oxopiperidine-1-carboxylate (1 g, 5.02 mmol, 1.00 equiv), N,N-dimethylformamide (5 mL), DMF-DMA (598 mg, 1.10 equiv). The resulting solution was stirred for 6 h at 80 °C in an oil bath. The crude product (1 g) was purified by flash-prep-HPLC; mobile phase, CH_3CN/ H_2O (NH_4HCO_3) =30%/70% increasing to $CH_3CN/H_2O(NH_4HCO_3)$=40%/60% within 10 min, detector, UV 254 nm. This resulted in 800 mg (63%) of the title compound as a yellow oil.

[0514] LC-MS: (ES, *m/z*): RT = 0.95min, LCMS34: m/z = 255 [M+1].

[0515] **Step 1:** Synthesis of (2-methoxy-5-nitrophenyl)hydrazine:

[0516] Into a 250-mL 3-necked round-bottom flask was placed 2-methoxy-5-nitroaniline (2 g, 11.89 mmol, 1.00 equiv), and hydrogen chloride (16 mL). To this solution was added $NaNO_2$ (904 mg, 13.10 mmol, 1.10 equiv) at -10 °C, and the resulting mixture was stirred for 1 h. To this solution was added $SnCl_2 \cdot 2\ H_2O$ (5.45 g, 24.15 mmol, 2.20 equiv) dissolved in HCl. The resulting solution was stirred for 30 min at -25 °C. The solids were collected by filtration. The solids of the solution were dissolved in potassium hydroxide (25%). This resulted in 1.3 g (60%) of the title compound as a red solid.

[0517] LC-MS: (ES, *m/z*): RT = 0.34 min, LCMS45: m/z = 184.07 [M+1]. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.79 (d, *J* = 2.9 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.65 (s, 1H), 4.17 (s, 2H), 3.90 (s, 3H).

[0518] **Step 2:** Synthesis of tert-butyl 1-(2-methoxy-5-nitrophenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate:

[0519] Into a 50-mL round-bottom flask was placed (2-methoxy-5-nitrophenyl)hydrazine (200 mg, 1.09 mmol, 1.00 equiv), HOAc (197 mg, 3.28 mmol, 3.00 equiv), tert-butyl (3E)-3-[(dimethylamino)methylidene]-4-oxopiperidine-1-carboxylate (278 mg, 1.09 mmol, 1.00 equiv), and methanol (10 mL). The resulting solution was stirred for 3 h at 65 °C in an oil bath. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 10 mL of H_2O. The resulting solution was extracted with 3x20 mL of chloromethane and the organic layers combined. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (20%B). This resulted in 240 mg (59%) of the title compound as a yellow solid.

[0520] LC-MS: (ES, *m/z*): RT = 1.43 min, LCMS31: m/z = 375.16 [M+1].

[0521] **Step 3:** Synthesis of tert-butyl 1-(5-amino-2-methoxyphenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate:

[0522] Into a 50-mL round-bottom flask was placed tert-butyl 1-(2-methoxy-5-nitrophenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate (200 mg, 0.53 mmol, 1.00 equiv), methanol (20 mL), Raney-Ni, hydrogen. The resulting solution was stirred for 1 h at 20 °C. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 130 mg (71%) of as yellow oil.

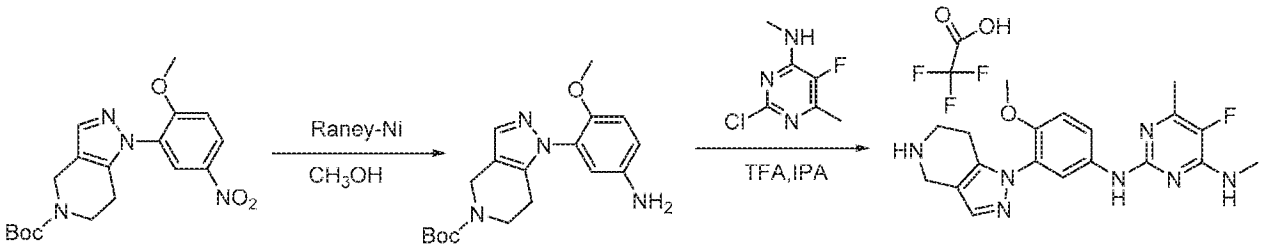
[0523] LC-MS: (ES, *m/z*): RT = 1.00min, LCMS33: m/z = 345.16 [M+1].

[0524] **Step 4:** Synthesis of 5-fluoro-2-N-(4-methoxy-3-[2H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-2-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0525] Into a 50-mL round-bottom flask was placed tert-butyl 2-(5-amino-2-methoxyphenyl)-2H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate (110 mg, 0.32 mmol, 1.00 equiv), trifluoroacetic acid (180.7 mg, 1.60 mmol, 5.00 equiv), IPA (5 mL), and 2-chloro-5-fluoro-N,6-dimethylpyrimidin-4-amine (56 mg, 0.32 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at 80 °C in an oil bath. The resulting mixture was concentrated under vacuum. The crude product (110 mg) was purified by flash-prep-HPLC; mobile phase, H_2O(TFA):CH_3CN increasing to H_2O(TFA):CH_3CN=20% within 20 min, detector, UV 254 nm. This resulted in 18.3 mg (12%) of the title compound as a light yellow solid.

Example 14: Synthesis of Compound 28

[0526] **Synthesis of 5-fluoro-2-N-(4-methoxy-3-[1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine trifluoroacetic acid:**



[0527] **Step 1:** Synthesis of tert-butyl 1-(5-amino-2-methoxyphenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate:

[0528] Into a 50-mL round-bottom flask was placed tert-butyl 1-(2-methoxy-5-nitrophenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate (200 mg, 0.53 mmol, 1.00 equiv), methanol (20 mL), Raney-Ni, and hydrogen. The resulting solution was stirred for 1 h at 20 °C. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted

in 130 mg (71%) of tert-butyl 1-(5-amino-2-methoxyphenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate as a yellow oil.

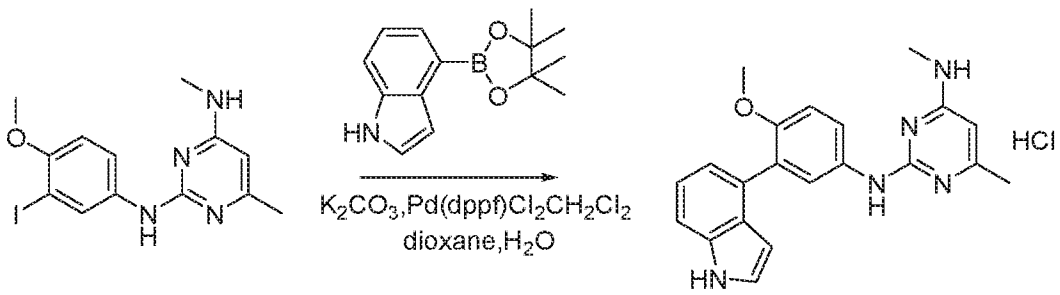
[0529] LC-MS: (ES, *m/z*): RT = 0.99 min, LCMS15: m/z = 345.19 [M+1].

[0530] **Step 2:** Synthesis of 5-fluoro-2-N-(4-methoxy-3-[1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0531] Into a 50-mL round-bottom flask was placed tert-butyl 1-(5-amino-2-methoxyphenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate (100 mg, 0.29 mmol, 1.00 equiv), IPA (10 mL), 2-chloro-5-fluoro-N,6-dimethylpyrimidin-4-amine (50.9 mg, 0.29 mmol, 1.00 equiv), trifluoroacetic acid (98.5 mg, 0.87 mmol, 3.00 equiv). The resulting solution was stirred for 2 h at 80 °C in an oil bath. The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC; mobile phase, water (0.05%TFA) and ACN (5.0% ACN up to 73.0% in 7 min), detector, UV 254/220 nm. This resulted in 78.6 mg (54%) of the title compound as a light yellow solid.

Example 15: Synthesis of Compound 33

[0532] **Synthesis of 2-N-[3-(1H-indol-4-yl)-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine hydrochloride:**

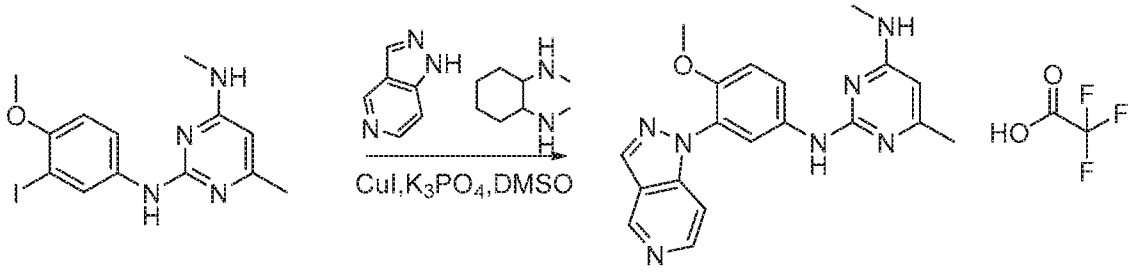


[0533] Synthesis of 2-N-[3-(1H-indol-4-yl)-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine:

[0534] Into a 30-mL round-bottom flask was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (300 mg, 0.81 mmol, 1.00 equiv), dioxane (10 mL), water(3 mL), potassium carbonate (336 mg, 2.43 mmol, 3.00 equiv), Pd(dppf)Cl2CH2Cl2 (66 mg), and 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (295 mg, 1.21 mmol, 1.50 equiv). The resulting solution was stirred for 3 h at 80 °C. The crude product was purified by prep-HPLC; Mobile Phase A:Water/0.05%HCl, Mobile Phase B: ACN. This resulted in 44.1 mg (14%) of the title compound as a solid.

Example 16: Synthesis of Compound 35

[0535] **Synthesis of 2-N-(4-methoxy-3-[1H-pyrazolo[4,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine; trifluoroacetic acid:**

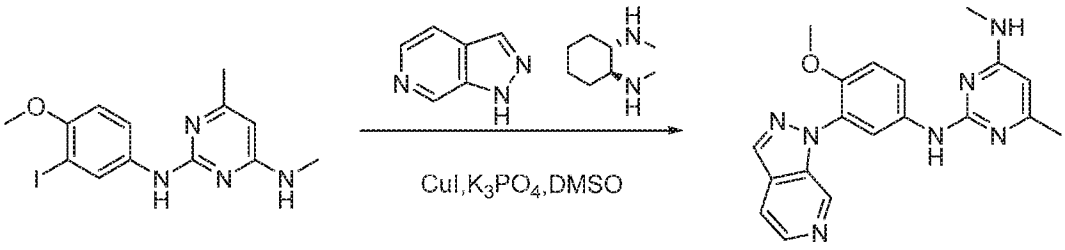


[0536] Synthesis of2-N-(4-methoxy-3-[1H-pyrazolo[4,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0537] Into a 30-mL round-bottom flask was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (300 mg, 0.81 mmol, 1.00 equiv), DMSO (4 mL), CuI (61 mg, 0.32 mmol, 0.40 equiv), K_3PO_4 (516 mg, 2.43 mmol, 3.00 equiv), 1H-pyrazolo[4,3-c]pyridine (385 mg, 3.23 mmol, 3.99 equiv), and 1-N,2-N-dimethylcyclohexane-1,2-diamine (92 mg, 0.65 mmol, 0.80 equiv). The resulting solution was stirred for 12 h at 120 °C. The crude product was purified by prep-HPLC; Mobile Phase A:Water/0.05%TFA, Mobile Phase B: ACN. This resulted in 102.7 mg (27%) of the title compound as a white solid.

Example 17: Synthesis of Compound 36

[0538] **Synthesis of 2-N-(4-methoxy-3-[1H-pyrrolo[2,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:**



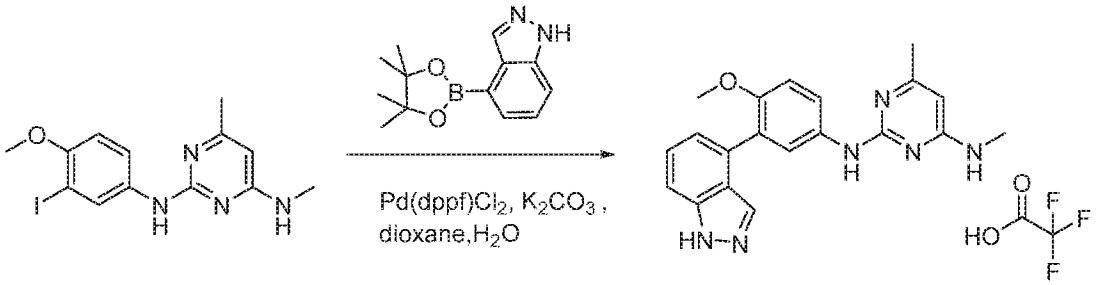
[0539] Synthesis of 2-N-(4-methoxy-3-[1H-pyrrolo[2,3-c]pyridin-1-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine:

[0540] Into a 20-mL vial purged and maintained with an inert atmosphere of nitrogen was placed 1H-pyrrolo[2,3-c]pyridine (289 mg, 2.45 mmol, 3.02 equiv), CuI (61.6 mg, 0.32 mmol, 0.40 equiv), K_3PO_4 (516 mg, 2.43 mmol, 3.00 equiv), DMSO (5 mL), 2-N-(3-iodo-4-methoxyphenyl)-

4-N,6-dimethylpyrimidine-2,4-diamine (300 mg, 0.81 mmol, 1.00 equiv), and (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (92.1 mg, 0.65 mmol, 0.80 equiv). The resulting solution was stirred for 1 overnight at 100 °C. The crude product was purified by Prep-HPLC; mobile phase, Water(10 mmol/L NH_4HCO_3) and ACN (25.0% ACN up to 31.0% in 12 min), detector, UV 254/220 nm. This resulted in 114.5 mg (39%) of the title compound as a white solid.

Example 18: Synthesis of Compound 37

[0541] **Synthesis of 2-N-[3-(1H-indazol-4-yl)-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine; trifluoroacetic acid:**

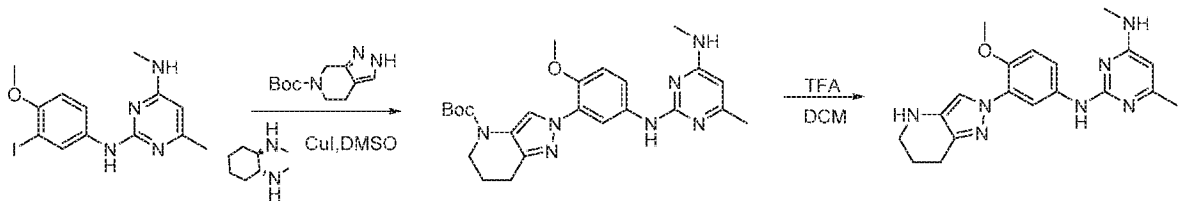


[0542] Synthesis of 2-N-[3-(1H-indazol-4-yl)-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine:

[0543] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (200 mg, 0.54 mmol, 1.00 equiv), 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (224 mg, 0.92 mmol, 1.70 equiv), potassium carbonate (224 mg, 1.62 mmol, 3.00 equiv), dioxane (10 mL), water(2 mL), and $Pd(dppf)Cl_2CH_2Cl_2$ (49 mg, 0.07 mmol, 0.10 equiv). The resulting solution was stirred for 1 overnight at 80 °C in an oil bath, then concentrated under vacuum. The resulting solution was extracted with 3x80 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 3x50 mL of water and 2x50 mL of Brine. The mixture was dried over anhydrous sodium sulfate. The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC; mobile phase, Mobile Phase A:Water/0.05% TFA, Mobile Phase B: ACN; detector, 254 nm. This resulted in 37.8 mg (15%) of the title compound as an off-white solid.

Example 19: Synthesis of Compound 56

[0544] **Synthesis of N2-(4-methoxy-3-(4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-2-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine hydrochloride:**

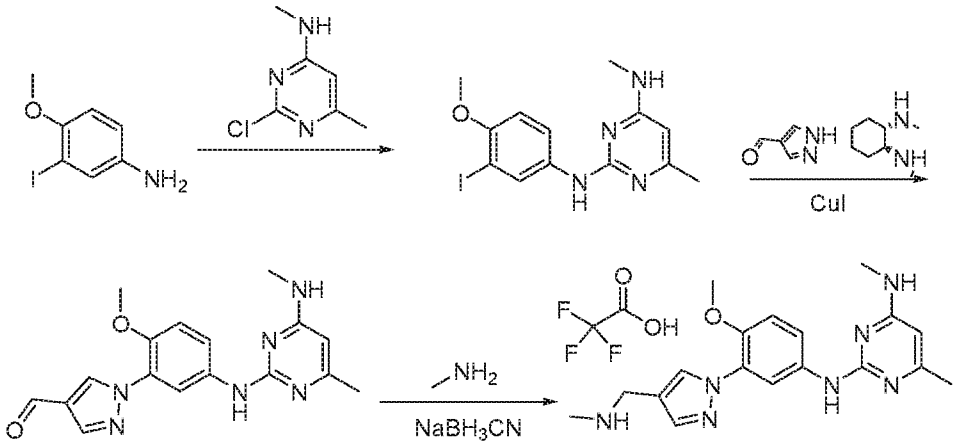


[0545] Synthesis of N2-(4-methoxy-3-(4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-2-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0546] Into a 25-mL round-bottom flask, was placed tert-butyl 2-(2-methoxy-5-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-b]pyridine-4-carboxylate (100 mg, 0.21 mmol, 1.00 equiv), trifluoroacetic acid (73 mg, 0.65 mmol, 3.00 equiv), and dichloromethane (5 mL). The resulting solution was stirred for 24 h at 25 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with H_2O (0.05% TFA):ACN (1:1). This resulted in 16.1 mg (9%) of the title compounds as a light yellow solid.

Example 20: Synthesis of Compound 108

[0547] **Synthesis of N2-(4-methoxy-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine**



[0548] **Step 1:** Synthesis of 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine

[0549] Into a 500-mL round-bottom flask, was placed 3-iodo-4-methoxyaniline (20 g, 80.31 mmol, 1.00 equiv), IPA (240 mL), trifluoroacetic acid (17.6 g, 155.70 mmol, 2.00 equiv), 2-chloro-N,6-dimethylpyrimidin-4-amine (12.7 g, 80.58 mmol, 1.00 equiv). The resulting solution

was stirred for 2 h at room temperature. The solids were collected by filtration. This resulted in 26 g (87%) of the title compound as a brown solid.

[0550] Analytical Data: LC-MS: (ES, *m/z*): RT = 1.058 min; LCMS33: m/z = 371 [M+1]. **2.**

[0551] **Step 2:** Synthesis of 1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazole-4-carbaldehyde

[0552] Into a 50-mL round-bottom flask, was placed 2-N-(3-iodo-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (1 g, 2.70 mmol, 1.00 equiv), Tol (10 mL), CuI (154 mg, 0.81 mmol, 0.30 equiv), K3PO4 (1.72 g, 8.10 mmol, 3.00 equiv), 1H-pyrazole-4-carbaldehyde (262 mg, 2.73 mmol, 1.00 equiv), (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (230 mg, 1.62 mmol, 0.60 equiv). The resulting solution was stirred for 24 h at 140°C. The residue was applied onto a silica gel column with water/ACN (1:50-1:10). The collected fractions were combined and concentrated under vacuum. This resulted in 550 mg (60%) of the title compound as an off-white solid.

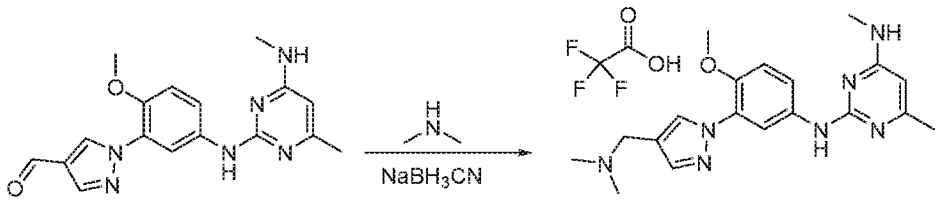
[0553] Analytical Data: LC-MS: (ES, *m/z*): RT = 0.981 min; LCMS33: m/z = 339 [M+1]. ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.91 (s, 1H), 8.77 (d, J = 0.6 Hz, 1H), 8.38 (s, 1H), 8.16 (s, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 9.0 Hz, 1H), 5.82 (s, 1H), 3.91 (s, 3H), 2.89 (s, 3H), 2.18 (s, 3H).

[0554] **Step 3:** Synthesis of N2-(4-methoxy-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine

[0555] Into a 25-mL round-bottom flask, was placed 1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazole-4-carbaldehyde (140 mg, 0.41 mmol, 1.00 equiv), $NaBH_3CN$ (5 g, 79.57 mmol, 192.30 equiv), methanol (233 mg, 7.27 mmol, 6.00 equiv), methanamine (104 mg, 3.35 mmol, 4.00 equiv). The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XSelect CSH Prep C18 OBD Column,, 19*250mm,5um; mobile phase, Water(0.05%TFA) and ACN (10.0% ACN up to 30.0% in 7 min); Detector, uv 254/220nm. This resulted in 47.5 mg (25%) of the title compound as a trifluoroacetic acid salt as a white solid.

Example 21: Synthesis of Compound 109

[0556] **Synthesis of N2-(3-(4-((dimethylamino)methyl)-1H-pyrazol-1-yl)-4-methoxyphenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**

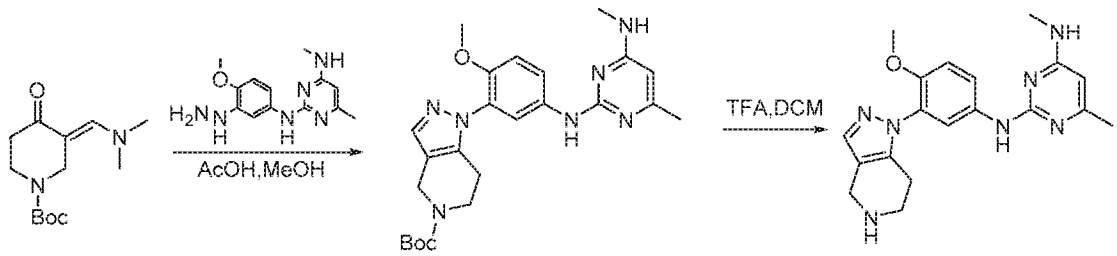


[0557] **Step 1:** Synthesis of N2-(3-(4-((dimethylamino)methyl)-1H-pyrazol-1-yl)-4-methoxyphenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0558] Into a 25-mL round-bottom flask, was placed 1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazole-4-carbaldehyde (160 mg, 0.47 mmol, 1.00 equiv), $NaBH_3CN$ (5 g, 79.57 mmol, 168.27 equiv), methanol (240 mg, 7.49 mmol, 4.00 equiv), dimethylamine (119 mg, 2.64 mmol, 4.00 equiv). The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XSelect CSH Prep C18 OBD Column, 19*250mm,5um; mobile phase, Water(0.05%TFA) and ACN (15.0% ACN up to 35.0% in 7 min); Detector, uv 254/220nm. This resulted in 89.2 mg (39%) of the title compound as the trifluoroacetic acid salt as a white solid.

Example 22: Synthesis of Compound 113:

[0559] **Synthesis of N2-(4-methoxy-3-(4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**



[0560] **Step 1:** Synthesis of tert-butyl 1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate:

[0561] Into a 100-mL round-bottom flask, was placed tert-butyl (3E)-3-[(dimethylamino)methylidene]-4-oxopiperidine-1-carboxylate (500 mg, 1.87 mmol, 1.00 equiv), AcOH (225 mg, 3.75 mmol, 2.00 equiv), methanol (10 mL), 2-N-(3-hydrazinyl-4-methoxyphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (580 mg, 1.87 mmol, 1.00 equiv). The resulting solution was stirred for 15 h at 65 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with H_2O (0.05% TFA):ACN (1:1). This resulted in 300 mg (26%) of as a yellow oil.

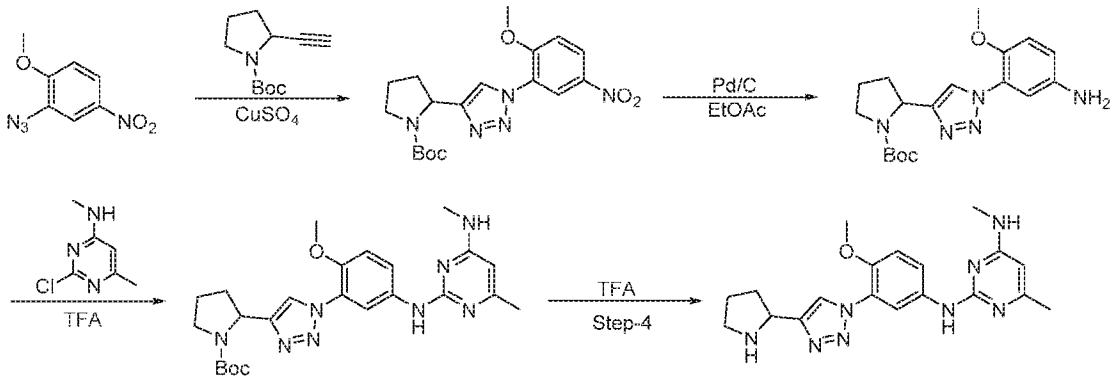
[0562] Analytical Data: LC-MS: (ES, *m/z*): RT = 1.18 min, LCMS 33: *m/z* = 466 [M+1].

[0563] **Step 2:** Synthesis of N2-(4-methoxy-3-(4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0564] Into a 50-mL round-bottom flask, was placed tert-butyl 1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxylate (300 mg, 0.64 mmol, 1.00 equiv), trifluoroacetic acid (290 mg, 1.92 mmol, 3.00 equiv), dichloromethane (10 mL). The resulting solution was stirred for 24 h at 25 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with H_2O(0.05%NH_4HCO_3):ACN (3:1). This resulted in 16.5 mg (7%) of the title compound as a light yellow solid.

Example 23: Synthesis of Compound 137:

[0565] **Synthesis of N2-(4-methoxy-3-(4-(pyrrolidin-2-yl)-1H-1,2,3-triazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**



[0566] **Step 1:** Synthesis of tert-butyl 2-[1-(2-methoxy-5-nitrophenyl)-1H-1,2,3-triazol-4-yl]pyrrolidine-1-carboxylate:

[0567] Into a 100-mL round-bottom flask, was placed 2-azido-1-methoxy-4-nitrobenzene (1 g, 5.15 mmol, 1.00 equiv), tert-butanol (10 mL), water(20 mL), dioxo(sulfonylidene)copper (80 mg,

0.50 mmol, 0.10 equiv), tert-butyl 2-ethynylpyrrolidine-1-carboxylate (1.1 g, 5.53 mmol, 1.10 equiv). The resulting solution was stirred for 3 h at 80 °C in an oil bath. The resulting solution was extracted with 20 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. This resulted in 550 mg (25%) of the title compound as a yellow solid.

[0568] Analytical Data: LC-MS: (ES, *m/z*): RT = 1.12 min, LCMS 53: *m/z* = 390 [M+1].

[0569] **Step 2:** Synthesis of tert-butyl 2-[1-(5-amino-2-methoxyphenyl)-1H-1,2,3-triazol-4-yl]pyrrolidine-1-carboxylate:

[0570] Into a 25-mL round-bottom flask, was placed tert-butyl 2-[1-(2-methoxy-5-nitrophenyl)-1H-1,2,3-triazol-4-yl]pyrrolidine-1-carboxylate (50 mg, 0.13 mmol, 1.00 equiv), palladium carbon (10 mg), ethyl acetate (2 mL). The resulting solution was stirred for 12 h at 25 °C. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 30 mg (62%) of the title compound as a yellow solid.

[0571] Analytical Data: LC-MS: (ES, *m/z*): RT = 1.02 min, LCMS 33: *m/z* = 360 [M+1].

[0572] **Step 3:** Synthesis of tert-butyl 2-[1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-1,2,3-triazol-4-yl]pyrrolidine-1-carboxylate:

[0573] Into a 50-mL round-bottom flask, was placed tert-butyl 2-[1-(5-amino-2-methoxyphenyl)-1H-1,2,3-triazol-4-yl]pyrrolidine-1-carboxylate (400 mg, 1.21 mmol, 1.00 equiv), trifluoroacetic acid (400 mg, 3.64 mmol, 3.00 equiv), IPA (10 mL), 2-chloro-N,6-dimethylpyrimidin-4-amine (174 mg, 1.20 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at 80 °C in an oil bath. The solids were collected by filtration. The resulting mixture was concentrated under vacuum. This resulted in 200 mg (36%) of the title compound as a pink solid.

[0574] Analytical Data: LC-MS: (ES, *m/z*): RT = 1.32 min, LCMS 27: *m/z* = 481 [M+1].

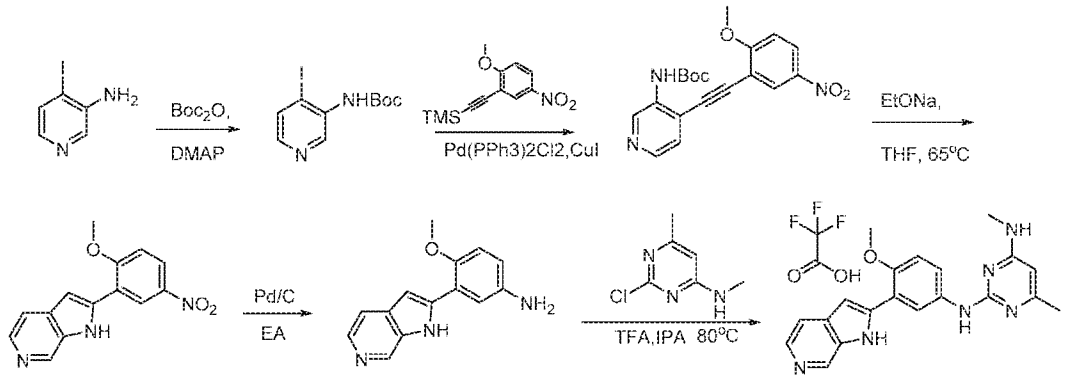
[0575] **Step 4:** Synthesis of tert-butyl 2-[1-(2-methoxy-5-nitrophenyl)-1H-1,2,3-triazol-4-yl]pyrrolidine-1-carboxylate:

[0576] Into a 50-mL round-bottom flask, was placed tert-butyl 2-[1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-1,2,3-triazol-4-yl]pyrrolidine-1-carboxylate (200 mg, 0.42 mmol, 1.00 equiv), trifluoroacetic acid (200 mg, 1.27 mmol, 3.00 equiv), dichloromethane (8 mL). The resulting solution was stirred for 24 h at 25 °C. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XSelect CSH Prep C18 OBD Column,, 5um,19*150mm; mobile phase, Water (0.05% TFA) and ACN (5.0% ACN

up to 20.0% in 8 min); Detector, UV 254/220nm. This resulted in 21.8 mg of the title compound as the trifluoroacetic acid salt as a white solid.

Example 24: Synthesis of Compound 157:

[0577] **Synthesis of N2-(4-methoxy-3-(1H-pyrrolo[2,3-c]pyridin-2-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**



[0578] **Step 1:** Synthesis of tert-butyl N-(4-iodopyridin-3-yl)carbamate:

[0579] Into a 100-mL round-bottom flask, was placed 4-iodopyridin-3-amine (2 g, 9.09 mmol, 1.00 equiv), Boc_2O (2.4 g, 11.00 mmol, 1.21 equiv), 4-dimethylaminopyridine (1 g, 8.19 mmol, 0.90 equiv), dichloromethane (50 mL). The resulting solution was stirred for 1 overnight at room temperature. The resulting solution was extracted with of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1: 10).This resulted in 1.9 g (65%) of the title compound as an off-white solid.

[0580] Analytical Data: LC-MS: (ES, *m/z*): RT = 0.719min, LCMS45: *m/z* =321 [M+1].

[0581] **Step 2:** Synthesis of tert-butyl N-[4-[2-(2-methoxy-5-nitrophenyl)ethynyl]pyridin-3-yl]carbamate

[0582] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl N-(4-iodopyridin-3-yl)carbamate (700 mg, 2.19 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (144 mg, 0.21 mmol, 0.09 equiv), CuI (83 mg, 0.44 mmol, 0.20 equiv), TEA (1.1 g, 10.87 mmol, 4.97 equiv), DMSO (5 mL), [2-(2-methoxy-5-nitrophenyl)ethynyl]trimethylsilane (544 mg, 2.18 mmol, 1.00 equiv). The resulting solution was stirred for 4 h at 50 °C. The resulting solution was extracted with of ethyl acetate and the organic layers combined. This resulted in 420 mg (52%) of the title compound as a yellow solid.

[0583] Analytical Data: LC-MS: (ES, *m/z*): RT 0.880= min, LCMS45: *m/z* = 370 [M+1].

[0584] **Step 3:** Synthesis of 2-(2-methoxy-5-nitrophenyl)-1H-pyrrolo[2,3-c]pyridine:

[0585] Into a 10-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl N-[4-[2-(2-methoxy-5-nitrophenyl)ethynyl]pyridin-3-yl]carbamate (30 mg, 0.08 mmol, 1.00 equiv), EtONa (11 mg), ethanol (2 mL). The final reaction mixture was irradiated with microwave radiation for 2 h at 65 °C. The crude product was used in the next reaction without further purification.

[0586] Analytical Data: LC-MS: (ES, *m/z*): RT =1.715 min, LCMS30: *m/z* = 270 [M+1].

[0587] **Step 4:** Synthesis of 4-methoxy-3-[1H-pyrrolo[2,3-c]pyridin-2-yl]aniline:

[0588] Into a 50-mL 3-necked round-bottom flask, was placed 2-(2-methoxy-5-nitrophenyl)-1H-pyrrolo[2,3-c]pyridine (109 mg, 0.40 mmol, 1.00 equiv), ethyl acetate (20 mL), Palladium carbon (30 mg), hydrogen. The resulting solution was stirred for 1 h at room temperature. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 100 mg of the title compound as a brown solid.

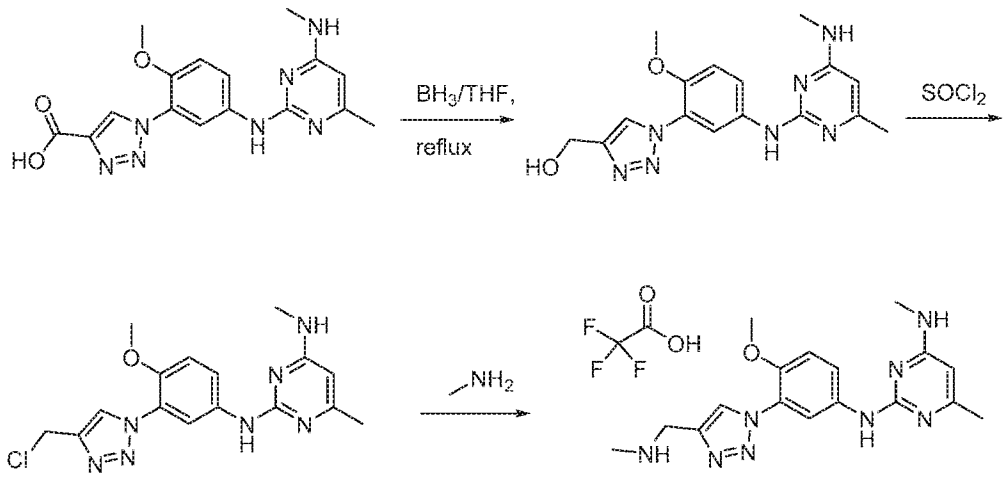
[0589] Analytical Data: LC-MS: (ES, *m/z*): RT = 1.041min, LCMS31: *m/z* = 270 [M+1].

[0590] **Step 5:** Synthesis of N2-(4-methoxy-3-(1H-pyrrolo[2,3-c]pyridin-2-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0591] Into a 40-mL vial, was placed 4-methoxy-3-[1H-pyrrolo[2,3-c]pyridin-2-yl]aniline (100 mg, 0.42 mmol, 1.00 equiv), IPA (15 mL, 1.09 equiv), trifluoroacetic acid (156 mg, 1.38 mmol, 3.30 equiv), 2-chloro-N,6-dimethylpyrimidin-4-amine (71.6 mg, 0.45 mmol, 3.30 equiv). The resulting solution was stirred for 3 h at 80 °C in an oil bath. The crude product (100 g) was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XSelect CSH Prep C18 OBD Column,, 19*250mm,5um; mobile phase, Water (0.05%TFA) and ACN (10.0% ACN up to 35.0% in 7 min); Detector, UV 254/220nm. 19.2 mg product was obtained and concentrated under vacuum. This resulted in 19.2 mg (10%) of the title compound as the trifluoroacetic acid salt as an off-white solid.

Example 25: Synthesis of Compound 159:

[0592] **Synthesis of N2-(4-methoxy-3-(4-((methylamino)methyl)-1H-1,2,3-triazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**



[0593] **Step 1:** Synthesis of [1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-1,2,3-triazol-4-yl]methanol:

[0594] Into a 50-mL round-bottom flask, was placed 1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-1,2,3-triazole-4-carboxylic acid (700 mg, 1.97 mmol, 1.00 equiv), BH_3/THF (15 mL). The resulting solution was stirred for 20 h at 20 °C. The resulting mixture was concentrated under vacuum. The reaction was then quenched by the addition of 5 mL of. The residue was applied onto a silica gel column with methanol/H_2O(0.05% TFA) (1/1). This resulted in 350 mg (52%) of the title compound as an off-white solid.

[0595] Analytical Data: LC-MS: (ES, *m/z*): RT = 0.856 min; LCMS53: *m/z* = 342 [M+1]. ^{1}H NMR (300 MHz, Methanol-*d*4) δ 8.42 – 8.28 (m, 2H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 6.01 (q, *J* = 0.9 Hz, 1H), 4.78 (d, *J* = 0.7 Hz, 2H), 3.96 (s, 3H), 3.01 (s, 3H), 2.44 – 2.28 (m, 3H).

[0596] **Step 2:** Synthesis of 2-N-[3-[4-(chloromethyl)-1H-1,2,3-triazol-1-yl]-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine:

[0597] Into a 100-mL round-bottom flask, was placed [1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-1,2,3-triazol-4-yl]methanol (200 mg, 0.59 mmol, 1.00 equiv), dichloromethane (40 mL), thionyl chloride (346 mg, 5.00 equiv), N,N-dimethylformamide (2 drop). The resulting solution was stirred for 1 h at 20 °C. The resulting solution was diluted with 30 mL of H_2O. The resulting solution was extracted with 3x80 mL of dichloromethane and the organic layers combined and concentrated under vacuum. This resulted in 137 mg (65%) of the title compound as an off-white solid.

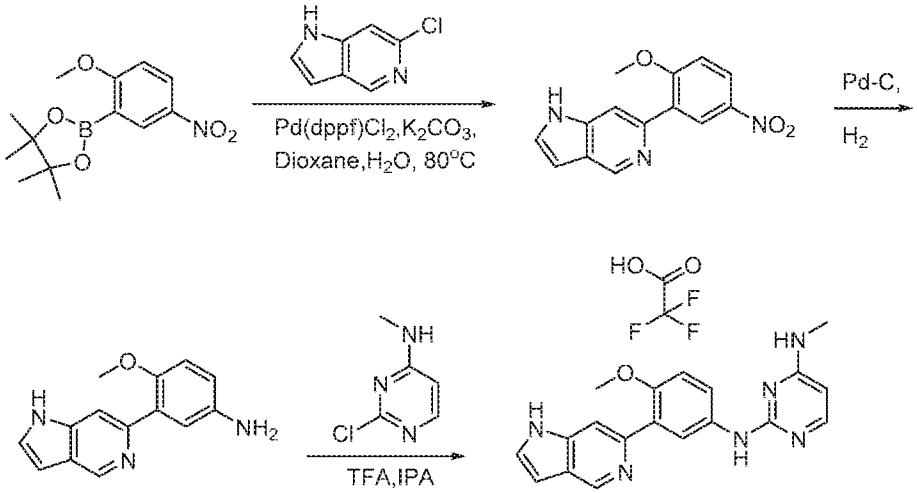
[0598] Analytical Data: LC-MS: (ES, *m/z*): RT = 0.994 min; LCMS15: *m/z* = 360 [M+1].

[0599] **Step 3:** Synthesis of N2-(4-methoxy-3-(4-((methylamino)methyl)-1H-1,2,3-triazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0600] Into a 50-mL round-bottom flask, was placed 2-N-[3-[4-(chloromethyl)-1H-1,2,3-triazol-1-yl]-4-methoxyphenyl]-4-N,6-dimethylpyrimidine-2,4-diamine (137 mg, 0.38 mmol, 1.00 equiv), methanamine hydrochloride (127 mg, 1.88 mmol, 5.00 equiv), potassium carbonate (420 mg, 3.04 mmol, 8.00 equiv), ACN (15 mL). The resulting solution was stirred for 2 days at 20 °C. The solids were filtered out. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XSelect CSH Prep C18 OBD Column,, 5um,19*150mm; mobile phase, Water (0.05% TFA) and ACN (5.0% ACN up to 20.0% in 7 min); Detector, UV 254/220nm. This resulted in 62.8 mg (35%) of the title compound as the trifluoroacetic acid salt as a white solid.

Example 26: Synthesis of Compound 175:

[0601] **Synthesis of N2-(4-methoxy-3-(1H-pyrrolo[3,2-c]pyridin-6-yl)phenyl)-N4-methylpyrimidine-2,4-diamine:**



[0602] **Step 1:** Synthesis of 6-(2-methoxy-5-nitrophenyl)-1H-pyrrolo[3,2-c]pyridine:

[0603] Into a 30-mL vial purged and maintained with an inert atmosphere of nitrogen, was placed 6-chloro-1H-pyrrolo[3,2-c]pyridine (500 mg, 3.28 mmol, 1.00 equiv), 2-(2-methoxy-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.1 g, 3.94 mmol, 1.20 equiv), $Pd(dppf)Cl_2$ (270 mg, 0.37 mmol, 0.11 equiv), potassium carbonate (1.36 g, 9.84 mmol, 3.00 equiv), Dioxane (10 mL), water(1 mL). The resulting solution was stirred for 4 h at 80 °C in an oil bath. The resulting solution was extracted with 3x30 mL of ethyl acetate and the organic layers combined.

The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (60%). This resulted in 280 mg (crude) of the title compound as a yellow solid.

[0604] Analytical Data: LC-MS: (ES, *m/z*): RT = 0.543 min, LCMS30: m/z = 270 [M+1].

[0605] **Step 2:** Synthesis of 4-methoxy-3-[1H-pyrrolo[3,2-c]pyridin-6-yl]aniline:

[0606] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of H2, was placed 6-(2-methoxy-5-nitrophenyl)-1H-pyrrolo[3,2-c]pyridine (280 mg, 1.04 mmol, 1.00 equiv), methanol (5 mL), Palladium on carbon (190 mg). The resulting solution was stirred for 2 h at 20 °C. The solids were filtered out. This resulted in 190 mg (76%) of the title compound as a brown solid.

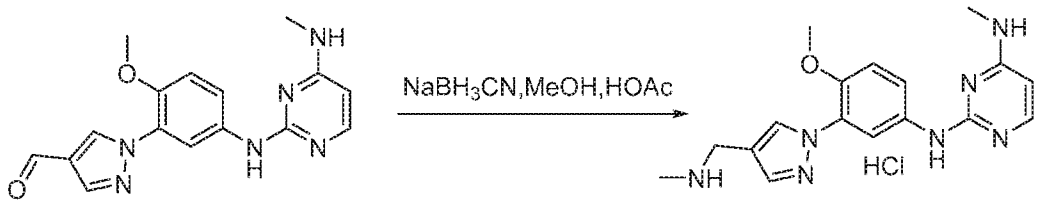
[0607] Analytical Data: LC-MS: (ES, *m/z*): RT = 0.702 min, LCMS15: m/z = 240 [M+1]. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.82 (d, *J* = 1.1 Hz, 1H), 7.74 (t, *J* = 1.0 Hz, 1H), 7.41 (d, *J* = 3.2 Hz, 1H), 7.32 (s, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 6.67 (s, 1H), 3.75 (s, 3H).

[0608] **Step 3:** Synthesis of N2-(4-methoxy-3-(1H-pyrrolo[3,2-c]pyridin-6-yl)phenyl)-N4-methylpyrimidine-2,4-diamine:

[0609] Into a 50-mL round-bottom flask, was placed 4-methoxy-3-[1H-pyrrolo[3,2-c]pyridin-6-yl]aniline (180 mg, 0.75 mmol, 1.00 equiv), 2-chloro-N-methylpyrimidin-4-amine (107 mg, 0.75 mmol, 0.99 equiv), trifluoroacetic acid (171.7 mg, 1.52 mmol, 2.02 equiv), IPA (5 mL). The resulting solution was stirred for 2 h at 80 °C in an oil bath. The crude product was purified by Prep-HPLC with the following conditions :Column: X Select C18, 19*250 mm, 5 um; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 25% B to 64% B in 15min. This resulted in 67.8 mg (20%) of the title compound as the trifluoroacetic acid salt as a white solid.

Example 27: Synthesis of Compound 181:

[0610] **Synthesis of N2-(4-methoxy-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)-N4-methylpyrimidine-2,4-diamine:**

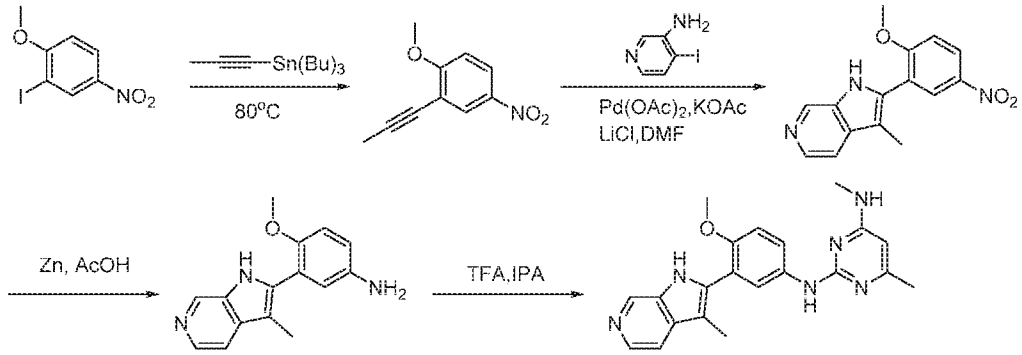


[0611] **Step 1:** Synthesis of N2-(4-methoxy-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)-N4-methylpyrimidine-2,4-diamine:

[0612] Into a 25-mL round-bottom flask, was placed 1-(2-methoxy-5-[[4-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazole-4-carbaldehyde (80 mg, 0.25 mmol, 1.00 equiv), methanol (2 mL), methanamine (34 mg, 1.09 mmol, 2.00 equiv) and stirred for 15min. Then $NaBH_3CN$ (93 mg, 1.48 mmol, 6.00 equiv), acetic acid (0.002 mL). The resulting solution was stirred for 2 h at 25 °C. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XSelect CSH Prep C18 OBD Column, 5um,19*150mm; mobile phase, CH_3CN: Water (0.05% HCl) = 1/9; Detector, UV 254/220nm. This resulted in 36.6 mg (37%) of the title compound as the hydrochloride salt as a white solid.

Example 28: Synthesis of Compound 200:

[0613] **Synthesis of N2-(4-methoxy-3-(3-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**



[0614] **Step 1:** Synthesis of 1-methoxy-4-nitro-2-(prop-1-yn-1-yl)benzene:

[0615] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-iodo-1-methoxy-4-nitrobenzene (2.8 g, 10.03 mmol, 1.00 equiv), tributyl(prop-1-yn-1-yl)stannane (5 g, 15.19 mmol, 1.51 equiv), $Pd(PPh_3)_2Cl_2$ (200 mg, 0.28 mmol, 0.03 equiv), dioxane (30 mL). The resulting solution was stirred overnight at 80 °C. The solids were filtered out. The resulting solution was extracted with of ethyl acetate and the organic layers combined. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (5%). This resulted in 1.06 g (55%) of the title compound.

[0616] **Step 2:** Synthesis of 2-(2-methoxy-5-nitrophenyl)-3-methyl-1H-pyrrolo[2,3-c]pyridine:

[0617] Into a 20-mL vial purged and maintained with an inert atmosphere of nitrogen, was placed 1-methoxy-4-nitro-2-(prop-1-yn-1-yl)benzene (500 mg, 2.62 mmol, 1.00 equiv), 4-iodopyridin-3-amine (1.1 g, 5.00 mmol, 1.91 equiv), $Pd(OAc)_2$ (110 mg, 0.49 mmol, 0.19 equiv), KOAc (750 mg, 7.64 mmol, 2.92 equiv), LiCl (0.11 g), N,N-dimethylformamide (10 mL). The resulting solution was stirred overnight at 100 °C. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, mobile phase, Detector, Xbridge C18 OBD 19*150mm. This resulted in 167 mg (23%) of the title compound.

[0618] **Step 3:** Synthesis of 4-methoxy-3-(3-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)aniline:

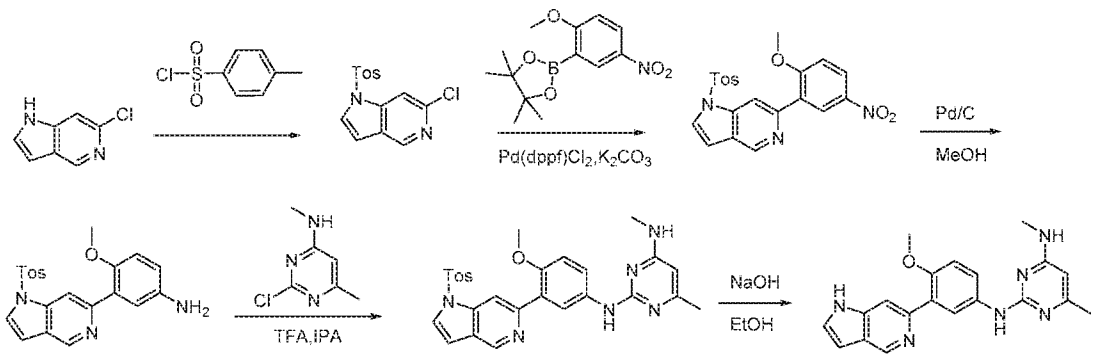
[0619] Into a 20-mL vial, was placed 2-(2-methoxy-5-nitrophenyl)-3-methyl-1H-pyrrolo[2,3-c]pyridine (150 mg, 0.53 mmol, 1.00 equiv), Zn (300 mg), AcOH (8 mL). The resulting solution was stirred for 2 h at 25 °C. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 115 mg (86%) of the title compound as a yellow solid.

[0620] **Step 4:** Synthesis of N2-(4-methoxy-3-(3-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0621] Into a 20-mL vial purged and maintained with an inert atmosphere of nitrogen, was placed 4-methoxy-3-[3-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl]aniline (100 mg, 0.39 mmol, 1.00 equiv), 2-chloro-N,6-dimethylpyrimidin-4-amine (50 g, 317.26 mmol, 803.61 equiv), trifluoroacetic acid (150 g, 1.33 mol, 3361.19 equiv), IPA (8 mL). The resulting solution was stirred for 1 h at 80 °C. The resulting mixture was concentrated under vacuum. This resulted in 22 mg (11%) of the title compound as the trifluoroacetyl fluoride salt.

Example 29: Synthesis of Compound 206:

[0622] **Synthesis of N2-(4-methoxy-3-(1H-pyrrolo[3,2-c]pyridin-6-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**



[0623] Step 1: Synthesis of 6-chloro-1-tosyl-1H-pyrrolo[3,2-c]pyridine:

[0624] Into a 50-mL round-bottom flask, was placed 6-chloro-1H-pyrrolo[3,2-c]pyridine (500 mg, 3.28 mmol, 1.00 equiv), tetrahydrofuran (20 mL), sodium hydride (473 mg, 19.71 mmol, 6.00 equiv), 4-methylbenzene-1-sulfonyl chloride (937 mg, 4.91 mmol, 1.50 equiv). The resulting solution was stirred for 4 h at 80 °C. The resulting solution was extracted with 200 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. This resulted in 900 mg (crude) of the title compound that was used without further purification.

[0625] Step 2: Synthesis of 6-(2-methoxy-5-nitrophenyl)-1-tosyl-1H-pyrrolo[3,2-c]pyridine:

[0626] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 6-chloro-1-[(4-methylbenzene)sulfonyl]-1H-pyrrolo[3,2-c]pyridine (500 mg, 1.63 mmol, 1.00 equiv), 2-(2-methoxy-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1094.1 mg, 3.92 mmol, 2.40 equiv), $Pd(dppf)Cl_2$ (676.5 mg, 0.92 mmol, 3.00 equiv), potassium carbonate (133.3 mg, 0.96 mmol, 0.10 equiv), water(20 mL), dioxane (2 mL). The resulting solution was stirred for 3 h at 80 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (2:3). This resulted in 600 mg (crude) of the title compound.

[0627] Step 3: Synthesis of 4-methoxy-3-(1-tosyl-1H-pyrrolo[3,2-c]pyridin-6-yl)aniline:

[0628] Into a 50-mL vial, was placed 6-(2-methoxy-5-nitrophenyl)-1-[(4-methylbenzene)sulfonyl]-1H-pyrrolo[3,2-c]pyridine (400 mg, 0.94 mmol, 1.00 equiv), Palladium carbon (200 mg), methanol (20 mL), hydrogen. The resulting solution was stirred for 2 h at room temperature. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 250 mg (crude) of the title compound.

[0629] Step 4: Synthesis of N2-(4-methoxy-3-(1-tosyl-1H-pyrrolo[3,2-c]pyridin-6-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

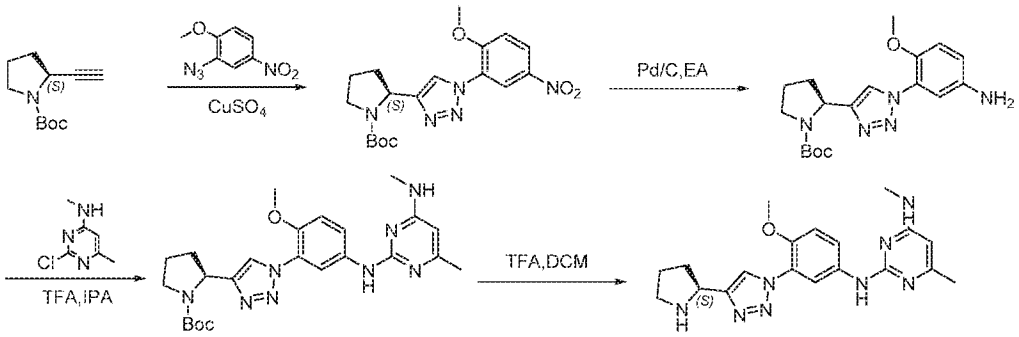
[0630] Into a 50-mL round-bottom flask, was placed 4-methoxy-3-[1-[(4-methylbenzene)sulfonyl]-1H-pyrrolo[3,2-c]pyridin-6-yl]aniline (200 mg, 0.51 mmol, 1.00 equiv), 2-chloro-N,6-dimethylpyrimidin-4-amine (80 mg, 0.51 mmol, 1.00 equiv), trifluoroacetic acid (147 mg, 1.30 mmol, 2.00 equiv), IPA (10 mL). The resulting solution was stirred for 5 h at 80 °C. The resulting mixture was concentrated under vacuum. This resulted in 250 mg (96%) of the title compound.

[0631] Step 5: Synthesis of N2-(4-methoxy-3-(1H-pyrrolo[3,2-c]pyridin-6-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0632] Into a 50-mL round-bottom flask, was placed 2-N-(4-methoxy-3-[1-[(4-methylbenzene)sulfonyl]-1H-pyrrolo[3,2-c]pyridin-6-yl]phenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (200 mg, 0.39 mmol, 1.00 equiv), sodium hydroxide (156 mg, 3.90 mmol, 10.00 equiv), ethanol (20 mL). The resulting solution was stirred for 3 h at 80 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XBridge Shield RP18 OBD Column, 30*150mm,5um; mobile phase, Water(10 mmol/L NH_4HCO_3) and ACN (30.0% ACN up to 43.0% in 7 min); Detector, UV 254220nm. This resulted in 24 mg (17%) of the title compound as a white solid.

Example 30: Synthesis of Compound 212:

[0633] **Synthesis of (S)-N2-(4-methoxy-3-(4-(pyrrolidin-2-yl)-1H-1,2,3-triazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**



[0634] Step 1: Synthesis of tert-butyl (S)-2-(1-(2-methoxy-5-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazol-4-yl)pyrrolidine-1-carboxylate:

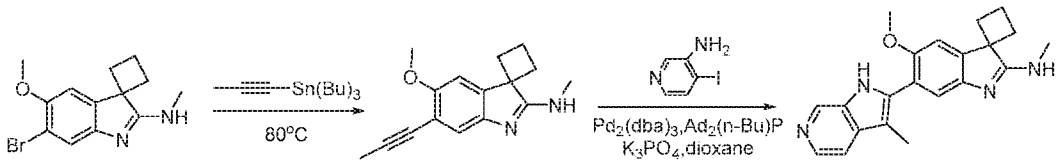
[0635] Into a 20-mL vial, was placed tert-butyl (S)-2-(1-(5-amino-2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)pyrrolidine-1-carboxylate (prepared as for compound 137 starting with tert-butyl (S)-2-ethynylpyrrolidine-1-carboxylate, 1 g, 2.78 mmol, 1.00 equiv), 2-chloro-N,6-dimethylpyrimidin-4-amine (525 mg, 3.33 mmol, 1.20 equiv), trifluoroacetic acid (958 mg, 8.47 mmol, 3.05 equiv), IPA (9 mL). The resulting solution was stirred for 1 h at 80 °C. The solids were collected by filtration. This resulted in 800 mg (60%) of title compound.

[0636] Step 2: Synthesis of (S)-N2-(4-methoxy-3-(4-(pyrrolidin-2-yl)-1H-1,2,3-triazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0637] Into a 20-mL vial, was placed tert-butyl (2S)-2-[1-(2-methoxy-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-1,2,3-triazol-4-yl]pyrrolidine-1-carboxylate (200 mg, 0.42 mmol, 1.00 equiv), trifluoroacetic acid (3 mL), dichloromethane (3 mL). The resulting solution was stirred for 1 h at 25 °C. The resulting mixture was concentrated under vacuum. This resulted in 57.8 mg (37%) of the title compound.

Synthesis of Compound 238

[0638] **Synthesis of 5'-methoxy-N-methyl-6'-(3-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)spiro[cyclobutane-1,3'-indol]-2'-amine:**



[0639] Step 1: Synthesis of 5'-methoxy-N-methyl-6'-(prop-1-yn-1-yl)spiro[cyclobutane-1,3'-indol]-2'-amine:

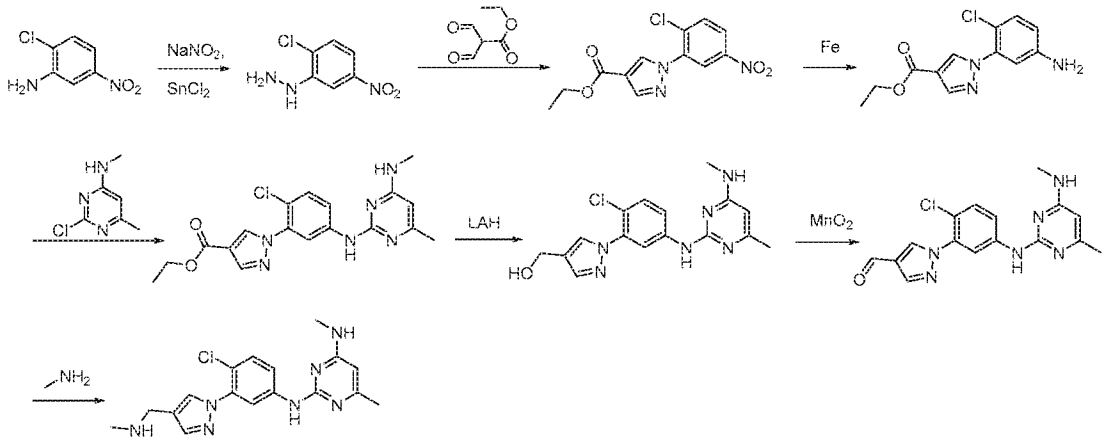
[0640] Into a 20-mL vial purged and maintained with an inert atmosphere of nitrogen, was placed 6-romo-5-ethoxy-N-methylspiro[cyclobutane-1,3-ndole]-2-amine (300 mg, 1.02 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (142 mg, 0.20 mmol, 0.20 equiv), dioxane (8 mL), tributyl(prop-1-yn-1-yl)stannane (500 mg, 1.52 mmol, 1.49 equiv). The resulting solution was stirred overnight at 80 °C. The resulting solution was extracted with of ethyl acetate and the organic layers combined. The residue was applied onto a silica gel column with ethyl acetate/hexane (30%). This resulted in 193 mg (75%) of the title compound.

[0641] Step 2: Synthesis of 5'-methoxy-N-methyl-6'-(3-methyl-1H-pyrrolo[2,3-c]pyridin-2-yl)spiro[cyclobutane-1,3'-indol]-2'-amine:

[0642] Into a 20-mL vial purged and maintained with an inert atmosphere of nitrogen, was placed 5-ethoxy-N-methyl-6-prop-1-yn-1-yl)spiro[cyclobutane-1,3-ndole]-2-mine (50 mg, 0.20 mmol, 1.00 equiv), $Pd_2(dba)_3$ (40 mg, 0.04 mmol, 0.22 equiv), $Ad_2(n\text{-}Bu)P$ (38 mg), K_3PO_4 (80 mg, 0.38 mmol, 1.92 equiv), dioxane (5 mL), 4-iodopyridin-3-amine (90 mg, 0.41 mmol, 2.08 equiv). The resulting solution was stirred overnight at 120 °C. The resulting solution was extracted with of ethyl acetate and the organic layers combined. This resulted in 29.7 mg (33%) of the title compound as the trifluoroacetic acid salt as a yellow solid.

Synthesis of Compound 262:

[0643] **Synthesis of N2-(4-chloro-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**



[0644] Step 1: 1. Synthesis of (2-chloro-5-nitrophenyl)hydrazine:

[0645] Into a 250-mL round-bottom flask, was placed 2-chloro-5-nitroaniline (3 g, 17.38 mmol, 1.00 equiv), hydrogen chloride (60 mL), $NaNO_2$ (1.5 g, 21.74 mmol, 1.25 equiv), $SnCl_2$ (10 g, 52.74 mmol, 3.03 equiv). The resulting solution was stirred for 1.5 h at 0 °C in an ice/salt bath. The solids were collected by filtration. This resulted in 8 g (crude) of the title compound as a yellow solid.

[0646] Step 2: Synthesis of ethyl 1-(2-chloro-5-nitrophenyl)-1H-pyrazole-4-carboxylate:

[0647] Into a 100-mL round-bottom flask, was placed (2-chloro-5-nitrophenyl)hydrazine (1 g, 5.33 mmol, 1.00 equiv), ethanol (40 mL), methyl 2-formyl-3-oxopropanoate (760 mg, 5.34 mmol, 1.00 equiv). The final reaction mixture was irradiated with microwave radiation for 2 h at 80 °C. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 600 mg (crude) of the title compound that was used without further purification.

[0648] Analytical Data: 1H NMR (300 MHz, Methanol-d4) δ 8.69 (d, J = 0.6 Hz, 1H), 8.52 (d, J = 2.6 Hz, 1H), 8.39 (q, J = 2.7 Hz, 1H), 8.20 (d, J = 0.6 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H).

[0649] Step 3: Synthesis of ethyl 1-(5-amino-2-chlorophenyl)-1H-pyrazole-4-carboxylate:

[0650] Into a 100-mL round-bottom flask, was placed ethyl 1-(2-chloro-5-nitrophenyl)-1H-pyrazole-4-carboxylate (900 mg, 3.04 mmol, 1.00 equiv), Fe (900 mg, 5.00 equiv), NH_4Cl (900 mg, 15.13 mmol, 5.00 equiv), ethanol/H2O (15 mL). The resulting solution was stirred for 2 h at 80 °C in an oil bath. The solids were filtered out. The residue was applied onto a silica gel column with H_2O (0.05%NH_4HCO_3):ACN (1:1). This resulted in 600 mg (67%) of the title compound.

[0651] Step 4: Synthesis of ethyl 1-(2-chloro-5-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)-1H-pyrazole-4-carboxylate:

[0652] Into a 100-mL round-bottom flask, was placed ethyl 1-(5-amino-2-chlorophenyl)-1H-pyrazole-4-carboxylate (532 mg, 2.00 mmol, 1.00 equiv), trifluoroacetic acid (458 mg, 4.05 mmol, 2.00 equiv), IPA (15 mL), 2-chloro-N,6-dimethylpyrimidin-4-amine (316 mg, 2.01 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at 60 °C in an oil bath. The solids were collected by filtration. The resulting mixture was concentrated under vacuum. This resulted in 500 mg (61%) of the title compound as a light yellow

[0653] Step 5: Synthesis of (1-(2-chloro-5-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)-1H-pyrazol-4-yl)methanol:

[0654] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed ethyl 1-(2-chloro-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazole-4-carboxylate (500 mg, 1.29 mmol, 1.00 equiv), LAH (450 mg, 11.86 mmol, 9.00 equiv), tetrahydrofuran (30 mL). The resulting solution was stirred for 2 h at 25 °C. The reaction was then quenched by the addition of. The resulting solution was extracted with 2x30 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. This resulted in 300 mg (61%) of the title compound.

[0655] Step 6: Synthesis of 1-(2-chloro-5-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)-1H-pyrazole-4-carbaldehyde:

[0656] Into a 50-mL round-bottom flask, was placed [1-(2-chloro-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazol-4-yl]methanol (500 mg, 1.45 mmol, 1.00 equiv), MnO_2 (500 mg, 5.75 mmol, 3.97 equiv), dichloromethane (10 mL). The resulting solution was stirred for 14 h at 40 °C in an oil bath. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 300 mg (54%) of the title compound.

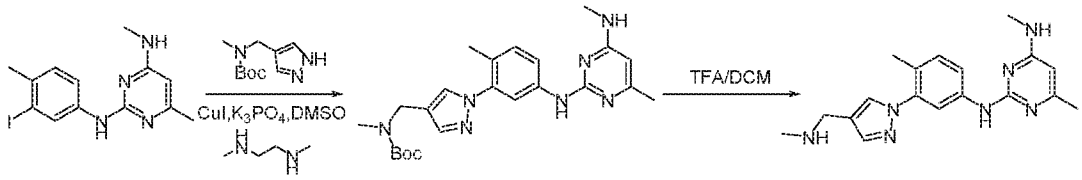
[0657] Step 7: Synthesis of N2-(4-chloro-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0658] Into a 50-mL round-bottom flask, was placed 1-(2-chloro-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazole-4-carbaldehyde (300 mg, 0.88 mmol, 1.00 equiv), $NaBH_3CN$ (150 mg, 2.59 mmol, 3.00 equiv), methanol (10 mL), AcOH (0.01 mL), methanamine (300 mg, 4.46 mmol, 5.00 equiv). The resulting solution was stirred for 12 h at 25 °C. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column,

XSelect CSH Prep C18 OBD Column,, 5um,19*150mm; mobile phase, Water(0.05%TFA) and ACN (5.0% ACN up to 15.0% in 12 min); Detector, UV 254220nm. This resulted in 88.8 mg (22%) of the title compound as the trifluoroacetic acid salt as a white solid.

Synthesis of Compound 286:

[0659] **Synthesis of N4,6-dimethyl-N2-(4-methyl-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)pyrimidine-2,4-diamine:**



[0660] Step 1: Synthesis of tert-butyl methyl((1-(2-methyl-5-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)-1H-pyrazol-4-yl)methyl)carbamate:

[0661] Into a 20-mL sealed tube, was placed 2-N-(3-iodo-4-methylphenyl)-4-N,6-dimethylpyrimidine-2,4-diamine (100 mg, 0.28 mmol, 1.00 equiv), tert-butyl N-methyl-N-(1H-pyrrol-3-ylmethyl)carbamate (62 mg, 0.29 mmol, 1.04 equiv), CuI (11 mg, 0.06 mmol, 0.20 equiv), K_3PO_4 (178 mg, 0.84 mmol, 2.97 equiv), methyl[2-(methylamino)ethyl]amine (10 mg, 0.11 mmol, 0.40 equiv), DMSO (8 mL). The resulting solution was stirred overnight at 120 °C. The resulting solution was diluted with of H_2O. The resulting solution was extracted with of ethyl acetate and the organic layers combined. The resulting mixture was washed with H_2O. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 100 mg (81%) of the title compound.

[0662] Analytical Data: LC-MS: (ES, m/z): RT=0.815 min, m/z =438 [M+1].

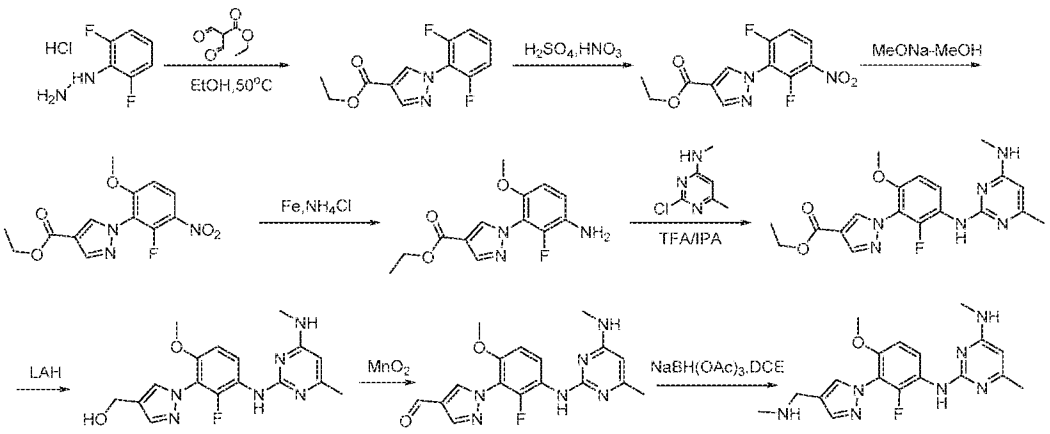
[0663] Step 2: Synthesis of N4,6-dimethyl-N2-(4-methyl-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)pyrimidine-2,4-diamine:

[0664] Into a 25-mL round-bottom flask, was placed tert-butyl N-methyl-N-[[1-(2-methyl-5-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrrol-3-yl]methyl]carbamate (100 mg, 0.23 mmol, 1.00 equiv), trifluoroacetic acid (1 mL), dichloromethane (5 mL). The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XSelect CSH Prep C18 OBD Column,,

5um,19*150mm; mobile phase, Water(0.05%TFA) and ACN (5.0% ACN up to 23.0% in 12 min); Detector, UV 254/220nm. This resulted in 41.7 mg (40%) of the title compound as the trifluoroacetic acid salt as light yellow oil.

Synthesis of Compound 317:

[0665] **Synthesis of N2-(2-fluoro-4-methoxy-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:**



[0666] Step 1: Synthesis of ethyl 1-(2,6-difluorophenyl)-1H-pyrazole-4-carboxylate:

[0667] Into a 100-mL round-bottom flask, was placed (2,6-difluorophenyl)hydrazine (1 g, 6.94 mmol, 1.00 equiv), ethanol (12 mL), ethyl 2-formyl-3-oxopropanoate (1.2 g, 8.33 mmol, 1.20 equiv). The resulting solution was stirred for 2h at 50 °C in an oil bath. The solvent was removed under vacuum. The residue was applied onto a silica gel column with PE/EA = 50/1. The collected fractions were combined and concentrated under vacuum. This resulted in 1.18 g (67%) of the title compound.

[0668] Analytical Data: LC-MS: (ES, m/z): RT = 1.269 min; LCMS53: m/z = 253 [M+1]+

[0669] Step 2: Synthesis of ethyl 1-(2,6-difluoro-3-nitrophenyl)-1H-pyrazole-4-carboxylate:

[0670] Into a 50-mL 3-necked round-bottom flask, was placed ethyl 1-(2,6-difluorophenyl)-1H-pyrazole-4-carboxylate (1.1 g, 4.36 mmol, 1.00 equiv), H2SO4 (5 mL), HNO_3 (2 mL) was added dropwise at 0 °C with a water/ice bath. The resulting solution was stirred for 4 h at 25 °C. The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers combined. Dried over anhydrous Na_2SO_4 , concentrated under vacuum. The residue was applied onto a silica gel column with PE/EA = 3/1. The collected fractions were combined and concentrated under vacuum. This resulted in 1 g (77%) of the title compound.

[0671] Analytical Data: LC-MS: (ES, m/z): RT = 1.264 min; LCMS15: m/z = 298[M+1]+

[0672] Step 3: Synthesis of ethyl 1-(2-fluoro-6-methoxy-3-nitrophenyl)-1H-pyrazole-4-carboxylate:

[0673] Into a 100-mL round-bottom flask, was placed ethyl 1-(2,6-difluoro-3-nitrophenyl)-1H-pyrazole-4-carboxylate (1 g, 3.36 mmol, 1.00 equiv), methanol (20 mL), sodium methoxide in methanol solution (m/z = 35%, 0.5 ml, 1.0 equiv) was added dropwise at 0 °C,. The resulting solution was stirred for 2 h at 0oC. Then the resulting mixture was quenched by NH_4Cl (aq) 10ml, extracted by EA 20 ml*3, dried over anhydrous Na_2SO_4, concentrated under vacuum. The residue was applied onto a silica gel column with PE/EA = 10/1. The collected fractions were combined and concentrated under vacuum. This resulted in 500 mg (48%) of the title compound as yellow oil.

[0674] Step 4: Synthesis of ethyl 1-(3-amino-2-fluoro-6-methoxyphenyl)-1H-pyrazole-4-carboxylate:

[0675] Into a 50-mL round-bottom flask, was placed ethyl 1-(2-fluoro-6-methoxy-3-nitrophenyl)-1H-pyrazole-4-carboxylate (500 mg, 1.62 mmol, 1.00 equiv), ethanol (10 mL), water (3 mL), Fe (453 mg, 8.08 mmol, 5 equiv), NH_4Cl (857 mg, 16.02 mmol, 9.91 equiv). The resulting solution was stirred for 2 h at 80 oC in an oil bath. The solids were filtered out. The resulting solvent was concentrated under vacuum. The resulting was extracted with 3x20 mL of ethyl acetate and the organic layers combined, dried over anhydrous Na_2SO_4, concentrated under vacuum. This resulted in 400 mg (89%) of the title compound.

[0676] Step 5: Synthesis of ethyl 1-(2-fluoro-6-methoxy-3-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)-1H-pyrazole-4-carboxylate:

[0677] Into a 50-mL round-bottom flask, was placed ethyl 1-(3-amino-2-fluoro-6-methoxyphenyl)-1H-pyrazole-4-carboxylate (400 mg, 1.43 mmol, 1.00 equiv), 2-chloro-N,6-dimethylpyrimidin-4-amine (270 mg, 1.71 mmol, 1.20 equiv), IPA (20 mL), trifluoroacetic acid (3 mL). The resulting solution was stirred for 3 h at 80 °C in an oil bath. The resulting mixture was allowed to cooled to r.t. Then filtered, the solid was collected. This resulted in 500 mg (87%) of the title compound.

[0678] Step 6: Synthesis of (1-(2-fluoro-6-methoxy-3-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)-1H-pyrazol-4-yl)methanol:

[0679] Into a 50-mL round-bottom flask, was placed ethyl 1-(2-fluoro-6-methoxy-3-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazole-4-carboxylate (400 mg, 1.00 mmol, 1.00 equiv), tetrahydrofuran (10 mL), LAH (114 mg, 3.00 mmol, 3.01 equiv) was added batch-

wise. The resulting solution was stirred for 1 h at 25 °C. The reaction was then quenched by the addition of 114 mg water. Then 114 mg NaOH (aq, m/z = 15%) and 342 mg water, 20 ml EA was added. Stirred at r.t. for 30 min. The solids were filtered out, the resulting solution was dried over anhydrous Na2SO4, concentrated under vacuum. This resulted in 300 mg (84%) of the title compound.

[0680] Step 7: Synthesis of 1-(2-fluoro-6-methoxy-3-((4-methyl-6-(methylamino)pyrimidin-2-yl)amino)phenyl)-1H-pyrazole-4-carbaldehyde:

[0681] Into a 50-mL round-bottom flask, was placed [1-(2-fluoro-6-methoxy-3-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazol-4-yl]methanol (300 mg, 0.84 mmol, 1.00 equiv), chloroform (15 mL), MnO_2 (730 mg, 8.40 mmol, 10.03 equiv). The resulting solution was stirred for 8 h at 70 °C in an oil bath. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 200 mg (67%) of the title compound.

[0682] Step 8: Synthesis of N2-(2-fluoro-4-methoxy-3-(4-((methylamino)methyl)-1H-pyrazol-1-yl)phenyl)-N4,6-dimethylpyrimidine-2,4-diamine:

[0683] Into a 50-mL round-bottom flask, was placed 1-(2-fluoro-6-methoxy-3-[[4-methyl-6-(methylamino)pyrimidin-2-yl]amino]phenyl)-1H-pyrazole-4-carbaldehyde (100 mg, 0.28 mmol, 1.00 equiv), DCE (10 mL), methanamine (200 mg, 6.44 mmol, 22.95 equiv), STAB (180 mg, 0.85 mmol, 3.03 equiv). The resulting solution was stirred for 2 h at 25 °C. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#SHIMADZU (HPLC-01)): Column, XBridge Prep C18 OBD Column, 19*150mm 5um; mobile phase, Water(0.05%TFA) and ACN (5.0% ACN up to 23.0% in 10 min); Detector, UV 220/254nm. This resulted in 66.5 mg (49%) of the title compound.

[0684] Other compounds were synthesized in the similar manner and the characterization data are listed in Table 2 below.

Table 2

Cpd #	Data
1	LC-MS: (ES, *m/z*): RT = 0.958 min, LCMS 33: *m/z* = 366 [M+1]. ^{1}H-NMR: (400 MHz, Methanol-d_4) δ 8.18 (s, 1H), 7.87 (s, 1H), 7.54 – 7.51 (m, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 5.82 (s, 1H), 4.02 (s, 2H), 3.86 (s, 3H), 3.24 (t, *J* = 6.0 Hz, 2H), 2.94 – 2.83 (m, 5H), 2.19 (s, 3H).

2	LC-MS: (ES, *m/z*): RT = 1.504min, LCMS 33: *m/z* =380 [M+1]. ^{1}H NMR: (400 MHz, Methanol-*d*$_4$) δ 8.22 – 8.10 (m, 2H), 7.59 – 7.50 (m, 1H), 7.28 (d, *J* = 9.1 Hz, 1H), 6.02 (d, *J* = 1.2 Hz, 1H), 4.47 (s, 2H), 3.95 (s, 3H), 3.88 – 3.52 (m, 2H), 3.20 – 3.16(m, 2H), 3.10 (s, 3H), 3.03 (s, 3H), 2.32 (d, *J* = 2.4 Hz, 3H).
3	LC-MS: (ES, *m/z*): RT = 1.022 min, LCMS 33: *m/z* = 380.2 [M+1]. ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ 8.15 (d, J = 3.9 Hz, 2H), 7.53 (d, *J* = 2.7 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 1H), 6.02 (d, *J* = 0.8 Hz, 1H), 4.62 (s, 2H), 3.95 (s, 3H), 3.82 (s, 1H), 3.77 (s, 1H), 3.17 – 2.94 (m, 8H), 2.32 (d, *J* = 0.9 Hz, 3H).
4	LC-MS: (ES, *m/z*): RT=1.06min, LCMS28, m/z=394.2 [M+1]. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.26 (d, *J* = 2.5 Hz, 1H), 8.12 (d, *J* = 2.7 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 5.99 (d, *J* = 1.1 Hz, 1H), 4.48 (s, 2H), 3.93 (d, *J* = 5.7 Hz, 3H), 3.65 (s, 2H), 3.30 (d, *J* = 7.4 Hz, 2H), 3.02 (s, 3H), 2.34 – 2.29 (m, 3H), 2.21 – 2.11 (m, 2H), 2.10 – 1.99 (m, 2H).
5	LC-MS: (ES, *m/z*): RT =1.020 min, LCMS28, m/z =394.2 [M+1] ^{1}H NMR (400 MHz, Methanol-d4) δ 8.47 (s, 1H), 8.20 (d, *J* = 2.7 Hz, 1H), 7.87 (s, 1H), 7.61 – 7.51 (m, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 6.02 (d, *J* = 1.2 Hz, 1H), 4.41 (s, 2H), 3.97 (s, 3H), 3.64 – 3.56 (m, 2H), 3.30 – 3.18 (m, 2H), 3.02 (s, 3H), 2.33 (d, *J* = 1.0 Hz, 3H), 2.20 (d, *J* = 7.9 Hz,2H), 2.12 – 2.01 (m, 2H).
6	LC-MS: (ES, *m/z*): RT = 0.963 min, LCMS27: *m/z* = 380.1 [M+1]. ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ 8.08 (d, *J* = 2.8 Hz, 1H), 7.54 (s, 2H), 6.98 (d, *J* = 8.9 Hz, 1H), 5.79 (d, *J* = 0.8 Hz, 1H), 4.12 (t, *J* = 5.7 Hz, 2H), 3.92 (s, 3H), 3.71 (s, 2H), 2.99 – 2.93 (m, 2H), 2.91 (d, *J* = 8.0 Hz, 3H), 2.54 (s, 3H), 2.18 (s, 3H).
7	LC-MS: (ES, *m/z*): RT = 0.901 min, LCMS15: *m/z* = 366.2 [M+1]. ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ 8.06 (d, *J* = 2.8 Hz, 1H), 7.56 – 7.53 (m, 2H), 6.98 (d, *J* = 8.9 Hz, 1H), 5.79 (d, *J* = 0.8 Hz, 1H), 4.07 – 4.03 (m, 4H), 3.91 (s, 3H), 3.28 – 3.18 (m, 2H), 2.89 (s, 3H), 2.18 (s, 3H).
8	LC-MS: (ES, *m/z*): RT = 2.985 min, LCMS 07: *m/z* = 367 [M+1]. ^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 8.23 (d, *J* = 2.7 Hz, 1H), 7.64 (d, *J* = 9.0, 2.8 Hz, 1H), 7.27 – 7.19 (m, 1H), 6.06 (d, *J* = 1.3 Hz, 1H), 4.74 (s, 2H), 4.63 (t, *J* = 5.7 Hz, 2H), 3.94 (d, *J* = 5.6 Hz, 5H), 2.99 (d, *J* = 3.1 Hz, 3H), 2.42 (s, 3H), 2.32 (s, 3H).
9	LC-MS: (ES, *m/z*): RT=1.696 min, LCMS 07, *m/z*=381 [M+1]. ^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 8.30 (d, *J* = 2.8 Hz, 1H), 7.61 (d, *J* = 9.0, 2.7 Hz, 1H), 7.21 (d, *J* = 9.1 Hz, 1H), 5.99 (d, *J* = 1.1 Hz, 1H), 4.64 – 4.52 (m, 4H), 3.93 (d, *J* = 7.8 Hz, 3H), 3.82 (d, *J* = 5.7 Hz, 2H), 3.11 (s, 3H), 3.02 (s, 3H), 2.31 (d, *J* = 0.9 Hz, 3H).
10	LC-MS: (ES, *m/z*): RT = 0.863 min, LCMS 07: *m/z* = 380 [M+1]. ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ 7.81 – 7.63 (m, 3H), 7.30 (d, *J* = 8.1 Hz, 1H), 6.01 (d, *J* = 1.2 Hz, 1H), 4.34 (s, 2H), 3.89 (s, 3H), 3.46 – 3.42 (m, 2H), 3.04 – 3.01 (m, 8H), 2.30 (s, 3H).
11	LC-MS: (ES, *m/z*): RT=1.039 min, LCMS 28, m/z=326 [M+1]. ^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 8.39 (d, *J* = 2.7 Hz, 1H), 7.75 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.31 (dd, *J* = 16.7, 9.0 Hz, 1H), 6.04 (d, *J* = 1.2 Hz, 1H), 4.06 (s, 3H), 3.01 (s, 3H), 2.61 (s, 3H), 2.33 (s, 3H).

12	LC-MS: (ES, *m/z*): RT = 1.175 min; LCMS53: m/z = 311 [M+1]. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.03 (s, 2H), 7.92 (s, 1H), 7.48 (d, *J* = 8.8Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 1H), 5.80 (s, 1H), 3.89 (s, 3H), 2.92 (s, 3H), 2.18 (s, 3H).
13	LC-MS: (ES, *m/z*): RT=1.531 min, LCMS28, *m/z*=352 [M+1]. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.10 (d, *J* = 2.8 Hz, 1H), 7.58 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 6.58 (s, 1H), 6.01 (s, 1H), 3.96 (s, 3H), 3.01 (s, 3H), 2.32 (s, 3H), 2.225 – 2.137 (m, 1H), 1.181 – 1.116 (m, 2H), 1.06 – 0.94 (m, 2H).
14	LC-MS: (ES, *m/z*): RT = 1.463 min, LCMS07: m/z = 351 [M+1]. ^{1}H NMR: (400 MHz, Methanol-d_4): δ 8.23 – 7.98 (m, 1H), 7.83 – 7.77(m, 1H), 7.53 (d, *J* = 8.9, 1H), 7.45 (d, *J* = 0.8 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 5.80 (d, *J* = 0.8 Hz, 1H), 3.84 (s, 3H), 2.88 (s, 3H), 2.17 (s, 3H), 1.83 – 1.77 (m, 1H), 1.09 – 0.71 (m, 2H), 0.70 – 0.39 (m, 2H).
15	LC-MS: (ES, *m/z*): RT = 1.30 min, LCMS 28: *m/z* = 311 [M+1]. ^{1}H NMR: (300 MHz, Methanol-d_4) δ 8.21 – 8.12 (m, 1H), 8.06 (d, *J* = 2.7 Hz, 1H), 7.78 – 7.67 (m, 1H), 7.50 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 1H), 6.57 – 6.47 (m, 1H), 6.28 – 5.98 (m, 1H), 3.95 (s, 3H), 3.00 (s, 3H), 2.44 – 2.28 (m, 3H).
19	LC-MS: (ES, *m/z*): RT = 1.407 min, LCMS28: *m/z* = 367.1 [M+1]. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.53 (d, *J* = 2.5 Hz, 1H), 8.34 (d, *J* = 2.6 Hz, 1H), 7.54 (s, 1H), 5.85 (d, *J* = 0.8 Hz, 1H), 3.94 (d, *J* = 2.1 Hz, 5H), 3.12 (t, *J* = 5.9 Hz, 2H), 2.87 (s, 3H), 2.67 (t, *J* = 5.9 Hz, 2H), 2.19 (s, 3H).
21	LC-MS: (ES, *m/z*): RT = 0.834 min, LCMS 07: *m/z* = 367 [M+1]. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.89 – 7.76 (m, 2H), 7.31 (d, *J* = 15.3, 9.0 Hz, 1H), 6.06 (d, *J* = 1.3 Hz, 1H), 4.77 (d, *J* = 2.0 Hz, 2H), 4.34 (t, *J* = 5.7 Hz, 2H), 3.96 (d, *J* = 2.8 Hz, 3H), 3.78 (d, *J* = 6.5, 4.9 Hz, 2H), 2.99 (d, *J* = 4.5 Hz, 3H), 2.43 (d, *J* = 0.9 Hz, 1H), 2.33 (d, *J* = 1.0 Hz, 3H).
22	LC-MS: (ES, *m/z*): RT = 0.992min LCMS 33: m/z =366 [M+1]. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.18 – 8.07 (m, 2H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 6.04 (d, *J* = 1.2 Hz, 1H), 4.44 (d, *J* = 6.9 Hz, 2H), 3.95 (s, 3H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.11 – 2.95 (m, 5H), 2.45 – 2.29 (m, 3H).
23	LC-MS: (ES, *m/z*): RT=0.963min，LCMS31，m/z=340.4 [M+1]. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.38 (d, *J* = 2.0 Hz, 1H), 8.16 (s, 1H), 7.81 (s, 1H), 7.55 (s, 1H), 7.29 (s, 1H), 6.02 (s, 1H), 4.16 (s, 2H), 3.96 (d, *J* = 1.6 Hz, 3H), 3.01 (d, *J* = 2.4 Hz, 3H), 2.32 (s, 3H).
24	LC-MS: (ES, *m/z*):RT = 1.357 min; LCMS07: *m/z* = 340 [M+1]. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 – 7.70 (m, 3H), 7.51 – 7.15 (m, 1H), 6.79 – 6.53(m, 1H), 6.21 (s, 1H), 4.10 (s, 2H), 3.89 (s, 3H), 2.86(s, 3H), 2.55 (s, 3H).
26	LC-MS: (ES, *m/z*): RT=2.978min, LCMS31, m/z=365.4[M+1]. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.70 – 7.58 (m, 2H), 7.45 (d, *J* = 5.0 Hz, 1H), 7.29 – 7.17 (m, 1H), 6.00 (d, *J* = 1.1 Hz, 1H), 3.85 (d, *J* = 5.1 Hz, 3H), 2.96 (d, *J* = 3.6 Hz, 3H), 2.64 – 2.57 (m, 2H), 2.51 – 2.44 (m, 2H), 2.31 (d, *J* = 1.0 Hz, 3H), 1.88 – 1.75 (m, 4H).
27	LC-MS: (ES, *m/z*): RT = 0.99min, LCMS28: m/z = 384.19 [M+1]. 1H NMR (400 MHz, Methanol-d_4) δ 8.18 (s, 1H), 8.12 (d, *J* = 2.7 Hz, 1H), 7.51 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 4.39 (s, 2H), 3.95 (s, 3H), 3.62 (t, *J* = 6.3 Hz, 2H), 3.18 – 3.02 (m, 5H), 2.36 (d, *J* = 2.9 Hz, 3H).

28	LC-MS: (ES, *m/z*): RT = 0.99min, LCMS15: m/z = 384.19 [M+1]. 1H NMR (400 MHz, Methanol-*d*4) δ 7.77 – 7.71 (m, 2H), 7.68 (s, 1H), 7.35-7.2 (m, 1H), 4.36 (s, 2H), 3.89 (s, 3H), 3.55 (t, *J* = 6.2 Hz, 2H), 3.05 (s, 3H), 2.94 (t, *J* = 6.2 Hz, 2H), 2.37 (d, *J* = 2.9 Hz, 3H).
30	LC-MS: (ES, *m/z*): RT=0.929 min,LCMS28, *m/z*=380 [M+1]. ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.00 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.53 (d, *J* = 2.7 Hz, 1H), 7.27 (dd, *J* = 20.3, 9.1 Hz, 1H), 6.01 (d, *J* = 1.2 Hz, 1H), 4.90 – 4.73 (m, 2H), 4.35 – 4.23 (m, 1H), 4.20 – 4.05 (m, 1H), 3.89 (d, *J* = 5.1 Hz, 4H), 3.75 – 3.63 (m, 1H), 2.98 (d, *J* = 2.8 Hz, 3H), 2.35 – 2.27 (m, 6H).
31	LC-MS: (ES, *m/z*): RT=1.221 min, LCMS 07, *m/z*=381 [M+1]. ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.02 (d, *J* = 7.8 Hz, 1H), 7.93 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 0H), 7.42 (d, *J* = 8.3 Hz, 1H), 6.07 (s, 1H), 5.05 – 4.99 (m, 3H), 4.64 (d, *J* = 12.0 Hz, 2H), 4.01 (d, *J* = 8.4 Hz, 6H), 3.28 (d, *J* = 5.0 Hz, 4H), 3.00 (s, 3H), 2.35 (s, 3H).
32	LC-MS: (ES, *m/z*): RT = 1.81 min, LCMS 33: *m/z* = 366.2 [M+1]. ^{1}H NMR (300 MHz, Methanol-*d*4) δ 7.87 – 7.68 (m, 3H), 7.35 – 7.25 (m, 1H), 6.05 – 5.98 (m, 1H), 3.89 (s, 3H), 3.61 – 3.50 (m, 2H), 2.98 (s, 3H), 2.73 (t, *J* = 6.3 Hz, 2H), 2.32 (d, *J* = 1.2 Hz, 3H), 2.19 (d, *J* = 6.3 Hz, 2H).
33	LC-MS: (ES, *m/z*): RT=1.375min, LCMS15, m/z=360.2 [M+1]. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.38 (s, 1H), 11.16 (s, 1H), 10.22 (s, 1H), 8.92 (s, 1H), 7.63 – 7.52 (m, 2H), 7.43 – 7.29 (m, 2H), 7.25 – 7.07 (m, 2H), 7.04 – 6.95 (s, 1H), 6.20 (s, 1H), 6.01 (d, *J* = 1.2 Hz, 1H), 3.72 (s, 3H), 2.85 (d, *J* = 4.6 Hz, 3H), 2.25 (s, 3H).
35	LC-MS: (ES, *m/z*): RT=0.966min, LCMS15, m/z=362.2 [M+1]. ^{1}H NMR (400 MHz, Methanol-d4) δ 9.58 (s, 1H), 8.93 – 8.88 (m, 1H), 8.56 (s, 1H), 8.11 – 8.05 (m, 1H), 7.88 – 7.75 (m, 2H), 7.42 (d, *J* = 9.1 Hz, 1H), 6.06 – 6.00 (m, 1H), 3.89 (s, 3H), 3.00 (s, 3H), 2.33 (d, *J* = 0.9 Hz, 3H).
36	LC-MS: (ES, *m/z*): RT=1.045 min, LCMS28, m/z=362 [M+1]. ^{1}H NMR (300 MHz, Methanol-*d*4) δ 8.75 (d, *J* = 1.2 Hz, 1H), 8.38 (d, *J* = 0.8 Hz, 1H), 8.28 (d, *J* = 5.7 Hz, 1H), 8.16 (s, 1H), 7.87 (dd, *J* = 5.7, 1.3 Hz, 1H), 7.68 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.23 (d, *J* = 9.1 Hz, 1H), 5.80 (s, 1H), 3.80 (s, 3H), 2.82 (s, 3H), 2.16 (s, 3H).
37	LC-MS: (ES, *m/z*): RT=1.274min LCMS 15, *m/z* =361 [M+1]. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.85 (s, 1H), 7.67 (d, *J* = 2.7 Hz, 1H), 7.62 – 7.39 (m, 3H), 7.26 – 7.13 (m, 2H), 5.98 (d, *J* = 1.3 Hz, 1H), 3.82 (s, 3H), 2.94 (s, 3H), 2.30 (s, 3H).
38	LC-MS: (ES, m/z): RT = 1.077 min, LCMS 07: m/z = 363 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.37 – 9.16 (m, 1H), 8.97 – 8.77 (m, 1H), 8.46 (d, J = 4.9, 2.7 Hz, 1H), 8.35 – 8.21 (m, 1H), 7.72 – 7.49 (m, 1H), 7.33 – 7.21 (m, 1H), 6.07 – 5.91 (m, 1H), 3.97 (d, J = 12.7, 5.6, 2.5 Hz, 3H), 2.98 (d, J = 17.2, 8.0, 4.1 Hz, 3H), 2.35 – 2.24 (m, 3H).
39	LC-MS: (ES, m/z): RT=1.358 min,LCMS45, m/z=376 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.35 (s, 1H), 8.27 (s, 2H), 8.02 (dd, J = 9.0, 2.7 Hz, 1H), 7.70 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 6.25 – 5.94 (m, 1H), 3.87 (d, J = 2.1 Hz, 3H), 2.96 (s, 3H), 2.60 (s, 3H), 2.46 – 2.23 (m, 3H).
40	LC-MS: (ES, m/z): RT = 1.028 min, LCMS 28: m/z = 361 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.75 (s, 1H), 9.69 (s, 1H), 8.67 (d, J = 2.7 Hz, 1H), 8.41 – 8.21(m, 1H), 8.12 (d, J = 7.0 Hz, 1H), 7.72 (dd, J = 9.1, 2.7 Hz, 1H), 7.46 (d, J = 9.1 Hz, 1H), 5.97 - 6.31 (m, 1H), 4.07 (s, 3H), 3.09 (s, 3H), 2.35 (d, J = 1.0 Hz, 3H).
41	LC-MS: (ES, m/z): RT=1.041 min,LCMS28, m/z=362 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.18 (t, J = 1.1 Hz, 1H), 8.82 (d, J = 1.0 Hz, 1H), 8.55 (s, 1H), 8.09 (d, J = 6.1 Hz, 1H), 7.77 (dd, J = 6.1, 1.4 Hz, 1H), 7.66 (dd, J = 9.0, 2.7 Hz, 1H), 7.23 (d, J =

	9.1 Hz, 1H), 5.82 (d, J = 0.8 Hz, 1H), 3.91 (s, 3H), 2.91 (s, 3H), 2.18 (s, 3H).
42	LC-MS: (ES, m/z): RT = 0.847 min; LCMS48: m/z = 361 [M+1]. 1H NMR (400 MHz, DMSO-d6) δ 11.58 (s, 1H), 8.85 (s, 1H), 8.15 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.87 – 7.76 (m, 1H), 7.56 – 7.38 (m, 2H), 7.01 (d, J = 8.9 Hz, 1H), 6.88 (s, 1H), 6.55 – 6.41 (m, 1H), 5.74 (s, 1H), 3.75 (s, 3H), 2.81 (d, J = 4.5 Hz, 3H), 2.11 (s, 3H).
43	LC-MS: (ES, m/z): RT = 1.243 min; LCMS53: m/z = 367 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.14 (s, 1H), 7.82 (s, 1H), 7.52 – 7.50 (m, 1H), 7.13 (d, J = 9.0 Hz, 1H), 5.85 (d, J = 0.8 Hz, 1H), 4.76 (d, J = 1.0 Hz, 2H), 4.00 (t, J = 5.7 Hz, 2H), 3.86 (s, 3H), 2.95 – 2.92 (m, 3H), 2.88 – 2.80 (m, 2H), 2.20 (s, 3H).
45	LC-MS: (ES, m/z): RT = 0.911 min, LCMS15: m/z = 280 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.49 (s, 1H), 7.77 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.20 – 7.10 (m, 2H), 6.90-6.85 (m, 1H), 5.82 (d, J = 1.2 Hz, 1H), 4.05 (s, 3H), 3.87 (s, 3H), 2.91 (s, 3H), 2.20 (s, 3H), 2.04 (s, 3H).
47	LC-MS: (ES, m/z): RT = 0.997 min; LCMS53: m/z = 362 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.91 (d, J = 1.0 Hz, 1H), 8.70 (d, J = 2.8 Hz, 1H), 8.32 (d, J = 5.7 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 5.84 (d, J = 0.8 Hz, 1H), 4.09 (s, 3H), 2.94 (s, 3H), 2.21 (s, 3H).
48	LC-MS: (ES, m/z): RT=1.092 min; m/z = 361 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.85 – 8.71 (m, 1H), 8.18 – 8.09 (m, 1H), 7.78 – 7.42 (m, 3H), 6.91 (d, J = 6.5 Hz, 2H), 5.66 (s, 1H), 3.86 (d, J = 2.3 Hz, 3H), 2.85 – 2.69 (m, 3H), 2.12 – 1.97 (m, 3H).
50	LC-MS: (ES, m/z):RT = 0.652 min; LCMS45: m/z = 367 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.73 (d, J = 2.5 Hz, 1H), 8.39 – 8.27 (m, 2H), 6.02 (d, J = 1.1 Hz, 1H), 4.38 (d, J = 1.1 Hz, 2H), 4.08 (s, 3H), 3.61 (t, J = 6.4 Hz, 2H), 3.11 (t, J = 6.3 Hz, 2H), 3.03 (s, 3H), 2.32 (s, 3H).
54	LC-MS: (ES, m/z): RT =0.397 min, LCMS53: m/z = 382 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 7.87 – 7.63 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 6.01 (d, J = 1.2 Hz, 1H), 4.19 (d, J = 3.2 Hz, 2H), 3.87 (s, 3H), 3.83 – 3.42 (m, 2H), 3.11 (s, 5H), 2.98 (d, J = 2.7 Hz, 3H), 2.44 – 2.29 (m, 3H).
56	LC-MS: (ES, *m/z*): RT = 0.966min; LCMS 33: m/z =366 [M+1]. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.48 (s, 1H), 8.24 (d, *J* = 2.7 Hz, 1H), 7.52 (d, *J* = 2.7 Hz, 1H), 7.31 (d, *J* = 9.0 Hz, 1H), 6.05 (d, *J* = 0.9 Hz, 1H), 3.98 (s, 3H), 3.63 – 3.53 (m, 2H), 3.10 (s, 3H), 3.00 – 2.85 (m, 2H), 2.42 (s, 3H), 2.30 – 2.24 (m, 2H).
57	LC-MS: (ES, m/z): RT = 0.935 min, LCMS53: m/z = 381.3 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.67 (s, 1H), 8.35 (d, J = 2.6 Hz, 1H), 8.08 (s, 1H), 5.85 (d, J = 0.8 Hz, 1H), 4.02 (s, 3H), 3.74 (s, 2H), 3.06 – 2.88 (m, 7H), 2.61 (s, 3H), 2.20 (s, 3H).
60	LC-MS: (ES, m/z): RT =1.116 min, LCMS 28: m/z = 364 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.33 (d, J = 1.4 Hz, 1H), 8.96 – 8.88 (m, 2H), 8.47 (d, J = 2.8 Hz, 1H), 8.30 (d, J = 4.6 Hz, 1H), 6.06 (s, 1H), 4.14 (s, 3H), 3.03 (s, 3H), 2.34 (s, 3H).
61	LC-MS: (ES, m/z): RT=0.992 min,LCMS28, m/z=369 [M+1]. 1H-NMR: δ 9.08 (s, 1H), 8.24 (d, J = 2.7 Hz, 1H), 7.68 (dd, J = 9.0, 2.7 Hz, 1H), 7.34 (d, J = 9.1 Hz, 1H), 6.01 (q, J = 0.8 Hz, 1H), 4.54 (s, 2H), 4.00 (s, 3H), 3.02 (d, J = 3.4 Hz, 9H), 2.32 (d, J = 1.0 Hz, 3H).
62	LC-MS: (ES, m/z): RT = 0.97min, LCMS28: m/z = 370.17 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.25-9.2 (m, 1H), 8.81 – 8.57 (m, 1H), 8.54 – 8.35 (m, 1H), 6.34 – 6.00 (m, 1H), 4.60-4.55 (m, 2H), 4.16-4.13 (m, 3H), 3.05-2.96 (m, 9H), 2.57 – 2.26 (m, 3H).

65	LC-MS: (ES, m/z): RT = 1.412 min; LCMS07: m/z = 381 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.57 (s, 1H), 8.37 (s, 1H), 7.82 (s, 1H), 6.12 (s, 1H), 4.73 – 4.25 (m, 2H), 4.12 (s, 3H), 3.93 – 3.42 (m, 2H), 3.24 (t, J = 6.4 Hz, 2H), 3.18 – 2.95(m, 6H), 2.67 – 2.36 (m, 3H).
66	LC-MS: (ES, m/z): RT = 0.974 min, LCMS33: m/z = 369.3 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.71 (s, 1H), 8.37 (s, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.38 (d, J = 9.1 Hz, 1H), 6.03 (s, 1H), 4.58 (s, 2H), 3.99 (s, 3H), 3.08 – 2.99 (m, 9H), 2.34 (s, 3H).
67	LC-MS: (ES, m/z): RT=1.008 min,LCMS28, m/z=381 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.04 (s, 1H), 8.18 (d, J = 2.5 Hz, 1H), 7.75 (dd, J = 8.9, 2.3 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 6.02 (s, 1H), 4.62 (s, 2H), 4.36 (t, J = 8.2 Hz, 4H), 4.00 (s, 3H), 3.04 (s, 3H), 2.58 (s, 2H), 2.33 (s, 3H).
68	LC-MS: (ES, m/z): RT=1.766 min,LCMS28, m/z=399 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.05 (s, 1H), 8.18 (d, J = 2.6 Hz, 1H), 7.74 (dd, J = 9.0, 2.6 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 6.03 (d, J = 1.1 Hz, 1H), 5.63 – 5.30 (m, 1H), 4.81 – 4.66 (m, 4H), 4.59 – 4.46 (m, 2H), 4.00 (s, 3H), 3.04 (s, 3H), 2.33 (s, 3H).
69	LC-MS: (ES, m/z): RT = 0.933 min; LCMS07: m/z = 422 [M+1]. 1H NMR (300 MHz, DMSO-d6) δ 8.93 (s, 1H), 8.35 (s, 1H), 7.86 (s, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 9.0 Hz, 1H), 6.92 (s, 1H), 5.75 (s, 1H), 4.60 (t, J = 6.5 Hz, 2H), 4.50 (t, J = 6.1 Hz, 2H), 3.78 (s, 3H), 3.65 (t, J = 6.4 Hz, 1H), 3.37 (s, 2H), 2.84 (d, J = 4.5 Hz, 3H), 2.70 (t, J = 5.7 Hz, 2H), 2.58 (t, J = 5.8 Hz, 2H), 2.10 (s, 3H).
70	LC-MS: (ES, m/z): RT= 0.999 min; LCMS33: m/z = 394 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.17 (s, 1H), 7.86 (s, 1H), 7.61 – 7.48 (m, 1H), 7.11 (d, J = 9.0 Hz, 1H), 5.82 (s, 1H), 3.85 (s, 3H), 3.73 (s, 2H), 3.26 – 2.82 (m, 7H), 2.82 – 2.7 (m, 2H), 2.18 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H).
73	LC-MS: (ES, m/z): RT = 1.663 min, LCMS15: m/z = 369.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.49 (s, 1H), 7.75 – 7.65 (m, 1H), 7.29 (d, J = 8.9 Hz, 1H), 6.05 – 5.98 (m, 1H), 4.49 (s, 2H), 4.08 (s, 3H), 3.01 (s, 9H), 2.32 (d, J = 0.9 Hz, 3H).
74	LC-MS: (ES, m/z): RT = 0.992 min; LCMS33: m/z = 369 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.86 – 8.52 (m, 2H), 8.49 – 8.19 (m, 1H), 8.05 – 7.73 (m, 1H), 6.15 – 5.79 (m, 1H), 4.34 (s, 2H), 4.11 (s, 3H), 3.02 (d, J = 5.1 Hz, 3H), 2.90 (s, 6H), 2.33 (d, J = 1.0 Hz, 3H).
75	LC-MS: (ES, m/z): RT = 1.161 min, LCMS 33: m/z = 408.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 7.74 – 7.70 (m, 2H), 7.58 – 7.50 (m, 1H), 7.33 – 7.28 (m, 1H), 6.01 (d, J = 2.4 Hz, 1H), 4.56 (d, J = 3.3 Hz, 2H), 3.96 – 3.75 (m, 5H), 2.97 (d, J = 7.2 Hz, 3H), 2.79 (t, J = 5.7 Hz, 2H), 2.32 (t, J = 5.8 Hz, 3H), 2.22 (s, 3H).
76	LC-MS: (ES, m/z): RT = 1.462 min; LCMS28: m/z = 382 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 7.73 – 7.61 (m, 3H), 7.45 –7.15 (m, 1H), 6.45 – 6.40 (m, 1H), 5.81(s, 1H), 4.24 (s, 2H), 3.95 (s, 3H), 2.97 (s, 3H), 2.44 (s, 3H),1.97 –1.73 (m, 3H).
77	LC-MS: (ES, m/z): RT=1.290 min, LCMS 07, m/z=467 [M+1]. 1H-NMR (400 MHz, Methanol-d4) δ 7.87 – 7.75 (m, 2H), 7.22 (d, J = 9.2, 2.5 Hz, 1H), 5.98 – 5.97 (m, 0H), 5.96 (s, 1H), 4.868 (s, 2H), 3.98 (d, J = 6.2, 4.5 Hz, 2H), 3.93 – 3.82 (m, 5H), 2.94 (s, 3H), 2.27 (s, 3H), 1.54 (s, 10H).
78	LC-MS: (ES, m/z): RT=1.426 min,LCMS28, m/z=366 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.05 (d, J = 2.5 Hz, 1H), 7.94 – 7.69 (m, 1H), 7.34 (d, J = 9.1 Hz, 1H), 6.01 (d, J = 1.0 Hz, 1H), 4.42 (s, 2H), 4.07 (d, J = 5.9 Hz, 3H), 3.65 (t, J = 6.0 Hz, 2H), 3.13 (t, J = 6.0 Hz, 2H), 2.97 (s, 3H),2.32 (s, 3H).

79	LC-MS: (ES, m/z): RT=0.923 min,LCMS28, m/z=380 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.07 (d, J = 2.6 Hz, 1H), 7.86 (dd, J = 9.0, 2.6 Hz, 1H), 7.33 (d, J = 9.1 Hz, 1H), 6.01 (d, J = 1.0 Hz, 1H), 4.50 (s, 2H), 4.07 (d, J = 5.8 Hz, 3H), 3.72 (t, J = 6.0 Hz, 2H), 3.16 (d, J = 14.2 Hz, 5H), 2.98 (d, J = 4.6 Hz, 3H), 2.32 (d, J = 1.0 Hz, 3H).
81	LC-MS: (ES, m/z): RT = 5.04 min, HPLC 07, m/z = 393.2 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 7.69 (d, J = 2.7 Hz, 1H), 7.50 (dd, J = 8.9, 2.7 Hz, 1H), 7.04 (d, J = 8.9 Hz, 1H), 6.47 (d, J = 1.1 Hz, 1H), 5.81 (d, J = 0.8 Hz, 1H), 3.74 (s, 3H), 3.49 (t, J = 1.5 Hz, 2H), 2.87 (s, 3H), 2.76 (t, J = 5.9 Hz, 2H), 2.61 (t, J = 5.9 Hz, 2H), 2.52 (s, 3H), 2.18 (s, 3H), 2.01 (d, J = 1.0 Hz, 3H).
82	LC-MS: (ES, m/z): RT = 1.045 min, LCMS33: m/z = 406.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.17 (s, 1H), 7.82 (s, 1H), 7.54 – 7.50 (m, 1H), 7.10 (d, J = 9.0 Hz, 1H), 5.80 (d, J = 0.8 Hz, 1H), 3.84 (s, 3H), 3.77 (d, J = 0.9 Hz, 2H), 3.06 (t, J = 6.0 Hz, 2H), 2.90 – 2.84 (m, 5H), 2.17 (s, 3H), 2.04 – 1.91 (m, 1H), 0.67 – 0.48 (m, 4H).
83	LC-MS: (ES, m/z): RT=1.021 min,LCMS28, m/z=380 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.29 (d, J = 2.8 Hz, 1H), 7.47 (dd, J = 8.9, 2.8 Hz, 1H), 7.13 (d, J = 8.9 Hz, 1H), 6.84 (s, 1H), 5.97 (s, 1H), 4.65 (s, 2H), 4.52 (t, J = 5.9 Hz, 2H), 3.92 (d, J = 3.6 Hz, 5H), 3.15 (s, 3H), 3.02 (s, 3H), 2.30 (s, 3H).
84	LC-MS: (ES, m/z): RT=1.015 min,LCMS28, m/z=366 [M+H]. 1H NMR (300 MHz, Methanol-d4) δ 8.25 (d, J = 2.8 Hz, 1H), 7.47 (dd, J = 8.9, 2.8 Hz, 1H), 7.18 – 7.07 (m, 1H), 6.85 (d, J = 1.0 Hz, 1H), 6.01 – 5.94 (m, 1H), 4.58 (d, J = 0.9 Hz, 2H), 4.53 – 4.43 (m, 2H), 3.93 (s, 3H), 3.88 – 3.79 (m, 2H), 3.02 (s, 3H), 2.29 (d, J = 1.0 Hz, 3H).
86	LC-MS: (ES, m/z): RT = 2.172 min, LCMS27: m/z = 426.1 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.16 (s, 1H), 8.51 (s, 1H), 8.32 (s, 1H), 5.94 (d, J = 0.8 Hz, 1H), 4.73 – 4.70 (m, 2H), 4.50 (t, J = 6.1 Hz, 2H), 4.07 (s, 3H), 3.78 – 3.70 (m, 4H), 2.35 (s, 7H), 2.21 (s, 3H).
87	LC-MS: (ES, m/z): RT =1.376 min, LCMS07: m/z = 451 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.17 (s, 1H), 7.84 (s, 1H),7.56 – 7.51(m, 1H) 7.11 (d, J = 9.0 Hz, 1H), 5.82 (s, 1H), 3.85 (s, 3H), 3.68 (d, J = 6.3 Hz, 2H), 3.59 (s, 2H), 2.95 – 2.80 (m, 4H), 2.64 (s, 3H), 2.51 (s, 3H), 2.44 – 2.40 (m, 2H), 2.16 (s, 3H).
88	LC-MS: (ES, m/z): RT = 1.24 min, LCMS 33: m/z = 492 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.20 – 8.13 (m, 2H), 7.39 – 7.38 (m, 1H), 7.27 (d, J = 9.0 Hz, 1H), 6.03 (d, J = 1.1 Hz, 1H), 4.62 (s, 1H), 4.34 (s, 1H), 3.94 (s, 3H), 3.82 (t, J = 8.2 Hz, 3H), 3.65 (d, J = 7.2 Hz, 2H), 3.52 (d, J = 5.4 Hz, 3H), 3.31 (s, 2H), 3.16 – 3.14 (m, 4H), 2.68 (s, 3H), 2.34 (d, J = 0.9 Hz, 3H).
93	LC-MS: (ES, m/z): RT=1.268 min,LCMS28, m/z=362 [M+H]. 1H NMR (300 MHz, DMSO-d6) δ 9.18 (d, J = 1.4 Hz, 1H), 8.93 (s, 1H), 8.81 – 8.66 (m, 2H), 7.88 (d, J = 4.7 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.41 (d, J = 1.0 Hz, 1H), 7.07 (d, J = 9.0 Hz, 1H), 6.96 (s, 1H), 5.76 (s, 1H), 3.89 (s, 3H), 2.91 (s, 3H), 2.12 (s, 3H).
94	LC-MS: (ES, m/z): RT=2.462 min, LCMS31, m/z=396 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.11 (d, J = 2.7 Hz, 1H), 7.91 (d, J = 14.9 Hz, 1H), 7.44 (dd, J = 8.9, 2.7 Hz, 1H), 7.24 (d, J = 8.9 Hz, 1H), 6.00 (d, J = 1.1 Hz, 1H), 4.43 (d, J = 6.6 Hz, 2H), 3.93 (d, J = 5.6 Hz, 3H), 3.00 (d, J = 15.7 Hz, 3H), 2.44 – 2.28 (m, 3H), 2.13 (d, J = 0.9 Hz, 3H), 1.99 (s, 3H).
95	LC-MS: (ES, m/z):RT = 1.113 min; LCMS07: m/z = 382 [M+1]. 1H-NMR (400 MHz, Methanol-d4) δ 8.19 – 8.05 (m, 2H), 7.49 – 7.39 (m, 1H), 7.51 – 7.13(m, 1H), 6.61 – 6.29 (m, 1H), 5.85 (s, 1H), 4.61 – 4.33 (m, 2H), 3.94 (s, 3H), 3.04 (s, 3H), 2.54 – 2.19 (m, 3H), 2.01 (s, 3H).

96	LC-MS: (ES, m/z):RT = 3.599 min; LCMS07: m/z = 396 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.23 – 8.06 (m, 2H), 7.57 – 7.43 (m, 1H), 7.45 – 7.06 (m, 1H), 6.48 – 6.36 (m, 1H), 5.87 (s, 1H), 4.63 (s, 2H), 3.97 – 3.89 (m, 3H), 3.21 – 2.87 (m, 6H), 2.51 – 2.17 (m, 6H).
99	LC-MS: RT= 1.04 min, LCMS 28: m/z = 376 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 9.83 (s, 1H), 8.66 (d, J = 2.7 Hz, 1H), 8.15 (d, J = 7.1 Hz, 1H), 7.95 (d, J = 7.1 Hz, 1H), 7.73 (dd, J = 9.0, 2.7 Hz, 1H), 7.44 (d, J = 9.0 Hz, 1H), 6.04 (s, 1H), 4.06 (s, 3H), 3.16 (s, 3H), 3.09 (s, 3H), 2.34 (d, J = 0.9 Hz, 3H).
100	LC-MS: (ES, m/z): RT= 2.13 min, LCMS 28: m/z = 392 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 9.09 (s, 1H), 8.46 (d, J = 2.7 Hz, 1H), 7.85 – 7.74 (m, 1H), 7.62 (dd, J = 9.0, 2.7 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.25 (dd, J = 6.6, 1.0 Hz, 1H), 6.02 (s, 1H), 4.25 (s, 3H), 4.01 (s, 3H), 3.05 (s, 3H), 2.33 (s, 3H).
102	LC-MS: (ES, m/z): RT=1.124 min, LCMS45, m/z=382 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.08 (s, 1H), 7.99 (s, 1H), 7.61 (dd, J = 8.9, 2.9 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 6.00 (s, 1H), 4.38 (s, 2H), 3.94 (s, 3H), 2.98 (d, J = 7.9 Hz, 9H), 2.31 (s, 3H), 2.22 (d, J = 0.8 Hz, 3H).
103	LC-MS: (ES, m/z): RT = 2.178 min, LCMS15: m/z = 382 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.58 (d, J = 6.0 Hz, 1H), 8.24 (d, J = 2.7 Hz, 1H), 7.47–7.42 (m, J = 5.1 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.03 (d, J = 1.2 Hz, 1H), 3.97 (d, J = 6.9 Hz, 3H), 3.03 (s, 3H), 2.88 (s, 3H), 2.49 (s, 3H), 2.32 (d, J = 0.9 Hz, 3H).
104	LC-MS: (ES, m/z): RT = 1.16min, LCMS33: m/z = 368.18 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.87-8.54 (m, 1H), 8.29 – 7.91 (m, 2H), 7.65-7.4 (m, 1H), 7.39-7.12 (m, 1H), 6.35-5.65 (m, 1H), 4.12-3.85 (m, 3H), 2.95-3.18 (m, 3H), 2.92 (s, 3H), 2.49-2.25 (m, 3H).
105	LC-MS: (ES, m/z): RT = 0.11min, LCMS28: m/z = 396.21 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 7.89 (d, J = 2.7 Hz, 1H), 7.70 (dd, J = 9.0, 2.7 Hz, 1H), 7.14 (d, J = 9.1 Hz, 1H), 5.83 (d, J = 0.8 Hz, 1H), 3.80 (s, 3H), 2.92 (s, 3H), 2.87 (s, 3H), 2.39 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H).
106	LC-MS: (ES, m/z): RT=0.99min, LCMS28: m/z=382.23 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 7.85 (s, 1H), 7.70 (dd, J = 9.0, 2.8 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 5.82 (d, J = 0.8 Hz, 1H), 3.76 (d, J = 8.2 Hz, 5H), 2.86 (s, 3H), 2.52 (s, 3H), 2.30 (s, 3H), 2.17 (d, J = 7.9 Hz, 6H).
108	LC-MS: (ES, m/z): RT = 0.942 min; LCMS53: m/z = 354 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.40 (s, 1H), 8.25 – 8.15 (m, 1H), 7.81 (d, J = 0.7 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.00 (d, J = 1.2 Hz, 1H), 4.21 (d, J = 2.1 Hz, 2H), 3.95 (s, 3H), 3.00 (s, 3H), 2.74 (s, 3H), 2.31 (s, 3H).
109	LC-MS: (ES, m/z): RT = 0.948; LCMS53: m/z = 368 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.46 (s, 1H), 8.21 (d, J = 2.6 Hz, 1H), 7.85 (s, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 6.00 (d, J = 1.1 Hz, 1H), 4.34 (s, 2H), 3.95 (s, 3H), 3.01 (s, 3H), 2.90 (s, 6H), 2.31 (d, J = 0.9 Hz, 3H).
113	LC-MS: (ES, m/z): RT = 0.85 min, LCMS 27: m/z = 366.0 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 7.89 (d, J = 2.7 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.48 (s, 1H), 7.12 (d, J = 9.0 Hz, 1H), 5.81 (d, J = 0.8 Hz, 1H), 3.91 (s, 2H), 3.79 (s, 3H), 3.08 (t, J = 5.7 Hz, 2H), 2.86 (s, 3H), 2.61 (t, J = 5.7 Hz, 2H), 2.18 (s, 3H).
116	LC-MS: (ES, m/z): RT=1.637 min, LCMS28, m/z=397 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.40 (s, 1H), 8.04 (s, 1H), 7.50 (s, 1H), 6.74 (s, 1H), 4.16 – 4.07 (m, 2H), 3.99 (s, 3H), 3.83 – 3.72 (m, 4H), 3.47-3.53 (m, 1H), 3.01 (s, 3H), 2.36 (s, 6H),

	1.99 – 1.77 (m, 4H).
117	LC-MS: (ES, m/z): RT = 1.659 min; LCMS07: m/z = 369 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.74 (s, 1H), 8.49 (s, 1H), 7.64 (d, J =2.7 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 5.71 (s, 1H), 3.91 (s, 3H), 2.98 (s, 3H), 2.90 (s, 3H), 2.18 (s, 3H).
119	LC-MS: (ES, m/z): RT = 1.22 min, LCMS 33: m/z = 362 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.67 (d, J = 1.2 Hz, 1H), 8.54 – 8.45 (m, 1H), 8.04 – 7.88 (m, 2H), 7.75 – 7.51 (m, 2H), 7.37 (d, J = 9.3 Hz, 1H), 6.01 (q, J = 0.9 Hz, 1H), 3.87 (d, J = 5.7 Hz, 3H), 2.97 (d, J = 7.2 Hz, 3H), 2.32 (d, J = 1.2 Hz, 3H).
121	LC-MS: (ES, m/z): RT = 1.568 min, LCMS15: m/z = 381.2 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.64 (s, 1H), 8.36 (d, J = 2.6 Hz, 1H), 7.69 – 7.67 (m, 1H), 7.36 (d, J = 9.1 Hz, 1H), 6.03 (d, J = 1.2 Hz, 1H), 4.62 (s, 2H), 4.30 – 4.28 (m, 4H), 3.98 (s, 3H), 3.03 (s, 3H), 2.65 – 2.45 (m, 2H), 2.33 (s, 3H).
122	LC-MS: (ES, m/z): RT=0.912 min, LCMS 28, m/z =313.2 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.80 (s, 1H), 8.45 (s, 1H), 7.70 (s, 1H), 7.02 (s, 1H), 4.48 (s, 2H), 4.13 (s, 3H), 3.20 (s, 3H), 2.85 (s, 3H), 2.76 (s, 3H).
125	LC-MS: (ES, m/z): RT=0.957 min, LCMS 28, m/z =339.1 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.79 (s, 1H), 8.42 (s, 1H), 7.68 (s, 1H), 7.01 (s, 1H), 5.07 – 4.99 (m, 1H), 4.12 (s, 3H), 3.61 – 3.46 (m, 2H), 3.20 (s, 3H), 2.76 (s, 3H), 2.66 – 2.54 (m, 1H), 2.51 – 2.32 (m, 2H), 2.31 – 2.17 (m, 1H).
134	LC-MS: (ES, m/z): RT=2.426 min, LCMS34, m/z=382 [M+1]. 1H NMR (300 MHz, DMSO-d6) δ 10.52 (s, 1H), 8.85 (q, J = 4.6 Hz, 1H), 8.24 (d, J = 2.6 Hz, 1H), 8.84-8.87 (m, 1H), 7.98-7.95 (m, 1H), 7.46 (dd, J = 8.9, 2.7 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 6.02 (d, J = 1.1 Hz, 1H), 2.90 (d, J = 4.6 Hz, 3H), 2.74 (d, J = 4.7 Hz, 3H), 2.25 (s, 6H).
136	LC-MS: (ES, m/z): RT = 1.66 min, LCMS 15: m/z = 395.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.72 (s, 1H), 8.36 (d, J = 2.7 Hz, 1H), 7.69 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.03 (q, J = 0.9 Hz, 1H), 4.74 (t, J = 9.0 Hz, 1H), 3.98 (s, 4H), 3.40 (t, J = 9.6 Hz, 1H), 3.03 (d, J = 5.1 Hz, 6H), 2.75 – 2.51 (m, 2H), 2.33 (d, J = 0.9 Hz, 5H).
137	LC-MS: (ES, m/z): RT = 1.06 min, LCMS 33: m/z = 381 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.65 – 8.55 (m, 1H), 8.32 (d, J = 2.7 Hz, 1H), 7.80 – 7.60 (m, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.03 (q, J = 0.9 Hz, 1H), 5.04 – 4.92 (m, 1H), 3.96 (d, J = 7.2 Hz, 3H), 3.57 – 3.43 (m, 2H), 3.03 (s, 3H), 2.67 – 2.13 (m, 7H).
138	LC-MS: (ES, m/z): RT=0.910 min, LCMS 07, m/z=383 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.04 (s, 1H), 7.75 (d, J = 9.0, 2.8 Hz, 1H), 7.18 (d, J = 9.1 Hz, 1H), 5.83 (d, J = 0.7 Hz, 1H), 3.79 (s, 3H), 3.48 (s, 2H), 2.85 (s, 3H), 2.42 (s, 3H), 2.18 (s, 3H), 2.08 (s, 6H).
139	LC-MS: (ES, m/z): RT=0.976 min, LCMS 27, m/z=383 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.02 (s, 1H), 7.75 (d, J = 9.0, 2.8 Hz, 1H), 7.21 (d, J = 9.1 Hz, 1H), 5.83 (d, J = 0.8 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 2H), 2.85 (s, 3H), 2.36 (s, 6H), 2.24 (s, 3H), 2.18 (s, 3H).
143	LC-MS: (ES, m/z): RT = 1.694 min; LCMS15: m/z = 397 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.42 (s, 1H), 8.30 (s, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H), 5.82 (s, 1H), 3.88 (d, J = 5.7 Hz, 5H), 2.89 (s, 3H), 2.61 (q, J = 7.2 Hz, 4H), 2.18 (s, 3H), 1.16 (t, J = 7.2 Hz, 6H).
144	LC-MS: (ES, m/z): RT = 1.381 min, LCMS27: m/z = 375.0 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.57 (d, J = 1.0 Hz, 1H), 8.22 (d, J = 2.7 Hz, 1H), 7.63 – 7.46 (m, 3H), 7.34 (d, J = 9.0 Hz, 1H), 7.28 – 7.17 (m, 1H), 6.05 – 5.97 (m, 1H), 3.97 (s, 3H), 3.00 (s, 3H), 2.47 – 2.37 (m, 3H), 2.31 (d, J = 0.9 Hz, 3H).

145	LC-MS: (ES, m/z): RT = 2.711 min, LCMS33: m/z = 401.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.47 (d, J = 1.0 Hz, 1H), 8.37 (s, 1H), 7.63 – 7.60 (m, 1H), 7.56 – 7.53 (m, 1H), 7.45 (s, 1H), 7.19 (d, J = 9.0 Hz, 1H), 7.13 – 7.10 (m, 1H), 5.81 (s, 1H), 3.87 (s, 3H), 2.88 (s, 3H), 2.18 (s, 3H), 2.06 – 1.96 (m, 1H), 1.04 – 0.88 (m, 2H), 0.83 – 0.68 (m, 2H).
146	LC-MS: (ES, m/z): RT = 1.094 min, LCMS32: m/z = 361.3 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.73 (d, J = 1.0 Hz, 1H), 8.28 (d, J = 3.4 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.75 – 7.53 (m, 2H), 7.45 – 7.29 (m, 2H), 7.14 – 7.12 (m, 1H), 6.03 (d, J = 1.2 Hz, 1H), 4.00 (s, 3H), 3.03 (s, 3H), 2.34 (d, J = 1.0 Hz, 3H).
148	LC-MS: (ES, m/z): RT = 1.737 min, LCMS33: m/z = 441.1 [M+1]. 1H-NMR: (CDCl3, ppm): 1H NMR (300 MHz, Methanol-d4) δ 8.74 (s, 1H), 8.33 (s, 1H), 8.00 (d, J = 3.0 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.49 – 7.31 (m, 2H), 6.02 (s, 1H), 3.99 (s, 3H), 3.03 (s, 3H), 2.33 (s, 3H).
151	LC-MS: (ES, m/z): RT=1.085 min,LCMS28, m/z=376 [M+1]. 1H NMR (400 MHz, DMSO-d6) δ 9.74 (s, 1H), 9.60 (s, 1H), 8.52 (d, J = 2.7 Hz, 1H), 8.24 – 8.12 (m, 1H), 7.61 (dd, J = 9.1, 2.8 Hz, 1H), 7.42 (d, J = 9.2 Hz, 1H), 6.03 (d, J = 1.2 Hz, 1H), 3.93 (s, 3H), 2.96 (s, 3H), 2.59 (s, 3H), 2.24 (s, 3H).
155	LC-MS: (ES, m/z): RT = 1.028 min; LCMS27: m/z = 375 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 7.76 (s, 1H), 7.65 (s, 1H), 7.58 – 7.46 (m, 2H), 7.54 – 7.23 (m, 1H), 7.18 – 6.89 (m, 1H), 5.80 (s, 1H), 3.78 (s, 3H), 2.90 (s, 3H), 2.60 (s, 3H), 2.19 (s, 3H).
156	LC-MS: (ES, m/z): RT=1.58min, LCMS28: m/z=374.19 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 7.63 (d, J = 2.7 Hz, 1H), 7.50 – 7.31 (m, 3H), 7.19 – 7.00 (m, 2H), 6.29 – 5.75 (m, 1H), 3.88 – 3.78 (m, 3H), 3.02 – 2.91 (m, 3H), 2.5 – 2.36 (m, 3H), 2.28 (d, J = 1.0 Hz, 3H).
157	LC-MS: (ES, m/z): RT =1.125 min, LCMS28: m/z = 361 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.98 (s, 1H), 8.20 (d, J = 6.7 Hz, 2H), 8.08 (d, J = 6.5 Hz, 1H), 7.79 (d, J = 9.4 Hz, 1H), 7.45 – 7.33 (m, 2H), 6.05 (s, 1H), 4.14 (s, 3H), 3.00 (s, 3H), 2.35 (s, 3H).
158	LC-MS: (ES, m/z): RT = 1.090 min; LCMS28: m/z = 375 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.14 (s, 1H), 8.42 (d, J = 6.8, 1.0 Hz, 1H), 8.08 (d, J = 6.8, 0.8 Hz, 1H), 7.85 (dd, J = 9.0, 2.7 Hz, 1H), 7.69 – 7.54 (m, 1H), 7.36 – 7.18 (m, 1H), 7.14 – 7.05 (m, 1H), 6.32 – 5.95 (m, 1H), 3.95 – 3.79 (m, 3H), 3.83 (s, 3H), 3.24 – 3.07 (m, 3H), 2.39 – 2.26 (m, 3H).
159	LC-MS: (ES, m/z): RT = 1.879 min; LCMS33: m/z = 355 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.62 (s, 1H), 8.38 – 8.31 (m, 1H), 7.67 (d, J = 9.1 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 6.06 – 6.01 (m, 1H), 4.45 (s, 2H), 3.98 (d, J = 0.8 Hz, 3H), 3.03 (s, 3H), 2.83 (s, 3H), 2.34 (d, J = 0.9 Hz, 3H).
160	LC-MS: (ES, m/z): RT = 1.420 min, LCMS 07: m/z = 382 [M+1]. 1H-NMR (400 MHz, Methanol-d4) δ 8.46 (s, 1H), 8.21 (d, J = 2.8 Hz, 1H), 7.50 – 7.46(m, 1H), 7.29 (d, J = 2.4 Hz, 1H), 6.04 (s, 1H), 4.32 (s, 2H), 3.98 (s, 3H), 3.05 (s, 3H), 2.92 (s, 6H), 2.44 – 2.31 (m, 6H).
161	LC-MS: (ES, m/z): RT=1.016 min,LCMS28, m/z=367 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.26 (d, J = 2.7 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.19 – 7.03 (m, 2H), 5.99 (q, J = 0.7 Hz, 1H), 4.41 (d, J = 2.3 Hz, 2H), 3.96 (d, J = 9.6 Hz, 6H), 3.03 (s, 3H), 2.82 (s, 3H), 2.30 (s, 3H).
163	LC-MS: (ES, m/z): RT = 1.501 min; LCMS53: m/z = 316 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.18 (s, 1H), 7.45 (s, 1H), 7.08 (d, J = 2.4 Hz, 1H), 4.01 (s, 0H), 3.88 (s,

	3H), 3.73 (s, 2H), 3.57 (d, J = 1.3 Hz, 3H), 3.27 (s, 0H), 3.04 (s, 3H), 2.34 (s, 6H).
164	LC-MS: (ES, m/z): RT=0.932 min, LCMS27, m/z=369 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.43 (s, 1H), 8.28 (d, J = 1.7 Hz, 1H), 7.63 (dd, J = 9.0, 2.7 Hz, 1H), 7.20 (dd, J = 9.1, 2.9 Hz, 1H), 5.83 (d, J = 1.0 Hz, 1H), 3.98-4.03 (m, 1H), 3.90 (d, J = 1.8 Hz, 3H), 2.91 (s, 3H), 2.38 (d, J = 1.5 Hz, 3H), 2.19 (s, 3H), 1.53 (d, J = 6.8 Hz, 3H).
165	LC-MS: RT = 1.077min; m/z= 423.2 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.77 (s, 1H), 8.36 (d, J = 2.6 Hz, 1H), 7.67 (dd, J = 9.0, 2.7 Hz, 1H), 7.39 (d, J = 9.0 Hz, 1H), 6.17 – 6.02 (m, 1H), 5.46 (d, J = 8.4 Hz, 1H), 4.00 (s, 3H), 3.03 (s, 3H), 2.73 (s, 3H), 2.34 (s, 3H).
166	LC-MS: (ES, m/z): RT = 1.526 min, LCMS 33, m/z = 383 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.62 (s, 1H), 8.29 (d, J = 2.7 Hz, 1H), 7.69 (dd, J = 9.0, 2.7 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 6.03 (d, J = 1.2 Hz, 1H), 3.98 (s, 3H), 3.03 (s, 3H), 2.63 (s, 3H), 2.33 (d, J = 1.0 Hz, 3H), 1.86 (s, 6H).
169	LC-MS: (ES, m/z): RT= 0.95 min, LCMS 33: m/z = 353 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 7.84 (d, J = 2.7 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.26 (d, J = 9.0 Hz, 1H), 6.92 (s, 1H), 6.19 (d, J = 7.3 Hz, 1H), 4.38 (s, 2H), 4.02 (s, 3H), 3.05 – 2.85 (m, 9H).
170	LC-MS: (ES, m/z): RT= 0.95 min, LCMS 27: m/z = 354 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 8.10 (s, 1H), 7.77 – 7.58 (m, 4H), 7.34 (d, J = 9.0 Hz, 1H), 6.21 (d, J = 7.3 Hz, 1H), 4.33 (s, 2H), 3.93 (s, 3H), 2.97 (d, J = 20.4 Hz, 9H).
171	LC-MS: (ES, m/z): RT = 0.875 min, LCMS07, m/z = 355.10 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.75 (s, 1H), 8.32 (s, 1H), 7.65 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 9.0 Hz, 1H), 6.22 (d, J = 7.3 Hz, 1H), 4.59 (s, 2H), 3.99 (s, 3H), 3.05 (s, 3H), 2.99 (s, 6H).
172	LC-MS: (ES, m/z): RT = 0.907 min, LCMS27: m/z = 355.0 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.40 (s, 1H), 8.33 (s, 1H), 7.74 (s, 1H), 7.65 – 7.60 (m, 1H), 7.21 (d, J = 9.1 Hz, 1H), 5.95 (d, J = 6.1 Hz, 1H), 3.98 – 3.90 (m, 5H), 2.92 (s, 3H), 2.76 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H).
173	LC-MS: (ES, m/z): RT = 1.015 min, LCMS28: m/z = 381.2 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.66 (s, 1H), 8.28 (s, 1H), 7.68 – 7.60 (m, 2H), 7.40 (d, J = 9.1 Hz, 1H), 6.23 (d, J = 7.3 Hz, 1H), 4.49 (s, 2H), 4.00 (s, 3H), 3.11 – 3.02 (m, 5H), 1.24 – 1.12 (m, 1H), 0.82 – 0.72 (m, 2H), 0.51 – 0.42 (m, 2H).
174	LC-MS: (ES, m/z): RT = 0.953 min, LCMS28: m/z = 348.1 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.11 (d, J = 1.2 Hz, 1H), 8.30 (d, J = 1.1 Hz, 1H), 8.03 (s, 1H), 7.90 (t, J = 1.2 Hz, 1H), 7.71 (d, J = 6.2 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.09 (d, J = 8.9 Hz, 1H), 5.90 (d, J = 6.0 Hz, 1H), 3.85 (s, 3H), 2.89 (s, 3H).
175	LC-MS: (ES, m/z): RT = 1.621 min, LCMS15: m/z = 347.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.14 (d, J = 0.7 Hz, 1H), 8.11 – 8.02 (m, 1H), 7.93 – 7.73 (m, 3H), 7.63 (d, J = 7.3 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.11 – 7.09 (m, 1H), 6.20 (d, J = 7.3 Hz, 1H), 3.96 (s, 3H), 3.00 (s, 3H).
176	LC-MS: (ES, m/z): RT = 2.222 min, LCMS15: m/z = 338.2 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.21 (s, 1H), 8.16 (s, 1H), 7.65 – 7.53 (m, 2H), 7.34 (d, J = 9.0 Hz, 1H), 6.20 (d, J = 7.3 Hz, 1H), 3.97 (s, 3H), 3.04 (s, 3H), 2.08 – 2.01 (m, 1H), 1.09 – 0.98 (m, 2H), 0.93 – 0.84 (m, 2H).
177	LC-MS: (ES, m/z): RT = 1.828 min; LCMS28: m/z = 354 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.46 – 8.36 (m, 1H), 8.26 (s, 1H), 7.71 – 7.56 (m, 2H), 7.40 – 7.27 (m, 1H), 6.20 (dd, J = 7.3, 1.9 Hz, 1H), 5.10 (dd, J = 8.5, 5.9 Hz, 2H), 4.99 – 4.90 (m, 2H),

	4.55 (tt, J = 8.5, 7.0 Hz, 1H), 4.03 – 3.91 (m, 3H), 3.08 (s, 3H).
178	LC-MS: (ES, m/z): RT = 1.214 min, LCMS27: m/z = 346.0 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 7.71 (s, 2H), 7.61 – 7.46 (m, 3H), 7.28 – 7.18 (m, 2H), 7.03 (d, J = 8.9 Hz, 1H), 6.51 – 6.41 (m, 1H), 5.91 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H), 2.92 (s, 3H).
179	LC-MS: (ES, m/z): RT = 0.790 min; LCMS33: m/z = 301 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.32 (d, J = 0.7 Hz, 1H), 7.86 (d, J = 0.7 Hz, 1H), 7.67 (s, 1H), 7.42 (s, 1H), 4.24 (s, 2H), 4.01 (s, 3H), 3.73 (s, 3H), 3.18 (s, 3H), 2.77 (s, 3H).
181	LC-MS: (ES, m/z): RT = 1.839 min; LCMS33: m/z = 340 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.46 (s, 1H), 8.09 (s, 1H), 7.87 (d, J = 2.1Hz, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.51–7.48 (m, 1H), 7.34 (d, J = 2.7 Hz, 1H), 6.21 (d, J = 2.4 Hz, 1H), 4.23 (s, 2H), 3.99 (s, 3H), 3.04 (s, 3H), 2.76 (s, 3H).
182	LC-MS: (ES, m/z): RT = 1.47 min, LCMS 31: m/z = 356 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.72 (d, J = 2.4 Hz, 1H), 8.60 (s, 1H), 8.38 (d, J = 2.4 Hz, 1H), 7.86 (s, 1H), 6.08 – 6.01 (m, 1H), 4.23 (s, 2H), 4.12 (s, 3H), 3.02 (s, 3H), 2.76 (s, 3H), 2.34 (s, 3H).
184	LC-MS: (ES, m/z): RT = 1.503 min, LCMS 33, m/z =382.3 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.68 (s, 1H), 8.44 (s, 1H), 7.94 (s, 1H), 7.72 (s, 1H), 6.98 (s, 1H), 4.25 (s, 2H), 4.19 – 4.10 (m, 5H), 3.86 – 3.75 (m, 2H), 3.68 (t, J = 11.8 Hz, 1H), 3.20 (s, 3H), 2.77 (s, 3H), 2.08 – 1.81 (m, 5H).
185	LC-MS: (ES, m/z): RT = 1.019 min, LCMS07: m/z = 354 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.47 (d, J = 2.1 Hz, 1H), 8.08 (s, 1H), 7.90 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 3.0 Hz, 1H), 7.52–7.48 (m, 1H), 7.34–7.31 (m, 1H), 6.21 (d, J = 2.7Hz, 1H), 4.23 (s, 2H), 3.99 (d, J = 1.5 Hz, 3H), 3.22 – 2.18 (m, 5H), 1.37-1.34 (m, 3H).
186	LC-MS: (ES, m/z): RT = 0.871 min, LCMS33: m/z = 312.2 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.04 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 0.8 Hz, 1H), 7.47 (s, 1H), 7.14 (s, 1H), 3.90 (s, 3H), 3.85 (s, 2H), 2.76 – 2.65 (m, 2H), 2.62 – 2.40 (m, 6H), 2.36 – 2.28 (m, 1H).
187	LC-MS: (ES, m/z): RT = 1.320 min; LCMS53: m/z = 326 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.40 (s, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.50 (s, 1H), 4.21 (s, 2H), 4.03 (s, 3H), 3.22 (s, 3H), 2.84 - 2.78 (m, 5H), 2.74 - 2.62 (m, 3H), 2.37 - 2.32 (m, 1H).
188	LC-MS: (ES, m/z): RT = 0.981 min, LCMS15: m/z = 381.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.66 (s, 1H), 8.58 (s, 1H), 8.36 (s, 1H), 7.89 (s, 1H), 6.05 (s, 1H), 4.74 (t, J = 7.5 Hz, 1H), 4.11 (s, 3H), 3.50 – 3.39 (m, 2H), 3.00 (s, 3H), 2.57 – 2.38 (m, 1H), 2.36 – 2.15 (m, 6H).
191	LC-MS: (ES, m/z): RT=1.01min, LCMS28: m/z=381.21 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.40 (s, 1H), 8.30 (s, 1H), 7.74 (s, 1H), 7.62 (dd, J = 9.0, 2.7 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 5.95 (d, J = 6.1 Hz, 1H), 3.92 – 3.86 (m, 5H), 3.43 – 3.33 (m, 1H), 2.92 (s, 3H), 2.28-2.18 (m, 2H), 1.92 – 1.65 (m, 4H).
192	LC-MS: (ES, m/z): RT= 0.96 min, LCMS 28: m/z = 353 [M+1]. 1H-NMR: (Methanol-d4, ppm):δ 8.60 (s, 1H), 7.79 (s, 1H), 7.53 (s, 1H), 4.99 (t, J = 7.8 Hz, 1H), 4.05 (s, 3H), 3.62 – 3.41 (m, 2H), 3.25 (s, 3H), 2.95 – 2.84 (m, 2H), 2.84 – 2.62 (m, 4H), 2.67 – 2.16 (m, 4H).
193	LC-MS: (ES, m/z): RT= 0.86 min, LCMS 07: m/z = 339 [M+1]. 1H-NMR: (Methanol-d4, ppm):δ 8.59 (s, 1H), 7.79 (s, 1H), 7.53 (s, 1H), 4.98 (t, J = 7.9 Hz, 1H), 4.05 (s, 3H), 3.60 – 3.43 (m, 2H), 2.96 – 2.81 (m, 2H), 2.79 – 2.63 (m, 3H), 2.59 – 2.53 (m,1H), 2.49 – 2.16 (m, 4H).

194	LC-MS: (ES, m/z): RT= 0.94 min, LCMS 28: m/z = 339 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 8.59 (s, 1H), 7.79 (s, 1H), 7.53 (s, 1H), 4.98 (t, J = 7.9 Hz, 1H), 4.05 (s, 3H), 3.60 – 3.43 (m, 2H), 2.98 – 2.82 (m, 2H), 2.79 – 2.51 (m, 4H), 2.49 – 2.16 (m, 4H).
195	LC-MS: (ES, m/z): RT= 0.87 min, LCMS 07: m/z = 339 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 8.58 (s, 1H), 7.79 (s, 1H), 7.53 (s, 1H), 4.98 (t, J = 7.9 Hz, 1H), 4.05 (s, 3H), 3.60 – 3.43 (m, 2H), 2.96 – 2.81 (m, 2H), 2.79 – 2.63 (m, 3H), 2.67 – 2.51 (m, 1H), 2.49 – 2.32 (m, 3H), 2.35 – 2.16 (m, 1H).
196	LC-MS: (ES, m/z): RT=0.938 min, LCMS07, m/z=409 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.80 (s, 1H), 8.47 (s, 1H), 8.21 (d, J = 18.4 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.05 (s, 1H), 5.08 – 4.98 (m, 1H), 4.16 – 4.12 (m, 4H), 4.05 (s, 1H), 3.78 – 3.85 (m, 2H), 3.67 – 3.74 (m, 1H), 3.58 – 3.47 (m, 2H), 3.21 (d, J = 2.0 Hz, 3H), 2.69 – 2.57 (m, 1H), 2.49 – 2.23 (m, 3H), 2.05 – 1.97 (m, 2H), 1.84 – 1.93 (m, 2H).
199	LC-MS: (ES, m/z): RT=1.128 min, LCMS28, m/z=379 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.75 (dd, J = 2.5, 1.1 Hz, 1H), 8.30 (d, J = 2.7 Hz, 1H), 8.11 (d, J = 5.7 Hz, 1H), 7.68 (dd, J = 9.0, 2.7 Hz, 1H), 7.59 (dd, J = 5.7, 1.1 Hz, 1H), 7.16 (d, J = 9.0 Hz, 1H), 5.85 (d, J = 0.8 Hz, 1H), 4.00 (s, 3H), 2.92 (s, 3H), 2.22 (s, 3H).
200	LC-MS: (ES, m/z): RT=1.180 min, LCMS28: m/z=375 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.90 (t, J = 0.8 Hz, 1H), 8.20 (dd, J = 6.5, 0.8 Hz, 1H), 8.10 (dd, J = 6.5, 0.8 Hz, 1H), 7.87 (dd, J = 9.0, 2.7 Hz, 1H), 7.83 – 7.70 (m, 1H), 7.33 (d, J = 9.0 Hz, 1H), 6.02 (d, J = 1.1 Hz, 1H), 3.95 (s, 3H), 2.96 (s, 3H), 2.45 (s, 3H), 2.33 (d, J = 1.0 Hz, 3H).
201	LC-MS: (ES, m/z): RT=4.116min, HPLC06: m/z =362 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.05 (s, 1H), 8.96 (s, 1H), 8.25 (d, J = 2.6 Hz, 1H), 7.82 (dd, J = 9.0, 2.7 Hz, 1H), 7.44 – 7.28 (m, 2H), 6.03 (d, J = 1.1 Hz, 1H), 4.13 (s, 3H), 3.01 (s, 3H), 2.34 (s, 3H).
202	LC-MS: (ES, m/z): RT= 1.00 min, LCMS53: m/z = 319 [M+1]. 1H-NMR: (Methanol-d4, ppm):δ 8.97 (s, J = 0.9 Hz, 1H), 8.30 – 8.05 (m, 2H), 7.75 (s, 1H), 7.70 (s, 1H) 7.39 (s, 1H), 4.22 (s, 3H), 2.97 – 2.84 (m, 2H), 2.81 – 2.64 (m, 3H), 2.49 – 2.35 (m, 1H).
203	LC-MS: (ES, m/z): RT=0.579 min, LCMS 07, m/z = 362 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.02 (s, 1H), 8.64 – 8.56 (m, 2H), 8.23 (d, J = 6.5, 0.8 Hz, 1H), 8.15 – 8.08 (m, 1H), 7.52 (s, 1H), 6.07 (s, 1H), 4.25 (s, 3H), 2.98 (s, 3H), 2.36 (s, 3H).
204	LC-MS: (ES, m/z): RT=0.579 min, LCMS 07, m/z = 362 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.02 (s, 1H), 8.64 – 8.56 (m, 2H), 8.23 (d, J = 6.5, 0.8 Hz, 1H), 8.15 – 8.08 (m, 1H), 7.52 (s, 1H), 6.07 (s, 1H), 4.25 (s, 3H), 2.98 (s, 3H), 2.36 (s, 3H).
205	LC-MS: (ES, m/z): RT=0.787 min, LCMS 07: m/z=324 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.65 (s, 1H), 8.30 (s, 1H), 8.02 (d, J = 9.1 Hz, 1H), 7.51 (d, J = 0.8 Hz, 1H), 6.81 (s, 1H), 6.23 (s, 1H), 4.03 (s, 3H), 3.97 (d, 1H), 3.12 (d, J = 7.5 Hz, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.01 (d, 2H), 1.42 (t, J = 5.9 Hz, 2H).
206	LC-MS: (ES, m/z): RT = 1.018 min, LCMS27: m/z = 361.0 [M+1]. 1H NMR (300 MHz, DMSO-d6) δ 11.45 (s, 1H), 8.85 (s, 1H), 8.77 (s, 1H), 8.34 – 8.30 (m, 1H), 7.87 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.00 (d, J = 8.9 Hz, 1H), 6.83 (s, 1H), 6.57 (s, 1H), 5.73 (s, 1H), 3.78 (s, 3H), 2.83 (d, J = 4.5 Hz, 3H), 2.09 (s, 3H).
207	LC-MS: (ES, m/z): RT = 0.781 min, LCMS28: m/z = 375 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ8.95 (s, 1H), 8.00 – 7.74 (m, 3H), 7.42 – 7.27 (m, 1H), 6.84 – 6.77 (m, 1H), 6.06 (d, J = 1.1 Hz, 1H), 3.97 (d, J = 3.3 Hz, 3H), 2.99 (s, 3H), 2.63 (d, J = 1.1 Hz, 3H), 2.35 (d, J = 1.0 Hz, 3H).

208	LC-MS: (ES, m/z): RT=0.739 min, LCMS 07: m/z=324 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.65 (s, 1H), 8.30 (s, 1H), 8.02 (d, J = 9.1 Hz, 1H), 7.51 (d, J = 0.8 Hz, 1H), 6.81 (s, 1H), 6.23 (s, 1H), 4.03 (s, 4H), 3.97 (d, 2H), 3.12 (d, J = 7.5 Hz, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.01 (d, 2H).
209	LC-MS: (ES, m/z): RT = 1.079 min, LCMS 28: m/z = 308 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.14 (s, 1H), 8.05 (s, 1H), 7.89 (d, J = 3.4 Hz, 1H), 7.65 (s, 1H), 7.44 (s, 1H), 7.15 – 7.09 (m, 1H), 4.01 (s, 3H), 3.76 (s, 3H), 3.20 (s, 3H).
210	LC-MS: (ES, m/z): RT = 1.000 min, LCMS28: m/z = 362 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.29 (s, 1H), 8.83 (s, 1H), 8.28 (s, 1H), 7.98 – 7.84 (m, 2H), 7.39 – 7.27 (m, 1H), 6.21 – 6.02 (m, 1H), 3.97 (s, 3H), 2.99 (s, 3H), 2.43 (s, 1H), 2.54 – 2.15 (m, 2H).
212	LC-MS: (ES, m/z): RT=0.941 min, LCMS07, m/z=381 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.42 (s, 1H), 8.30 (s, 1H), 7.63 (dd, J = 9.0, 2.7 Hz, 1H), 7.20 (d, J = 9.0 Hz, 1H), 5.83 (d, J = 0.8 Hz, 1H), 4.38 (t, J = 6.9 Hz, 1H), 3.89 (s, 3H), 3.22 – 3.11 (m, 1H), 3.07 – 2.96 (m, 1H), 2.91 (s, 3H), 2.38 – 2.24 (m, 1H), 2.19 (s, 3H), 2.09 – 1.89 (m, 3H).
213	LC-MS: (ES, m/z): RT=0.952 min, LCMS07, m/z=381 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.41 (s, 1H), 8.29 (s, 1H), 7.63 (dd, J = 9.0, 2.7 Hz, 1H), 7.19 (d, J = 9.0 Hz, 1H), 5.83 (s, 1H), 4.37 (t, J = 6.9 Hz, 1H), 3.89 (s, 3H), 3.16 – 3.19 (m, 1H), 3.07 – 2.96 (m, 1H), 2.91 (s, 3H), 2.38 – 2.24 (m, 1H), 2.19 (s, 3H), 2.08 – 1.89 (m, 3H).
214	LC-MS: (ES, m/z): RT= 1.10 min, LCMS28: m/z = 333 [M+1]. 1H-NMR: (Methanol-d4, ppm):δ 9.16 (s, 1H), 8.04 (s, 1H), 7.90 (d, J = 3.3 Hz, 1H), 7.75 (s, 1H), 7.40 (s, 1H), 7.13 (dd, J = 3.4, 0.8 Hz, 1H), 4.04 (s, 3H), 3.26 (s, 3H), 2.97 – 2.40 (m, 6H).
215	LC-MS: (ES, m/z): RT=1.107 min, LCMS28: m/z=333 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.73 (d, J = 1.0 Hz, 1H), 8.04 (d, J = 5.6 Hz, 1H), 7.57 (dd, J = 5.6, 1.1 Hz, 1H), 7.50 (s, 1H), 7.45 (s, 1H), 6.95 (d, J = 0.9 Hz, 1H), 4.08 (s, 3H), 3.06 (s, 3H), 2.71 – 2.57 (m, 2H), 2.60 – 2.44 (m, 3H), 2.30 (tq, J = 9.7, 5.6, 4.8 Hz, 1H).
216	LC-MS: (ES, m/z): RT=1.148 min, LCMS28: m/z=367 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.71 (d, J = 1.1 Hz, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.58 (dd, J = 5.6, 1.1 Hz, 1H), 7.46 (d, J = 8.9 Hz, 2H), 3.96 (s, 3H), 3.06 (s, 3H), 2.74 – 2.62 (m, 2H), 2.64 – 2.43 (m, 3H), 2.35 – 2.22 (m, 1H).
217	LC-MS: (ES, m/z): RT=2.121 min, LCMS28: m/z=351[M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.05 (d, J = 2.2 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 8.12 (dd, J = 6.6, 0.8 Hz, 1H), 7.80 (d, J = 1.4 Hz, 2H), 4.19 (s, 3H), 3.25 (s, 3H), 2.93 – 2.62 (m, 5H), 2.48 – 2.35 (m, 1H).
218	LC-MS: (ES, m/z): RT = 2.136 min, LCMS53: m/z = 376.3 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 7.70 (s, 1H), 7.55 – 7.51 (m, 1H), 7.27 – 7.24 (m, 1H), 7.16 – 7.15 (m, 1H), 7.09 – 6.98 (m, 1H), 7.01 (d, J = 8.9 Hz, 1H), 5.79 (d, J = 0.7 Hz, 1H), 3.77 (s, 3H), 3.34 – 3.16 (m, 2H), 2.88 (s, 3H), 2.17 (s, 3H).
219	LC-MS: (ES, m/z): RT = 0.969 min, LCMS33: m/z = 377.3 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.43 (s, 1H), 7.92 (s, 1H), 7.86 (d, J = 2.7 Hz, 1H), 7.47 (s, 1H), 7.34 (d, J = 9.1 Hz, 1H), 6.02 (s, 1H), 3.96 (s, 3H), 2.97 (s, 3H), 2.33 (s, 3H).
220	LC-MS: (ES, m/z): RT = 0.977 min, LCMS07: m/z = 391.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.86 (s, 1H), 8.54 (d, J = 2.7 Hz, 1H), 7.49 – 7.41 (m, 2H), 6.87 (d, J = 2.4 Hz, 1H), 6.72 (s, 1H), 5.85 (s, 1H), 3.72 (s, 3H), 3.37 (s, 3H), 2.97 (s, 3H), 2.21 (s, 3H).

221	LC-MS: (ES, m/z): RT = 1.022 min, LCMS33: m/z = 379.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.23 (s, 1H), 8.03 – 7.98 (m, 3H), 7.24 – 7.18 (m, 2H), 6.05 (s, 1H), 3.94 (s, 3H), 2.94 (s, 3H), 2.34 (s, 3H).
222	LC-MS: (ES, m/z): RT = 0.926min, LCMS33: m/z = 384 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.61 (d, J = 2.8 Hz, 1H), 7.79 (s, 2H), 6.92 (d, J = 3.2 Hz, 1H), 5.86 (s, 1H), 3.90 (s, 2H), 3.76 (s, 3H), 3.44 (s, 3H), 2.95 (s, 3H), 2.54 (s, 3H), 2.20 (s, 3H).
223	LC-MS: (ES, m/z): RT =1.757 min, LCMS53: m/z = 361 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.49 (d, J = 1.9 Hz, 1H), 8.05 – 7.98 (m, 1H), 7.86 (s, 1H), 7.65 – 7.53 (m, 2H), 7.09 (d, J = 8.9 Hz, 1H), 6.69 – 6.60 (m, 1H), 5.83 (s, 1H), 3.83 (s, 3H), 2.92 (s, 3H), 2.21 (s, 3H).
225	LC-MS: (ES, m/z): RT = 1.022 min, LCMS33: m/z = 352.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.43 (d, J = 1.2 Hz, 1H), 8.10 – 8.02 (m, 1H), 7.69 – 7.66 (m, 1H), 7.05 (d, J = 9.0 Hz, 1H), 6.95 (d, J = 1.2 Hz, 1H), 5.79 (d, J = 0.7 Hz, 1H), 3.85 (s, 3H), 2.94 (s, 3H), 2.89 (s, 3H), 2.17 (s, 3H).
227	LC-MS: (ES, m/z): RT=0.875 min, LCMS07: m/z=326 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.65 (s, 1H), 8.30 (s, 1H), 8.02 (s, 1H), 6.81 (s, 1H), 4.03 (s, 4H), 3.97 (d, 2H), 3.12 (d, J = 7.5 Hz, 2H), 2.86 (t, J = 6.3 Hz, 3H), 2.01 (d, 2H), 1.86 (t, J = 5.9 Hz, 2H), 1.42 (t, J = 6.3 Hz, 2H).
228	LC-MS: (ES, m/z): RT=0.668 min, LCMS30: m/z=375 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 7.66 (dd, J = 8.9, 2.8 Hz, 1H), 7.60 (d, J = 1.0 Hz, 1H), 7.56 (d, J = 2.7 Hz, 1H), 7.53 (d, J = 3.3 Hz, 1H), 7.03 (d, J = 8.9 Hz, 1H), 6.57 (dd, J = 3.2, 1.0 Hz, 1H), 5.83 – 5.75 (m, 1H), 3.75 (s, 3H), 2.85 (s, 3H), 2.42 (s, 3H), 2.18 (s, 3H).
229	LC-MS: (ES, m/z): RT = 1.203 min, LCMS28: m/z = 379 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.24 (s, 1H), 8.02 (d, J = 2.3 Hz, 1H), 7.96 – 7.84 (m, 2H), 7.78 (d, J = 2.9 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 6.03 (d, J = 1.1 Hz, 1H), 3.96 (s, 2H), 2.99 (s, 2H), 2.36 – 2.31 (m, 2H).
230	LC-MS: (ES, m/z): RT=1.055 min, LCMS33, m/z=366 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.05 (s, 1H), 7.67 (dd, J = 8.9, 2.8 Hz, 1H), 7.05 (d, J = 8.9 Hz, 1H), 6.69 (s, 1H), 5.80 (d, J = 0.7 Hz, 1H), 3.84 (s, 3H), 2.93 (d, J = 16.2 Hz, 6H), 2.48 (s, 3H), 2.18 (s, 3H).
231	LC-MS: (ES, m/z): RT = 0.926 min, LCMS15: m/z = 323 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.96 (s, 1H), 7.93 (s, 1H), 7.78 (s, 1H), 7.45 (d, J = 2.7 Hz,1H), 7.01 (d, J = 3.3 Hz, 1H), 6.54 – 6.46 (m, 2H), 3.94 (m, 3H), 3.84 – 3.74 (m, 1H), 3.55 – 3.45 (m, 2H), 3.27 – 3.17 (m, 2H), 2.35 – 2.24 (m, 2H), 1.85 – 1.69 (m, 2H).
232	LC-MS: (ES, m/z): RT = 1.356 min, LCMS15: m/z = 363 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.92 (d, J = 4.0 Hz, 1H), 8.28 (s, 1H), 7.86 (s, 1H), 7.76 – 7.71 (m, 1H), 7.11 (d, J = 8.0 Hz, 1H), 5.82 (s, 1H), 3.91 (s, 3H), 2.92 (s, 3H), 2.19 – 2.05 (m, 4H), 1.20 – 1.13 (m, 4H).
233	LC-MS: (ES, m/z): RT = 1.215 min, LCMS15 m/z = 363 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.01 (s, 1H), 8.01 (s, 1H), 7.95 – 7.87 (m, 1H), 7.81 – 7.62 (m, 1H), 7.33 – 7.21 (m, 1H), 6.23 – 5.97 (m, 1H), 3.97 – 3.90 (d, J = 6.0 Hz, 3H), 3.02 – 2.96 (m, 3H), 2.45 – 2.29 (m, 3H), 2.20 – 2.11 (m, 1H), 1.41 – 1.30 (m, 2H), 1.14 – 1.04 (m, 2H).
234	LC-MS: (ES, m/z): RT = 0.98 min, LCMS27: m/z = 361.9 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.14 – 9.02 (m, 2H), 8.44 (s, 1H), 8.10 (t, J = 1.2 Hz, 1H), 7.83 (d, J = 1.2 Hz, 1H), 7.66 (q, J = 2.7 Hz, 1H), 7.10 (d, J = 9.3 Hz, 1H), 5.82 (d, J = 0.9 Hz, 1H), 3.94 (s, 3H), 2.95 (s, 3H), 2.19 (s, 3H).

235	LC-MS: (ES, m/z): RT = 2.256 min, LCMS15: m/z = 363 [M+1]. 1H NMR (400 MHz, DMSO-d6) δ 12.79 – 11.73(m, 2H), 10.27 (s, 1H), 8.77 (s, 1H), 8.49 (s, 1H), 8.25 (s, 1H), 8.13 (s, 1H), 7.54 (d, J = 4.0 Hz, 1H), 7.19 (d, J = 4.0 Hz, 1H), 6.01 (s, 1H), 3.88 (s, 3H), 2.93 (d, J = 4.0 Hz, 3H), 2.26 (s, 3H).
236	LC-MS: (ES, m/z): RT = 0.942 min, LCMS34: m/z = 325 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.73 (s, 1H), 7.67 (s, 1H), 7.57 – 7.51(m, 1H), 6.44 – 6.37(m, 2H), 3.84 (s, 3H), 3.63 – 3.51(m, 1H), 3.27 – 3.15 (m, 2H), 2.88 – 2.82 (m, 2H), 2.19 – 2.07 (m, 2H), 2.05 – 1.95(m, 1H), 1.59 – 1.44 (m, 2H), 1.28 – 1.16 (m, 2H), 0.99 – 0.86 (m, 2H).
238	LC-MS: (ES, m/z): RT=1.313 min, LCMS28, m/z=347 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.93 (d, J = 0.9 Hz, 1H), 8.21 (dd, J = 6.5, 0.8 Hz, 1H), 8.09 (dd, J = 6.6, 0.8 Hz, 1H), 7.73 (s, 1H), 7.34 (s, 1H), 4.03 (s, 3H), 3.25 (s, 3H), 2.94 – 2.80 (m, 2H), 2.78 – 2.63 (m, 3H), 2.43 (s, 4H).
241	LC-MS: (ES, m/z): RT = 3.62 min, HPLC05: m/z = 345 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.01 (q, J = 0.9 Hz, 1H), 8.25 (q, J = 6.6 Hz, 1H), 8.14 (d, J = 6.3 Hz, 1H), 7.94 – 7.80 (m, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.19 – 7.10 (m, 1H), 6.07 – 6.00 (m, 1H), 2.99 (s, 3H), 2.52 (s, 3H), 2.34 (s, 3H).
242	LC-MS: (ES, m/z): RT = 0.971 min, LCMS15: m/z = 335 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.91 (d, J = 2.2Hz, 1H), 8.49 (s, 1H), 8.26 – 8.35(m, 2H), 7.82 – 7.87 (m, 1H), 7.55 – 7.39 (m, 3H), 5.88 (s, 1H), 2.95 (s, 3H), 2.22 (s, 3H).
243	LC MS: (ES, m/z): RT=0.810 min, LCMS28: m/z=307 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.02 (s, 1H), 8.30 (m, 2H), 8.16 – 8.06 (m, 1H), 7.12 (d, J = 15.9 Hz, 1H), 6.97 (s, 1H), 4.12 (s, 1H), 3.54 (d, J = 12.1 Hz, 2H), 3.21 (s, J = 12.5 Hz, 2H), 2.53 (d, J = 12.3 Hz, 3H), 2.36 – 2.27 (m, 2H), 1.85 (s, 2H).
244	LC-MS: (ES, m/z): RT = 1.08 min, LCMS 33: m/z = 363 [M+1]. 1H NMR (400 MHz, Chloroform-d) δ 8.85 (s, 1H), 8.83 – 8.24 (m, 2H), 8.09 (s, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 6.3 Hz, 1H), 5.84 (s, 1H), 2.89 (s, 3H), 2.83 (q, J = 9.0 Hz, 2H), 2.20 (s, 3H), 1.24 (t, J = 0.9 Hz, 3H).
245	LC-MS: (ES, m/z): RT=1.122 min, LCMS28: m/z=370 [M+1]. 1H NMR (400 MHz, DMSO-d6) δ 11.18 (s, 1H), 9.42 – 9.35 (m, 2H), 9.10 (dd, J = 5.9, 1.0 Hz, 1H), 8.33 (s, 1H), 8.06 (dd, J = 5.9, 2.7 Hz, 1H), 7.93 – 7.85 (m, 1H), 7.42 (d, J = 8.9 Hz, 1H), 7.06 (s, 1H), 5.84 (s, 1H), 2.78 (d, J = 4.7 Hz, 3H), 2.14 (s, 3H).
246	LC-MS: (ES, m/z): RT=1.341 min, LCMS28: m/z=375 [M+1]. 1H NMR (400 MHz, DMSO-d6) δ 12.62 (s, 1H), 9.33 (s, 1H), 8.15 (s, 1H), 7.97 (dd, J = 8.9, 2.6 Hz, 1H), 7.54 (d, J = 3.5 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 3.5 Hz, 1H), 7.05 (s, 1H), 5.84 (s, 1H), 2.79 (d, J = 4.6 Hz, 3H), 2.14 (s, 3H).
247	LC-MS: (ES, m/z): RT=0.760 min, LCMS07: m/z=308 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.65 (s, 1H), 8.30 (s, 1H), 8.02 (d, J = 9.1 Hz, 2H), 7.51 (d, J = 0.8 Hz, 1H), 6.81 (s, 1H), 4.23 (s, 1H), 4.03 (s, 2H), 3.97 (d, 2H), 3.12 (d, J = 7.5 Hz, 5H), 2.86 (t, J = 6.3 Hz, 2H), 2.01 (d, 1H).
248	LC-MS: (ES, m/z): RT = 1.183 min, LCMS33: m/z = 370 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.00 (dd, J = 4.8, 1.4 Hz, 1H), 8.66 – 8.58 (m, 1H), 8.16 (d, J = 2.6 Hz, 1H), 7.79 (dd, J = 9.1, 4.8 Hz, 1H), 7.71 (dd, J = 8.8, 2.7 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 6.07 (d, J = 1.1 Hz, 1H), 3.02 (s, 3H), 2.35 (d, J = 1.0 Hz, 3H).
249	LC-MS: (ES, m/z): RT = 1.181 min, LCMS28: m/z = 359 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.25 (s, 1H), 7.79 – 7.68 (m, 2H), 7.38 (d, J = 8.8 Hz, 1H), 7.15 (s, 1H), 5.88 (s, 1H), 2.92 (s, 3H), 2.21 (s, 3H).

250	LC-MS: (ES, m/z): RT =1.274 min, LCMS27: m/z = 368 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.23 (s, 1H), 7.78 – 7.64 (m, 3H), 7.45 – 7.32 (m, 3H), 7.24 – 7.11 (m, 1H), 5.87 (d, J = 0.7 Hz, 1H), 2.91 (s, 3H), 2.21 (s, 3H).
251	LC-MS: (ES, m/z): RT = 1.04 min, LCMS27: m/z = 369.9 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.52 (d, J = 1.5 Hz, 1H), 8.47 – 8.35 (m, 2H), 8.29 – 8.22 (m, 1H), 7.77 (q, J = 2.7 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 5.88 (s, 1H), 2.90 (s, 3H), 2.21 (s, 3H).
252	LC-MS: (ES, m/z): RT= 1.36 min, LCMS28: m/z = 375 [M+1]. 1H-NMR: (Methanol-d4, ppm): 8.86 (d, J = 2.3 Hz, 1H), 8.06 (d, J = 2.6 Hz, 1H), 7.85 (d, J = 2.2 Hz, 1H), 7.69 (dd, J = 8.8, 2.7 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 6.07 (d, J = 1.1 Hz, 1H), 3.01 (s, 3H), 2.34 (s, 3H).
253	LC-MS: (ES, m/z): RT=2.424 min, LCMS07: m/z=358.7 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.26 (d, J = 1.1 Hz, 1H), 8.05 (dd, J = 13.5, 1.9 Hz, 2H), 7.69 (dd, J = 8.8, 2.7 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 6.07 (s, 1H), 3.01 (s, 3H), 2.34 (s, 3H).
254	LC-MS: (ES, m/z): RT= 1.10 min, LCMS28: m/z = 371 [M+1]. 1H-NMR: (Methanol-d4, ppm): 8.68 (d, J = 1.7 Hz, 1H), 8.07 (d, J = 2.7 Hz, 1H), 7.98 – 7.85 (m, 1H), 7.60 – 7.49 (m, 2H), 6.06 (d, J = 1.0 Hz, 1H), 3.96 (s, 3H), 3.01 (s, 3H), 2.35 (s, 3H).
255	LC-MS: (ES, m/z): RT=2.004 min, LCMS28: m/z=365 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.24 (d, J = 3.8 Hz, 1H), 8.13 – 8.05 (m, 2H), 8.01 (d, J = 2.7 Hz, 1H), 7.94 (d, J = 3.3 Hz, 1H), 7.76 – 7.64 (m, 1H), 7.17 (dd, J = 3.4, 0.9 Hz, 1H), 6.07 (d, J = 1.1 Hz, 1H), 2.99 (d, J = 7.7 Hz, 3H), 2.38 – 2.33 (m, 3H).
256	LC-MS: (ES, m/z): RT=1.716 min, LCMS53: m/z=345 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.19 (d, J = 0.9 Hz, 1H), 7.96 (t, J = 0.8 Hz, 1H), 7.93 – 7.87 (m, 2H), 7.85 – 7.78 (m, 1H), 7.49 (dd, J = 15.3, 8.4 Hz, 1H), 7.15 (dd, J = 3.4, 0.9 Hz, 1H), 6.23 – 6.03 (m, 1H), 2.97 (d, J = 3.5 Hz, 3H), 2.46 – 2.26 (m, 6H).
257	LC-MS: (ES, m/z): RT=1.342 min, LCMS53: m/z=292 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.20 (d, J = 0.9 Hz, 1H), 7.96 (d, J = 0.9 Hz, 1H), 7.93 (d, J = 3.4 Hz, 1H), 7.60 (s, 1H), 7.55 (s, 1H), 7.16 (dd, J = 3.4, 0.9 Hz, 1H), 3.73 (s, 3H), 3.20 (s, 3H), 2.42 (d, J = 0.6 Hz, 3H).
258	LC-MS: (ES, m/z): RT = 0.91 min, LCMS 27: m/z = 370 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.68 (d, J = 4.8 Hz, 2H), 8.25 (s, 1H), 7.74 (q, J = 2.7 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.23 (t, J = 4.9 Hz, 1H), 5.87 (d, J = 0.9 Hz, 1H), 2.90 (s, 3H), 2.21 (s, 3H).
259	LC-MS: (ES, m/z): RT = 1.02 min, LCMS 53: m/z = 369.9 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.92 – 8.85 (m, 1H), 8.70 (q, J = 5.7 Hz, 1H), 8.33 (q, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.77 (q, J = 2.7 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 5.88 (d, J = 0.9 Hz, 1H), 2.90 (s, 3H), 2.21 (s, 3H).
260	LC-MS: (ES, m/z): RT = 1.797 min, LCMS31: m/z = 381.2 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.33 (d, J = 0.9 Hz, 1H), 8.04 (d, J = 4.3 Hz, 1H), 7.77 – 7.73 (m, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.14 (s, 1H), 5.84 (s, 1H), 3.36 (s, 2H), 2.86 (s, 3H), 2.18 (s, 3H).
261	LC-MS: (ES, m/z): RT = 0.969 min, LCMS33: m/z = 377.3 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.43 (s, 1H), 7.92 (s, 1H), 7.86 (d, J = 2.7 Hz, 1H), 7.47 (s, 1H), 7.34 (d, J = 9.1 Hz, 1H), 6.02 (s, 1H), 3.96 (s, 3H), 2.97 (s, 3H), 2.33 (s, 3H).
262	LC-MS: (ES, m/z): RT = 1.03 min, LCMS 27: m/z = 358 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.32 – 8.15 (m, 2H), 7.95 – 7.86 (m, 1H), 7.77 (q, J = 8.7 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 6.07 (d, J = 1.2 Hz, 1H), 4.24 (s, 2H), 3.02 (s, 3H), 2.76 (s, 3H), 2.35 (d, J = 0.9 Hz, 3H).

263	LC-MS: (ES, m/z): RT= 1.04 min, LCMS28: m/z = 224 [M+1]. 1H-NMR: (Methanol-d4, ppm):δ 9.07 – 9.00 (m, 1H), 8.26 (dd, J = 6.5, 0.8 Hz, 1H), 8.14 (dd, J = 6.4, 0.8 Hz, 1H), 7.52 – 7.37 (m, 2H), 7.28 (dd, J = 8.2, 2.4 Hz, 1H), 7.11 (d, J = 0.8 Hz, 1H), 2.49 (s, 3H).
264	LC-MS: (ES, m/z): RT=0.970 min, LCMS 27: m/z =225.0 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.95 (s, 1H), 8.22 (d, J = 6.5 Hz, 1H), 8.10 (d, J = 6.5 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.08 – 7.02 (m, 2H), 6.91 (dd, J = 8.3, 2.7 Hz, 1H), 2.41 (s, 3H).
266	LC-MS: (ES, m/z): RT=1.137 min, LCMS 07: m/z= 280 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.82 (s, 1H), 7.45 (d, J = 9.0, 2.8 Hz, 2H), 6.91 (d, J = 9.1 Hz, 2H), 6.73 (d, J = 0.8 Hz, 1H), 4.61 (s, 2H), 2.21 (s, 3H).
267	LC-MS: (ES, m/z): RT=0.74min, LCMS33: m/z=210.15 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.75 (s, 1H), 8.68 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.13 (d, J = 5.6 Hz, 1H), 7.67 (dd, J = 5.6, 1.1 Hz, 1H), 7.47 (d, J = 5.3 Hz, 1H), 6.79 (d, J = 0.8 Hz, 1H), 2.70 – 2.42 (m, 3H).
268	LC-MS: (ES, m/z): RT=0.659 min, LCMS 07, m/z=210 [M+H]. 1H NMR (400 MHz, Methanol-d4) δ 8.95 (s, 1H), 8.30 (s, 1H), 8.02 (s, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 7.40 (d, 1H), 6.72 (s, 1H), 2.35 (s, 3H).
271	LC-MS: (ES, m/z): RT = 1.849 min, LCMS33: m/z =370 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.26 (s, 1H), 8.53 (d, J = 6.4 Hz, 1H), 8.32 (d, J = 6.4 Hz, 1H), 7.93 – 7.90 (m, 2H), 7.57 (d, J = 8.1 Hz, 1H), 6.04 (s, 1H), 2.99 (s, 3H), 2.47 – 2.34 (m, 6H).
273	LC-MS: (ES, m/z): RT = 1.428 min, LCMS53: m/z = 231 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.87 (s, 1H), 8.17 (d, J = 6.5 Hz, 1H), 8.05 (d, J = 6.5 Hz, 1H), 7.13 (s, 1H), 2.61 (s, 3H).
274	LC-MS: (ES, m/z): RT = 1.806 min, LCMS53: m/z = 344 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 7.91 (s, 1H), 7.62 – 7.50 (m, 2H), 7.44 – 7.34 (m, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.16 – 7.04 (m, 1H), 7.07 – 6.95 (m, 1H), 6.52 (d, J = 0.9 Hz, 1H), 5.81 (d, J = 0.7 Hz, 1H), 2.89 (s, 3H), 2.44 (s, 3H), 2.19 (s, 3H).
275	LC-MS: (ES, m/z): RT = 1.062 min, LCMS28: m/z = 231 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.91 – 8.84 (m, 1H), 8.26 – 8.15 (m, 1H), 8.08 – 8.97 (m, 1H), 7.06 (d, J = 0.8 Hz, 1H), 2.55 (s, 3H).
276	LC-MS: (ES, m/z): RT = 0.975 min, LCMS33: m/z = 365.3 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 7.52 – 7.40 (m, 2H), 7.36 – 7.20 (m, 3H), 5.98 (s, 1H), 3.21 – 3.18 (m, 2H), 2.97 (s, 3H), 2.31 – 2.19 (m, 6H), 1.34 – 1.29 (m, 3H).
278	LC-MS: (ES, m/z): RT=1.130 min, LCMS28: m/z=292 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.04 – 8.98 (m, 1H), 8.26 (d, J = 6.4 Hz, 1H), 8.15 (d, J = 6.5 Hz, 1H), 7.63 (s, 1H), 7.58 (s, 1H), 7.13 (d, J = 0.7 Hz, 1H), 3.72 (s, 3H), 3.20 (s, 3H), 2.62 (s, 3H).
279	LC-MS: (ES, m/z): RT=1.948 min, LCMS 27: m/z =346.0 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.93 (d, J = 1.0 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.21 (d, J = 2.4 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.67 (dd, J = 5.6, 1.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 5.83 (s, 1H), 2.87 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H).
280	LC-MS: (ES, m/z): RT=2.2min, LCMS33: m/z=355.15 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.85 (d, J = 2.2 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 2.3 Hz, 1H), 7.58 (dd, J = 8.3, 2.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 6.03 (d, J = 1.1 Hz, 1H), 3.002-2.98(m, 3H), 2.5-2.42 (m, 3H), 2.33 (s, 3H).
282	LC-MS: (ES, m/z): RT=2.054 min, LCMS28: m/z=346 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.28 (d, J = 1.3 Hz, 1H), 8.84 (d, J = 1.0 Hz, 1H), 8.32 – 8.21 (m, 2H),

	7.74 – 7.62 (m, 2H), 7.35 (d, J = 8.5 Hz, 1H), 5.85 (d, J = 0.7 Hz, 1H), 2.84 (s, 3H), 2.18 (d, J = 7.7 Hz, 6H).
284	LC-MS: (ES, m/z): RT=1.313 min, LCMS28: m/z=347 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.93 (d, J = 0.9 Hz, 1H), 8.21 (dd, J = 6.5, 0.8 Hz, 1H), 8.09 (dd, J = 6.6, 0.8 Hz, 1H), 7.73 (s, 1H), 7.34 (s, 1H), 4.03 (s, 3H), 3.25 (s, 3H), 2.94 – 2.80 (m, 2H), 2.78 – 2.63 (m, 3H), 2.43 (s, 4H).
285	LC-MS: (ES, m/z): RT = 0.942 min; LCMS53: m/z = 354 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.40 (s, 1H), 8.25 – 8.15 (m, 1H), 7.81 (d, J = 0.7 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.00 (d, J = 1.2 Hz, 1H), 4.21 (d, J = 2.1 Hz, 2H), 3.95 (s, 3H), 3.00 (s, 3H), 2.74 (s, 3H), 2.31 (s, 3H).
286	LC-MS: (ES, m/z): RT=1.290 min, LCMS 28: m/z =338.1 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.10 – 8.07 (m, 1H), 7.90 – 7.86 (m, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.75 – 7.62 (m, 1H), 7.47 – 7.39 (m, 1H), 6.25 – 6.02 (m, 1H), 4.24 (s, 2H), 2.98 (d, J = 1.4 Hz, 3H), 2.77 (d, J = 2.4 Hz, 3H), 2.44 – 2.30 (m, 3H), 2.23 (d, J = 6.9 Hz, 3H).
287	LC-MS: (ES, m/z): RT=2.288 min, LCMS 07: m/z=350 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.53 (s, 1H), 7.58 (s, 1H), 8.47 (s, 1H), 8.35 (s, 1H), 8.13 (d, J = 10.1 Hz, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.22 (d, J = 3.7 Hz, 1H), 5.81 (s, 1H), 2.93 (s, 3H), 2.41 (s, 3H), 2.17 (s, 3H).
288	LC-MS: (ES, m/z): RT=1.107 min, LCMS28: m/z=333 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.73 (d, J = 1.0 Hz, 1H), 8.04 (d, J = 5.6 Hz, 1H), 7.57 (dd, J = 5.6, 1.1 Hz, 1H), 7.50 (s, 1H), 7.45 (s, 1H), 6.95 (d, J = 0.9 Hz, 1H), 4.08 (s, 3H), 3.06 (s, 3H), 2.71 – 2.57 (m, 2H), 2.60 – 2.44 (m, 3H), 2.30 (tq, J = 9.7, 5.6, 4.8 Hz, 1H).
289	LC-MS: (ES, m/z): RT=1.313 min, LCMS28, m/z=347 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.93 (d, J = 0.9 Hz, 1H), 8.21 (dd, J = 6.5, 0.8 Hz, 1H), 8.09 (dd, J = 6.6, 0.8 Hz, 1H), 7.73 (s, 1H), 7.34 (s, 1H), 4.03 (s, 3H), 3.25 (s, 3H), 2.94 – 2.80 (m, 2H), 2.78 – 2.63 (m, 3H), 2.43 (s, 4H).
292	LC-MS: (ES, m/z): RT= 1.39 min, LCMS28: m/z = 386 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 8.33 – 8.24 (m, 2H), 7.68 (d, J = 3.3 Hz, 1H), 7.48 (dd, J = 8.8, 2.8 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.82 – 6.74 (m, 1H), 6.01 (d, J = 1.1 Hz, 1H), 3.96 (s, 3H), 3.11 (s, 3H), 2.32 (d, J = 1.0 Hz, 3H).
293	LC-MS: (ES, m/z): RT= 1.01 min, LCMS33: m/z = 432 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 8.03 – 7.75 (m, 4H), 7.32 (dd, J = 12.6, 8.9 Hz, 1H), 7.19 (dd, J = 3.4, 0.9 Hz, 1H), 6.02 (s, 1H), 5.00 (s, 2H), 3.97 (d, J = 4.7 Hz, 3H), 2.98 (s, 3H), 2.34 (d, J = 0.9 Hz, 3H), 2.07 (s, 3H).
294	LC-MS: (ES, m/z): RT=0.98min, LCMS33:m/z=333.17 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.75 (d, J = 1.5 Hz, 1H), 8.69 (t, J = 1.2 Hz, 1H), 8.20 (d, J = 3.3 Hz, 1H), 7.70 (s, 1H), 7.30 (s, 1H), 6.94 (dd, J = 3.3, 1.0 Hz, 1H), 4.00 (s, 3H), 3.25 (s, 3H), 2.9-2.82 (m, 2H), 2.75-2.62 (m, 3H), 2.48 – 2.34 (m, 1H).
295	LC-MS: (ES, m/z): RT=0.90min, LCMS33: m/z=308.16 [M +1]. 1H NMR (400 MHz, Methanol-d4) δ 8.73 (d, J = 1.5 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 3.3 Hz, 1H), 7.54 (s, 1H), 7.38 (s, 1H), 6.92 (dd, J = 3.3, 0.9 Hz, 1H), 3.98 (s, 3H), 3.74 (s, 3H), 3.19 (s, 3H).
296	LC-MS: (ES, m/z): RT= 1.30 min, LCMS07: m/z = 390 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.11 (d, J = 1.0 Hz, 1H), 8.02 – 7.86 (m, 2H), 7.74 (d, J = 3.4 Hz, 1H), 7.32 – 7.18 (m, 1H), 7.01 (dd, J = 3.4, 1.0 Hz, 1H), 6.00 (d, J = 1.0 Hz, 1H), 4.75 (s, 2H), 3.95 (s, 3H), 2.99 (s, 3H), 2.33 (d, J = 0.9 Hz, 3H).
297	LC-MS: (ES, m/z): RT=1.163 min, LCMS28, m/z=296 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.84 (t, J = 0.8 Hz, 1H), 8.15 (dd, J = 6.5, 0.8 Hz, 1H), 8.02 (dd, J = 6.5,

	0.7 Hz, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.29 (dd, J = 8.4, 1.9 Hz, 1H), 3.92 (s, 3H), 2.41 (s, 3H), 2.20 (s, 3H).
298	LC-MS: (ES, m/z): RT=1.138 min, LCMS28, m/z=311 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.80 (d, J = 0.8 Hz, 1H), 8.14 (dd, J = 6.5, 0.8 Hz, 1H), 8.01 (dd, J = 6.5, 0.8 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.4, 2.0 Hz, 1H), 3.93 (s, 3H), 2.83 (s, 3H), 2.42 (s, 3H).
299	LC-MS: (ES, m/z): RT=1.56min, LCMS33: m/z=353.18 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.26 (s, 1H), 7.94 (s, 1H), 7.57 (dd, J = 8.3, 2.4 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 6.04 (s, 1H), 4.14 (s, 3H), 3.00 (s, 3H), 2.47 (s, 3H), 2.33 (s, 3H).
300	LC-MS: (ES, m/z): RT=0.941 min, LCMS07: m/z=347 [M+1]. 1H-NMR-PH-EPI-K-1211-200: 1H NMR (400 MHz, Methanol-d4) δ 8.31 (s, 1H), 7.58 (s, 1H), 8.07 (s, 1H), 7.65 (s, 1H), 7.13 (s, 1H), 6.87 (d, J = 9.1 Hz, 1H), 3.91 (s, 3H), 3.21 (s, 3H), 2.87 (d, J = 9.1 Hz, 2H), 2.65 (d, J = 10.3 Hz, 3H), 2.57 (s, 3H), 2.33 (s, J = 10.3 Hz, 1H).
301	LC-MS: RT = 0.623 min, LCMS 32: m/z = 282 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.92 (s, 1H), 8.20 (d, J = 6.5 Hz, 1H), 8.09 (d, J = 6.5 Hz, 1H), 7.73 – 7.61 (m, 2H), 7.41 – 7.28 (m, 1H), 4.26 (s, 2H), 3.96 (s, 3H), 2.76 (s, 3H), 2.43 (s, 3H).
302	LC-MS: (ES, m/z): RT = 1.029 min, LCMS53: m/z = 352 [M+1]. 1H NMR (400 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.97 (s, 1H), 8.00 – 7.75 (m, 2H), 7.41 – 7.32 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 5.77 (s, 1H), 3.65 (s, 3H), 2.79 (d, J = 4.0 Hz, 3H), 2.25 (s, 3H), 2.12 (s, 3H).
306	LC-MS: (ES, m/z): RT = 0.856 min, LCMS27: m/z = 352 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.10 (s, 1H), 7.91 (s, 1H), 7.79 – 7.69 (m, 1H), 7.06 (d, J = 8.9 Hz, 1H), 6.45 (d, J = 6.2 Hz, 1H), 5.81 (s, 1H), 3.83 (s, 3H), 2.97 (s, 3H), 2.89 (s, 3H), 2.19 (s, 3H).
307	LC-MS: (ES, m/z): RT = 0.868 min, LCMS07: m/z = 360 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 8.47 – 8.43 (m, 1H), 7.88 (s, 1H), 7.80 (s, 1H), 7.14 – 7.11 (m, 1H), 5.88 (d, J = 1.2Hz, 1H), 3.74 (s, 2H), 2.88 (s, 3H), 2.43 (s, 3H), 2.19 (s, 3H).
308	LC-MS: (ES, m/z): RT= 1.94 min, LCMS07: m/z = 376 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 8.22 (d, J = 1.0 Hz, 1H), 7.76 (d, J = 3.3 Hz, 1H), 7.68 (d, J = 2.5 Hz, 2H), 7.30 (dd, J = 3.3, 0.8 Hz, 1H), 4.06 (s, 3H), 3.25 (s, 3H), 2.87 (s, 2H), 2.68 (d, J = 8.6 Hz, 3H), 2.41 (d, J = 13.8 Hz, 1H).
309	LC-MS: RT = 1.014 min, LCMS 07: m/z = 376 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 9.14 (s, 1H), 8.03 (s, 1H), 7.88 (d, J = 3.3 Hz, 1H), 7.75 (s, 1H), 7.39 (s, 1H), 7.11 (d, J = 3.3 Hz, 1H), 4.37 (s, 2H), 4.04 (s, 3H), 3.03 – 2.85 (m, 2H), 2.79 – 2.65 (m, 3H), 2.48 – 2.34 (m, 1H).
310	LC-MS: (ES, m/z): RT=1.063 min, LCMS28: m/z=337 [M+1]. 1H NMR (400 MHz, Methanol-d4) δ 8.73 (s, 1H), 8.08 (dd, J = 6.6, 0.8 Hz, 1H), 7.95 – 7.88 (m, 1H), 7.41 (d, J = 8.3 Hz, 1H), 6.52 – 6.44 (m, 2H), 3.91 (s, 3H), 3.85 – 3.73 (m, 1H), 3.47 – 3.52 (m, 2H), 3.18 – 3.25 (m, 2H), 2.42 (s, 3H), 2.30 (dd, J = 14.7, 3.8 Hz, 2H), 1.72 – 1.82 (m, 2H).
317	LC-MS: (ES, m/z): RT= 1.68 min, LCMS07: m/z = 372 [M+1]. 1H-NMR: (Methanol-d4, ppm): δ 8.04 (s, 1H), 7.91 (s, 1H), 7.82 – 7.65 (m, 1H), 7.18 – 7.12 (m, 1H), 6.03 (s, 1H), 4.23 (s, 2H), 3.88 (s, 3H), 2.94 (s, 3H), 2.76 (s, 3H), 2.32 (s, 3H).
386	LC-MS: (ES, m/z): RT = 0.784 min, LCMS28: m/z = 375 [M+1]. 1H NMR (300 MHz, Methanol-d4) δ 9.09 (s, 1H), 8.01 – 7.98 (m, 1H), 7.94 – 7.74 (m, 2H), 7.64 (d, J = 1.3 Hz, 1H), 7.41 – 7.27 (m, 1H), 6.07 (d, J = 1.2 Hz, 1H), 3.97 (d, J = 3.3 Hz, 3H), 2.99 (s, 3H), 2.53 (d, J = 1.2 Hz, 3H), 2.39 – 2.32 (m, 3H).

Example 20: Bioactivity Assays

[0685] MATERIALS AND EQUIPMENT:

[0686] Recombinant purified human EHMT2 913-1193 (55 μM) synthesized by Viva was used for all experiments. Biotinylated histone peptides were synthesized by Biopeptide and HPLC-purified to > 95% purity. Streptavidin Flashplates and seals were purchased from PerkinElmer and 384 Well V-bottom Polypropylene Plates were from Greiner. ^{3}H-labeled *S*-adenosylmethionine (^{3}H-SAM) was obtained from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. Unlabeled SAM and *S*-adenosylhomocysteine (SAH) were obtained from American Radiolabeled Chemicals and Sigma-Aldrich respectively. Flashplates were washed in a Biotek ELx-405 with 0.1% Tween. 384-well Flashplates and 96-well filter binding plates were read on a TopCount microplate reader (PerkinElmer). Compound serial dilutions were performed on a Freedom EVO (Tecan) and spotted into assay plates using a Thermo Scientific Matrix PlateMate (Thermo Scientific). Reagent cocktails were added by Multidrop Combi (Thermo Scientific).

[0687] MDA-MB-231 cell line was purchased from ATCC (Manassas, VA, USA). RPMI/Glutamax medium, Penicillin-Streptomycin, Heat Inactivated Fetal Bovine Serum, and D-PBS were purchased from Life Technologies (Grand Island, NY, USA). Odyssey blocking buffer, 800CW goat anti-mouse IgG (H+L) antibody, and Licor Odyssey Infrared Scanner were purchased from Licor Biosciences, Lincoln, NE, USA. H3K9me2 mouse monoclonal antibody (Cat #1220) was purchased from Abcam (Cambridge, MA, USA). 16% Paraformaldehyde was purchased from Electron Microscopy Sciences, Hatfield, PA, USA).MDA-MB-231 cells were maintained in complete growth medium (RPMI supplemented with 10% v/v heat inactivated fetal bovine serum) and cultured at 37 °C under 5% CO_2. UNC0638 was purchased from Sigma-Aldrich (St. Louis, MO, USA).

[0688] Various *In vitro* or *in vivo* biological assays are may be suitable for detecting the effect of the compounds of the present disclosure. These i*n vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[0689] **General Procedure for EHMT2 Enzyme Assay on Histone Peptide Substrate.** 10-point curves of test compounds were made on a Freedom EVO (Tecan) using serial 3-fold dilutions in DMSO, beginning at 2.5 mM (final top concentration of compound was 50 μM and

the DMSO was 2%). A 1 μL aliquot of the inhibitor dilution series was spotted in a polypropylene 384-well V-bottom plate (Greiner) using a Thermo Scientific Matrix PlateMate (Thermo Scientific). The 100% inhibition control consisted of 1 mM final concentration of the product inhibitor S-adenosylhomocysteine (SAH, Sigma-Aldrich). Compounds were incubated for 30 minutes with 40 μL per well of 0.031 nM EHMT2 (recombinant purified human EHMT2 913-1193, Viva) in 1X assay buffer (20 mM Bicine [pH 7.5], 0.002% Tween 20, 0.005% Bovine Skin Gelatin and 1 mM TCEP). 10 μL per well of substrate mix comprising assay buffer, ^{3}H-SAM (^{3}H-labeled *S*-adenosylmethionine, American Radiolabeled Chemicals, specific activity of 80 Ci/mmol), unlabeled SAM (American Radiolabeled Chemicals), and peptide representing histone H3 residues 1-15 containing C-terminal biotin (appended to a C-terminal amide-capped lysine, synthesized by Biopeptide and HPLC-purified to greater than 95% purity) were added to initiate the reaction (both substrates were present in the final reaction mixture at their respective K_m values, an assay format referred to as "balanced conditions"). Reactions were incubated for 60 minutes at room temperature and quenched with 10 μL per well of 400 μM unlabeled SAM, then transferred to a 384-well streptavidin Flashplate (PerkinElmer) and washed in a Biotek ELx-405 well washer with 0.1% Tween after 60 minutes. 384-well Flashplates were read on a TopCount microplate reader (PerkinElmer).

[0690] **General Procedure for MDA-MB-231 HEK9me2 in-cell Western Assay.** Compound (100 nL) was added directly to 384-well cell plate. MDA-MB-231 cells (ATCC) were seeded in assay medium (RPMI/Glutamax supplemented with 10% v/v heat inactivated fetal bovine serum and 1% Penicillin/Streptomycin, Life Technologies) at a concentration of 3,000 cells per well to a Poly-D-Lysine coated 384-well cell culture plate with 50 μL per well. Plates were incubated at 37°C, 5% CO_2 for 48 hours (BD Biosciences 356697). Plates were incubated at room temperature for 30 minutes and then incubated at 37°C, 5% CO_2 for additional 48 hours. After the incubation, 50 μL per well of 8% paraformaldehyde (Electron Microscopy Sciences) in PBS was added to the plates and incubated at room temperature for 20 minutes. Plates were transferred to a Biotek 406 plate washer and washed 2 times with 100 μL per well of wash buffer (1X PBS containing 0.3% Triton X-100 (v/v)). Next, 60 μL per well of Odyssey blocking buffer (Licor Biosciences) was added to each plate and incubated for 1 hour at room temperature. Blocking buffer was removed and 20 μL of monoclonal primary antibody α-H3K9me2 (Abcam) diluted 1:800 in Odyssey buffer with 0.1% Tween 20 (v/v) were added and plates were incubated overnight (16 hours) at 4 °C. Plates were washed 5 times with 100 μL per well of wash buffer. Next 20 μL per well of

secondary antibody was added (1:500 800CW donkey anti-mouse IgG (H+L) antibody (Licor Biosciences), 1:1000 DRAQ5 (Cell Signaling Technology) in Odyssey buffer with 0.1% Tween 20 (v/v)) and incubated for 1 hour at room temperature. The plates were washed 5 times with 100 µL per well wash buffer then 2 times with 100 µL per well of water. Plates were allowed to dry at room temperature then imaged on a Licor Odyssey Infrared Scanner (Licor Biosciences) which measured integrated intensity at 700 nm and 800 nm wavelengths. Both 700 and 800 channels were scanned.

[0691] **% Inhibition Calculation.** First, the ratio for each well was determined by: $\left(\frac{H3K9me2\ 800nm\ value}{DRAQ5\ 700nm\ value}\right)$.

[0692] Each plate included fourteen control wells of DMSO only treatment (Minimum Inhibition) as well as fourteen control wells (background wells) for maximum inhibition treated with control compound UNC0638 (Background wells).

[0693] The average of the ratio values for each well was calculated and used to determine the percent inhibition for each test well in the plate. Control compound was serially diluted three-fold in DMSO for a total of 10 test concentrations beginning at 1 µM. Percent inhibition was calculated as: Percent Inhibition = $100-\left(\left(\frac{\text{(Individual Test Sample Ratio) - (Background Avg Ratio)}}{\text{(Minimum Inhibition Ratio) - (Background Average Ratio)}}\right) * 100\right)$

[0694] IC_{50} curves were generated using triplicate wells per concentration of compound. The IC_{50} is the concentration of compound at which measured methylation is inhibited by 50% as interpolated from the dose response curves. IC_{50} values were calculated using a non-linear regression (variable slope–four parameter fit model) with by the following formula:

$\%\ inhibition = Bottom + \left(\frac{Top - Bottom}{(1 + (IC_{50}/[I])^n)}\right)$, where *Top* is fixed at 100% and *Bottom* is fixed to 0%, [I] = concentration of inhibitor, IC_{50} = half maximal inhibitory concentration and n = Hill Slope.

[0695] The IC_{50} values are listed in Table 3 below ("A" means IC_{50} <100 nM; "B" means IC_{50} ranging between 100 nM and 1 µM; "C" means IC_{50} ranging between >1 µM and 10 µM; "D" means IC_{50} >10 µM; "-" or "ND" means not determined).

Table 3

Compound No.	EHMT2 PEP (IC50 µM)	EHMT1 PEP (IC50 µM)	EHMT2 ICW (IC50 µM)

Compound No.	EHMT2 PEP (IC50 μM)	EHMT1 PEP (IC50 μM)	EHMT2 ICW (IC50 μM)
1	A	A	B
2	A	A	B
3	C	B	D
4	C	C	C
5	C	B	C
6	D	D	D
7	C	B	C
8	D	C	D
9	D	D	D
10	B	B	B
11	D	D	D
12	D	D	D
13	C	B	C
14	C	B	C
15	D	D	D
19	C	C	C
21	D	D	D
22	D	C	D
23	A	A	C
24	C	C	D
26	D	C	D
27	B	B	C
28	C	C	C
30	D	D	D
31	D	D	D
32	D	D	D
33	D	D	D
35	C	C	C
36	D	C	D
37	D	D	D
38	D	C	D
39	D	D	D
40	B	A	B
41	D	C	D
42	D	D	D
43	D	C	D
45	D	D	D
47	C	C	D
48	B	A	C
49	D	D	D
50	B	B	D
54	D	D	D
56	D	C	D
57	C	B	C

Compound No.	EHMT2 PEP (IC50 μM)	EHMT1 PEP (IC50 μM)	EHMT2 ICW (IC50 μM)
60	D	C	C
61	D	C	D
62	D	C	D
65	D	C	D
66	B	A	B
67	D	C	D
68	D	D	D
69	D	D	D
70	B	B	C
73	D	C	D
74	B	A	B
75	D	D	D
76	D	D	D
77	D	D	D
78	C	C	D
79	C	C	D
81	C	C	C
82	B	B	C
83	D	D	D
84	C	C	C
86	D	D	D
87	B	A	B
88	B	B	D
93	D	C	D
94	D	C	D
95	D	D	D
96	D	D	D
99	C	C	C
100	D	D	C
102	C	B	C
103	D	D	D
104	D	C	D
105	D	D	D
106	D	D	D
108	A	A	A
109	A	A	A
113	A	A	B
116	C	C	C
117	D	D	D
119	D	C	D
121	B	B	B
122	C	B	C
125	B	A	B
134	D	D	D

Compound No.	EHMT2 PEP (IC50 μM)	EHMT1 PEP (IC50 μM)	EHMT2 ICW (IC50 μM)
136	B	B	B
137	A	A	B
138	D	D	D
139	D	D	D
143	B	B	C
144	C	C	D
145	D	D	D
146	D	B	C
148	C	B	C
151	B	B	B
155	D	D	D
156	D	D	C
157	A	A	B
158	B	A	B
159	A	A	B
160	A	A	B
161	C	B	C
163	C	C	C
164	B	B	B
165	D	D	D
166	D	C	D
169	C	B	C
170	B	A	B
171	A	A	B
172	B	B	C
173	C	A	C
174	D	D	C
175	A	A	B
176	C	B	C
177	D	C	D
178	D	D	D
179	B	B	C
181	A	A	B
182	B	A	B
184	B	B	C
185	B	B	C
186	A	A	B
187	A	A	B
188	B	B	C
191	C	B	D
192	A	A	B
193	A	A	B
194	A	A	B
195	B	B	C

Compound No.	EHMT2 PEP (IC50 μM)	EHMT1 PEP (IC50 μM)	EHMT2 ICW (IC50 μM)
196	B	B	C
199	A	A	C
200	A	A	A
201	C	C	D
202	A	A	C
203	C	B	C
204	C	C	D
205	D	C	D
206	A	A	A
207	A	A	B
208	C	C	D
209	C	B	D
210	C	A	C
212	A	A	B
213	B	A	B
214	A	A	B
215	A	A	B
216	A	A	B
217	A	A	B
218	D	D	C
219	C	B	D
220	D	C	D
221	B	A	B
222	B	A	B
223	A	A	B
225	C	A	C
227	C	C	D
228	A	A	B
229	B	A	B
230	B	A	C
231	C	C	D
232	D	C	C
233	C	B	C
234	D	B	C
235	D	D	D
236	D	D	D
237	A	A	B
238	A	A	A
239	D	D	D
240	D	C	D
241	A	A	B
242	D	D	D
243	C	B	D
244	D	D	D

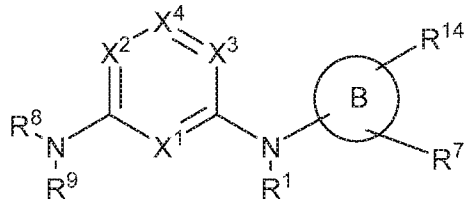
Compound No.	EHMT2 PEP (IC50 μM)	EHMT1 PEP (IC50 μM)	EHMT2 ICW (IC50 μM)
245	D	D	D
246	C	B	C
247	C	C	D
248	D	C	D
249	C	B	C
250	D	C	D
251	C	B	C
252	C	B	C
253	D	C	D
254	D	D	D
255	A	A	B
256	A	A	B
257	C	B	C
258	C	B	C
259	D	C	D
260	C	B	D
261	C	B	D
262	A	A	A
263	D	D	D
264	D	D	D
266	D	D	D
267	D	D	D
268	D	D	D
269	A	A	B
270	D	D	D
271	C	C	D
273	D	D	D
274	D	C	D
275	D	D	D
276	C	C	C
278	A	A	B
279	A	A	C
280	D	C	D
282	A	A	A
284	A	A	A
285	A	A	A
286	A	A	A
287	C	B	C
288	A	A	B
289	A	A	A
291	C	C	C
292	B	A	B
293	B	A	C
294	A	A	C

Compound No.	EHMT2 PEP (IC50 μM)	EHMT1 PEP (IC50 μM)	EHMT2 ICW (IC50 μM)
295	C	B	C
296	B	A	C
297	D	D	D
298	D	D	D
299	D	C	D
300	B	A	B
301	C	C	D
302	D	D	D
303	C	C	D
304	B	B	D
305	B	C	D
306	C	C	D
307	A	A	B
308	C	B	D
309	C	B	D
310	C	C	D
311	D	D	D
312	D	D	D
313	B	B	C
314	A	A	B
315	B	B	C
316	A	A	B
317	A	A	A
318	B	B	B
319	A	A	A
320	A	A	B
321	A	A	A
322	A	A	B
323	A	A	B
324	B	B	C
325	A	A	B
326	A	A	A
327	A	A	A
328	A	A	A
329	A	A	A
330	A	A	A
331	A	A	B
332	A	A	ND
333	A	A	ND
334	A	A	ND
386	A	A	A

[0696] 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 (I0), (II0), (III0), or (IV0):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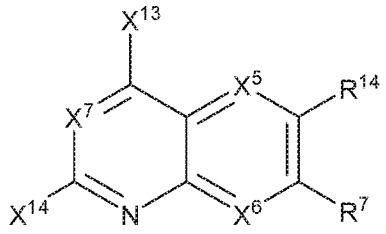
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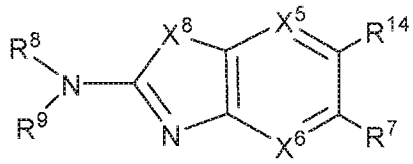
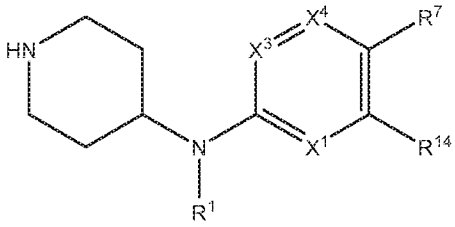

(III0), or


(IV0),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein

X^1 is N or CR^2;

X^2 is N or CR^3;

X^3 is N or CR^4;

X^4 is N or CR^5;

X^5 is N or CH;

X^6 is N or CR^{15};

X^7 is N or CH;

X^8 is NR^{13} or $CR^{11}R^{12}$;

one of X^{13} and X^{14} independently is NR^8R^9, and the other is R^{10};

B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl optionally substituted with one or more R^{15};

R^1 is H or C_1-C_4 alkyl;

each of R^2, R^3, R^4, and R^5, independently is selected from the group consisting of H, halo, cyano, C_1-C_6 alkoxyl, C_6-C_{10} aryl, OH, NR^aR^b, $C(O)NR^aR^b$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^b$, $NR^aC(O)OR^b$, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein the C_6-C_{10} aryl, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, C_1-C_6 alkoxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, are each optionally substituted with one or more of halo, OR^a, or NR^aR^b, in which each of R^a and R^b independently is H or C_1-C_6 alkyl;

R^6 is $–Q^1$-T^1, in which Q^1 is a bond, or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, oxo, or C_1-C_6 alkoxyl, and T^1 is H, halo, cyano, or R^{S1}, in which R^{S1} is C_3-C_8 cycloalkyl, phenyl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- or 6-membered heteroaryl and R^{S1} is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, $-C(O)R^c$, $-C(O)OR^c$, $-SO_2R^c$, $-SO_2N(R^c)_2$, $-NR^cC(O)R^d$, $-C(O)NR^cR^d$, $-NR^cC(O)OR^d$, $-OC(O)NR^cR^d$, NR^cR^d, or C_1-C_6 alkoxyl, in which each of R^c and R^d independently is H or C_1-C_6 alkyl;

R^7 is $–Q^2$-T^2, in which Q^2 is a bond, $C(O)NR^e$, or $NR^eC(O)$, R^e being H or C_1-C_6 alkyl and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, and wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $–Q^3$-T^3, wherein each Q^3 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^3 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^f, $C(O)R^f$, $C(O)OR^f$, $OC(O)R^f$, $S(O)_2R^f$, NR^fR^g, $OC(O)NR^fR^g$, $NR^fC(O)OR^g$, $C(O)NR^fR^g$, and $NR^fC(O)R^g$, each of R^f and R^g independently being H, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl, in which the C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy; or $–Q^3$-T^3 is oxo;

R^8 is H or C_1-C_6 alkyl;

R^9 is $-Q^4$-T^4, in which Q^4 is a bond or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxyl, and T^4 is H, halo, OR^h, NR^hR^i, $NR^hC(O)R^i$, $C(O)NR^hR^i$, $C(O)R^h$, $C(O)OR^h$, $NR^hC(O)OR^i$, $OC(O)NR^hR^i$, $S(O)_2R^h$, $S(O)_2NR^hR^i$, or R^{S2}, in which each of R^h and R^i independently is H or C_1-C_6 alkyl, and R^{S2} is C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- to 10-membered heteroaryl, and R^{S2} is optionally substituted with one or more $-Q^5$-T^5, wherein each Q^5 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^5 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^j, $C(O)R^j$, $C(O)OR^j$, $OC(O)R^j$, $S(O)_2R^j$, NR^jR^k, $OC(O)NR^jR^k$, $NR^jC(O)OR^k$, $C(O)NR^jR^k$, and $NR^jC(O)R^k$, each of R^j and R^k independently being H or C_1-C_6 alkyl; or $-Q^5$-T^5 is oxo;

R^{10} is halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein each of the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and 4- to 12-membered heterocycloalkyl is optionally substituted with one or more halo, cyano, hydroxyl, oxo, amino, mono- or di- alkylamino, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, $C(O)NR^jR^k$, or $NR^jC(O)R^k$;

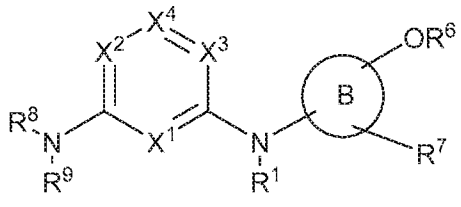
R^{11} and R^{12} together with the carbon atom to which they are attached form a C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein the C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, amino, mono- or di- alkylamino, or C_1-C_6 alkoxyl;

R^{13} is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} cycloalkyl, or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S;

R^{14} is H, halo, cyano, $P(O)R^lR^m$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, or $-OR^6$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is optionally substituted with one or more of halo or OR^6, and each of R^l and R^m independently is C_1-C_6 alkyl; and

R^{15} is H, halo, cyano, or $-OR^6$.

2. The compound of claim 1, being of Formula (I), (II), or (III):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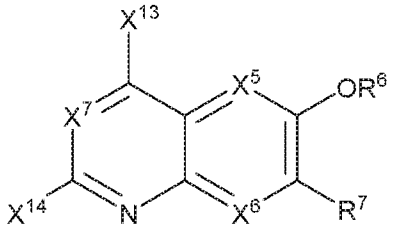
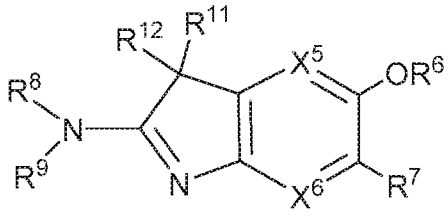

(II), or


(III),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein

X^1 is N or CR^2;

X^2 is N or CR^3;

X^3 is N or CR^4;

X^4 is N or CR^5;

X^5 is N or CH;

X^6 is N or CR^{15};

X^7 is N or CH;

one of X^{13} and X^{14} independently is NR^8R^9, and the other is R^{10};

B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl optionally substituted with one or more R^{15};

R^1 is H or C_1-C_4 alkyl;

each of R^2, R^3, R^4, and R^5, independently is selected from the group consisting of H, halo, cyano, C_1-C_6 alkoxyl, C_6-C_{10} aryl, OH, NR^aR^b, $C(O)NR^aR^b$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^b$, $NR^aC(O)OR^b$, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-

membered heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein the C_6-C_{10} aryl, C_3-C_8 cycloalkyl, 4- to 7- membered heterocycloalkyl, 5- to 6-membered heteroaryl, C_1-C_6 alkoxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, are each optionally substituted with one or more of halo, OR^a, or NR^aR^b, in which each of R^a and R^b independently is H or C_1-C_6 alkyl;

R^6 is $-Q^1$-T^1, in which Q^1 is a bond, or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, oxo, or C_1-C_6 alkoxyl, and T^1 is H, halo, cyano, or R^{S1}, in which R^{S1} is C_3-C_8 cycloalkyl, phenyl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- or 6-membered heteroaryl and R^{S1} is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, $-C(O)R^c$, $-C(O)OR^c$, $-SO_2R^c$, $-SO_2N(R^c)_2$, $-NR^cC(O)R^d$, $-C(O)NR^cR^d$, $-NR^cC(O)OR^d$, $-OC(O)NR^cR^d$, NR^cR^d, or C_1-C_6 alkoxyl, in which each of R^c and R^d independently is H or C_1-C_6 alkyl;

R^7 is $-Q^2$-T^2, in which Q^2 is a bond, $C(O)NR^e$, or $NR^eC(O)$, R^e being H or C_1-C_6 alkyl and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, and wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $-Q^3$-T^3, wherein each Q^3 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^3 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^f, $C(O)R^f$, $C(O)OR^f$, $OC(O)R^f$, $S(O)_2R^f$, NR^fR^g, $OC(O)NR^fR^g$, $NR^fC(O)OR^g$, $C(O)NR^fR^g$, and $NR^fC(O)R^g$, each of R^f and R^g independently being H, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl, in which the C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy; or $-Q^3$-T^3 is oxo;

R^8 is H or C_1-C_6 alkyl;

R^9 is $-Q^4$-T^4, in which Q^4 is a bond or C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxyl, and T^4 is H, halo, OR^h, NR^hR^i, $NR^hC(O)R^i$, $C(O)NR^hR^i$, $C(O)R^h$, $C(O)OR^h$, $NR^hC(O)OR^i$, $OC(O)NR^hR^i$, $S(O)_2R^h$, $S(O)_2NR^hR^i$, or R^{S2}, in which each of R^h and R^i independently is H or C_1-C_6 alkyl, and R^{S2} is C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- to 10-membered

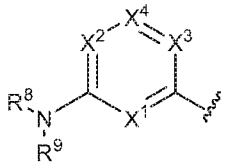
heteroaryl, and R^{S2} is optionally substituted with one or more $-Q^5$-T^5, wherein each Q^5 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^5 independently is selected from the group consisting of H, halo, cyano, 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 containing 1-4 heteroatoms selected from N, O, and S, 5- to 6-membered heteroaryl, OR^j, $C(O)R^j$, $C(O)OR^j$, $OC(O)R^j$, $S(O)_2R^j$, NR^jR^k, $OC(O)NR^jR^k$, $NR^jC(O)OR^k$, $C(O)NR^jR^k$, and $NR^jC(O)R^k$, each of R^j and R^k independently being H or C_1-C_6 alkyl; or $-Q^5$-T^5 is oxo;

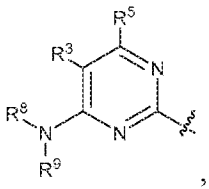
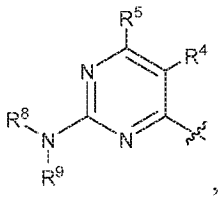
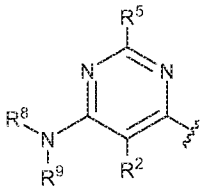
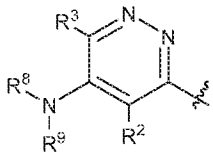
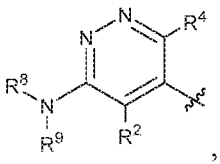
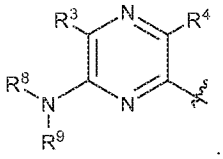
R^{10} is halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein each of the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and 4- to 12-membered heterocycloalkyl is optionally substituted with one or more halo, cyano, hydroxyl, oxo, amino, mono- or di- alkylamino, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, $C(O)NR^jR^k$, or $NR^jC(O)R^k$;

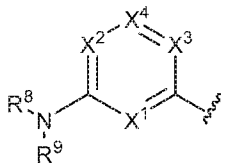
R^{11} and R^{12} together with the carbon atom to which they are attached form a C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein the C_3-C_{12} cycloalkyl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxyl, oxo, amino, mono- or di- alkylamino, or C_1-C_6 alkoxyl; and

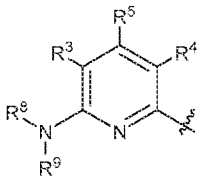
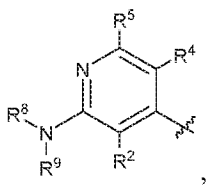
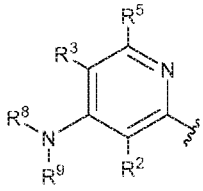
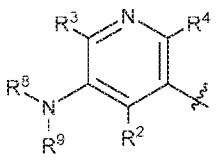
R^{15} is H, halo, cyano, or $-OR^6$.

3. The compound of claim 1, wherein the compound is of Formula (I0) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

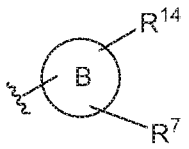
4. The compound any one of the preceding claims, wherein  is

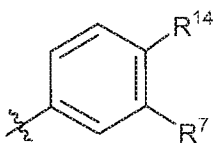
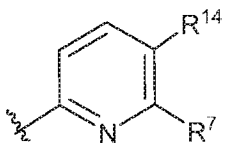
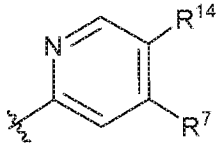
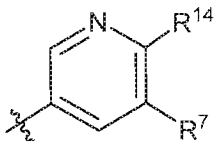
 ,  ,  ,  ,  , or  .

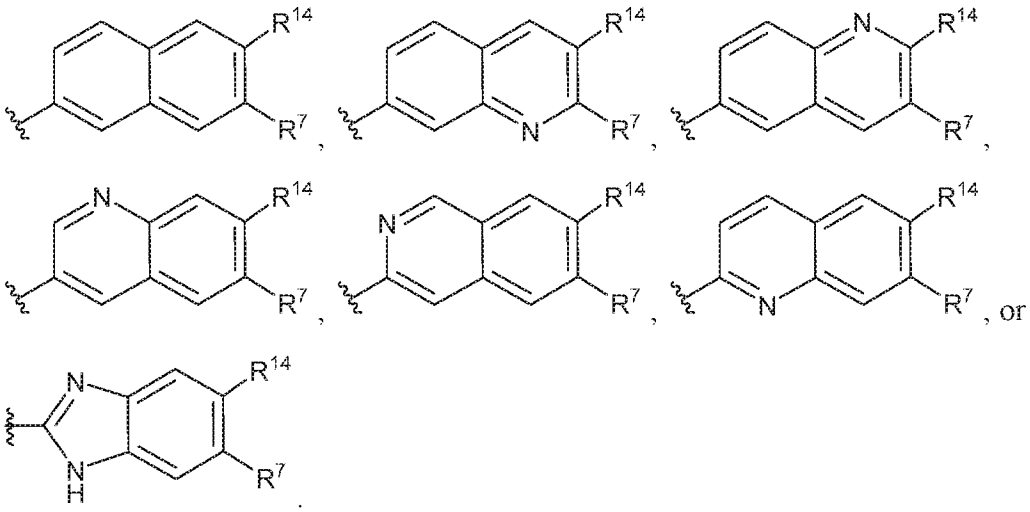
5. The compound any one of the preceding claims, wherein  is

 ,  ,  , or  .

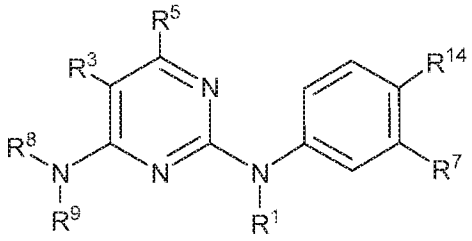
6. The compound any one of the preceding claims, wherein ring B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl.

7. The compound any one of the preceding claims, wherein  is

 ,  ,  ,  ,



8. The compound any one of the preceding claims, being of any one of Formulae (I0a)-(I0l):



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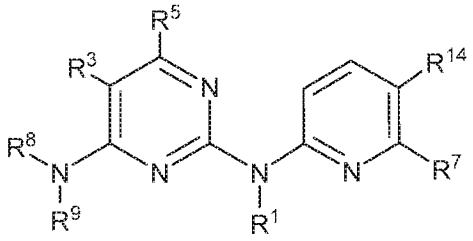

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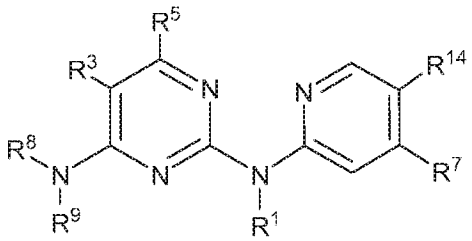

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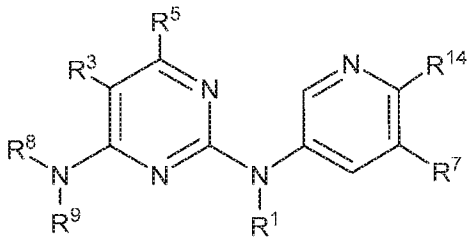

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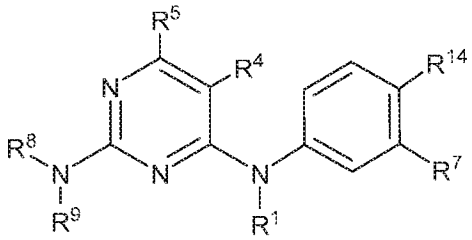

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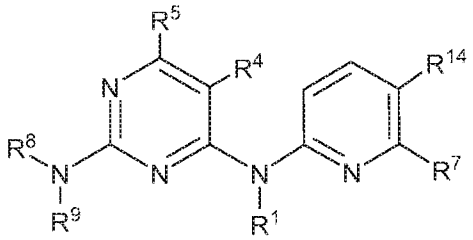

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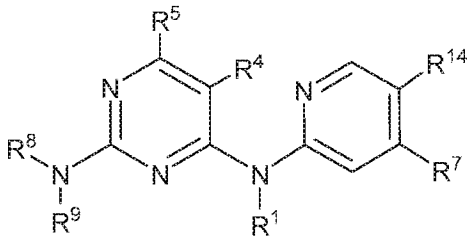

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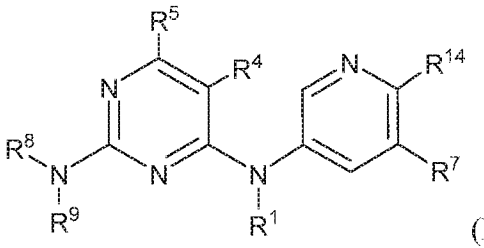

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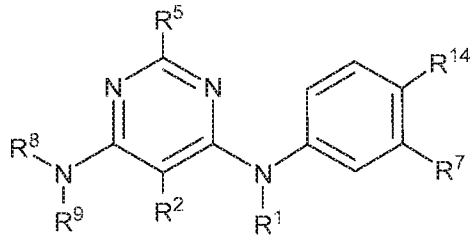
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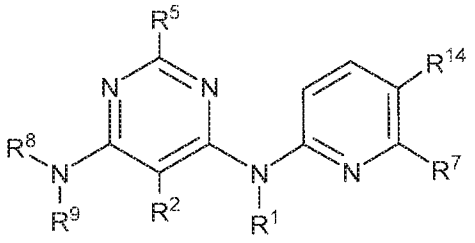
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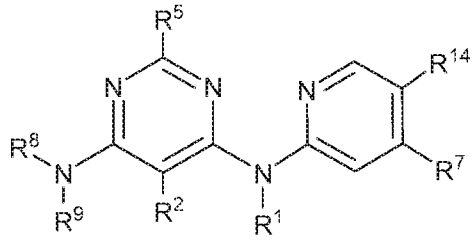
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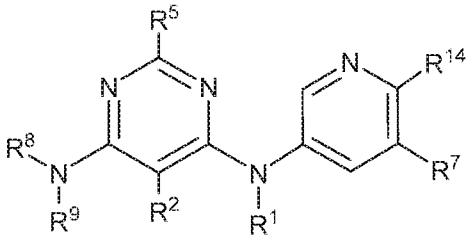
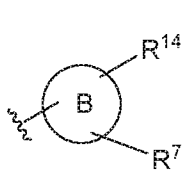
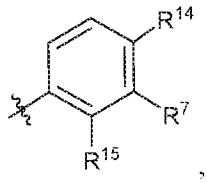
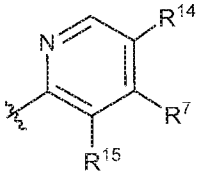
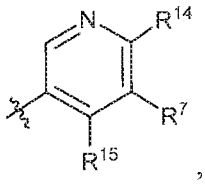
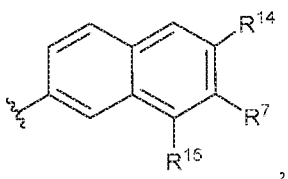
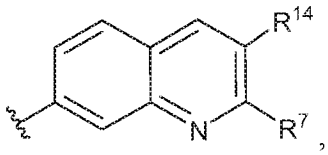
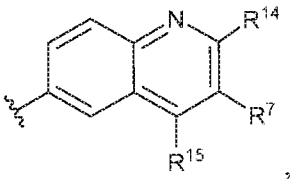
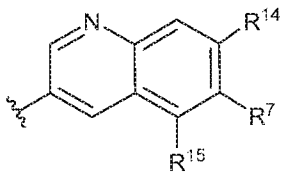
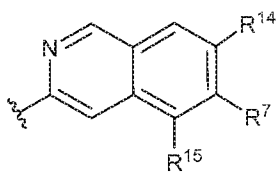
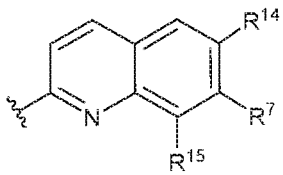
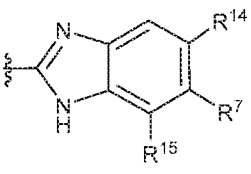

(I0l),

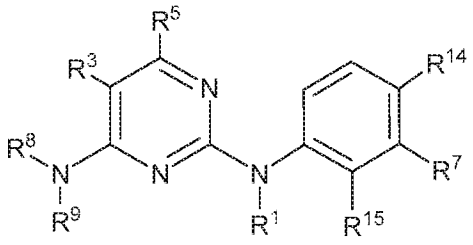
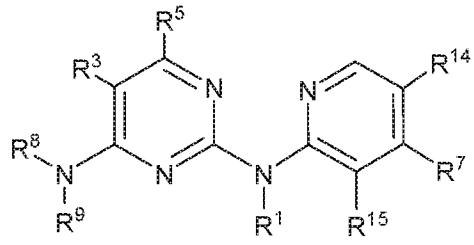
or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

9. The compound any one of the preceding claims, wherein ring B is C_6-C_{10} aryl or 5- to 10-membered heteroaryl substituted with one R^{15}.

10. The compound any one of the preceding claims, wherein  is  ,

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 , or
 .

11. The compound any one of the preceding claims, being of any one of Formulae (I0a')-(I0i'):


(I0a'),

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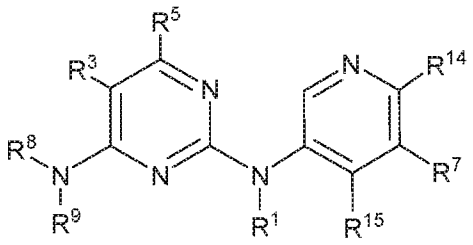
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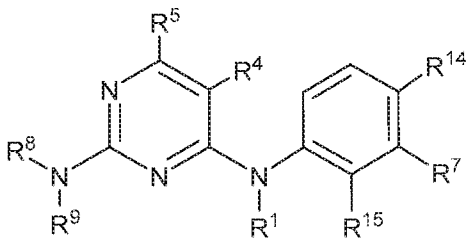
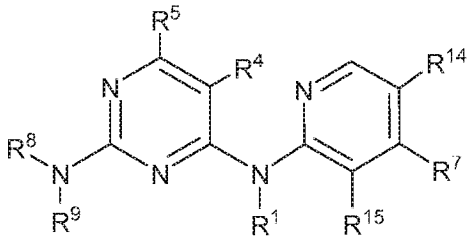
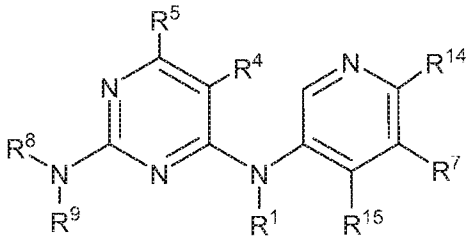

(I0d'),

(I0e'),

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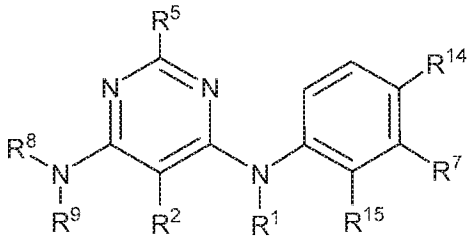
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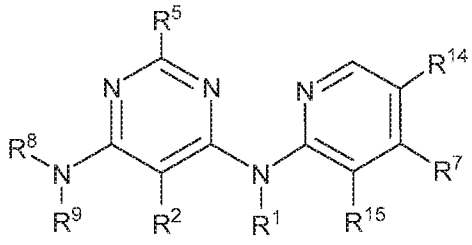
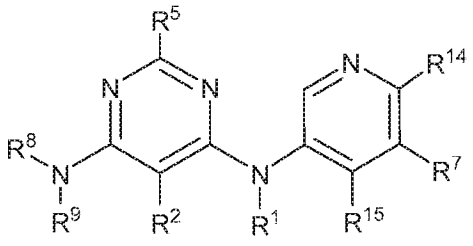
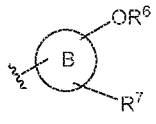
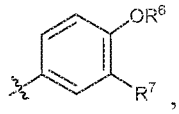
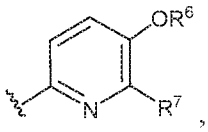
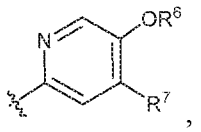
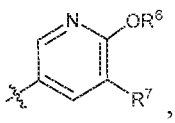
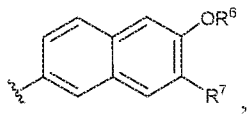
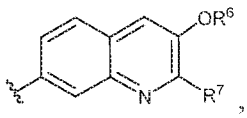
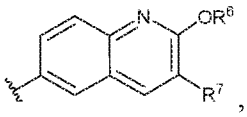
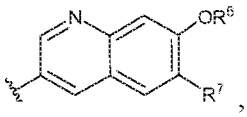
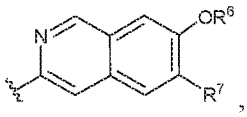
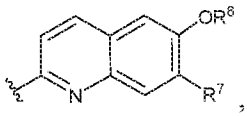

(I0h'),

(I0i'),

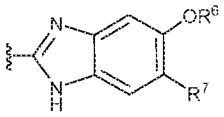
or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

12. The compound of claim 2, being of Formula (I) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

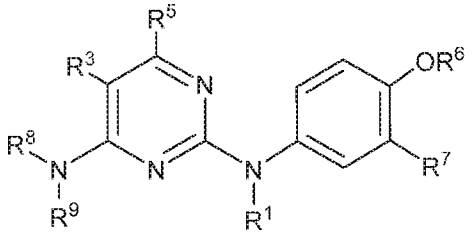
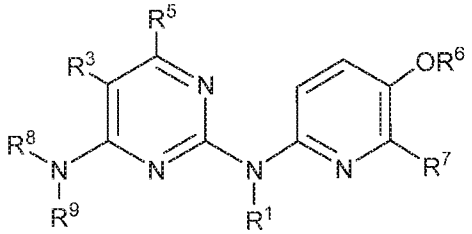
13. The compound any one of the preceding claims, wherein  is  ,

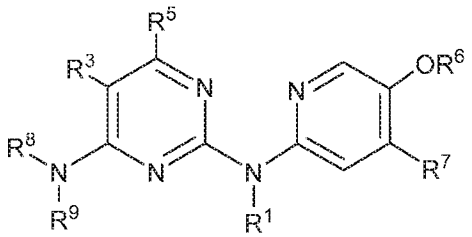
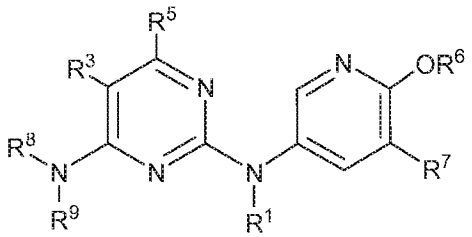
 ,  ,  ,  ,  ,

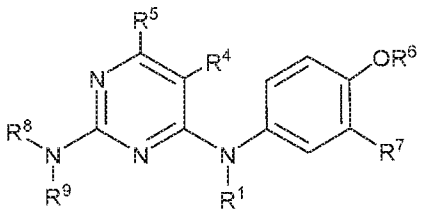
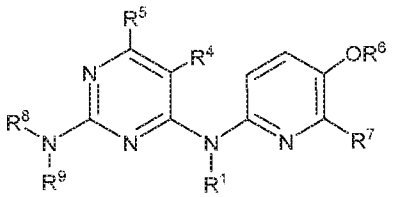
 ,  ,  ,  , or

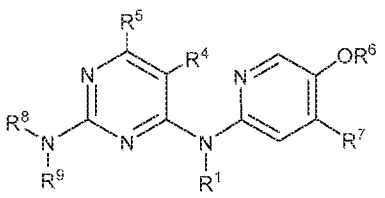
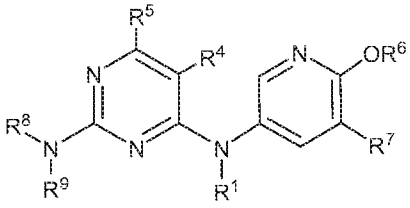
 .

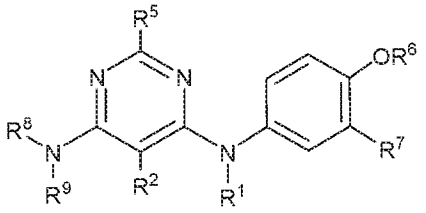
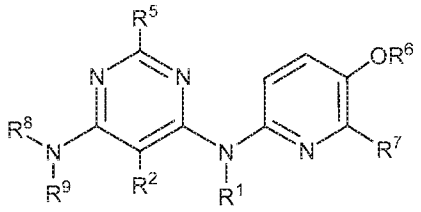
14. The compound any one of the preceding claims, being of Formula (Ia)-(Il):

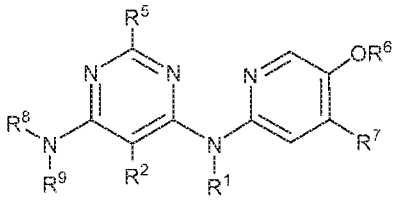
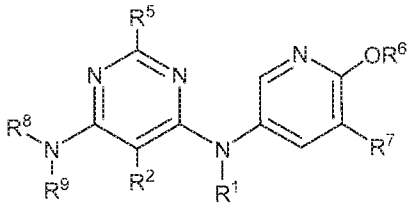
 (Ia),  (Ib),

 (Ic),  (Id),

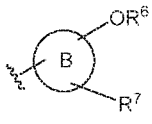
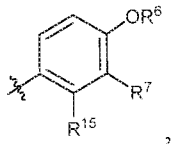
 (Ie),  (If),

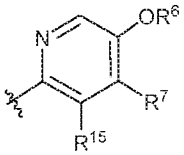
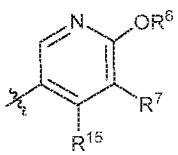
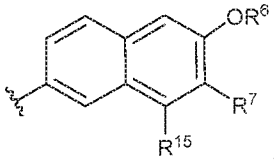
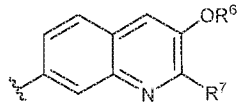
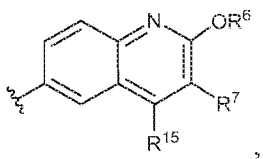
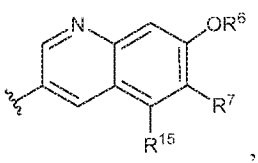
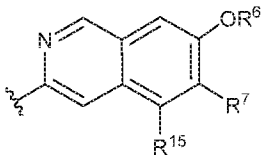
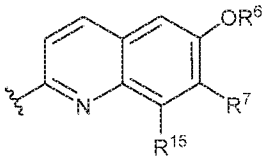
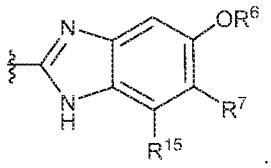
 (Ig),  (Ih),


(Ii),

(Ij),

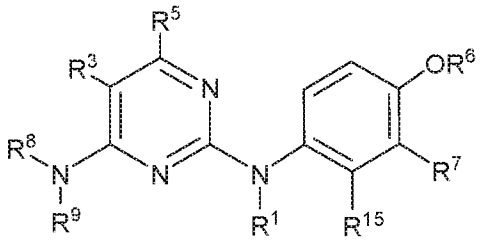
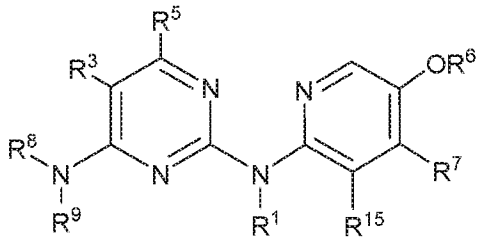

(Ik),

(Il),

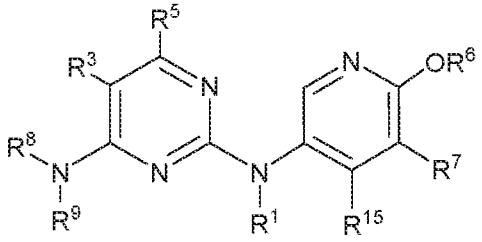
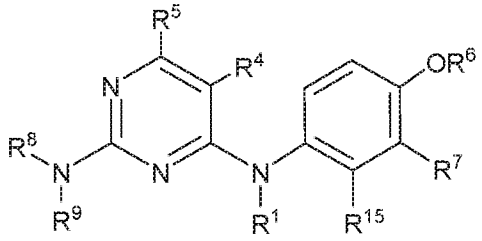
or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

15. The compound any one of the preceding claims, wherein  is  ,

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 , or
 .

16. The compound any one of the preceding claims, being of Formula (Ia')-(Ii'):


(Ia'),

(Ib'),


(Ic'),

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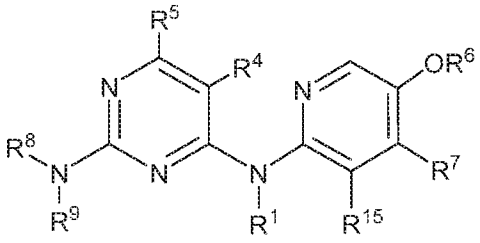
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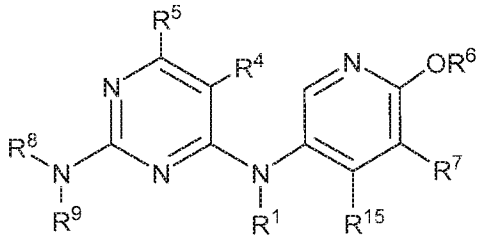
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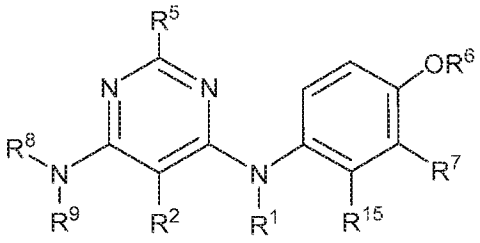
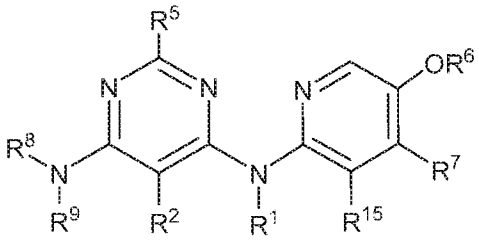
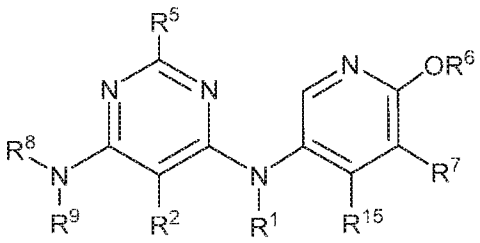

(Ig'),


(Ih'),


(Ii'),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

17. The compound of any one of the preceding claims, wherein at least one of X^1, X^2, X^3 and X^4 is N.

18. The compound of any one of the preceding claims, wherein X^1 and X^3 are N.

19. The compound of any one of the preceding claims, wherein X^1 and X^3 are N, X^2 is CR^3 and X^4 is CR^5.

20. The compound of any one of the preceding claims, wherein R^1 is C_1-C_4 alkyl.

21. The compound of any one of the preceding claims, wherein R^1 is H.

22. The compound of any one of the preceding claims, wherein at most one of R^3 and R^5 is not H.

23. The compound of any one of the preceding claims, wherein R^3 is H or halo.

24. The compound of any one of the preceding claims, wherein R^3 is H.

25. The compound of any one of the preceding claims, wherein R^5 is C_1-C_6 alkyl.

26. The compound of any one of the preceding claims, wherein at most one of R^4 and R^5 is not H.

27. The compound of any one of the preceding claims, wherein at least one of R^4 and R^5 is not H.

28. The compound of any one of the preceding claims, wherein R^4 is H, C_1-C_6 alkyl, or halo.

29. The compound of any one of the preceding claims, wherein at most one of R^2 and R^5 is not H.

30. The compound of any one of the preceding claims, wherein at least one of R^2 and R^5 is not H.

31. The compound of any one of the preceding claims, wherein R^2 is H, C_1-C_6 alkyl, or halo.

32. The compound of any one of the preceding claims, wherein R^5 is C_1-C_6 alkyl.

33. The compound of any one of the preceding claims, wherein R^6 is $-Q^1$-T^1, in which Q^1 is a bond or C_1-C_6 alkylene linker optionally substituted with one or more of halo, and T^1 is H, halo, cyano, or R^{S1}, in which R^{S1} is C_3-C_8 cycloalkyl, phenyl, 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, or a 5- or 6-membered heteroaryl and R^{S1} is optionally substituted with one or more of halo, C_1-C_6 alkyl, hydroxyl, oxo, NR^cR^d, or C_1-C_6 alkoxyl.

34. The compound of any one of the preceding claims, wherein R^6 is C_1-C_6 alkyl optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxyl.

35. The compound of any one of the preceding claims, wherein R^6 is unsubstituted C_1-C_6 alkyl.

36. The compound of any one of the preceding claims, wherein R^7 is $-Q^2$-T^2, in which Q^2 is a bond or $C(O)NR^e$, and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $-Q^3$-T^3.

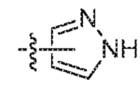
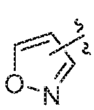
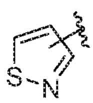
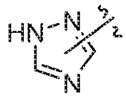
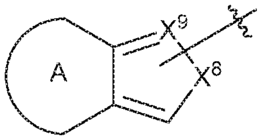
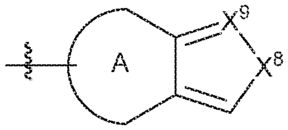
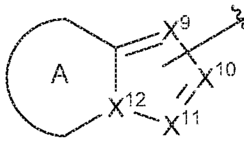
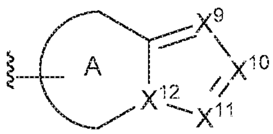
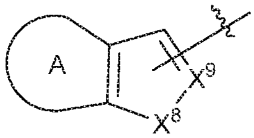
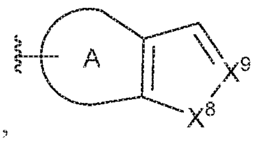
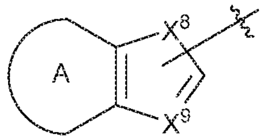
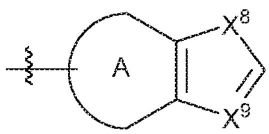
37. The compound of any one of the preceding claims, wherein R^7 is $-Q^2$-T^2, in which Q^2 is a bond, and T^2 is 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl, wherein the 5- to 10-membered heteroaryl or 4- to 12-membered heterocycloalkyl is optionally substituted with one or more $-Q^3$-T^3.

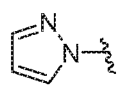
38. The compound of any one of the preceding claims, wherein T^2 is 4- to 12-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, which is optionally substituted with one or more $-Q^3$-T^3.

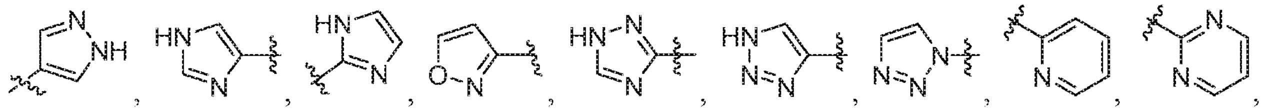
39. The compound of any one of the preceding claims, wherein T^2 is 8- to 12-membered bicyclic heterocycloalkyl that comprises a 5- or 6-membered aryl or heteroaryl ring fused with a non-aromatic ring.

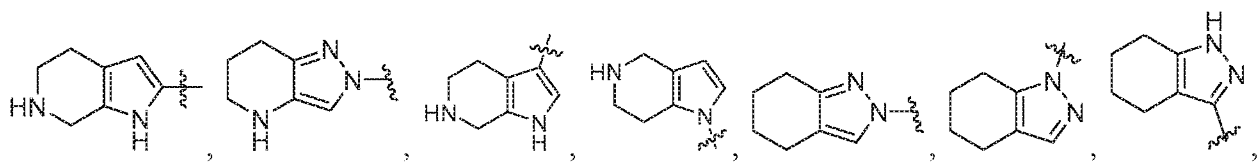
40. The compound of any one of the preceding claims, wherein T^2 is 8- to 12-membered bicyclic heterocycloalkyl that comprises a 5- or 6-membered aryl or heteroaryl ring fused with a non-aromatic ring, in which the 5- or 6-membered aryl or heteroaryl ring is connected to Q^2.

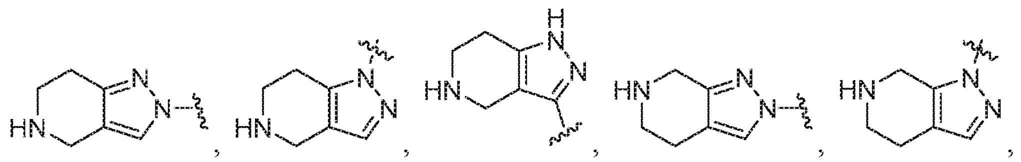
41. The compound of any one of the preceding claims, wherein T^2 is 5- to 10-membered heteroaryl.

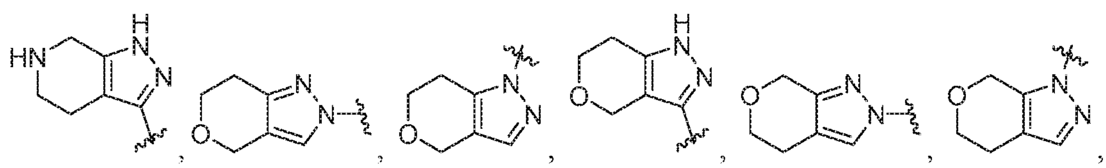
42. The compound of any one of the preceding claims, wherein T^2 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and tautomers thereof, each of which is optionally substituted with one or more $-Q^3-T^3$, wherein X^8 is NH, O, or S, each of X^9, X^{10}, X^{11}, and X^{12} is independently CH or N, and at least one of X^9, X^{10}, X^{11}, and X^{12} is N, and ring A is a C_5-C_8 cycloalkyl, phenyl, 6-membered heteroaryl, or 4- to 8-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S.

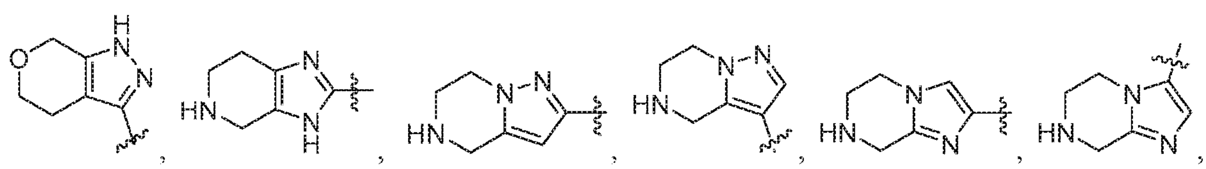
43. The compound of any one of the preceding claims, wherein T^2 is selected from  ,

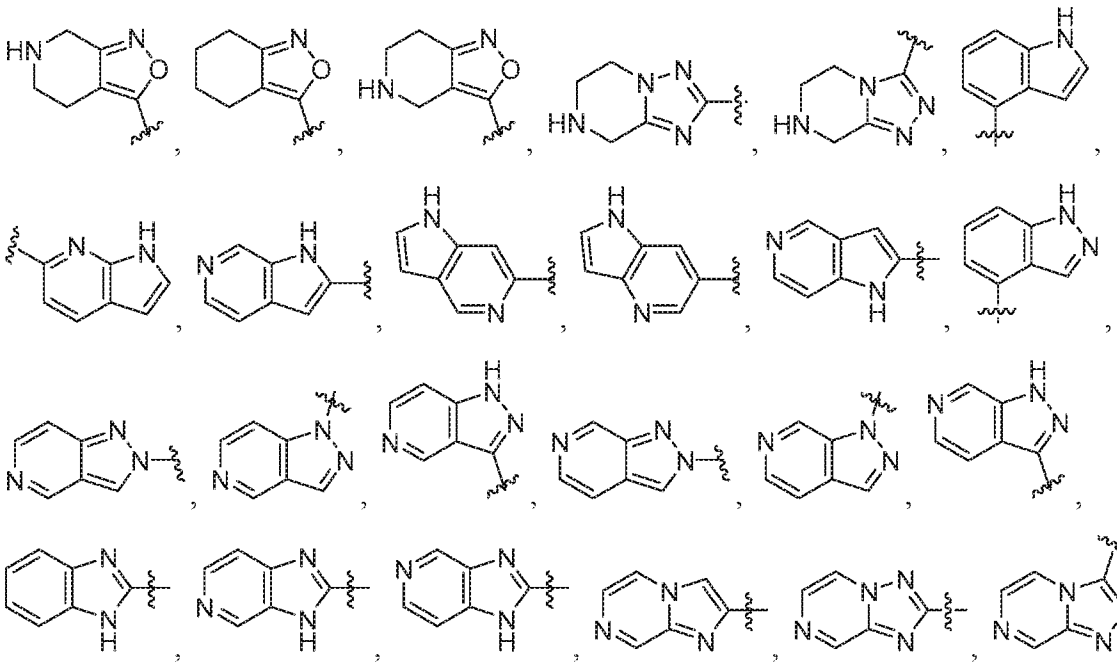




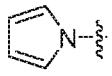


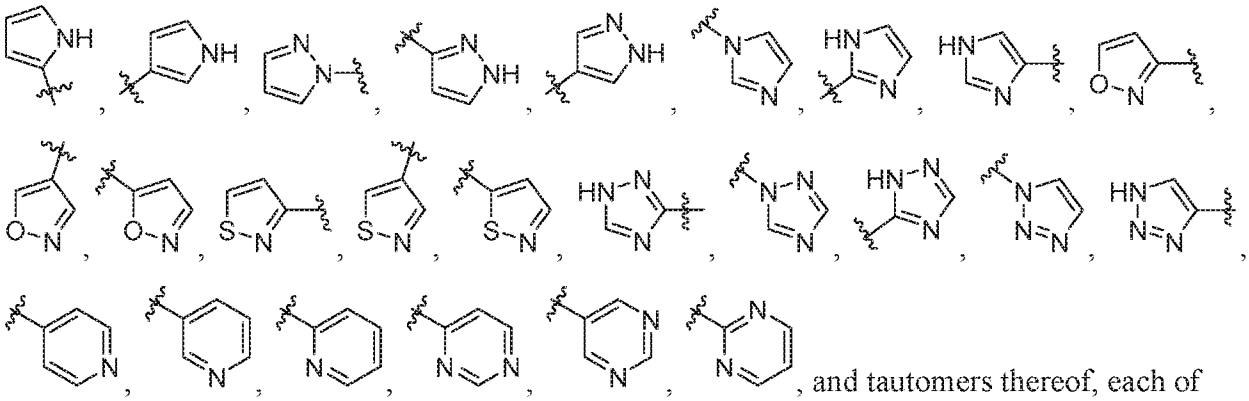




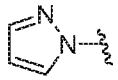


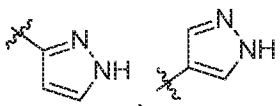
, and tautomers thereof, each of which is optionally substituted with one or more –Q^3-T^3.

44. The compound of any one of the preceding claims, wherein T^2 is selected from  ,



, and tautomers thereof, each of which is optionally substituted with one or more –Q^3-T^3.

45. The compound of any one of the preceding claims, wherein T^2 is selected from  ,



, and tautomers thereof, each of which is optionally substituted with one or more –Q^3-T^3.

46. The compound of any one of the preceding claims, wherein each Q^3 independently is a bond or C_1-C_3 alkylene linker each optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxy, and each T^3 independently is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocycloalkyl, OR^f, $C(O)R^f$, $C(O)OR^f$, NR^fR^g, $C(O)NR^fR^g$, and $NR^fC(O)R^g$, in which the C_3-C_8 cycloalkyl or 4- to 7-membered heterocycloalkyl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl or C_1-C_6 alkoxy.

47. The compound of any one of the preceding claims, wherein each Q^3 independently is a C_1-C_3 alkylene linker, and each T^3 independently is NR^fR^g, each of R^f and R^g independently being H, C_3-C_8 cycloalkyl, or C_1-C_6 alkyl optionally substituted with C_3-C_8 cycloalkyl, in which the C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl is optionally substituted with one or more halo, cyano, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy.

48. The compound of any one of the preceding claims, wherein at least one of R^8 and R^9 is H.

49. The compound of any one of the preceding claims, wherein each of R^8 and R^9 is H.

50. The compound of any one of the preceding claims, wherein R^8 is H.

51. The compound of any one of the preceding claims, wherein R^9 is $-Q^4$-T^4, in which Q^4 is a bond or C_1-C_6 alkylene linker optionally substituted with one or more of halo, cyano, hydroxyl, or C_1-C_6 alkoxyl, and T^4 is H, halo, OR^h, NR^hR^i, $NR^hC(O)R^i$, $C(O)NR^hR^i$, $C(O)R^h$, $C(O)OR^h$, or R^{S2}, in which R^{S2} is C_3-C_8 cycloalkyl or 4- to 7-membered heterocycloalkyl, and R^{S2} is optionally substituted with one or more $-Q^5$-T^5.

52. The compound of any one of the preceding claims, wherein Q^4 is C_1-C_6 alkylene, and T^4 is H.

53. The compound of any one of the preceding claims, wherein each Q^5 independently is a bond or C_1-C_3 alkylene linker.

54. The compound of any one of the preceding claims, wherein each T^5 independently is selected from the group consisting of H, halo, cyano, C_1-C_6 alkyl, OR^j, $C(O)R^j$, $C(O)OR^j$, NR^jR^k, $C(O)NR^jR^k$, and $NR^jC(O)R^k$.

55. The compound of any one of the preceding claims, wherein R^9 is C_1-C_3 alkyl.

56. The compound of any one of the preceding claims, wherein R^{14} is H, halo, or C_1-C_6 alkyl.

57. The compound of any one of the preceding claims, wherein R^{14} is halo or $-OR^6$.

58. The compound of any one of the preceding claims, wherein R^{14} is halo.

59. The compound of any one of the preceding claims, wherein R^{14} is $-OR^6$.

60. The compound of any one of the preceding claims, wherein R^{15} is H or halo.

61. The compound of any one of the preceding claims, wherein R^{15} is H.

62. The compound of any one of the preceding claims, wherein R^{15} is H or halo.

63. The compound of any one of the preceding claims, wherein R^{14} is halo, and R^{15} is H.

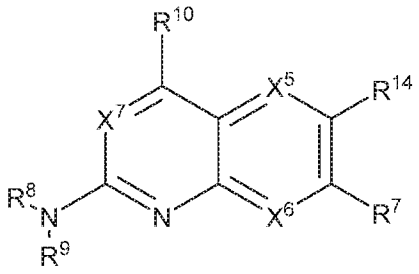
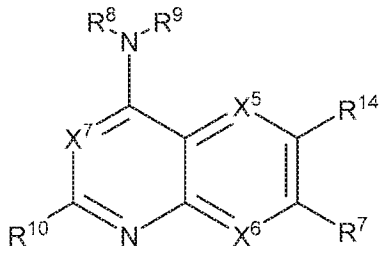
64. The compound of any one of the preceding claims, wherein R^{14} is $-OR^6$, and R^{15} is H.

65. The compound of any one of the preceding claims, wherein R^{14} is halo, and R^{15} is halo.

66. The compound of any one of the preceding claims, wherein R^{14} is $-OR^6$, and R^{15} is halo.

67. The compound of claim 1, being of Formula (II0) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

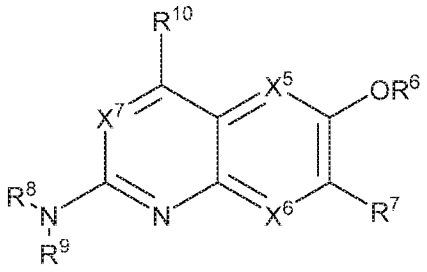
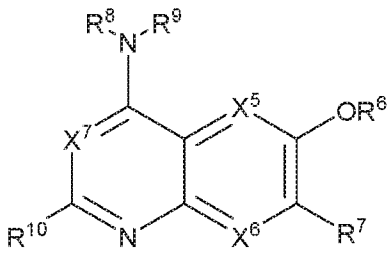
68. The compound of any one of the preceding claims, being of Formulae (II0a) or (II0b):


(II0a),

(II0b),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

69. The compound of claim 2, wherein the compound is of Formula (II), or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

70. The compound of any one of the preceding claims, being of Formula (IIa) or (IIb):


(II0a),

(II0b),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

71. The compound of any one of the preceding claims, wherein each of X^5, X^6 and X^7 is CH.

72. The compound of any one of the preceding claims, wherein at least one of X^5, X^6 and X^7 is N.

73. The compound of any one of the preceding claims, wherein at most one of X^5, X^6 and X^7 is N.

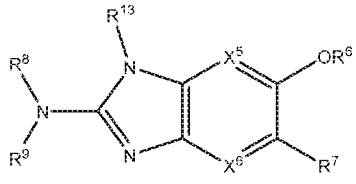
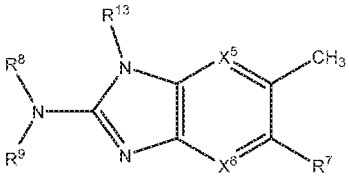
74. The compound of any one of the preceding claims, wherein R^{10} is optionally substituted 4- to 7-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S.

75. The compound of any one of the preceding claims, wherein R^{10} is connected to the bicyclic group of Formula (II) via a carbon-carbon bond.

76. The compound of any one of the preceding claims, wherein R^{10} is connected to the bicyclic group of Formula (II) via a carbon-nitrogen bond.

77. The compound of claim 1, wherein the compound is of Formula (III0) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

78. The compound of any one of the preceding claims, being of Formula (III0a) or (III0b):


(III0a),

(III0b),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

79. The compound of claim 2, being of Formula (III) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

80. The compound of any one of the preceding claims, wherein R^{11} and R^{12} together with the carbon atom to which they are attached form a 4- to 7-membered heterocycloalkyl containing 1-4 heteroatoms selected from N, O, and S, wherein the 4- to 7-membered heterocycloalkyl is optionally substituted with one or more of halo, C_1-C_6 alkyl, hydroxyl, oxo, amino, mono- or di-alkylamino, or C_1-C_6 alkoxyl.

81. The compound of any one of the preceding claims, wherein R^{11} and R^{12} together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl which is optionally substituted with one or more of halo, C_1-C_6 alkyl, hydroxyl, oxo, amino, mono- or di- alkylamino, or C_1-C_6 alkoxyl.

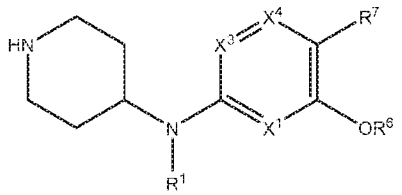
82. The compound of any one of the preceding claims, wherein each of X^5 and X^6 is CH.

83. The compound of any one of the preceding claims, wherein each of X^5 and X^6 is N.

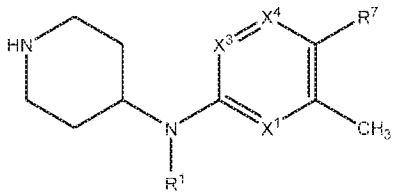
84. The compound of any one of the preceding claims, wherein one of X^5 and X^6 is CH and the other is CH.

85. The compound of claim 1, being of Formula (IV0) or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

86. The compound of any one of the preceding claims, being of Formula (IV0a) or (IV0b):



(IV0a), or



(IV0b),

or a tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

87. The compound of any one of the preceding claims, wherein the compound is selected from those in Table 1 and pharmaceutically acceptable salts thereof.

88. The compound of any one of the preceding claims, wherein the compound inhibits a kinase with an enzyme inhibition IC_{50} value of about 100 nM or greater, 1 μM or greater, 10 μM or greater, 100 μM or greater, or 1000 μM or greater.

89. The compound of any one of the preceding claims, wherein the compound inhibits a kinase with an enzyme inhibition IC_{50} value of about 1 mM or greater.

90. The compound of any one of the preceding claims, wherein the compound inhibits a kinase with an enzyme inhibition IC_{50} value of 1 μM or greater, 2 μM or greater, 5 μM or greater, or 10 μM or greater, wherein the kinase is one or more of the following: AbI, AurA, CHK1, MAP4K, IRAK4, JAK3, EphA2, FGFR3, KDR, Lck, MARK1, MNK2, PKCb2, SIK, and Src.

91. A pharmaceutical composition comprising a compound of any one of the preceding claims and a pharmaceutically acceptable carrier.

92. A method of preventing or treating a blood disorder via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of the preceding claims.

93. The method of any one of the preceding claims, wherein the blood disorder is sickle cell anemia or β-thalassemia.

94. The method of any one of the preceding claims, wherein the blood disorder is a hematological cancer.

95. A method of preventing or treating a cancer via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of the preceding claims.

96. The method of claim 95, wherein the cancer is lymphoma, leukemia, melanoma, breast cancer, ovarian cancer, hepatocellular carcinoma, prostate carcinoma, lung cancer, brain cancer, or hematological cancer.

97. The method of any one of the preceding claims, wherein the hematological cancer is acute myeloid leukemia (AML) or chronic lymphocytic leukemia (CLL).

98. The method claim 96, wherein the lymphoma is diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma or Non-Hodgkin's Lymphoma.

99. The method of claim 95, wherein the cancer is chronic myelogenous leukemia (CML), acute myeloid leukemia, acute lymphocytic leukemia or mixed lineage leukemia, or myelodysplastic syndromes (MDS).

100. The method of any one of the preceding claims, wherein a compound of any of Formulae (I0)-(IV0) or (I)-(III) is a selective inhibitor of EHMT2.

101. A compound of any one of the preceding claims for use in preventing or treating a blood disorder via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2.

102. The compound of any one of the preceding claims, wherein the blood disorder is sickle cell anemia or β-thalassemia.

103. The compound of any one of the preceding claims, wherein the blood disorder is a hematological cancer.

104. A compound of any one of the preceding claims for use in preventing or treating a cancer via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2.

105. The compound of any one of the preceding claims, wherein the cancer is lymphoma, leukemia, melanoma, breast cancer, ovarian cancer, hepatocellular carcinoma, prostate carcinoma, lung cancer, brain cancer, or hematological cancer.

106. The compound of any one of the preceding claims, wherein the hematological cancer is acute myeloid leukemia (AML) or chronic lymphocytic leukemia (CLL).

107. The compound of any one of the preceding claims, wherein the lymphoma is diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma or Non-Hodgkin's Lymphoma.

108. The compound of any one of the preceding claims, wherein the cancer is chronic myelogenous leukemia (CML), acute myeloid leukemia, acute lymphocytic leukemia or mixed lineage leukemia, or myelodysplastic syndromes (MDS).

109. The compound of any one of the preceding claims, wherein the compound of any of Formulae (I0)-(IV0) or (I)-(III) is a selective inhibitor of EHMT2.

110. Use of a compound of any one of the preceding claims in manufacture of a medicament for preventing or treating a blood disorder via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2.

111. The use of any one of the preceding claims, wherein the blood disorder is sickle cell anemia or β-thalassemia.

112. The use of any one of the preceding claims, wherein the blood disorder is a hematological cancer.

113. Use of a compound of any one of the preceding claims in manufacture of a medicament for preventing or treating a cancer via inhibition of a methyltransferase enzyme selected from EHMT1 and EHMT2.

114. The use of any one of the preceding claims, wherein the cancer is lymphoma, leukemia, melanoma, breast cancer, ovarian cancer, hepatocellular carcinoma, prostate carcinoma, lung cancer, brain cancer, or hematological cancer.

115. The use of any one of the preceding claims, wherein the hematological cancer is acute myeloid leukemia (AML) or chronic lymphocytic leukemia (CLL).

116. The use of any one of the preceding claims, wherein the lymphoma is diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma or Non-Hodgkin's Lymphoma.

117. The use of any one of the preceding claims, wherein the cancer is chronic myelogenous leukemia (CML), acute myeloid leukemia, acute lymphocytic leukemia or mixed lineage leukemia, or myelodysplastic syndromes (MDS).

118. The use of any one of the preceding claims, wherein the compound of any of Formulae (I0)-(IV0) or (I)-(III) is a selective inhibitor of EHMT2.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/067192

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D403/14 C07D413/12 C07D471/04 C07D487/04
C07D491/04 C07D491/14 C07D498/04 A61P35/00 A61K31/519
ADD.
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)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FENG LIU ET AL: "Discovery of an in Vivo Chemical Probe of the Lysine Methyltransferases G9a and GLP", JOURNAL OF MEDICINAL CHEMISTRY, vol. 56, no. 21, 31 October 2013 (2013-10-31), pages 8931-8942, XP055456510, ISSN: 0022-2623, DOI: 10.1021/jm401480r table 4, compounds 7,13-18; abstract ----- -/--	1-66, 87-118

[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
7 March 2018	16/05/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schmid, Arnold

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/067192

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HUANG ET AL: "N^4-Phenyl modifications of N^2-(2-hydroxyl)ethyl-6-(pyrrolidin-1-yl)-1,3,5-triazine-2,4-diamines enhance glucocerebrosidase inhibition by small molecules with potential as chemical chaperones for Gaucher disease", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 17, no. 21, 1 November 2007 (2007-11-01), pages 5783-5789, XP022267173, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2007.08.050 abstract; compound 44	1-66
X	US 2002/143176 A1 (LIU CHUNJIAN [US] ET AL) 3 October 2002 (2002-10-03) page 1, paragraph 2; examples 17,18,23-25,27,29,31,32,35-37,40,43-45	1-66
X	PITTS W J ET AL: "Rapid synthesis of triazine inhibitors of inosine monophosphate dehydrogenase", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 12, no. 16, 1 January 2002 (2002-01-01), pages 2137-2140, XP002378610, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(02)00351-7 abstract; compounds 5a-5r (table 1)	1-66
X	WO 00/25780 A1 (SQUIBB BRISTOL MYERS CO [US]) 11 May 2000 (2000-05-11) page 1, line 9 - page 1, line 16; examples 104-108,110-194,209,212,214-241,244	1-66
X,P	WO 2017/181177 A1 (EPIZYME INC [US]) 19 October 2017 (2017-10-19) CAPLUS-RN: 2140155-56-0, 2140155-57-1, 2140157-62-4, 2140157-63-5, 2140162-26-9, 2140162-27-0, 2140163-48-8, 2140163-49-9, 2140163-50-2	1-66, 87-118

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/067192

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
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:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an 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.:

3-35(completely); 1, 2, 36-66, 87-118(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3-35(completely); 1, 2, 36-66, 87-118(partially)

   compounds (I0), compositions comprising them, their use and methods

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2. claims: 67-76(completely); 1, 2, 36-66, 87-118(partially)

   compounds (II0), compositions comprising them, their use and methods

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3. claims: 77-84(completely); 1, 2, 36-66, 87-118(partially)

   compounds (III0), compositions comprising them, their use and methods

   ---

4. claims: 85, 86(completely); 1, 2, 36-66, 87-118(partially)

   compounds (IV0), compositions comprising them, their use and methods

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/067192

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		EP 1448187 A2	25-08-2004
		US 2002143176 A1	03-10-2002
		WO 03047512 A2	12-06-2003
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