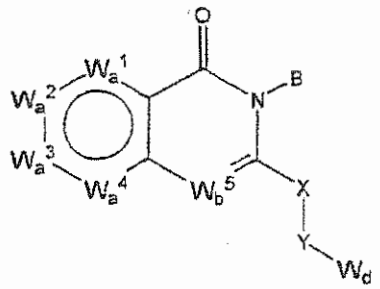
[0007] The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3K δ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3K δ is integrally involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its integral role in immune system function, PI3K δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. Other class I PI3K involved in immune system function includes PI3K γ, which plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

[0008] Downstream mediators of the PI3K signal transduction pathway include Akt and mammalian target of rapamycin (mTOR). Akt possesses a pleckstrin homology (PH) domain that binds PIP3, leading to Akt kinase activation. Akt phosphorylates many substrates and is a central downstream effector of PI3K for diverse cellular responses. One important function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechanisms. mTOR is a serine-threonine kinase related to the lipid kinases of the PI3K family. mTOR has been implicated in a wide range of biological processes including cell growth, cell proliferation, cell motility and survival. Disregulation of the mTOR pathway has been reported in various types of cancer. mTOR is a multifunctional kinase that integrates growth factor and nutrient signals to regulate protein translation, nutrient uptake, autophagy, and mitochondrial function.

[0009] As such, kinases, particularly PI3Ks are prime targets for drug development. There remains a need for PI3K inhibitors suitable for drug development. The present invention addresses this need and provides related advantages as well by providing new classes of kinase inhibitors.

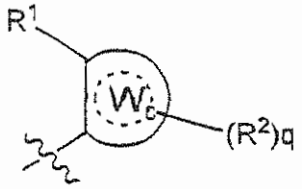
SUMMARY ~~OF THE INVENTION~~

[0010] The disclosure provides~~In a first aspect of the invention,~~ compounds ~~are provided~~ which are of Formula I, or their pharmaceutically acceptable salts thereof, wherein



Formula I

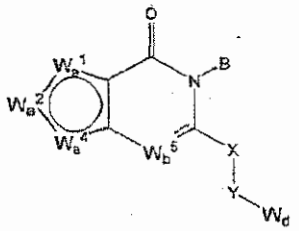
[0011] W_a^1 is CR^3 or N; W_a^2 is CR^5 or N; W_a^3 is CR^6 or N; W_a^4 is N or CR^7; W_b^5 is CR^8, CHR^8, or N, wherein no more than two adjacent ring atoms selected from W_a^1, W_a^2, W_a^3, W_a^4, and W_b^5 are heteroatoms. W_d is heterocycloalkyl, aryl or heteroaryl. B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II;



Formula II

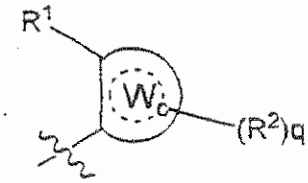
[0012] wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4. X is absent or is –(CH(R^9))$_z$-and each instance of z is independently an integer of 1, 2, 3, or 4. Y is absent, –O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^9)-, -C(=O)-(CHR^9)$_z$-, -C(=O)-, -N(R^9)-C(=O)-, or -N(R^9)-C(=O)NH-,-N(R^9)C(R^9)$_2$-, or -C(=O)-(CHR^9)$_z$-;, wherein when W_b^5 is N, no more than one of X or Y is absent. R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate. R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate. R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxy or nitro. R^5, R^6, R^7, and R^8 are independently hydrogen, C_1-C_6alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, heterocycloalkyl, C_1-C_6heteroalkyl, C_1-C_6alkoxy, C_1-C_4amido, amino, acyl, C_1-C_4acyloxy, C_1-C_4sulfonamido, halo, cyano, hydroxy or nitro. Each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_2-C_7cycloalkyl, or C_2-C_{10}heteroalkyl.

[0013] The disclosure also provides~~In another aspect of the invention,~~ compounds ~~are provided~~ which are of Formula IX or their pharmaceutically acceptable salts thereof, wherein



Formula IX

W_a^1 and W_a^2 are independently CR^5, S, N, or NR^4, and W_a^4 is independently CR^7, S, N, or NR^4 wherein no more than two adjacent ring atoms are nitrogen or sulfur, and when W_a^1 is S, one of W_a^2 and W_a^4 is N or NR^4. W_b^5 is CR^8, N, or NR^8. B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II:

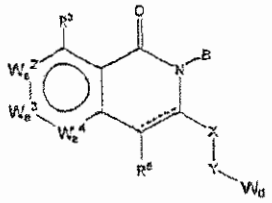


Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4. W_d is absent or is a heterocycloalkyl, aryl or heteroaryl moiety. X is absent or is –(CH(R^9))$_z$-and each instance of z independently is an integer of 1, 2, 3, or 4. Y is absent, -O-, -S-, -S(=O)-, -S(=O)2-, -N(R9)-, -C(=O)-(CHR9)z-, -C(=O)-, -N(R9)-C(=O)-, or -N(R9)-C(=O)NH-,-N(R9)C(R9)2-, or -C(=O)-(CHR9)z-. R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy,

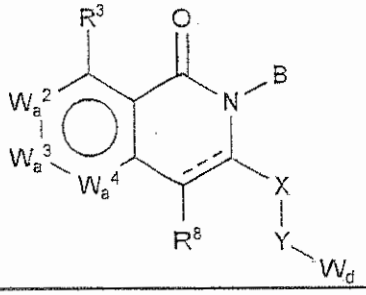
amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate. R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl,sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate. R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxy or nitro. R^4 is hydrogen, acyl, C_1-C_6alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, or C_1-C_6heteroalkyl; R^5, R^7, and R^8 are independently hydrogen, C_1-C_6alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, C_1-C_6heteroalkyl, acyl, C_1-C_6alkoxy, C_1-C_6amido, amino, C_1-C_6acyloxy, C_1-C_6sulfonamido, halo, cyano, hydroxy or nitro. Each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, or C_2-C_{10}heteroalkyl.

[0014] In some embodiments, the compound of Formula I has a structure of Formula IV:



Formula IV

[0014a] In a first aspect, there is provided a compound of Formula IV:



Formula IV,

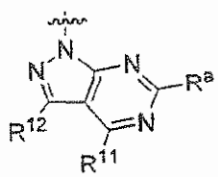
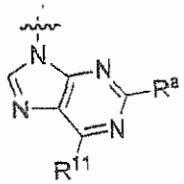
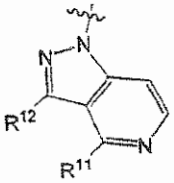
or a pharmaceutically acceptable salt thereof, wherein

W_a^2 is CR^5 or N;

W_a^3 is CR^6 or N;

W_a^4 is CR^7 or N;

wherein no more than two adjacent ring atoms selected from W_a^2, W_a^3, and W_a^4 are heteroatoms;

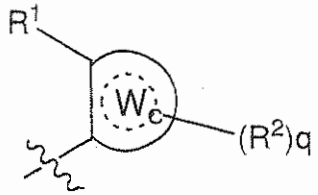
W_d is  ,  , or  ;

R^a is hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl;

R^{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, or alkoxy;

R^{12} is hydrogen, alkyl, cyano, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, amino, carboxylic acid, alkoxycarbonyl, or amido;

B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II:



Formula II;

W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

q is an integer of 0, 1, 2, 3, or 4;

X is $-(CH(R^9))_z-$;

Y is absent;

z is 1;

R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

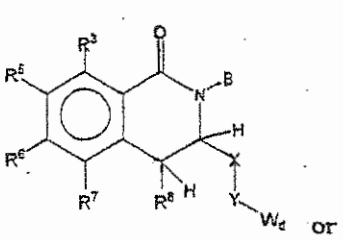
R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, or nitro;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl, or heteroaryl;

R^5, R^6, R^7, and R^8 are independently hydrogen, C_1–C_4alkyl, C_2–C_5alkenyl, C_2–C_5alkynyl, C_3–C_5cycloalkyl, C_1–C_4heteroalkyl, C_1–C_4alkoxy, C_1–C_4amido, amino, acyl, C_1–C_4acyloxy, C_1–C_4sulfonamido, halo, cyano, hydroxy, or nitro; and

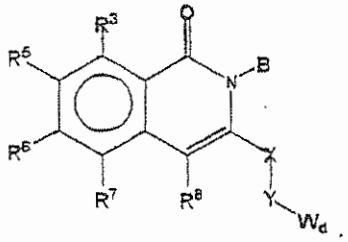
each instance R^9 is independently hydrogen, C_1–C_{10}alkyl, C_3–C_7cycloalkyl, or C_2–C_{10}heteroalkyl.

[0015] In some embodiments a compound of Formula IV is of Formula V or VI:



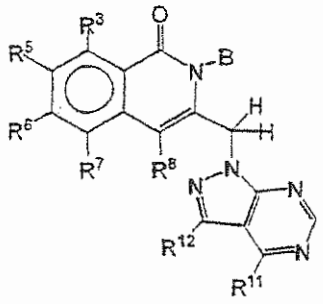
Formula V

or



Formula VI

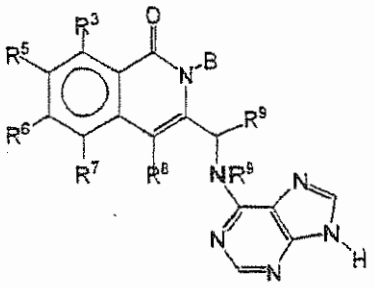
[0016] In some embodiments, the compound of Formula VI has the structure of Formula VI-A:



Formula VI-A

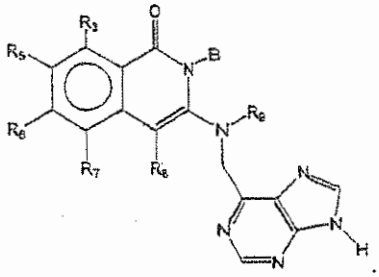
[0017] In some embodiments of the compound of Formula VI-A, R^{11} is amino. In some embodiments of the compound of Formula VI-A, R^{12} is alkyl, alkenyl, alkynyl, heteroaryl, aryl, heterocycloalkyl, cyano, amino, carboxylic acid, or amido. In some embodiments of the compound of Formula VI-A, R^{12} is a monocyclic heteroaryl or a bicyclic heteroaryl.

[0018] In some embodiments of the compound of Formula VI, the compound has the structure of Formula VI-C:

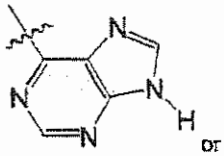
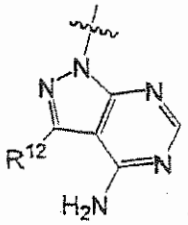


Formula VI-C

[0019] In some of the embodiments of Formula VI, the compound has a structure of Formula VI-D;



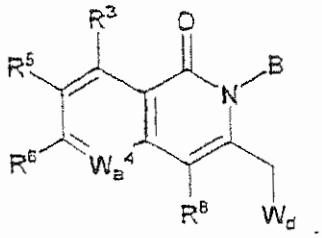
Formula VI-D

[0020] The disclosure also provides~~In another aspect of the invention~~ a compound or its pharmaceutically acceptable salts having the structure of Formula VI is provided, wherein: B is alkyl, amino, heteroalkyl, or a moiety of Formula II; wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4; X is absent or $-(CH(R^9))_z$-and z is an integer of 1, 2, 3, or 4; Y is absent, $-N(R^9)-$, or $-N(R^9)-CH(R^9)-$; W_d is:  or ;

[0021] R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate; R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, or phosphate;

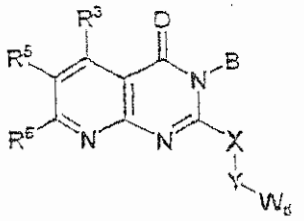
[0022] R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl or heteroaryl; each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, or C_2-C_{10}heteroalkyl; andR^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, cyano, amino, carboxylic acid, alkoxycarbonyl or amido.

[0023] In some embodiments, the compound of Formula VI has the structure of Formula 6-A:



Formula VII

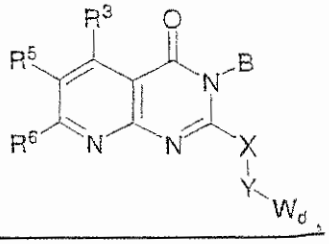
[0028] In some embodiments, the compound of Formula I has a structure of Formula VIII:



Formula VIII

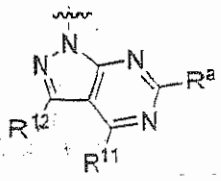
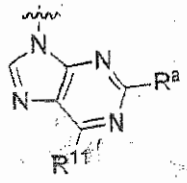
where X is absent and Y is -O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^5)-, -C(=O)-(CHR^5)$_z$-, -C(=O)-, -N(R^5)(C=O)-, or -N(R^5)(C=O)NH-;or X is –(CH(R^5))$_z$-, and Y is absent; or X is –(CH(R^5))$_z$-, and Y is O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^5)-, -C(=O)-(CHR^5)$_z$-, -C(=O)-, -N(R^5)-C(=O)-, or -N(R^5)-C(=O)NH-,-N(R^5)C(R^5)$_2$-, or -C(=O)-(CHR^5)$_z$. Each instance of z independently is an integer of 1, 2, 3, or 4. W_d is bicyclic aryl or bicyclic heteroaryl.

[0028a] In a second aspect, there is provided a compound of Formula VIII-A:



Formula VIII-A

or a pharmaceutically acceptable salt thereof, wherein

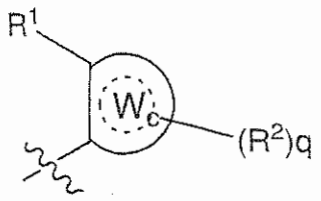
W_d is  or ;

R^a is hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl;

R^{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, or alkoxy;

R^{12} is hydrogen, alkyl, cyano, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, amino, carboxylic acid, alkoxycarbonyl, or amido;

B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II:



Formula II;

W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

q is an integer of 0, 1, 2, 3, or 4;

X is $-(CH(R^9))_z-$;

Y is absent;

z is 1;

R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

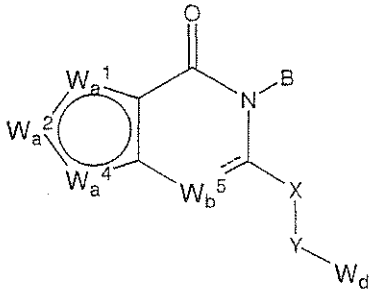
R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, or nitro;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl, or heteroaryl;

R^5 and R^6 are independently hydrogen, C_1–C_4alkyl, C_2–C_5alkenyl, C_2–C_5alkynyl, C_3–C_5cycloalkyl, C_1–C_4heteroalkyl, C_1–C_4alkoxy, C_1–C_4amido, amino, acyl, C_1–C_4acyloxy, C_1–C_4sulfonamido, halo, cyano, hydroxy, or nitro; and

each R^9 is independently hydrogen, C_1–C_{10}alkyl, C_3–C_7cycloalkyl, or C_2–C_{10}heteroalkyl.

[0028b] In a third aspect, there is provided a compound of Formula IX:



Formula IX

or a pharmaceutically acceptable salt thereof,

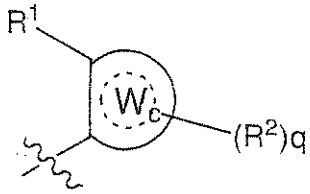
wherein W_a^1 and W_a^2 are independently CR^5, S, N, or NR^4, and

W_a^4 is independently CR^7, S, N, or NR^4;

wherein no more than two adjacent ring atoms are nitrogen or sulfur, and when W_a^1 is S, one of W_a^2 and W_a^4 is N or NR^4;

W_b^5 is CR^8, N, or NR^8;

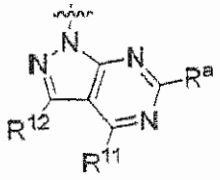
B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II;



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

q is an integer of 0, 1, 2, 3, or 4;



W_d is ;

R_a is hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl;

R_{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, or alkoxy;

R_{12} is hydrogen, alkyl, cyano, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, amino, carboxylic acid, alkoxycarbonyl, or amido;

X is $-(CH(R^9))_z-$;

each instance of z independently is an interger of 1;

Y is absent;

R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro;

R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

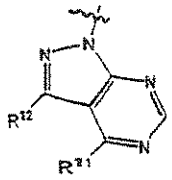
R^4 is hydrogen, acyl, C_1-C_4alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, or C_1-C_4heteroalkyl;

R^5, R^7, and R^8 are independently hydrogen, C_1-C_4alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, C_1-C_4heteroalkyl, acyl, C_1-C_4alkoxy, C_1-C_4amido, amino, C_1-C_4acyloxy, C_1-C_4sulfonamido, halo, cyano, hydroxy or nitro; and

each instance R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, or C_2-C_{10}heteroalkyl.

[0029] In some embodiments of the compound of Formula IX, the compound has a structure which is a member of the group consisting of : (*i*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is CR^7, and W_b^5 is CR^8; (*ii*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is CR^7, and W_b^5 is CHR^8; (*iii*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is CR^7, and W_b^5 is N; (*iv*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is CR^7, and W_b^5 is NR^8; (*v*) W_a^1 is NR^4, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CR^8; (*vi*) W_a^1 is NR^4, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CHR^8; (*vii*) W_a^1 is NR^4, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is N; (*viii*) W_a^1 is NR^4, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is NR^8; (*ix*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is CR^8; (*x*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is CHR^8; (*xi*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is N; (*xii*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is NR^8; (*xiii*) W_a^1 is S, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is CR^8; (*xiv*) W_a^1 is S, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is CHR^8; (*xv*) W_a^1 is S, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is N; (*xvi*) W_a^1 is S, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is NR^8; (*xvii*) W_a^1 is N, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is CR^8; (*xviii*) W_a^1 is N, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is CHR^8; (*xix*) W_a^1 is N, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is N; (*xx*) W_a^1 is N, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is NR^8; (*xxi*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is CR^8; (*xxi*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is CHR^8; (*xxii*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is N; (*xxiii*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is NR^8; (*xxiv*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CR^8; (*xxv*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CHR^8; (*xxvi*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is N; (*xxvii*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is NR^8; (*xxviii*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is NR^4, and W_b^5 is CR^8; (*xxix*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is NR^4, and W_b^5 is CHR^8; (*xxx*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is NR^4, and W_b^5 is N; (*xxxi*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is NR^4, and W_b^5 is NR^8; (*xxxii*) W_a^1 is CR^5, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is CHR^8; (*xxxiii*) W_a^1 is CR^5, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is CR^8; (*xxxiv*) W_a^1 is CR^5, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is N; and (*xxxv*) W_a^1 is CR^5, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is NR^8.

[0030] In some embodiments of the invention, the compound of Formula IX is of Formula X:



Formula III

wherein R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} is is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl including but not limited to monocyclic or bicyclic heteroaryl, heterocycloalkyl, cycloalkyl, cyano, amino, carboxylic acid, alkoxycarbonyl, or amido.

[0047] The disclosure also provides~~In another aspect of the invention~~, a method of inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase)~~, is provided~~ comprising: contacting the PI3 kinase with an effective amount of one or more compounds disclosed herein. For instance, the step of contacting involves the use of one or more compounds of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, and/or XIV. In some embodiments, the step of contacting comprises contacting a cell that contains said PI3 kinase. In some embodiments of the method, the inhibition takes place in a subject suffering from a disorder involving malfunctioning of one or more types of PI3 kinase. Some exemplary diseases involving malfunctioning of PI3 kinases are selected from the group consisting of autoimmune diseases, rheumatoid arthritis, respiratory disease, and various types of cancers. Where desired, the compound used in the method has the structure of Formula 6-A, wherein R^{11} is amino and R^{12} is substituted phenyl.

[0048] In some embodiments of the method, the inhibition takes place in a subject suffering from rheumatoid arthritis or a respiratory disease, and wherein the compound has the structure of Formula 6-A, and wherein R^{11} is amino and R^{12} is bicyclic heteroaryl.

[0049] In some embodiments, the method comprises administering a second therapeutic agent to the subject.

[0050] The disclosure also~~In yet another aspect, the present invention~~ provides a method of treating a disease manifesting an undesired immune response. The method comprises the step of administering to a subject in need thereof, one or more compounds disclosed herein including compounds of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, and/or XIV, in an amount that is effective in ameliorating said undesired immune response. In some embodiments, the one or more compounds inhibit T-cell independent B-cell activation as evidenced by a reduction in production of anti-TNP IgG3 by at least about five folds when administered in an amount less than about 30mg/kg BID dose to a test animal.

[0051] In some embodiments, the disease treated is associated with swelling or pain of a joint of a subject. The method can be effective in ameliorating one or more rheumatoid arthritis symptoms as evidenced by reduction in mean joint diameter by at least about 10% after 17 days and/or reduction in ankle diameter by at least 5-10% or more after several days to weeks of treatment, including for example reduction in ankle diameter by at least 5% after 7 days of treatment. In another embodiment, the undesired immune response is evidenced by enhanced production of anti-type II collagen antibodies, and the use of one or more subject compounds reduces the serum anti-type II collagen level at an ED50 of less than about 10 mg/kg.

[0052] The disclosure also provides~~In another aspect of the invention,~~ a composition~~is provided~~ which comprises a pharmaceutically acceptable excipient and one or more compounds of Formula I, IV, V, VI, VII, VIII , IX, X, XI, XII, XIII and/or XIV. In some of the embodiments of the invention, the composition is a liquid, solid, semi-solid, gel, or an aerosol form.

[0052a] In a fourth aspect, there is provided a composition comprising a pharmaceutically acceptable excipient and a compound as defined above.

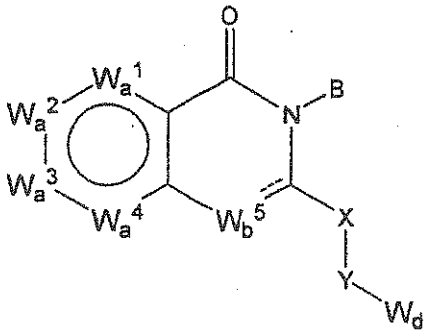
INCORPORATION BY REFERENCE

[0053] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

W_a^1 is CR^3 or N;

W_a^2 is CR^5 or N;

W_a^3 is CR^6 or N;

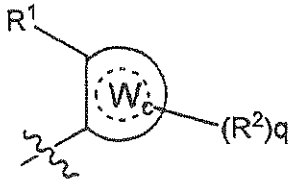
W_a^4 is N or CR^7;

W_b^5 is CR^8, CHR^8, or N,

wherein no more than two adjacent ring atoms selected from W_a^1, W_a^2, W_a^3, W_a^4, and W_b^5 are heteroatoms;

W_d is heterocycloalkyl, aryl or heteroaryl;

B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II;



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and
q is an integer of 0, 1, 2, 3, or 4;

X is absent or is $-(CH(R^9))_z-$ and each instance of z is independently an integer of 1, 2, 3, or 4;

Y is absent, -O-, -S-, $-S(=O)-$, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^9)_z-$, $-C(=O)-$, $-N(R^9)-C(=O)-$, or $-N(R^9)-C(=O)NH-$, $-N(R^9)C(R^9)_2-$, or $-C(=O)-(CHR^9)_z$, wherein when W_b^5 is N, no more than one of X or Y is absent;

R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

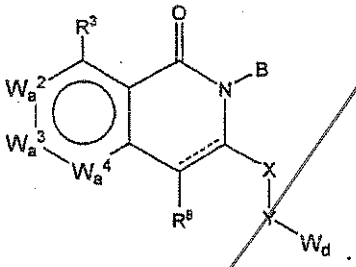
R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxy or nitro;

R^5, R^6, R^7, and R^8 are independently hydrogen, C_1-C_4alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, C_1-C_4heteroalkyl, C_1-C_4alkoxy, C_1-C_4amido, amino, acyl, C_1-C_4acyloxy, C_1-C_4sulfonamido, halo, cyano, hydroxy or nitro; and

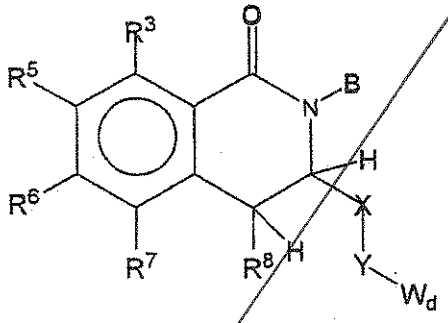
each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, or C_2-C_{10}heteroalkyl.

2. The compound of Formula I having a structure of Formula IV:



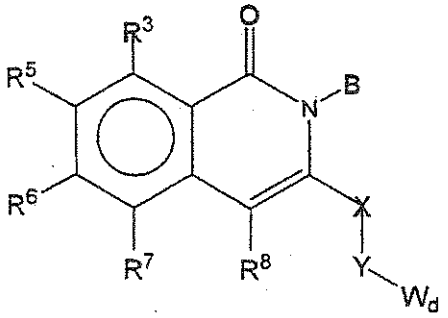
Formula IV

3. The compound of claim 1 of Formula V or VI:



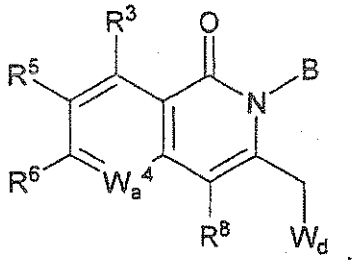
Formula V

or



Formula VI

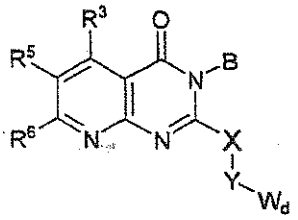
4. The compound of claim 1 of Formula VII:



Formula VII

5. The compound of claim 5 wherein W_a^4 is N.

6. The compound of claim 1 having a structure of Formula VIII-A:



Formula VIII-A

wherein X is absent and Y is -O-, -S-, -S(=O)-, -S(=O)$_2$-, -NH(R^9)-, -C(=O)-(CHR^9)$_z$-, -C(=O)-, -N(R^9)(C=O)-, or -N(R^9)(C=O)NH-;

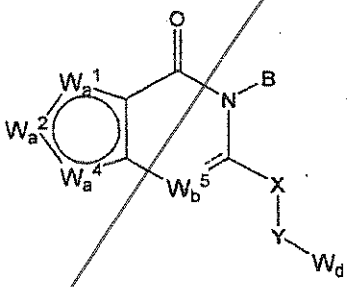
or X is –(CH(R^9))$_z$-, and Y is absent;

or X is –(CH(R^9))$_z$-, and Y is -O-, -S-, -S(=O)-, -S(=O)$_2$-, -NH(R^9)-, -C(=O)-(CHR^9)$_z$-, -C(=O)-, -N(R^9)(C=O)-, or -N(R^9)(C=O)NH-,;

each instance of z independently is an integer of 1, 2, 3, or 4; and,

W_d is bicyclic aryl or bicyclic heteroaryl.

7. A compound of Formula IX:



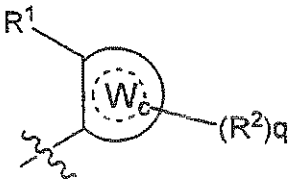
Formula IX

or a pharmaceutically acceptable salt thereof, wherein

wherein W_a^1 and W_a^2 are independently CR^5, S, N, or NR^4, and W_a^4 is independently CR^7, S, N, or NR^4 wherein no more than two adjacent ring atoms are nitrogen or sulfur, and when W_a^1 is S, one of W_a^2 and W_a^4 is N or NR^4;

W_b^5 is CR^8, N, or NR^8;

B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II;



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

q is an integer of 0, 1, 2, 3, or 4 ;

W_d is absent or is a heterocycloalkyl, aryl or heteroaryl moiety;

X is absent or is –(CH(R^9))$_z$-and each instance of z independently is an integer of 1, 2, 3, or 4;

Y is absent, - O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^9)-, -C(=O)-(CHR^9)$_z$-, -C(=O)-, -N(R^9)-C(=O)-, or -N(R^9)-C(=O)NH-,-N(R^9)C(R^9)$_2$-, or -C(=O)-(CHR^9)$_z$;

R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro;

R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxy or nitro;

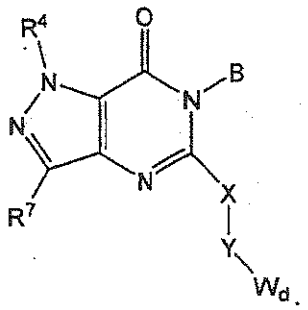
R^4 is hydrogen, acyl, C_1-C_4alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, or C_1-C_4heteroalkyl;

R^5, R^7, and R^8 are independently hydrogen, C_1-C_4alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, C_1-C_4heteroalkyl, acyl, C_1-C_4alkoxy, C_1-C_4amido, amino, C_1-C_4acyloxy, C_1-C_4sulfonamido, halo, cyano, hydroxy or nitro; and

each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, or C_2-C_{10}heteroalkyl.

8. The compound of claim 7 having a structure selected from the group consisting of:
(*i*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is CR^7, and W_b^5 is CR^8; (*ii*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is CR^7, and W_b^5 is CHR^8; (*iii*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is CR^7, and W_b^5 is N; (*iv*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is CR^7, and W_b^5 is NR^8; (*v*) W_a^1 is NR^4, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CR^8; (*vi*) W_a^1 is NR^4, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CHR^8; (*vii*) W_a^1 is NR^4, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is N; (*viii*) W_a^1 is NR^4, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is NR^8; (*ix*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is CR^8; (*x*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is CHR^8; (*xi*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is N; (*xii*) W_a^1 is NR^4, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is NR^8; (*xiii*) W_a^1 is S, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is CR^8; (*xiv*) W_a^1 is S, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is CHR^8; (*xv*) W_a^1 is S, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is N; (*xvi*) W_a^1 is S, W_a^2 is CR^5, W_a^4 is N, and W_b^5 is NR^8; (*xvii*) W_a^1 is N, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is CR^8; (*xviii*) W_a^1 is N, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is CHR^8; (*xix*) W_a^1 is N, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is N; (*xx*) W_a^1 is N, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is NR^8; (*xxi*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is CR^8;
(*xxi*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is CHR^8; (*xxii*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is N; (*xxiii*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is NR^8; (*xxiv*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CR^8; (*xxv*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CHR^8; (*xxvi*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is N; (*xxvii*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is NR^8; (*xxviii*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is NR^4, and W_b^5 is CR^8; (*xxix*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is NR^4, and W_b^5 is CHR^8; (*xxx*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is NR^4, and W_b^5 is N; (*xxxi*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is NR^4, and W_b^5 is NR^8; (*xxxii*) W_a^1 is CR^5, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is CHR^8; (*xxxiii*) W_a^1 is CR^5, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is CR^8; (*xxxiv*) W_a^1 is CR^5, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is N; and (*xxxv*) W_a^1 is CR^5, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is NR^8.

9. A compound of claim 7 of Formula X:

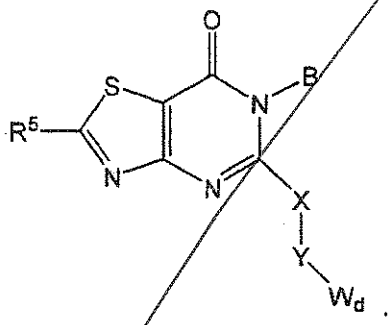


Formula X

10. The compound of claim 9 wherein R^4 is C_1-C_4alkyl or C_3-C_5cycloalkyl.

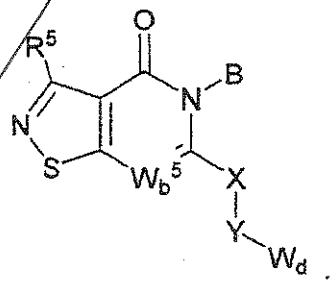
11. The compound of claim 10 wherein R^4 is methyl or ethyl.

12. A compound of claim 7 of Formula XI:



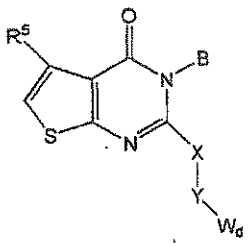
Formula XI

13. A compound of claim 7 of Formula XII:

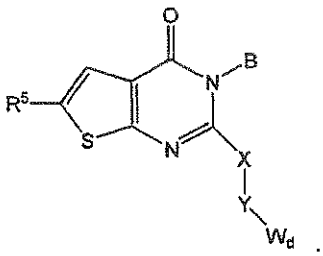


Formula XII

14. A compound of claim 7 of Formula XIII or XIV



Formula XIII



Formula XIV

15. The compound of claim 1 or 2 wherein R^3 is -H, halo, alkyl, alkoxy, or cycloalkyl.

16. The compound of claim 15 wherein R^3 is -H, -CH_3, -CH_2CH_3, -CF_3, -Cl or -F.

17. The compound of claim 1, 2, or 7 wherein R^5 is H, -CN, -NH_2, C_1-C_4alkyl, C_1-C_4alkoxy, -CF_3, NO_2, or halo.

18. The compound of claim 1, 2, or 7 wherein R^5 is H, -CH_3, -CH_2CH_3, -OCH_3, -OCH_2CH_3, -CF_3, or halo.

19. The compound of claim 18 wherein R^5 is H, -CH_3, -OCH_3, -CF_3, -Cl or -F.

20. The compound of claim 1 or 2 wherein R^6 is H, -CN, -NH_2, C_1-C_4alkyl, C_1-C_4alkoxy, -CF_3, NO_2, or halo.

21. The compound of claim 20 wherein R^6 is H, -CH_3, -CH_2CH_3, -OCH_3, -OCH_2CH_3, -CF_3, or halo.

22. The compound of claim 20 wherein R^6 is H, -CH_3, -OCH_3, -CF_3, or halo.

23. The compound of claim 1, 2, or 7 wherein R^7 is H, -CN, -NH_2, C_1-C_4alkyl, C_1-C_4alkoxy, -CF_3, NO_2, or halo.

24. The compound of claim 23 wherein R^7 is H, -CH_3, -CH_2CH_3, -OCH_3, -OCH_2CH_3, -CF_3, or halo.

25. The compound of claim 23 wherein R^7 is H, -CH_3, -OCH_3, -CF_3, or halo.

26. The compound of claim 1, 2, or 7 wherein R^8 is H, -CN, -NH_2, C_1-C_4alkyl, C_1-C_4alkoxy, -CF_3, NO_2, or halo.

27. The compound of claim 26 wherein R^8 is H, -CH_3, -CH_2CH_3, -OCH_3, -OCH_2CH_3, -CF_3, or halo.

28. The compound of claim 1, 2, or 7 wherein X is -CH_2- or -$CH(CH_3)$-.

29. The compound of claim 28 wherein -$CH(CH_3)$- is in an (S) stereochemical configuration.

30. The compound of claim 28 wherein -$CH(CH_3)$- is in a (R) stereochemical configuration.

31. The compound of claim 1, 2, or 7 wherein Y is absent, -O-, -$NH(R^9)$-, or -$S(=O)_2$-.

32. The compound of claim 31 wherein R^9 is methyl or hydrogen.

33. The compound of claim 1, 2, or 7 wherein X-Y is -CH_2-$N(CH_3)$.

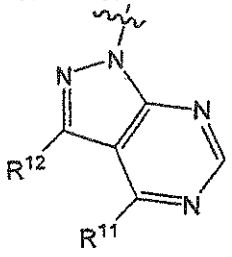
34. The compound of claim 1, 2, or 7 wherein X-Y is (S) -$CH(CH_3)$-NH-.

35. The compound of claim 1, 2, or 7 wherein X-Y is (R) -$CH(CH_3)$-NH-.

36. The compound of claim 1, 2, or 7 wherein W_d is 4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 6-amino-9H-purin-9-yl, 7-amino-2-methyl-2*H*-pyrazolo[4,3-d]pyrimidin-3-yl, or 6-methylenyl-9H-purin-6-yl.

37. The compound of claim 36 wherein W_d is pyrazolopyrimidine.

38. The compound of claim 37wherein the pyrazolopyrimidine is of Formula III:

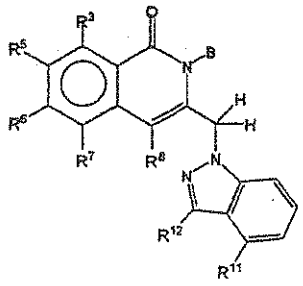


Formula III

wherein R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and

R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

39. The compound of claim 38 of Formula VI-A:

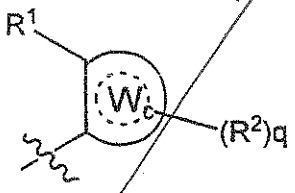


Formula VI-A

40. The compound of claim 38 or 39 wherein R^{11} is amino.

41. The compound of claim 1, 2, 7, or 39 wherein B is alkyl, amino, heteroalkyl, heterocycloalkyl, or cycloalkyl.

42. The compound of claim 1, 2, 7, or 39 wherein B is a moiety of Formula II;



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl,

and q is an integer of 0, 1, 2, 3, or 4.

43. The compound of claim 42 wherein W_c is aryl or heteroaryl.

44. The compound of claim 42 wherein W_c is phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, pyrimidin-2-yl, pyrimidin-5-yl, or pyrazin-2-yl.

45. The compound of claim 42 wherein W_c is heterocycloalkyl or cycloalkyl.

46. The compound of claim 45 wherein W_c is cyclopentyl, cyclohexyl, morpholinyl, or piperazinyl.

47. The compound of claim 42 wherein R^1 is hydrogen.

48. The compound of claim 42 wherein R^1 is alkoxy, amido, amino, acyloxy, hydroxy, sulfonamido, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl.

49. The compound of claim 48 wherein R^1 is substituted with phosphate.

50. The compound of claim 42 wherein R^1 is –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate.

51. The compound of claim 42 wherein q is 0 or 1.

52. The compound of claim 42 wherein R^2 is halo, hydroxy, cyano, nitro, or phosphate.

53. The compound of claim 42 wherein R^2 is hydroxy or cyano.

54. A composition comprising a pharmaceutically acceptable excipient and a compound of any one of claims 1-53.

55. The composition of claim 54 wherein the composition is a liquid, solid, semi-solid, gel, or an aerosol form.

56. A method of inhibiting a catalytic activity of a PI3 kinase present in a cell, comprising; contacting said cell with an effective amount of a compound of any of claims 1-55.

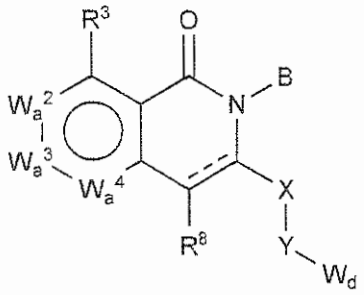
57. The method of claim 56 wherein the inhibiting takes place in a subject suffering from a disorder which is cancer, bone disorder, inflammatory disease, immune disease, nervous system disease, metabolic disease, respiratory disease, thrombosis, or cardiac disease.

58. The method of claim 56 wherein a second therapeutic agent is administered to the subject.

59. The method of claim 58, wherein the second agent is an agent that inhibits IgE production.

CLAIMS

1. A compound of Formula IV:



Formula IV,

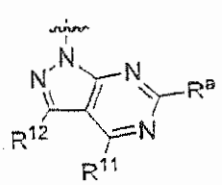
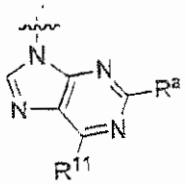
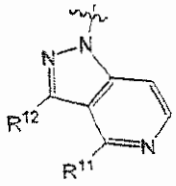
or a pharmaceutically acceptable salt thereof, wherein

W_a^2 is CR^5 or N;

W_a^3 is CR^6 or N;

W_a^4 is CR^7 or N;

wherein no more than two adjacent ring atoms selected from W_a^2, W_a^3, and W_a^4 are heteroatoms;

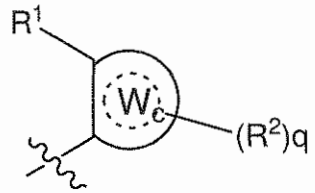
W_d is , , or ;

R^a is hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl;

R^{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, or alkoxy;

R^{12} is hydrogen, alkyl, cyano, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, amino, carboxylic acid, alkoxycarbonyl, or amido;

B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II:



Formula II;

W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

q is an integer of 0, 1, 2, 3, or 4;

X is $-(CH(R^9))_z-$;

Y is absent;

z is 1;

R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

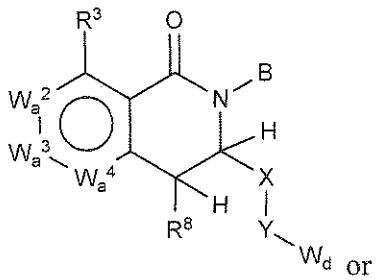
R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, or nitro;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl, or heteroaryl;

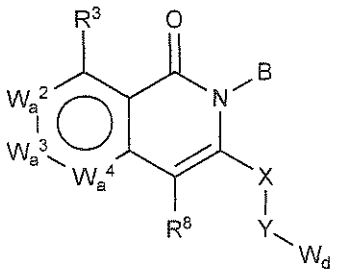
R^5, R^6, R^7, and R^8 are independently hydrogen, C_1–C_4alkyl, C_2–C_5alkenyl, C_2–C_5alkynyl, C_3–C_5cycloalkyl, C_1–C_4heteroalkyl, C_1–C_4alkoxy, C_1–C_4amido, amino, acyl, C_1–C_4acyloxy, C_1–C_4sulfonamido, halo, cyano, hydroxy, or nitro; and

each instance R^9 is independently hydrogen, C_1–C_{10}alkyl, C_3–C_7cycloalkyl, or C_2–C_{10}heteroalkyl.

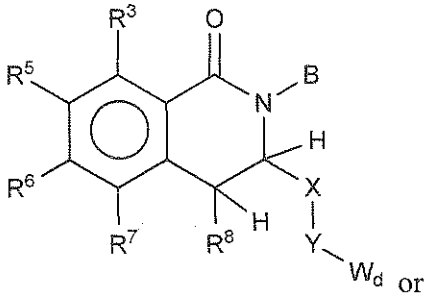
2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, having a structure of Formula 2-A or Formula 2-B, Formula V, Formula VI or Formula VII:



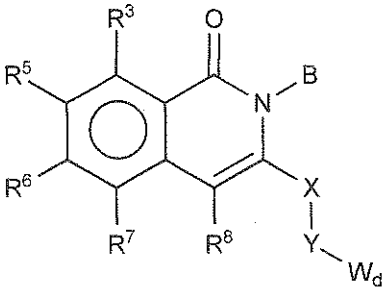
or



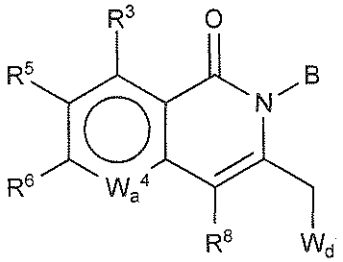
Formula 2-A Formula 2-B,



or



Formula V Formula VI,



Formula VII,

wherein in Formula VII, W_a^4 is N.

3. The compound of claim 1 to 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from hydrogen, alkyl, or halo.

4. The compound of claim 3 or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen, methyl, isopropyl, or fluoro.

5. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, halo, alkyl, alkoxy, or cycloalkyl.

6. The compound of claim 5 or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, methyl, ethyl, $-CF_3$, chloro, or fluoro.

7. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein R^3 is methyl or chloro.

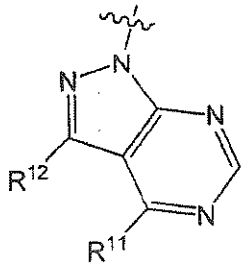
8. The compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein R^5, R^6, R^7, and R^8 are independently selected from hydrogen, cyano, $-NH_2$, C_1–C_4alkyl, C_1–C_4alkoxy, $-CF_3$, $-NO_2$, or halo.

9. The compound of any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, wherein X is $-CH_2-$ or $-CH(CH_3)-$.

10. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein $-CH(CH_3)-$ is in an (S) stereochemical configuration.

11. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, wherein X is $-CH_2-$ and Y is absent.

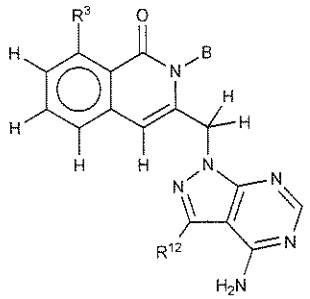
12. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, wherein W_c is aryl or heterocycloalkyl.

13. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, wherein W_d is 

,

wherein R^{12} is hydrogen, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

14. The compound of claim 13 or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula 6-A:



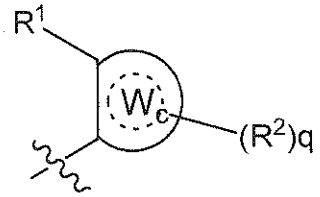
Formula 6-A,

or a pharmaceutically acceptable salt thereof.

15. The compound of claim 14 or a pharmaceutically acceptable salt thereof, wherein B is alkyl, amino, aryl, heteroalkyl, heteroaryl, heterocycloalkyl, or cycloalkyl.

16. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein B is optionally substituted phenyl, methyl, ethyl, isopropyl, cyclopropyl, cyclopentyl, optionally substituted pyridinyl, or tetrahydropyranyl.

17. The compound of claim 14 or a pharmaceutically acceptable salt thereof, wherein B is a moiety of Formula II:



Formula II;

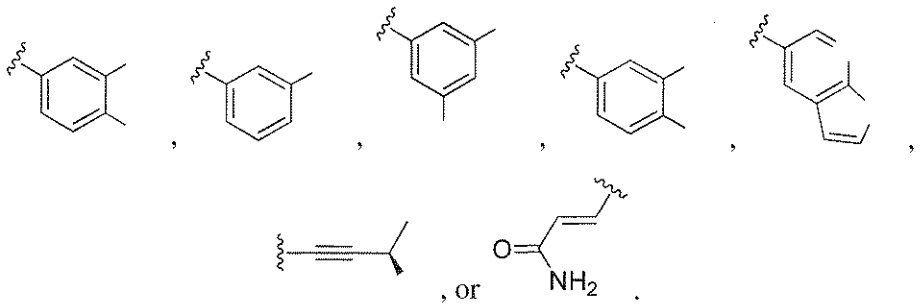
wherein W_c is phenyl;

R^1 is hydrogen, fluoro, chloro, cyano, methyl, isopropyl, $-CF_3$, methoxy, nitro, or phosphate;

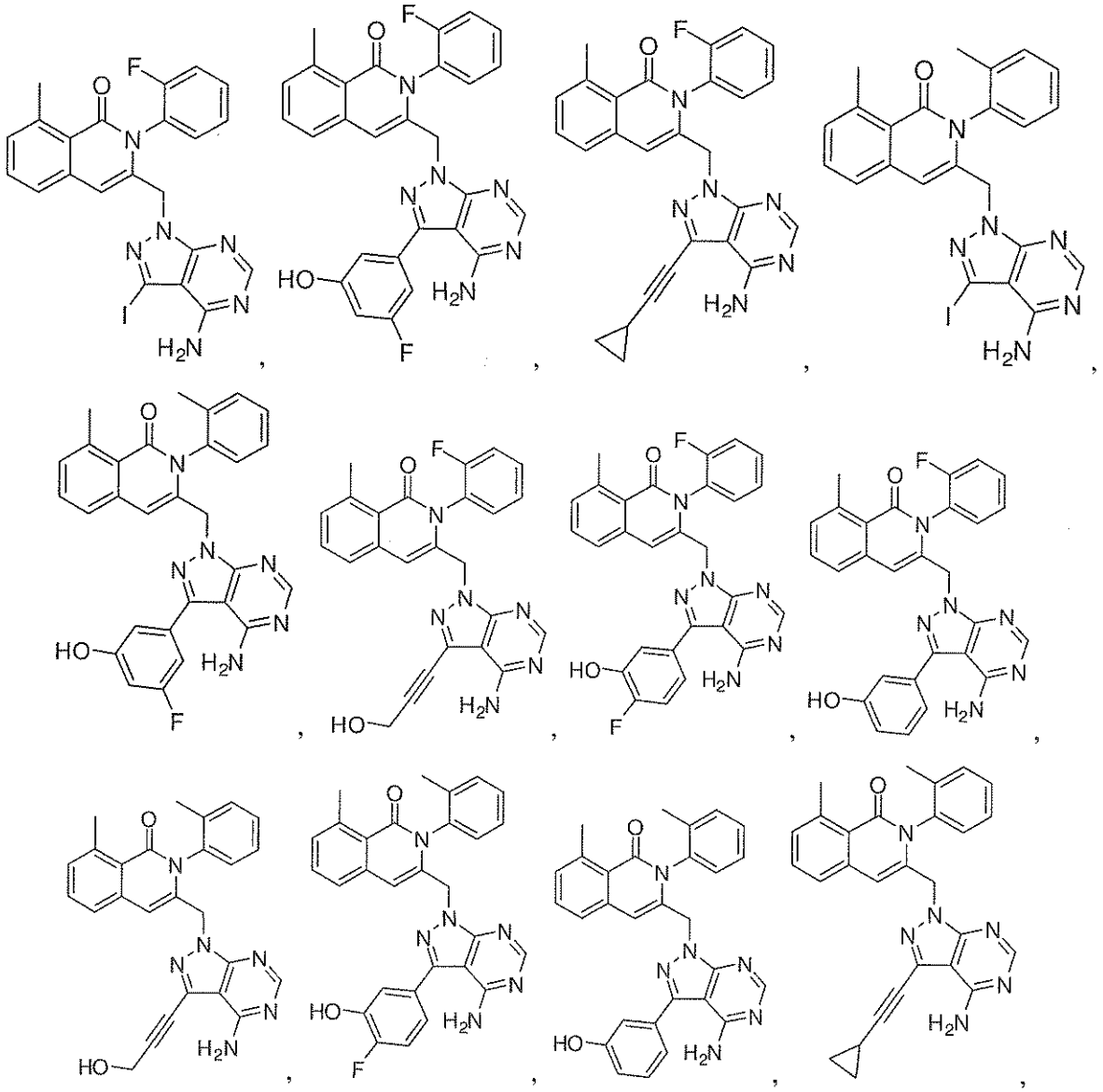
R^2 is hydroxy or cyano; and

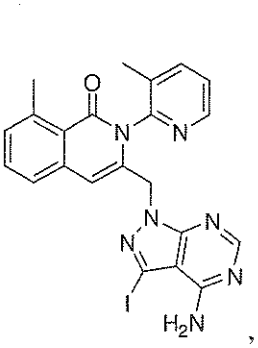
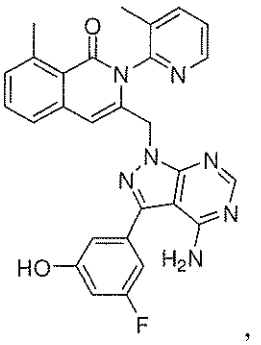
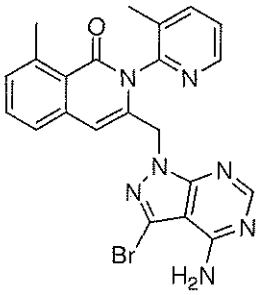
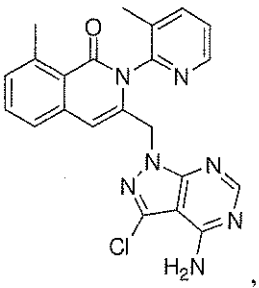
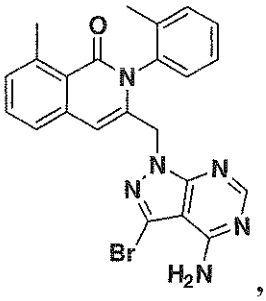
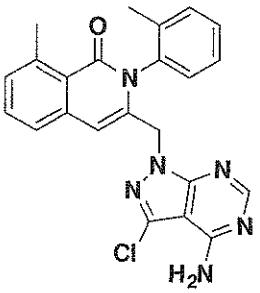
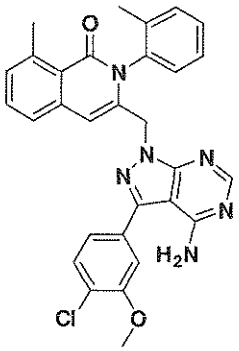
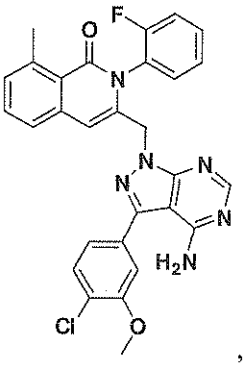
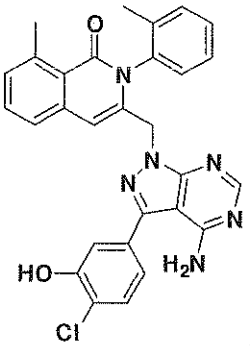
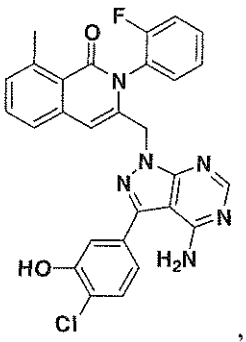
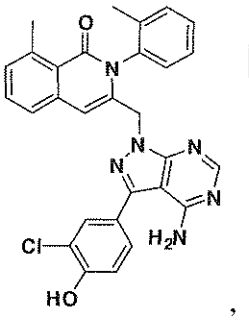
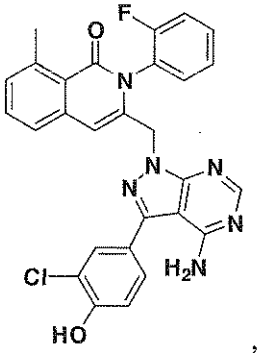
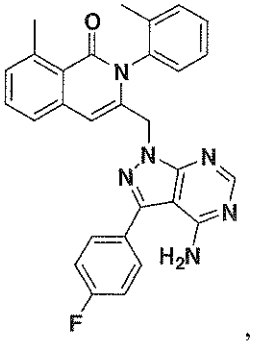
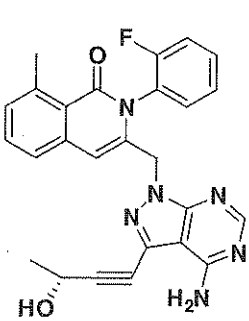
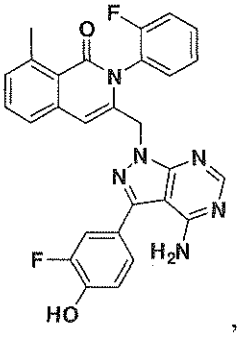
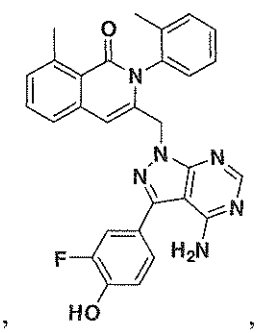
q is an integer of 0 or 1.

18. The compound of any one of claims 14 to 17 or a pharmaceutically acceptable salt thereof, wherein R^{12} is iodo, bromo,



19. The compound of claim 1, wherein the compound is:



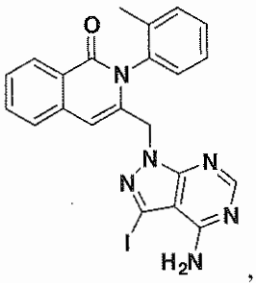
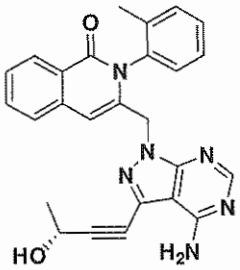
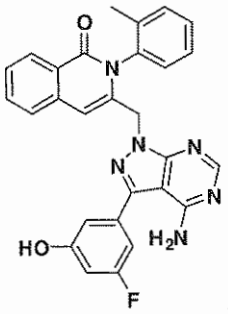
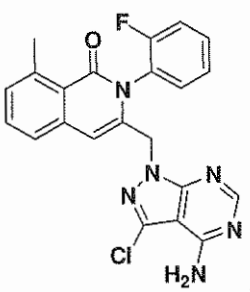
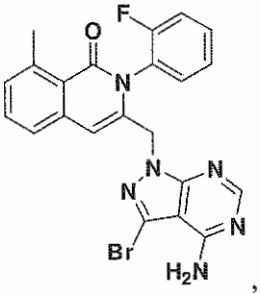
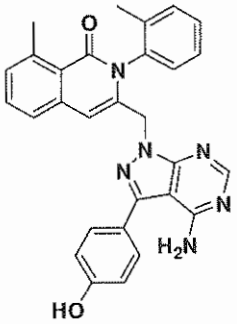
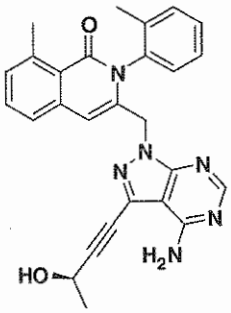
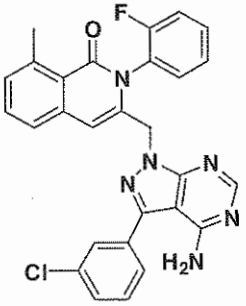
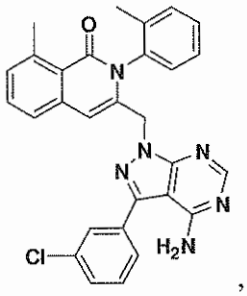
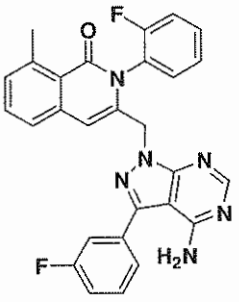
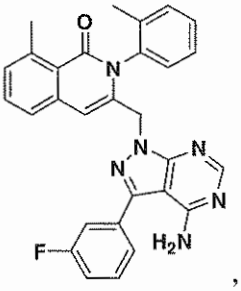
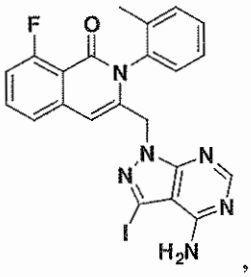
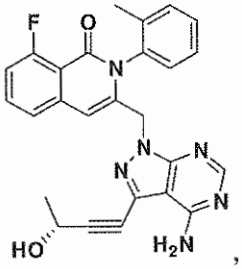
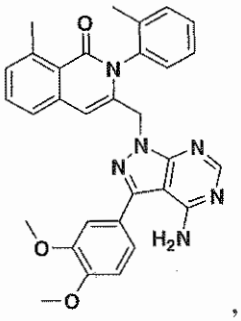
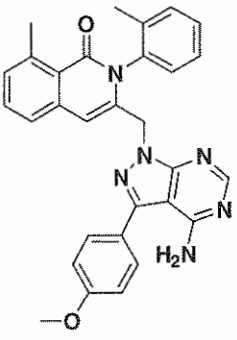
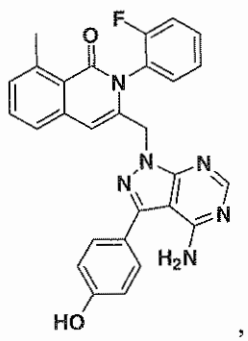

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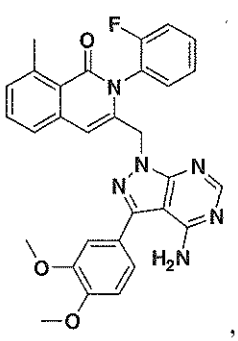
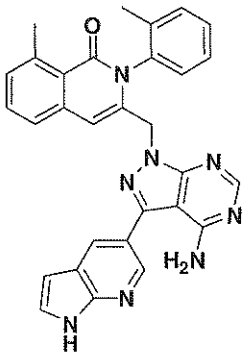
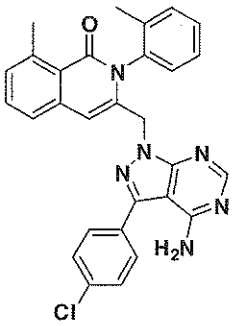

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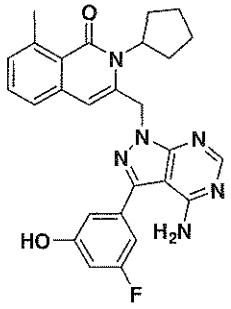
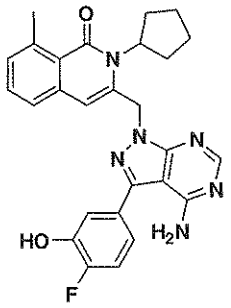
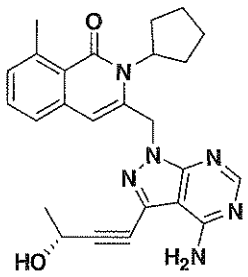
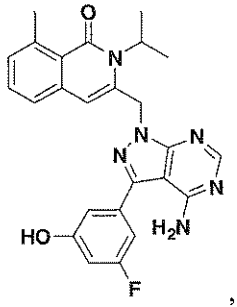
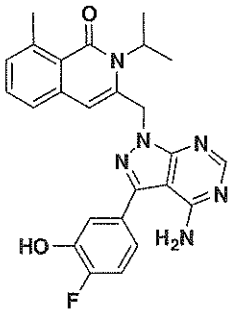
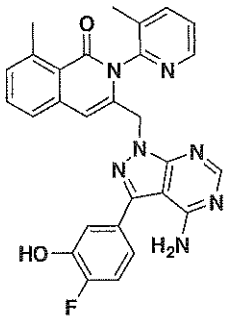
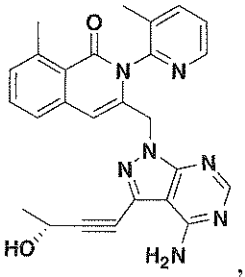
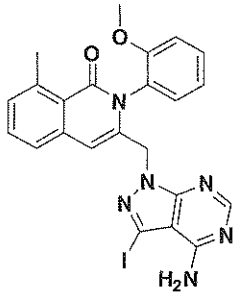
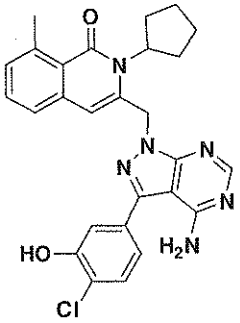
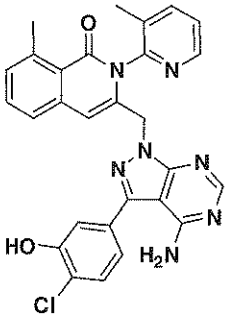
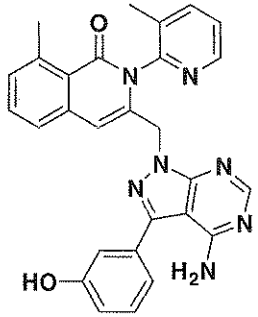
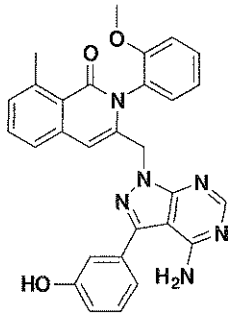
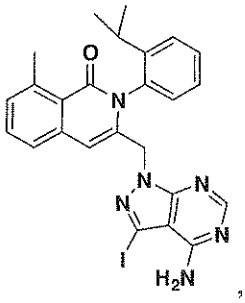
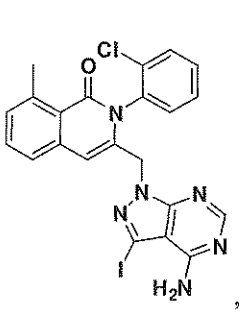
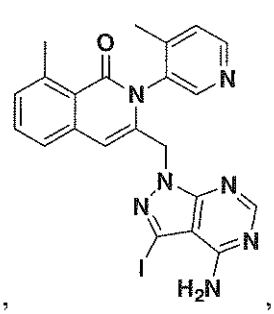
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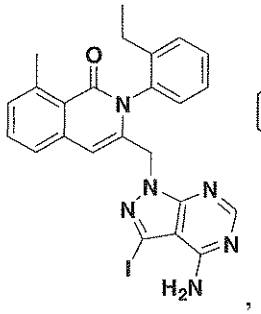
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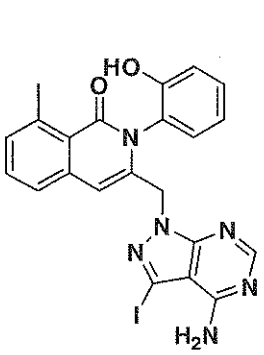
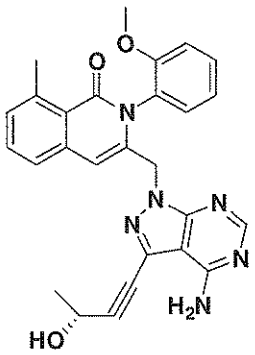
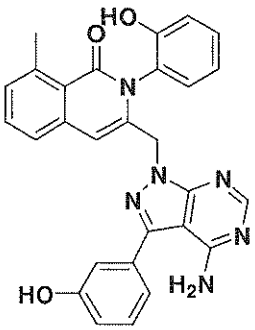
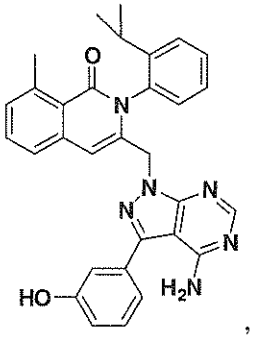
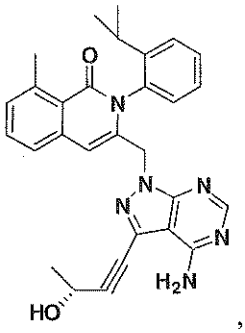
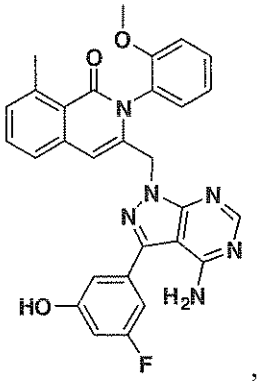
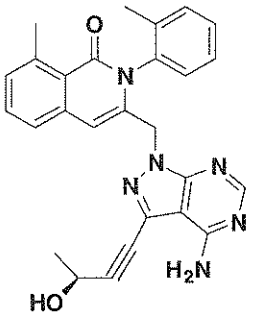
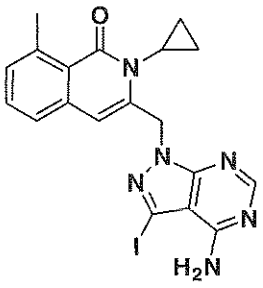
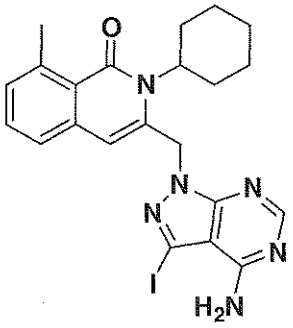
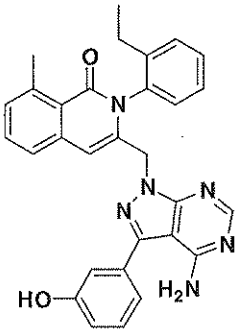
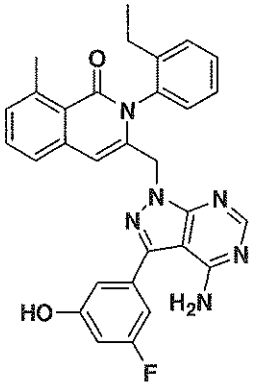
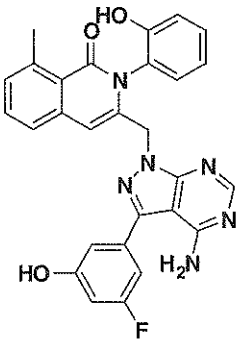
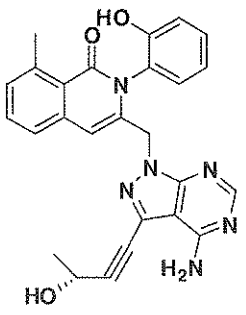
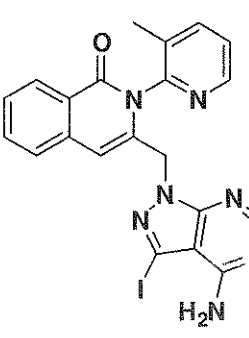
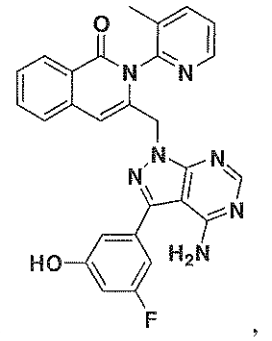
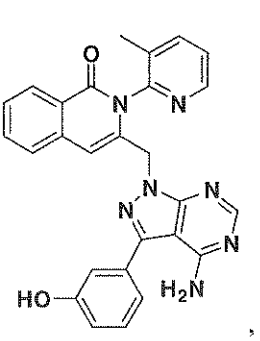
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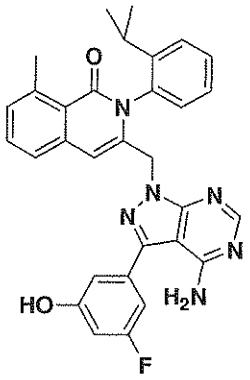
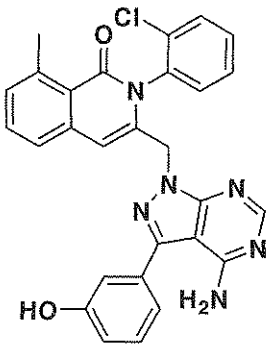
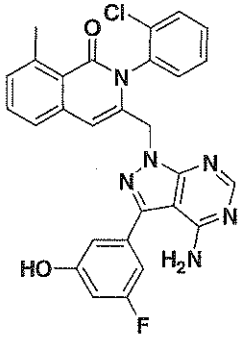
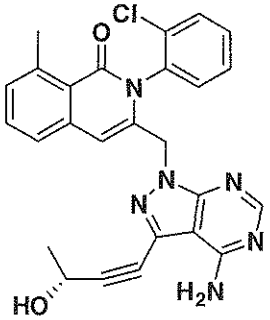
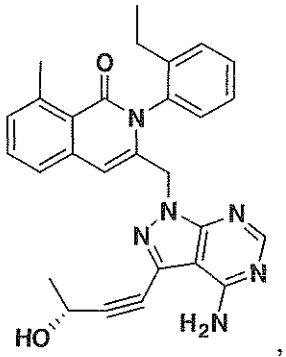
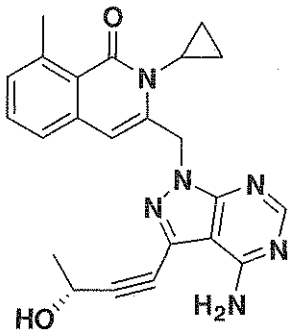
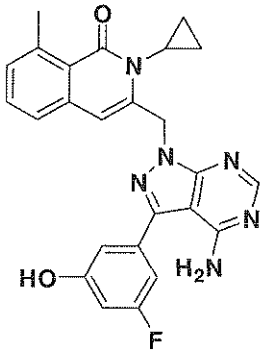
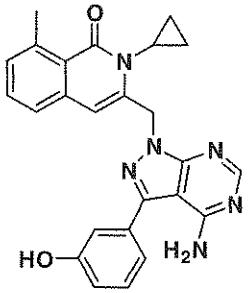
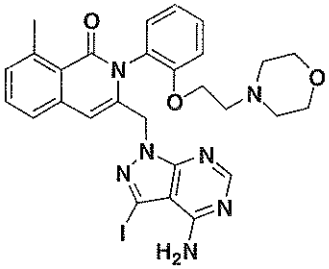
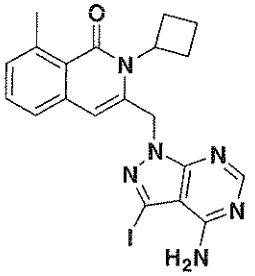
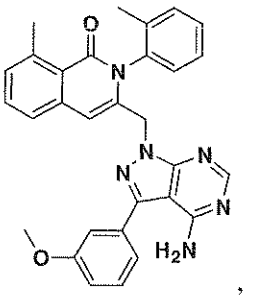
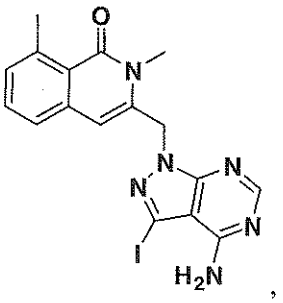
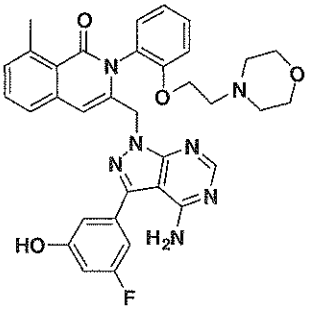
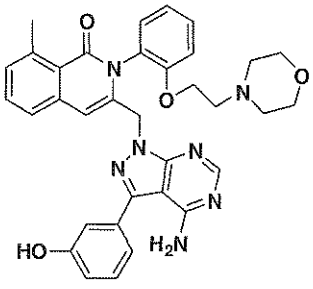
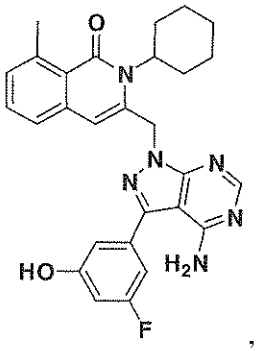
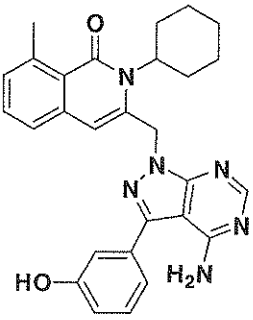

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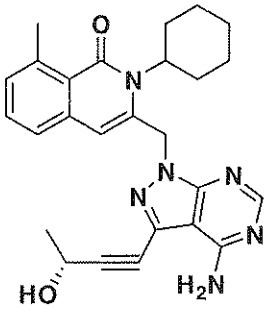
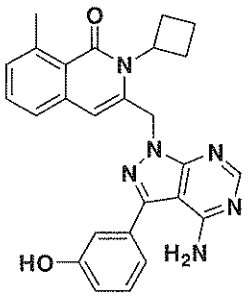
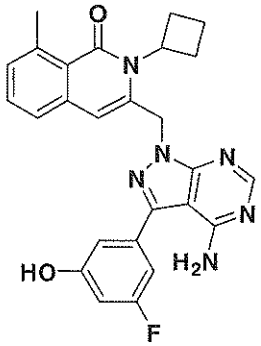
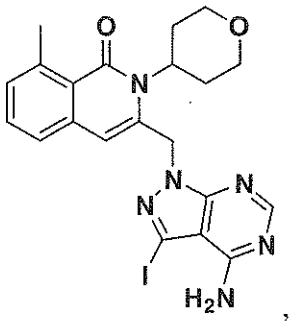
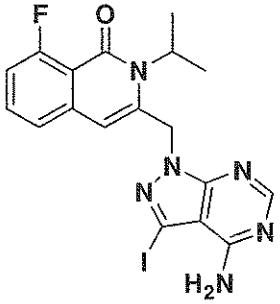
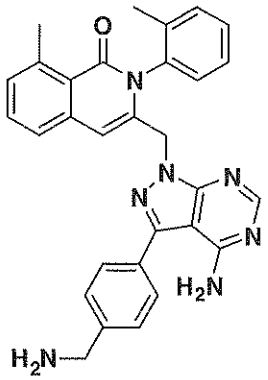
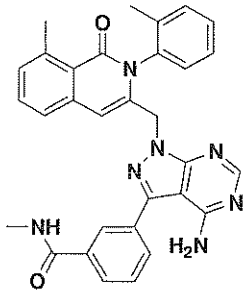
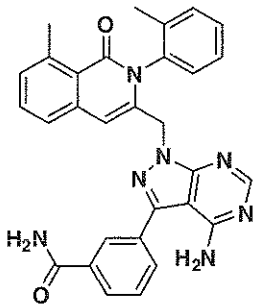
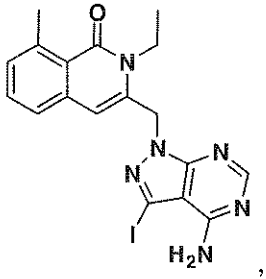
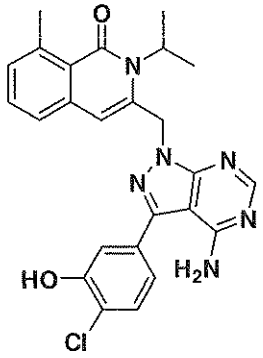
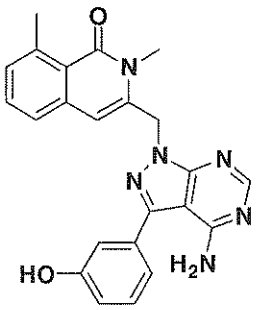
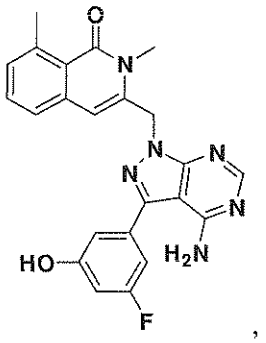
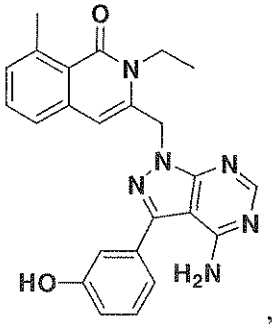
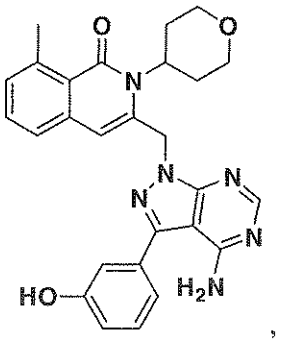
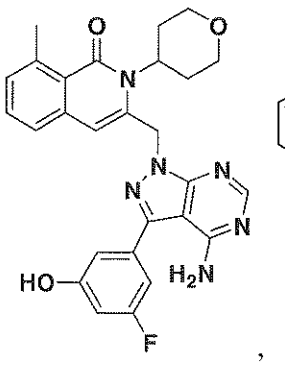
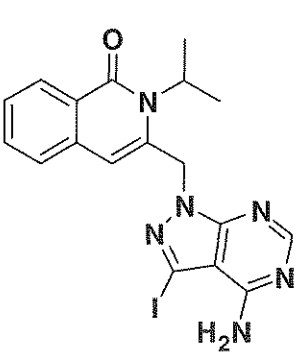
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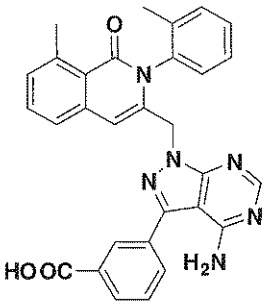
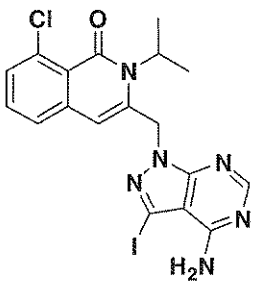
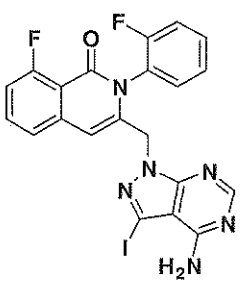
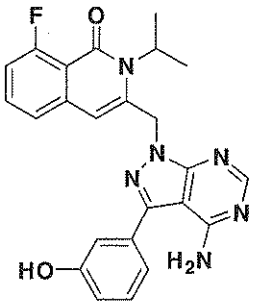
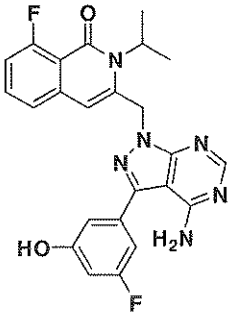
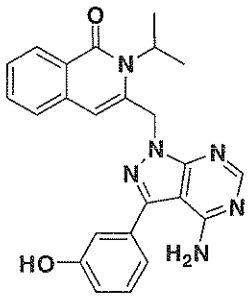
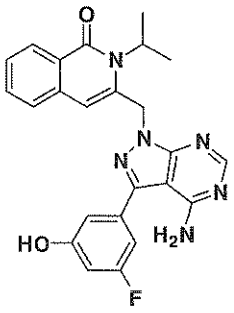
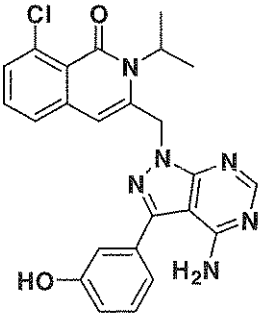
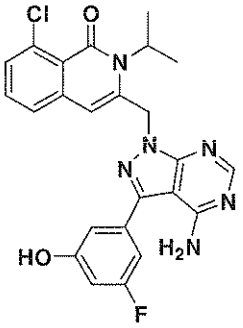
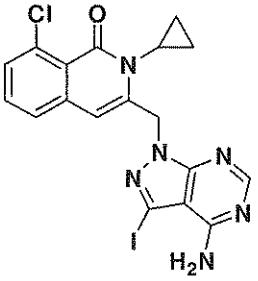
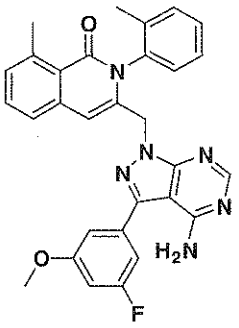
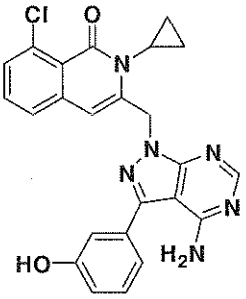
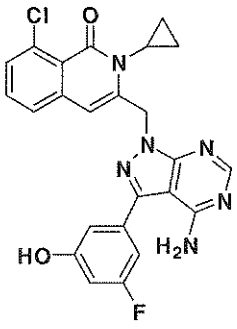
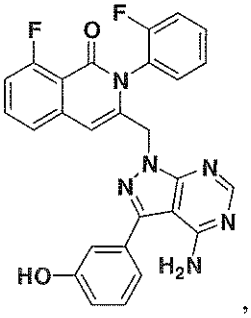
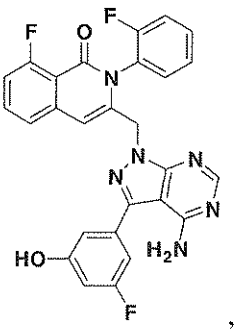
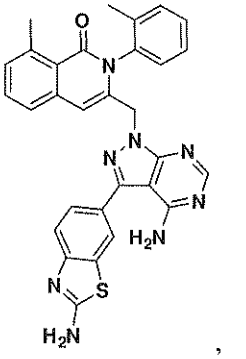
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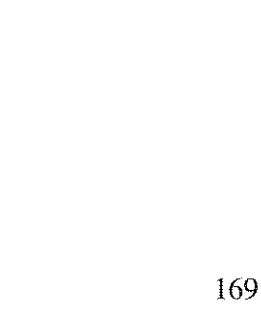
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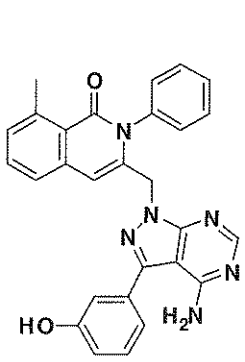
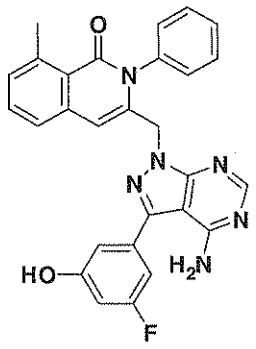
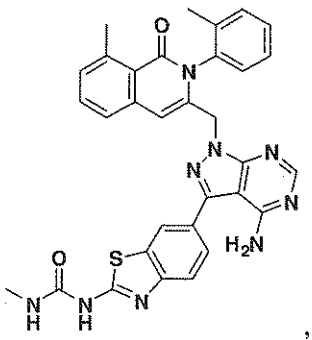
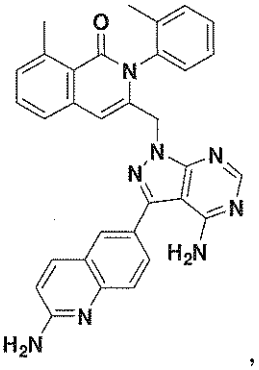
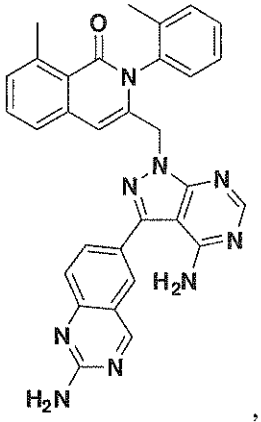
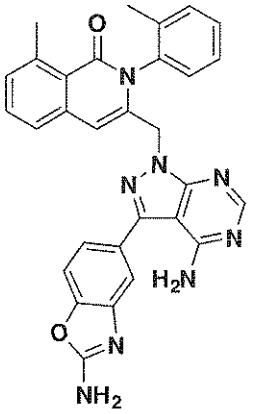
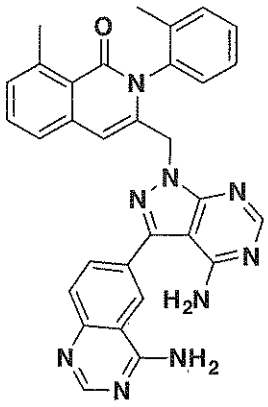
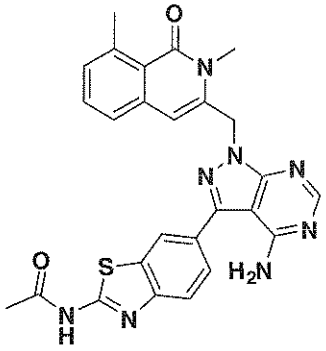
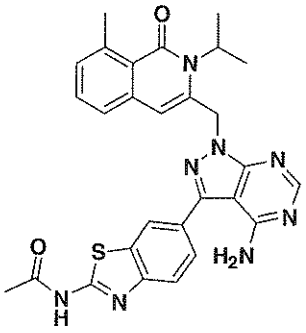
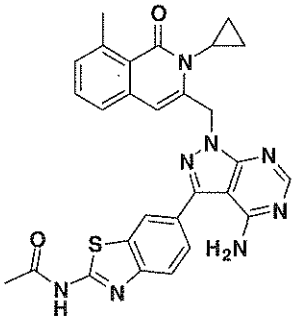
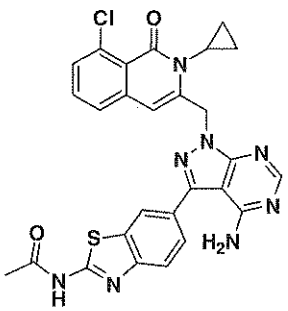
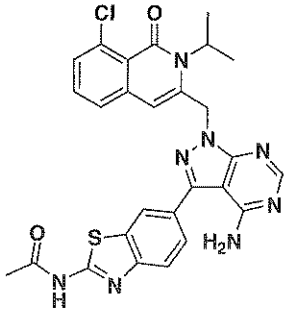
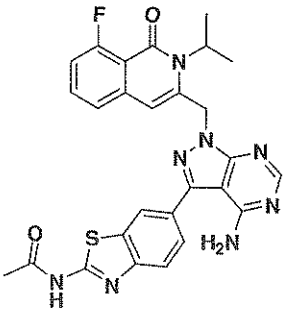
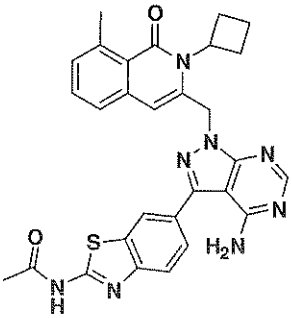
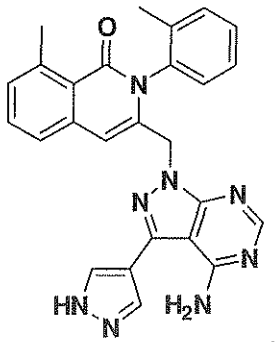
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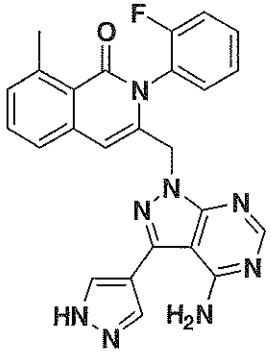
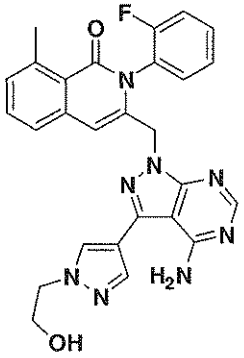
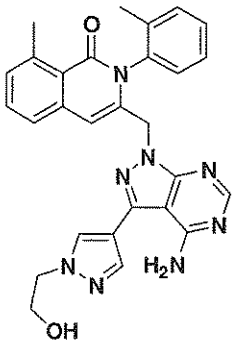
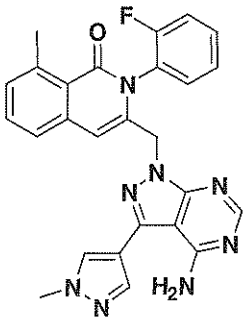
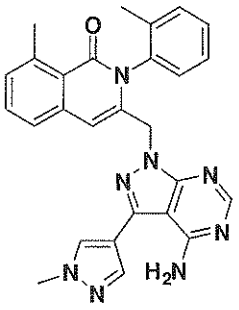
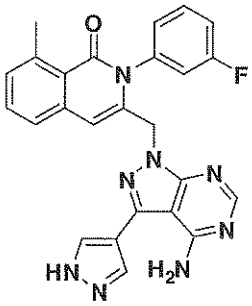
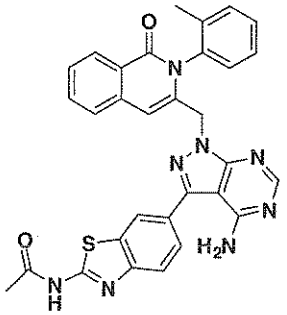
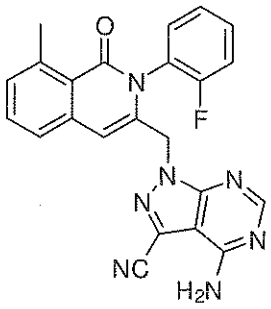
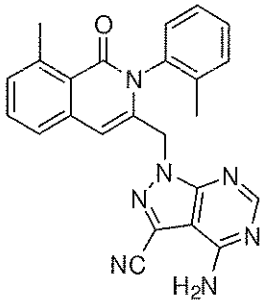
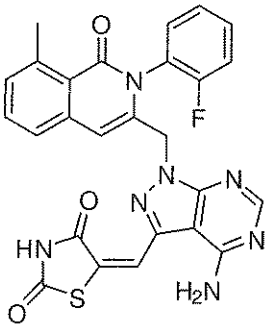
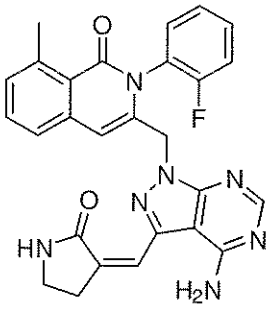
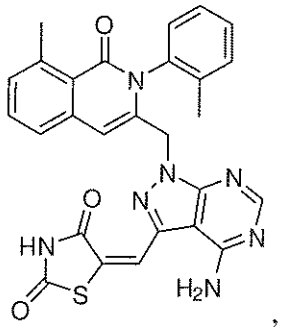
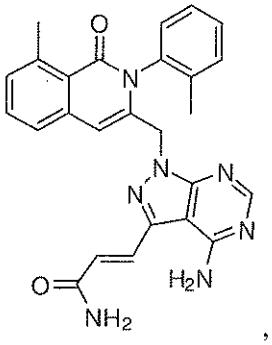
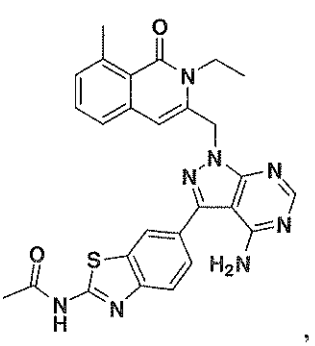
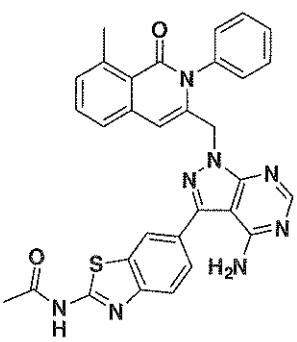

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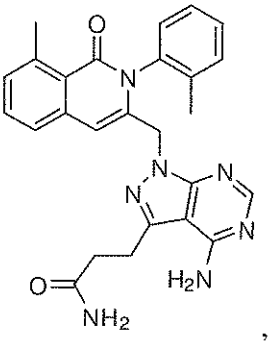
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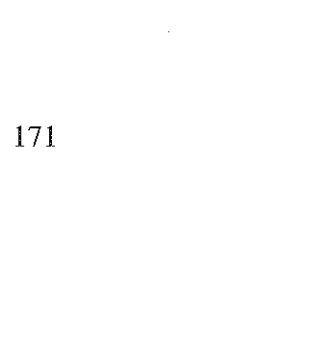

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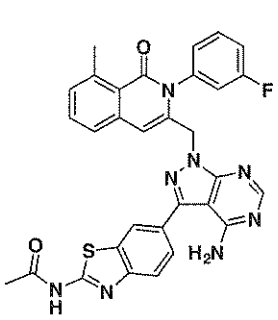
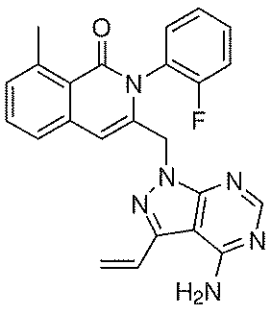
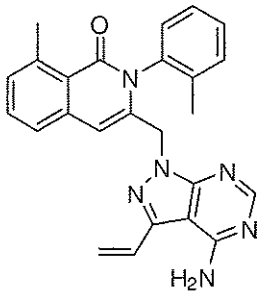
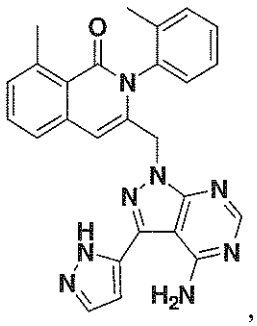
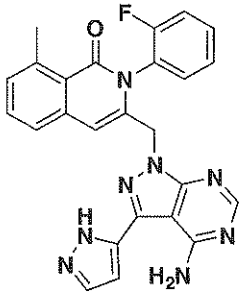
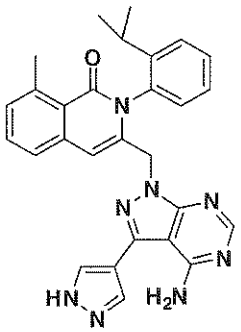
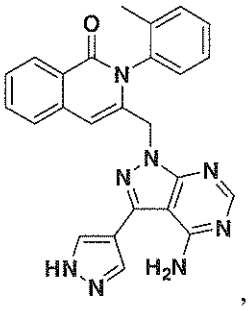
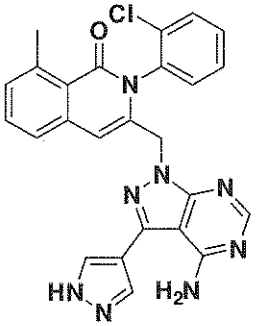
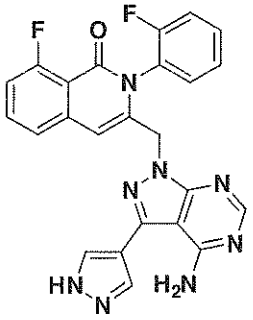
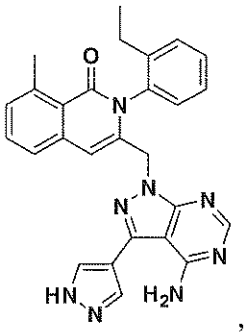
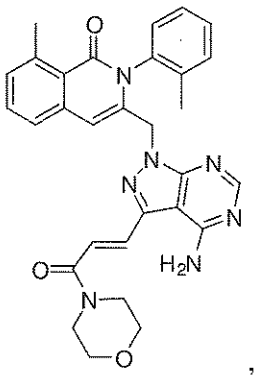
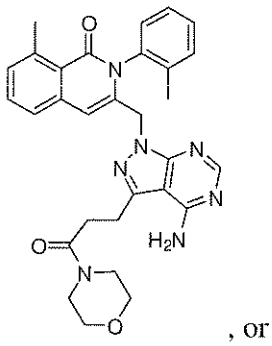
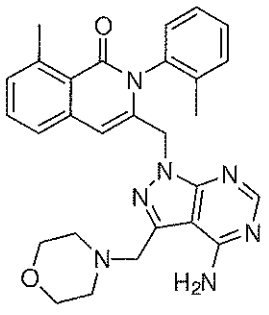
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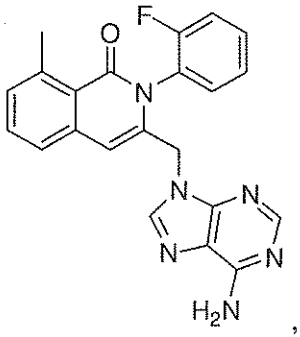
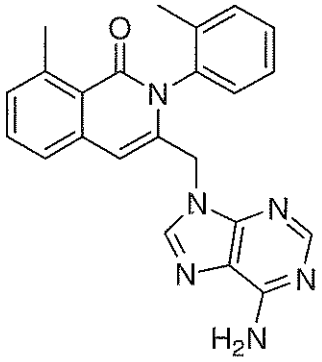
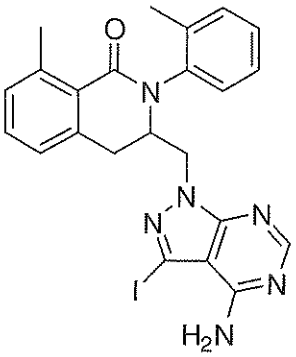
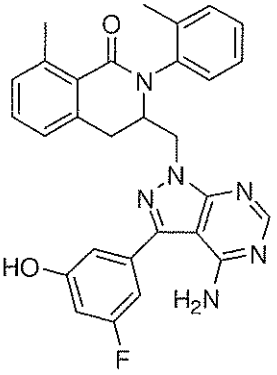
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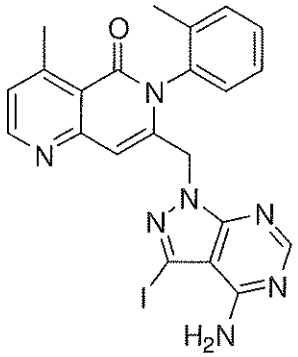
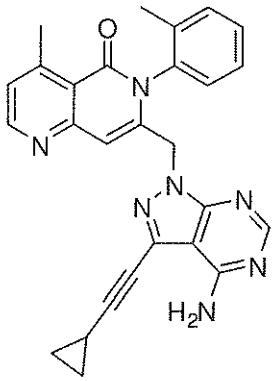
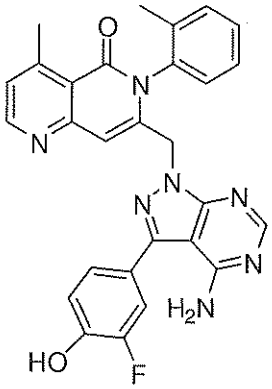
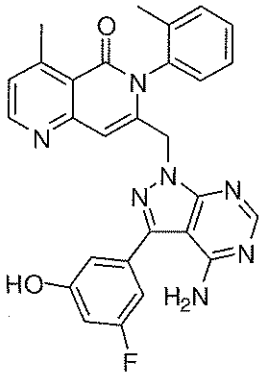
or a pharmaceutically acceptable salt thereof.

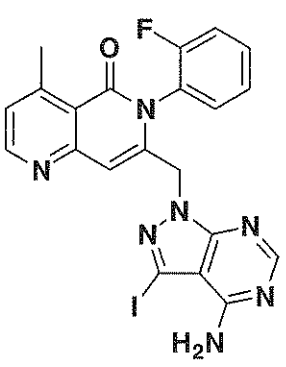
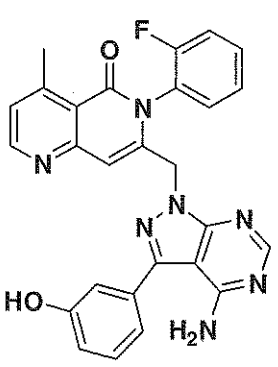
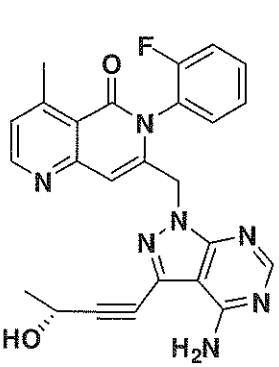
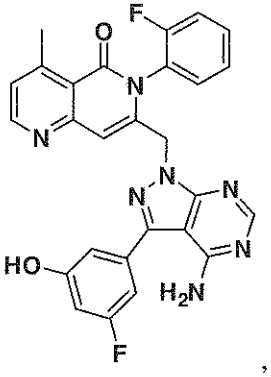
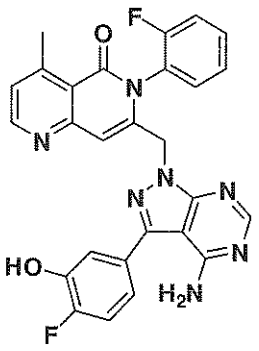
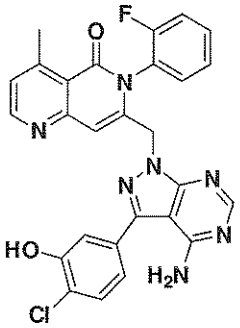
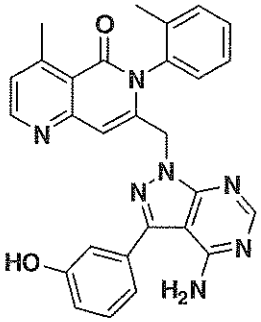
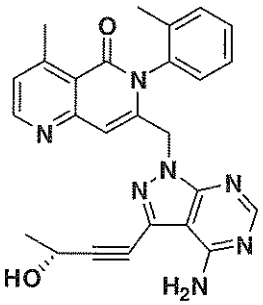
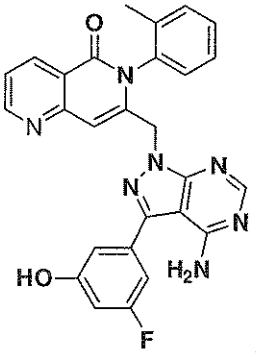
20. The compound of claim 1, wherein the compound is:


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or a pharmaceutically acceptable salt thereof.

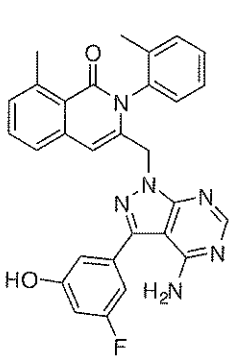
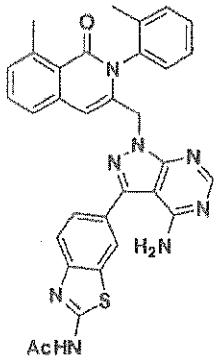
21. The compound of claim 1, wherein the compound is:


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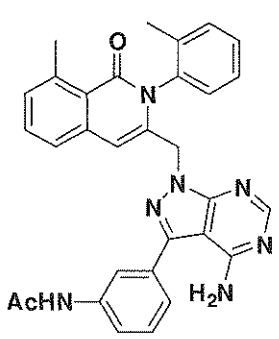
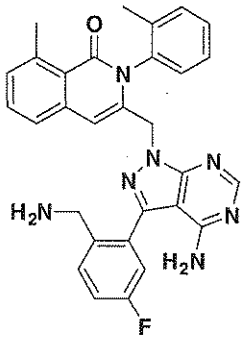
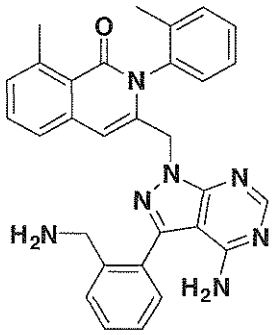
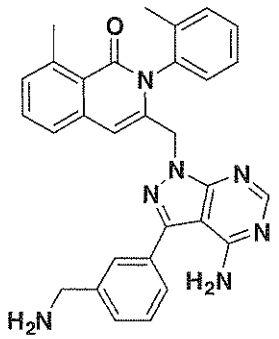
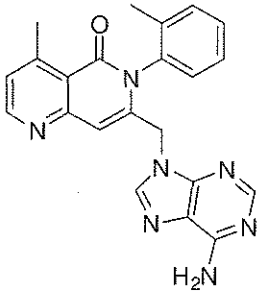
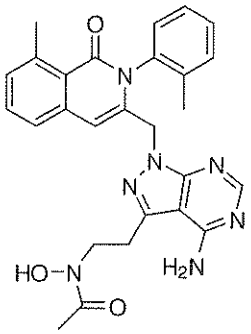
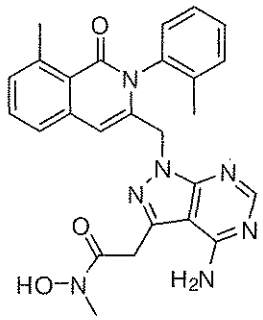
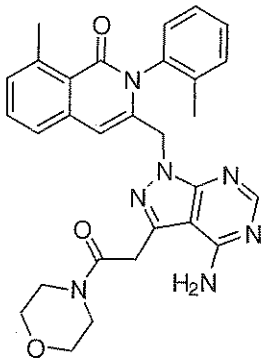
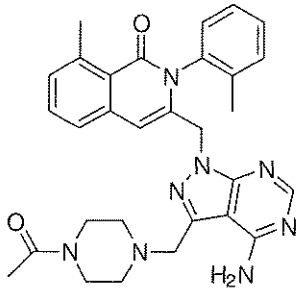
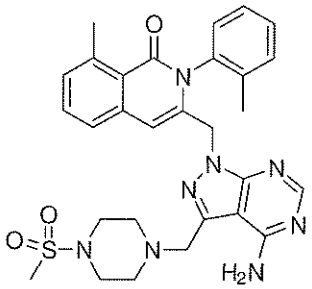
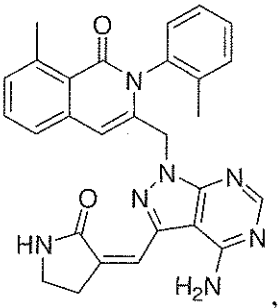
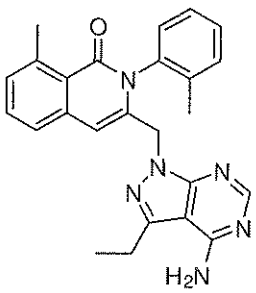
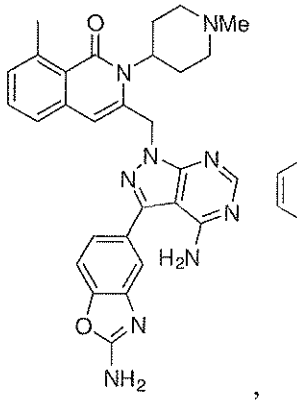
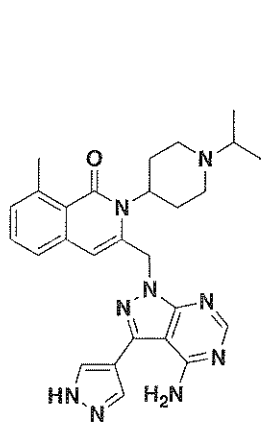
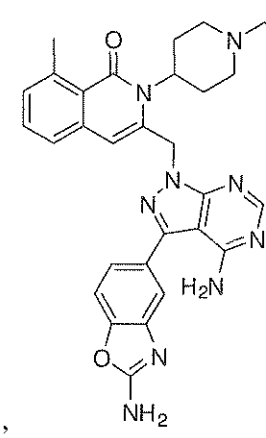
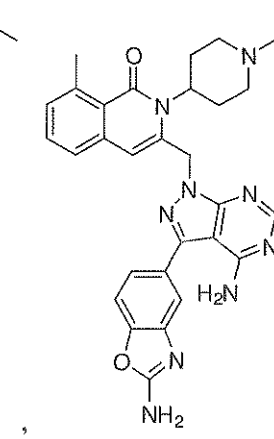
or a pharmaceutically acceptable salt thereof.

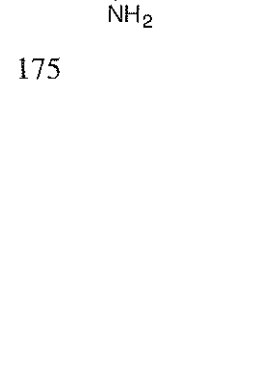
22. The compound of claim 1, wherein the compound is:

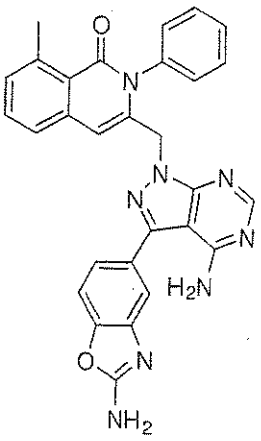
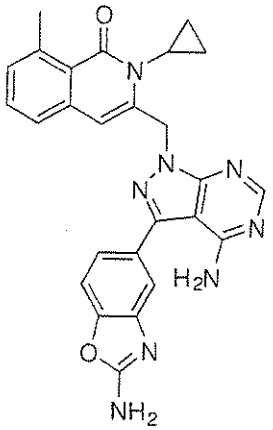
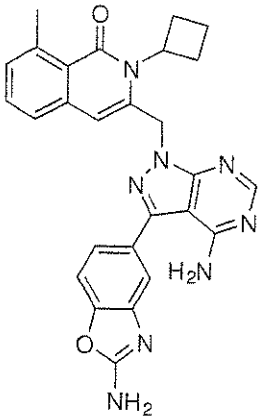
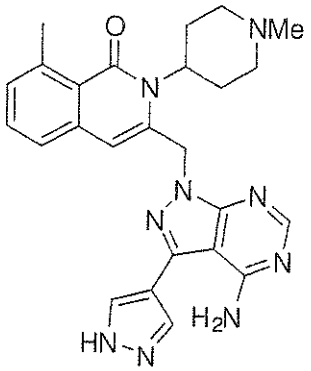
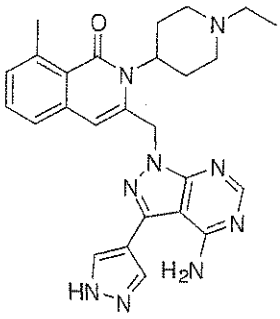
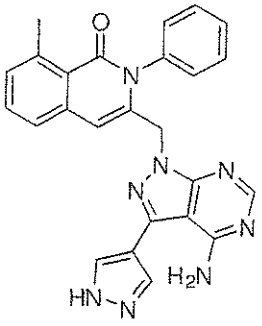
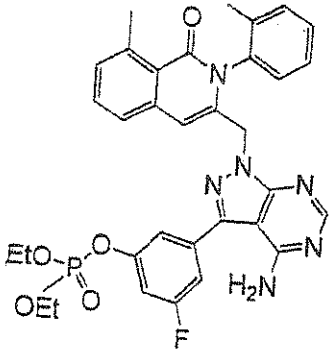
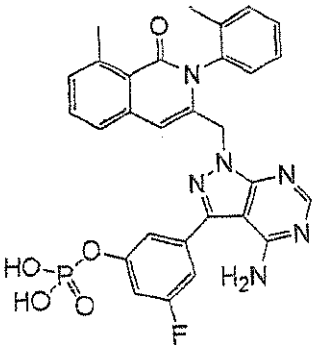

or


or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1, wherein the compound is:

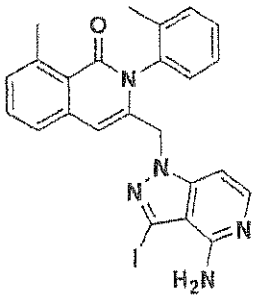
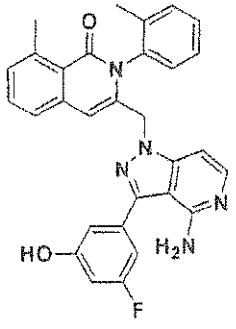
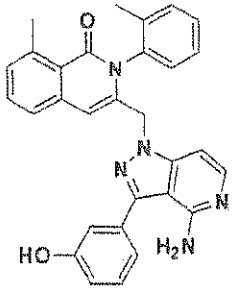



















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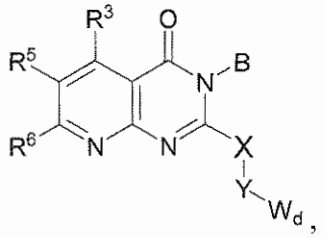
or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1, wherein the compound is


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, or


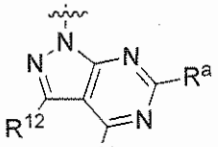
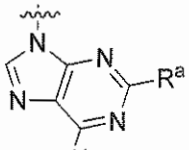
or a pharmaceutically acceptable salt thereof.

25. A compound of Formula VIII-A:



Formula VIII-A

or a pharmaceutically acceptable salt thereof, wherein

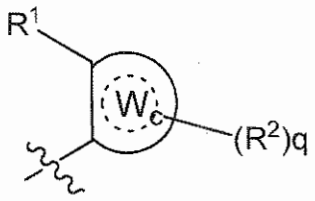
W_d is  or  ;

R^a is hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl;

R^{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, or alkoxy;

R^{12} is hydrogen, alkyl, cyano, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, amino, carboxylic acid, alkoxycarbonyl, or amido;

B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II:



Formula II;

W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

q is an integer of 0, 1, 2, 3, or 4;

X is $-(CH(R^9))_z-$;

Y is absent;

z is 1;

R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

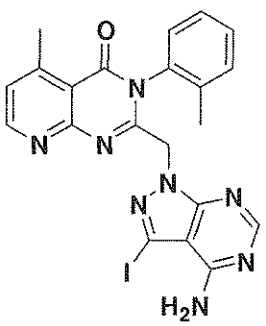
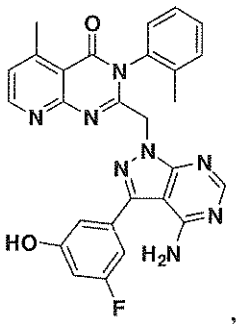
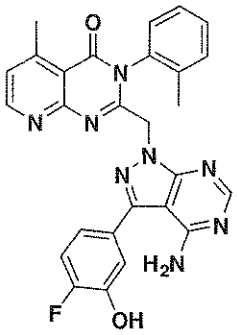
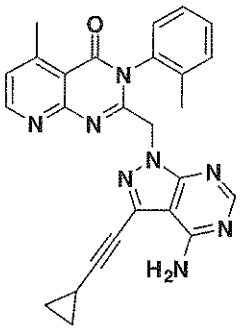
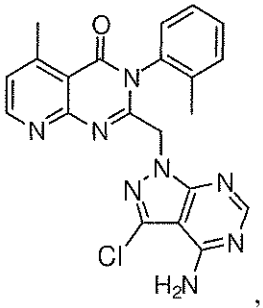
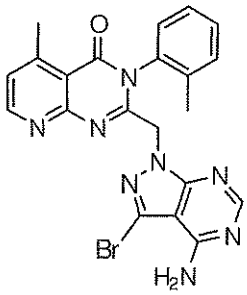
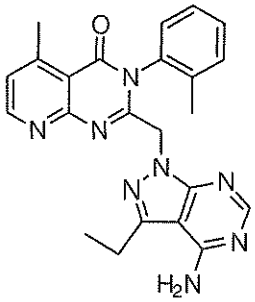
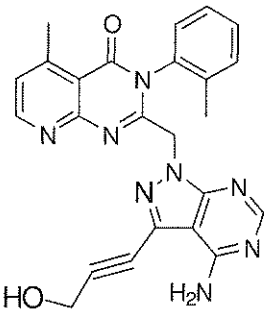
R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, or nitro;

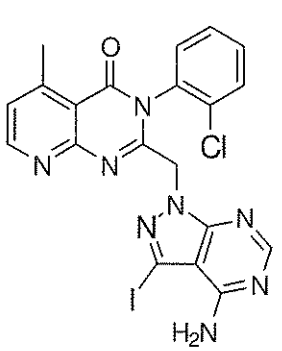
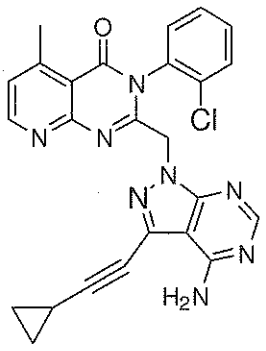
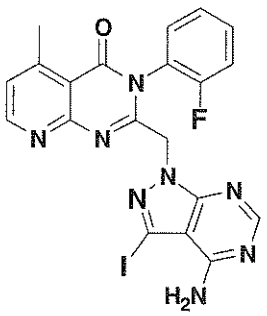
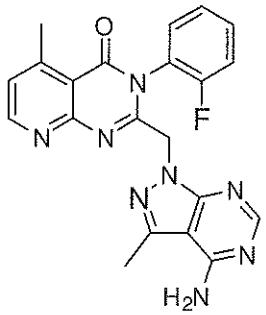
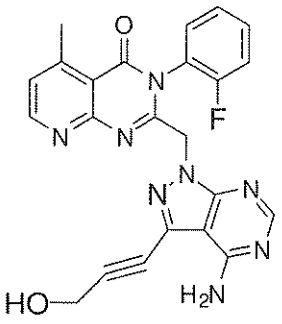
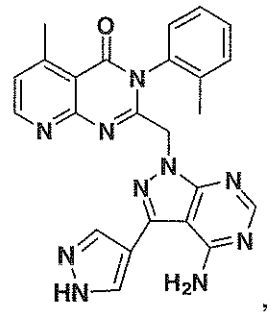
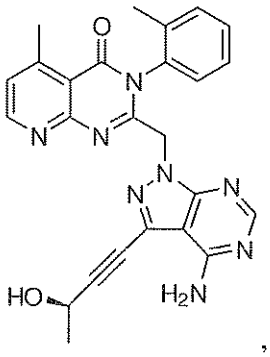
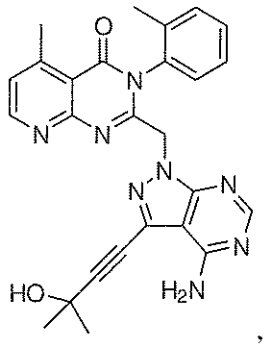
R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl, or heteroaryl;

R^5 and R^6 are independently hydrogen, C_1–C_4alkyl, C_2–C_5alkenyl, C_2–C_5alkynyl, C_3–C_5cycloalkyl, C_1–C_4heteroalkyl, C_1–C_4alkoxy, C_1–C_4amido, amino, acyl, C_1–C_4acyloxy, C_1–C_4sulfonamido, halo, cyano, hydroxy, or nitro; and

each R^9 is independently hydrogen, C_1–C_{10}alkyl, C_3–C_7cycloalkyl, or C_2–C_{10}heteroalkyl.

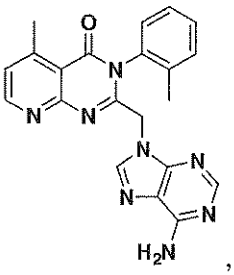
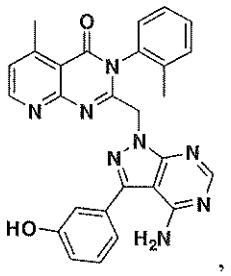
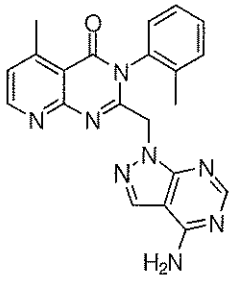
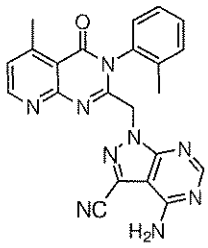
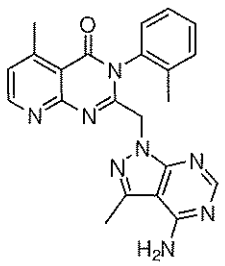
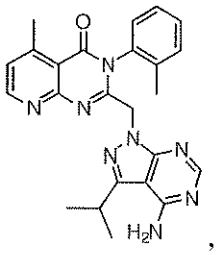
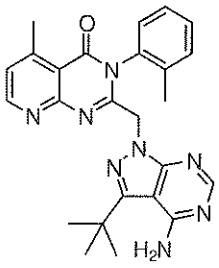
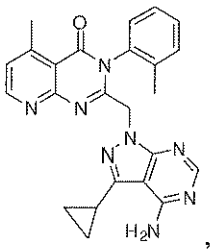
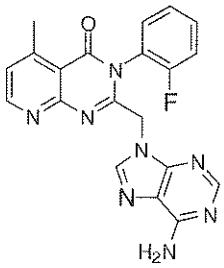
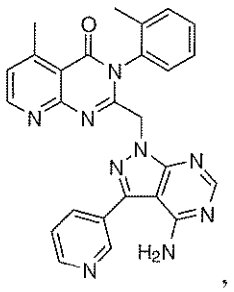
26. The compound of claim 25, wherein the compound is:

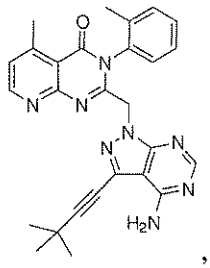

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or a pharmaceutically acceptable salt thereof.

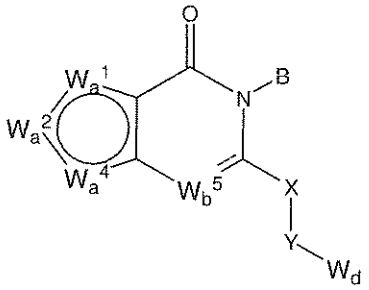
27. The compound of claim 25, wherein the compound is:


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or  ,

or a pharmaceutically acceptable salt thereof.

28. A compound of Formula IX:



Formula IX

or a pharmaceutically acceptable salt thereof,

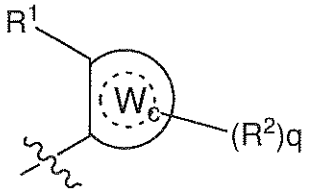
wherein W_a^1 and W_a^2 are independently CR^5, S, N, or NR^4, and

W_a^4 is independently CR^7, S, N, or NR^4;

wherein no more than two adjacent ring atoms are nitrogen or sulfur, and when W_a^1 is S, one of W_a^2 and W_a^4 is N or NR^4;

W_b^5 is CR^8, N, or NR^8;

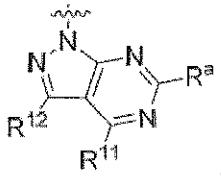
B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II;



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

q is an integer of 0, 1, 2, 3, or 4;

W_d is  ;

R_a is hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl;

R_{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, or alkoxy;

R_{12} is hydrogen, alkyl, cyano, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, amino, carboxylic acid, alkoxycarbonyl, or amido;

X is $-(CH(R^9))_z-$;

each instance of z independently is an interger of 1;

Y is absent;

R^1 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro;

R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

R^4 is hydrogen, acyl, C_1-C_4alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, or C_1-C_4heteroalkyl;

R^5, R^7, and R^8 are independently hydrogen, C_1-C_4alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, C_1-C_4heteroalkyl, acyl, C_1-C_4alkoxy, C_1-C_4amido, amino, C_1-C_4acyloxy, C_1-C_4sulfonamido, halo, cyano, hydroxy or nitro; and

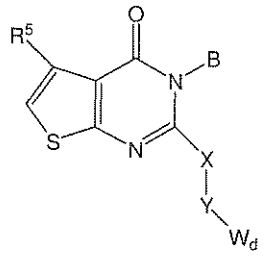
each instance R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, or C_2-C_{10}heteroalkyl.

29. The compound of claim 28 or a pharmaceutically acceptable salt thereof, wherein W_a^1 is NR^4, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is N; and R^4 and R^7 are each independently C_1-C_4alkyl.

30. The compound of claim 28 or a pharmaceutically acceptable salt thereof, wherein W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, W_b^5 is N, and R^5 is C_1-C_4alkyl.

31. The compound of claim 28 or a pharmaceutically acceptable salt thereof, wherein W_a^1 is CR^5, W_a^2 is CR^5, W_a^4 is S, and W_b^5 is N.

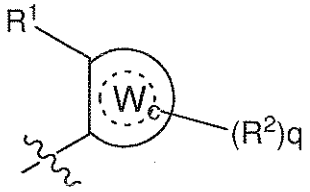
32. The compound of claim 28 of Formula XIII:



Formula XIII

or a pharmaceutically acceptable salt thereof, wherein

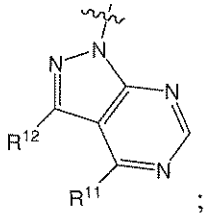
B is a moiety of Formula II;



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

q is an integer of 0, 1, or 2;

W_d is:  ;

X is $-(CH_2)_z-$;

Y is absent;

z is 1;

R^1 is hydrogen, fluoro, chloro, cyano, methyl, isopropyl, $-CF_3$, methoxy, or nitro;

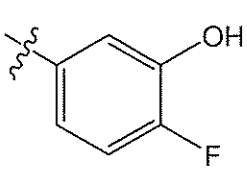
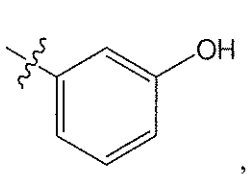
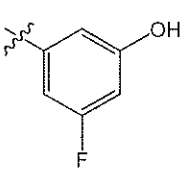
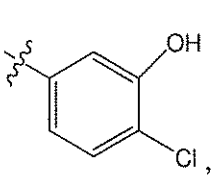
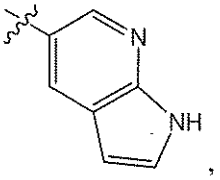
R^2 is halo, hydroxy, cyano, or nitro;

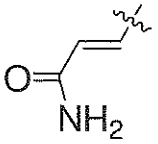
R^5 is hydrogen or methyl;

R^{11} is amino; and

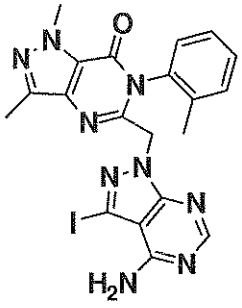
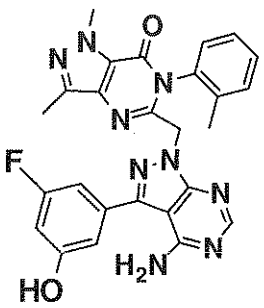
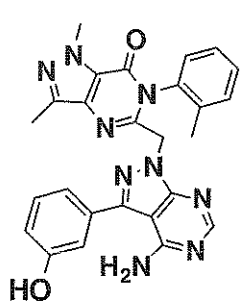
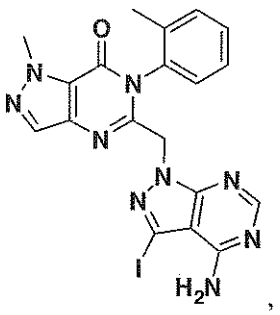
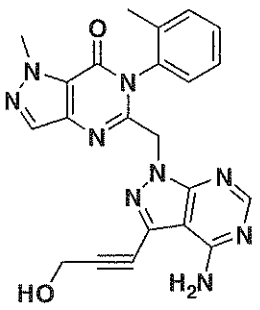
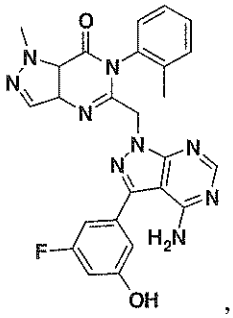
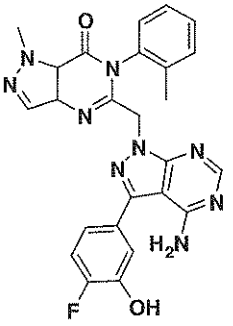
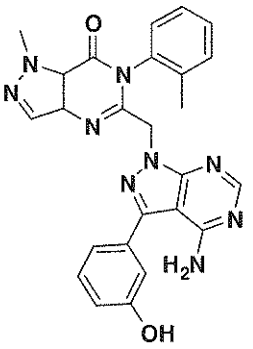
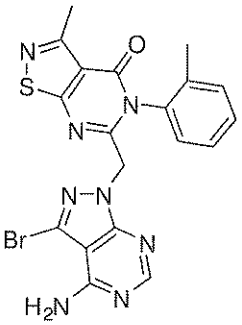
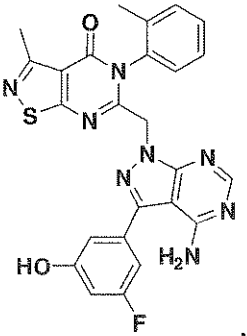
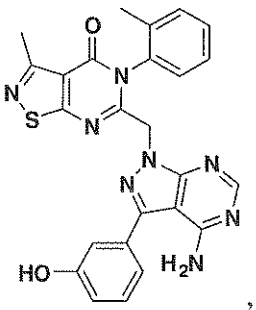
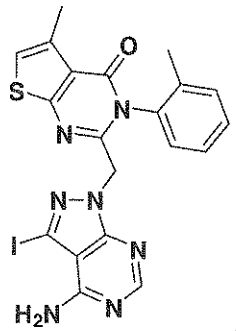
R^{12} is hydrogen, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

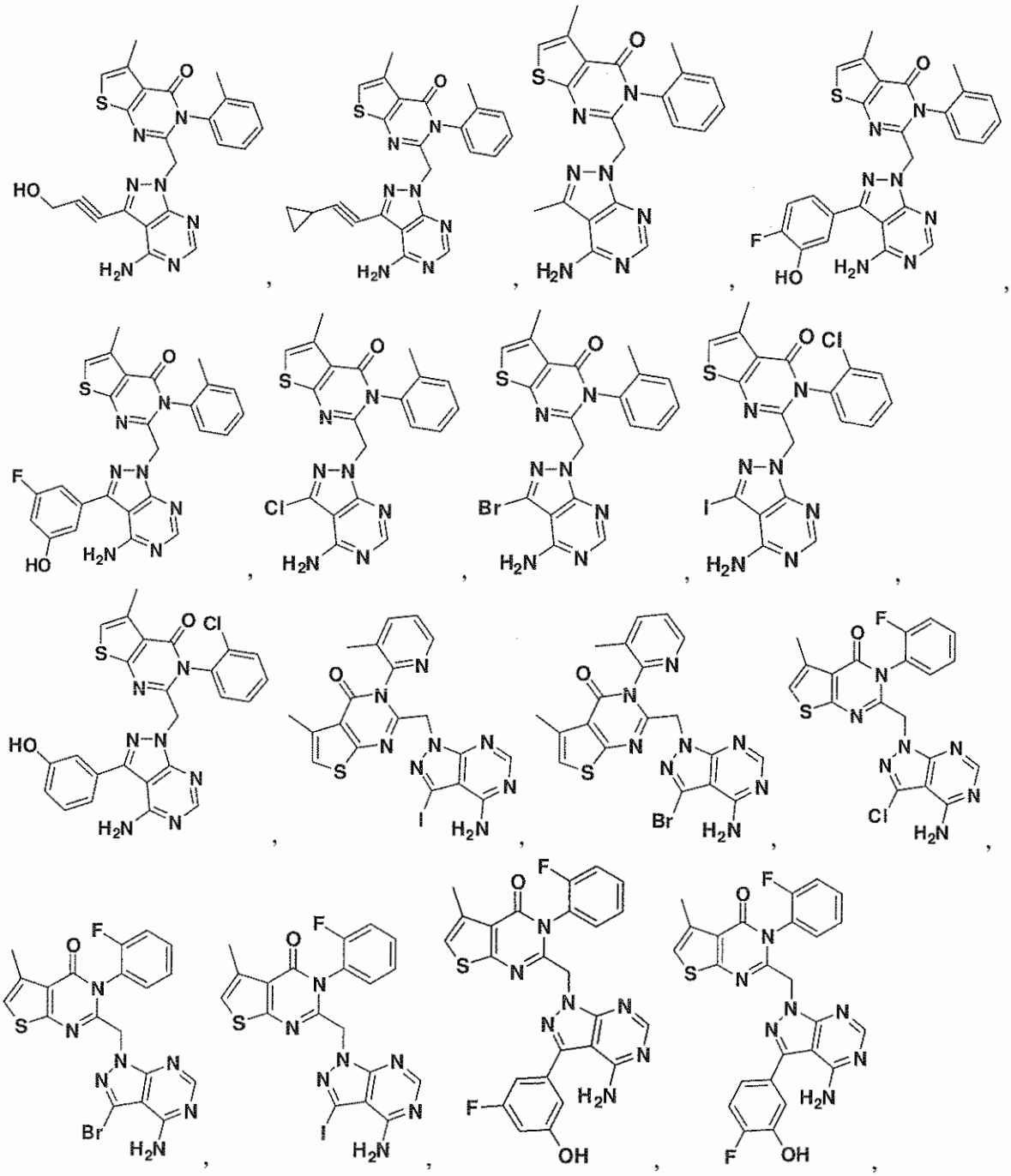
33. The compound of claim 32 or a pharmaceutically acceptable salt thereof, wherein R^{12} is iodo, bromo,

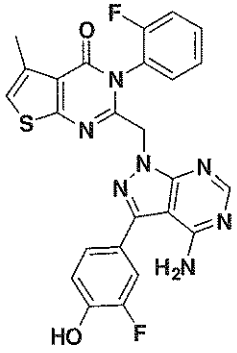
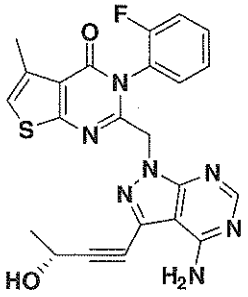
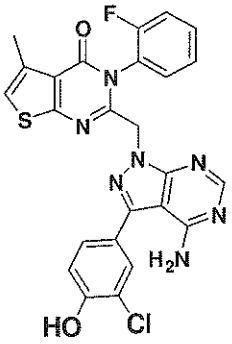
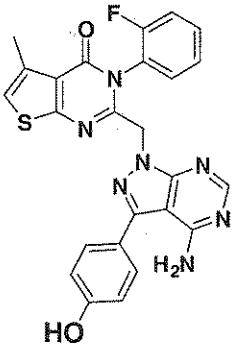
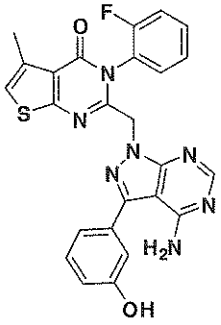
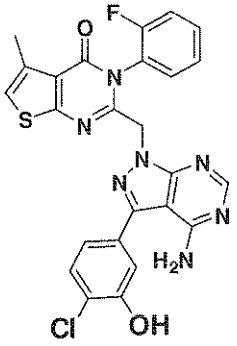
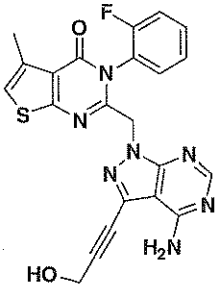
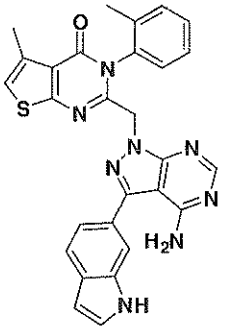
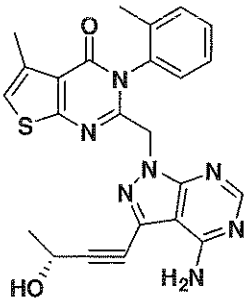
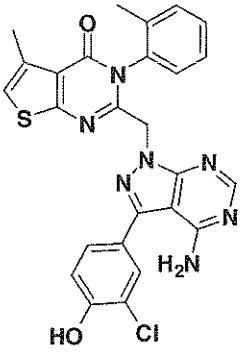
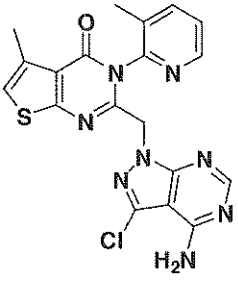
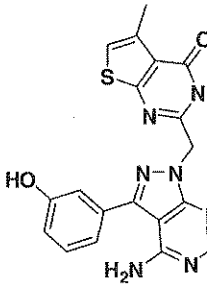
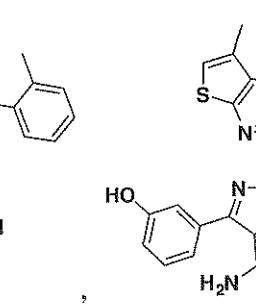
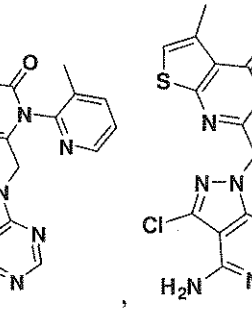






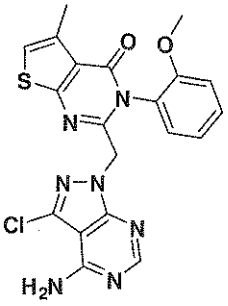


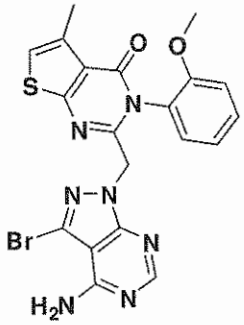
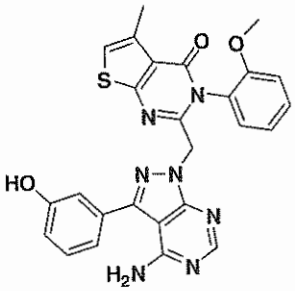
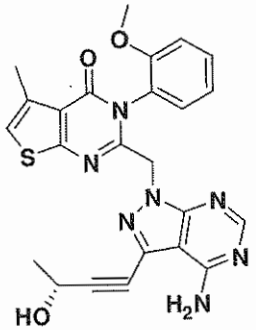
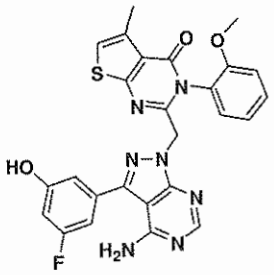
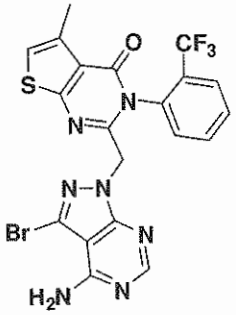
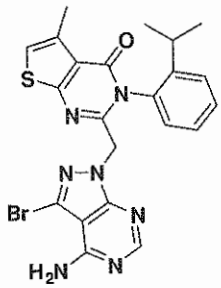
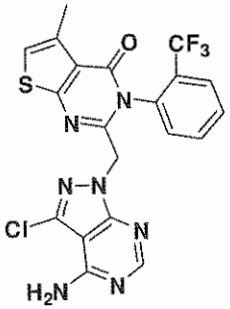
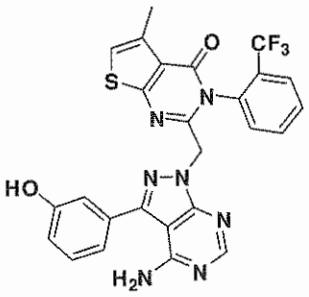
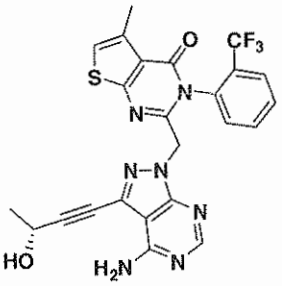
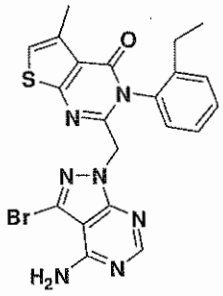
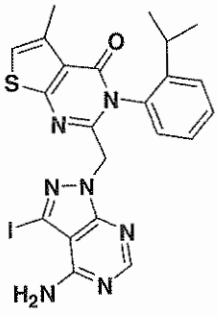
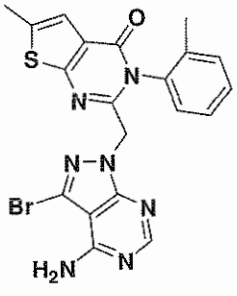
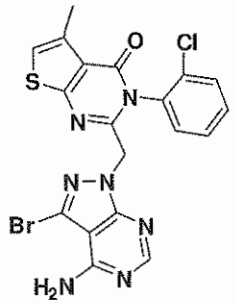
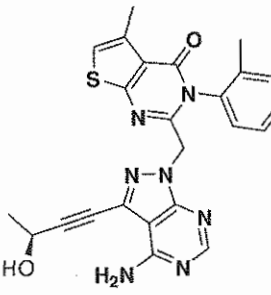
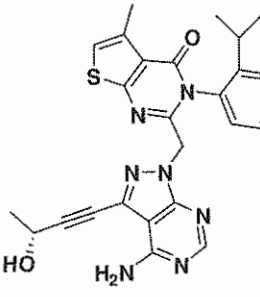
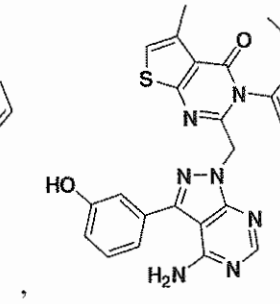
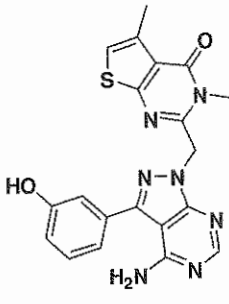
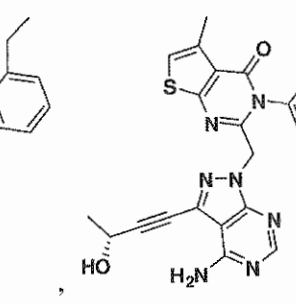
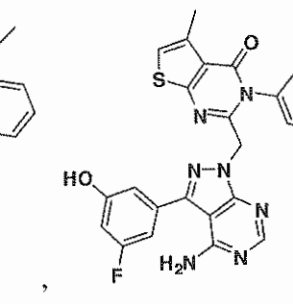
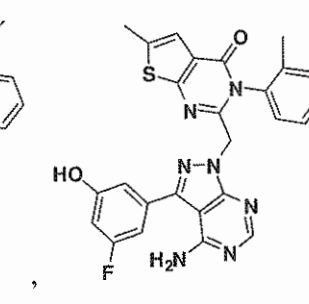
34. The compound of claim 28, wherein the compound is:

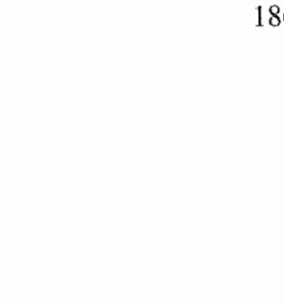
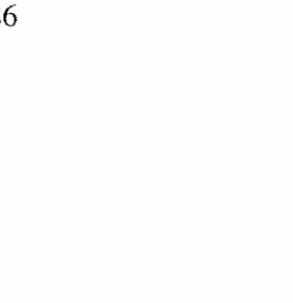













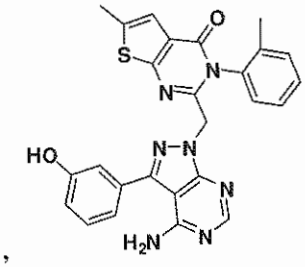
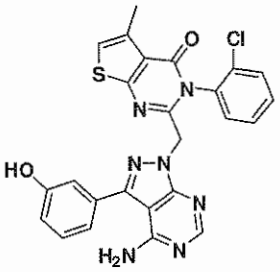
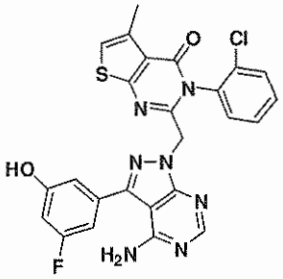
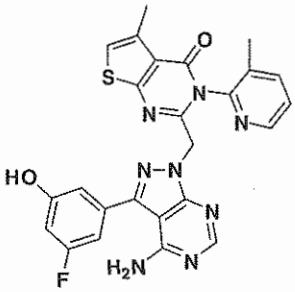
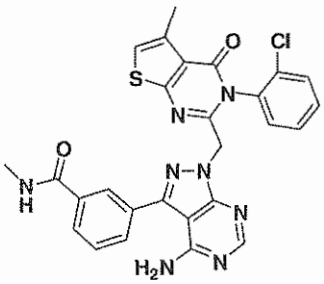
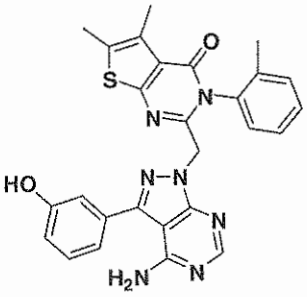
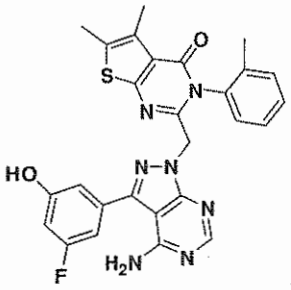
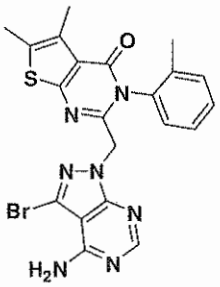
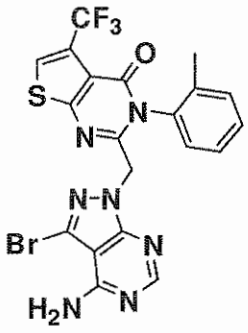
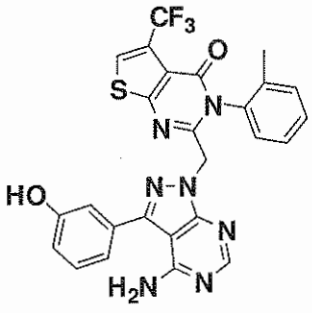
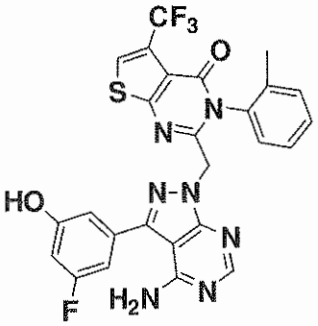




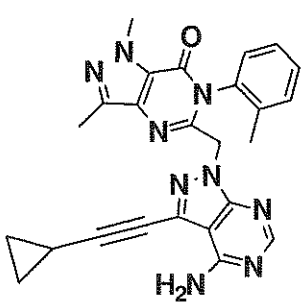
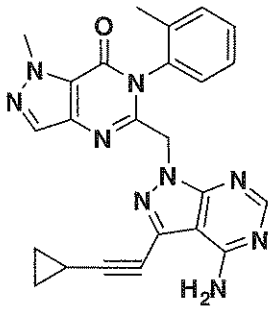
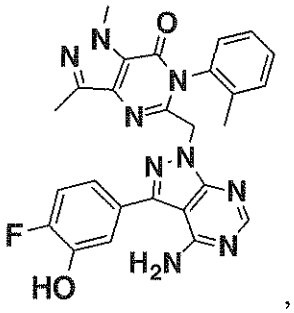
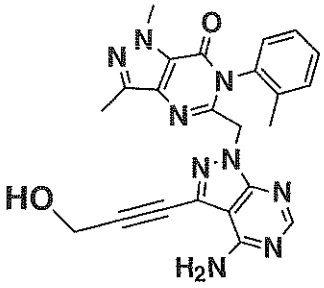
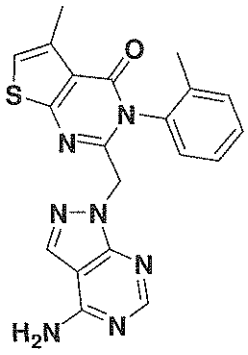
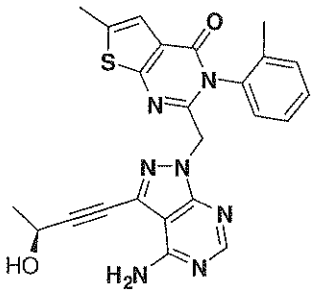

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or a pharmaceutically acceptable salt thereof.

35. The compound of claim 28, wherein the compound is:


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or a pharmaceutically acceptable salt thereof.

36. A composition comprising a pharmaceutically acceptable excipient and a compound of any one of claims 1 to 35.

37. The composition of claim 36 wherein the composition is a liquid, solid, semi-solid, gel, or an aerosol form.