CERTAIN CHEMICAL ENTITIES, COMPOSITIONS AND METHODS

[0001] This application claims the benefit of U.S. Provisional Application Serial Nos. 61/009,971, filed on January 4, 2008; 61/194,294 filed on September 26, 2008, and 61/201,146 filed December 5, 2008, and the co-pending case under attorney docket number 35280-714.602 filed herewith, each of which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The activity of cells can be regulated by external signals that stimulate or inhibit intracellular events. The process by which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response is referred to as signal transduction. Over the past decades, cascades of signal transduction events have been elucidated and found to play a central role in a variety of biological responses. Defects in various components of signal transduction pathways have been found to account for a vast number of diseases, including numerous forms of cancer, inflammatory disorders, metabolic disorders, vascular and neuronal diseases (Gaestel et al. *Current Medicinal Chemistry* (2007) 14:2214-2234).

[0003] Kinases represent a class of important signaling molecules. Kinases can generally be classified into protein kinases and lipid kinases, and certain kinases exhibit dual specificities. Protein kinases are enzymes that phosphorylate other proteins and/or themselves (i.e., autophosphorylation). Protein kinases can be generally classified into three major groups based upon their substrate utilization: tyrosine kinases which predominantly phosphorylate substrates on tyrosine residues (e.g., erb2, PDGF receptor, EGF receptor, VEGF receptor, src, abl), serine/threonine kinases which predominantly phosphorylate substrates on serine and/or threonine residues (e.g., mTorC1, mTorC2, ATM, ATR, DNA-PK, Akt), and dual-specificity kinases which phosphorylate substrates on tyrosine, serine and/or threonine residues.

[0004] Lipid kinases are enzymes that catalyze the phosphorylation of lipids. These enzymes, and the resulting phosphorylated lipids and lipid-derived biologically active organic molecules, play a role in many different physiological processes, including cell proliferation, migration, adhesion, and differentiation. Certain lipid kinases are membrane associated and they catalyze the phosphorylation of lipids contained in or associated with cell membranes. Examples of such enzymes include phosphoinositide(s) kinases (such as PI3-kinases, PI4-Kinases), diacylglycerol kinases, and sphingosine kinases.

[0005] The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated systems in human cancers. PI3K signaling is also a key factor in many other diseases in humans. PI3K signaling is involved in many disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

[0006] PI3Ks are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation (Katso et al., 2001). The class I PI3Ks (p110α, p110β, p110δ, and p110γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases. The class II and III PI3-Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2. The PIKKs are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

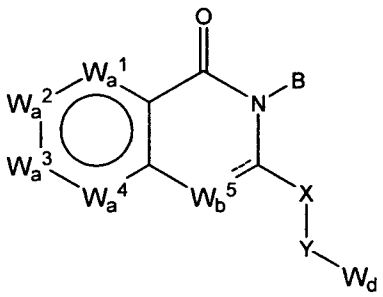
[0007] The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3K δ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3K δ is integrally 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 plckstrin 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.

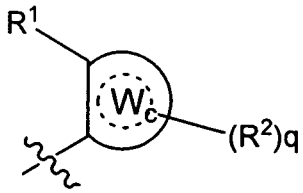
SUMMARY OF THE INVENTION

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



Formula I

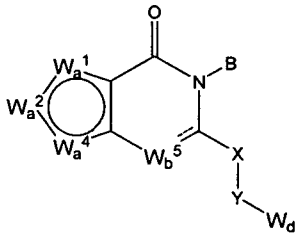
[0011] W_a^1 is CR^3 or N; W_a^2 is CR^5 or N; W_a^3 is CR^6 or N; W_a^4 is N or CR^7; W_b^5 is CR^8, CHR^8, or N, wherein no more than two adjacent ring atoms selected from W_a^1, W_a^2, W_a^3, W_a^4, and W_b^5 are heteroatoms. W_d is heterocycloalkyl, aryl or heteroaryl. B is alkyl, amino, heteroalkyl,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



Formula II

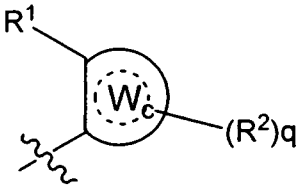
[0012] wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4. X is absent or is $-(CH(R^9))_z$-and each instance of z is independently an integer of 1, 2, 3, or 4. Y is absent, --O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^9)-, -C(=O)-(CHR^9)$_z$-, -C(=O)-, -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_4alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, heterocycloalkyl, 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. Each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, or C_2-C_{10}heteroalkyl.

[0013] 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:

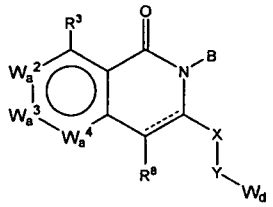


Formula II

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,

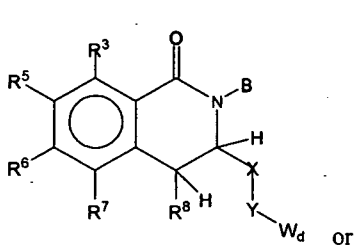
amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate. R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl,sulfonamido,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



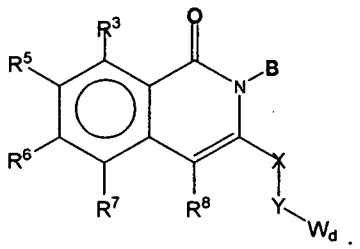
Formula IV

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



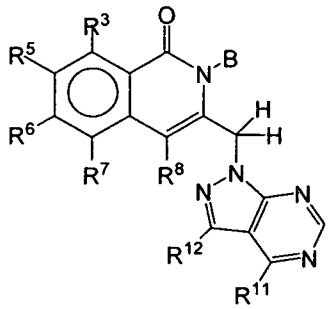
Formula V

or



Formula VI

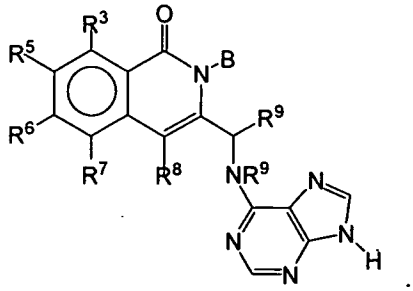
[0016] In some embodiments, the compound of Formula VI has the structure of Formula VI-A:



Formula VI-A

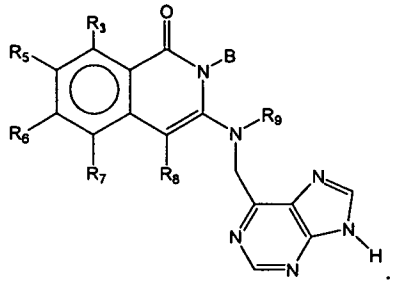
[0017] In some embodiments of the compound of Formula VI-A, R^{11} is amino. In some embodiments of the compound of Formula VI-A, R^{12} is alkyl, alkenyl, alkynyl, heteroaryl, aryl, heterocycloalkyl, cyano, amino, carboxylic acid, or amido. In some embodiments of the compound of Formula VI-A, R^{12}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

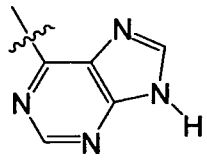
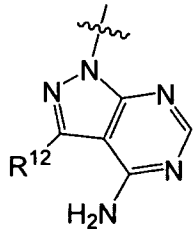


Formula VI-C

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



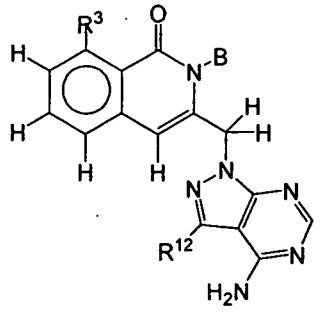
Formula VI-D

[0020] 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;

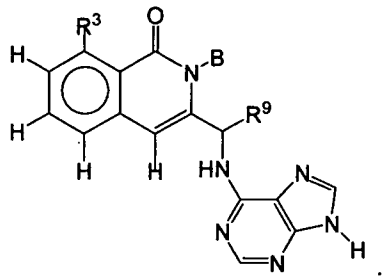
[0022] R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl or heteroaryl; each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, or C_2-C_{10}heteroalkyl;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



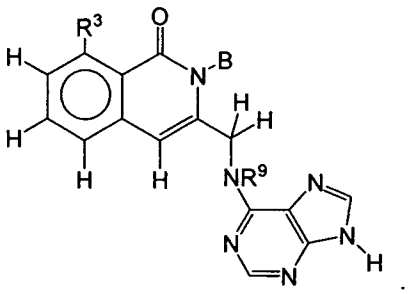
Formula 6-A

[0024] In some embodiments, the compound of Formula VI has the structure of Formula 6-C1:



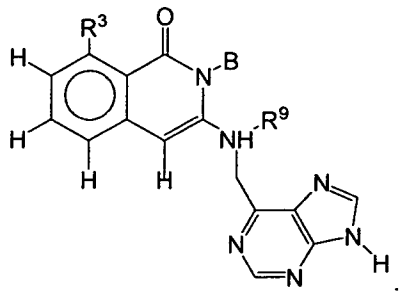
Formula 6-C1

[0025] In some embodiments, the compound of Formula VI has the structure of Formula 6-C2:



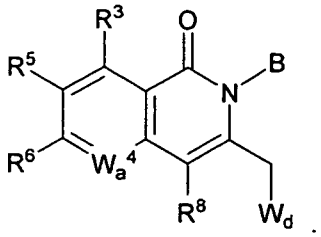
Formula 6-C2

[0026] In some embodiments, the compound of Formula VI has the structure of Formula 6-D:



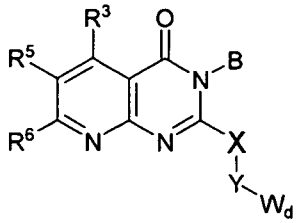
Formula 6-D

[0027] In some embodiments a compound of Formula I is of Formula VII:



Formula VII

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

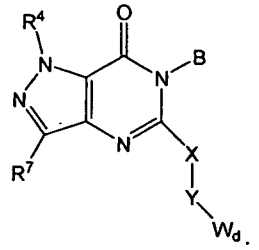


Formula VIII

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

[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.

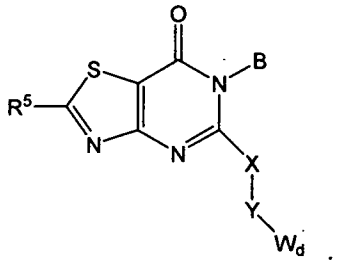
[0030] In some embodiments of the invention, the compound of Formula IX is of Formula X:



Formula X

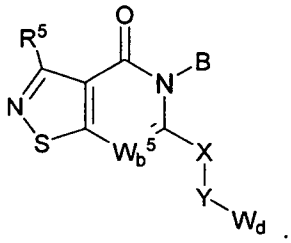
[0031] In some embodiments of the invention, the compound of Formula IX is the compound wherein R^4 is C_1-C_4alkyl or C_3-C_5cycloalkyl. In some embodiments of the invention, the compound of Formula IX is the compound wherein R^4 is methyl or ethyl.

[0032] In some embodiments of the invention, the compound of Formula IX is the compound of Formula XI:



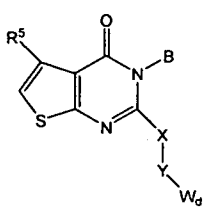
Formula XI

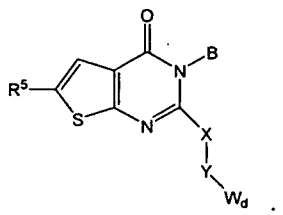
[0033] In some embodiments of the invention, the compound of Formula IX is the compound of Formula XII:



Formula XII

[0034] In some embodiments of the invention, the compound of Formula VIII is the compound of Formula XII or XIII





Formula XIII Formula XIV

[0035] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VI-A, VI-C, VI-D, 6-A, 6-C1, 6-C2, 6-D, VII, VIII, IX, X, XI, XII, XIII, or XIV is the compound wherein B is a member of the group consisting of a moiety of Formula II, wherein W_c is aryl including but not limited to substituted phenyl, heteroaryl including but not limited to monocyclic heteroaryl, heterocycloalkyl, or cycloalkyl, heterocycloalkyl, alkyl, including but not limited to a moiety having the formula $-(CH_2)_2-NR^aR^a$, wherein each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, or $-NR^aR^a$ are combined together to form a cyclic moiety.

[0036] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VI-A, VI-C, VI-D, 6-A, 6-C1, 6-C2, 6-D, VII, VIII, IX, X, XI, XII, XIII, or XIV is the compound wherein R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate.

[0037] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VI-A, VI-C, VI-D, 6-A, 6-C1, 6-C2, 6-D, VII, VIII, IX, X, XI, XII, XIII, or XIV is the compound wherein R^2 is a alkyl, halo, hydroxy, cyano, nitro, or phosphate and q is 1 or 2.

[0038] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VI-A, VI-C, VI-D, 6-A, 6-C1, 6-C2, 6-D, VII, or VIII is the compound wherein R^3 is -H, halo including but not limited to -Cl or -F , alkyl including but not limited to $-CH_3$ or-CH_2CH_3, alkoxy, cycloalkyl, or - CF_3.

[0039] In some embodiments of the invention, the compound of Formula IX, or X, R^4 is selected from –H, methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, cyclobutyl, and cyclopentyl.

[0040] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VI-A, VI-C, VI-D,VII, VIII, IX, XI, XII, XIII or XIV is the compound wherein R^5 is H, -CN, $-NH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, $-CF_3$, NO_2, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, or halo, which includes but is not limited to -Cl or -F.

[0041] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VI-A, VI-C, VI-D, VII, or VIII is the compound wherein R^6 is H, -CN, $-NH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, $-CF_3$, NO_2, $-CH_3$, or halo.

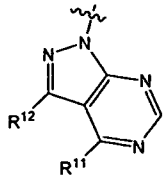
[0042] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VI-A, VI-C, VI-D, VII, VIII, IX, or X is the compound wherein R^7 is H, -CN, $-NH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, $-CF_3$, NO_2, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, or halo.

[0043] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VI-A, VI-C, VI-D, VII, IX, or XII is the compound wherein R^8 is H, -CN, $-NH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, $-CF_3$, NO_2, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, or halo.

[0044] In some of the embodiments of Formula I, IV, VI, or VII, R^5, R^6, R^7, and R^8 are hydrogen.

[0045] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VI-A, VI-C, VI-D, VII, VIII, IX, X, XI, XII, XIII or XIV is the compound wherein X is $-CH_2$-, $-CH(CH_2CH_3)$-or $-CH(CH_3)$-, inlcuding but not limited wherein $-CH(CH_2CH_3)$-or $-CH(CH_3)$- is in a (S) or (R) stereochemical configuration. In some embodiments of the invention, the compound of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII or XIV is the compound wherein Y is absent, -O-, $-NH(R^9)$-, or $-S(=O)_2$-. In some embodiments of the invention, the compound of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII or XIV is the compound wherein R^9 is methyl or hydrogen. In some embodiments of the invention, the compound of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII or XIV is the compound wherein X-Y is $-CH_2N(CH_3)$, $-CH_2$-$N(CH_2CH_3)$, $-CH(CH_3)NH$-,$-CH(CH_2CH_3)$-NH-, -N(H)CH_2-, $-N(CH_2CH_3)$ CH_2- or -$N(CH_3)CH_2$-, including but not limited to $-CH(CH_3)NH$- or $-CH(CH_2CH_3)$-NH having a (S) or (R) sterochemical configuration.

[0046] In some embodiments of the invention, the compound of Formula I, IV, V, VI, VII, VIII , IX, X, XI, XII, XIII or XIV is the compound wherein W_d is pyrazolopyrimidine including but not limited to 4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl or 7-amino-2-methyl-2*H*-pyrazolo[4,3-d]pyrimidin-3-yl, purine including but not limited to6-amino-9H-purin-9-yl or 6-methylenyl-9H-purin-6-yl. In some embodiments of the invention, the compound of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII or XIV is the compound wherein the pyrazolopyrimidine is of Formula III:



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] 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] 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] 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.

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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0054] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0055] FIG. 1 depicts an exemplary protocol for measuring T-cell independent production of TNP specific antibodies *in vivo*.

[0056] FIG. 2 depicts the fold reduction in TNP specific IgG3 response to antigens provided by compounds 7 and 53 of formula IV as compared to a vehicle control, when administered orally.

[0057] FIG. 3 depicts the dose-dependent effect of twice daily oral administration of compound 53 of formula IV in reducing the increase in ankle diameter over time in a collagen-induced developing arthritis model in rats. Also depicted are the results from non-arthritic control rats, arthritic control rats administered with a negative control vehicle, and arthritic control rats treated twice daily with methotrexate.

[0058] FIG. 4 depicts the dose-dependent effect of compounds 7 and 53 of formula IV in improving ankle histopathology when administered in a collagen-induced developing arthritis model in rats. Also depicted are the results from arthritic control rats administered with negative control vehicle or methotrexate.

[0059] FIG. 5 depicts the dose-dependent effect of compounds 7 and 53 of formula IV in improving knee histopathology when administered in a collagen-induced developing arthritis model in rats. Also depicted are the results from arthritic control rats administered with negative control vehicle or positive control methotrexate.

[0060] FIG. 6 depicts the dose-dependent effect of compounds 7 and 53 of formula IV in reducing the level of anti-type II collagen antibodies *in vivo* when administered to a collagen-induced developing arthritis rat model. Also depicted are the results from arthritic rats administered with negative control vehicle or methotrexate.

[0061] FIG. 7 depicts the dose-dependent effect of compound 7 of formula IV on improving ankle histopathology when administered in collagen-induced developing arthritis model in rats. Also depicted are the results from arthritic vehicle control rats and methotrexate-treated arthritic rats.

[0062] FIG. 8 depicts the dose-dependent effect of compound 53 of formula IV administered daily on ankle histopathology in a collagen-induced established arthritis model in rats. Also depicted are the results from arthritic arthritic vehicle control rats and Enbrel-treated arthritic rats.

[0063] FIG. 9 depicts the dose-dependent effect of compound 53 of formula IV administered twice daily on ankle histopathology in a collagen-induced established arthritis model in rats. Also depicted are the results from arthritic vehicle control rats and Enbrel-treated arthritic rats.

[0064] FIG 10 depicts the dose-dependent effect of compound 53 of formula IV on the increase in average paw volume in an adjuvant induced arthritis model.

[0065] FIG 11 depicts the effect of compound 53 of formula IV on the average weight over time of rats in an adjuvant induced arthritis model in rats.

DETAILED DESCRIPTION OF THE INVENTION

[0066] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in

practicing the invention. It is intended that the appended claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[0067] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

[0068] As used in the specification and claims, the singular form "a", "an" and "the" includes plural references unless the context clearly dictates otherwise.

[0069] As used herein, "agent" or "biologically active agent" refers to a biological, pharmaceutical, or chemical compound or other moiety. Non-limiting examples include simple or complex organic or inorganic molecule, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, antibody fragment, a vitamin derivative, a carbohydrate, a toxin, or a chemotherapeutic compound. Various compounds can be synthesized, for example, small molecules and oligomers (e.g., oligopeptides and oligonucleotides), and synthetic organic compounds based on various core structures. In addition, various natural sources can provide compounds for screening, such as plant or animal extracts, and the like. A skilled artisan can readily recognize that there is no limit as to the structural nature of the agents of the present invention.

[0070] The term "agonist" as used herein refers to a compound having the ability to initiate or enhance a biological function of a target protein, whether by inhibiting the activity or expression of the target protein. Accordingly, the term "agonist" is defined in the context of the biological role of the target polypeptide. While preferred agonists herein specifically interact with (e.g. bind to) the target, compounds that initiate or enhance a biological activity of the target polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

[0071] The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound having the ability to inhibit a biological function of a target protein, whether by inhibiting the activity or expression of the target protein. Accordingly, the terms "antagonist" and "inhibitors" are defined in the context of the biological role of the target protein. While preferred antagonists herein specifically interact with (e.g. bind to) the target, compounds that inhibit a biological activity of the target protein by interacting with other members of the signal transduction pathway of which the target protein is a member are also specifically included within this definition. A preferred biological activity inhibited by an antagonist is associated with the development, growth, or spread of a tumor, or an undesired immune response as manifested in autoimmune disease.

[0072] An "anti-cancer agent", "anti-tumor agent" or "chemotherapeutic agent" refers to any agent useful in the treatment of a neoplastic condition. One class of anti-cancer agents comprises chemotherapeutic agents. "Chemotherapy" means the administration of one or more chemotherapeutic drugs and/or other agents to a cancer patient by various methods, including intravenous, oral, intramuscular, intraperitoneal, intravesical, subcutaneous, transdermal, buccal, or inhalation or in the form of a suppository.

[0073] The term "cell proliferation" refers to a phenomenon by which the cell number has changed as a result of division. This term also encompasses cell growth by which the cell morphology has changed (e.g., increased in size) consistent with a proliferative signal.

[0074] The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompasses administration of two or more agents to an animal so that both agents and/or their metabolites are present in the animal at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[0075] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound described herein that is sufficient to effect the intended application including but not limited to disease treatment, as defined below. The therapeutically effective amount may vary depending upon the intended application (*in vitro or in vivo)*, or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g. reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0076] As used herein, "treatment" or "treating," or "palliating" or "ameliorating" are used interchangeably herein. These terms refers to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0077] A "therapeutic effect," as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0078] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0079] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0080] "Signal transduction" is a process during which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response. A modulator of a signal transduction pathway refers to a compound which modulates the activity of one or more cellular proteins mapped to the same specific signal transduction pathway. A modulator may augment (agonist) or suppress (antagonist) the activity of a signaling molecule.

[0081] The term "selective inhibition" or "selectively inhibit" as applied to a biologically active agent refers to the agent's ability to selectively reduce the target signaling activity as compared to off-target signaling activity, via direct or interact interaction with the target.

[0082] The term "B-ALL" as used herein refers to B-cell Acute Lymphoblastic Leukemia.

[0083] "Subject" refers to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics and veterinary applications. In some embodiments, the patient is a mammal, and in some embodiments, the patient is human.

[0084] "Radiation therapy" means exposing a patient, using routine methods and compositions known to the practitioner, to radiation emitters such as alpha-particle emitting radionuclides (e.g., actinium and thorium radionuclides), low linear energy transfer (LET) radiation emitters (i.e. beta emitters), conversion electron emitters (e.g. strontium-89 and samarium-153-EDTMP, or high-energy radiation, including without limitation x-rays, gamma rays, and neutrons.

[0085] "Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.,* Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound in vivo when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like.

[0086] The term "*in vivo*" refers to an event that takes place in a subject's body.

[0087] The term "*in vitro*" refers to an event that takes places outside of a subject's body. For example, an *in vitro* assay encompasses any assay run outside of a subject assay. *In vitro* assays encompass cell-based assays in which cells alive or dead are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

[0088] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0089] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0090] When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, that "consist of" or "consist essentially of" the described features.

[0091] The following abbreviations and terms have the indicated meanings throughout

PI3-K = Phosphoinositide 3-kinase; PI = phosphatidylinositol; PDK = Phosphoinositide Dependent Kinase; DNA-PK = Deoxyribose Nucleic Acid Dependent Protein Kinase; PTEN = Phosphatase and Tensin homolog deleted on chromosome Ten; PIKK = Phosphoinositide Kinase Like Kinase; AIDS = Acquired Immuno Deficiency Syndrome; HIV = Human Immunodeficiency Virus; MeI = Methyl Iodide; $POCl_3$ = Phosphorous Oxychloride; KCNS = Potassium IsoThiocyanate; TLC = Thin Layer Chromatography; MeOH = Methanol; and $CHCl_3$ = Chloroform.

[0092] Abbreviations used herein have their conventional meaning within the chemical and biological arts.

[0093] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, C_1-C_{10} alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; e.g., "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, it is a C_1-C_4 alkyl group. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl isobutyl, tertiary butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl, decyl, and the like. The alkyl is attached to the rest of the molecule by a single bond, for example, methyl (Me), ethyl (Et), *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, and the like. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$ where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0094] "Alkylaryl" refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0095] "Alkylhetaryl" refers to an -(alkyl)hetaryl radical where hetaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0096] "Alkylheterocycloalkyl" refers to an –(alkyl) heterocycyl radical where alkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and alkyl respectively.

[0097] An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[0098] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (i.e. C_2-C_{10} alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; e.g., "2 to 10 carbon atoms" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to five carbon atoms (e.g., C_2-C_5 alkenyl). The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0099] "Alkenyl-cycloalkyl" refers to refers to an -(alkenyl)cycloalkyl radical where alkenyl and cyclo alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively.

[00100] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (i.e. C_2-C_{10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; e.g., "2 to 10 carbon atoms" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to five carbon atoms (e.g., C_2-C_5 alkynyl). The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00101] "Alkynyl-cycloalkyl" refers to refers to an -(alkynyl)cycloalkyl radical where alkynyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkynyl and cycloalkyl respectively.

[00102] "Carboxaldehyde" refers to a –(C=O)H radical.

[00103] "Carboxyl" refers to a –(C=O)OH radical.

[00104] "Cyano" refers to a –CN radical.

[00105] "Cycloalkyl" refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and may be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms (i.e. C_2-C_{10} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range; e.g., "3 to 10 carbon atoms" means that the cycloalkyl group may consist of 3 carbon atoms, etc., up to and including 10 carbon atoms. In some embodiments, it is a C_3-C_8 cycloalkyl radical. In some embodiments, it is a C_3-C_5 cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloseptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, and the like. Unless stated otherwise specifically in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00106] "Cycloalkyl-alkenyl" refers to a –(cycloalkyl) alkenyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively.

[00107] "Cycloalkyl-heterocycloalkyl" refers to a –(cycloalkyl) heterocycyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively.

[00108] "Cycloalkyl-heteroaryl" refers to a –(cycloalkyl) heteroaryl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively.

[00109] The term "alkoxy" refers to the group -O-alkyl, including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. "Lower alkoxy" refers to alkoxy groups containing one to six carbons. In some embodiments, C_1-C_4 alkyl, is an alkyl group which encompasses both straight and branched chain alkyls of from 1 to 4 carbon atoms.

[00110] The term "substituted alkoxy" refers to alkoxy wherein the alkyl constituent is substituted (i.e., -O-(substituted alkyl)). Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, SR^a, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently

hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00111] The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a C_1-C_6 alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkoxy group is a lower alkoxy group. In some embodiments, C_1-C_4 alkoxy, is an alkoxy group which encompasses both straight and branched chain alkoxy groups of from 1 to 4 carbon atoms.

[00112] The term "substituted alkoxycarbonyl" refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality. Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxycarbonyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, SR^a, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00113] "Acyl" refers to the groups (alkyl)-C(O)-, (aryl)-C(O)-, (heteroaryl)-C(O)-, (heteroalkyl)-C(O)-, and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality. In some embodiments, it is a C_1-C_{10} acyl radical which refers to the total number of chain or ring atoms of the alkyl, aryl, heteroaryl or heterocycloalkyl portion of the acyloxy group plus the carbonyl carbon of acyl, i.e three other ring or chain atoms plus carbonyl. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, SR^a, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00114] "Acyloxy" refers to a R(C=O)O- radical wherein "R" is alkyl, aryl, heteroaryl, heteroalkyl, or heterocycloalkyl, which are as described herein. In some embodiments, it is a C_1-C_4 acyloxy radical which refers to the total number of chain or ring atoms of the alkyl, aryl, heteroaryl or heterocycloalkyl portion of the acyloxy group plus the carbonyl carbon of acyl, i.e three other ring or chain atoms plus carbonyl. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2-$S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$

(where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00115] "Amino" or "amine" refers to a $-N(R^a)_2$ radical group, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, unless stated otherwise specifically in the specification. When a $-N(R^a)_2$ group has two Ra other than hydrogen they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, $-N(R^a)_2$ is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise specifically in the specification, an amino group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl and each of these moieties may be optionally substituted as defined herein.

[00116] The term "substituted amino" also refers to N-oxides of the groups $-NHR^d$, and NR^dR^d each as described above. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid. The person skilled in the art is familiar with reaction conditions for carrying out the N-oxidation.

[00117] "Amide" or "amido" refers to a chemical moiety with formula $-C(O)N(R)_2$ or $-NHC(O)R$, where R is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), each of which moiety may itself be optionally substituted. In some embodiments it is a C_1-C_4 amido or amide radical, which includes the amide carbonyl in the total number of carbons in the radical. The R_2 of $-N(R)_2$ of the amide may optionally be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6-, or 7-membered ring. Unless stated otherwise specifically in the specification, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. An amide may be an amino acid or a peptide molecule attached to a compound of Formula (I), thereby forming a prodrug. Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be amidified. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3.sup.rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety.

[00118] "Aromatic" or "aryl" refers to an aromatic radical with six to ten ring atoms (e.g., C_6-C_{10} aromatic or C_6-C_{10} aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (e.g., phenyl, fluorenyl, and naphthyl). Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10" refers to each integer in the given range; e.g., "6 to 10 ring atoms" means that the aryl group may consist of 6 ring atoms, 7 ring atoms, etc., up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, an aryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl,

alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -$N(R^a)_2$, -C(O)R^a, -C(O)OR^a, -OC(O)$N(R^a)_2$, -C(O)$N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00119] "Aralkyl" or "arylalkyl" refers to an (aryl)alkyl— radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[00120] "Ester" refers to a chemical radical of formula –COOR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be esterified. The procedures and specific groups to make such esters are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3.sup.rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety. Unless stated otherwise specifically in the specification, an ester group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -$N(R^a)_2$, -C(O)R^a, -C(O)OR^a, -OC(O)$N(R^a)_2$, -C(O)$N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00121] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical may be optionally substituted as defined above for an alkyl group.

[00122] "Halo", "halide", or, alternatively, "halogen" means fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

[00123] "Heteroalkyl" "heteroalkenyl" and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given, e.g. C_1-C_4 heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. For example, a $–CH_2OCH_2CH_3$ radical is referred to as a "C_4" heteroalkyl, which includes the heteroatom center in the atom chain length description. Connection to the rest of the molecule may be through either a heteroatom or a carbon in the heteroalkyl chain. A heteroalkyl group may be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -$N(R^a)_2$, -C(O)R^a, -C(O)OR^a, -C(O)$N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00124] "Heteroalkylaryl" refers "to an -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl respectively.

[00125] "Heteroalkylheteroaryl" refers "to an -(heteroalkyl)heteroaryl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl respectively

[00126] "Heteroalkylheterocycloalkyl" refers "to an -(heteroalkyl)heterocycloalkyl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl respectively

[00127] "Heteroalkylcycloalkyl" refers "to an -(heteroalkyl) cycloalkyl radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl respectively.

[00128] "Heteroaryl" or, alternatively, "heteroaromatic" refers to a 5- to 18-membered aromatic radical (e.g., C_5-C_{13} heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur, and which may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range; e.g., "5 to 18 ring atoms" means that the heteroaryl group may consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a pyridyl group with two points of attachment is a pyridylidene. An N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl,isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.* thienyl). Unless stated

otherwise specifically in the specification, a heteraryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00129] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as pyridinyl N-oxides.

[00130] "Heteroarylalkyl" refers to a moiety having an aryl moiety, as described herein, connected to an alkylene moiety, as described herein, wherein the connection to the remainder of the molecule is through the alkylene group.

[00131] "Heterocycloalkyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Whenever it appears herein, a numerical range such as "3 to 18" refers to each integer in the given range; e.g., "3 to 18 ring atoms" means that the heterocycloalkyl group may consist of 3 ring atoms, 4 ring atoms, etc., up to and including 18 ring atoms. In some embodiments, it is a C_5-C_{10} heterocycloalkyl. In some embodiments, it is a C_4-C_{10} heterocycloalkyl. In some embodiments, it is a C_3-C_{10} heterocycloalkyl. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. The heterocycloalkyl may be attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl moiety is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl.

[00132] "Heterocycloalkyl" also includes bicyclic ring systems wherein one non-aromatic ring, usually with 3 to 7 ring atoms, contains at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms; and the other ring, usually with 3 to 7 ring atoms, optionally contains 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and is not aromatic.

[00133] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the

stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[00134] "Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00135] "Nitro" refers to the $-NO_2$ radical.

[00136] "Oxa" refers to the -O- radical.

[00137] "Oxo" refers to the =O radical.

[00138] "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[00139] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[00140] A "leaving group or atom" is any group or atom that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable examples of such groups unless otherwise specified are halogen atoms, mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

[00141] "Protecting group" has the meaning conventionally associated with it in organic synthesis, i.e. a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and such that the group can readily be removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T.H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, New York (1999). For example, a hydroxy protected form is where at least one of the hydroxy groups present in a compound is protected with a hydroxy protecting group. Likewise, amines and other reactive groups may similarly be protected.

[00142] "Solvate" refers to a compound (e.g., a compound selected from Formula I or a pharmaceutically acceptable salt thereof) in physical association with one or more molecules of a pharmaceutically acceptable solvent. It will be

understood that "a compound of Formula I" encompass the compound of Formula I and solvates of the compound, as well as mixtures thereof.

[00143] "Substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from acyl, alkyl, alkylaryl, cycloalkyl, aralkyl, aryl, carbohydrate, carbonate, heteroaryl, heterocycloalkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, ester, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, oxo, perhaloalkyl, perfluoroalkyl, phosphate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Di-substituted amino groups encompass those which form a ring together with the nitrogen of the amino group, such as for instance, morpholino. The substituents themselves may be substituted, for example, a cycloalkyl substituent may have a halide substituted at one or more ring carbons, and the like. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above.

[00144] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl), and -S-(optionally substituted heterocycloalkyl).

[00145] "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-(optionally substituted amino), -S(O)-(optionally substituted aryl), -S(O)-(optionally substituted heteroaryl), and -S(O)-(optionally substituted heterocycloalkyl).

[00146] "Sulfonyl" refers to the groups: $-S(O_2)$-H, $-S(O_2)$-(optionally substituted alkyl), $-S(O_2)$-(optionally substituted amino), $-S(O_2)$-(optionally substituted aryl), $-S(O_2)$-(optionally substituted heteroaryl), and $-S(O_2)$-(optionally substituted heterocycloalkyl).

[00147] "Sulfonamidyl" or "sulfonamido" refers to a $-S(=O)_2-NRR$ radical, where each R is selected independently from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The R groups in –NRR of the $-S(=O)_2-NRR$ radical may be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6-, or 7-membered ring. In some embodiments, it is a C_1-C_{10} sulfonamido, wherein each R in sulfonamido contains 1 carbon, 2 carbons, 3 carbons, or 4 carbons total. A sulfonamido group is optionally substituted by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl respectively

[00148] "Sulfoxyl" refers to a $-S(=O)_2OH$ radical.

[00149] "Sulfonate" refers to a $-S(=O)_2-OR$ radical, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl respectively.

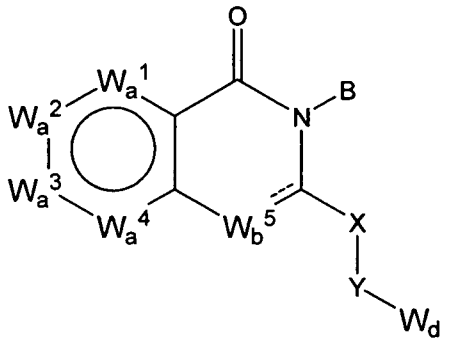
[00150] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[00151] Compounds of the present invention also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form," "polymorph," and "novel form" may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to.

[00152] Chemical entities include, but are not limited to, compounds of Formula I, IV, V. VI, VII, VIII, IX, X, XI, XII, XIII, and XIV and all pharmaceutically acceptable forms thereof. Pharmaceutically acceptable forms of the compounds recited herein include pharmaceutically acceptable salts, chelates, non-covalent complexes, prodrugs, and mixtures thereof. In certain embodiments, the compounds described herein are in the form of pharmaceutically acceptable salts. Hence, the terms "chemical entity" and "chemical entities" also encompass pharmaceutically acceptable salts, chelates, non-covalent complexes, prodrugs, and mixtures.

[00153] In addition, if the compound of Formula I, IV, V. VI, VII, VIII, IX, X, XI, XII, XIII, or XIV is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

[00154] In one aspect, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof:,



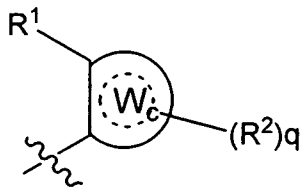
Formula I

[00155] 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,

[00156] 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;

[00157] W_d is heterocycloalkyl, aryl or heteroaryl;

[00158] B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II;



Formula II

[00159] wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4;

[00160] X is absent or is $-(CH(R^9))z$ and each instance of z independently is an integer of 1, 2, 3, or 4;

[00161] 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 $-C(=O)-(CHR^9)_z-$;

[00162] 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;

[00163] 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;

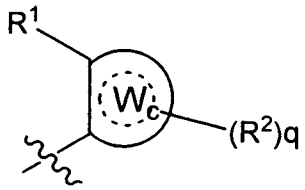
[00164] R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl, or heteroaryl;

[00165] R^5, R^6, R^7, and R^8 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxy or nitro; and

[00166] each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, or C_2-C_{10}heteroalkyl.

[00167] In some embodiments, W_a^1 is CR^3. In some embodiments, W_a^1 is N. In some embodiments, W_a^2 is CR^5. In some embodiments, W_a^2 is N. In some embodiments, W_a^3 is CR^6. In some embodiments, W_a^3 is N. In some embodiments, W_a^4 is CR^7. In some embodiments, W_a^4 is N. In some embodiments, W_b^5 is CR^8. In some embodiments, W_b^5 is CHR^8. In some embodiments, W_b^5 is N. In some embodiments, W_a^2 is CR^5, W_a^3 is CR^6 and W_a^4 is CR^7. In some embodiments, W_a^2 is N, W_a^3 is CR^6, and W_a^4 is CR^7. In some embodiments, W_a^2 is CR^5, W_a^3 is N, and W_a^4 is CR^7. In some embodiments, W_a^2 is CR^5, W_a^3 is CR^6, and W_a^4 is N. In some embodiments, W_a^2 and W_a^3 are N and W_a^4 is CR^7. In some embodiments, W_a^2 is CR^5, and W_a^3 and W_a^4 are N. In some embodiments, W_b^5 is CR^8. In some embodiments, W_b^5 is CHR^8. In some embodiments, W_b^5 is N. In some embodiments, W_a^2 is CR^5, W_a^3 is CR^6, W_a^4 is CR^7, and W_b^5 is CR^8. In some embodiments, W_a^2 is CR^5, W_a^3 is CR^6, W_a^4 is CR^7, and W_b^5 is CHR^8. In some embodiments, W_a^2 is CR^5, W_a^3 is CR^6, W_a^4 is CR^7, and W_b^5 is N. In some embodiments, W_a^2 is N, W_a^3 is CR^6, W_a^4 is CR^7, and W_b^5 is CR^8. In some embodiments, W_a^2 is N, W_a^3 is CR^6, W_a^4 is CR^7, and W_b^5 is CHR^8. In some embodiments, W_a^2 is N, W_a^3 is CR^6, W_a^4 is CR^7, and W_b^5 is N. In some embodiments, W_a^2 is CR^5, W_a^3 is N, W_a^4 is CR^7, and W_b^5 is CR^8. In some embodiments, W_a^2 is CR^5, W_a^3 is N, W_a^4 is CR^7, and W_b^5 is CHR^8. In some embodiments, W_a^2 is CR^5, W_a^3 is N, W_a^4 is CR^7, and W_b^5 is N. In some embodiments, W_a^2 is CR^5, W_a^3 is CR^6, W_a^4 is N, and W_b^5 is CR^8. In some embodiments, W_a^2 is CR^5, W_a^3 is CR^6, W_a^4 is N, and W_b^5 is CHR^8. In some embodiments, W_a^2 is CR^5, W_a^3 is CR^6, W_a^4 is N, and W_b^5 is N. In some embodiments, W_a^2 and W_a^3 are N, W_a^4 is CR^7, and W_b^5 is CR^8. In some embodiments, W_a^2 and W_a^3 are N, W_a^4 is CR^7, and W_b^5 is CHR^8. In some embodiments, W_a^2 and W_a^3 are N, W_a^4 is CR^7, and W_b^5 is N. In some embodiments, W_a^2 is CR^5, W_a^3 and W_a^4 are N, and W_b^5 is CR^8. In some embodiments, W_a^2 is CR^5, W_a^3 and W_a^4 are N, and W_b^5 is CHR^8. In some embodiments, W_a^2 is CR^5, W_a^3 and W_a^4 are N, and W_b^5 is N.

[00168] In some embodiments, B is unsubstituted or substituted alkyl, including but not limited to $-(CH_2)_2$-NR^aR^a ,wherein each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, or NR^aR^a are combined together to form a cyclic moiety, which includes but is not limited to piperidinyl, piperazinyl, and morpholinyl. In some embodiments, B is unsubstituted or substituted amino. In some embodiments, B is unsubstituted or substituted heteroalkyl.

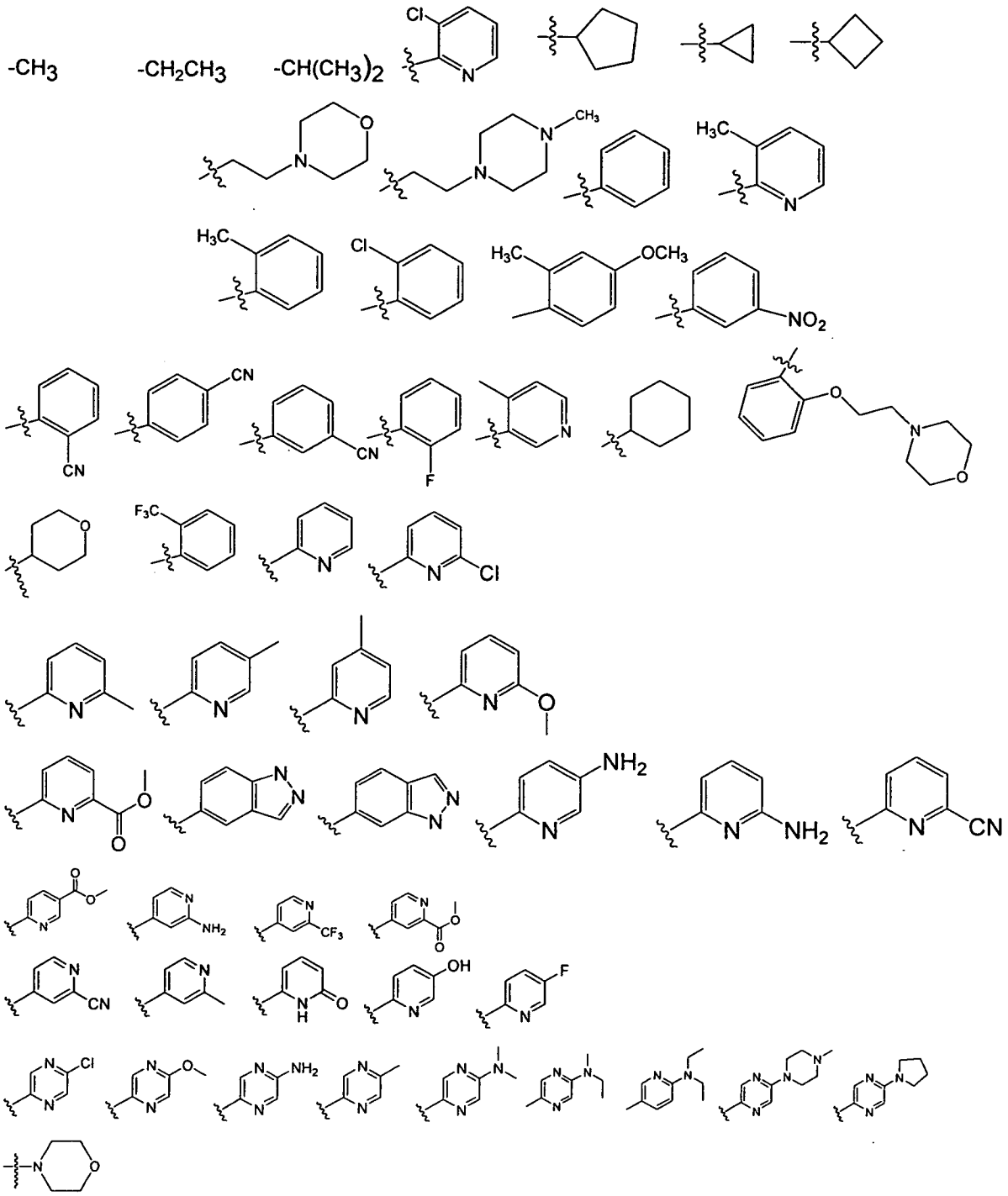


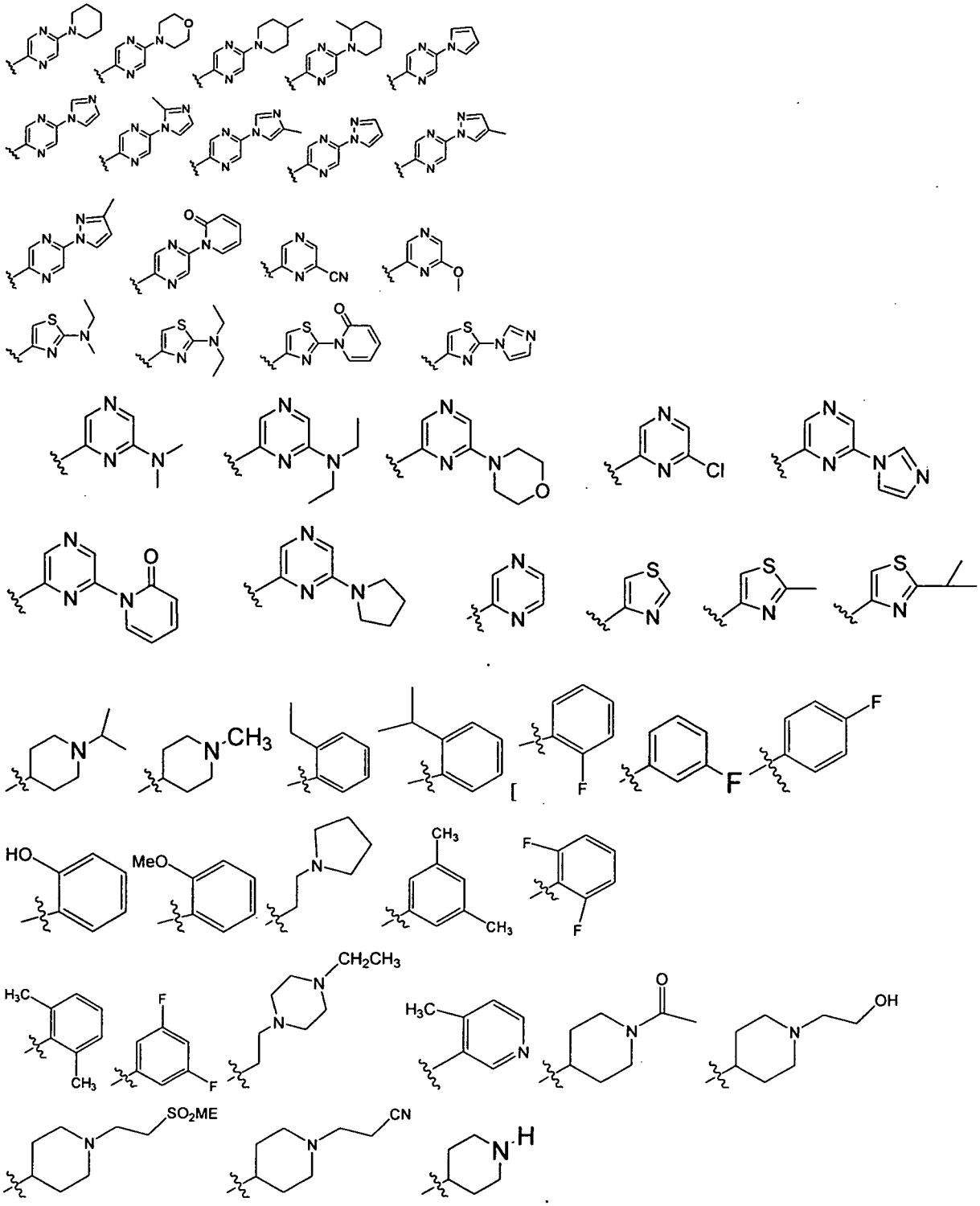
Formula II

[00169] In some embodiments, B is a moiety of Formula II and wherein W_c is a member selected from the group consisting of unsubstituted or substituted aryl, substituted phenyl, unsubstituted or substituted heteroaryl including but

not limited to pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, pyrimidin-2-yl, pyrimidin-5-yl, or pyrazin-2-yl, unsubstituted or substituted monocyclic heteroaryl, unsubstituted or substituted bicyclic heteroaryl, a heteroaryl comprising two heteroatoms as ring atoms, unsubstituted or substituted heteroaryl comprising a nitrogen ring atom, heteroaryl comprising two nitrogen ring atoms, heteroaryl comprising a nitrogen and a sulfur as ring atoms, unsubstituted or substituted heterocycloalkyl including but not limited to morpholinyl, tetrahydropyranyl, piperazinyl, and piperidinyl, unsubstituted or substituted cycloalkyl including but not limited to cyclopentyl and cyclohexyl.

[00170] In some embodiments, B is one of the following moieties:





[00171] In some embodiments, B is substituted by one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, or sulfonamido, may itself be substituted.

[00172] In some embodiments, R^1 is a member selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted heteroalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocycloalkyl. In some

embodiments, R^1 is unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroaryl, or unsubstituted or substituted heteroarylalkyl. In some embodiments, R^1 is unsubstituted or substituted alkoxy, unsubstituted or substituted amido, unsubstituted or substituted amino. In some embodiments, R^1 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, or unsubstituted or substituted sulfonamido. In some embodiments, R^1 is halo which includes –Cl, -F, -I, and -Br. In some embodiments, R^1 is selected from the group consisting of cyano, hydroxy, nitro, unsubstituted or substituted phosphate, unsubstituted or substituted urea, and carbonate.

[00173] In some embodiments, when R^1 is alkyl, R^1 is methyl, ethyl, propyl, isopropyl, *n*- butyl, *tert*- butyl, *sec*-butyl, pentyl, hexyl or heptyl.

[00174] In some embodiments, when R^1 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, or hydroxy, R^1 is substituted by phosphate, or unsubstituted urea, or substituted urea, or carbonic acid, or carbonate.

[00175] In some embodiments, when R^1 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido, R^1 is substituted by one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido may itself be substituted.

[00176] In some embodiments, R^2 is a member selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted heteroalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, and unsubstituted or substituted heterocycloalkyl. In some embodiments, R^2 is unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroaryl, or unsubstituted or substituted heteroarylalkyl. In some embodiments, R^2 is unsubstituted or substituted alkoxy, unsubstituted or substituted amido, unsubstituted or substituted amino. In some embodiments, R^2 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, or unsubstituted or substituted sulfonamido. In some embodiments, R^2 is halo, which is –I, -F, -Cl, or -Br. In some embodiments, R^2 is selected from the group consisting of cyano, hydroxy, nitro, a carbonic acid, and a carbonate. In some embodiments, R^2 is unsubstituted or substituted phosphate. In some embodiments, R^2 is unsubstituted or substituted urea. In some embodiments, when R^2 is alkyl, R^2 is methyl, ethyl, propyl, isopropyl, *n*- butyl, *tert*- butyl, *sec*-butyl, pentyl, hexyl or heptyl.

[00177] In some embodiments, when R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, or hydroxy, it is substituted by phosphate, substituted by urea, or substituted by carbonate.

[00178] In some embodiments, when R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido, it is substituted by one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido may itself be substituted.

[00179] In some embodiments, q is an integer of 0. In some embodiments, q is an integer of 1. In some embodiments, q is an integer of 2. In some embodiments, q is an integer of 3. In some embodiments, q is an integer of 4.

[00180] In some embodiments, R^3 is a member selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, and unsubstituted or substituted alkynyl. In some embodiments, R^3 is unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocycloalkyl. In some embodiments, R^3 is unsubstituted or substituted alkoxy, unsubstituted or substituted amido, unsubstituted or substituted amino. In some embodiments, R^3 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, or unsubstituted or substituted sulfonamido. In some embodiments, R^3 is halo, which is –I, -F, -Cl, or -Br.

[00181] In some embodiments, R^3 is selected from the group consisting of cyano, hydroxy, and nitro. In some embodiments, when R^3 is alkyl, R^3 is methyl, ethyl, propyl, isopropyl, *n*- butyl, *tert*- butyl, *sec*-butyl, pentyl, hexyl or heptyl. In some embodiments, R^3 is $-CF_3$.

[00182] In some embodiments, when R^3 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido, it is substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido may itself be substituted.

[00183] In some embodiments, R^5 is hydrogen, unsubstituted or substituted alkyl (including but not limited to unsubstituted or substituted C_1-C_4alkyl). In some embodiments, R^5 is unsubstituted or substituted alkenyl including but not limited to unsubstituted or substituted C_2-C_5alkenyl. In some embodiments, R^5 is unsubstituted or substituted alkynyl including but not limited to unsubstituted or substituted C_2-C_5alkynyl. In some embodiments, R^5 is unsubstituted or substituted cycloalkyl including but not limited to unsubstituted or substituted C_3-C_5cycloalkyl. In some embodiments, R^5 is unsubstituted or substituted heterocycloalkyl. In some embodiments, R^5 is unsubstituted or substituted heteroalkyl including but not limited to unsubstituted or substituted C_1-C_4heteroalkyl. In some embodiments, R^5 is unsubstituted or substituted alkoxy including but not limited to unsubstituted or substituted C_1-C_4alkoxy. In some embodiments, R^5 is unsubstituted or substituted amido including but not limited to unsubstituted or substituted C_1-C_4amido. In some embodiments, R^5 is unsubstituted or substituted amino. In some embodiments, R^5 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted C_1-C_4acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted sulfonamido, or unsubstituted or substituted C_1-C_4sulfonamido. In some embodiments, R^5 is halo, which is –I, -F, -Cl, or -Br. In some embodiments, R^5 is selected from the group consisting of cyano, hydroxy, and nitro. In some other embodiments, R^5 is $-CH_3$, $-CH_2CH_3$, n-propyl, isopropyl, $-OCH_3$, $-OCH_2CH_3$, or $-CF_3$.

[00184] In some embodiments, when R^5 is alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, acyl, alkoxy, amido, amino, acyloxy, alkoxycarbonyl, or sulfonamido, R^5 is optionally substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido may itself be substituted.

[00185] In some embodiments, R^6 is hydrogen, unsubstituted or substituted alkyl (including but not limited to unsubstituted or substituted C_1-C_4alkyl). In some embodiments, R^6 is unsubstituted or substituted alkenyl including but not limited to unsubstituted or substituted C_2-C_5alkenyl. In some embodiments, R^6 is unsubstituted or substituted alkynyl including but not limited to unsubstituted or substituted C_2-C_5alkynyl. In some embodiments, R^6 is unsubstituted or substituted cycloalkyl including but not limited to unsubstituted or substituted C_3-C_5cycloalkyl. In

some embodiments, R^6 is unsubstituted or substituted heterocycloalkyl. In some embodiments, R^6 is unsubstituted or substituted heteroalkyl including but not limited to unsubstituted or substituted C_1-C_4heteroalkyl. In some embodiments, R^6 is unsubstituted or substituted alkoxy including but not limited to unsubstituted or substituted C_1-C_4alkoxy. In some embodiments, R^6 is unsubstituted or substituted amido including but not limited to unsubstituted or substituted C_1-C_4amido. In some embodiments, R^6 is unsubstituted or substituted amino. In some embodiments, R^6 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted C_1-C_4acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted sulfonamido, or unsubstituted or substituted C_1-C_4sulfonamido. In some embodiments, R^6 is halo, which is –I, -F, -Cl, or -Br. In some embodiments, R^6 is selected from the group consisting of cyano, hydroxy, and nitro. In some other embodiments, R^6 is $-CH_3$, $-CH_2CH_3$, n-propyl, isopropyl, $-OCH_3$, $-OCH_2CH_3$, or $-CF_3$.

[00186] In some embodiments, when R^6 is alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, acyl, alkoxy, amido, amino, acyloxy, alkoxycarbonyl, or sulfonamido, R^6 is optionally substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido may itself be substituted.

[00187] In some embodiments, R^7 is hydrogen, unsubstituted or substituted alkyl (including but not limited to unsubstituted or substituted C_1-C_4alkyl). In some embodiments, R^7 is unsubstituted or substituted alkenyl including but not limited to unsubstituted or substituted C_2-C_5alkenyl. In some embodiments, R^7 is unsubstituted or substituted alkynyl including but not limited to unsubstituted or substituted C_2-C_5alkynyl. In some embodiments, R^7 is unsubstituted or substituted cycloalkyl including but not limited to unsubstituted or substituted C_3-C_5cycloalkyl. In some embodiments, R^7 is unsubstituted or substituted heterocycloalkyl. In some embodiments, R^7 is unsubstituted or substituted heteroalkyl including but not limited to unsubstituted or substituted C_1-C_4heteroalkyl. In some embodiments, R^7 is unsubstituted or substituted alkoxy including but not limited to unsubstituted or substituted C_1-C_4alkoxy. In some embodiments, R^7 is unsubstituted or substituted amido including but not limited to unsubstituted or substituted C_1-C_4amido. In some embodiments, R^7 is unsubstituted or substituted amino. In some embodiments, R^7 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted C_1-C_4acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted sulfonamido, or unsubstituted or substituted C_1-C_4sulfonamido. In some embodiments, R^7 is halo, which is –I, -F, -Cl, or -Br. In some embodiments, R^7 is selected from the group consisting of cyano, hydroxy, and nitro. In some other embodiments, R^7 is $-CH_3$, $-CH_2CH_3$, n-propyl, isopropyl, $-OCH_3$, $-OCH_2CH_3$, or $-CF_3$.

[00188] In some embodiments, when R^7 is alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, acyl, alkoxy, amido, amino, acyloxy, alkoxycarbonyl, or sulfonamido, R^7 is optionally substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido may itself be substituted.

[00189] In some embodiments, R^8 is hydrogen, unsubstituted or substituted alkyl (including but not limited to unsubstituted or substituted C_1-C_4alkyl). In some embodiments, R^8 is unsubstituted or substituted alkenyl including but not limited to unsubstituted or substituted C_2-C_5alkenyl. In some embodiments, R^8 is unsubstituted or substituted alkynyl including but not limited to unsubstituted or substituted C_2-C_5alkynyl. In some embodiments, R^8 is unsubstituted or substituted cycloalkyl including but not limited to unsubstituted or substituted C_3-C_5cycloalkyl. In

some embodiments, R^8 is unsubstituted or substituted heterocycloalkyl. In some embodiments, R^8 is unsubstituted or substituted heteroalkyl including but not limited to unsubstituted or substituted C_1-C_4heteroalkyl. In some embodiments, R^8 is unsubstituted or substituted alkoxy including but not limited to unsubstituted or substituted C_1-C_4alkoxy. In some embodiments, R^8 is unsubstituted or substituted amido including but not limited to unsubstituted or substituted C_1-C_4amido. In some embodiments, R^8 is unsubstituted or substituted amino. In some embodiments, R^8 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted C_1-C_4acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted sulfonamido, or unsubstituted or substituted C_1-C_4sulfonamido. In some embodiments, R^8 is halo, which is –I, -F, -Cl, or -Br. In some embodiments, R^8 is selected from the group consisting of cyano, hydroxy, and nitro. In some other embodiments, R^8 is $-CH_3$, $-CH_2CH_3$, n-propyl, isopropyl, $-OCH_3$, $-OCH_2CH_3$, or $-CF_3$.

[00190] In some embodiments, when R^8 is alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, acyl, alkoxy, amido, amino, acyloxy, alkoxycarbonyl, or sulfonamido, R^8 is optionally substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido may itself be substituted.

[00191] In some embodiments, R^5, R^6, R^7, and R^8 are H.

[00192] In some embodiments, X is absent. In some embodiments, X is $-(CH(R^9))_z$, and z is an integer of 1, 2, 3 or 4.

[00193] In some embodiments, R^9 is unsubstituted or substituted alkyl including but not limited to unsubstituted or substituted C_1-C_{10}alkyl. In some embodiments, R^9 is unsubstituted or substituted cycloalkyl including but not limited to unsubstituted or substituted C_3-C_7cycloalkyl. In some embodiments, R^9 is methyl or hydrogen. In some embodiments, R^9 is unsubstituted or substituted heterocycloalkyl including but not limited to unsubstituted or substituted C_2-C_{10}heteroalkyl. In some embodiments, R^9 is unsubstituted or substituted heteroalkyl including but not limited to unsubstituted or substituted C_2-C_{10}heteroalkyl.

[00194] When R^9 is any of the above, in some embodiments, X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, or $-CH(CH_2CH_3)-$. In some embodiments, when X is $-CH(CH_3)-$, $-CH(CH_3)-$ is in an (S)- or (R)-stereochemical configuration.

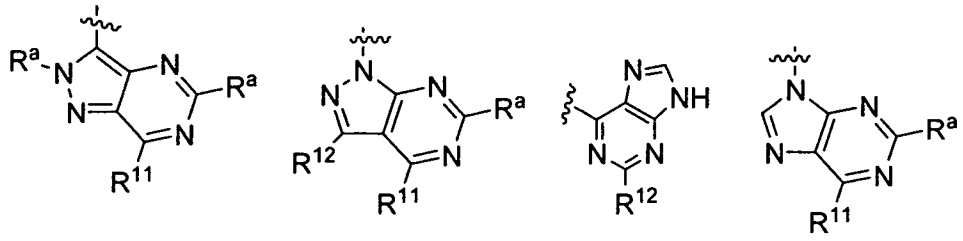
[00195] In some embodiments of the compound of Formula I, Y is absent. In some embodiments, Y is -O-, -S-, -S(=O)-, $-S(=O)_2-$, -C(=O)-, $-N(R^9)(C=O)-$, $-N(R^9)(C=O)NH-$, $-N(R^9)C(R^9)_2-$ (such as-$N(R^9)CH_2-$, specifically - $N(CH_3)CH_2-$, $N(CH(CH_3)_2)CH_2$ - or $N(CH_2CH_3)CH_2-$), $-N(R^9)-$, $-N(CH_3)-$, $-N(CH_2CH_3)-$, or $-N(CH(CH_3)_2)-$. In some embodiments, Y is $-C(=O)-(CHR^9)_z-$ and z is an integer of 1, 2, 3, or 4.

[00196] In some embodiments, X-Y is $-CH_2-$, $-CH_2-N(CH_3)$, $-CH(CH_3)-NH-$, (S) $-CH(CH_3)-NH-$, or (R) $-CH(CH_3)-NH-$. In some embodiments, X-Y is $-N(CH_3)CH_2-$, $N(CH_2CH_3)\ CH_2-$, $-N(CH(CH_3)_2)CH_2-$, or $-NHCH_2-$.

[00197] In some embodiments, W_d is a member selected from the group consisting of unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl. In some embodiments, W_d is unsubstituted or substituted monocyclic heteroaryl, or unsubstituted or substituted bicyclic heteroaryl. In some embodiments, W_d is a bicyclic heteroaryl having at least one heteroatom, e.g., a bicyclic heteroaryl having at least one nitrogen ring atom. In some embodiments, W_d is a bicyclic heteroaryl having at least two heteroatoms, e.g., a bicyclic heteroaryl having at least two nitrogen ring atoms. In some embodiments, W_d is a bicyclic heteroaryl having two heteroatoms in the ring which is connected to XY. In some embodiments, W_d is a bicyclic heteroaryl having two nitrogen ring atoms in the ring to which XY is connected. In some embodiments, W_d is a bicyclic heteroaryl having four heteroatoms, e.g., a bicyclic heteroaryl having four nitrogen ring atoms. In some embodiments, W_d is

unsubstituted or substituted 4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl, unsubstituted or substituted 7-amino-2-methyl-2*H*-pyrazolo[4,3-d]pyrimidin-3-yl. unsubstituted or substituted 6-methylenyl-9H-purin-6-yl, or unsubstituted or substituted 6-amino-9H-purin-9-yl.

[00198] In some embodiments W_d is one of the following:

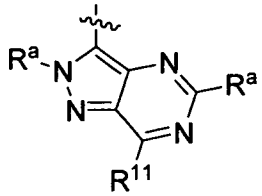


wherein R^a is hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl;

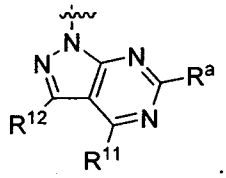
R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and

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

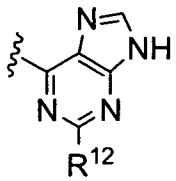
[00199] In some embodiments, Wd is:



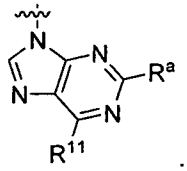
[00200] In some embodiments, W_d is:



[00201] In some embodiments, W_d is:



[00202] In some embodiments, W_d is:



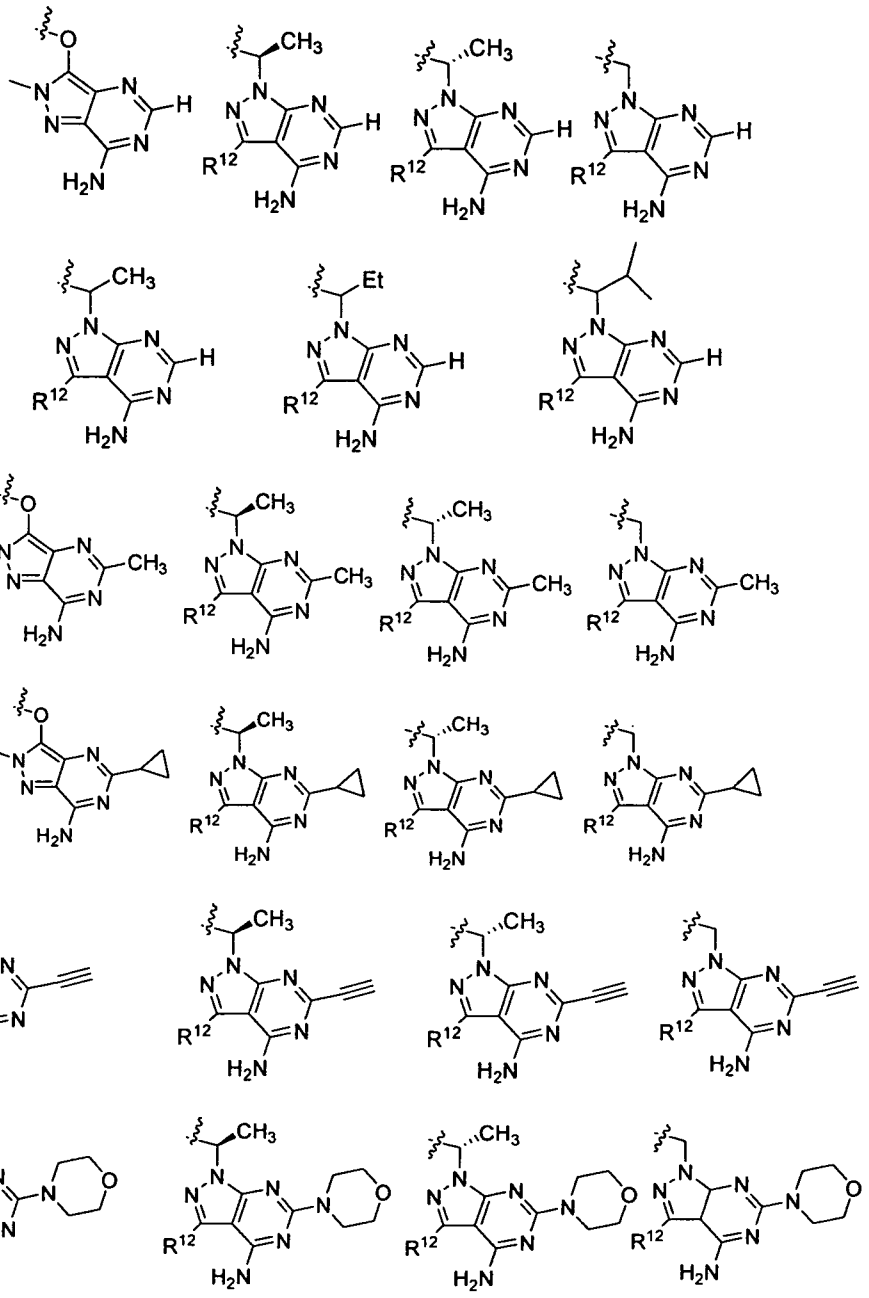
[00203] In some embodiments of W_d, R^a is a member selected from the group consisting of hydrogen, halo, phosphate, urea, a carbonate, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heteroalkyl, and unsubstituted or substituted heterocycloalkyl.

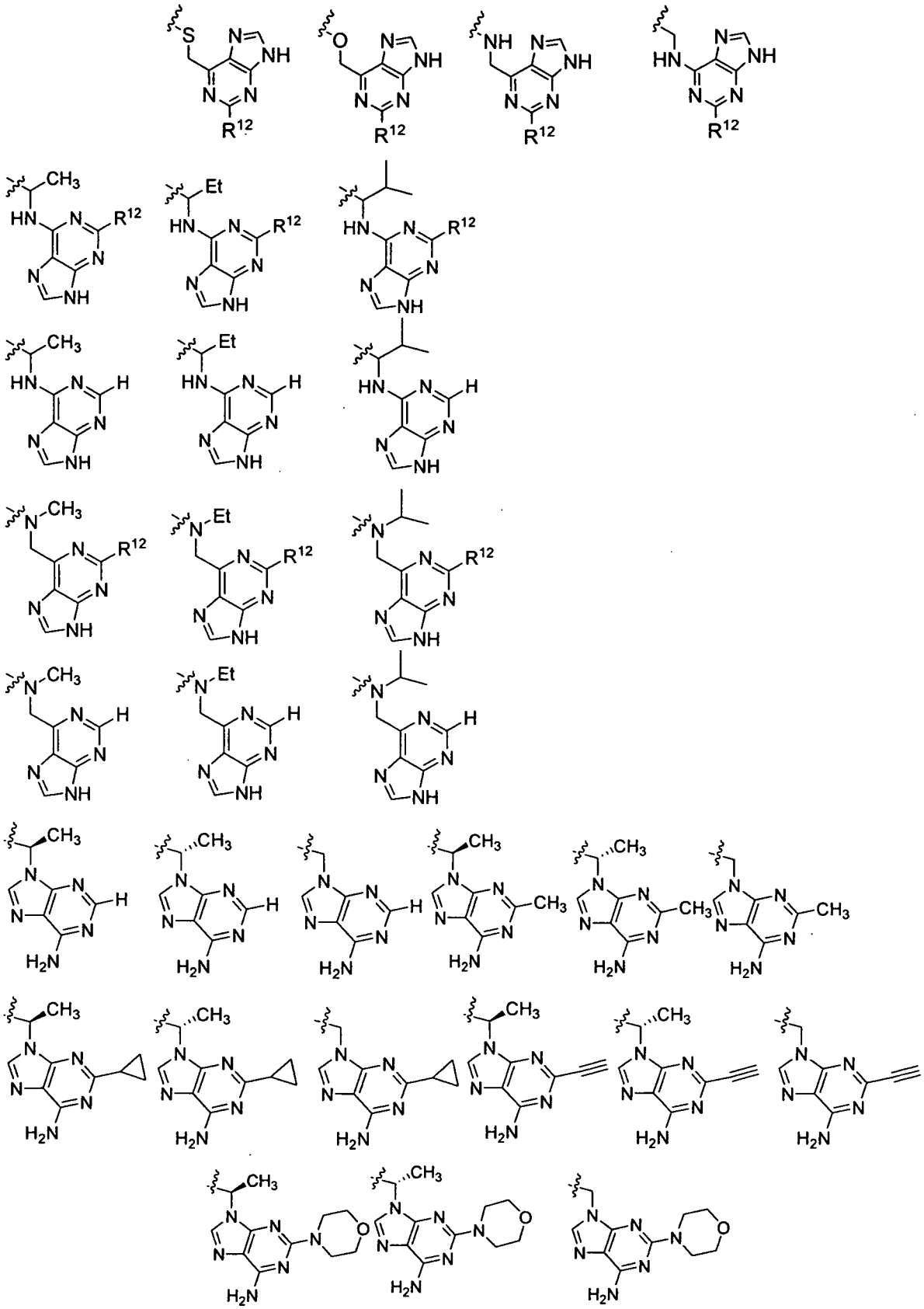
[00204] In some embodiments of W_d, when R^a is alkyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl, it is substituted by phosphate, urea, or carbonate.

[00205] In some embodiments, R^{11} is a member of the group consisting of hydrogen, unsubstituted or substituted alkyl, and halo, which includes –I, -F, -Cl, or –Br. In some embodiments, R^{11} is unsubstituted or substituted amino, unsubstituted or substituted amido, hydroxy, or unsubstituted or substituted alkoxy. In some embodiments, R^{11} is phosphate, unsubstituted or substituted urea, or carbonate.

[00206] In some embodiments, when R^{11} is alkyl, amino, amido, hydroxy, or alkoxy, it is substituted by phosphate, urea, or carbonate.

[00207] In some embodiments,-X-Y-W_d is one of the following moieties:





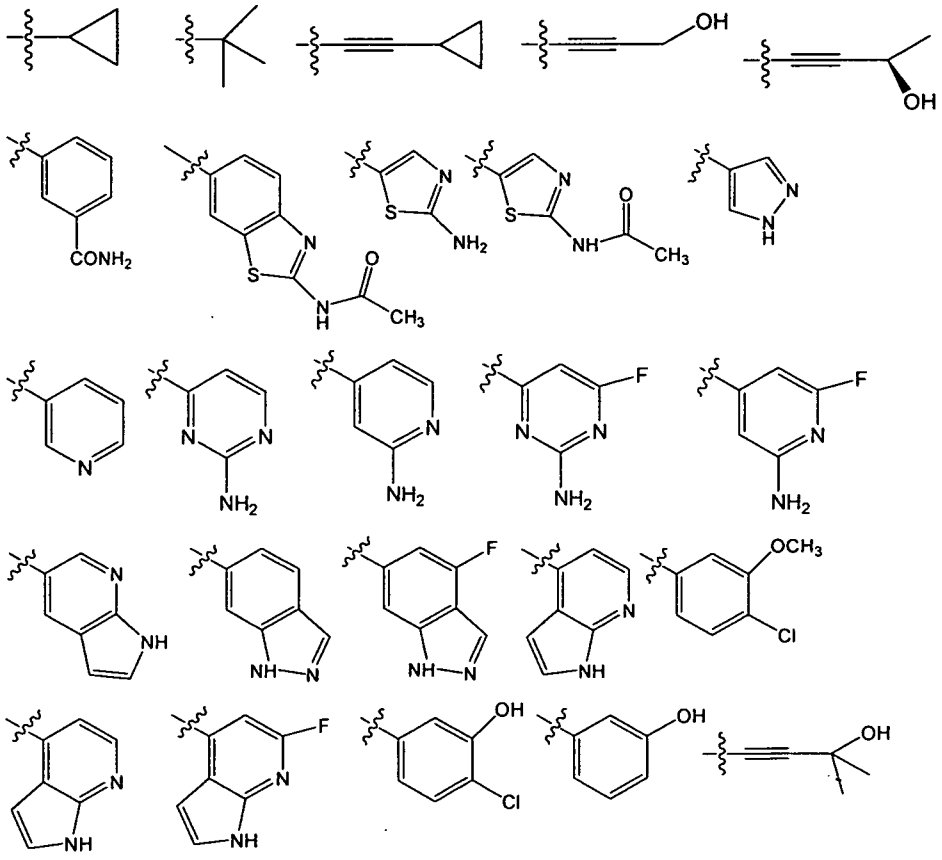
[00208] In some embodiments, R^{12} is a member of the group consisting of hydrogen, cyano, halo, unsubstituted or substituted alkyl, and unsubstituted or substituted alkynyl unsubstituted or substituted alkenyl. In some embodiments, R^{12} is unsubstituted or substituted aryl. In some embodiments, R^{12} is unsubstituted or substituted heteroaryl, which

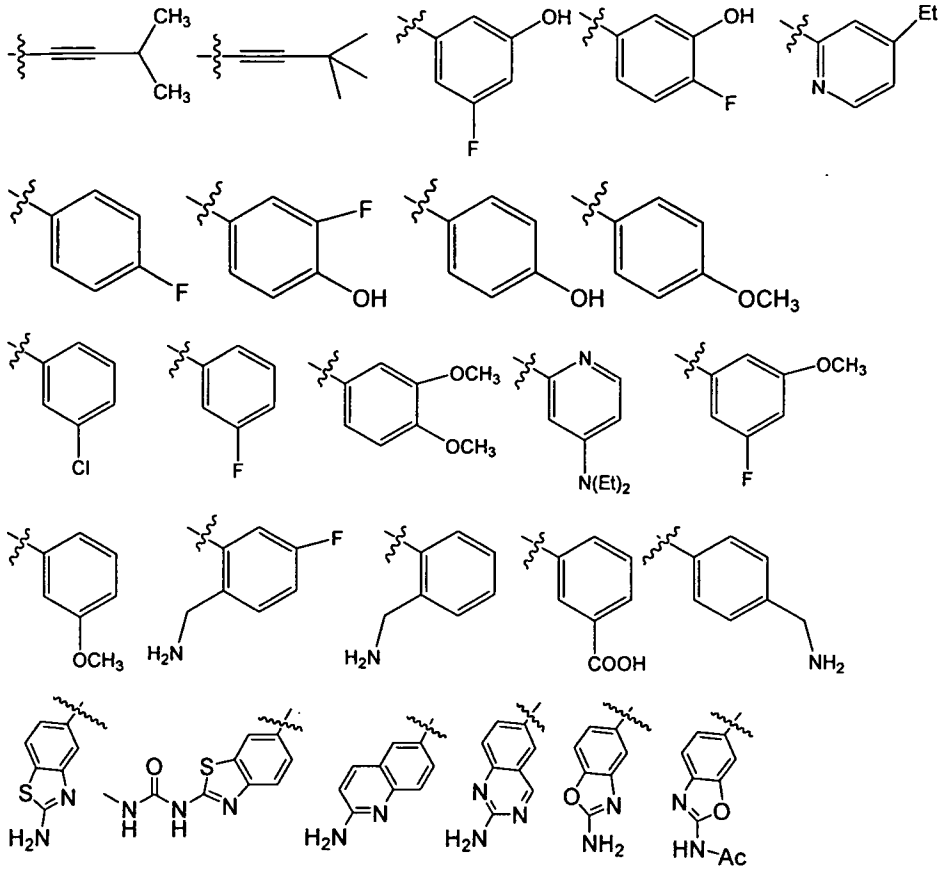
includes but is not limited to heteroaryl having a 5 membered ring, heteroaryl having a six membered ring, heteroaryl with at least one nitrogen ring atom, heteroaryl with two nitrogen ring atoms, monocylic heteroaryl, and bicyclic heteroaryl. In some embodiments, R^{12} is unsubstituted or substituted heterocycloalkyl, which includes but is not limited to heterocycloalkyl with one nitrogen ring atom, heterocycloalkyl with one oxygen ring atom, R^{12} is heterocycloalkyl with one sulfur ring atom, 5 membered heterocycloalkyl, 6 membered heterocycloalkyl, saturated heterocycloalkyl, unsaturated heterocycloalkyl, heterocycloalkyl having an unsaturated moiety connected to the heterocycloalkyl ring, heterocycloalkyl substituted by oxo, and heterocycloalkyl substituted by two oxo. In some embodiments, R^{12} is unsubstituted or substituted cycloalkyl, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkyl substituted by one oxo, cycloalkyl having an unsaturated moiety connected to the cycloalkyl ring. In some embodiments, R^{12} is unsubstituted or substituted amido, carboxylic acid, unsubstituted or substituted acyloxy, or unsubstituted or substituted alkoxycarbonyl.

[00209] In some embodiments, when R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, it is substituted with phosphate. In some embodiments, when R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, it is substituted with urea. In some embodiments, when R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, it is substituted with carbonate.

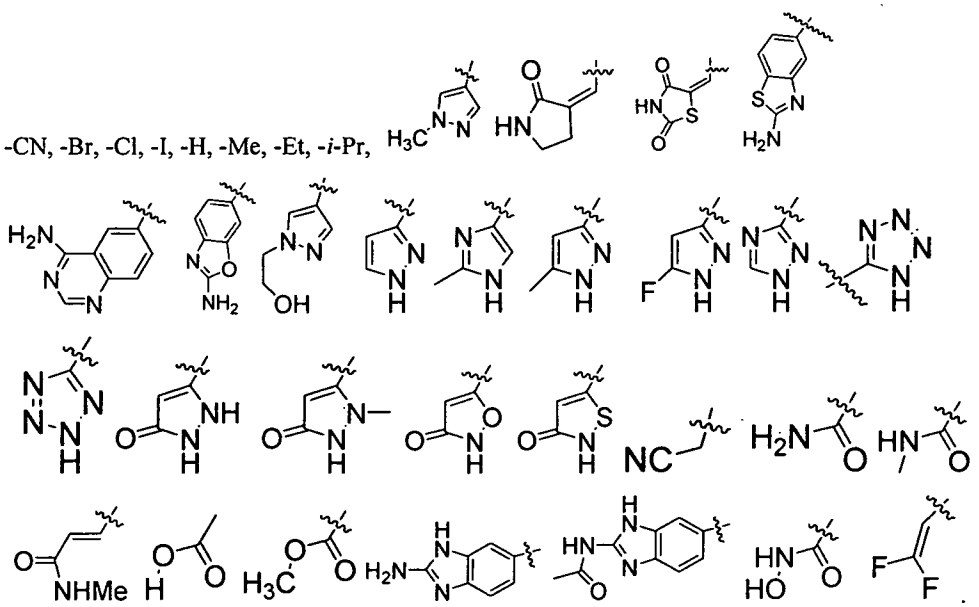
[00210] In some embodiments, when R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkoxycarbonyl, amido, or acyloxy, it is substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido may itself be substituted.

[00211] In some embodiments, R^{12} of W_d is one of the following moieties:

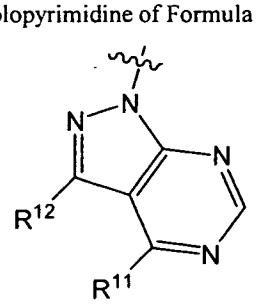




-CN, -Br, -Cl, -I, -H, -Me, -Et, -*i*-Pr,



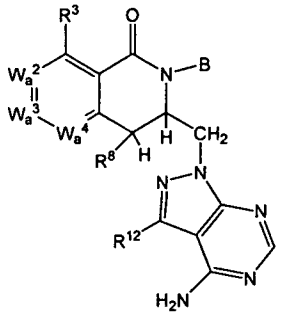
[00212] In some embodiments, W_d is a pyrazolopyrimidine of Formula III:



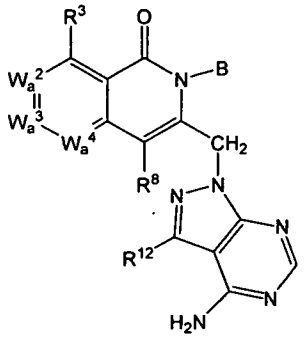
Formula III

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. In some embodiments, R^{11} is amino and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In some embodiments, R^{11} is amino and R^{12} is alkyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In some embodiments, R^{11} is amino and R^{12} is monocyclic heteroaryl. In some embodiments, R^{11} is amino and R^{12} is bicyclic heteroaryl. In some embodiments, R^{11} is amino and R^{12} is cyano, amino, carboxylic acid, acyloxy, alkoxycarbonyl, or amido.

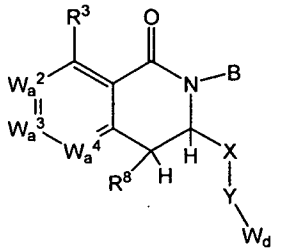
[00213] In some embodiments, the compound of Formula I is a compound which has a structure selected from the group consisting of Formula 1-A, 1-B, 2-A, 2-B. IV, V, V-A, VI, VI-A, VI-B, VI-C, 6-C1, 6-C2, V-I-D, and 6-D:



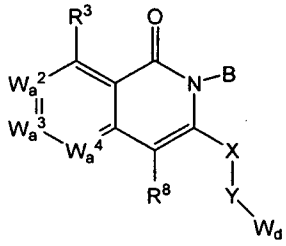
Formula 1-A



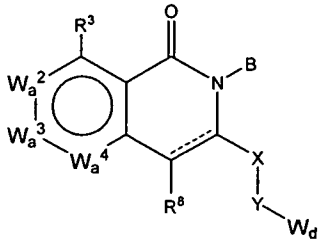
Formula 1-B



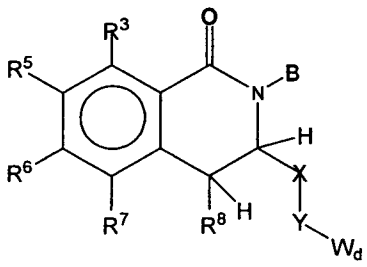
Formula 2-A



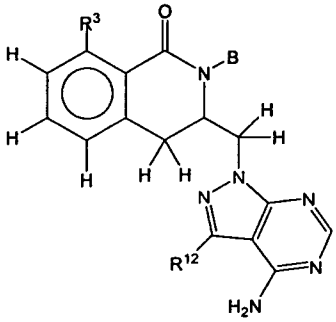
Formula 2-B



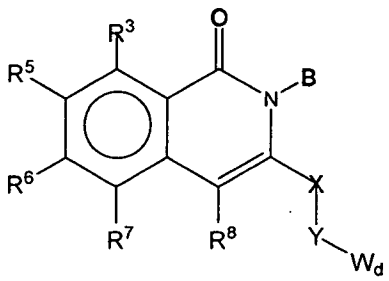
Formula IV



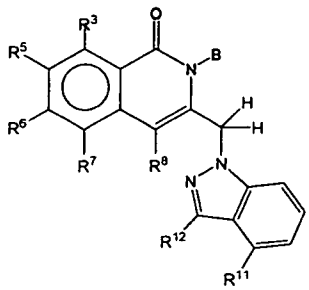
Formula V



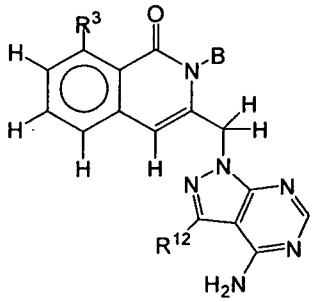
Formula V-A



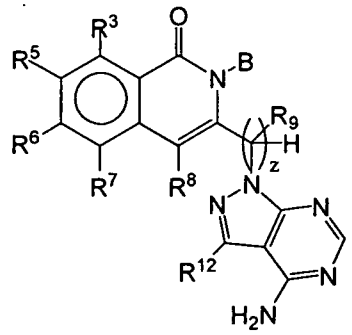
Formula VI



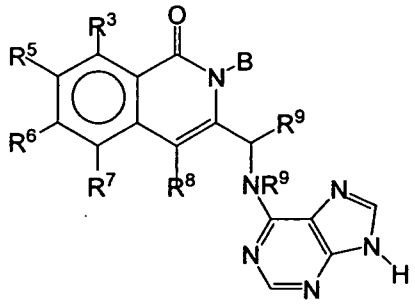
Formula VI-A



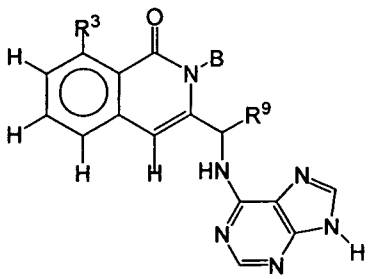
Formula 6-A



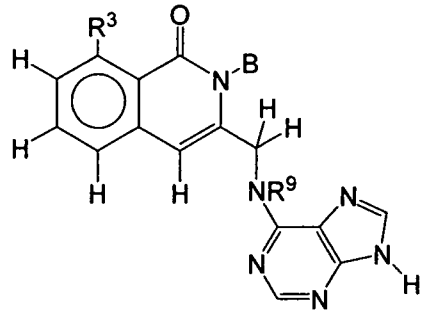
Formula VI-B



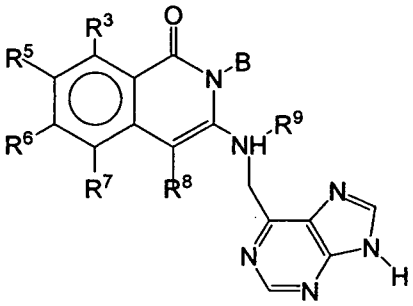
Formula VI-C



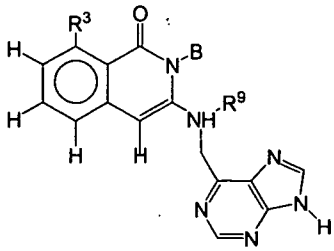
Formula 6-C1



Formula 6-C2

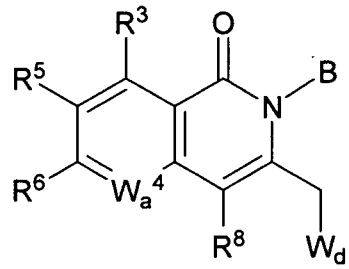


Formula VI-D

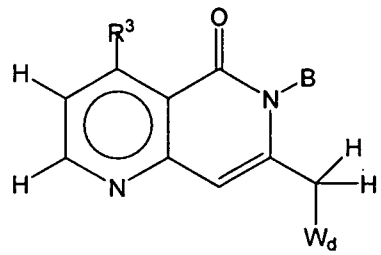


Formula 6-D

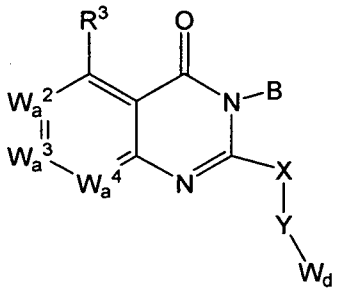
In another embodiment, the compound of Formula I is a compound which has a structure selected from the group consisting of Formula VII, 7-A, VIII, VIII-A, and 8-A:



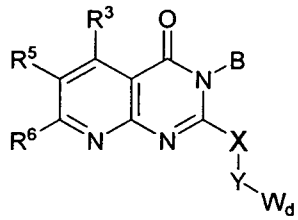
Formula VII



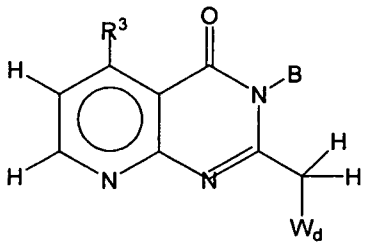
Formula 7-A



Formula VIII



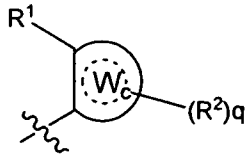
Formula VIII-A



Formula 8-A

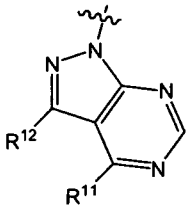
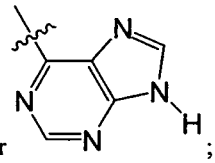
[00214] Any of the disclosed elements and their substituents for the compounds of Formula I can be used in any combination.

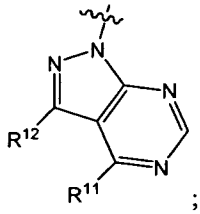
[00215] In one aspect, for compounds of Formula I, IV, V, VI, VII, or VIII, R_3 is H, CH_3, CF_3, Cl, F, aryl, or heteroaryl; B is alkyl or a moiety of Formula II;

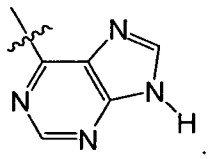


Formula II

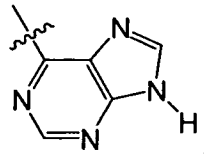
wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is an integer of 0, 1, 2, 3, or 4; R^5, R^6, R^7, and R^8 are H; X is absent or $(CH_2)_z$; z is 1; Y is absent , $-N(R^9)-$, or $-N(R^9)\,CH(R^9)-$; R^9 is hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, or C_2-C_{10}heteroalkyl; and W_d is pyrazolopyrimidine or purine.

[00216] In another aspect, for compounds of Formula I, IV, V, VI, VII, or VIII, R_3 is H, CH_3, CF_3, Cl, or F; B is alkyl or a moiety of Formula II which is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is 0, 1 or 2; R^5, R^6, R^7, and R^8 are H; X is absent or $(CH_2)_z$; z is 1; Y is absent , $-N(R^9)-$, or $-N(R^9)\,CH(R^9)-$; R^9 is hydrogen, methyl, or ethyl; W_d is:  or ; R^{11} is amino; and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, cyano, amino, carboxylic acid, alkoxycarbonyl, or amido.

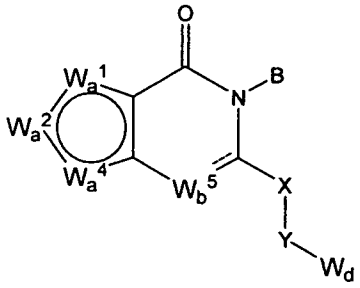
[00217] In another aspect, for compounds of Formula I, IV, V, VI, VII, or VIII, R_3 is H, CH_3, CF_3, Cl, or F; B is alkyl or a moiety of Formula II which is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro or phosphate; q is 0, 1 or 2; R^5, R^6, R^7, and R^8 are H; X is $(CH_2)_z$; z is 1; Y is absent and W_d is: ; R^{11} is amino; and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, cyano, amino, carboxylic acid, alkoxycarbonyl, or amido.

[00218] In another aspect, for compounds of Formula I, IV, V, VI, VII, or VIII, R_3 is H, CH_3, CF_3, Cl, or F; B is alkyl or a moiety of Formula II, which is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is 0, 1 or 2; R^5, R^6, R^7, and R^8 are H; X is $(CH_2)_z$; z is 1; Y is $-N(R^9)-$; R^9 is hydrogen, methyl, or ethyl; and W_d is .

[00219] In another aspect, for compounds of Formula I, IV, V, VI, VII, or VIII, R_3 is H, CH_3, CF_3, Cl, or F; B is alkyl or a moiety of Formula II, which is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$,

isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is 0, 1 or 2; R^5, R^6, R^7, and R^8 are H; X is absent; Y is–$N(R^9)$ $CH(R^9)$-; R^9 is hydrogen, methyl, or ethyl; and W_d is .

[00220] The invention also provides a compound of Formula IX or its pharmaceutically acceptable salt,

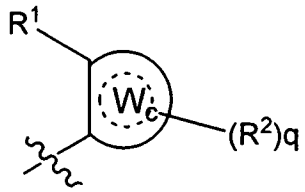


Formula IX

[00221] 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;

[00222] W_b^5 is CR^8, N, or NR^8;

[00223] B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II;



Formula II

[00224] wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

[00225] q is an integer of 0, 1, 2, 3, or 4;

[00226] W_d is absent or is a heterocycloalkyl, aryl or heteroaryl moiety;

[00227] X is absent or is $-(CH(R^9))_z$- and each instance of z independently is an integer of 1, 2, 3, or 4;

[00228] 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 $-C(=O)-(CHR^9)_z$-;

[00229] 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;

[00230] 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;

[00231] R^4 is hydrogen, acyl,alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, or C_1-C_4heteroalkyl;

[00232] R^5, R^7, and R^8 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro;

[00233] each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, or C_2-C_{10}heteroalkyl.

[00234] Substituents described for Formula I are equally applicable to compounds of Formula IX, except for W_a^1, W_a^2, W_a^4, and W_b^5 which are defined as follows:

[00235] In some embodiments, W_a^1 is CR^5, S, N, or NR^4.

[00236] In some embodiments, W_a^2 is CR^5, S, N, or NR^4.

[00237] In some embodiments, W_a^4 is CR^7, S, N, or NR^4.

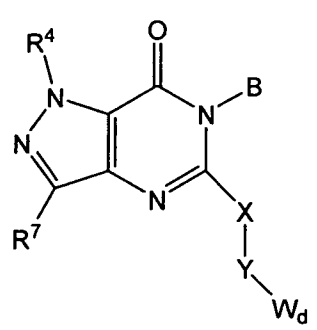
[00238] In some embodiments, W_b^5 is CR^8, N, or NR^8.

[00239] In some embodiments, the compound of Formula IX 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; (*xxii*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is CHR^8; (*xxiii*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is N; (*xxiv*) W_a^1 is CR^5, W_a^2 is N, W_a^4 is S, and W_b^5 is NR^8; (*xxv*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CR^8; (*xxvi*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is CHR^8; (*xxvii*) W_a^1 is S, W_a^2 is N, W_a^4 is CR^7, and W_b^5 is N; (*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.

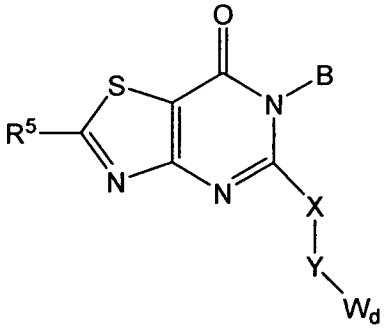
[00240] In some embodiments, R^4 is a member of the group consisting of hydrogen, unsubstituted or substituted acyl, unsubstituted or substituted alkyl which includes but is not limited to unsubstituted or substituted C_1-C_4alkyl, unsubstituted or substituted alkenyl which includes but is not limited to C_2-C_5alkenyl, unsubstituted or substituted alkynyl which includes but is not limited to C_2-C_5alkynyl, unsubstituted or substituted cycloalkyl which includes but is not limited to C_3-C_5cycloalkyl, unsubstituted or substituted heterocycloalkyl, and unsubstituted or substituted heteroalkyl which includes but is not limited to unsubstituted or substituted C_1-C_4heteroalkyl.

[00241] In some embodiments, when R^4 is acyl, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, or heteroalkyl, it is substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, or sulfonamido may itself be substituted.

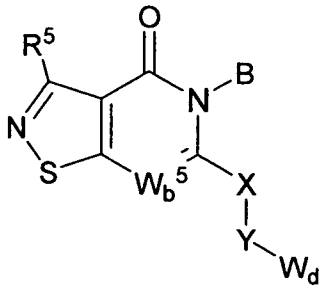
[00242] In some embodiments, the compound of Formula IX is a compound which has a structure selected from the group consisting of Formula X, XI, XII, XIII, and XIV:



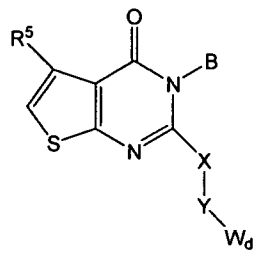
Formula X



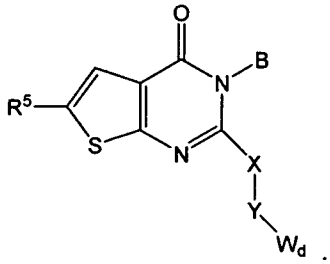
Formula XI



Formula XII



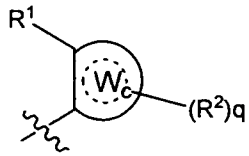
Formula XIII



Formula XIV

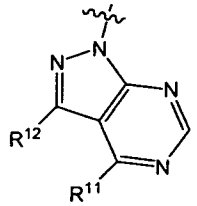
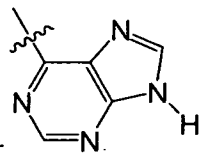
[00243] Any of the disclosed elements and their substituents for the compounds of Formula IX can be used in any combination.

[00244] In one aspect, for compounds of Formula IX, X, XI, XII, XIII or XIV, B is alkyl or a moiety of Formula II;

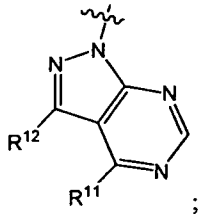


Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is an integer of 0, 1, 2, 3, or 4; R^4, R^5, R^7, and R^8 are H or methyl; X is absent or $(CH_2)_z$; z is 1; Y is absent , $-N(R^9)-$, or $-N(R^9)\,CH(R^9)-$; R^9 is hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, or C_2-C_{10}heteroalkyl; and W_d is pyrazolopyrimidine or purine.

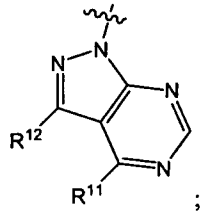
[00245] In another aspect, for compounds of Formula IX, X, XI, XII, XIII or XIV, B is alkyl or a moiety of Formula II wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is an integer of 0, 1, 2, 3, or 4; R^4, R^5, and R^7 are H or methyl; R^8 is H; X is absent or $(CH_2)_z$; z is 1; Y is absent or $-N(R^9)-$; R^9 is hydrogen, methyl, or ethyl; W_d is:  or ; R^{11} is amino; and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, cyano, amino, carboxylic acid, alkoxycarbonyl, or amido.

[00246] In another aspect, for compounds of Formula IX, X, XI, XII, XIII or XIV, B is a moiety of Formula II wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$,or nitro; R^2 is halo, hydroxy, cyano, or nitro; q is 0, 1 or 2; R^4, R^5, and R^7 are H or methyl; R^8 is H; X is $(CH_2)_z$; z is 1; Y



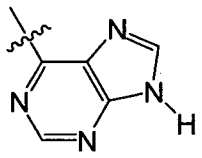
is absent and W_d is: ; R^{11} is amino; and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

[00247] In another aspect, for compounds of Formula IX, X, XI, XII, XIII or XIV, B is alkyl or a moiety of Formula II wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is 0, 1 or 2; R^4, R^5, and R^7 are H or methyl; R^8 is



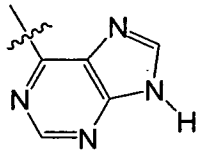
H; X is $(CH_2)_z$; z is 1; Y is absent and W_d is: ; R^{11} is amino; and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, cyano, amino, carboxylic acid, alkoxycarbonyl, or amido.

[00248] In another aspect, for compounds of Formula IX, X, XI, XII, XIII or XIV, B is alkyl or a moiety of Formula II wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is 0, 1 or 2; R^4, R^5, and R^7 are H or methyl; R^8 is

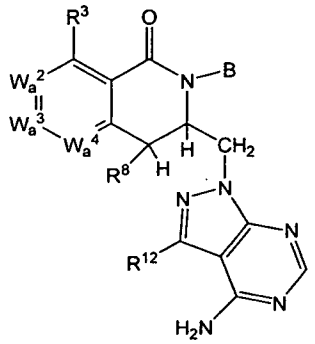


H; X is $(CH_2)_z$; z is 1; X is $(CH_2)_z$; z is 1; Y is–$N(R^9)$-; R^9 is hydrogen, methyl, or ethyl; and W_d is .

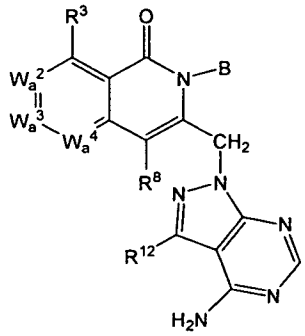
[00249] In another aspect, for compounds of Formula IX, X, XI, XII, XIII or XIV, B is alkyl or a moiety of Formula II wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is 0, 1 or 2; R^4, R^5, and R^7 are H or methyl; R^8 is



H; X is absent; Y is $-N(R^9)\ CH(R^9)$-; R^9 is hydrogen, methyl, or ethyl; W_d is: .



Formula 1-A

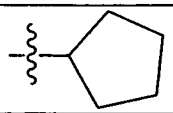
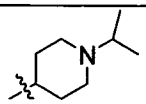
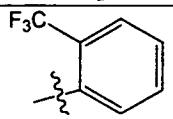
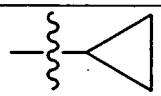
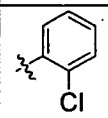
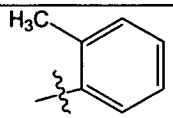
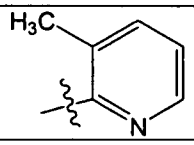
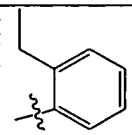
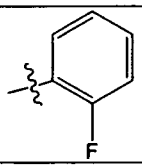
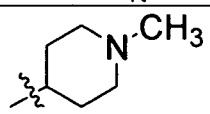
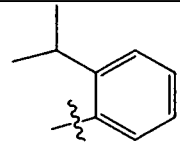
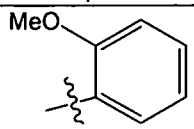
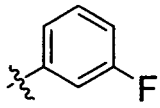
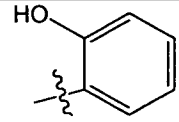
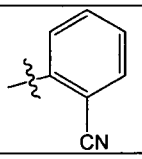
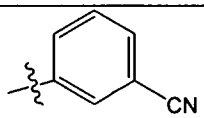
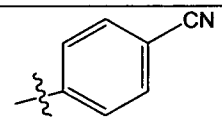
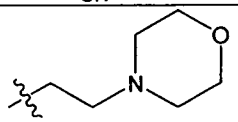
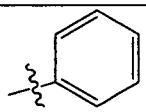
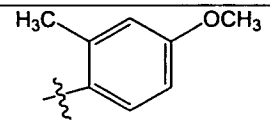
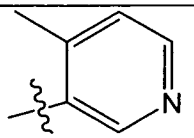
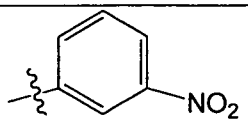
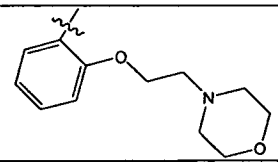
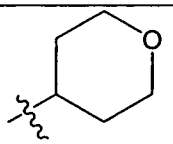
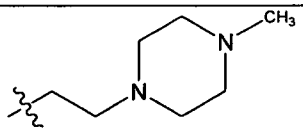
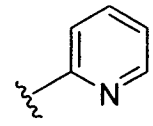
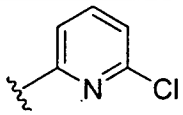
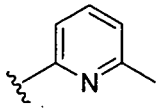
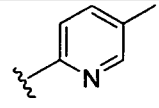
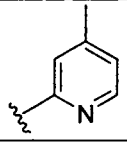
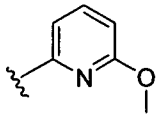
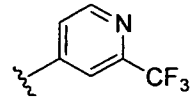


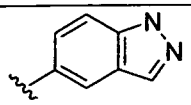
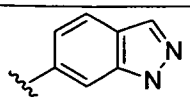
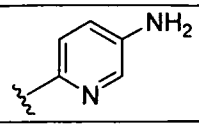
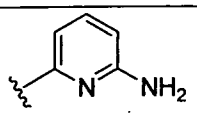
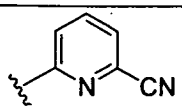
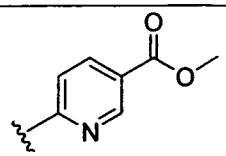
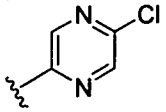
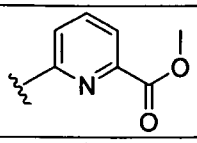
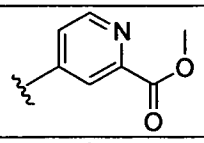
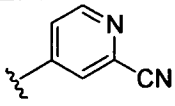
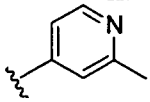
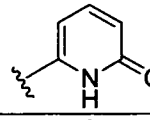
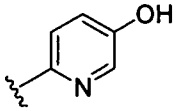
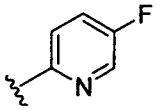
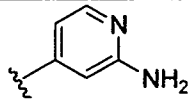
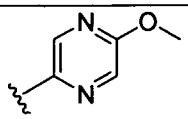
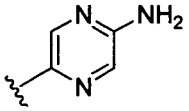
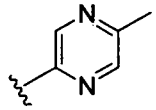
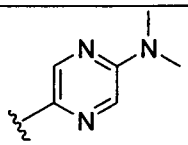
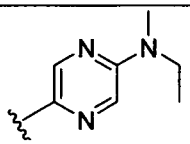
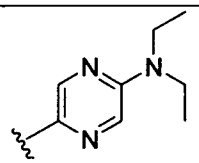
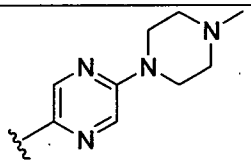
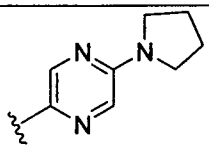
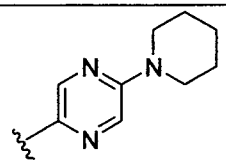
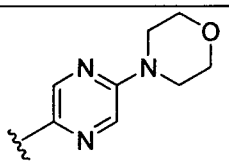
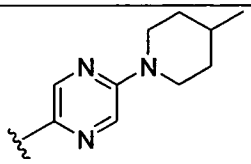
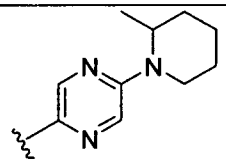
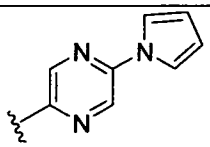
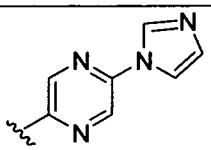
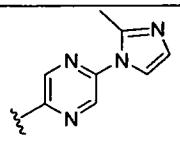
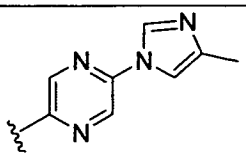
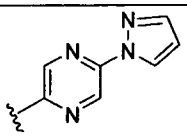
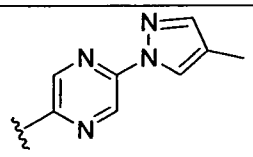
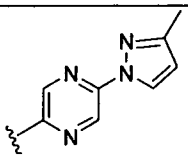
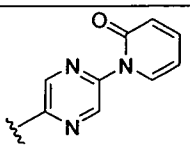
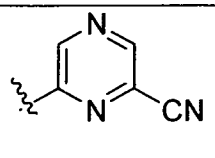
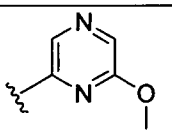
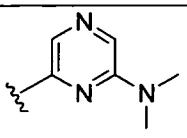
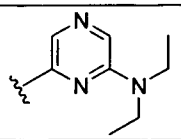
Formula 1-B

[00250] Illustrative embodiments of Formula 1-A and Formula 1-B are provided, wherein R^3 is selected from any of H, Cl, F, or methyl; any of W_a^2 is elected from CH, N, C-CN, or C-OCH_3; any of W_a^3 is selected from CH, N, C-CF_3, or C-CH_3; any of W_a^4 is selected from CH, N, or C-CF_3; any of R^8 is selected from H, Me, or Cl; any of B as described

in Table 1; and any of R^{12} as described in Table 2. The compounds of Formula 1-A and Formula 1-B can contain any substituents specified under R^3, W_a^2, W_a^3, W_a^4, R^8, B, and R^{12}. The specific embodiments described in no way limit the invention, but are descriptive of the compounds of the invention. Some additional exemplary compounds of Formulas 1-A and 1-B are illustrated in Table 5.

Table 1. Illustrative B of a compound having a structure of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, or XIV.

Sub-class #	B	Sub-class #	B	Sub-class #	B
B-1		B-2		B-3	-CH(CH$_3$)2
B-4		B-5		B-6	
B-7		B-8		B-9	
B-10		B-11		B-12	
B-13		B-14		B-15	
B-16		B-17		B-18	
B-19		B-20		B-21	
B-22		B-23		B-24	
B-25		B-26		B-27	
B-28		B-29		B-30	
B-31		B-32		B-33	

B-34		B-35		B-36	
B-37		B-38		B-39	
B-40		B-41		B-42	
B-43		B-44		B-45	
B-46		B-47		B-48	
B-49		B-50		B-51	
B-52		B-53		B-54	
B-55		B-56		B-57	
B-58		B-59		B-60	
B-61		B-62		B-63	
B-64		B-65		B-66	
B-67		B-68		B-69	
B-70		B-71		B-72	

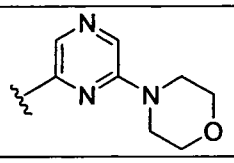
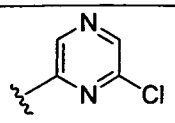
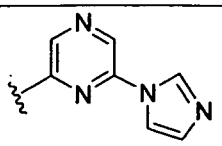
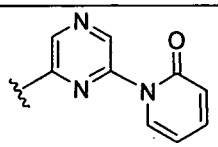
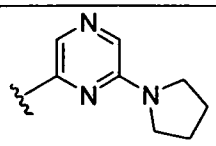
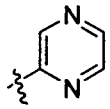
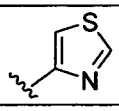
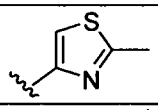
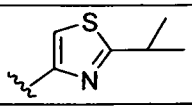
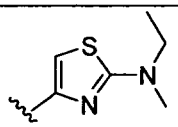
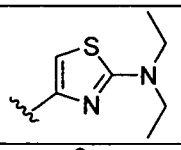
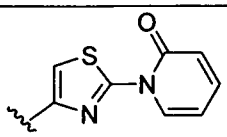
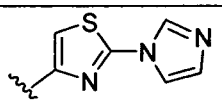
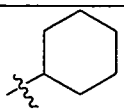
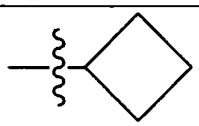
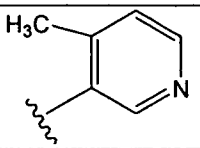
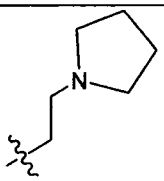
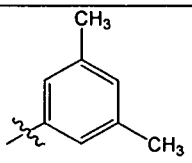
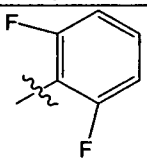
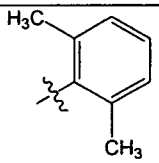
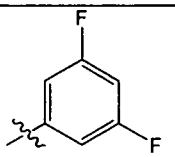
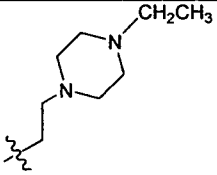
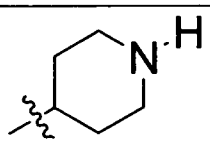
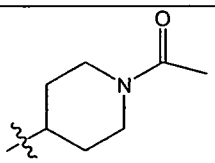
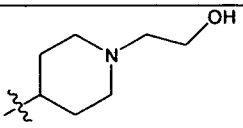
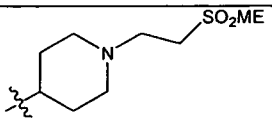
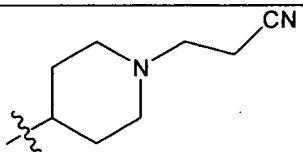
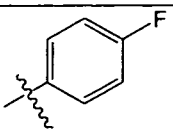
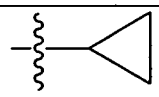
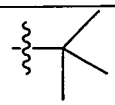
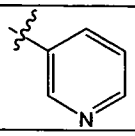
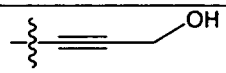
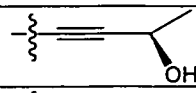
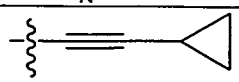
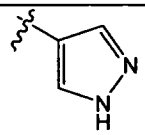
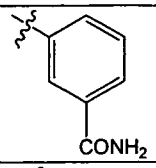
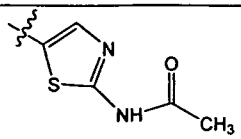
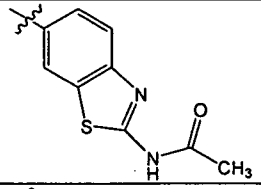
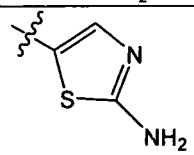
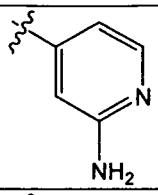
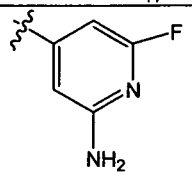
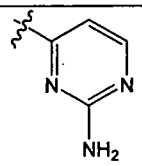
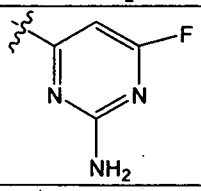
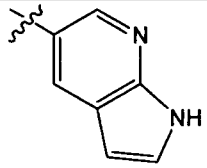
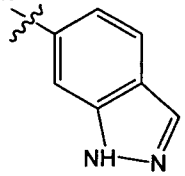
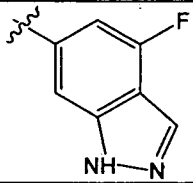
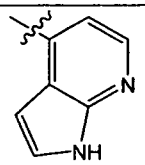
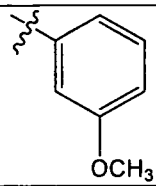
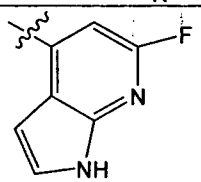
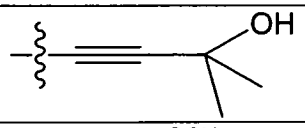
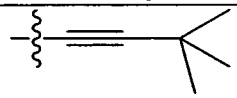
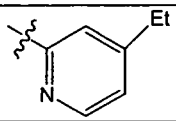
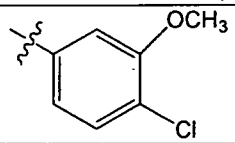
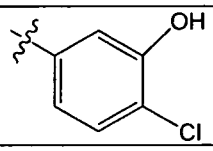
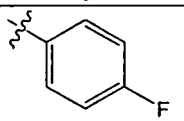
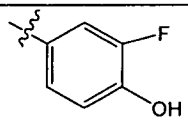
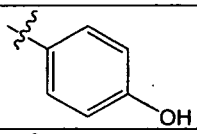
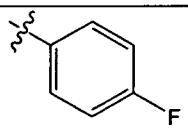
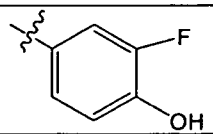
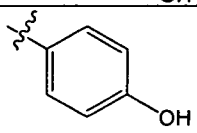
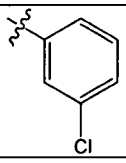
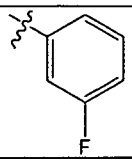
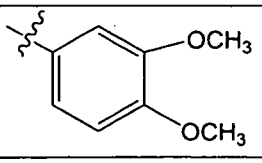
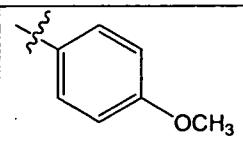
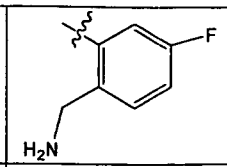
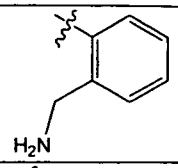
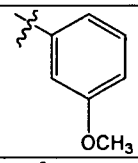
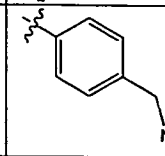
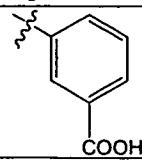
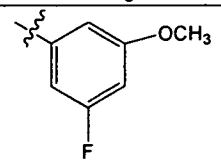
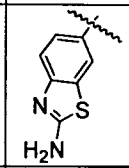
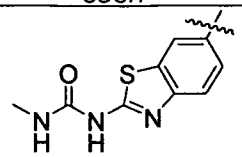
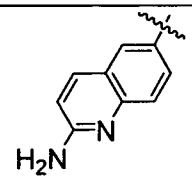
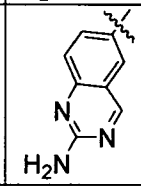
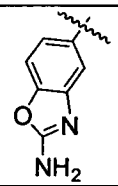
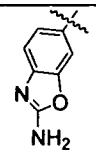
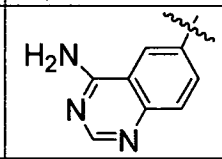
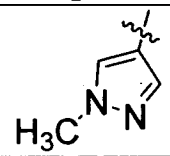
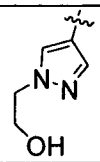
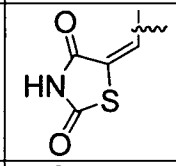
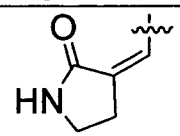
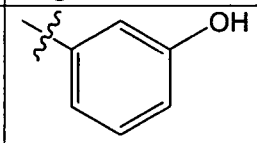
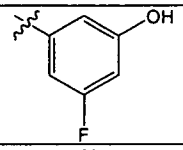
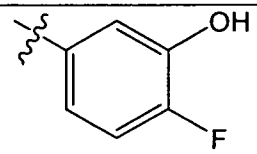
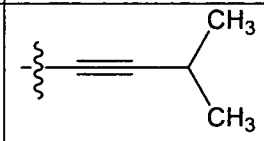
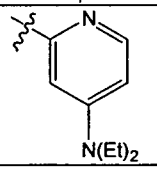
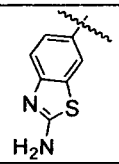
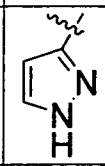
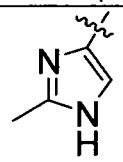
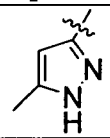
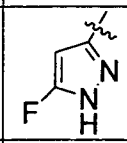
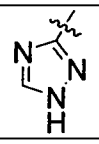
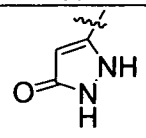
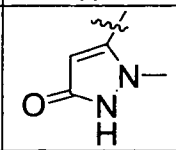
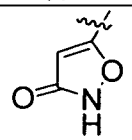
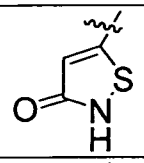
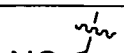
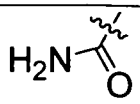
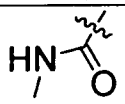
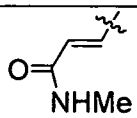
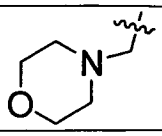
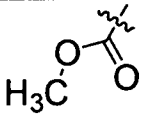
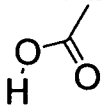
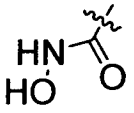
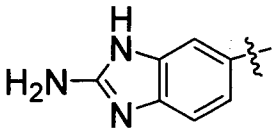
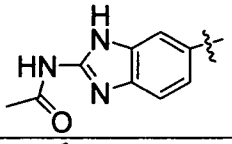
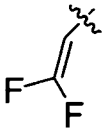
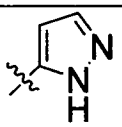
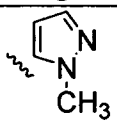
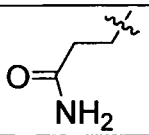
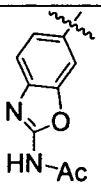
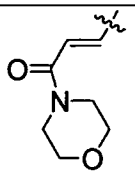
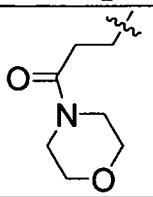
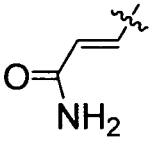
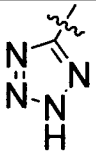
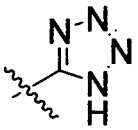
B-73		B-74		B-75	
B-76		B-77		B-78	
B-79		B-80		B-81	
B-82		B-83		B-84	
B-85		B-86		B-87	-CH_3
B-88	-CH_2CH_3	B-89		B-90	
B-91		B-92		B-93	
B-94		B-95		B-96	
B-97		B-98		B-99	
B-100		B-101		B-102	

Table 2. Illustrative R^{12} of a compound having a structure of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, or XIV.

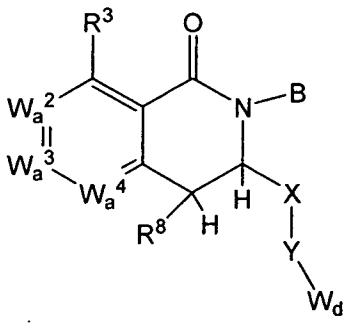
Sub-class #	R^{12}	Sub-class #	R^{12}	Sub-class #	R^{12}
12-1	-CN	12-2	-Br	12-3	-Cl
12-4	-CH_2CH_3	12-5	-CH_3	12-6	-$CH(CH_3)_2$

12-7		12-8		12-9	
12-10		12-11		12-12	
12-13		12-14		12-15	
12-16		12-17		12-18	
12-19		12-20		12-21	
12-22		12-23		12-24	
12-25		12-26		12-27	
12-28		12-29		12-30	
12-31		12-32		12-33	
12-34		12-35	-H	12-36	
12-37		12-38		12-39	
12-40		12-41		12-42	

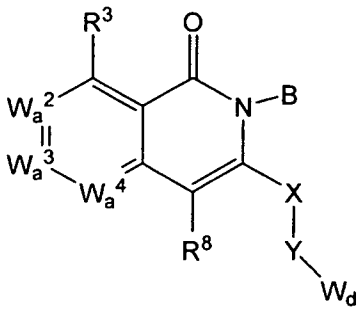
12-43		12-44		12-45	
12-46		12-47		12-48	
12-49		12-50		12-51	
12-52		12-53		12-54	
12-55		12-56		12-57	
12-58		12-59		12-60	
12-61	-I	12-62		12-63	
12-64		12-65		12-66	
12-67		12-68		12-69	
12-70		12-71		12-72	
12-73		12-74		12-75	

12-76		12-77		12-78	
12-79		12-80		12-81	
12-82		12-83		12-84	
12-85		12-86		12-87	
12-88		12-89		12-90	
12-91		12-92		12-93	
12-94		12-95		12-96	

[00251] Illustrative embodiments of Formula 2-A and Formula 2-B are provided, wherein R^3 is selected from any of H, Cl, F, or methyl; any of W_a^2 is elected from CH, N, C-CN, or C-OCH_3; any of W_a^3 is selected from CH, N, C-CF_3, or C-CH_3; any of W_a^4 is selected from CH, N, or C-CF_3; any of $R^{8\,is}$ selected from H, Me, or Cl; any of B as described in Table 1; any of R^{12} as described in Table 2, and any of X-Y-W_d as described in Table 3. The compounds of Formula 2-A and Formula 2-B can contain any substituents specified under R^3, W_a^2, W_a^3, W_a^4, R^8, B, R^{12}, and X-Y-W_d. The specific embodiments described in no way limit the invention, but are descriptive of the compounds of the invention. Some additional exemplary compounds of Formulas 2-A and 2-B are illustrated in Table 5.



Formula 2-A



Formula 2-B

Table 3. Exemplary X-Y-W_d for a compound having a structure of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, or XIV.

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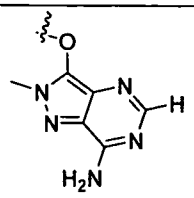
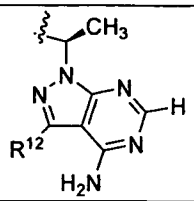
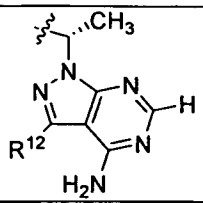
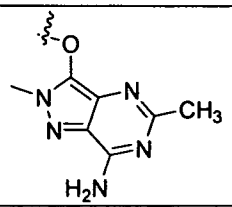
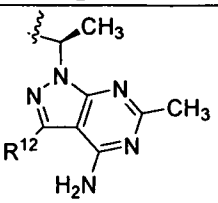
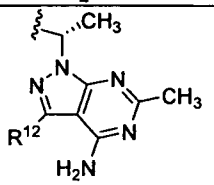
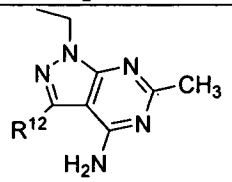
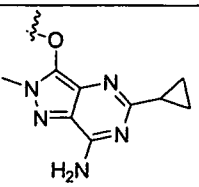
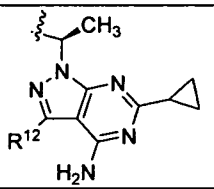
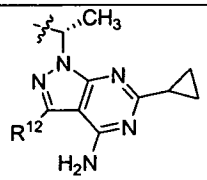
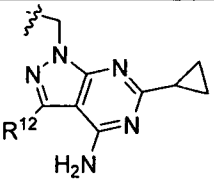
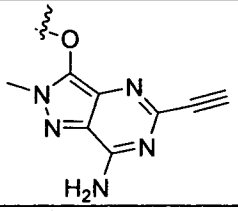
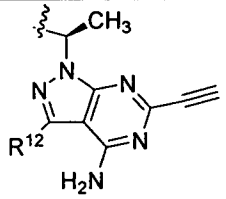
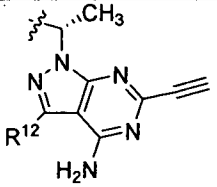
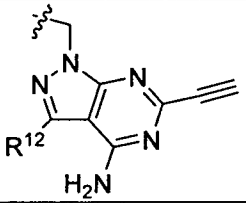
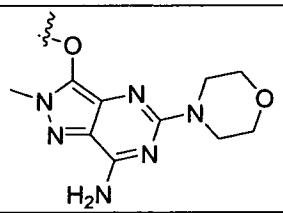
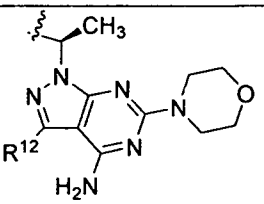
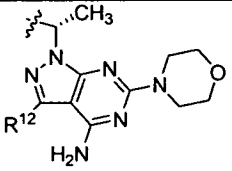
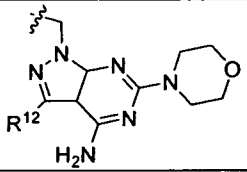
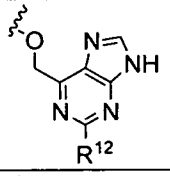
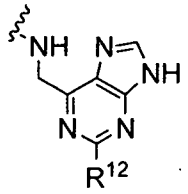
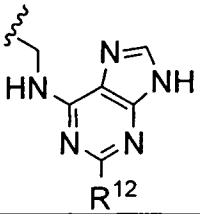
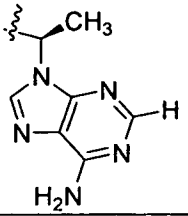
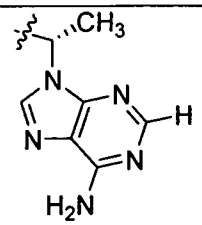
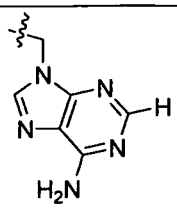
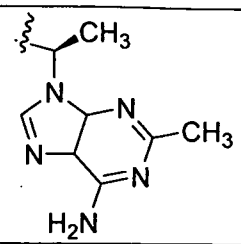
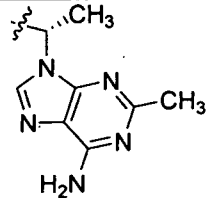
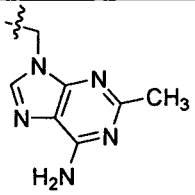
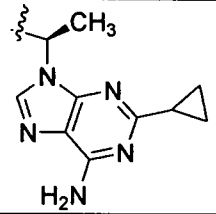
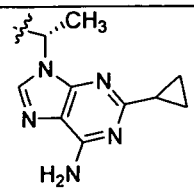
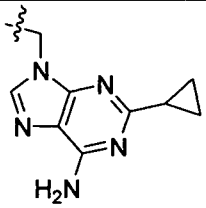
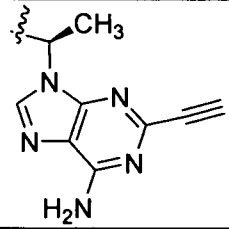
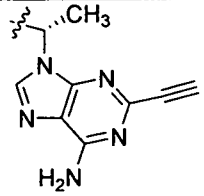
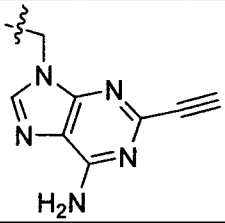
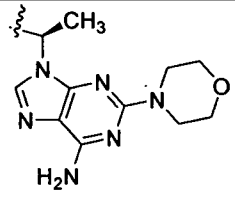
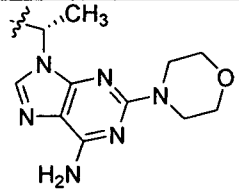
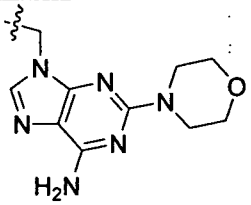
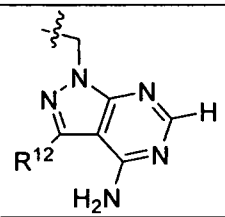
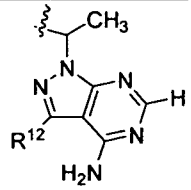
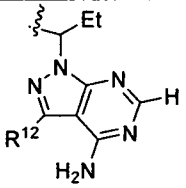
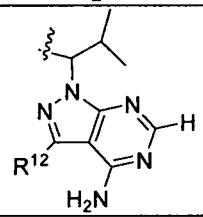
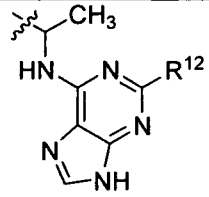
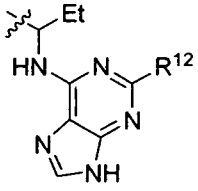
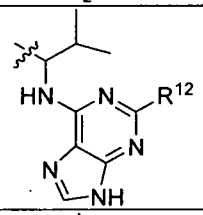
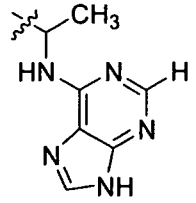
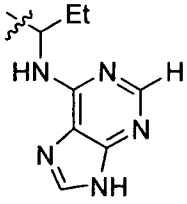
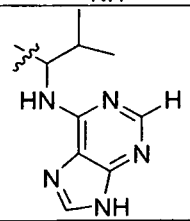
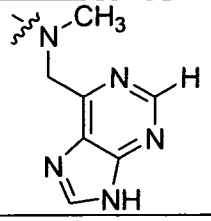
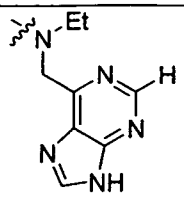
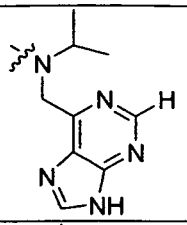
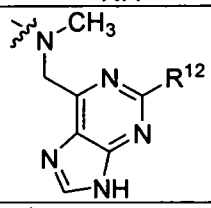
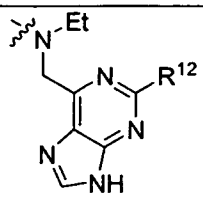
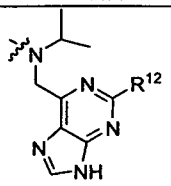
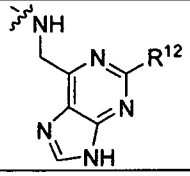
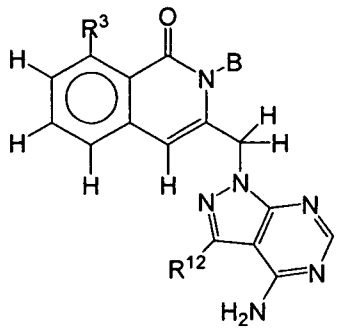
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	

25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	
46		47		48	

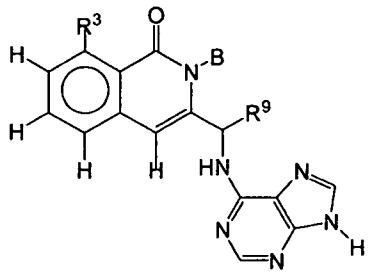
49		50		51	
52		53		54	
55					

[00252] Illustrative embodiments of Formula 6-A are provided, wherein R^3 is selected from any of H, Cl, F, or methyl; any of B as described in Table 1; and any of R^{12} as described in Table 2. The compounds of Formula 6-A can contain any substituents specified under R^3, B, and R^{12}. The specific embodiments described in no way limit the invention, but are descriptive of the compounds of the invention. Some additional exemplary compounds of Formulas 6-A are illustrated in Table 5.



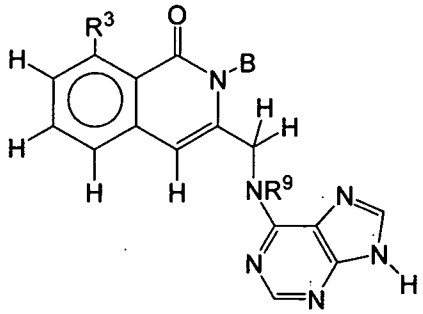
Formula 6-A

[00253] Illustrative embodiments of Formula 6-C1 are provided, wherein R^3 is selected from any of H, Cl, F, or methyl; any of B as described in Table 1; any of R^9, which is selected from –H, $-CH_3$, or $-CH_2CH_3$; and any of R^{12} as described in Table 2. The compounds of Formula 6-C1 can contain any substituents specified under R^3, B, R^9, and R^{12}. The specific embodiments described in no way limit the invention, but are descriptive of the compounds of the invention. Some additional exemplary compounds of Formulas 6-C1 are illustrated in Table 5.



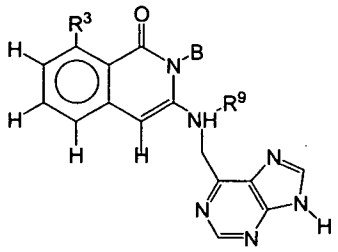
Formula 6-C1

[00254] Illustrative embodiments of Formula 6-C2 are provided, wherein R^3 is selected from any of H, Cl, F, or methyl; any of B as described in Table 1; and any of R^9, which is selected from –H, $-CH_3$, or $-CH_2CH_3$. The compounds of Formula 6-C2 can contain any substituents specified under R^3, B, and R^9. The specific embodiments described in no way limit the invention, but are descriptive of the compounds of the invention. Some additional exemplary compounds of Formulas 6-C2 are illustrated in Table 5.



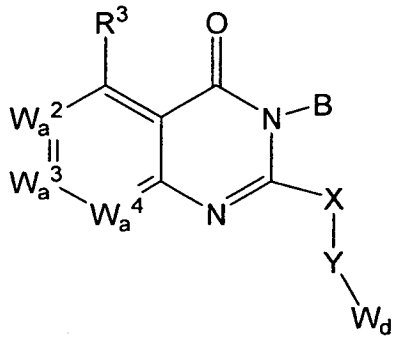
Formula 6-C2

[00255] Illustrative embodiments of Formula 6-D are provided, wherein R^3 is selected from any of H, Cl, F, or methyl; any of B as described in Table 1; and any of R^9, which is selected from –H, $-CH_3$, or $-CH_2CH_3$. The compounds of Formula 6-D can contain any substituents specified under R^3, B, and R^9. The specific embodiments described in no way limit the invention, but are descriptive of the compounds of the invention. Some additional exemplary compounds of Formulas 6-D are illustrated in Table 5.



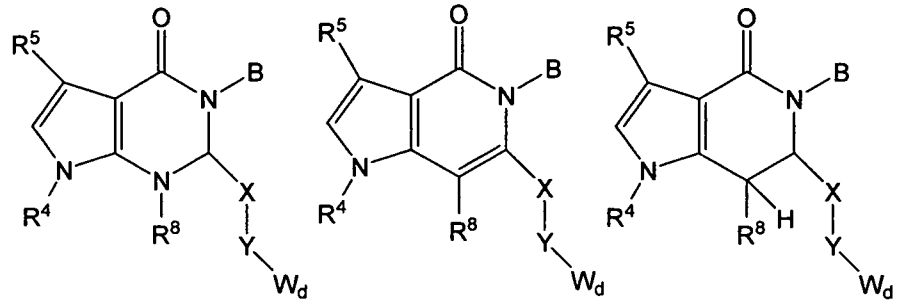
Formula 6-D

[00256] Illustrative embodiments of Formula VIII are provided, wherein R^3 is selected from any of H, Cl, F, or methyl; any of W_a^2 is elected from CH, N, C-CN, or $C-OCH_3$; any of W_a^3 is selected from CH, N, $C-CF_3$, or $C-CH_3$; any of W_a^4 is selected from CH, N, or $C-CF_3$; any of B as described in Table 1; any of R^{12} as described in Table 2, and any of X-Y-W_d as described in Table 3. The compounds of Formula VIII can contain any substituents specified under R^3, W_a^2, W_a^3, W_a^4, B, R^{12}, and X-Y-W_d. The specific embodiments described in no way limit the invention, but are descriptive of the compounds of the invention. Some additional exemplary compounds of Formula VIII are illustrated in Table 5.



Formula VIII

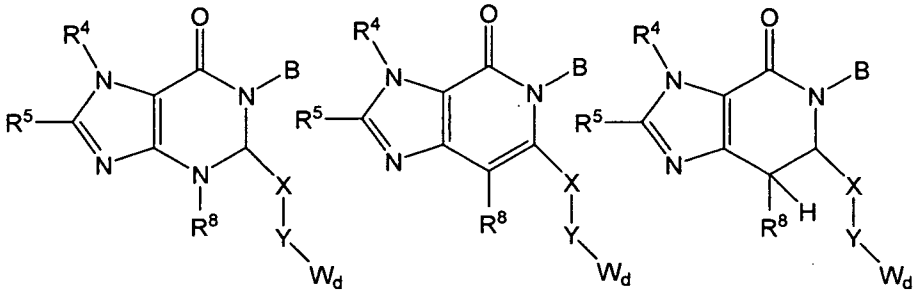
[00257] Also provided are compounds of substructure Formulae 9A-9BD under generic structure Formula IX, wherein R^4 is selected from –H, methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, cyclobutyl, and cyclopentyl; any of R^5 is selected from H, Cl, F, methyl, or trifluoromethyl; any of R^7 is selected from H, Cl, F, methyl, trifluoromethyl; cyano, hydroxyl, ethyl, iso-propyl, and cyclopropyl; any of R^8 is selected from H, methyl or iso-propyl; any of B as described in Table 1; any of X-Y-W_d as described in Table 3 , and any of R^{12} as described in Table 2. The compounds of Formulae 9A-9BD can contain any substituents specified under R^4, R^5, R^7 R^8 B, X-Y-W_d, and R^{12} . The specific embodiments described in no way limit the invention, but are descriptive of the compounds of the invention. Some additional exemplary compounds of Formulae 9-A to 9-BD are illustrated in Table 5.



Formula 9-A

Formula 9-B

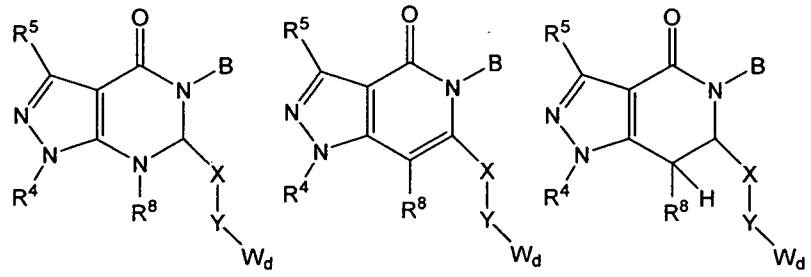
Formula 9-C



Formula 9-D

Formula 9-E

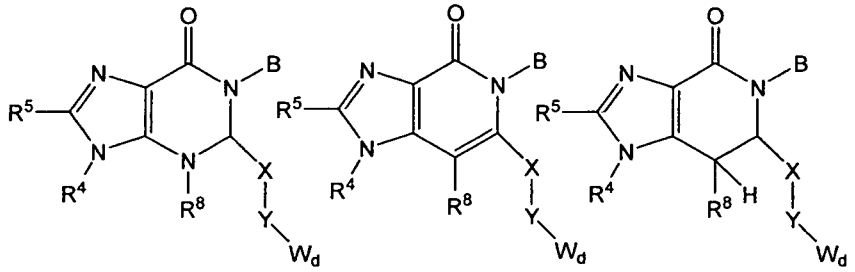
Formula 9-F



Formula 9-G

Formula 9-H

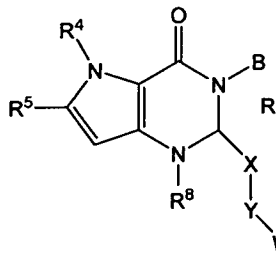
Formula 9-I



Formula 9-J

Formula 9-K

Formula 9-L



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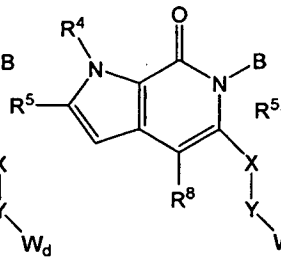
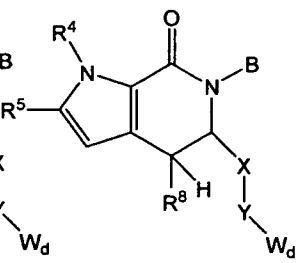


Formula 9-N



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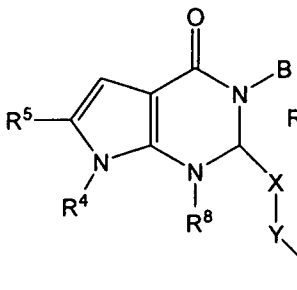

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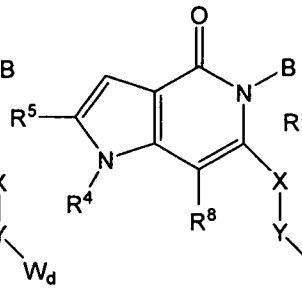

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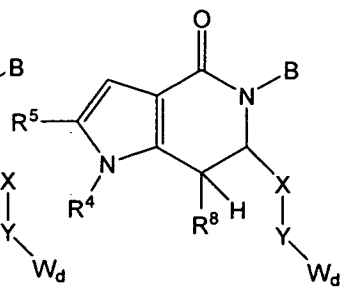

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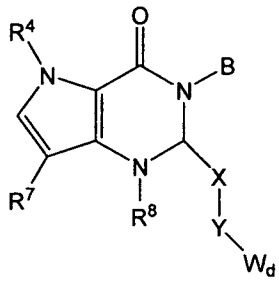

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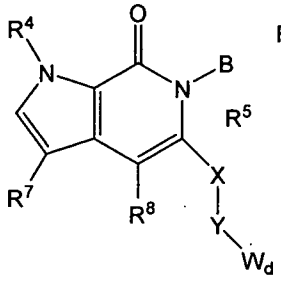

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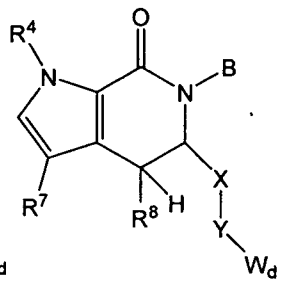

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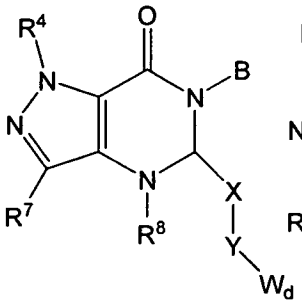

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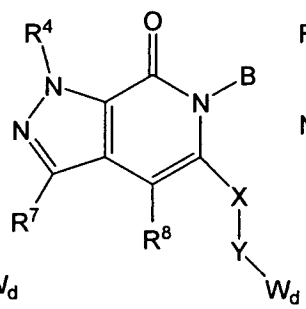

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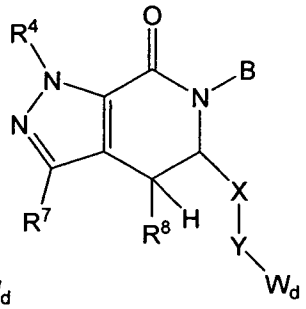

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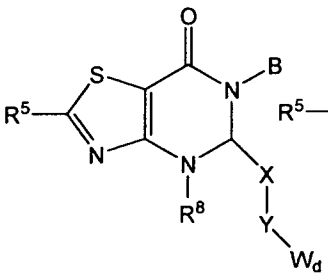

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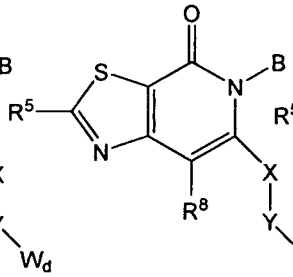

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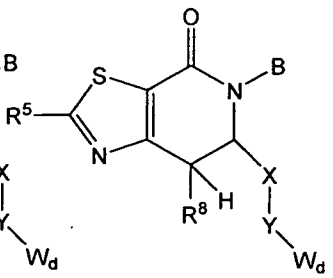

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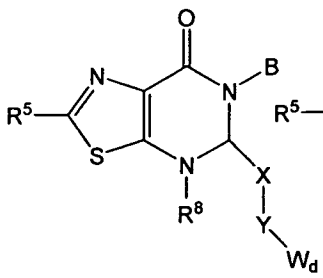

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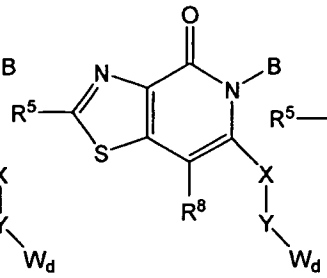

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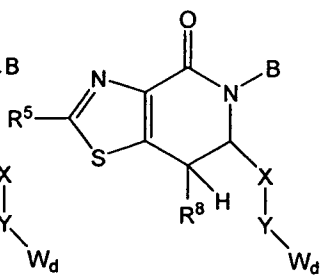

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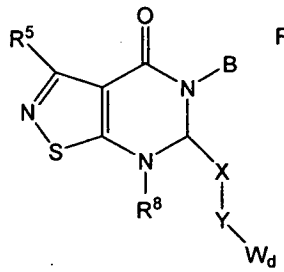

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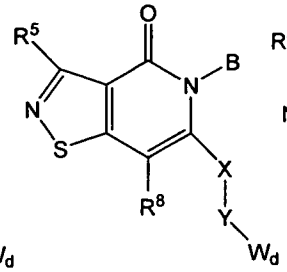

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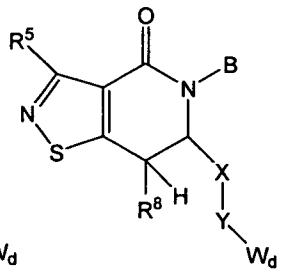

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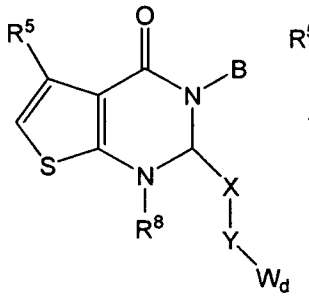

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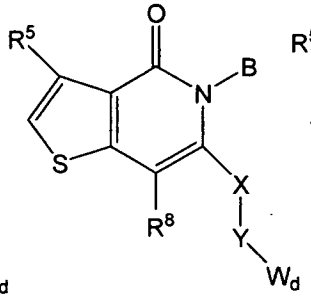

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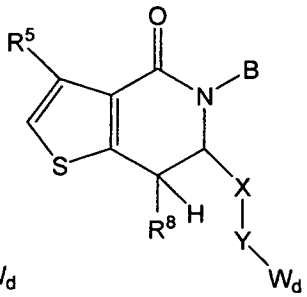

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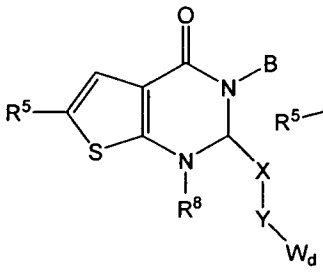

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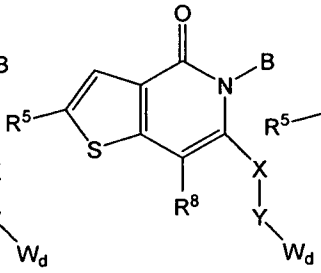

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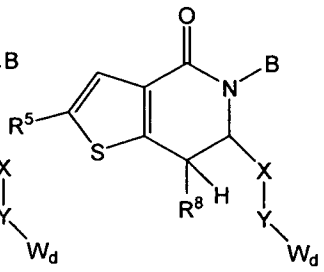

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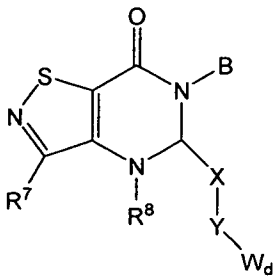

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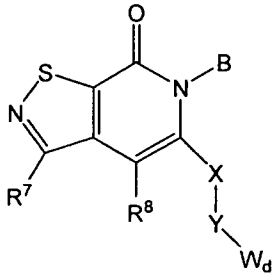

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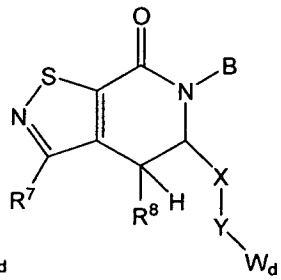
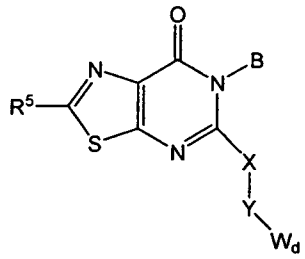


Formula 9-AP



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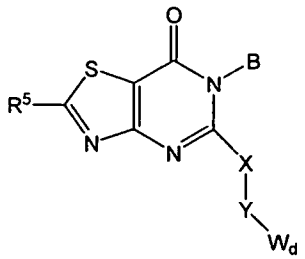

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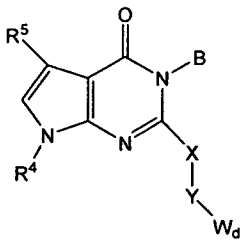

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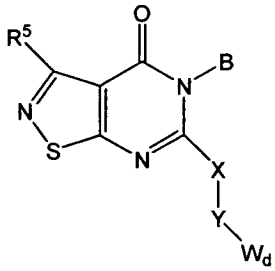

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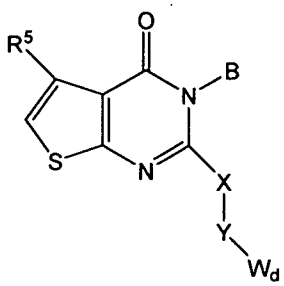

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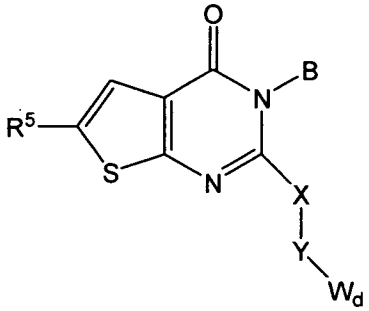

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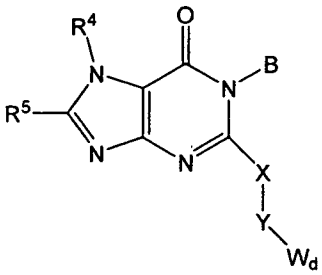

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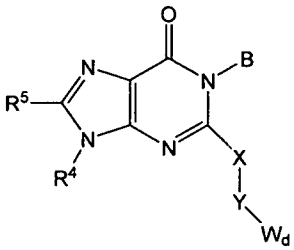

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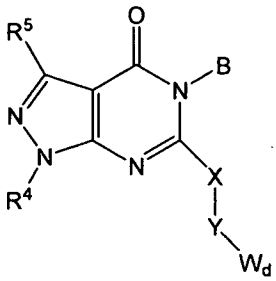

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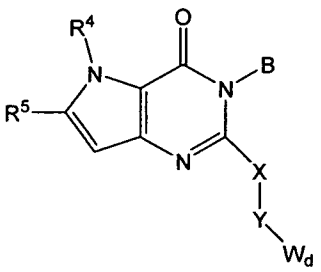

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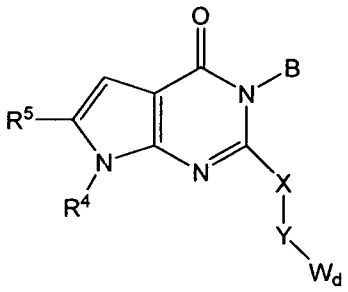
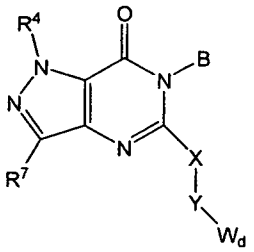
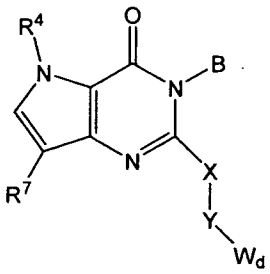


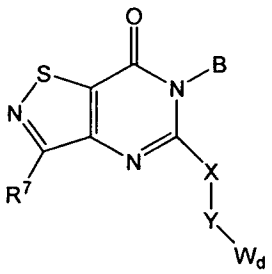
Formula 9-BA



Formula 9-BB

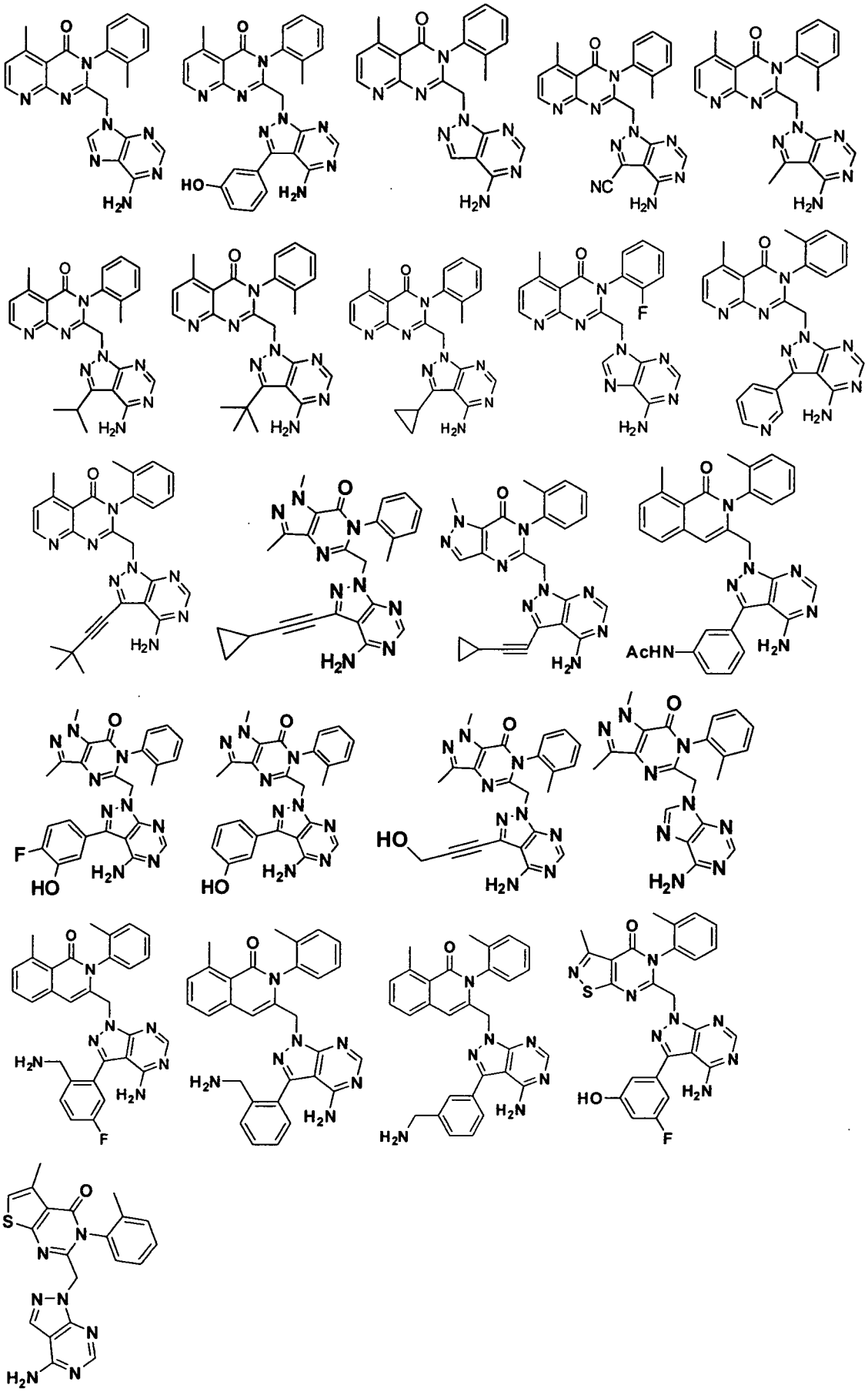


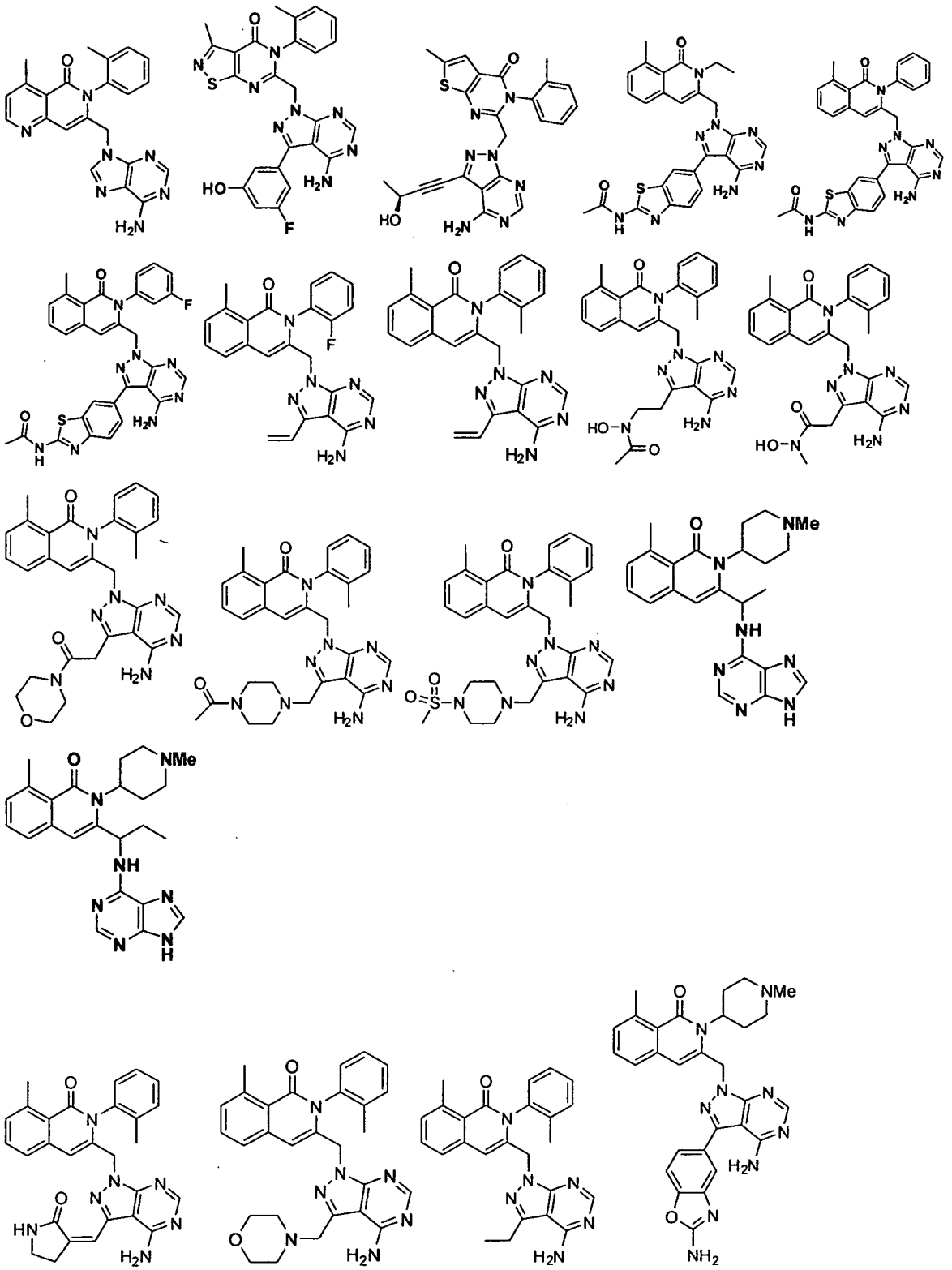
Formula 9-BC

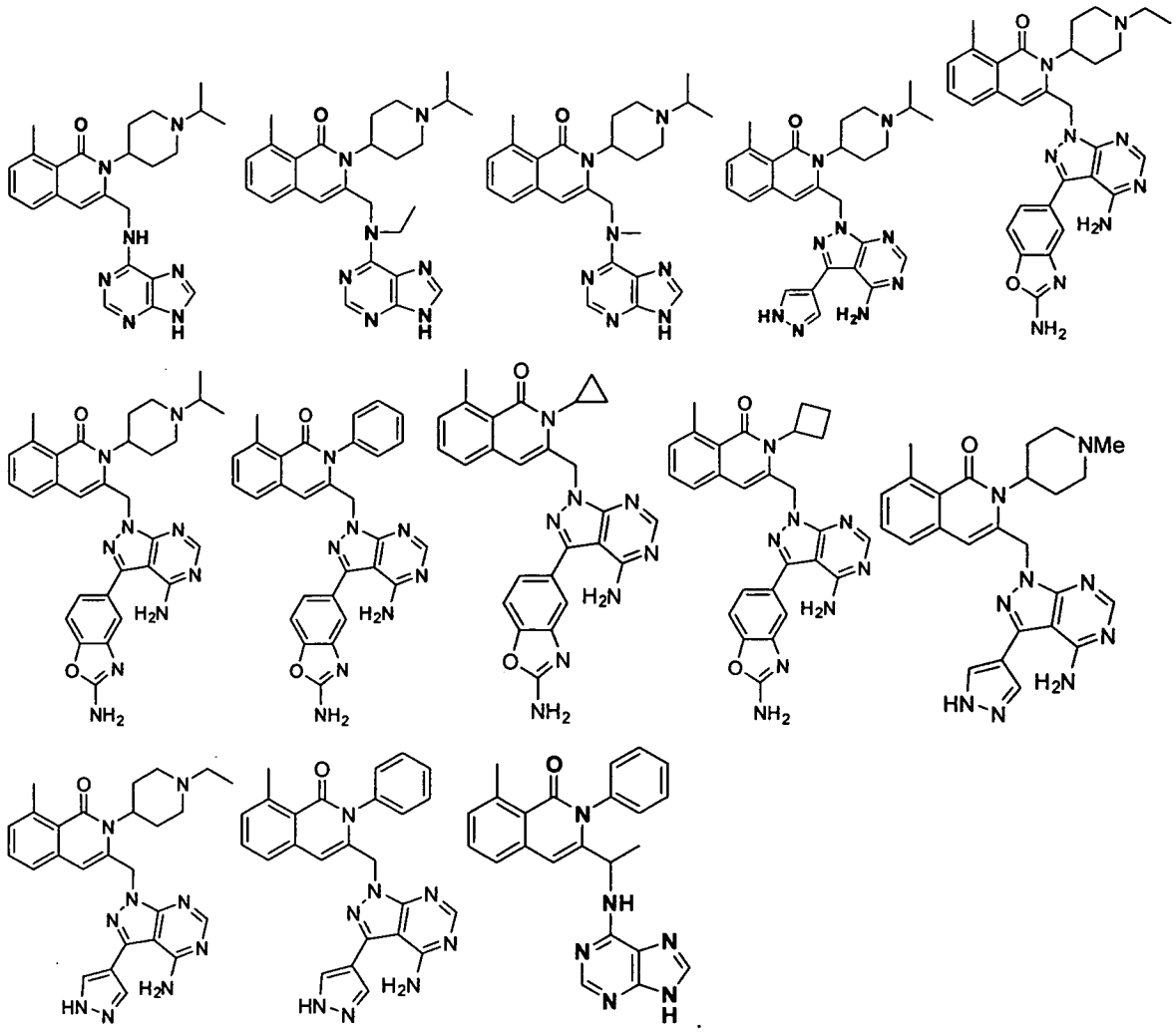


Formula 9-BD

[00258] Other illustrative compounds include but are not limited to the following:







[00259] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/ or techniques well known in the art.

[00260] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10 °C to 200 °C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, e.g., taking place at about atmospheric pressure within a temperature range of about -10 °C to about 110 °C over a period of about 1 to about 24 hours; reactions left to run overnight average a period of about 16 hours.

[00261] The terms "solvent," "organic solvent," or "inert solvent" each mean a solvent inert under the conditions of the reaction being described in conjunction therewith including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, N-methylpyrrolidone ("NMP"), pyridine and the like. Unless specified to the contrary, the solvents used in the reactions described herein are inert organic solvents. Unless specified to the contrary, for each gram of the limiting reagent, one cc (or mL) of solvent constitutes a volume equivalent.

[00262] Isolation and purification of the chemical entities and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can also be used.

[00263] When desired, the (R)- and (S)-isomers of the compounds of the present invention, if present, may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. Alternatively, a specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

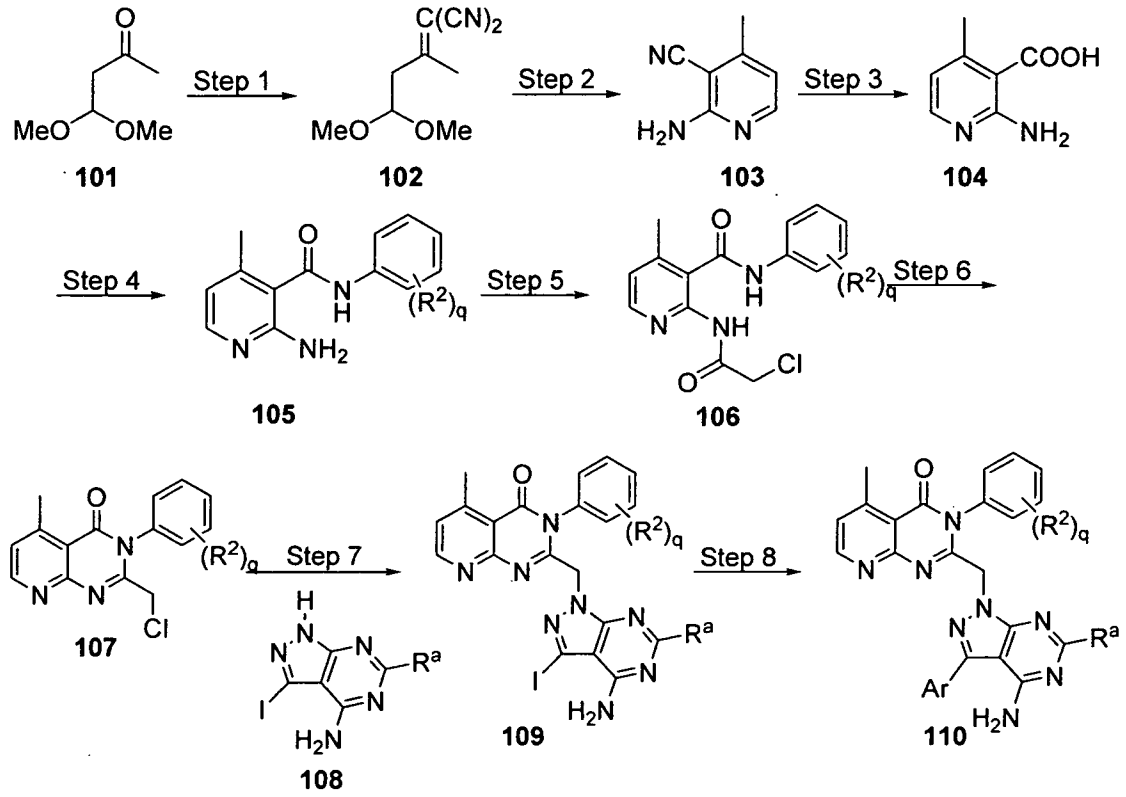
[00264] The compounds described herein can be optionally contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salts.

[00265] Many of the optionally substituted starting compounds and other reactants are commercially available, e.g., from Aldrich Chemical Company (Milwaukee, WI) or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

[00266] The compounds of the invention can generally be synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing these chemical entities are both readily apparent and accessible to those of skill in the relevant art, based on the instant disclosure.

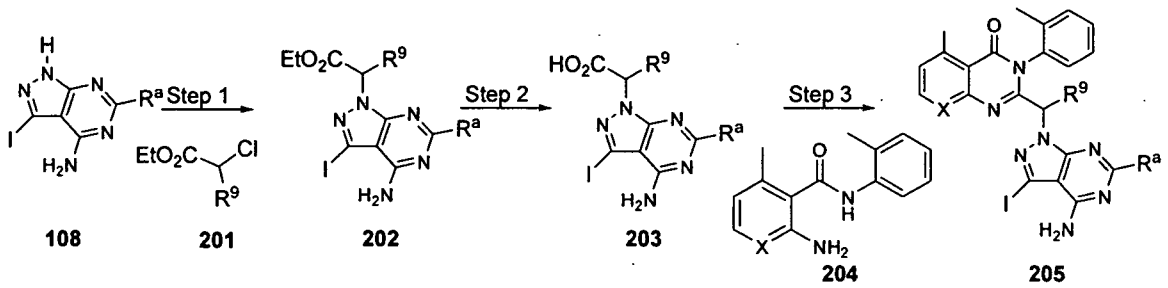
[00267] The compounds of the invention can be synthesized by an appropriate combination of known synthetic methods in the art. The discussion below is offered to illustrate certain of the diverse methods available for use in making the compounds of the invention and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds of the present invention.

Reaction Scheme 1



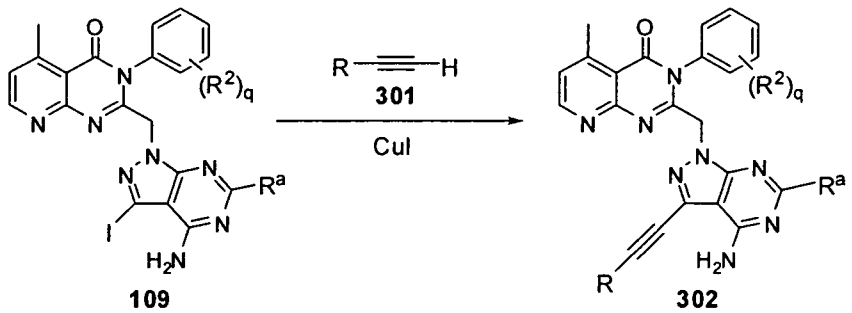
[00268] Referring to Scheme 1, Step 1, ketone 101 is converted to the corresponding alkene using, for example, malononitrile and piperidine in acetic acid. The product, a compound of Formula **102**, is isolated. Referring to Scheme 1, Step 2, a compound of Formula **102** is cyclized to a pyridine using, for example, ammonia in methanol. The product, a compound of Formula **103**, is isolated. Referring to Scheme 1, Step 3, a compound of Formula **103** is hydrolyzed to the corresponding carboxylic acid. The product, a compound of formula **104**, is isolated. Referring to Scheme 1, Step 4, a compound of Formula **104** is converted to an amide using, for example, a standard amide coupling reagent, such as EDCI. The product, a compound of Formula **105**, is isolated. Referring to Scheme 1, Step 5, a compound of Formula **105** is converted to the corresponding amide using, for example, chloroacetyl chloride. The product, a compound of Formula **106**, is isolated. Referring to Scheme 1, Step 6, a compound of Formula **106** is converted to a compound of Formula **107**, using, for example, acetic acid. The product, a compound of Formula **107**, is isolated. Referring to Scheme 1, Step 7, a compound of Formula **107** undergoes a displacement at the chlorine when reacted with a nucleophile and a base, such as pyrazolopyrimidine **108** and potassium carbonate. The product, a compound of Formula **109**, is isolated. Referring to Scheme 1, Step 8, a compound of Formula **109** is coupled with an aryl or heteroaryl boronic acid or boronic acid derivative such as, for example, a borolan, using, for example, palladium catalyzed coupling conditions. The product, a compound of Formula **110**, is isolated.

Reaction Scheme 2



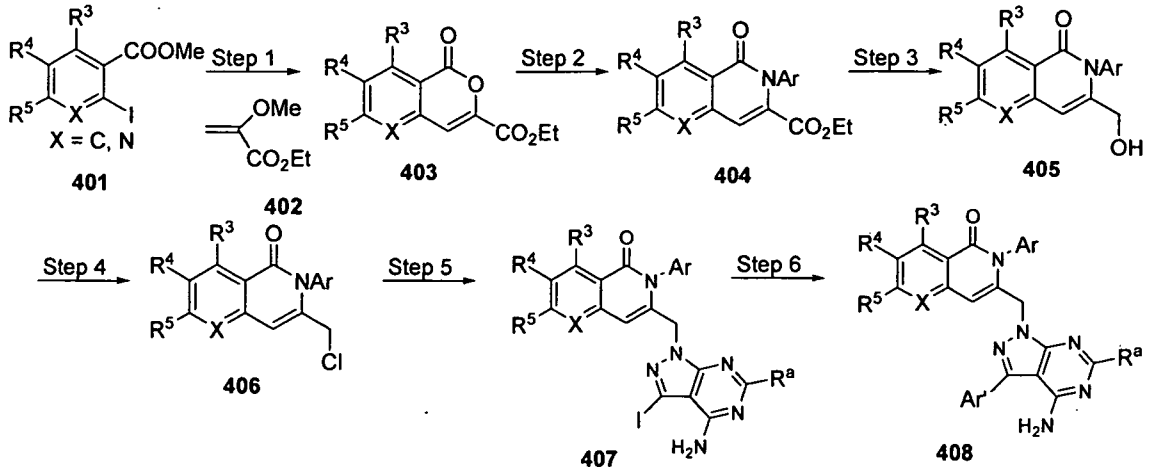
[00269] Referring to Scheme 2, Step 1, a compound of Formula **108** is converted to a compound of Formula **202**, for example, via an alkylation of a compound of Formula **201**. The product, a compound of Formula **202**, is isolated. Referring to Scheme 2, Step 2, a compound of Formula **202** is converted to a compound of Formula **203**, for example, via saponification. The product, a compound of Formula **203**, is isolated. Referring to Scheme 2, Step 3, a compound of Formula **203** is cyclized to a quinazoline of Formula **205**, for example, via sealed tube reaction with a compound of Formula **204** and a dehydrating agent, such as PCl_5. The product, a compound of Formula **205**, is isolated.

Reaction Scheme 3



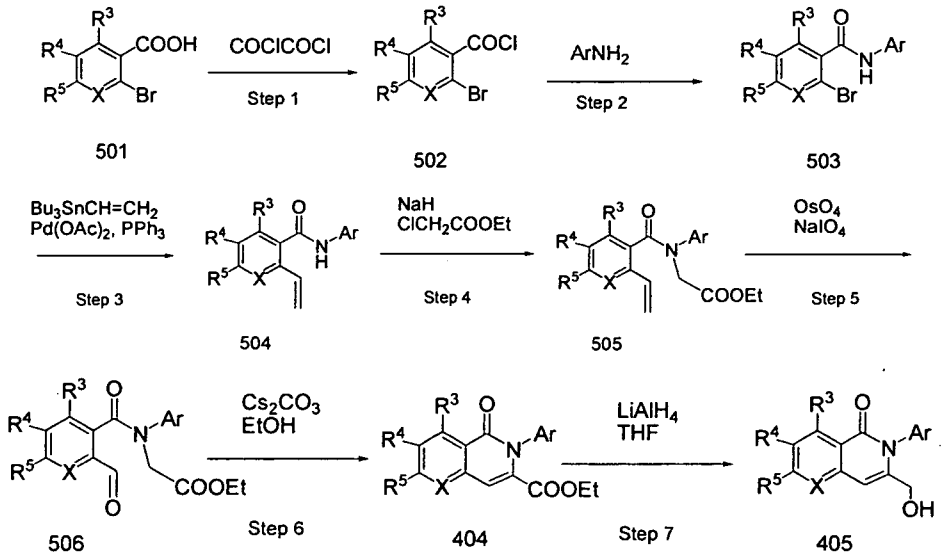
[00270] Referring to Scheme 3, a compound of Formula **109** is converted to a compound of Formula **302**, for example, via a Sonagashira coupling with a compound of Formula **301**. The product, a compound of Formula **302**, is isolated.

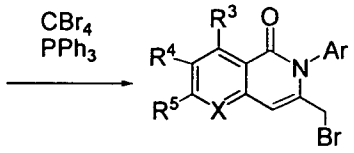
Reaction Scheme 4



[00271] Referring to Scheme 4, Step 1, a compound of Formula **401** is converted to a compound of Formula **403**, for example, via a two step process of Heck coupling with a compound of Formula **402**, followed by acid catalyzed cyclization in methanol. The product, a compound of Formula **403**, is isolated. Referring to Scheme 4, Step 2, a compound of Formula **403** is converted to a compound of Formula **404**, for example, via reaction with an appropriately substituted aniline. The product, a compound of Formula **404**, is isolated. Referring to Scheme 4, Step 3, a compound of Formula **404** is converted to a compound of Formula **405**, for example, though reduction with lithium aluminum hydride. The product, a compound of Formula **405**, is isolated. Referring to Scheme 4, Step 4, a compound of Formula **405** is converted to a compound of Formula **406**, for example, via reaction with thionyl chloride. The product, a compound of Formula **406**, is isolated. Referring to Scheme 4, Step 5, a compound of Formula **406** is converted to a compound of Formula **407**, for example, via alkylation with a pyrrazolopyrimidine using a base such as potassium carbonate. The product, a compound of Formula **407**, is isolated. Referring to Scheme 4, Step 6, a compound of Formula **407** is converted to a compound of Formula **408**, for example, via a Suzuki reaction. The product, a compound of Formula **408**, is isolated.

Reaction Scheme 5:



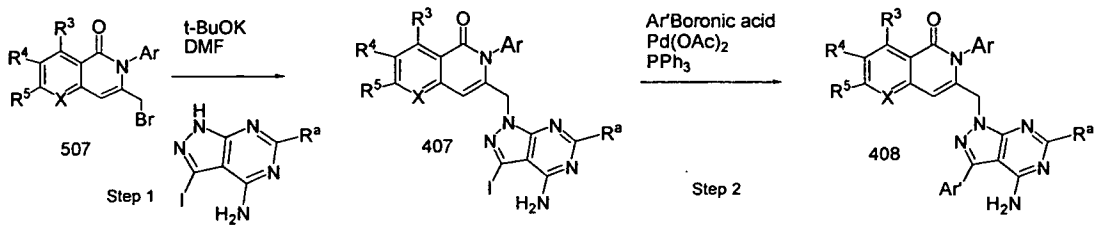


507

Step 8

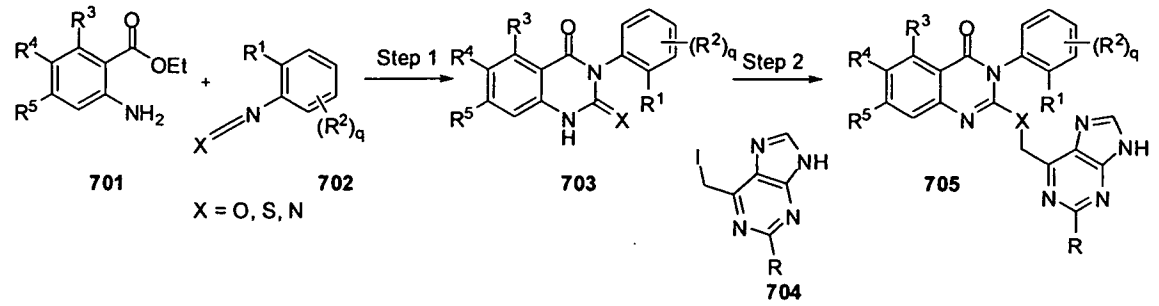
[00272] Referring to Scheme 5, Step 1, a compound of Formula **501** is converted to a compound of Formula **502**, for example, with a reagent suitable for introduction of an acid chloride, for example, oxalyl chloride. The product, a compound of Formula **502**, is optionally isolated. Referring to Scheme 5, Step 2, a compound of Formula **502** is converted to a compound of Formula **503** for example, reaction with, for example, an aryl amine . The product, a compound of Formula **503**, is isolated. Referring to Scheme 5, Step 3, a compound of Formula **503** is converted to a compound of Formula **504**, for example, via a Stille coupling using an appropriate vinyl-stannane. The product, a compound of Formula **504**, is isolated. Referring to Scheme 5, Step 4, a compound of Formula **504** is converted to a tertiary amide, a compound of Formula **505**, via reaction with chloroethyl acetate and sodium hydride base. The compound of Formula **505** is isolated. Referring to Scheme 5, Step 5, a compound of Formula **505** is oxidized to an aldehyde, using, for example, osmium tetraoxide and sodium periodinate. The product, a compound of Formula **506**, is isolated. Referring to Scheme 5, Step 6, a compound of Formula **506** is converted to a compound of Formula **404**, for example, though aldol reaction in ethanol with a base, such as cesium carbonate. The product, a compound of Formula **404**, is isolated. Referring to Scheme 5, Step 7, a compound of Formula **404** is reduced to a primary alcohol via reduction with, for example, lithium aluminum hydride, to produce a compound of Formula **405**, which is isolated. Referring to Scheme 5, Step 8, a compound of Formula **405** is converted to a compound of Formula **507** via reaction with carbon tetrabromide and triphenylphosphine. The compound of Formula **507** is optionally isolated. This compound can be a central intermediate in the synthesis of the compounds of the invention.

Reaction Scheme 6:



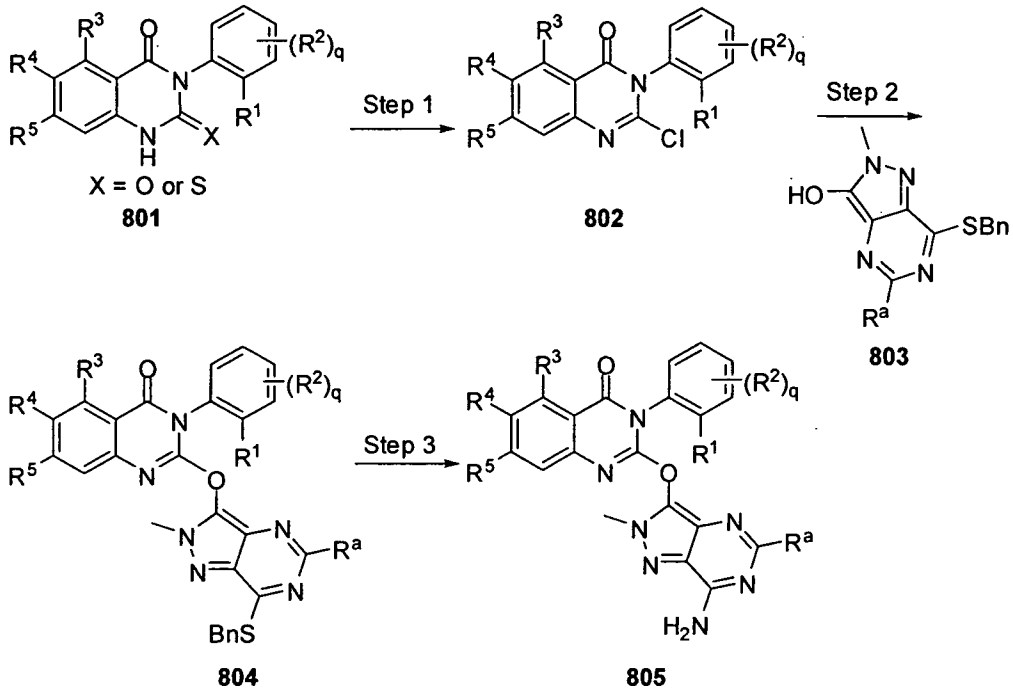
[00273] Referring to Scheme 6, Step 1, a compound of Formula **507**, synthesized as described in Reaction Scheme 5 is converted to a compound of Formula **407** via coupling with a compound of Formula **108** in the presence of base, for example, potassium *t*- butoxide. The compound of Formula **407** is isolated. Referring to Scheme 6, Step 2, a compound of Formula **407** is converted to a compound of Formula **408** via coupling with, for example, an aryl boronic acid, in the presence of coupling catalysts and base, for example, palladium acetate, triphenylphosphine and sodium carbonate, for example. The compound of Formula **408** is isolated.

Reaction Scheme 7:



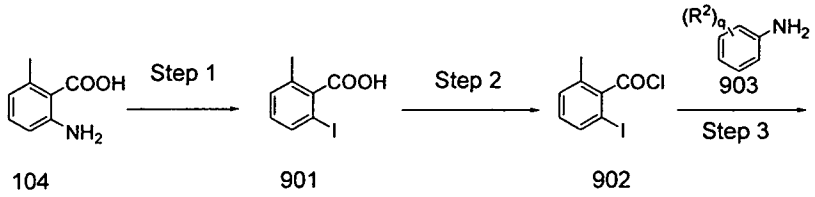
[00274] Referring to Scheme 7, Step 1, a compound of Formula **701** is reacted with a compound of Formula **702**. The product, a compound of Formula **703**, is isolated. Referring to Scheme 7, Step 2, a compound of Formula **703** is reacted with an optionally substituted purine such as a compound of Formula **704**. The product, a compound of Formula **705**, is isolated.

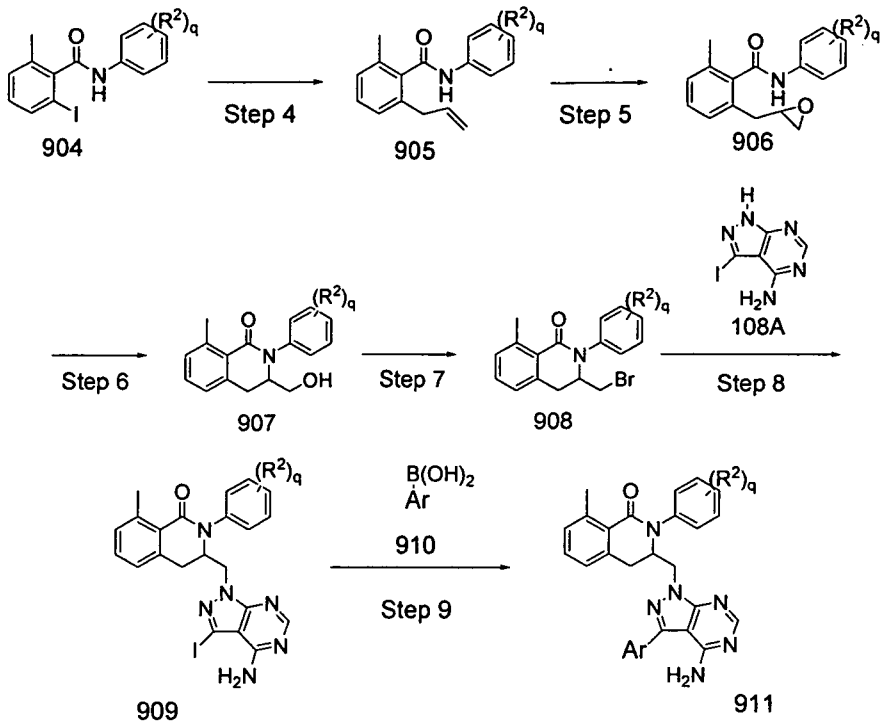
Reaction Scheme 8:



[00275] Referring to Scheme 8, Step 1, a compound of Formula **801** is treated with a reagent such as thionyl chloride to produce a compound of Formula **802**, which, is isolated. Referring to Scheme 8, Step 2, a compound of Formula **802** and a compound of Formula **803** are combined in the presence of base. The product, a compound of Formula **804**, is isolated. Referring to Scheme 8, Step 3, a compound of Formula **804** is converted to a compound of Formula **805**, which is isolated.

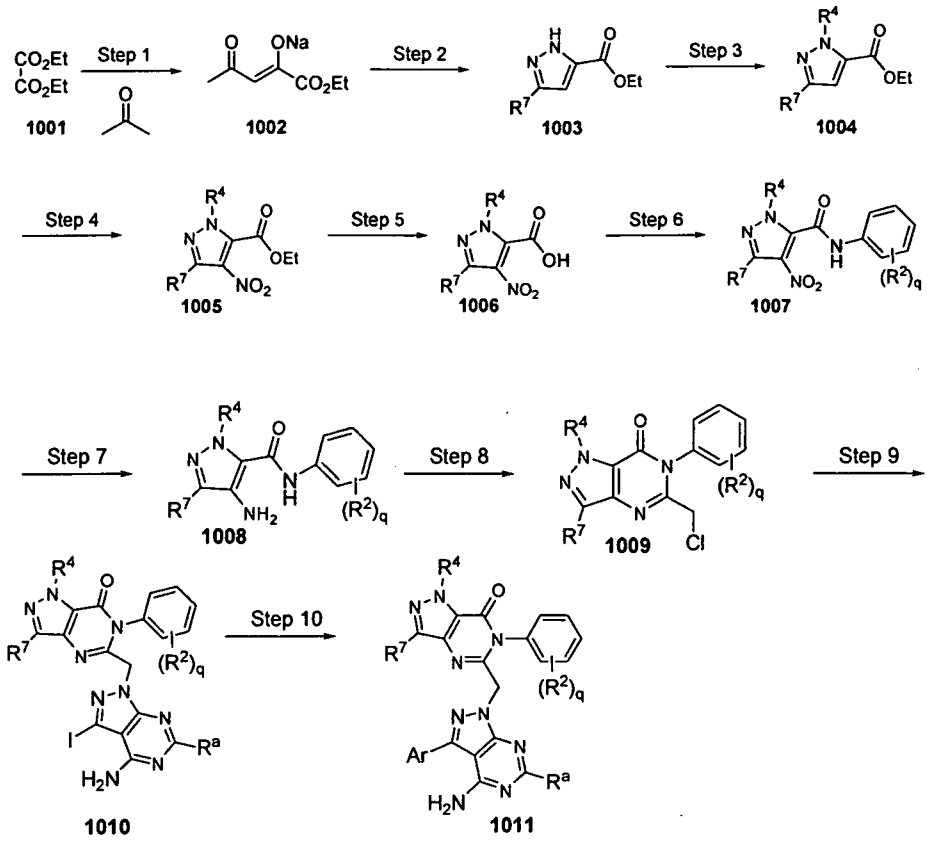
Reaction Scheme 9:





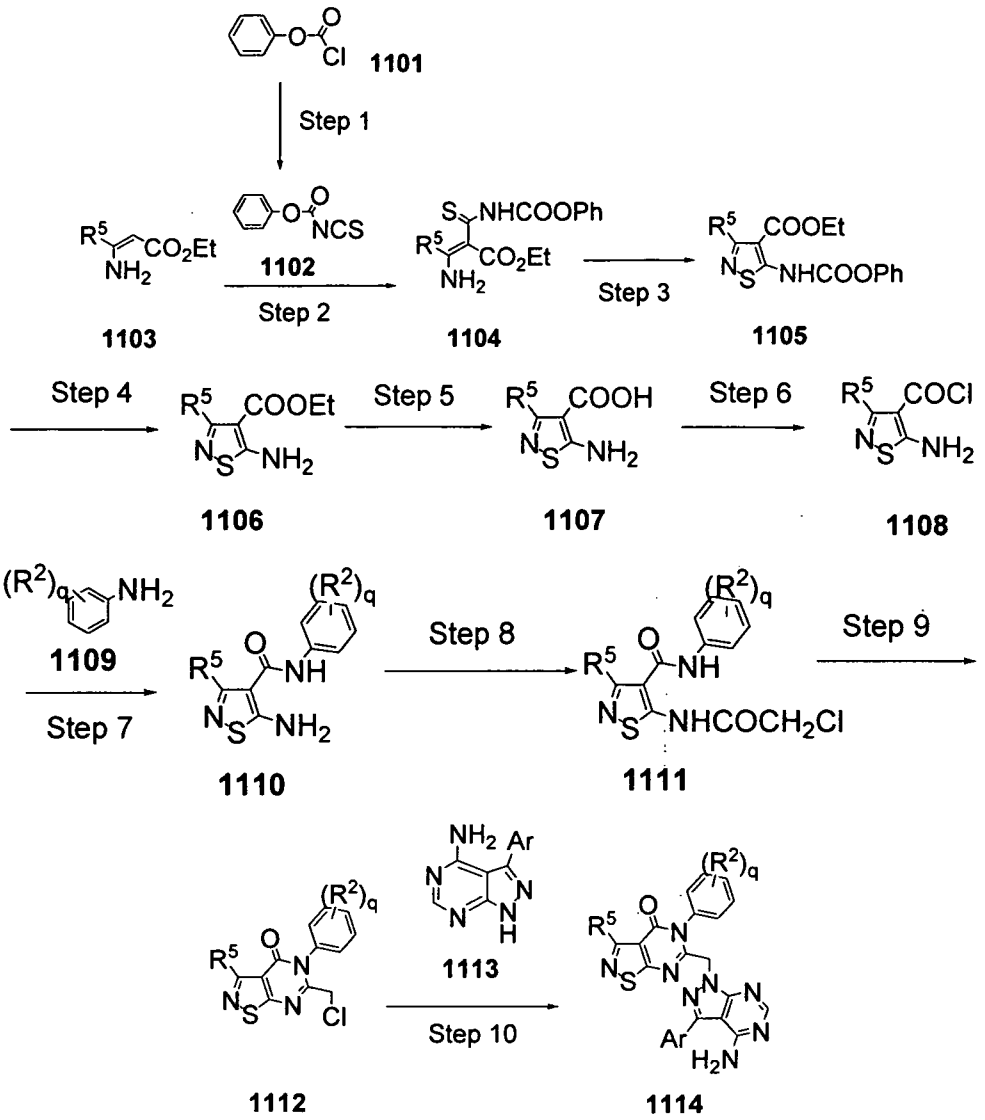
[00276] Referring to Scheme 9, Step 1, a compound of Formula **104** is reacted, for example, with sodium nitrite and potassium iodide under acidic conditions, to produce a compound of Formula **901**, which can be isolated. Referring to Scheme 9, Step 2, the compound of Formula **901** is converted to its acid chloride by reaction with, for example, oxalyl chloride, to obtain a compound of Formula **902**, which can be isolated. Referring to Scheme 9, Step 3, the acid chloride of Formula **902** is reacted with an optionally substituted amino- aryl or amino- hetaryl, compound **903**, to yield a compound of Formula **904**, which is isolated. Referring to Scheme 9, Step 4, the compound of Formula **904** is coupled, for example, with an allyl stannane, to produce a compound of Formula **905**, which is isolated. Referring to Scheme 9, Step 5, the compound of Formula **905** is converted to its epoxide by treatment with, for example, meta-chloroperbenzoic acid, to yield a compound of Formula **906**, which can be isolated. Referring to Scheme 9, Step 6, the compound of Formula **906** is cyclized by treatment, for example, sodium hydride in dimethyl formamide, to obtain a compound of Formula **907**, which is isolated. Referring to Scheme 9, Step 7, the primary hydroxyl of the compound of Formula **907** is converted to the bromide by treatment, for example, with carbon tetrabromide and triphenylphosphine, to produce a compound of Formula **908**, which is isolated. Referring to Scheme 9, Step 8, the compound of Formula **908** is coupled to a pyrazolopyrimidine of Formula **108A** by treatment, for example, with potassium carbonate in dimethylformamide, to yield a compound of Formula **909**, which is isolated. Referring to Scheme 9, Step 9, the dihydroisoquinolone of Formula **909** is coupled with an optionally substituted aryl or hetaryl boronic acid of Formula **910** to produce a compound of Formula **911**, which is isolated.

Reaction Scheme 10:



[00277] Referring to Scheme 10, Step 1, a compound of Formula **1001** is treated with a sodium acetate and acetone. The product, a compound of Formula **1002**, is isolated. Referring to Scheme 10, Step 2, a compound of Formula **1002** is cyclized to the corresponding pyrazole, for example, with hydrazine in acetic acid and water. The product, a compound of Formula **1003**, is isolated. Referring to Scheme 10, Step 3, a compound of Formula **1003** is, for example, alkylated using dimethyl sulfate. The product, a compound of Formula **1004**, is isolated. Referring to Scheme 10, Step 4, a compound of Formula **1004** is nitrated using, for example, a solution of nitric acid and sulfuric acid. The product, a compound of Formula **1005**, is isolated. Referring to Scheme 10, Step 5, a compound of Formula **1005** is saponified using a base, such as sodium hydroxide. The product, a compound of Formula **1006**, is isolated. Referring to Scheme 10, Step 6, a compound of Formula **1006** is first converted to an acid chloride using thionyl chloride, then reacted with an appropriately substituted aniline to create the corresponding amide. The product, a compound of Formula **1007**, is isolated. Referring to Scheme 10, Step 7, a compound of Formula **1007** is reduced to the corresponding amino-pyrazole using hydrogenation conditions with Pd/C as catalyst. The product, a compound of Formula **1008**, is isolated. Referring to Scheme 10, Step 8, a compound of Formula 1008 is cyclized to the corresponding quinazolinone using conditions such as chloroacetyl chloride and acetic acid. The product, a compound of Formula **1009**, is isolated. Referring to Scheme 10, Step 9, a compound of Formula **1009** is coupled with a pyrazolopyrmidine of Formula **108**, for example using conditions such as potassium *t*- butoxide in DMF at room temperature. The product, a compound of Formula **1010**, is isolated. Referring to Scheme 10, Step 9, a compound of Formula **1010** is coupled with an aryl boronic acid of Formula of 910, for example, using palladium acetate catalysis, in the presence of triphenyl phosphine and sodium carbonate in DMF to produce a compound of Formula **1011**. The product, a compound of Formula **1011**, is isolated.

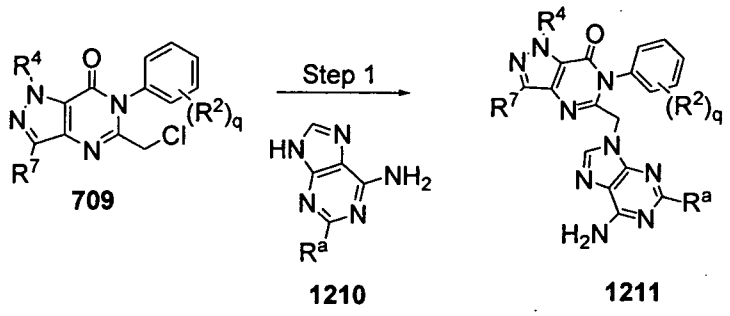
Reaction Scheme 11:



[00278] Referring to Scheme 11, Step 1, a compound of Formula **1101** is reacted with potassium thiocyanide in acetonitrile to produce a compound of Formula **1102**, which can be isolated. Referring to Scheme 11, Step 2, the compound of Formula **1102** is reacted with a conjugated ester of Formula **1103**, to produce a compound of Formula **1104**, which is isolated. Referring to Scheme 11, Step 3, the compound of Formula **1104** is cyclized, for example, by treating it with bromine in ethanol, to obtain a thiazole of Formula **1105**, which is isolated. Referring to Scheme 11, Step 4, the compound of Formula **1105** is deprotected with, for example, potassium carbonate in aqueous dimethylformamide, to yield a compound of Formula **1106**, which is isolated. Referring to Scheme 11, Step 5, the ester of the compound of Formula **1106** is saponified with, for example, sodium hydroxide in water, to produce the compound of Formula **1107**, which is isolated. Referring to Scheme 11, Step 6, the free acid of the compound of Formula **1107** is converted to the acid chloride by treating it with, for example, thionyl chloride, to produce a compound of Formula **1108**, which can be isolated. Referring to Scheme 11, Step 7, the acid chloride of the compound of Formula **1108** is reacted with an optionally substituted amino- aryl or amino-heteroaryl compound of Formula **1109**, to obtain a compound of Formula **1110**, which is isolated. Referring to Scheme 11, Step 8, the primary amine of the compound of Formula 1110 is reacted with a haloacyl chloride, for example, chloroacetyl chloride in

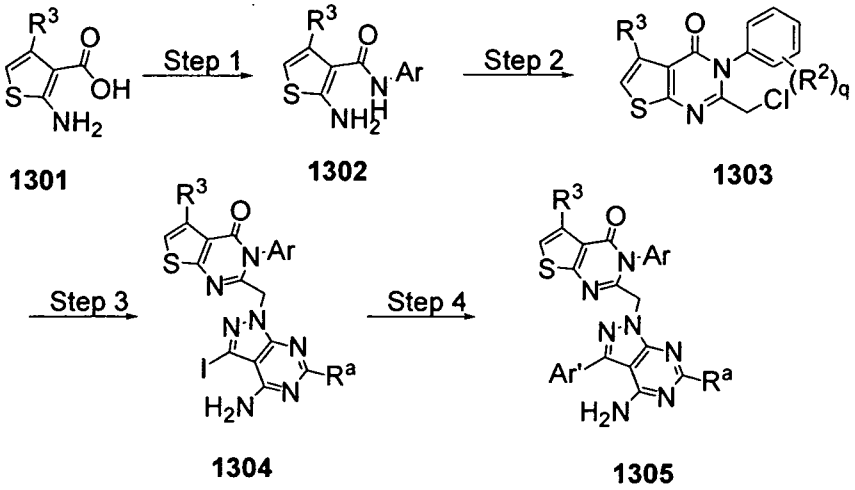
pyridine and methylene chloride to produce a compound of Formula **1111**, which is isolated. Referring to Scheme 11, Step 9, the compound of Formula **1111** is cyclized by, for example, heating in a sealed tube in the presence of phosphoryl chloride, to yield a compound of Formula **1112**, which is isolated. Referring to Scheme 11, Step 10, the thiazolopyrimidone compound of Formula **1112** is reacted with an pyazolopyrimidine of Formula **1113** in the presence of a base, for example potassium t-butoxide in dimethylformamide to produce a compound of Formula **1114**, which is isolated.

Reaction Scheme 12:



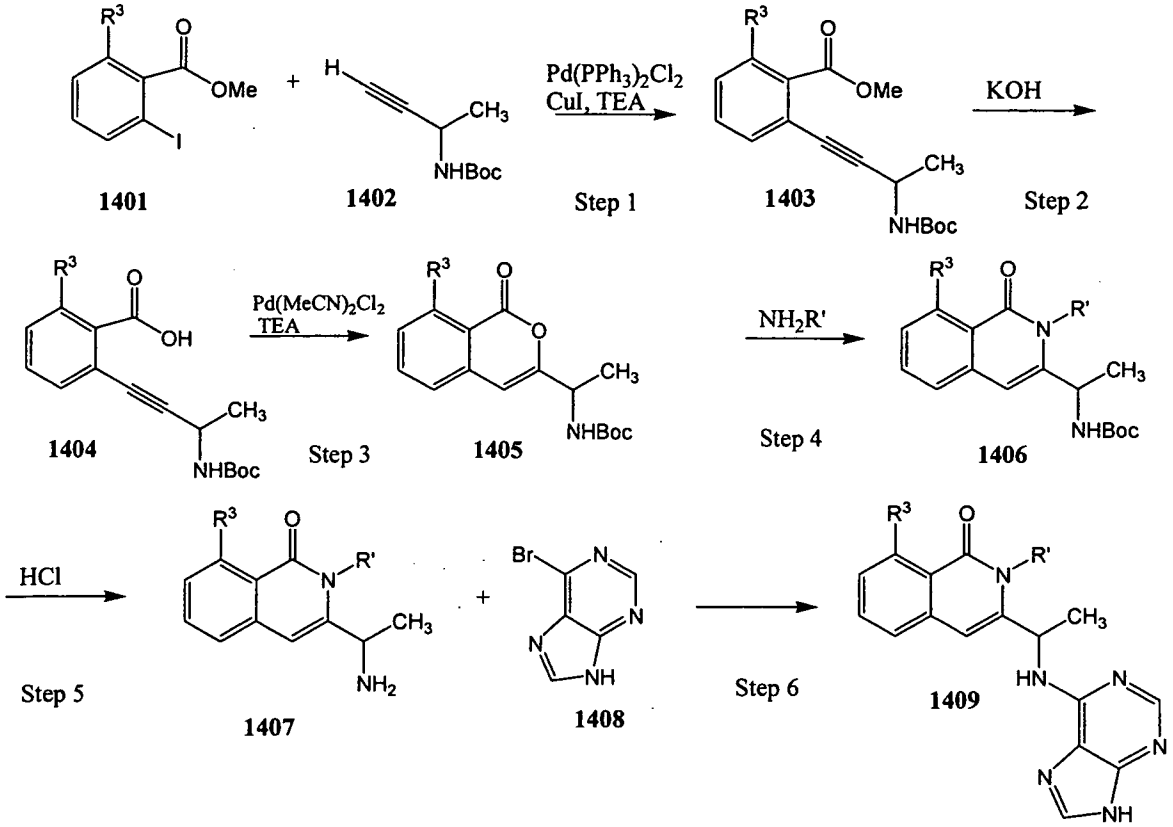
[00279] Referring to Scheme 12, Step 1, a compound of Formula **709** is alkylated with an optionally substituted purine of Formula **1210**. The product, a compound of Formula **1211**, is isolated.

Reaction Scheme 13:



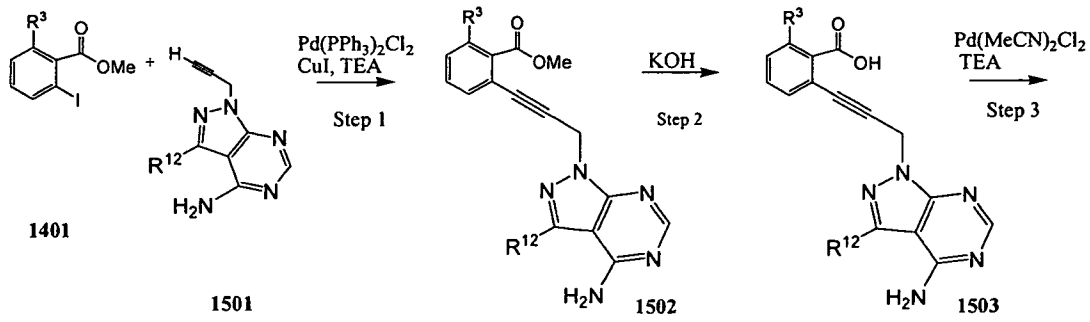
[00280] Referring to Scheme 13, Step 1, a compound of Formula **1301** is first converted to an acid chloride using thionyl chloride, then reacted with an appropriately substituted aniline. The product, a compound of Formula **1302**, is isolated. Referring to Scheme 13, Step 2, a compound of Formula **1302** is cyclized to the corresponding thieno-pyrimidinone, for example, with chloroacetyl chloride in acetic acid. The product, a compound of Formula **1303**, is isolated. Referring to Scheme 13, Step 3, a compound of Formula **1303** is, for example, alkylated using an appropriately substituted pyrazolo-pyrimidine. The product, a compound of Formula **1304**, is isolated. Referring to Scheme 13, Step 4, a compound of Formula **1304** is, for example, arylated using an appropriately substituted boronic acid. The product, a compound of Formula **1305**, is isolated.

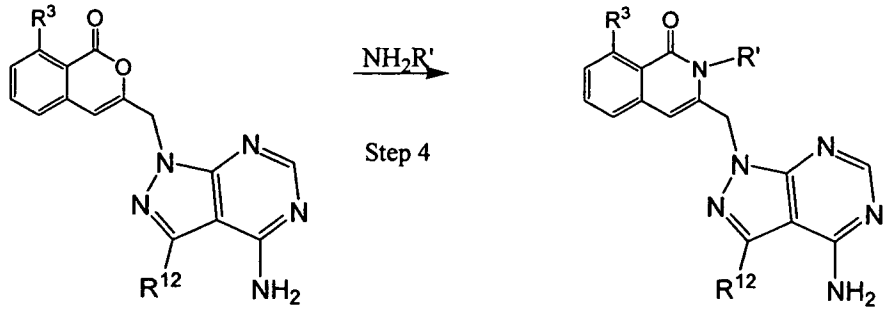
Reaction Scheme 14:



[00281] Referring to Reaction Scheme 14, Step 1, iodo ester **1401,** is reacted with an alkyne **1402** in the presence of a palladium catalyst, copper iodide and triethylamine (TEA) to couple the alkyne to the aryl core of **1401** to produce a compound of Formula **1403.** The compound of Formula **1403** is isolated. Referring to Reaction Scheme 14, Step 2, a compound of Formula **1403** is treated with potassium hydroxide base to obtain the carboxylic acid, a compound of Formula **1404,** if the reaction product is acidified, or its salt. The compound of Formula **1404** is isolated. Referring to Reaction Scheme 14, Step 3, a compound of Formula **1404** is treated with bis (acetonitrile)dichloropalladium (II) and TEA to effect intramolecular ring closure to produce a compound of Formula **1405.** The compound of Formula **1405** is isolated. Referring to Reaction Scheme 14, Step 4, a compound of Formula **1405** is reacted with a primary amine to produce a compound of Formula **1406.** The compound of Formula **1406** is isolated. Referring to Reaction Scheme 14, Step 5, a compound of Formula **1406** is treated with hydrochloric acid, removing the protecting group on nitrogen, and to obtain a compound of Formula **1407.** The compound of Formula **1407** can be isolated. Referring to Reaction Scheme 14, Step 6, a compound of Formula **1407** is reacted with a compound of Formula **1408,** to produce a compound of Formula **1409.** The compound of Formula **1409** is isolated.

Reaction Scheme 15:

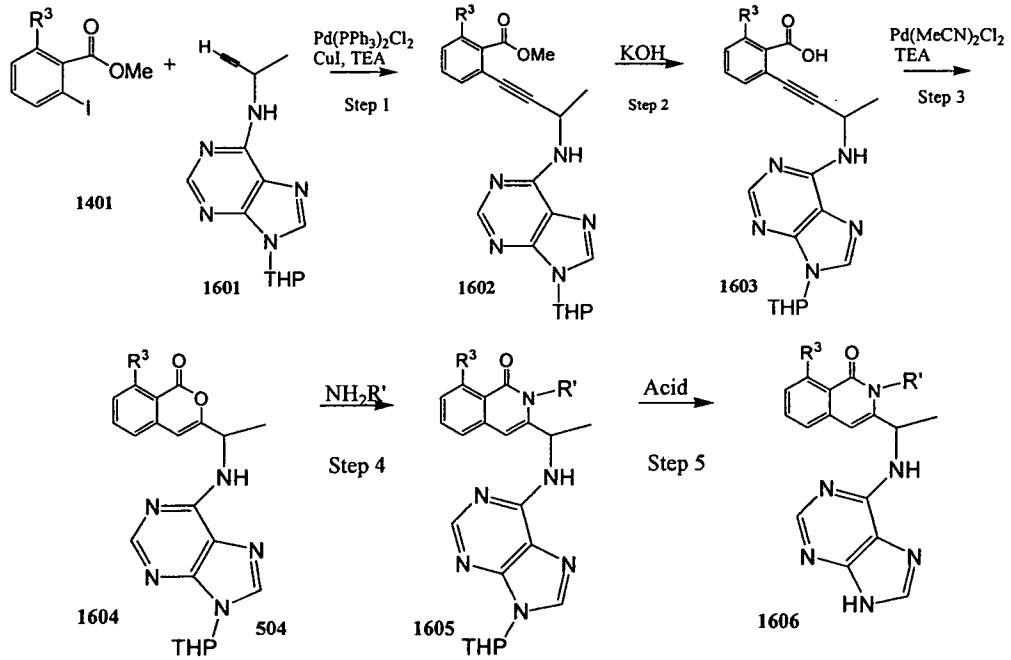




1504 1505

[00282] Referring to Reaction Scheme 15, Step 1, iodo ester **1401** is reacted with alkyne **1501** in the presence of palladium coupling catalyst, copper iodide, and TEA, to obtain a compound of Formula **1502**. The compound of Formula **1502** is isolated. Referring to Reaction Scheme 15, Step 2, the compound of Formula **1502** is treated with potassium hydroxide base to obtain the carboxylate or free acid of a compound of Formula **1503**. Referring to Reaction Scheme 15, Step 3, the compound of Formula **1503** is treated with bis (acetonitrile)dichloropalladium (II) and TEA to effect intramolecular ring closure to produce a compound of Formula **1504**. The compound of Formula **1504** is isolated. Referring to Reaction Scheme 15, Step 4, the compound of Formula **1504** is treated with a primary amine to produce a compound of Formula **1505**. The compound of Formula **1505** is isolated.

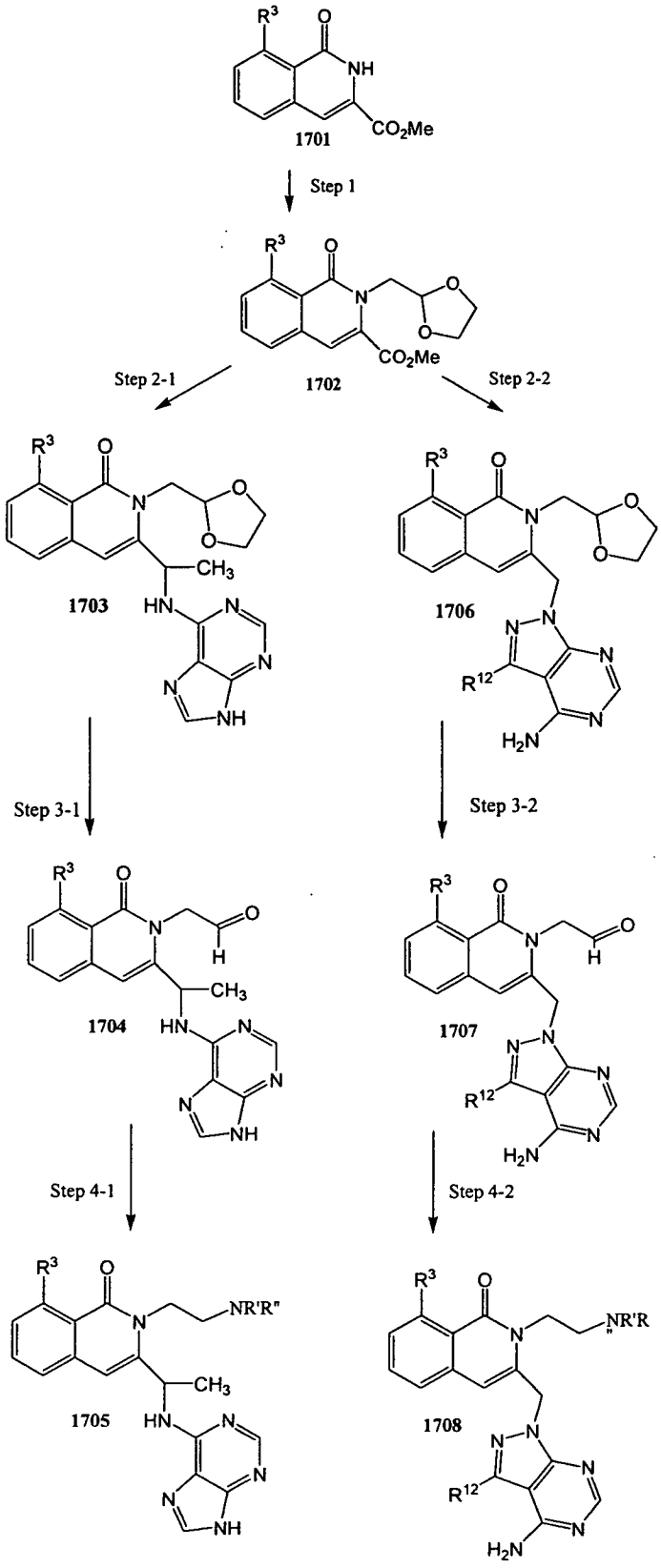
Reaction Scheme 16:



[00283] Referring to Reaction Scheme 16, Step 1, iodo ester **1401** is reacted with alkyne **1601** in the presence of palladium coupling catalyst, copper iodide, and TEA, to obtain a compound of Formula **1602**. The compound of Formula **1602** is isolated. Referring to Reaction Scheme 16, Step 2, the compound of Formula **1602** is treated with potassium hydroxide base to obtain the carboxylate or free acid of a compound of Formula **1603**. Referring to Reaction Scheme 16, Step 3, the compound of Formula **1603** is treated with bis (acetonitrile)dichoropalladium (II) and TEA to effect intramolecular ring closure to produce a compound of Formula **1604**. The compound of Formula **1604** is isolated. Referring to Reaction Scheme 16, Step 4, the compound of Formula **1604** is treated with a primary amine to produce a compound of Formula **1605**. The compound of Formula **1605** is isolated. Referring to Reaction Scheme

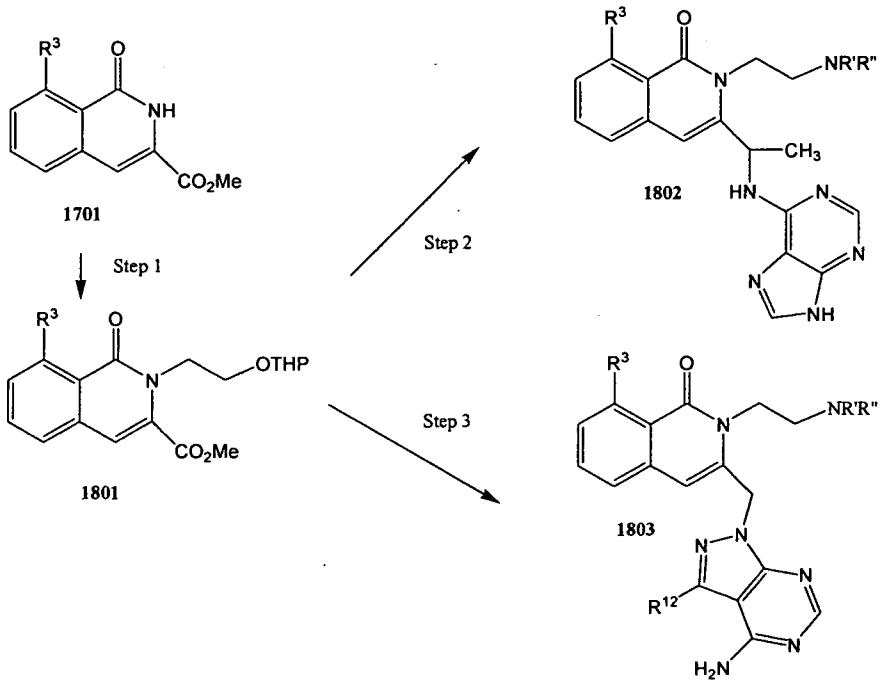
16, Step 5, the compound of Formula **1605** is treated with acid to remove the THP protecting group to obtain a compound of Formula **1606.** The compound of Formula **1606** is isolated.

Reaction Scheme 17:



[00284] Referring to Reaction Scheme 17, Step 1 the compound of Formula **1701** is synthesized by a variety of synthetic routes, including variations of Schemes 1 or 2 where, for example, a benzyl amine is used in the step of converting a compound of Formula **403** to a compound of Formula **404**. The benzyl protecting group of the amine may be removed by standard deprotection chemistry to produce a compound of **1701**. The compound of Formula **1701** is converted to a compound of Formula **1702** by alkylation of the amide nitrogen with a number of 2-carbon containing synthons which can be deprotected, oxidized and reprotected as the respective ketal, the compound of Formula **1702**, which can be isolated. Referring to Reaction Scheme 17, Step 2-1, the compound of Formula **1702** is transformed by, for example, reductive amination of the ester moiety to introduce the purinyl moiety of a compound of Formula **1703**, or alternatively, is alkylated to so introduce a purinyl moiety and obtain a compound of Formula **1703**. Referring to Reaction Scheme 17, Step 3-1, the compound of Formula **1703** is treated with acid to remove the ketal protecting group to produce a compound of Formula **1704**. The compound of Formula **1704** is isolated. Referring to Reaction Scheme 17, Step 4-1, the compound of Formula **1704** is reductively aminated with an amine to produce a compound of Formula **1705**. The compound of Formula **1705** is isolated. Referring to Reaction Scheme 17, Step 2-2, the compound of Formula **1702** is transformed by, steps 7 and 8 of Scheme 5 and step 1 of Scheme 6 to introduce the pyrazolopyrimidine moiety of a compound of Formula **1706**. The compound of Formula **1706** is isolated. Referring to Reaction Scheme 17, Step 3-2, the compound of Formula **1706** is treated with acid to remove the ketal protecting group to produce a compound of Formula **1707**. The compound of Formula **1707** can be isolated. Referring to Reaction Scheme 17, Step 4-2, the compound of Formula **1707** is reductively aminated with an amine to produce a compound of Formula **1708**. The compound of Formula **1708** is isolated.

Reaction Scheme 18:

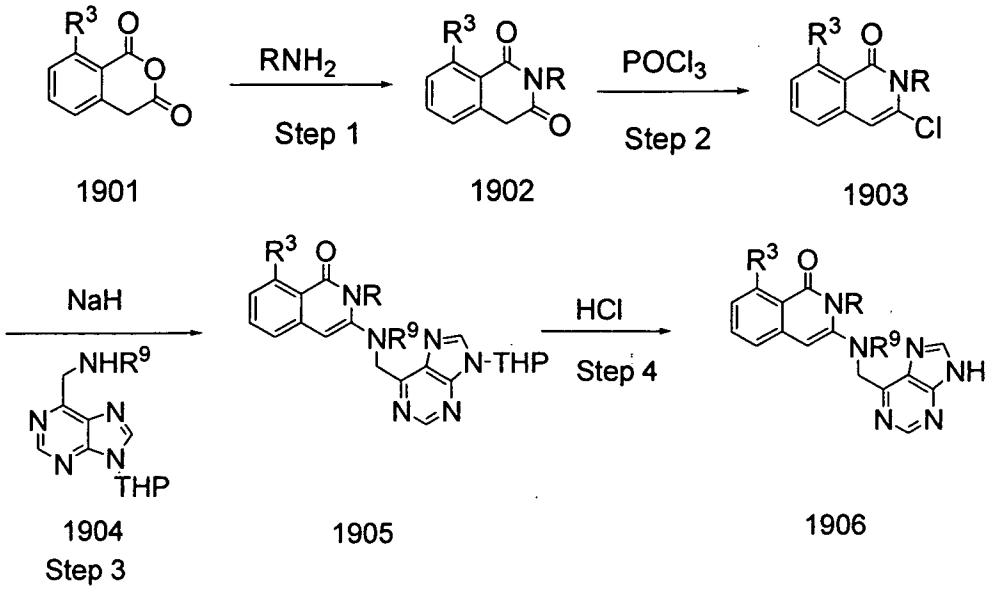


[00285] Referring to Reaction Scheme 18, Step 1, the compound of Formula **1701** is synthesized as described in Scheme 17 or any other generally known chemistry. The compound of Formula **1701** is transformed by alkylation of the amide nitrogen with a number of 2-carbon containing synthons which can be deprotected, and converted to the alkoxy protected species as shown in the compound of Formula **1801**, which can be isolated. Referring to Reaction Scheme 18, Step 2, the compound of Formula **1801** is converted via chemistry described in Step 2-1 of Scheme 17 to

introduce a purinyl moiety, and that resultant compound is transformed by deprotection, activation and amination with an amine to produce a compound of Formula **1802**, which is isolated.

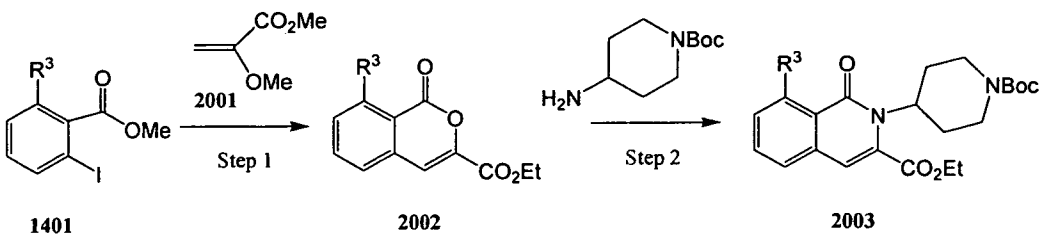
[00286] Referring to Reaction Scheme 18, Step 3, the compound of Formula **1801** is converted via chemistry described in Step 2-2 of Scheme 17 to introduce a pyrazolopyrimidine moiety, and that resultant compound is transformed by deprotection, activation and amination with an amine to produce a compound of Formula **1803**, which is isolated.

Reaction Scheme 19:



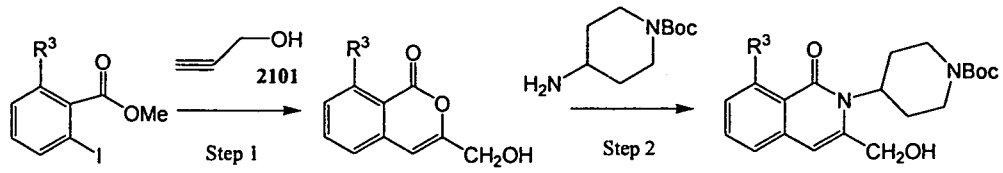
[00287] Referring to Reaction Scheme 19, Step 1, the compound of Formula **1901** is treated with an amine to produce a compound of Formula **1902**. The compound of Formula **1902** is isolated. Referring to Reaction Scheme 19, Step 2, the compound of Formula **1902** is treated with phosphorus oxychloride to generate a compound of Formula **1903**. The compound of Formula **1903** is isolated. Referring to Reaction Scheme 19, Step 3, the compound of Formula **1903** is reacted with an amino purine of Formula **1904** to obtain a compound of Formula **1905**. The compound of Formula **1905** is isolated. Referring to Reaction Scheme 19, Step 4, the compound of Formula **1905** is treated with hydrochloric acid to remove the protecting group at nitrogen on the purine moiety to produce a compound of Formula **1906**. The compound of **1906** is isolated.

Reaction Scheme 20:



[00288] Referring to Reaction Scheme 20, Step 1, the compound of Formula **1401** is treated with vinylogous ester **2001** using, for example a Heck reaction with subsequent cyclization, to produce a compound of Formula **2002**. The compound of Formula **2002** is isolated. Referring to Reaction Scheme 20, Step 2, the compound of Formula **2002** is reacted with 4- amino N-Boc piperidine to produce a compound of Formula **2002**. The compound of Formula **2003** is isolated. The compound of Formula **2003** can be used as an intermediate in the synthesis of the compounds of the invention.

Reaction Scheme 21:



1401 **2102** **2103**

[00289] Referring to Reaction Scheme 21, Step 1, the compound of Formula **1401** is treated with an alkynyl alcohol, for example, of Formula **2101**, the presence of copper iodide and palladium on carbon catalyst, to produce a compound of Formula **2102**. The compound of Formula **2102** is optionally isolated and optionally purified. Referring to Reaction Scheme 21, Step 1, the compound of Formula **2102** is reacted with 4- amino N-Boc piperidine to produce a compound of Formula **2103**. The compound of Formula **2103** is isolated. The compound of Formula **2103** can be used as an intermediate in the synthesis of the compounds of the invention.

[00290] Any of the compounds of Formula I, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, or XIV can be synthesized using the reaction schemes as disclosed herein or variants of these processes as well known in the art.

[00291] The chemical entities can be synthesized by an appropriate combination of generally well known synthetic methods.

[00292] In some embodiments, one or more subject compounds bind specifically to a PI3 kinase or a protein kinase selected from the group consisting of mTor, DNA-dependent protein kinase DNA-dependent protein kinase (Pubmed protein accession number (PPAN) AAA79184), Abl tyrosine kinase (CAA52387), Bcr-Abl, hemopoietic cell kinase (PPAN CAI19695), Src (PPAN CAA24495), vascular endothelial growth factor receptor 2 (PPAN ABB82619), vascular endothelial growth factor receptor-2 (PPAN ABB82619), epidermal growth factor receptor (PPAN AG43241), EPH receptor B4 (PPAN EAL23820), stem cell factor receptor (PPAN AAF22141), Tyrosine-protein kinase receptor TIE-2 (PPAN Q02858), fms-related tyrosine kinase 3 (PPAN NP_004110), platelet-derived growth factor receptor alpha (PPAN NP_990080), RET (PPAN CAA73131), and any other protein kinases listed in the appended tables and figures, as well as any functional mutants thereof. In some embodiments, the IC50 of a subject compound for p110α, p110β, p110γ, or p110δ is less than about 1 uM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM or even less than about 0.5nM. In some embodiments, the IC50 of a subject compound for mTor is less than about 1 uM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM or even less than about 0.5nM. In some other embodiments, one or more subject compounds exhibit dual binding specificity and are capable of inhibiting a PI3 kinase (e.g., a class I PI3 kinase) as well as a protein kinase (e.g., mTor) with an IC50 value less than about 1 uM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM or even less than about 0.5 nM. One or more subject compounds are capable of inhibiting tyrosine kinases including, for example, DNA-dependent protein kinase DNA-dependent protein kinase (Pubmed protein accession number (PPAN) AAA79184), Abl tyrosine kinase (CAA52387), Bcr-Abl, hemopoietic cell kinase (PPAN CAI19695), Src (PPAN CAA24495), vascular endothelial growth factor receptor 2 (PPAN ABB82619), vascular endothelial growth factor receptor-2 (PPAN ABB82619), epidermal growth factor receptor (PPAN AG43241), EPH receptor B4 (PPAN EAL23820), stem cell factor receptor (PPAN AAF22141), Tyrosine-protein kinase receptor TIE-2 (PPAN Q02858), fms-related tyrosine kinase 3 (PPAN NP_004110), platelet-derived growth factor receptor alpha (PPAN NP_990080), RET (PPAN CAA73131), and functional mutants thereof. In some embodiments, the tyrosine kinase is Abl, Bcr-Abl, EGFR, or Flt-3, and any other kinases listed in the Tables herein.

[00293] In some embodiments, the compounds of the present invention exhibits one or more functional characteristics disclosed herein. For example, one or more subject compounds bind specifically to a PI3 kinase. In some embodiments, the IC50 of a subject compound for p110α, p110β, p110γ, or p110δ is less than about 1 uM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than about 1 nM, less than about 0.5nM, less than about 100pM, or less than about 50 pM.

[00294] In some embodiments, one or more of the subject compound may selectively inhibit one or more members of type I or class I phosphatidylinositol 3-kinases (PI3-kinase) with an IC50 value of about 100 nM, 50 nM, 10 nM, 5 nM, 100 pM, 10 pM or 1 pM, or less as measured in an in vitro kinase assay.

[00295] In some embodiments, one or more of the subject compound may selectively inhibit one or two members of type I or class I phosphatidylinositol 3-kinases (PI3-kinase) consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ. In some aspects, some of the subject compounds selectively inhibit PI3-kinase δ as compared to all other type I PI3-kinases. In other aspects, some of the subject compounds selectively inhibit PI3-kinase δ and PI3-kinase γ as compared to the rest of the type I PI3-kinases. In yet other aspects, some of the subject compounds selectively inhibit PI3-kinase α and PI3-kinase β as compared to the rest of the type I PI3-kinases. In still yet some other aspects, some of the subject compounds selectively inhibit PI3-kinase δ and PI3-kinase α as compared to the rest of the type I PI3-kinases. In still yet some other aspects, some of the subject compounds selectively inhibit PI3-kinase δ and PI3-kinase β as compared to the rest of the type I PI3-kinases, or selectively inhibit PI3-kinase δ and PI3-kinase α as compared to the rest of the type I PI3-kinases, or selectively inhibit PI3-kinase α and PI3-kinase γ as compared to the rest of the type I PI3-kinases, or selectively inhibit PI3-kinase γ and PI3-kinase β as compared to the rest of the type I PI3-kinases.

[00296] In yet another aspect, an inhibitor that selectively inhibits one or more members of type I PI3-kinases, or an inhibitor that selectively inhibits one or more type I PI3-kinase mediated signaling pathways, alternatively can be understood to refer to a compound that exhibits a 50% inhibitory concentration (IC50) with respect to a given type I PI3-kinase, that is at least at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold, at least 1000-fold, at least 10,100-fold, or lower, than the inhibitor's IC50 with respect to the rest of the other type I PI3-kinases.

Pharmaceutical Compositions

[00297] The invention provides pharmaceutical compositions comprising one or more compounds of the present invention.

[00298] In some embodiments, the invention provides pharmaceutical compositions for treating diseases or conditions related to an undesirable, over-active, harmful or deleterious immune response in a mammal. Such undesirable immune response can be associated with or result in, e.g., asthma, emphysema, bronchitis, psoriasis, allergy, anaphylaxsis, auto-immune diseases, rhuematoid arthritis, graft versus host disease, and lupus erythematosus. The pharmaceutical compositions of the present invention can be used to treat other respiratory diseases including but not limited to diseases affecting the lobes of lung, pleural cavity, bronchial tubes, trachea, upper respiratory tract, or the nerves and muscle for breathing.

[00299] In some embodiments, the invention provides pharmaceutical compositions for the treatment of disorders such as hyperproliferative disorder including but not limited to cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal; kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS related AIDS-Related (e.g. Lymphoma and Kaposi's Sarcoma) or Viral-Induced cancer. In some embodiments, said pharmaceutical composition is for the treatment of a non-cancerous

hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

[00300] The invention also provides compositions for the treatment of liver diseases (including diabetes), pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes- induced renal disease) or pain in a mammal.

[00301] The invention further provides a composition for the prevention of blastocyte implantation in a mammal.

[00302] The invention also relates to a composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which can manifest as tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00303] The subject pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a compound of the present invention as the active ingredient, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Where desired, the pharmaceutical compositions contain pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[00304] The subject pharmaceutical compositions can be administered alone or in combination with one or more other agents, which are also typically administered in the form of pharmaceutical compositions. Where desired, the subject compounds and other agent(s) may be mixed into a preparation or both components may be formulated into separate preparations to use them in combination separately or at the same time.

[00305] In some embodiments, the concentration of one or more of the compounds provided in the pharmaceutical compositions of the present invention is less than 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%,14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v or v/v.

[00306] In some embodiments, the concentration of one or more of the compounds of the present invention is greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v, or v/v.

[00307] In some embodiments, the concentration of one or more of the compounds of the present invention is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%,

approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v. v/v.

[00308] In some embodiments, the concentration of one or more of the compounds of the present invention is in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[00309] In some embodiments, the amount of one or more of the compounds of the present invention is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

[00310] In some embodiments, the amount of one or more of the compounds of the present invention is more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5g, 7 g, 7.5g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

[00311] In some embodiments, the amount of one or more of the compounds of the present invention is in the range of 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

[00312] The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. An exemplary dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[00313] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

[00314] Pharmaceutical compositions for oral administration In some embodiments, the invention provides a pharmaceutical composition for oral administration containing a compound of the present invention, and a pharmaceutical excipient suitable for oral administration.

[00315] In some embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of a compound of the present invention; optionally (ii) an effective amount of a second agent; and (iii) a pharmaceutical excipient suitable for oral administration. In some embodiments, the composition further contains: (iv) an effective amount of a third agent.

[00316] In some embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a

predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00317] This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water may be added (e.g., 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[00318] An active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[00319] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00320] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00321] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which may disintegrate in the

bottle. Too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

[00322] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[00323] When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00324] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00325] Surfactant which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[00326] A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance (" HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (i.e., hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00327] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00328] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00329] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00330] Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00331] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose

monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00332] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00333] In one embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for compositions for non-oral use, e.g., compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[00334] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG ; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, .epsilon.-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00335] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00336] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%,

2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00337] The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00338] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00339] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like.

[00340] Pharmaceutical compositions for injection. In some embodiments, the invention provides a pharmaceutical composition for injection containing a compound of the present invention and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

[00341] The forms in which the novel compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00342] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[00343] Sterile injectable solutions are prepared by incorporating the compound of the present invention in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed

by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00344] Pharmaceutical compositions for topical (e.g., transdermal) delivery. In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing a compound of the present invention and a pharmaceutical excipient suitable for transdermal delivery.

[00345] Compositions of the present invention can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation may provide more immediate exposure of the active ingredient to the chosen area.

[00346] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (e.g., urea), glycols (e.g., propylene glycol), alcohols (e.g., ethanol), fatty acids (e.g., oleic acid), surfactants (e.g., isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (e.g., menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00347] Another exemplary formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of a compound of the present invention in controlled amounts, either with or without another agent.

[00348] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[00349] Pharmaceutical compositions for inhalation. Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[00350] Other pharmaceutical compositions. Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, e.g., See, *e.g.*, Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., *Principles of Drug Action*, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., *Basic and Clinical*

Pharmacology, Ninth Edition, McGraw Hill, 20037ybg; Goodman and Gilman, eds., *The Pharmacological Basis of Therapeutics*, Tenth Edition, McGraw Hill, 2001; *Remingtons Pharmaceutical Sciences*, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, *The Extra Pharmacopoeia*, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference herein in their entirety.

[00351] Administration of the compounds or pharmaceutical composition of the present invention can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (e.g. transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. Compounds can also abe administered intraadiposally or intrathecally.

[00352] The amount of the compound administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, preferably about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, e.g. bydividing such larger doses into several small doses for administration throughout the day.

[00353] In some embodiments, a compound of the invention is administered in a single dose. Typically, such administration will be by injection, e.g., intravenous injection, in order to introduce the agent quickly. However, other routes may be used as appropriate. A single dose of a compound of the invention may also be used for treatment of an acute condition.

[00354] In some embodiments, a compound of the invention is administered in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In another embodiment a compound of the invention and another agent are administered together about once per day to about 6 times per day. In another embodiment the administration of a compound of the invention and an agent continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[00355] Administration of the agents of the invention may continue as long as necessary. In some embodiments, an agent of the invention is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, an agent of the invention is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, an agent of the invention is administered chronically on an ongoing basis, e.g., for the treatment of chronic effects.

[00356] An effective amount of a compound of the invention may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[00357] The compositions of the invention may also be delivered via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer. Such a method of administration may, for example, aid in the prevention or amelioration of restenosis following procedures such as balloon angioplasty. Without being bound by theory, compounds of the invention may slow or inhibit the migration and proliferation of smooth muscle cells in the arterial wall which contribute to restenosis. A compound of the invention may be administered, for example, by local

delivery from the struts of a stent, from a stent graft, from grafts, or from the cover or sheath of a stent. In some embodiments, a compound of the invention is admixed with a matrix. Such a matrix may be a polymeric matrix, and may serve to bond the compound to the stent. Polymeric matrices suitable for such use, include, for eample, lactone-based polyesters or copolyesters such as polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides, polyaminoacids, polysaccharides, polyphosphazenes, poly (ether-ester) copolymers (e.g. PEO-PLLA); polydimethylsiloxane, poly(ethylene-vinylacetate), acrylate-based polymers or copolymers (e.g. polyhydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone), fluorinated polymers such as polytetrafluoroethylene and cellulose esters. Suitable matrices may be nondegrading or may degrade with time, releasing the compound or compounds. Compounds of the invention may be applied to the surface of the stent by various methods such as dip/spin coating, spray coating, dip-coating, and/or brush-coating. The compounds may be applied in a solvent and the solvent may be allowed to evaporate, thus forming a layer of compound onto the stent. Alternatively, the compound may be located in the body of the stent or graft, for example in microchannels or micropores. When implanted, the compound diffuses out of the body of the stent to contact the arterial wall. Such stents may be prepared by dipping a stent manufactured to contain such micropores or microchannels into a solution of the compound of the invention in a suitable solvent, followed by evaporation of the solvent. Excess drug on the surface of the stent may be removed via an additional brief solvent wash. In yet other embodiments, compounds of the invention may be covalently linked to a stent or graft. A covalent linker may be used which degrades *in vivo*, leading to the release of the compound of the invention. Any bio-labile linkage may be used for such a purpose, such as ester, amide or anhydride linkages. Compounds of the invention may additionally be administered intravascularly from a balloon used during angioplasty. Extravascular administration of the compounds via the pericard or via advential application of formulations of the invention may also be performed to decrease restenosis.

[00358] A variety of stent devices which may be used as described are disclosed, for example, in the following references, all of which are hereby incorporated by reference: U.S. Pat. No. 5451233; U.S. Pat. No. 5040548; U.S. Pat. No. 5061273; U.S. Pat. No. 5496346; U.S. Pat. No. 5292331; U.S. Pat. No. 5674278; U.S. Pat. No. 3657744; U.S. Pat. No. 4739762; U.S. Pat. No. 5195984; U.S. Pat. No. 5292331; U.S. Pat. No. 5674278; U.S. Pat. No. 5879382; U.S. Pat. No. 6344053.

[00359] The compounds of the invention may be administered in dosages. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. Dosing for a compound of the invention may be found by routine experimentation in light of the instant disclosure.

[00360] When a compound of the invention, is administered in a composition that comprises one or more agents, and the agent has a shorter half-life than the compound of the invention unit dose forms of the agent and the compound of the invention may be adjusted accordingly.

[00361] The subject pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

[00362] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[00363] The activity of the compounds of the present invention may be determined by the following procedure, as well as the procedure described in the examples below. The activity of the kinase is assessed by measuring the incorporation of γ-^{33}P-phosphate from γ -^{33}P-ATP onto N-terminal His tagged substrate, which is expressed in *E. coli* and is purified by conventional methods, in the presence of the kinase. The assay is carried out in 96-well polypropylene plate. The incubation mixture (100, µL) comprises of 25 mM Hepes, pH 7.4, 10 mM $MgCl_2$, 5 mM β-glycerolphosphate, 100 µM Na-orthovanadate, 5 mM DTT, 5 nM kinase, and 1 µM substrate. Inhibitors are suspended in DMSO, and all reactions, including controls are performed at a final concentration of 1% DMSO. Reactions are initiated by the addition of 10 µM ATP (with 0.5 µCi γ-^{33}P- ATP/well) and incubated at ambient temperature for 45 minutes. Equal volume of 25% TCA is added to stop the reaction and precipitate the proteins. Precipitated proteins are trapped onto glass fiber B filterplates, and excess labeled ATP washed off using a Tomtec MACH III harvestor. Plates are allowed to air-dry prior to adding 30 µL/well of Packard Microscint 20, and plates are counted using a Packard TopCount.

[00364] The invention also provides kits. The kits include a compound or compounds of the present invention as described herein, in suitable packaging, and written material that can include instructions for use, discussion of clinical studies, listing of side effects, and the like. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. The kit may further contain another agent. In some embodiments, the compound of the present invention and the agent are provided as separate compositions in separate containers within the kit. In some embodiments, the compound of the present invention and the agent are provided as a single composition within a container in the kit. Suitable packaging and additional articles for use (e.g., measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in some embodiments, be marketed directly to the consumer.

METHODS

[00365] The invention also provides methods of using the compounds or pharmaceutical compositions of the present invention to treat disease conditions, including but not limited to diseases associated with malfunctioning of one or more types of PI3 kinase. A detailed description of conditions and disorders mediated by p110δ kinase activity is set forth in Sadu et al., WO 01/81346, which is incorporated herein by reference in its entirety for all purposes.

[00366] The treatment methods provided herein comprise administering to the subject a therapeutically effective amount of a compound of the invention. In one embodiment, the present invention provides a method of treating an inflammation disorder, including autoimmune diseases in a mammal. The method comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Examples of autoimmune diseases includes but is not limited to acute disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, coeliac disease, Crohn's disease, Diabetes mellitus (type 1),

Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, lupus erythematosus, multiple sclerosis, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, oemphigus, polyarthritis, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis (also known as "giant cell arteritis"), warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis, Chagas' disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, and vulvodynia. Other disorders include bone-resorption disorders and thromobsis.

[00367] In some embodiments, the method of treating inflammatory or autoimmune diseases comprises administering to a subject (e.g. a mammal) a therapeutically effective amount of one or more compounds of the present invention that selectively inhibit PI3K-δ and/or PI3K-γ as compared to all other type I PI3 kinases. Such selective inhibition of PI3K-δ and/or PI3K-γ may be advantageous for treating any of the diseases or conditions described herein. For example, selective inhibition of PI3K-δ may inhibit inflammatory responses associated with inflammatory diseases, autoimmune disease, or diseases related to an undesirable immune response including but not limited to asthma, emphysema, allergy, dermatitis, rhuematoid arthritis, psoriasis, lupus erythematosus, or graft versus host disease. Selective inhibition of PI3K-δ may further provide for a reduction in the inflammatory or undesirable immune response without a concomittant reduction in the ability to reduce a bacterial, viral, and/or fungal infection. Selective inhibition of both PI3K-δ and PI3K-γ may be advantageous for inhibiting the inflammatory response in the subject to a greater degree than that would be provided for by inhibitors that selectively inhibit PI3K -δ or PI3K-γ alone. In one aspect, one or more of the subject methods are effective in reducing antigen specific antibody production *in vivo* by about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more. In another aspect, one or more of the subject methods are effective in reducing antigen specific IgG3 and/or IgGM production *in vivo* by about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more.

[00368] In one aspect, one of more of the subject methods are effective in ameliorating symptoms assoicated with rhuematoid arthritis including but not limited to a reduction in the swelling of joints, a reduction in serum anti-collagen levels, and/or a reduction in joint pathology such as bone resorption, cartilage damage, pannus, and/or inflammation. In another aspect, the subject methods are effective in reducing ankle inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, 60%, or about 75% to 90%. In another aspect, the subject methods are effective in reducing knee inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, 60%, or about 75% to 90% or more. In still another aspect, the subject methods are effective in reducing serum anti-type II collagen levels by at least about 10%, 12%, 15%, 20%, 24%, 25%, 30%, 35%, 50%, 60%, 75%, 80%, 86%, 87%, or about 90% or more. In another aspect, the subject methods are effective in reducing ankle histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 90% or more. In still another aspect, the subject methods are effective in reducing knee histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 90% or more.

[00369] In other embodiments, the present invention provides methods of using the compounds or pharmaceutical compositions to treat respiratory diseases including but not limited to diseases affecting the lobes of lung, pleural cavity, bronchial tubes, trachea, upper respiratory tract, or the nerves and muscle for breathing. For example, methods are provided to treat obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) is an umbrella term for a group of respiratory tract diseases that are characterized by airflow obstruction or limitation. Conditions included in this umbrella term are: chronic bronchitis, emphysema, and bronchiectasis.

[00370] In another embodiment, the compounds described herein are used for the treatment of asthma. Also, the compounds or pharmaceutical compositions described herein may be used for the treatment of endotoxemia and sepsis. In one embodiment, the compounds or pharmaceutical compositions described herein are used to for the treatment of rheumatoid arthritis (RA). In yet another embodiment, the compounds or pharmaceutical compositions described herein is used for the treatment of contact or atopic dermatitis. Contact dermatitis includes irritant dermatitis, phototoxic dermatitis, allergic dermatitis, photoallergic dermatitis, contact urticaria, systemic contact-type dermatitis and the like. Irritant dermatitis can occur when too much of a substance is used on the skin of when the skin is sensitive to certain substance. Atopic dermatitis, sometimes called eczema, is a kind of dermatitis, an atopic skin disease.

[00371] The invention also relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. In some embodiments, said method relates to the treatment of cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (e.g. Lymphoma and Kaposi's Sarcoma) or viral-induced cancer. In some embodiments, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

[00372] The invention also relates to a method of treating diseases related to vasculogenesis or angiogenesis in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. In some embodiments, said method is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00373] Patients that can be treated with compounds of the present invention, or pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative of said compounds, according to the methods of this invention include, for example, patients that have been diagnosed as having psoriasis; restenosis; atherosclerosis; BPH; breast cancer such as a ductal carcinoma in duct tissue in a mammary gland, medullary carcinomas, colloid carcinomas, tubular carcinomas, and inflammatory breast cancer; ovarian cancer, including epithelial ovarian tumors such as adenocarcinoma in the ovary and an adenocarcinoma that has migrated from the ovary into the abdominal cavity; uterine cancer; cervical cancer such as adenocarcinoma in the cervix epithelial including squamous cell carcinoma and adenocarcinomas; prostate cancer, such as a prostate cancer selected from the following: an adenocarcinoma or an adenocarinoma that has migrated to the bone; pancreatic cancer such as epitheliod carcinoma in the pancreatic duct tissue and an adenocarcinoma in a pancreatic duct; bladder cancer such as a transitional cell carcinoma in urinary bladder, urothelial carcinomas (transitional cell carcinomas), tumors in the urothelial cells that line the bladder, squamous cell carcinomas, adenocarcinomas, and small cell cancers; leukemia such as acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, myeloproliferative disorders, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), mastocytosis, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and myelodysplastic syndrome (MDS); bone cancer; lung cancer such as non-small cell lung cancer (NSCLC), which is divided into squamous cell

carcinomas, adenocarcinomas, and large cell undifferentiated carcinomas, and small cell lung cancer; skin cancer such as basal cell carcinoma, melanoma, squamous cell carcinoma and actinic keratosis, which is a skin condition that sometimes develops into squamous cell carcinoma; eye retinoblastoma; cutaneous or intraocular (eye) melanoma; primary liver cancer (cancer that begins in the liver); kidney cancer; thyroid cancer such as papillary, follicular, medullary and anaplastic; AIDS-related lymphoma such as diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma and small non-cleaved cell lymphoma; Kaposi's Sarcoma; viral-induced cancers including hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatocellular carcinoma; human lymphotropic virus-type 1 (HTLV-1) and adult T-cell leukemia/lymphoma; and human papilloma virus (HPV) and cervical cancer; central nervous system cancers (CNS) such as primary brain tumor, which includes gliomas (astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme), Oligodendroglioma, Ependymoma, Meningioma, Lymphoma, Schwannoma, and Medulloblastoma; peripheral nervous system (PNS) cancers such as acoustic neuromas and malignant peripheral nerve sheath tumor (MPNST) including neurofibromas and schwannomas, malignant fibrous cytoma, malignant fibrous histiocytoma, malignant meningioma, malignant mesothelioma, and malignant mixed Müllerian tumor; oral cavity and oropharyngeal cancer such as, hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, and oropharyngeal cancer; stomach cancer such as lymphomas, gastric stromal tumors, and carcinoid tumors; testicular cancer such as germ cell tumors (GCTs), which include seminomas and nonseminomas, and gonadal stromal tumors, which include Leydig cell tumors and Sertoli cell tumors; thymus cancer such as to thymomas, thymic carcinomas, Hodgkin disease, non-Hodgkin lymphomas carcinoids or carcinoid tumors; rectal cancer; and colon cancer.

[00374] The invention also relates to a method of treating diabetes in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof.

[00375] In addition, the compounds described herein may be used to treat acne.

[00376] In addition, the compounds described herein may be used for the treatment of arteriosclerosis, including atherosclerosis. Arteriosclerosis is a general term describing any hardening of medium or large arteries. Atherosclerosis is a hardening of an artery specifically due to an atheromatous plaque.

[00377] Further the compounds described herein may be used for the treatment of glomerulonephritis. Glomerulonephritis is a primary or secondary autoimmune renal disease characterized by inflammation of the glomeruli. It may be asymptomatic, or present with hematuria and/or proteinuria. There are many recognized types, divided in acute, subacute or chronic glomerulonephritis. Causes are infectious (bacterial, viral or parasitic pathogens), autoimmune or paraneoplastic.

[00378] Additionally, the compounds described herein may be used for the treatment of bursitis, lupus, acute disseminated encephalomyelitis (ADEM), addison's disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, coeliac disease, crohn's disease, diabetes mellitus (type 1), goodpasture's syndrome, graves' disease, guillain-barré syndrome (GBS), hashimoto's disease, inflammatory bowel disease, lupus erythematosus, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, ord's thyroiditis,ostheoarthritis, uveoretinitis, pemphigus, polyarthritis, primary biliary cirrhosis, reiter's syndrome, takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, wegener's granulomatosis, alopecia universalis, chagas' disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, vulvodynia, appendicitis, arteritis, arthritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, cholecystitis, chorioamnionitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, hepatitis, hidradenitis, ileitis, iritis,

laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, or vulvitis.

[00379] The invention also relates to a method of treating a cardiovascular disease in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Examples of cardiovascular conditions include, but are not limited to, atherosclerosis, restenosis, vascular occlusion and carotid obstructive disease.

[00380] In another aspect, the present invention provides methods of disrupting the function of a leukocyte or disrupting a function of an osteoclast. The method includes contacting the leukocyte or the osteoclast with a function disrupting amount of a compound of the invention.

[00381] In another aspect of the present invention, methods are provided for treating ophthalmic disease by administering one or more of the subject compounds or pharmaceutical compositions to the eye of a subject.

[00382] Methods are further provided for administering the compounds of the present invention via eye drop, intraocular injection, intravitreal injection, topically, or through the use of a drug eluting device, microcapsule, implant, or microfluidic device. In some cases, the compounds of the present invention are administered with a carrier or excipient that increases the intraocular penetrance of the compound such as an oil and water emulsion with colloid particles having an oily core surrounded by an interfacial film.

[00383] In some cases, the colloid particles include at least one cationic agent and at least one non-ionic sufactant such as a poloxamer, tyloxapol, a polysorbate, a polyoxyethylene castor oil derivative, a sorbitan ester, or a polyoxyl stearate. In some cases, the cationic agent is an alkylamine, a tertiary alkyl amine, a quarternary ammonium compound, a cationic lipid, an amino alcohol, a biguanidine salt, a cationic compound or a mixture thereof. In some cases the cationic agent is a biguanidine salt such as chlorhexidine, polyaminopropyl biguanidine, phenformin, alkylbiguanidine, or a mixture thereof. In some cases, the quaternary ammonium compound is a benzalkonium halide, lauralkonium halide, cetrimide, hexadecyltrimethylammonium halide, tetradecyltrimethylammonium halide, dodecyltrimethylammonium halide, cetrimonium halide, benzethonium halide, behenalkonium halide, cetalkonium halide, cetethyldimonium halide, cetylpyridinium halide, benzododecinium halide, chlorallyl methenamine halide, myristylalkonium halide, stearalkonium halide or a mixture of two or more thereof. In some cases, cationic agent is a benzalkonium chloride, lauralkonium chloride, benzododecinium bromide, benzethenium chloride, hexadecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, dodecyltrimethylammonium bromide or a mixture of two or more thereof. In some cases, the oil phase is mineral oil and light mineral oil, medium chain triglycerides (MCT), coconut oil; hydrogenated oils comprising hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenate castor oil or hydrogenated soybean oil; polyoxyethylene hydrogenated castor oil derivatives comprising poluoxyl-40 hydrogenated castor oil, polyoxyl-60 hydrogenated castor oil or polyoxyl-100 hydrogenated castor oil.

[00384] The invention further provides methods of modulating kinase activity by contacting a kinase with an amount of a compound of the invention sufficient to modulate the activity of the kinase. Modulate can be inhibiting or activating kinase activity. In some embodiments, the invention provides methods of inhibiting kinase activity by contacting a kinase with an amount of a compound of the invention sufficient to inhibit the activity of the kinase. In some embodiments, the invention provides methods of inhibiting kinase activity in a solution by contacting said solution with an amount of a compound of the invention sufficient to inhibit the activity of the kinase in said solution. In some embodiments, the invention provides methods of inhibiting kinase activity in a cell by contacting said cell

with an amount of a compound of the invention sufficient to inhibit the activity of the kinase in said cell. In some embodiments, the invention provides methods of inhibiting kinase activity in a tissue by contacting said tissue with an amount of a compound of the invention sufficient to inhibit the activity of the kinase in said tissue. In some embodiments, the invention provides methods of inhibiting kinase activity in an organism by contacting said organism with an amount of a compound of the invention sufficient to inhibit the activity of the kinase in said organism. In some embodiments, the invention provides methods of inhibiting kinase activity in an animal by contacting said animal with an amount of a compound of the invention sufficient to inhibit the activity of the kinase in said animal. In some embodiments, the invention provides methods of inhibiting kinase activity in a mammal by contacting said mammal with an amount of a compound of the invention sufficient to inhibit the activity of the kinase in said mammal. In some embodiments, the invention provides methods of inhibiting kinase activity in a human by contacting said human with an amount of a compound of the invention sufficient to inhibit the activity of the kinase in said human. In some embodiments, the % of kinase activity after contacting a kinase with a compound of the invention is less than 1, 5, 10, 20, 30, 40, 50, 60, 70, 80 90, 95, or 99% of the kinase activity in the absence of said contacting step.

[00385] In some embodiments, the kinase is a lipid kinase or a protein kinase. In some embodiments, the kinase is selected from the group consisting of PI3 kinase including different isorforms such as PI3 kinase α, PI3 kinase β, PI3 kinase γ, PI3 kinase δ; DNA-PK; mTor; Abl, VEGFR, Ephrin receptor B4 (EphB4); TEK receptor tyrosine kinase (TIE2); FMS-related tyrosine kinase 3 (FLT-3); Platelet derived growth factor receptor (PDGFR); RET; ATM; ATR; hSmg-1; Hck; Src; Epidermal growth factor receptor (EGFR); KIT; Inulsin Receptor (IR) and IGFR.

[00386] The invention further provides methods of modulating PI3 kinase activity by contacting a PI3 kinase with an amount of a compound of the invention sufficient to modulate the activity of the PI3 kinase. Modulate can be inhibiting or activating PI3 kinase activity. In some embodiments, the invention provides methods of inhibiting PI3 kinase activity by contacting a PI3 kinase with an amount of a compound of the invention sufficient to inhibit the activity of the PI3 kinase. In some embodiments, the invention provides methods of inhibiting PI3 kinase activity. Such inhibition can take place in solution, in a cell expressing one or more PI3 kinases, in a tissue comprising a cell expressing one or more PI3 kinases, or in an organism expressing one or more PI3 kinases. In some embodiments, the invention provides methods of inhibiting PI3 kinase activity in an animal (including mammal such as humans) by contacting said animal with an amount of a compound of the invention sufficient to inhibit the activity of the PI3 kinase in said animal.

COMBINATION TREATMENT

[00387] The present invention also provides methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound of the present invention, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. In one aspect, such therapy includes but is not limited to the combination of the subject compound with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect.

[00388] In one aspect, the compounds or pharmaceutical compositions of the present invention may present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Such combination can reduce the undesired effect of high level of IgE associated with the use of one or more PI3Kδ inhibitors, if such effect occurs. This may be particularly useful in treatment of autoimmune and inflammatory disorders (AIID) such as rheumatoid arthritis. Additionally, the administration of PI3Kδ or PI3Kδ/γ inhibitors of the

present invention in combination with inhibitors of mTOR may also exhibit synergy through enhanced inhibition of the PI3K pathway.

[00389] In a separate but related aspect, the present invention provides a combination treatment of a disease associated with PI3Kδ comprising administering to a PI3Kδ inhibitor and an agent that inhibits IgE production or activity. Other exemplary PI3Kδ inhibitors are applicable for this combination and they are described, e.g., US Patent No. 6,800,620. Such combination treatment is particularly useful for treating autoimmune and inflammatory diseases (AIID) including but not limited to rheumatoid arthritis.

[00390] Agents that inhibit IgE production are known in the art and they include but are not limited to one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (i.e. rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as for example Omalizumab and TNX-901.

[00391] For treatment of autoimmune diseases, the subject compounds or pharmaceutical compositions can be used in combination with commonly prescribed drugs including but not limited to Enbrel®, Remicade®, Humira®, Avonex®, and Rebif®. For treatment of respiratory diseaseses, the subject compounds or pharmaceutical compositions can be administered in combination with commonly prescribed drugs including but not limited to Xolair®, Advair®, Singulair®, and Spiriva®.

[00392] The compounds of the invention may be formulated or administered in conjunction with other agents that act to relieve the symptoms of inflammatory conditions such as encephalomyelitis, asthma, and the other diseases described herein. These agents include non-steroidal anti-inflammatory drugs (NSAIDs), e.g. acetylsalicylic acid; ibuprofen; naproxen; indomethacin; nabumetone; tolmetin; etc. Corticosteroids are used to reduce inflammation and suppress activity of the immune system. The most commonly prescribed drug of this type is Prednisone. Chloroquine (Aralen) or hydroxychloroquine (Plaquenil) may also be very useful in some individuals with lupus. They are most often prescribed for skin and joint symptoms of lupus. Azathioprine (Imuran) and cyclophosphamide (Cytoxan) suppress inflammation and tend to suppress the immune system. Other agents, e.g. methotrexate and cyclosporin are used to control the symptoms of lupus. Anticoagulants are employed to prevent blood from clotting rapidly. They range from aspirin at very low dose which prevents platelets from sticking, to heparin/coumadin.

[00393] In another one aspect, this invention also relates to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof, in combination with an amount of an anti-cancer agent (e.g. a chemotherapeutic agent). Many chemotherapeutics are presently known in the art and can be used in combination with the compounds of the invention.

[00394] In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens. Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec (Imatinib Mesylate), Velcade (bortezomib), Casodex (bicalutamide), Iressa (gefitinib), and Adriamycin as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine,

cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, Casodex™, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.R™; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethyla- mine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOL™, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERE™, Rhone-Poulenc Rorer, Antony, France); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen (Nolvadex™), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO). Where desired, the compounds or pharmaceutical composition of the present invention can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, and Velcade®.

[00395] This invention further relates to a method for using the compounds or pharmaceutical composition in combination with radiation therapy in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the invention in this combination therapy can be determined as described herein.

[00396] Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (e.g. At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-

212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner of the present invention include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

[00397] Without being limited by any theory, the compounds of the present invention can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of the present invention or pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof, which amount is effective is sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, or solvate in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

[00398] The compounds or pharmaceutical compositions of the present invention can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

[00399] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound of the present invention and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24,1996), WO 96/27583 (published March 7,1996), European Patent Application No. 97304971.1 (filed July 8,1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26,1998), WO 98/03516 (published January 29,1998), WO 98/34918 (published August 13,1998), WO 98/34915 (published August 13,1998), WO 98/33768 (published August 6,1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13,1994), European Patent Publication 931, 788 (published July 28,1999), WO 90/05719 (published May 31,1990), WO 99/52910 (published October 21,1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17,1999), PCT International Application No. PCT/IB98/01113 (filed July 21,1998), European Patent Application No. 99302232.1 (filed March 25,1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12,1999), United States Patent 5,863, 949 (issued January 26,1999), United States Patent 5,861, 510 (issued January 19,1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (i. e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-ll, MMP-12, andMMP-13). Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, and RS 13-0830.

[00400] The invention also relates to a method of and to a pharmaceutical composition of treating a cardiovascular disease in a mammal which comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof, or an isotopically-labeled derivative thereof, and an amount of one or more therapeutic agents use for the treatment of cardiovascular diseases.

[00401] Examples for use in cardiovascular disease applications are anti-thrombotic agents, e.g., prostacyclin and salicylates, thrombolytic agents, e.g., streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator complex (APSAC), anti-platelets agents, e.g., acetyl-salicylic acid (ASA) and clopidrogel, vasodilating agents, e.g., nitrates, calcium channel blocking drugs, anti-proliferative agents, e.g., colchicine and alkylating agents, intercalating agents, growth modulating factors such as interleukins, transformation growth factor-beta and congeners of platelet derived growth factor, monoclonal antibodies directed against growth factors, anti-inflammatory agents, both steroidal and non-steroidal, and other agents that can modulate vessel tone, function, arteriosclerosis, and the healing response to vessel or organ injury post intervention. Antibiotics can also be included in combinations or coatings comprised by the invention. Moreover, a coating can be used to effect therapeutic delivery focally within the vessel wall. By incorporation of the active agent in a swellable polymer, the active agent will be released upon swelling of the polymer.

[00402] The compounds describe herein may be formulated or administered in conjunction with liquid or solid tissue barriers also known as lubricants. Examples of tissue barriers include, but are not limited to, polysaccharides, polyglycans, seprafilm, interceed and hyaluronic acid.

[00403] Medicaments which may be administered in conjunction with the compounds described herein include any suitable drugs usefully delivered by inhalation for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; anti-infectives, e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimize the activity and/or stability of the medicament.

[00404] Other exemplary therapeutic agents useful for a combination therapy include but are not limited to agents as described above, radiation therapy, hormone antagonists, hormones and their releasing factors, thyroid and antithyroid drugs, estrogens and progestins, androgens, adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones, insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas, agents affecting calcification and bone turnover: calcium, phosphate, parathyroid hormone, vitamin D, calcitonin, vitamins such as water-soluble vitamins, vitamin B complex, ascorbic acid, fat-soluble vitamins, vitamins A, K, and E, growth factors, cytokines, chemokines, muscarinic receptor agonists and antagonists; anticholinesterase agents; agents acting at the neuromuscular junction and/or autonomic ganglia; catecholamines, sympathomimetic drugs, and adrenergic receptor agonists or antagonists; and 5-hydroxytryptamine (5-HT, serotonin) receptor agonists and antagonists.

[00405] Therapeutic agents can also include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids, prostaglandins, thromboxanes, leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-antipyretic

agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β-adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

[00406] Additional therapeutic agents contemplated herein include diuretics, vasopressin, agents affecting the renal conservation of water, rennin, angiotensin, agents useful in the treatment of myocardial ischemia, anti-hypertensive agents, angiotensin converting enzyme inhibitors, β-adrenergic receptor antagonists, agents for the treatment of hypercholesterolemia, and agents for the treatment of dyslipidemia.

[00407] Other therapeutic agents contemplated include drugs used for control of gastric acidity, agents for the treatment of peptic ulcers, agents for the treatment of gastroesophageal reflux disease, prokinetic agents, antiemetics, agents used in irritable bowel syndrome, agents used for diarrhea, agents used for constipation, agents used for inflammatory bowel disease, agents used for biliary disease, agents used for pancreatic disease. Therapeutic agents used to treat protozoan infections, drugs used to treat Malaria, Amebiasis, Giardiasis, Trichomoniasis, Trypanosomiasis, and/or Leishmaniasis, and/or drugs used in the chemotherapy of helminthiasis. Other therapeutic agents include antimicrobial agents, sulfonamides, trimethoprim-sulfamethoxazole quinolones, and agents for urinary tract infections, penicillins, cephalosporins, and other, β-Lactam antibiotics, an agent comprising an aminoglycoside, protein synthesis inhibitors, drugs used in the chemotherapy of tuberculosis, mycobacterium avium complex disease, and leprosy, antifungal agents, antiviral agents including nonretroviral agents and antiretroviral agents.

[00408] Examples of therapeutic antibodies that can be combined with a subject compound include but are not limited to anti-receptor tyrosine kinase antibodies (cetuximab, panitumumab, trastuzumab), anti CD20 antibodies (rituximab, tositumomab), and other antibodies such as alemtuzumab, bevacizumab, and gemtuzumab.

[00409] Moreover, therapeutic agents used for immunomodulation, such as immunomodulators, immunosuppressive agents, tolerogens, and immunostimulants are contemplated by the methods herein. In addition, therapeutic agents acting on the blood and the blood-forming organs, hematopoietic agents, growth factors, minerals, and vitamins, anticoagulant, thrombolytic, and antiplatelet drugs.

[00410] Further therapeutic agents that can be combined with a subject compound may be found in Goodman and Gilman's "The Pharmacological Basis of Therapeutics" Tenth Edition edited by Hardman, Limbird and Gilman or the Physician's Desk Reference, both of which are incorporated herein by reference in their entirety.

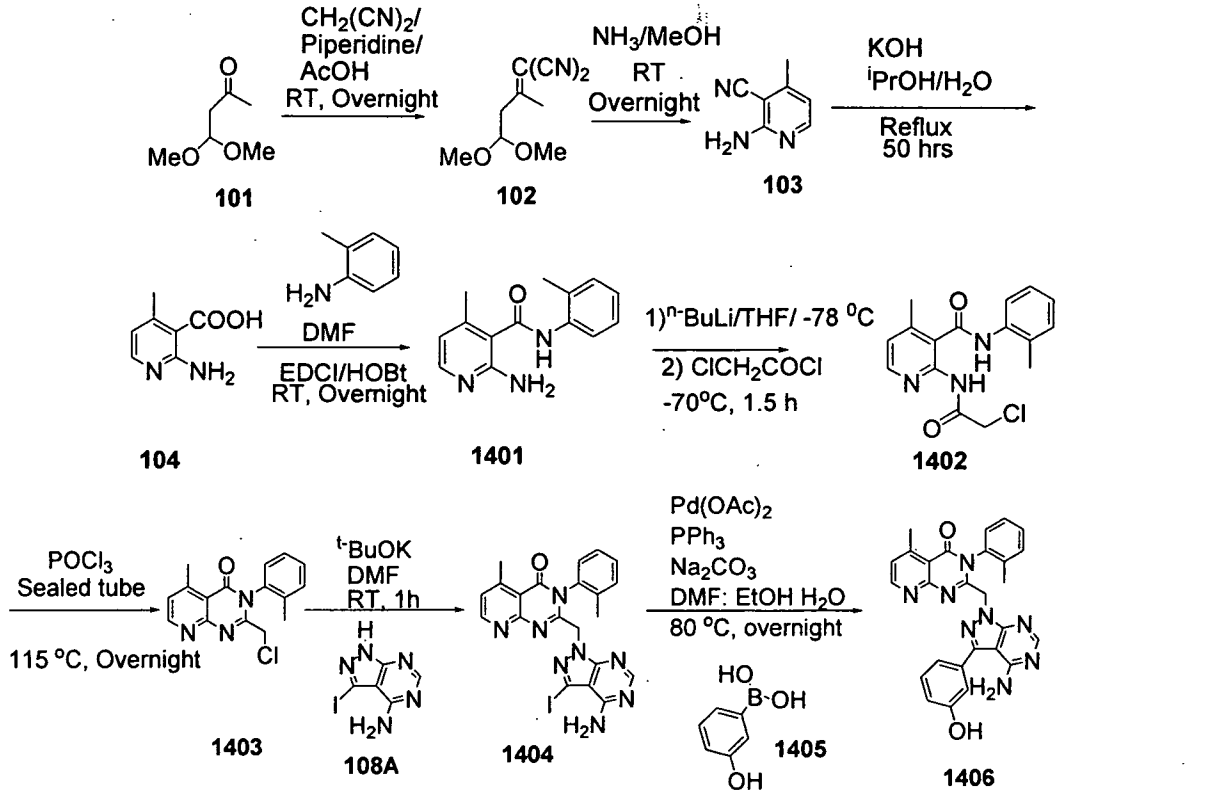
[00411] The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the compounds of the invention will be co-administer with other agents as described above. When used in combination therapy, the compounds described herein may be administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the present invention and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present invention can be administered just followed by and any of the agents described above, or vice versa. In the separate administration protocol, a compound of the present invention and any of the agents described above may be administered a few minutes apart, or a few hours apart, or a few days apart.

[00412] The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

EXAMPLES

[00413] **Example 1:** Synthesis of 2-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylpyrido[2,3-d]pyrimidin-4(3H)-one (Compound 1406).

[00414] **Scheme 14.** Synthesis of 2-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylpyrido[2,3-d]pyrimidin-4(3H)-one (Compound 1406) is described.



[00415] To a stirred solution of 4,4-dimethoxy-2-butanone (**101**)(61 g, 85%, 0.393 mol), acetic acid (2.2 mL, 0.038 mmol) and piperidine (3.8 mL, 0.038 mol) in toluene (150 mL), malononitrile (25 g, 0.394 mmol) was added in portions over 20 min. The reaction mixture was stirred overnight at room temperature. The resulting dark red solution was washed with H_2O (50 mL), dried over $MgSO_4$ and concentrated in vacuo to afford the desired product 2-(4,4-dimethoxybutan-2-ylidene) malononitrile (**102**) (70 g, 99%), which was used directly in the next step.

[00416] Ammonia gas was bubbled through a solution of **102** (32 g, 0.178 mmol) in MeOH (500 mL) for 3 h, the resulting deep-red solution was stirred overnight at room temperature. The mixture was concentrated and the residue was partitioned between HCl solution (2 N, 600 mL) and EtOAc (600 mL). The aqueous layer was separated and basified with ice-cold concentrated $NaHCO_3$ (600 mL) solution. The solid was precipitated out of the solution and collected by filtration to afford the desired product 2-amino-4-methylnicotinonitrile (**103**) (3.0 g, 33%).

[00417] Compound **103** (5.32 g, 40 mmol) was suspended in a solution of potassium hydroxide (26.88 g, 480 mmol) in water (26.85 mL) and iso-propanol (9.6 mL). The reaction mixture was heated to reflux for 50 h, then cooled to

room temperature and diluted with ice-water (100 mL) and neutralized with concentrated HCl solution until PH = 6 – 7. The mixture was concentrated in vacuo and the resulting residue was purified by flash chromatography eluting with ethanol to afford the desired product 2-amino-4-methylnicotinic acid (**104**) (3.284 g, 54.7%).

[00418] To a stirred solution of **104** (3.2 g, 21.2 mmol) in DMF (40 mL) and DCM (80 mL) was added EDCI (8.12 g, 42.4 mmol), HOBt (2.86 g, 21.4 mmol) and o-Toluidine (4.53 mL, 42.4 mmol). The reaction mixture was stirred overnight at room temperature and then poured into water (120 mL). The aqueous phase was extracted with DCM (60 mL × 2). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The solid was precipitated out of the solution. The solid was collected by filtration and dried to afford the desired product 2-amino-4-methyl-N-o-tolylnicotinamide (**1401**) (3. 6 g, 70.4%).

[00419] A suspension of **1401** (1.2 g, 4.96 mmol) in dry THF (60 mL) was added butyllithium (2.5M, 2.38 mL, 5.96 mmol) dropwise under Argon at -40 °C and stirred at this temperature for 1 h. Then the reaction mixture was cooled to -78 °C and chloroacetyl chloride (0.432 mL, 5.4 mmol) was added. After stirring for 2 h at -78 °C, the reaction mixture was poured into ice-water (100 mL). After most of THF was removed in vacuo, the solid was precipitated out of the solution. The solid was collected by filtration and washed with ether to afford the desired product 2-(2-chloroacetamido)-4-methyl-N-o-tolylnicotinamide (**1402**) (890 mg, 56.4%).

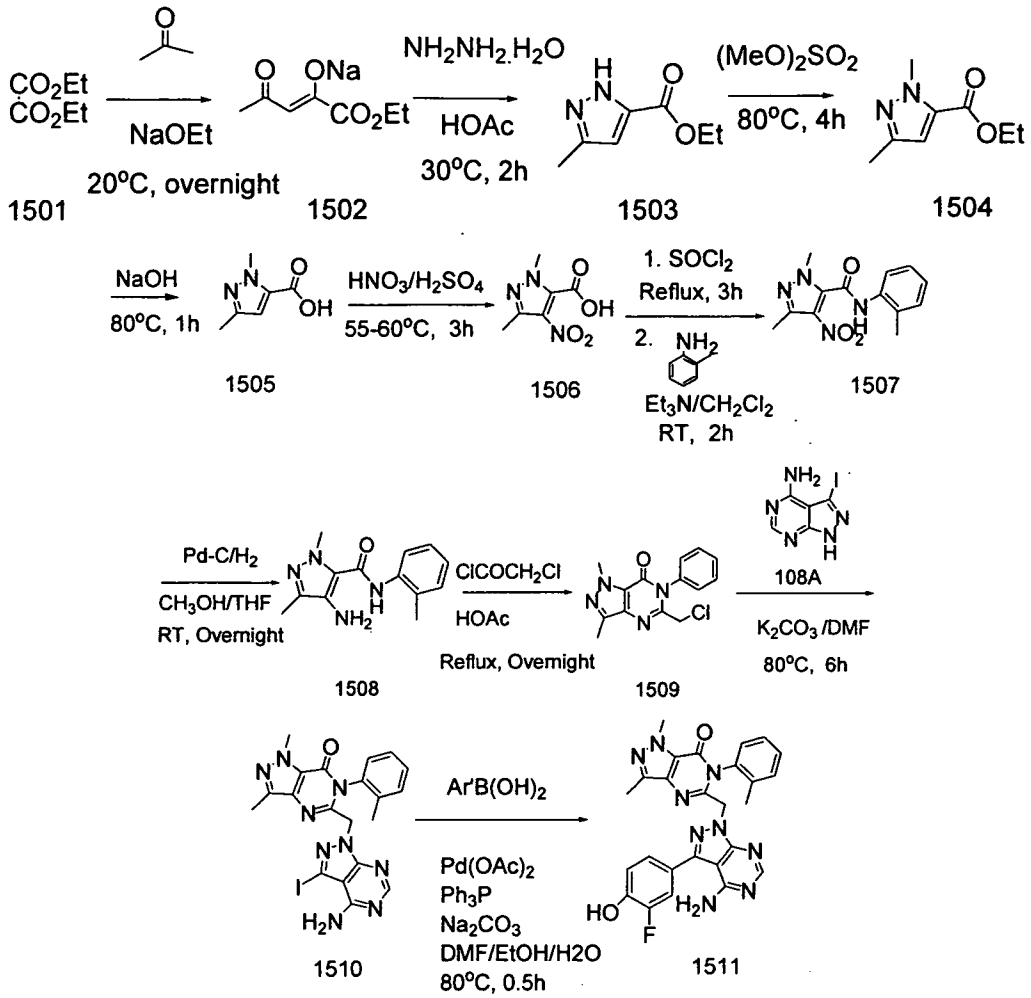
[00420] A mixture of **1402** (320 mg, 1 mmol) and phosphorus oxychloride (20 mL, 214mmol) was heated at 115 °C overnight in a sealed- tube. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was poured into ice-water and neutralized with saturated $NaHCO_3$ solution until PH 8 - 9, the resulting precipitate solid was collected by filtration and washed with ether to afford the desired product 2-(chloromethyl)-5-methyl-3-o-tolylpyrido[2,3-d]pyrimidin-4(3H)-one (**1403**) (200 mg, 66.8%).

[00421] To a solution of 3-iodo-4-amine-1H-pyrazolo[3,4-d]pyrimidin (**108A**)(261 mg, 1.2 mmol) in dry DMF (9 mL) under nitrogen, potassium tert-butoxide(123 mg,1.1 mmol) was added at 0 °C . The resulting mixture was stirred at this temperature for 45 min.. A solution of **1403** (300 mg, 1 mmol) in dry DMF (5 mL) was added. The reaction mixture was stirred for 1h at 0 °C and then an additional 1h at room temperature. The mixture was concentrated in vacuo and the resulting residue was purified by flash chromatography to afford the desired product 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylpyrido[2,3-d]pyrimidin-4(3H)-one (**1404**) (450 mg, 83.3%).

[00422] To a solution of **1404** (36 mg, 0.069 mmol) and 3-hydroxyphenylboronic acid (**1405**)(12 mg, 0.083 mmol) in DMF (2 mL), EtOH (1 mL) and water (1 mL) was added $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) and Na_2CO_3 solution (1M, 0.5 mL, 0.5 mmol) under Argon. The resulting mixture was degassed and back-filled with argon three times and then heated overnight at 80°C. The reaction mixture was allowed to cool to room temperature, concentrated. The residue was diluted with water (20 mL), neutralized with HCl solution (1M) until pH 6 -7 and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography to afford the desired product 2-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylpyrido[2,3-d]pyrimidin-4(3H)-one (**1406**) (8 mg, 23.7%).

[00423] **Example 2:** Synthesis of 5-((4-amino-3-(3-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1,3-dimethyl-6-o-tolyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one (Compound 1511).

[00424] **Scheme 15.** Synthesis of 5-((4-amino-3-(3-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-1,3-dimethyl-6-o-tolyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one (Compound **1512**) is described.



[00425] Sodium (5.2 g, 0.226 mol) was dissolved in anhydrous ethanol (120 mL). A mixture of diethyl oxalate (**1501**)(31.8 mL, 0.235 mol) and acetone (16.0 mL, 0.218 mol) was added to the above solution keeping the temperature under 10 °C. The reaction mixture was stirred overnight at RT. The resulting precipitate was collected by filtration, washed with petroether and dried to afford the desired product **1502** as a yellow solid. (30.4 g, 77.5%).

[00426] Hydrazine hydrate (9.7 mL, 85%, 0.200 mol) was added dropwise to acetic acid (34 mL). To this solution, compound **1502** (30.4g, 0.169mol) was added in portions at 25°C. The resulting mixture was stirred for 2 h at room temperature, then basified with saturated $NaHCO_3$ solution until pH 8 and extracted with DCM (200 mL × 3). The combined organic phases were washed with brine, dried and concentrated to afford the desired product, compound **1503**, as a yellow solid (22 g, 84.6%).

[00427] Dimethyl sulfate (3.2 mL, 33.8 mmol) was added dropwise to a solution of compound **1503** (4.2 g, 29.9 mmol) in toluene (20 mL). The reaction mixture was stirred for 4 h at 80 °C, then allowed to cool to room temperature and concentrated. A 40% NaOH solution (15 mL) was added to the residue. The resulting mixture was stirred for 1h at 80 °C, then cooled to room temperature and diluted with H_2O (30 mL), acidified with concentrated HCl solution until pH 3 – 4. The precipitated solid was collected by filtration, washed with cold water and dried to afford the desired product, compound **1505**, as an off-white solid. (3.54 g, 84.4%).

[00428] To a stirred mixture of concentrated H_2SO_4 (3.6 mL) and fuming HNO_3 (3.1 mL, 73.9 mmol), the acid **1505** (2.813 g, 20 mmol) was added at 70 - 80 °C. The reaction mixture was stirred for 6 h at 70 °C, and cooled to room temperature and then poured into ice-water. The precipitated solid was collected by filtration, washed with water and dried to afford the desired product, compound **1506**, as a yellow solid (0.795 g, 21.5%).

[00429] A mixture of compound **1506** (1.508 g, 8.15 mmol) and $SOCl_2$ (6 mL) was refluxed for 3 h, then concentrated to remove $SOCl_2$. The residue was dissolved in CH_2Cl_2 (8 mL). To this solution, Et_3N (1.13 mL) and o-toluidine (1.12 g, 12.23 mmol) was added at 0 °C. The resulting mixture was stirred for 2 h at 10 °C, concentrated and diluted with water. The solid was collected by filtration, washed with water and petroether, dried to afford the desired product, compound **1507**, as a yellow solid (1.74 g, 77.6%).

[00430] To a stirred mixture of compound **1507** (1.73 g, 6.31 mmol) in MeOH (100 mL) and THF (10 mL), 5% Pd/C (0.2 g) was added. The mixture was degassed and back-filled with hydrogen three times. The reaction mixture was stirred overnight at room temperature and then filtrated. The filtrate was concentrated in vacuo. The solid was dried to afford the desired product, compound **1508,** as a pale solid (1.47 g, 95.4%).

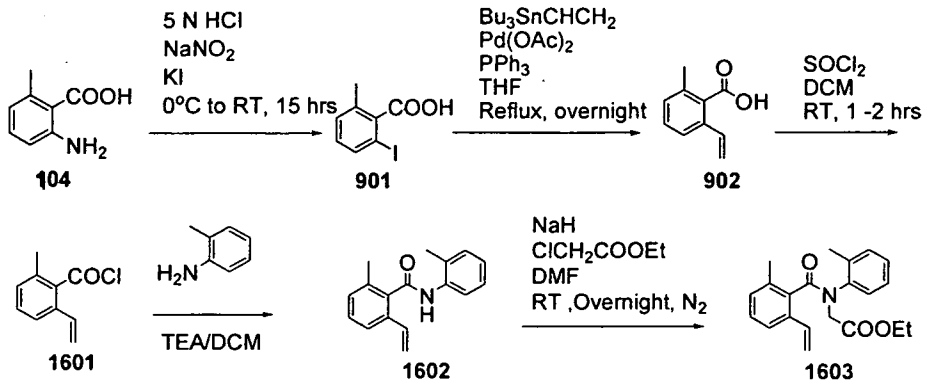
[00431] Chloroacetyl chloride (1.44 mL, 1.99 mmol) was added to a solution of compound **1508** (1.46 g, 5.98 mmol) in acetic acid (20 mL) and the reaction mixture was heated to reflux for 4 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was diluted in DCM (100 mL), washed with saturated $NaHCO_3$ solution and brine, dried and concentrated. The residue was purified by flash chromatography eluting with petroether in ethyl acetate (10 / 1) to afford the desired product, compound **1509**, as a off-white solid (0.48 g, 26.7%).

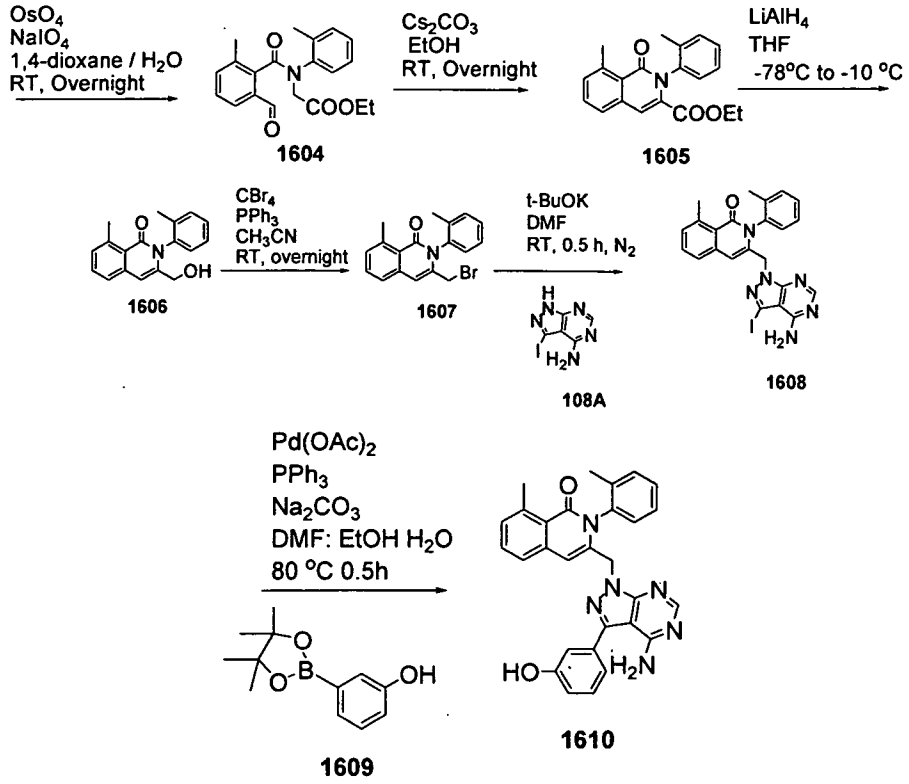
[00432] A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(108A)** (311 mg, 1.19 mmol) and K_2CO_3 (330 mg, 2.39 mmol) in DMF (10 mL) was stirred at room temperature for 15 min., a solution of compound **(1509)** (180 mg, 1.15 mmol, 1 eq.) in DMF (5 mL) was added dropwise at room temperature. The resulting mixture was stirred 2 h at 80°C. The reaction mixture was concentrated in vacuo to remove the organic solvent. The resulting residue was purified by a silica gel column chromatography to afford the desired product, compound **1509,** (142 mg, 44.9% yield) as a pale yellow solid.

[00433] Compound **1510** (40 mg, 0.076 mmol), Na_2CO_3 (40 mg, 0.38 mmol), $Pd(PPh_3)_4$ (17.6 mg, 0.015 mmol), and 3-fluoro-4-hydroxyphenylboronic acid (15.8 mg, 0.101 mmol) were dissolved in a solution of DMF, ethanol and water (4 mL / 2 mL / 2mL). The resulting mixture was degassed and back-filled with argon three times and then heated to 80 °C for 4 h with stirring. The reaction mixture was cooled to room temperature, neutralized with 1N HCl solution until pH 7, concentrated in vacuo and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography eluting with DCM / MeOH = 50 / 1 to afford the desired product **1511**(32 mg, 82%).

[00434] **Example 3**: Synthesis of 3-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound 1610) (method A).

Scheme 16. : Synthesis of 3-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound 1610) via method A is described.





[00435] A solution of 2-amino-6-methylbenzoic acid (**104**) (106.5 g, 705 mmol) in H_2O (200 mL) was cooled to 0 - 5 °C, con. HCl (250 mL) was added slowly. The solution was stirred for 15 min at 0-5 °C. A solution of sodium nitrite (58.4 g, 6.85 mol) in H_2O (120 mL) was added dropwise at 0-5 °C, and the resulting mixture was stirred for 30 min. Then above solution was added to a solution of KI (351 g, 2.11 mol) in H_2O (200 mL), and the resulting mixture was stirred at RT for 16 h. The solution was poured into ice water (2000 mL) and extracted with ethyl acetate (3 × 1000 mL). The combined organic layer was washed with aqueous NaOH (15%, 3 x 200 mL). The aqueous layer was acidified to PH = 1, and extracted with ethyl acetate (3 x 1000 mL). The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the desired product, 2-iodo-6-methylbenzoic acid (**901**) (145 g, 79% yield) as a yellow solid

[00436] To a stirred mixture of 2-iodo-6-methylbenzoic acid (**901**) (105 g, 400 mmol), $Pd(OAc)_2$ (27 g, 120 mmol) and PPh_3 (63 g 240 mol) in THF (1000 mL) at RT, tributyl(vinyl)tin (152 g, 480 mmol) was added. The resulting mixture was heated to reflux overnight. The mixture was allowed to cool to RT, filtered through silica gel (10 g), and then concentrated in vacuo. The residue was poured into ice water (1000 mL) and extracted with ethyl acetate (3 × 1000 mL). The combined organic layer was washed with aqueous NaOH (15%, 5 × 200 mL). The combined aqueous layer was acidified to PH = 1, extracted with ethyl acetate (3 × 1000 mL). The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the desired product, 2-methyl-6-vinylbenzoic acid (**902**) (61 g, 95% yield) as a yellow solid.

[00437] A mixture of 2-methyl-6-vinylbenzoic acid (**902**) (56 g, 350 mmol) and thionyl chloride (208 g, 1750 mmol) in toluene (400 mL) was stirred at reflux for 2 h. The mixture was concentrated *in vacuo* to afford the desired product, 2-methyl-6-vinylbenzoyl chloride (**1601**) (63 g, 95% yield) as a yellow oil. The product obtained was used directly in the next step without purification.

[00438] A mixture of o-toluidine (45 g, 420 mmol) and Triethylamine (71 g, 70 mmol) in CH_2Cl_2 (300 mL) was stirred for 10 min at RT. To this mixture, 2-methyl-6-vinylbenzoyl chloride (**1601**) (63 g, 35 mmol) was added, and the resulting mixture was stirred at RT for 30min. The solution was poured into water (300 mL) and extracted with CH_2Cl_2 (3 x 200 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the crude product. The crude product was suspended in IPE (isopropyl ether) (300 mL), stirred at reflux for 30min, and then cooled to 0 - 5°C. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, 2-methyl-N-o-tolyl-6-vinylbenzamide (**1602**) (81 g, 80% yield) as a yellow solid.

[00439] To a solution of 2-methyl-N-o-tolyl-6-vinylbenzamide (**1602**) (80 g, 320 mmol) in DMF (250 mL) at RT, NaH (60% in mineral oil, 25.6 g, 640 mmol) was slowly added and the resulting mixture was stirred at RT for 30 min. To this mixture, ethyl chloroacetate (78 g, 640 mmol) was added and the resulting mixture was stirred at RT for 2 h. The solution was poured into water (500 mL) and extracted with ethyl acetate (3 x 200 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude product was suspended in MeOH (160 mL), stirred at reflux for 10 min, and then cooled to 0 – 5°C. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, ethyl 2-(2-methyl-N-o-tolyl-6-vinylbenzamido) acetate (**1603**) (67 g, 62% yield) as a white solid.

[00440] To a stirred mixture of ethyl 2-(2-methyl-N-o-tolyl-6-vinylbenzamido) acetate (**1603**) (67 g, 200 mmol) in 1, 4-dioxane (300 mL) and H_2O (100 mL) at RT, Osmium tetroxide (20mg) was added was and stirred at RT for 30 min. To this mixture, sodium periodate (86 g, 400 mmol) was added and the resulting mixture was stirred at RT for 16h. The reaction mixture was filtered through silica gel (10 g), the filtrate was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was further dried *in vacuo* to afford the desired product, ethyl 2-(2-formyl-6-methyl-N-o-tolylbenzamido) acetate (**1604**) (38 g, 57% yield) as a yellow solid.

[00441] To a stirred solution of ethyl 2-(2-formyl-6-methyl-N-o-tolylbenzamido) acetate (**1604**) (38 g, 112 mmol) in EtOH (200 mL) and ethyl acetate (100 mL) at RT, cesium carbonate (22 g, 112 mmol) was added. The resulting mixture was degassed and back-filled with argon three times and then stirred at 50 °C for 5 h. The mixture was allowed to cool to RT, filtered through silica gel (10 g), and the filtrate was concentrated in vacuo. The residue was poured into H_2O (200 mL), extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude product was suspended in IPE (120 mL), heated to reflux for 10min, and then cooled to 0 - 5°C. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, ethyl 8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinoline-3- carboxylate (**1605**) (28 g, 77% yield) as a white solid.

[00442] To a stirred solution of lithium aluminum hydride (8.28 g, 218 mol) in anhydrous THF (500 mL) at -78° C under a nitrogen atmosphere, ethyl 8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinoline-3-carboxylate (**1605**) (28 g, 87 mmol) was slowly added over a 10 min period of time. The resulting mixture was allowed to warm to -30° C, stirred for 30min and TLC showed the completion of the reaction. Then the mixture was cooled to -78° C, and water (50 mL) was slowly added. The mixture was allowed to warm to RT, filtered through silica gel (10 g), and the filtrate was concentrated in vacuo. The crude product was poured into H_2O (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude product was suspended in ethyl acetate (30 mL) and stirred for 10min. The solid was collected by filtration and further dried *in vacuo* to afford the desired product, 3-(hydroxymethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1606**) (22 g, 92% yield) as a white solid.

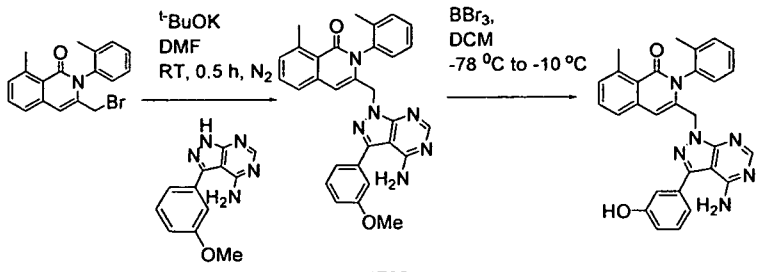
[00443] PBr_3 (25.6 g, 95 mmol) was slowly added to a stirred solution of DMF (11.5 g, 158 mol) in acetonitrile (200 mL) at 0° C, and the resulting mixture was stirred at 0C for 30 min. 3-(Hydroxymethyl)-8-methyl-2-o-tolylisoquinolin -1-(2H)-one (**1606**) (22 g, 78.8 mmol) was slowly added. Then the reaction mixture was allowed to warm to RT and stirred for 30 min. Saturated aqueous $NaHCO_3$ solution (50 mL) was slowly added and extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude product was suspended in IPE (50 mL) and then stirred for 10min. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, 3-(bromomethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1607**) (21 g, 80% yield) as a white solid.

[00444] 3-Iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**108A**) (10.8 g, 41.4 mmol) and potassium tert -butoxide (4.4 g, 40 mmol) were dissolved in anhydrous DMF (150 mL) and stirred at RT for 30 min. 3-(Bromomethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1607**) (13.7 g, 40 mmol) was added. The resulting mixture was stirred at RT for 30min, poured into ice water (300 mL) and then extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated to about 100 ml in vacuo, the precipitate was collected by filtration to afford the first batch of desired product, 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1608**) (12 g, 60% yield) as a white solid. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (2-20% MeOH/DCM) to afford the second batch of desired product, 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1608**) (6 g, 30% yield) as a white solid.

[00445] 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o- tolylisoquinolin-1(2H)-one (**1608**) (13 g, 24.9 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**1609**)(6.6 g, 30 mmol) were dissolved in DMF-EtOH-H_2O (120 mL, 40 mL, 40 mL). $Pd(OAc)_2$ (1.684 g, 7.5 mmol), PPh_3 (3.935 g 15 mmol) and Na_2CO_3 (13.25 g 125 mmol) were added sequentially. The resulting mixture was degassed and back-filled with argon three times and then stirred at 100 °C for 1h. The mixture was allowed to cool to RT, filtered through silica gel (10 g) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (2-20% MeOH/DCM) to afford the product (**1610**) (9 g, 76% yield) as a slight yellow solid. Then above product was suspended in EtOH (100 mL) and heated to reflux for 30 min. The mixture was allowed to cool to RT, and the solid was collected by filtration. The solid was then suspended in EA (100 mL) and stirred overnight. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product , 3-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1610**)(8.4 g, 69% yield) as a white solid.

[00446] **Example 4:** Synthesis of 3-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound 1610) (method B).

[00447] **Scheme 17.** Synthesis of 3-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound **1610**) via method B is described.



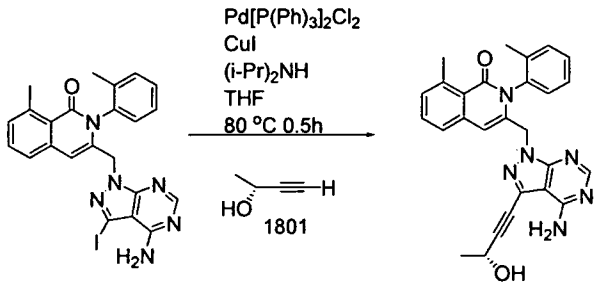
1607 1701 1702 1610

[00448] 3-(3-Methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**1701**)(964 mg, 4 mmol) and potassium tert - butoxide (0.44 g, 4 mmol) were dissolved in anhydrous DMF (150 mL) and stirred at RT for 30 min. 3-(Bromomethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1607**) (1.37 g, 4.0 mmol) was added. The resulting mixture was stirred at RT for 30min, poured into ice water (30 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (2-20% MeOH/DCM) to afford the desired product, 3-((4-amino-3-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1702**) (1.4 g, 70% yield) as a white solid.

[00449] To a solution of 3-((4-amino-3-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1702**)(100 mg, 0.2 mmol) in CH_2Cl_2 (20 mL) at -78 °C under a nitrogen atmosphere, BBr_3 (1 mL) was added and the resulting mixture was stirred at -78 °C for 3 h. The mixture was allowed to warm to RT, poured into ice-water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (10-50% MeOH/CH_2Cl_2) to afford the desired product, 3-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1610**)(87 mg, 91% yield) as a white solid.

[00450] Example 5: Synthesis of (R)-3-((4-amino-3-(3-hydroxybut-1-ynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound 1802).

Scheme 18. Synthesis of (R)-3-((4-amino-3-(3-hydroxybut-1-ynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound **1802**) is described.

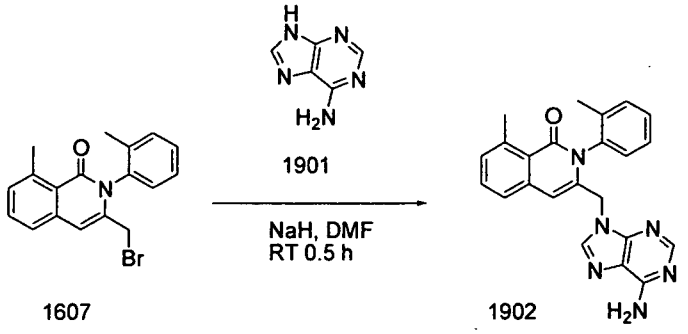


1608 1802

[00451] 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o- tolylisoquinolin-1(2H)-one (**1608**) (522 mg, 1 mmol) and (R)-but-3-yn-2-ol (84 mg, 1.2 mmol) were dissolved in anhydrous THF (40 mL). The mixture was degassed and back-filled with nitrogen three times. $Pd(PPh_3)_2Cl_2$ (12 mg, 0.1 mmol), CuI (47 mg 0.25 mmol) and $(i\text{-}Pr)_2NH$ (505 mg, 5 mmol) were added sequentially. The resulting mixture was degassed and back-filled with argon three times and then stirred at reflux for 4h. The mixture was allowed to cool to RT, filtered through silica gel (10 g) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (2-20% MeOH/DCM) to afford the product, 3 (R)-3-((4-amino-3-(3-hydroxybut-1-ynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1802**) (324 mg, 70% yield) as a slightly yellow solid.

[00452] Example 6: Synthesis of 3-((6-amino-9H-purin-9-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound 1902).

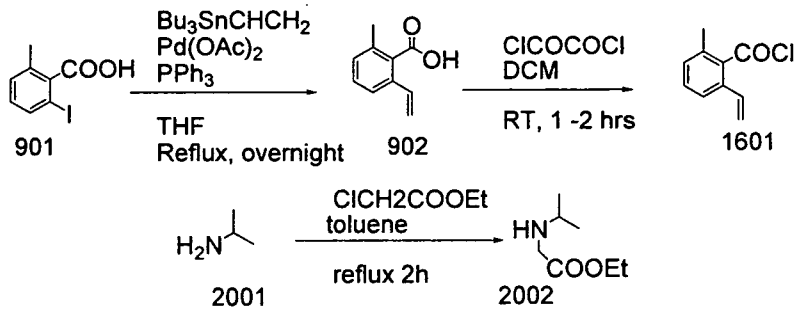
[00453] Scheme 19. Synthesis of 3-((6-amino-9H-purin-9-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound **1902**) is described.

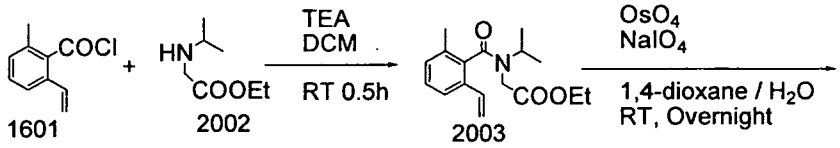


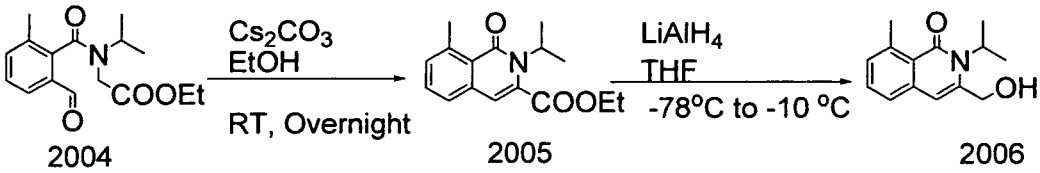
[00454] 9H-Purin-6-amine **(1901)**(540 mg, 4.0 mmol) was dissolved in anhydrous DMF (20 mL). NaH (60% in mineral oil, 160 mg, 4.0 mmol) was added and the resulting mixture was stirred at RT for 30 min. 3-(Bromomethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **(1607)**(1.37 g, 4.0 mmol) was added. The reaction mixture was stirred at RT for 30min, poured into ice-water (30 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (2-20% MeOH/DCM) to afford the desired product, 3-((6-amino-9H-purin-9-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **(1902)**(1.1 g, 70% yield) as a white solid.

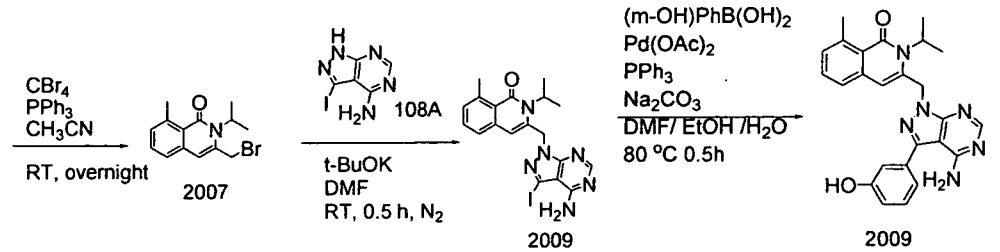
[00455] **Example 7**: Synthesis of 3-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (Compound 2009).

Scheme 20. Synthesis of 3-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (Compound **2009**) is described.









[00456] To a stirred mixture of 2-iodo-6-methylbenzoic acid (**901**) (105 g, 400 mmol), $Pd(OAc)_2$ (27 g, 120 mmol) and PPh_3 (63 g 240 mol) in THF (1000 mL) at RT, tributyl(vinyl)tin (152 g, 480 mmol) was added. The resulting mixture was heated to reflux overnight. The mixture was allowed to cool to RT, filtered through silica gel (10 g), and then concentrated *in vacuo*. The residue was poured into ice water (1000 mL) and extracted with ethyl acetate (3 × 1000 mL). The combined organic layer was washed with aqueous NaOH (15%, 5 × 200 mL). The combined aqueous layer was acidified to PH = 1, extracted with ethyl acetate (3 × 1000 mL). The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the desired product, 2-methyl-6-vinylbenzoic acid (**902**) (61 g, 95% yield) as a yellow solid.

[00457] A mixture of 2-methyl-6-vinylbenzoic acid (**902**) (56 g, 350 mmol) and thionyl chloride (208 g, 1750 mmol) in toluene (400 mL) was stirred at reflux for 2h. The mixture was concentrated *in vacuo* to afford the desired product, 2-methyl-6-vinylbenzoyl chloride (**1601**) (63 g, 95% yield) as a yellow oil. The product obtained was used directly in the next step without purification.

[00458] Propan-2-amine (**2001**)(59 g, 1.0 mol) and ethyl chloroacetate (122 g, 1.0 mol) were dissolved in toluene (200 mL) and the mixture was stirred at reflux for 2h. The reaction mixture was allowed to cool to RT, poured into ice-water (500 mL) and extracted with ethyl acetate (3 × 250 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (10-50% EA /PE) to afford the product, ethyl 2-(isopropylamino)acetate (**2002**) (70g, 51% yield) as an oil.

[00459] Ethyl 2-(isopropylamino)acetate (**2002**) (14.5 g, 100 mmol) and triethylamine (200 g, 200 mmol) were dissolved in CH_2Cl_2 (300mL) and the mixture was stirred for 10 min at RT. 2-Methyl-6-vinylbenzoyl chloride (**1601**) (18 g, 100 mmol) was added, and the resulting mixture was stirred at RT for 30min. The reaction mixture was poured into water (300 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the crude product. The crude product was suspended in IPE (isopropyl ether) (300 mL), stirred at reflux for 30min, and then cooled to 0-5°C. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, ethyl 2-(N-isopropyl-2-methyl-6-vinylbenzamido)acetate (**2003**) (14.5 g, 50% yield) as a yellow solid.

[00460] To a stirred solution of ethyl 2-(N-isopropyl-2-methyl-6-vinylbenzamido)acetate (**2003**) (14.0 g, 48.0 mmol) in 1,4-dioxane (100 mL) and H_2O (30 mL), Osmium tetroxide (20 mg) was added and the resulting mixture was stirred at RT for 30 min. To this mixture, sodium periodate (22 g, 100 mmol) was added and then stirred at RT for 16h. The reaction mixture was filtered through silica gel (10 g), the filtrate was extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was further dried *in vacuo* to afford the desired product, ethyl 2-(2-formyl-N-isopropyl-6-methylbenzamido)acetate (**2004**) (8.33 g, 57% yield) as a yellow solid.

[00461] To a stirred solution of ethyl 2-(2-formyl-N-isopropyl-6-methylbenzamido)acetate (**2004**) (8.3 g, 28.0 mmol) in EtOH (100 mL) and ethyl acetate (50 mL) at RT, cesium carbonate (5.9 g, 30 mmol) was added. The resulting mixture was degassed and back-filled with argon three times and then stirred at 50°C for 5 h. The mixture was allowed to cool to RT, filtered through silica gel (10 g), and the filtrate was concentrated in vacuo. The residue was poured into H_2O (200 mL), extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The crude product was suspended in IPE (120 mL), stirred at reflux for 10min, and then cooled to 0-5°C. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, ethyl 2-isopropyl-8-methyl-1-oxo-1,2-dihydroisoquinoline-3- carboxylate (**2005**) (5.35 g, 70% yield) as a white solid.

[00462] To a stirred solution of lithium aluminum hydride (2.88 g, 76 mol) in anhydrous THF (200 mL) at -78° C under a nitrogen atmosphere, ethyl 2-isopropyl-8-methyl-1-oxo-1,2-dihydroisoquinoline-3- carboxylate (**2005**) (5.2 g, 19 mmol) was slowly added over a 10 min period of time. The resulting mixture was allowed to warm to -30° C, stirred for 30min and TLC showed the completion of the reaction. Then the mixture was cooled to -78° C, and water (50 mL) was slowly added. The mixture was allowed to warm to RT, filtered through silica gel (10 g), and the filtrate was concentrated in vacuo. The crude product was poured into H_2O (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude product was suspended in ethyl acetate (30 mL) and stirred for 10min. The solid was collected by filtration and further dried *in vacuo* to afford the desired product, 3-(hydroxymethyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (**2006**) (3.51 g, 80% yield) as a white solid.

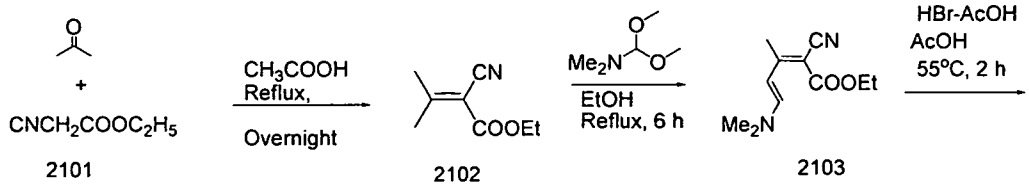
[00463] To a solution of 3-(hydroxymethyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (**2006**) (1.61 g, 7.0 mmol) in CH_2Cl_2, PPh_3 (3.67 g, 14.0 mmol) was added and the mixture was stirred at RT for 30 min. The mixture was cooled to 0°C, and CBr_4 (4.64 g, 14.0 mmol) was added in portions. The resulting mixture was stirred from 0°C to RT for 30 min, and then concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (30-50% EA/PE) to afford the desired product, 3-(bromomethyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (**2007**) (1.65 g, 80% yield) as a white solid.

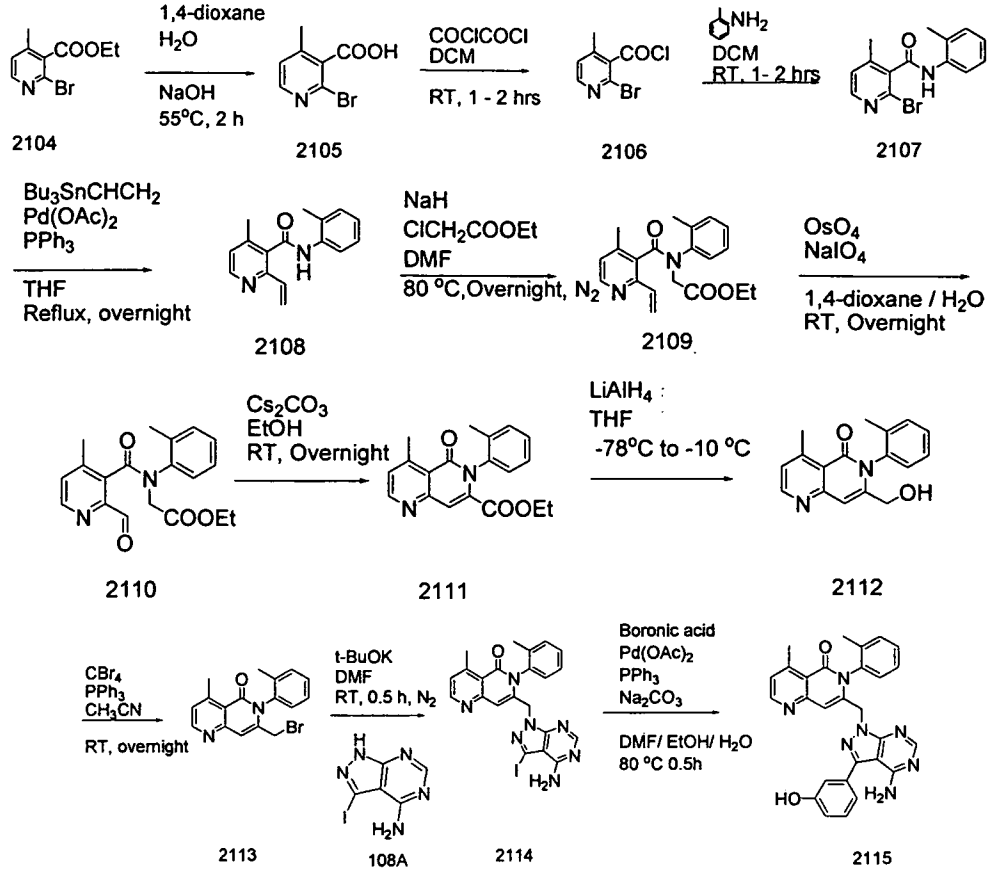
[00464] A mixture of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**108A**) (1.3 g, 5 mmol) and potassium tert - butoxide (0.55 g, 5 mmol) in anhydrous DMF (20 mL) was stirred at RT for 30 min and then 3-(bromomethyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (**2007**) (1.47 g, 5 mmol) was added. The resulting mixture was stirred at RT for 30min, poured into ice-water (30 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (2-20% MeOH/DCM) to afford the desired product, 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (**2008**) (1.66 g, 70% yield) as a white solid.

[00465] To a stirred mixture of 3-((4-Amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (**2008**) (95 mg, 0.2 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (66 mg, 0.3 mmol) in DMF-EtOH-H_2O (3:1:1, 20 mL), $Pd(OAc)_2$ (16 mg, 0.075 mmol), PPh_3 (39.3 mg 0.15 mmol) and Na_2CO_3 (132 mg, 1.25 mmol) were added sequentially. The resulting mixture was degassed and back-filled with argon three times and then stirred at 100 °C for 1 h. The mixture was allowed to cool to RT, filtered through silica gel (10 g) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (2-20% MeOH/DCM) to afford the product, 3-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (**2009**) (53 mg, 61% yield) as a slightly yellow solid.

[00466] Example 8: Synthesis of 7-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-4-methyl-6-o-tolyl-1,6-naphthyridin-5(6H)-one (Compound 2115).

[00467] Scheme 21. Synthesis of 7-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-4-methyl-6-o-tolyl-1,6-naphthyridin-5(6H)-one (Compound **2115**) is described.





[00468] To a mixture of ethyl 2-cyanoacetate (**2101**) (45.2 g, 400 mmol) and acetone (46.4 g, 800 mmol) in glacial acetic acid (50 mL), piperidine (2 mL, 20 mmol) was added and the resulting mixture stirred at reflux for 24 h. The reaction mixture was allowed to cool to RT, and then concentrated *in vacuo*. The residue was diluted with water (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (0-2% EA / PE) to afford the desired product, ethyl 2-cyano-3-methylbut- 2-enoate (**2102**) (49.6 g, 81% yield) as a white solid.

[00469] To a solution of ethyl 2-cyano-3-methylbut-2-enoate (**2102**) (43.6 g, 285 mol) in absolute EtOH (300 mL), N,N-dimethylformamide dimethyl acetal (37.3 g, 313 mmol) was added dropwise and the resulting mixture was stirred at reflux 6 h. The mixture was allowed to cool to RT, concentrated *in vacuo* to afford the crude desired product, ethyl 2-cyano-5-(dimethylamino)-3-methylpenta-2,4- dienoate (**2103**) (39.8 g, 67% yield) as a yellow solid.

[00470] Ethyl 2-cyano-5-(dimethylamino)-3-methylpenta-2,4-dienoate (**2103**) (30.8 g, 148 mmol) was dissolved in AcOH (120 mL) and the mixture was stirred at 40 °C. A solution of 45% HBr-AcOH (120 mL) was added dropwise, and then the mixture was stirred at 55 °C for 2 h. The mixture was allowed to cool to RT, poured onto ice, neutralized with solid Na_2CO_3, and extracted with ethyl acetate (3 x 150 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (5-20% EA/PE) to afford the desired product, ethyl 2-bromo-4-methylnicotinate (**2104**) (17.6 g, 49% yield) as a yellow oil.

[00471] To a solution of ethyl 2-bromo-4-methylnicotinate (**2104**) (12.8 g, 52 mmol) in 1,4-dioxane (15 mL), a solution of NaOH (8.0 g, 200 mmol) in H_2O (15 mL) was added and the resulting mixture was stirred at reflux for 12 h. The mixture was allowed to cool to RT, diluted with H_2O, washed with ethyl acetate (3 x 30 mL). The aqueous

layer was acidified with concentrated hydrochloric acid to pH=1, and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the desired product, 2-bromo-4-methylnicotinic acid (**2105**) (9.7 g, 85% yield) as a white solid.

[00472] To a solution of 2-bromo-4- methylnicotinic acid (**2105**) (13 g, 60 mmol) and DMF (3 drops) in CH_2Cl_2 (150 mL), oxalyl chloride (11.4 g, 90 mmol) was added dropwise and the resulting mixture was stirred at RT for 2h. The reaction mixture was concentrated *in vacuo* to afford the desired product, 2-bromo-4-methylnicotinoyl chloride (**2106**) (13.4 g, 95% yield) as a yellow oil. The product obtained was used directly in the next step without further purification.

[00473] o-Toluidine (7.7 g, 72 mmol) and triethylamine (9.1 g, 90 mmol) were dissolved in CH2Cl2 (100mL) and stirred for 10 min at RT. 2-Bromo-4-methylnicotinoyl chloride (**2106**) (13.4 g, 57 mmol) was added, and the resulting mixture was stirred at RT for 1 h. The mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the crude product. The crude product was suspended in IPE (isopropyl ether) (50 mL). The mixture was stirred at reflux for 30min and then was cooled to 0-5°C. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, 2-bromo-4-methyl-N-o-tolylnicotinamide (**2107**) (13 g, 75% yield) as a yellow solid.

[00474] To a solution of 2-bromo-4-methyl-N-o- tolylnicotinamide (**2107**) (13 g, 43 mmol) and tributyl(vinyl)tin (16.4 g, 52 mmol) in THF (200 mL) under a nitrogen atmosphere, $Pd(OAc)_2$ (2.9 g, 13 mmol) and PPh_3 (6.8 g, 26 mol) were added. The resulting mixture was stirred at reflux for 16 h. The mixture was then allowed to cool to RT, filtered through silica gel (10 g), and concentrated in vacuo. The residue was poured into water (200 mL), extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (20-50% EA/PE) to afford the desired product, 4-methyl-N-o-tolyl-2-vinylnicotinamide (**2108**) (8.7 g, 80% yield) as a yellow solid.

[00475] To a stirred solution of 4-methyl-N-o-tolyl-2-vinylnicotinamide (**2108** (8.1 g, 32 mmol) in DMF (50 mL) at RT, NaH (60% in mineral oil, 2.6 g, 65 mmol) was added slowly and the resulting mixture was stirred at RT for 30 min. Ethyl chloroacetate (78 g, 640 mmol) was added dropwise to this mixture at RT, and stirred for 2 h. The solution was poured into water (300 mL) and extracted with ethyl acetate (3 x 80 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude product was suspended in MeOH (60 mL) and stirred at reflux for 10 min. The mixture was then cooled to 0 -5°C. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, ethyl 2-(4-methyl-N-o-tolyl-2-vinylnicotinamido) acetate (**2109**) (6.3 g, 58% yield) as a white solid.

[00476] To a solution of ethyl 2-(4-methyl-N-o-tolyl-2- vinylnicotinamido) acetate (**2109**) (6.1 g, 18 mmol) in 1, 4-dioxane (90 mL) and H_2O (30 mL) at RT, Osmium tetroxide (5 mg) was added and the resulting mixture was stirred for 30 min. Sodium periodate (7.7 g, 36 mmol) was added and the mixture was stirred at RT for 16 h. The mixture was filtered through silica gel (5 g), and the filtrate was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was further dried under reduced pressure to afford the desired product, ethyl 2-(2-formyl-4-methyl-N-o-tolylnicotinamido)acetate (**2110**) (4.4 g, 72% yield) as a yellow solid.

[00477] To a stirred solution of ethyl 2-(2-formyl-4-methyl-N-o-tolylnicotinamido)acetate (**2110**) (4.4 g, 13 mmol) in EtOH (30mL) and ethyl acetate (10 mL) at RT, cesium carbonate (4.3 g, 13 mmol) was added. The resulting mixture was degassed and back-filled with argon three times and then stirred at 50 °C for 5 h. The mixture was allowed to cool

to RT, filtered through silica gel (5 g), and the filtrate was concentrated in vacuo. The residue was poured into H_2O (200 mL), extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The crude product was suspended in IPE (30 mL), stirred at reflux for 10min, and then cooled to 0 -5 °C. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, ethyl 4-methyl-5-oxo-6-o-tolyl- 5,6-dihydro-1,6-naphthyridine-7-carboxylate (**2111**) (3.0 g, 72% yield) as a white solid.

[00478] To a stirred solution of lithium aluminum hydride (0.86 g, 23 mol) in anhydrous THF (100 mL) at -78 °C under a nitrogen atmosphere, a solution of ethyl 4-methyl-5-oxo-6-o-tolyl-5,6-dihydro- 1,6- naphthyridine-7-carboxylate (**2111**) (2.9 g, 9.0 mmol) in anhydrous THF (20 mL) was added dropwise. The resulting mixture was allowed to warm to -10°C, stirred for 30min and TLC showed the completion of the reaction. Then the mixture was cooled to -78°C, and water (50 mL) was slowly added. The mixture was allowed to warm to RT, filtered through silica gel (5 g), and the filtrate was concentrated in vacuo. The crude product was poured into H_2O (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude product was suspended in ethyl acetate (10 mL) and stirred for 10min. The solid was collected by filtration and further dried *in vacuo* to afford the desired product, 7-(hydroxymethyl)-4-methyl-6-o-tolyl- 1,6-naphthyridin-5(6H)-one (**2112**) (2.1 g, 83% yield) as a white solid.

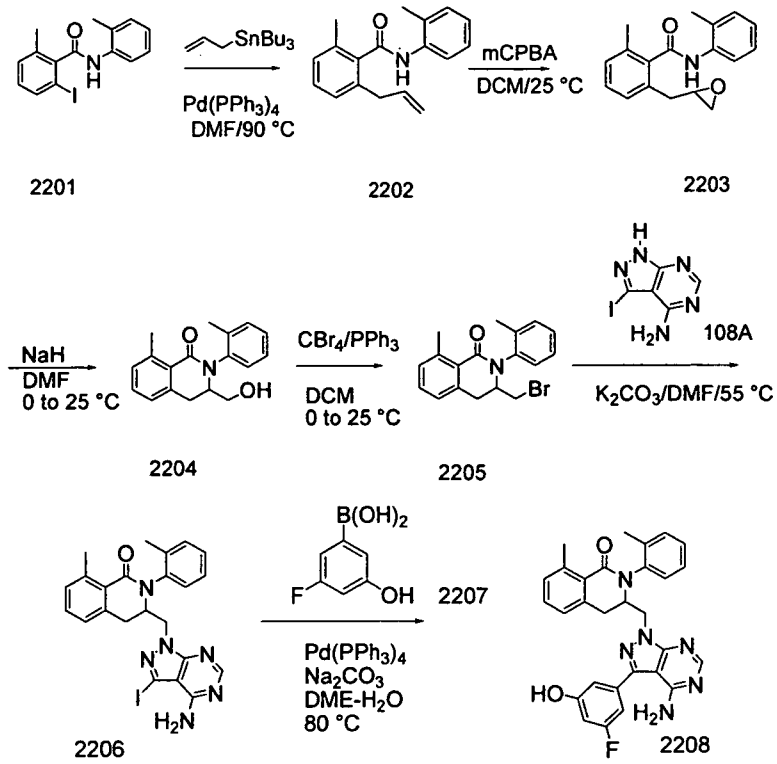
[00479] To a solution of 7-(hydroxymethyl)-4-methyl-6-o-tolyl- 1,6-naphthyridin-5(6H)-one (**2112**) (1.96 g, 7.0 mmol) in CH_2Cl_2, PPh_3 (3.67 g, 14.0 mmol) was added and stirred at RT for 30 min. CBr_4 (4.64 g, 14.0 mmol) was added to the mixture in portions at 0 °C. The resulting mixture was allowed to warm to RT, stirred for 30 min, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (30-50% EA/PE) to afford the desired product, 7-(bromomethyl)-4-methyl-6-o-tolyl-1,6-naphthyridin-5(6H)-one (**2113**) (1.92 g, 80% yield) as a white solid.

[00480] A mixture of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**108A**) (1.08 g, 4.14 mmol) and potassium tert - butoxide (0.44 g, 4.0 mmol) in anhydrous DMF (50 mL) was stirred at RT for 30 min and then 7-(bromomethyl)-4-methyl-6-o-tolyl-1,6-naphthyridin-5(6H)-one (**2113**) (1.37 g, 4.0 mmol) was added. The resulting mixture was stirred at RT for 30 min, poured into ice water (300 mL) and then extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (0-2% MeOH/DCM) to afford the desired product, 7-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-4-methyl-6-o-tolyl-1,6- naphthyridin-5(6H)-one (**2114**) (1.07 g, 50% yield) as a white solid.

[00481] To a stirred mixture of 7-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-4- methyl-6-o-tolyl-1,6-naphthyridin-5(6H)-one (**2114**) (1.05 g, 2.0 mmol) and 3-hydroxyphenylboronic acid (0.33 g, 2.4 mmol) in DMF-EtOH-H_2O (3:1:1, 50 mL), $Pd(OAc)_2$ (0.14 g, 0.60 mmol), PPh_3 (0.31 g, 1.2 mmol) and Na_2CO_3 (1.06 g, 10.0 mmol) were added sequentially. The resulting mixture was degassed and back-filled with argon three times and then stirred at 80 °C for 1 h. The mixture was allowed to cool to RT, filtered through silica gel (5 g) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (2-5% MeOH/DCM) to afford the desired product, 7-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-4- methyl-6-o-tolyl- 1,6-naphthyridin-5(6H)-one (**2115**) (0.68 g, 69% yield) as a slight yellow solid. Then the product was dissolved in EtOH (5 mL), and stirred at reflux for 30 min. The solution was allowed to cool to RT and the solid was collected by filtration. The solid was then suspended in ethyl acetate (5 mL), and stirred at RT for 16 h. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, 7-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-4- methyl-6-o-tolyl- 1,6-naphthyridin-5(6H)-one (**2115**) (0.59 g, 60% yield) as a white solid.

[00482] Example 9: 3-((4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolyl-3,4-dihydroisoquinolin-1(2H)-one (Compound 2208).

Scheme 22. 3-((4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolyl-3,4-dihydroisoquinolin-1(2H)-one (Compound **2208**) is described.



[00483] 2-Iodo-6-methyl-N-o-tolylbenzamide (**2201**)(1.5 g, 4.27 mmol), which has been prepared from the reaction of compound **902** and 2-methyl aniline, and allyltributyl tin (2.10 g, 1.5 mmol) were dissolved in anhydrous DMF (12 mL). The solution was degassed and back-filled with argon (three times). $Pd(PPh_3)_4$ (148 mg, 0.13 mmol) was added. The reaction mixture was degassed and back-filled with argon (three times), and then stirred at 90°C for 16 h. The mixture was allowed to cool to RT, partitioned between ethyl acetate and H_2O. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with EtOAc and Hexanes to afford the desired product, 2-allyl-6-methyl-N-o-tolylbenzamide (**2202**) (1.1 g, 95% yield).

[00484] 2-Allyl-6-methyl-N-o-tolylbenzamide (2202) (800 mg, 3.01 mmol) was dissolved in anhydrous dichloromethane (20 mL). mCPBA (70%, 1.11 g, 4.52 mmol) was added and the resulting mixture was stirred at RT for 24 h. Na_2SO_3 (1.0 g) was added and stirred for 1 h. The mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with EtOAc and Hexanes to afford the desired product, 2-methyl-6-(oxiran-2-ylmethyl)-N-o-tolylbenzamide (**2203**)(660 mg, 83% yield).

[00485] 2-Methyl-6-(oxiran-2-ylmethyl)-N-o-tolylbenzamide (**2203**) (860 mg, 3.06 mmol) was dissolved in anhydrous DMF (15 mL) and cooled to 0 °C under an argon atmosphere. NaH (60% in mineral oil, 245 mg, 6.12 mmol) was added in portions and the resulting mixture was stirred at 0 °C for 3 h. H_2O (30 mL) was slowly added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography

on silica gel eluting with EtOAc and Hexanes to afford the desired product, 3-(hydroxymethyl)-8-methyl-2-o-tolyl-3,4-dihydroisoquinolin-1(2H)-one (**2204**) (435 mg, 51% yield).

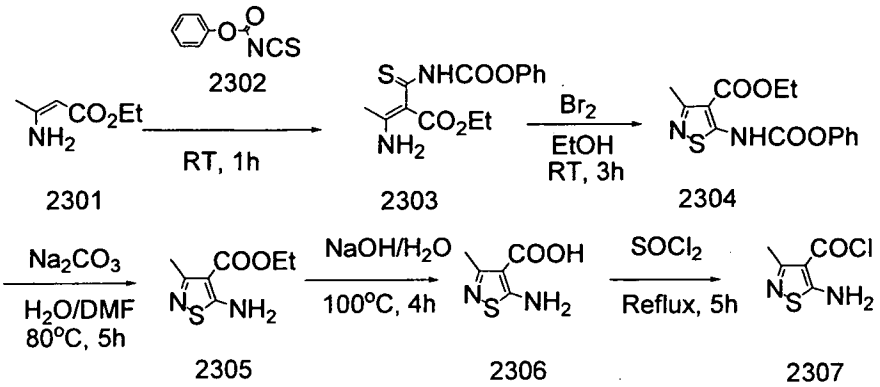
[00486] 3-(Hydroxymethyl)-8-methyl-2-o-tolyl-3,4-dihydroisoquinolin-1(2H)-one (**2204**) (430 mg, 1.53 mmol) was dissolved in anhydrous dichloromethane (25 mL) and cooled to 0°C under an argon atmosphere. PPh_3 (600 mg, 2.29 mmol) and CBr_4 (761 mg, 2.29 mmol) were added sequentially and the resulting mixture was stirred from 0°C to RT for 16 h. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with EtOAc and Hexanes to afford the desired product, 3-(bromomethyl)-8-methyl-2-o-tolyl-3,4-dihydroisoquinolin-1(2H)-one(**2205**) (480 mg, 91% yield).

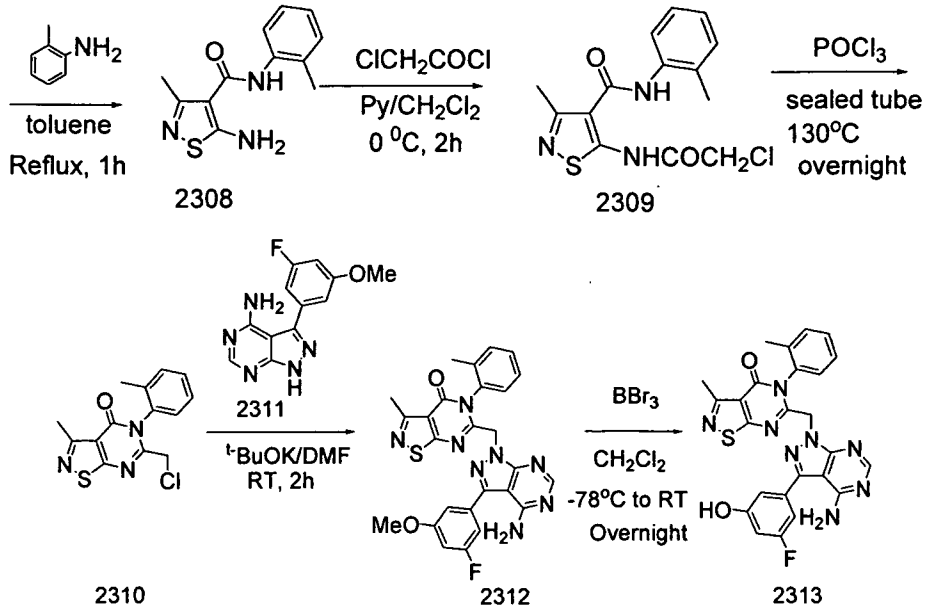
[00487] 3-(Bromomethyl)-8-methyl-2-o-tolyl-3,4-dihydroisoquinolin-1(2H)-one (**2205**) (387 mg, 1.12 mmol) and 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**108A**)(440 mg, 1.69 mmol) were dissolved in anhydrous DMF (20 mL). K_2CO_3 (309 mg, 2.24 mmol) was added and the resulting mixture was stirred at 50°C for 3h. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel eluting with methanol and dichloromethane to afford the desired product, 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolyl-3,4-dihydroisoquinolin-1(2H)-one (**2206**) (100 mg, 17% yield).

[00488] 3-((4-Amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolyl-3,4-dihydroisoquinolin-1(2H)-one (**2206**) (100 mg, 0.11 mmol) and 3-fluoro-5-hydroxyphenylboronic acid (**2207**) (36 mg, 0.23 mmol) were dissolved in DME (4 mL). The solution was degassed and back-filled with argon (three times). $Pd(PPh_3)_4$ (6.4 mg, 5.5 μmol) and aqueous Na_2CO_3 solution (1.0 M, 0.44 mL, 0.44 mmol) were added sequentially. The reaction mixture was degassed and back-filled with argon (three times), and then stirred at 80 °C for 24h. The mixture was allowed to cool to RT, partitioned between ethyl acetate and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with methanol and dichloromethane to afford the desired product, 3-((4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolyl-3,4-dihydroisoquinolin-1(2H)-one (**2208**) (12 mg, 22% yield).

[00489] Example 10: Synthesis of 6-((4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methyl-5-o-tolylisothiazolo[5,4-d]pyrimidin-4(5H)-one (Compound 2313).

Scheme 23. Synthesis of 6-((4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-methyl-5-o-tolylisothiazolo[5,4-d]pyrimidin-4(5H)-one (Compound **2313**) is described.





[00490] A solution of compound **2302** (24.9 g, 0.19 mol) in CH_3CN (50 mL) was added to a solution of compound **2301** (30 g, 0.19 mol) in at 0 °C. The mixture was stirred for 1 hour at room temperature and poured into 500 mL of water. The reaction mixture was allowed to stand for 1 h. The solid was precipitated out of the solution, collected by filtration, washed with water and dried to afford the desired compound **2303** as a red-orange solid (50 g, 85.5%).

[00491] To a solution of compound **2303** (54 g, 0.175 mol) in ethyl acetate (200 mL), a solution of Br_2 (56 g, 0.35 mol) in ethyl acetate (50 mL) was added dropwise at room temperature. The resulting mixture was stirred for 3 h at room temperature. The solid was collected by filtration, washed with ethyl acetate to afford the desired product, compound **2304** (40 g, 74.6%).

[00492] A mixture of compound **2304** (40 g, 0.13 mol) and saturated Na_2CO_3 solution (10 mL) in DMF (100 mL) was heated for 5 h at 80 °C. The reaction mixture was cooled to room temperature and 1 L of water was added. The solid was collected by filtration and dried to afford the desired product, compound **2305** (16 g, 66%).

[00493] A mixture of compound **2305** (16 g, 0.086 mol), NaOH (6.88 g, 0.172 mol) in water (50 mL) was heated for 4 h at reflux. The reaction mixture was cooled to room temperature and acidified with 1N HCl solution until PH = 3 – 4. The solid was collected by filtration and dried to afford the desired product, compound **2306** (12 g, 88%).

A mixture of compound **2306** (1 g, 0.0063 mol) in $SOCl_2$ (15 mL) was stirred for 5 h at reflux, the reaction mixture was cooled to room temperature and concentrated to remove excess $SOCl_2$. Anhydrous toluene (30 mL) was added to the residue and concentrated. This process was repeated twice to remove the residue of $SOCl_2$.

[00494] The crude compound **2307** was dissolved in dry toluene (5 mL). 2-Methyl- aniline (2 g, 0.0187 mol) was added to the above solution. The resulting mixture was heated for 1h at reflux, cooled to room temperature and filtered. The filtrate was concentrated to dryness and partitioned between ethyl acetate and brine. The aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried with $MgSO_4$ and filtered. The residue was purified by flash chromatography eluting with petroether ethyl acetate from 50:1 to 5:1 to afford the desired product, compound **2308** (600 mg, 38.55%).

[00495] A solution of compound **2308** (600 mg, 2.43 mmol) and pyridine (0.78 mL) in DCM (30 mL) was stirred for 10 min at 0°C. Chloroacetyl chloride (423 mg, 3.74 mmol) was added. The reaction mixture was stirred for 2 h and quenched with water. The organic phase was separated and washed with water, brine, dried, filtered and concentrated to afford the desired product, compound **2309** (700 mg, 89%).

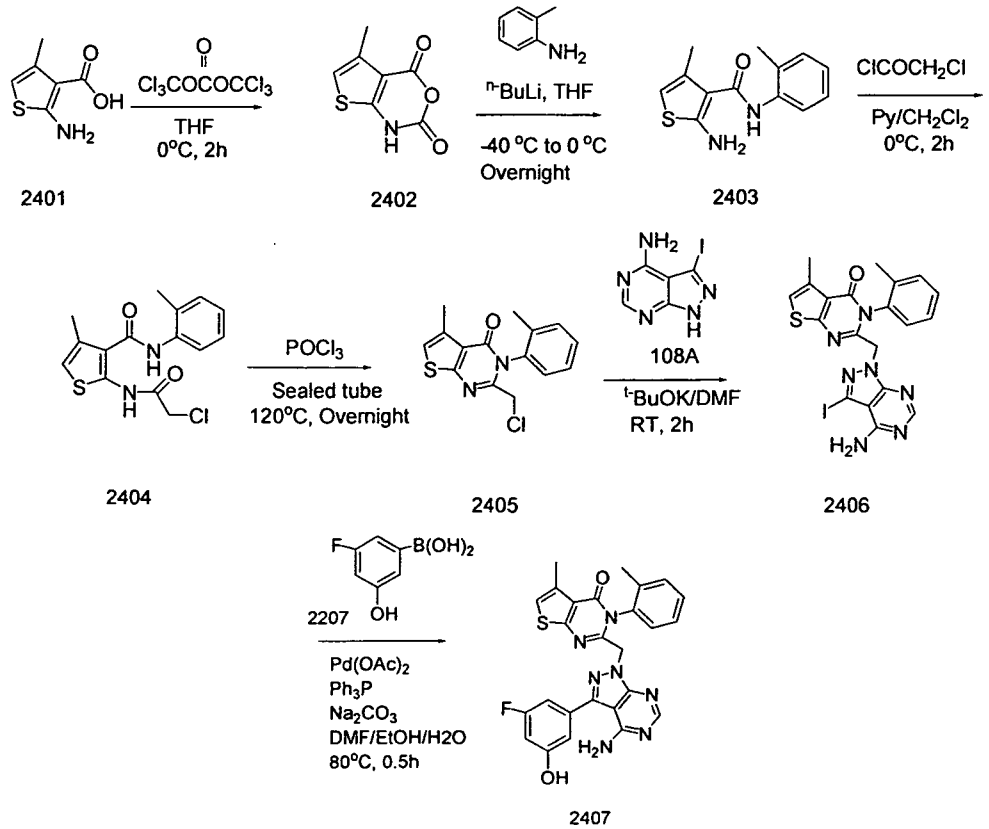
[00496] A mixture of compound **2309** (600 mg, 1.85 mmol) and $POCl_3$ (10 mL) was heated overnight at 120 - 130°C (oil bath) in a sealed tube. The reaction mixture was cooled to room temperature and concentrated. The residue was partitioned between ethyl acetate and water, and then basified with saturated Na_2CO_3 solution until PH 7 – 8. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography eluting with petroether in ethyl acetate (PE/EA=20/1) to afford the desired product, compound **2310** as a yellow powder (300 mg, 53.0%).

[00497] tert-BuOK (28.7 mg, 0.256 mmol) was added to a solution of compound **2311** (76 mg, 0.295 mmol) in dry DMF (3 mL) at RT. The reaction mixture was stirred for 30 min., and a solution of compound **2310** (60 mg, 0.196 mmol) in DMF (2 mL) was added dropwise. The resulting mixture was stirred for 2 h and concentrated. The residue was purified by flash chromatography eluting with (DCM/MeOH=50/1) to afford the desired product **2312** as off-white solid (65 mg, 62.7%).

[00498] To a solution of compound **2312** (40 mg, 0.076 mmol) in dry DCM (10 mL), BBr_3(190.4 mg, 0.76 mmol) was added dropwise at -78°C, then the reaction mixture was allowed to warm to room temperature and stirred for overnight. The reaction mixture was poured into ice-water, basified with saturated $NaHCO_3$ solution until PH 8 – 9 and extracted with DCM. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography eluting with DCM / MeOH = 30 / 1 to afford the desired product, compound **2313** (15 mg, 38.5%).

[00499] Example 11: Synthesis of 2-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylthieno[2,3-d]pyrimidin-4(3H)-one (Compound 2407).

[00500] Scheme 24. Synthesis of 2-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylthieno[2,3-d]pyrimidin-4(3H)-one (Compound **2407**) is described.



[00501] To a stirred solution of 2-amino-4-methylthiophene-3-carboxylic acid (**2401**) (2.4 g, 15.2 mmol) in THF (50 mL), a solution of triphosgene (9.0 g, 30 mmol, 2 eq.) in THF (10 mL) was added slowly dropwise at 0 °C in 20 min. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with water (20 mL) at 0 °C, and then concentrated *in vacuo* to remove the organic solvent. A brown solid was precipitated out of solution. The solid was collected by filtration, washed with water (5 mL x 2) and dried *in vacuo* to afford the desired product 5-methyl-1H-thieno[2,3-d][1,3]oxazine-2,4-dione (**2402**) (2.5 g, 89.3% yield) as a brown solid.

[00502] To a stirred solution of o-toluidine, (1.4 g, 12.8 mmol, 1.2 eq) in dry THF (20 mL), n-BuLi (2.5 N, 7.7 mL, 19.3 mmol, 1.8 eq.) was added slowly dropwise at -40 °C under argon atmosphere in 30 min. The resulting mixture was stirred at -40 °C for another 30 min. A solution of 5-methyl-1H-thieno[2,3-d][1,3]oxazine-2,4-dione (**2402**) (1.95 g, 10.7 mmol, 1eq) in dry THF (50 mL) was added slowly dropwise at -40 °C in 20 min. The reaction mixture was stirred at -40 °C for 1h and then allowed to warm to room temperature for overnight. The reaction mixture was quenched with water (20 mL) at 0°C, and then neutralized with concentrated HCl solution until pH 8-9. The mixture was concentrated *in vacuo* to remove the organic solvent. The residue was extracted with ethyl acetate (25 mL x 3). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by a silica gel column chromatography using 5% to 20% ethyl acetate in petroether as an eluent to afford the desired product 2-amino-4-methyl-N-o-tolylthiophene-3-carboxamide (**2403**) (0.74 g, 28.1% yield) as a yellow solid.

[00503] To a stirred solution of 2-amino-4-methyl-N-o-tolylthiophene-3-carboxamide (**2403**) (740 mg, 3 mmol) and pyridine (406.8 mg, 3.6 mmol, 1.2 eq) in dry DCM (20 mL), 2-chloroacetyl chloride (284.8 mg, 3.6 mmol, 1.2 eq.) was added slowly dropwise at 0 °C in 30 min. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with water (20 mL) at 0 °C and extracted with DCM. The combined organic phases were washed with 1N of HCl solution (10 mL), brine (10 mL) , dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product 2-(2-chloroacetamido)-4-methyl -N-o-tolylthiophene-3-carboxamide (**2404**) (950 mg, 98.1% yield) as a yellow solid.

[00504] A mixture of 2-(2-chloroacetamido)-4-methyl-N-o-tolylthiophene-3-carboxamide (**2404**) (1.07 g, 3.32 mmol) and $POCl_3$ (25 mL) was stirred overnight in a sealed tube at 120 °C. The reaction mixture was concentrated in vacuo to remove excess $POCl_3$. The residue was partitioned between DCM (30 mL) and saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and washed with sat. $NaHCO_3$ (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by a silica gel column chromatography to afford the desired product 2-(chloromethyl)-5-methyl-3-o-tolylthieno[2,3-d]pyrimidin-4(3H)-one (**2405**) (760 mg, 75.2% yield) as a yellow solid.

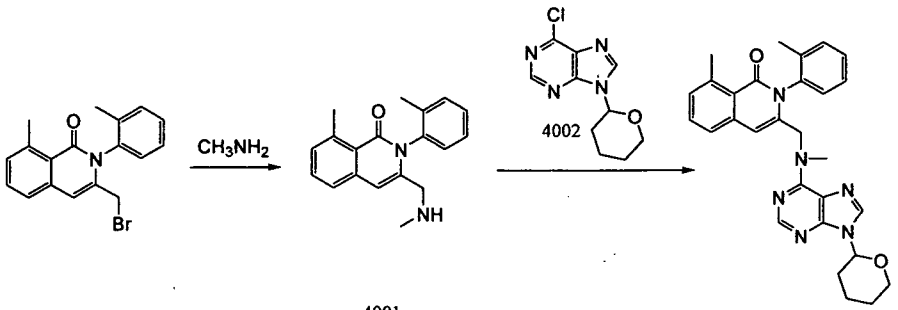
[00505] A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**108A**) (314.3 mg, 1.2 mmol, 1.5eq) and t-BuOK (155 mg, 1.38 mmol, 1.2 eq) in DMF (10 mL) was stirred at room temperature for 15 min., a solution of 2-(chloromethyl)-5-methyl-3-o-tolylthieno[2,3-d] pyrimidin-4(3H)-one (**2405**) (350 mg, 1.15 mmol, 1 eq.) in DMF (5 mL) was added dropwise at room temperature. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo to remove the organic solvent. The resulting residue was purified by a silica gel column chromatography to afford the desired product 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5- methyl-3-o-tolylthieno[2,3-d]pyrimidin-4(3H)-one (**2406**) (250 mg, 41.1% yield) as a yellow solid.

[00506] 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o- tolylthieno[2,3-d]pyrimidin-4(3H)-one (**2406**) (50 mg, 0.092 mmol), PPh_3 (14.5 mg, 0.056 mmol, 0.6 eq) and 3-fluoro-5-hydroxyphenylboronic acid (**2207**) (17.2 mg, 0.11 mmol,1.2 eq) were dissolved in a solution of DMF, ethanol and water (5 mL / 2 mL / 2mL). To this mixture $Pd(OAc)_2$ (4.14 mg, 0.018 mmol, 0.2 eq) and sodium carbonate (48.7 mg, 0.46 mmol, 5 eq)

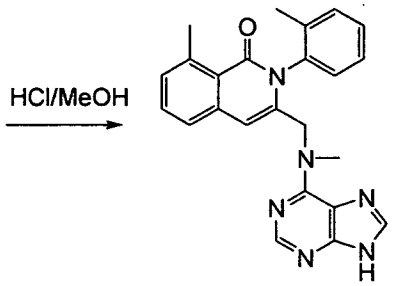
were added sequentially. The resulting mixture was degassed and back-filled with argon three times and then heated to 80°C for 0.5h with stirring. The reaction mixture was concentrated in vacuo to remove the organic solvent. The resulting residue was purified by a silica gel column chromatography to afford the desired product 2-((4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylthieno[2,3-d]pyrimidin-4(3H)-one (**2407**)(22.8mg, 48.2% yield) as a yellow solid.

[00507] Example 12: Synthesis of 8-methyl-3-((methyl(9H-purin-6-yl)amino)methyl)-2-o-tolylisoquinolin-1(2H)-one.

[00508] Scheme 25: The synthesis of 8-methyl-3-((methyl(9H-purin-6-yl)amino)methyl)-2-o-tolylisoquinolin-1(2H)-one (Compound 4004) is described.



1607 4001 4003



4004

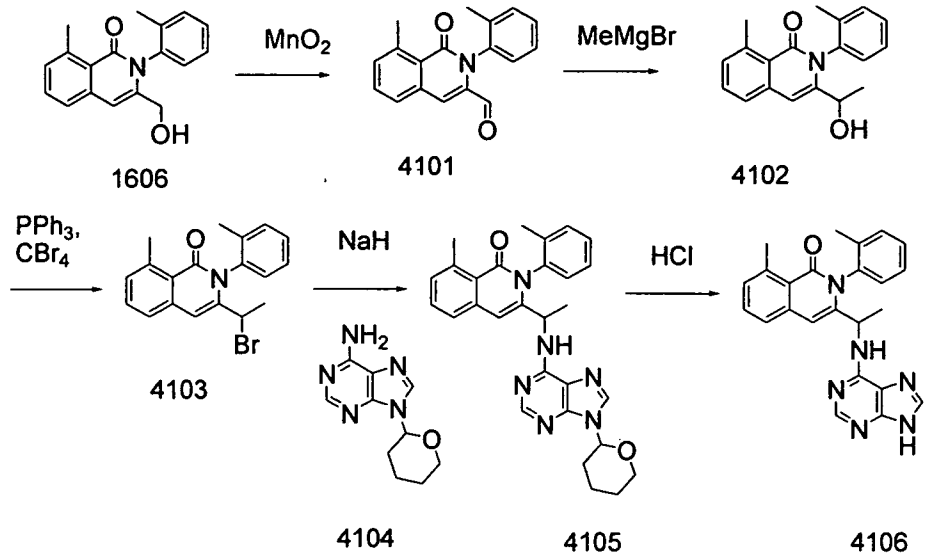
[00509] 3-(Bromomethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (342 mg, 1.0 mmol) (**1607**) was dissolved in methylamine solution (100 mL) and stirred for 2 h. The mixture was poured into ice-water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the desired product, 8-methyl-3-((methylamino)methyl)-2-o-tolylisoquinolin-1(2H)-one (**4001**) (250 mg, 86% yield) as a yellow solid. The product obtained was used directly in the next step without purification.

[00510] 8-Methyl-3-((methylamino)methyl)-2-o-tolylisoquinolin-1(2H)-one (233 mg, 0.8 mmol) (**4001**) and 6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (**4002**) (238 mg, 1.0 mmol) were dissolved in EtOH (50 mL) and the resulting mixture was stirred at reflux for 2 h. The mixture was allowed to cool to RT, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (2-20% MeOH/DCM) to afford the product, 8-Methyl-3-((methyl(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl)amino)methyl)-2-o-tolylisoquinolin-1(2H)-one (**4003**) (200 mg, 51% yield) as a slight yellow solid.

[00511] 8-Methyl-3-((methyl(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl)amino)methyl)-2-o-tolylisoquinolin-1(2H)-one (**4003**) (180 mg 0.36mmol) was dissolved in MeOH (HCl) (50 mL) and the mixture was stirred at RT for 2 h. Aqueous $NaHCO_3$ solution was added to the reaction mixture and the pH was adjusted to 9. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford the desired product, 8-methyl-3-((methyl(9H-purin-6-yl)amino)methyl)-2-o-tolylisoquinolin-1(2H)-one (**4004**) (80 mg, 54% yield) as a yellow solid.

[00512] Example 13: Synthesis of 3-(1-(9H-purin-6-ylamino)ethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one

[00513] Scheme 26: The synthesis of 3-(1-(9H-purin-6-ylamino)ethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound **4106**) is described.



[00514] To a stirred solution of 3-(hydroxymethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **1606** (2.79 g, 10 mmol) in CH_2Cl_2 (200 mL), MnO_2 (5 g) was added and the resulting mixture was stirred at reflux for 3 h. The mixture was allowed to cool to RT, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (10-50% EA/PE) to afford the product, 8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinoline-3-carbaldehyde **4101** (2.5 g, 90% yield) as a white solid.

[00515] 8-Methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinoline-3-carbaldehyde **4101** (2.4 g, 8.6 mmol) was dissolved in anhydrous THF (280 mL) and cooled to -78°C under a nitrogen atmosphere. Methyl MgBr (2 M, 5 mL, 10 mmol) was added slowly, and the resulting mixture was stirred at -78 °C for 2h. H_2O (5 mL) was added and then the solution was poured into ice-water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue product was purified by flash column chromatography on silica gel (10-50% EA/PE) to afford the product, 3-(1-hydroxyethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **4102** (1.8 g, 71% yield) as a white solid.

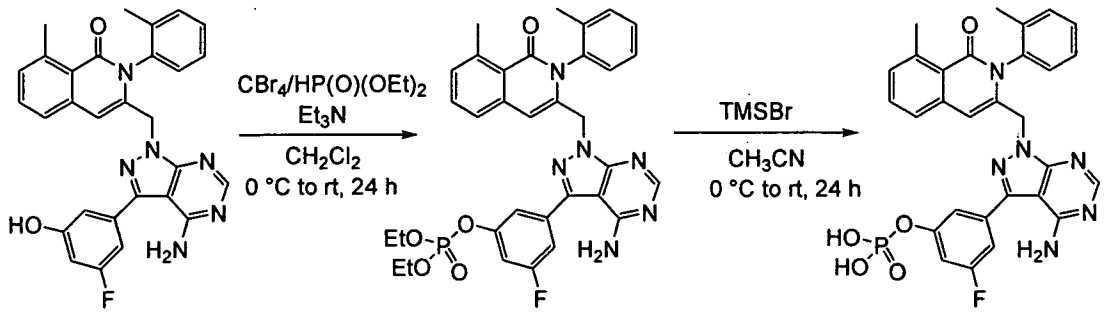
[00516] To a solution of 3-(1-hydroxyethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **4102** (1.6 g, 5.5 mmol) in CH_2Cl_2, PPh_3 (2.88g, 11.0 mmol) was added and the resulting mixture was stirred at RT for 30 min. Then CBr_4 (3.64 g, 11.0 mmol) was added in portions to the mixture at 0 °C. The resulting mixture was allowed to warm to RT, stirred for 30 min, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (30-50% EA/PE) to afford the desired product, 3-(1-bromoethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **4103** (1.8 g, 91% yield) as a white solid.

[00517] To a stirred solution of 9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine **4103** (436 mg 2mmol) in anhydrous DMF (10 mL), NaH (60% in mineral oil, 77 mg, 2 mmol) was added and the mixture was stirred for 30 min. 3-(1-Bromoethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **4104** (700 mg, 2 mmol) was added. The mixture was stirred for 2h, poured into ice-water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (10-50% MeOH/DCM) to afford the product, 8-methyl-3-(1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)-2-o-tolylisoquinolin-1(2H)-one **4105** (500 mg, 51% yield) as a white solid.

[00518] 8-Methyl-3-(1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)-2-o-tolylisoquinolin-1(2H)-one **4105** (180 mg, 0.36mmol) was dissolved in MeOH (HCl) (50 mL) and stirred for 2 h. Aqueous $NaHCO_3$ solution was added to the reaction mixture and the pH value was adjusted to 9. The mixture was then filtered and the filtrate was concentrated *in vacuo* to afford the desired product, 3-(1-(9H-purin-6-ylamino)ethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **4106** (80 mg, 54% yield) as a yellow solid.

[00519] Example 14: Synthesis of 3-(4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenyl dihydrogen phosphate.

[00520] Scheme 27. The synthesis of 3-(4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenyl dihydrogen phosphate (Compound **4903**)is described.



4301 4302 4303

[00521] 3-((4-Amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **4301** (250 mg, 0.5 mmol) was dissolved in anhydrous THF (15 mL) in a round bottom flask in dark (covered by aluminum foil) and cooled to 0°C under an argon atmosphere. CBr_4 (498 mg, 1.5 mmol) was added followed by diethylphosphite (129 µL, 1.0 mmol) and triethylamine (417 µL, 1.5 mmol). The resulting mixture was stirred in dark from 0°C to RT for 16 h. The mixture was then partitioned between ethyl acetate and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with methanol and dichloromethane to afford the desired product, 3-(4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenyl diethyl phosphate **4302** (200 mg, 62% yield) as an off-white solid.

[00522] 3-(4-Amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenyl diethyl phosphate **4302** (170 mg, 0.26 mmol) was dissolved in anhydrous CH_3CN (5 mL) and cooled to 0°C under an argon atmosphere. TMSBr (0.34 mL, 2.64 mmol) was slowly added via a syringe and the resulting mixture was stirred from 0°C to RT for 16 h. LC-MS showed small amount of starting material left, additional amount of TMSBr (0.1 mL) was added and stirred at RT for 5 h. LC-MS showed the complete conversion. The mixture was concentrated *in vacuo*, and the residue was dissolved in Et_2O (10 mL) and H_2O (0.5 mL) and stirred for 30 min. The mixture was concentrated *in vacuo* to affords the desired product, 3-(4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenyl dihydrogen phosphate **4903** (140 mg, 91% yield).

[00523] Example 15: IC50 Values for Selected Compounds

Table 4. *In Vitro* IC_{50} data for selected compounds.

IC50(nM)	+ (greater than 10 microMolar)	++ (less than 10 microMolar)	+++ (less than 1 microMolar	++++ (less than 100 nM)
PI3K δ	Compound No.	Compound No.	Compound No.	Compound No.

		1, 5, 22, 27, 38, 39, 40, 41, 46, 92, 117, 118, 120, 129, 132, 164, 165, 172, 188, 190, 197, 198, 205, 208, 210, 212, 214, 217, 218, 220, 222, 237, 263, 285, 294, 298	4, 14, 15, 17, 18, 21, 26, 29, 31, 32, 34, 35, 36, 42, 43, 44, 45, 47, 49, 57, 69, 71, 85, 87, 94, 106, 107, 140, 143, 175, 179, 183, 184, 191, 193, 196, 199, 200, 201, 202, 206, 207, 211, 213, 215, 219, 224, 225, 228, 229, 230, 232, 233, 239, 241, 243, 245, 253, 254, 255, 260, 262, 270, 293, 299	2, 3, 6, 7, 8, 9, 10, 11, 12, 13, 16, 19, 20, 23, 24, 25, 28, 30, 33, 37, 48, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 70, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 86, 88, 89, 90, 91, 93, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 108, 109, 110, 111, 112, 113, 114, 115, 119, 123, 124, 125, 126, 128, 134, 135, 136, 137, 138, 139, 141, 142, 144, 145, 146, 147, 148, 149, 150, 151. 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 166, 167, 168, 169, 170, 171, 173, 174, 176, 177, 178, 180, 189, 192, 194, 195, 203, 204, 209, 216, 221, 223, 226, 227, 231, 234, 235, 236, 238, 240, 242, 244, 246, 247, 248, 249, 250, 251, 252, 256, 257, 258, 259, 261, 264, 265, 266, 267, 268, 269, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 286, 287, 288,

				289, 290, 291, 292, 295, 296, 297, 300, 301, 302, 303, 304
PI3K γ	Compound No. 1, 4, 5, 18, 38, 43, 60, 69, 169, 172, 196, 197, 198, 200, 201, 202, 204, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 217, 218, 219, 220, 221, 222, 223, 225, 228, 230, 236, 237, 239, 245, 266, 285, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304	Compound No. 17, 34, 35, 37, 38, 40, 42, 57, 61, 65, 91, 92, 94, 105, 107, 140, 164, 170, 175, 179, 184, 188, 190, 191, 193, 199,203, 216, 224, 229, 232, 235, 241, 243, 244, 251, 253, 254, 255, 263, 264, 268, 270, 272, 276, 282, 287	Compound No. 2, 8, 9, 10, 11, 14, 15, 20, 22, 27, 28, 39, 41, 46, 47, 49, 51, 55, 58, 66, 70, 71, 73, 76, 78, 80, 93, 98, 99, 100, 103, 104, 106, 108, 109, 161, 162, 163, 165, 166, 180, 192, 205, 226, 227, 231, 233, 240, 242, 249, 250, 252, 256, 257, 259, 262, 265, 273, 274, 275, 278, 280, 286, 288, 291	Compound No. 3, 6, 7, 12, 13, 16, 19, 21, 23, 24, 25, 26, 29, 30, 31, 33, 36, 44, 45, 48, 50, 52, 53, 54, 56, 59, 62, 63, 64, 67, 68, 72, 74, 75, 77, 79, 81, 82, 83, 84, 86, 87, 88, 89, 90, 95, 96, 97, 101, 102, 142, 145, 146, 147, 148, 149, 150, 151, 152, 160, 167, 168, 171, 173, 174, 176, 177, 178. 183, 189, 194, 195, 234, 238, 246, 247, 248, 258, 260, 261, 267, 269, 271, 277, 279, 281, 283, 284, 289, 290, 292
PI3K α	Compound No. 6, 8, 9, 10,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 54, 55, 56, 57, 58, 59, 60, 61, 62, 64, 65, 67, 68, 69, 70, 71, 72, 73, 74, 79, 80, 81,	Compound No. 3, 7, 63, 66, 84, 86, 89, 90, 97, 108, 113, 115, 152, 168, 171, 173, 189, 194, 296	Compound No. 53, 95, 101, 102, 145, 147, 149, 151, 177	Compound No. 142, 148, 150, 153, 154, 155, 156, 157, 158, 159, 176

	82, 83, 85, 87, 88, 91, 93, 96, 98, 99, 100, 103, 104, 105, 106, 107, 109, 110, 111, 112, 114, 140, 146, 160, 161, 162, 163, 164, 165, 166, 167, 169, 170, 172, 174, 175, 179, 180, 183, 184, 188, 190, 191, 192, 193 , 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 297, 298, 299, 300, 301, 302, 303, 304			
PI3K β	Compound No. 8, 9, 10, 11, 14, 21, 22, 24, 26, 27, 28,	Compound No. 3, 12, 13, 23, 25, 53, 55, 58, 61, 63, 65,	Compound No. 7, 62, 66, 82, 89, 90, 95, 97, 100, 102,	Compound No. 101, 142, 155, 156, 157

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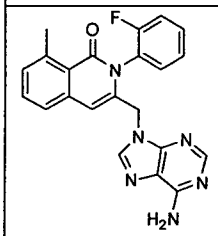
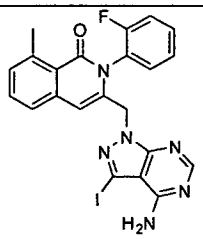
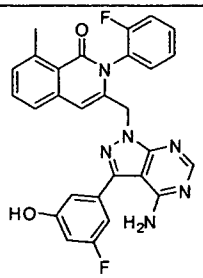
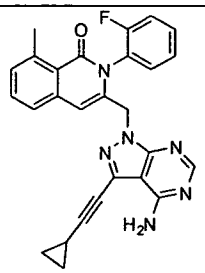
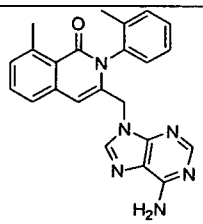
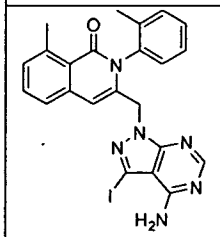
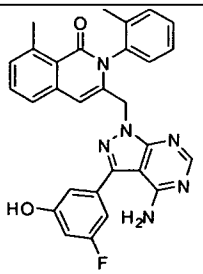
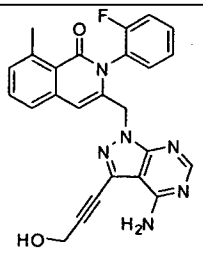
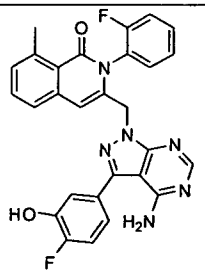
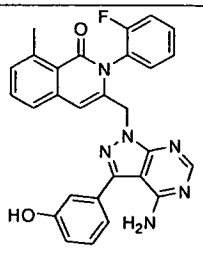
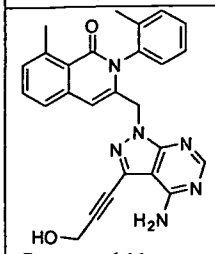
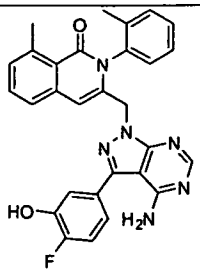
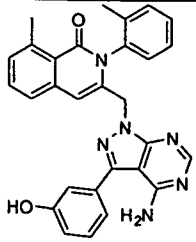
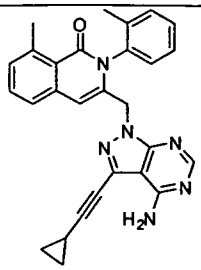
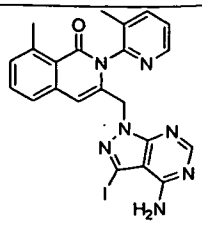
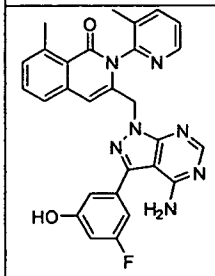
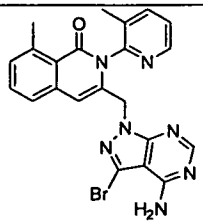
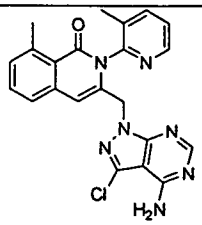
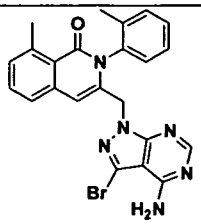
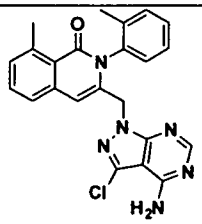
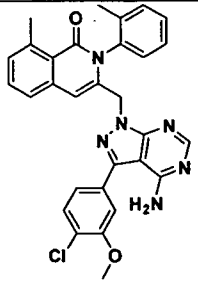
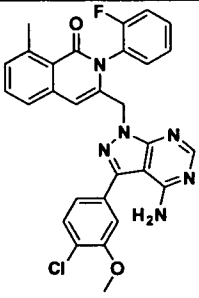
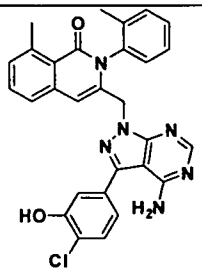
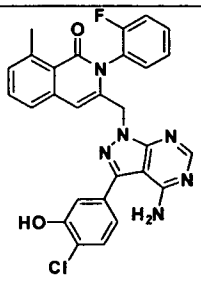
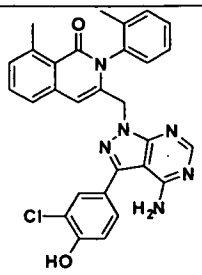
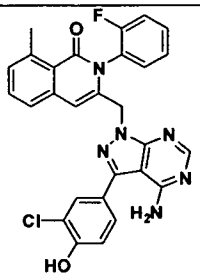
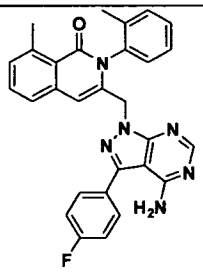
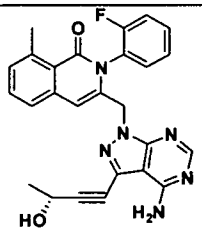
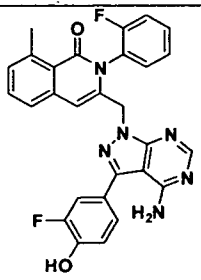
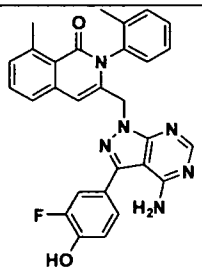
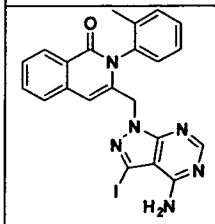
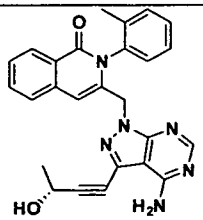
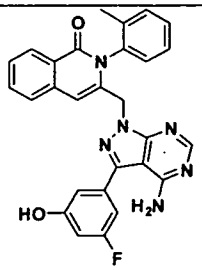
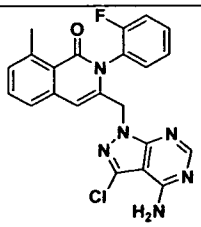
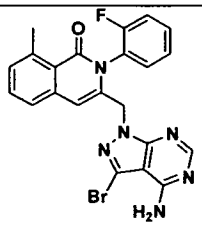
B cell proliferation EC_{50} (nM)	Compound No. 38, 162, 205, 228, 229	Compound No. 1, 2, 5, 22, 26, 27, 39, 40, 43, 49, 57, 71, 87, 112, 200, 201, 202, 208, 209,	Compound No. 4, 8, 9, 10, 11, 14, 15, 18, 19, 20, 21, 24, 25, 28, 29, 30, 31, 32, 34, 35, 36,	Compound No. 3, 6, 7, 12, 13, 16, 17, 23, 33, 37, 44, 48, 53, 54, 55, 62, 63, 66, 67, 68, 72,

		210, 211, 212, 213, 214, 215, 217, 218, 219, 220, 222, 223, 232, 233, 237, 262, 263, 293	41, 42, 45, 46, 47, 50, 51, 61, 69, 70, 76, 77, 78, 79, 80, 85, 86, 91, 98, 100, 103, 104, 105, 106, 107, 110, 111, 114, 119, 124, 133, 135, 145, 152, 161, 162, 163, 169, 203, 204, 206, 207, 216, 221, 224, 225, 226, 230, 243, 245, 246, 251, 252, 253, 254, 256, 257, 260, 261, 264, 265, 272, 276, 287, 288	73, 74, 75, 81, 82, 83, 84, 88, 89, 90, 93, 95, 96, 97, 99, 101, 102, 108, 109, 113, 115, 123, 125, 126, 128, 134, 136, 137, 138, 139, 141, 142, 144, 146, 147, 148, 149, 150, 151, 153, 154, 155, 156, 157, 158, 159, 160, 166, 167, 168, 170, 171, 173, 174, 176, 177, 178, 180, 189, 192, 194, 195, 199, 227, 231, 234, 235, 236, 238, 242, 244, 247, 248, 249, 250, 255, 258, 259, 266, 268, 271, 275, 277, 278, 279, 280, 281, 282, 283, 284, 286, 289, 290, 291, 292, 295, 296, 297

Table 5. Structures of the Compounds for the IC50 results described in Table 4.

Structure				
 Compound 1	 Compound 2	 Compound 3	 Compound 4	 Compound 5
 Compound 6	 Compound 7	 Compound 8	 Compound 9	 Compound 10

Structure				
 Compound 11	 Compound 12	 Compound 13	 Compound 14	 Compound 15
 Compound 16	 Compound 17	 Compound 18	 Compound 19	 Compound 20
 Compound 21	 Compound 22	 Compound 23	 Compound 24	 Compound 25
 Compound 26	 Compound 27	 Compound 28	 Compound 29	 Compound 30
 Compound 31	 Compound 32	 Compound 33	 Compound 34	 Compound 35

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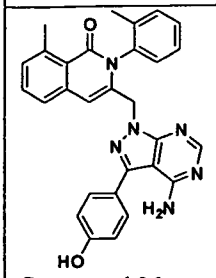
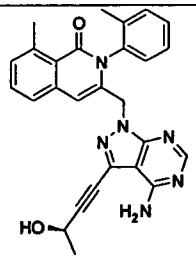
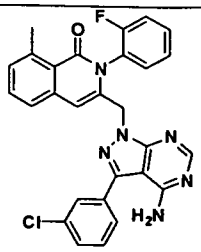
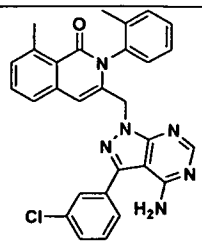
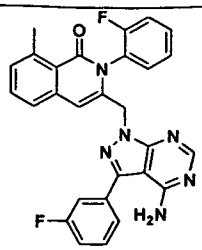
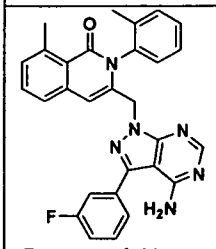
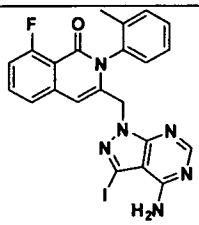
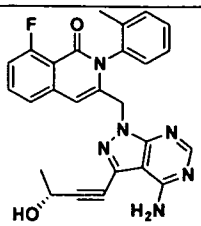
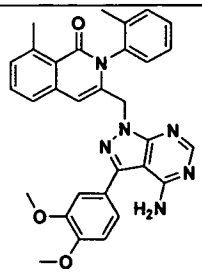
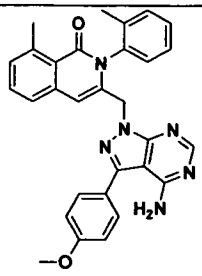
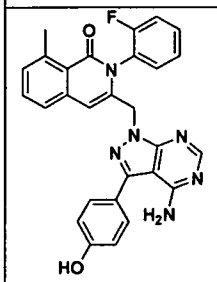
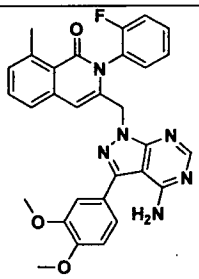
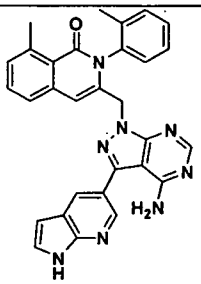
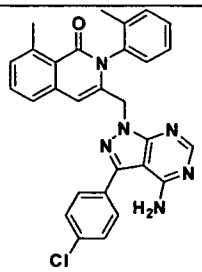
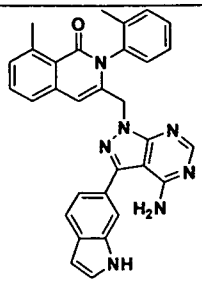
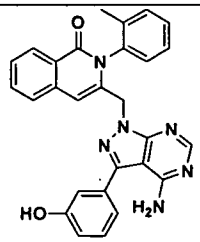
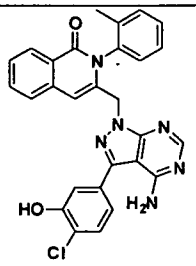
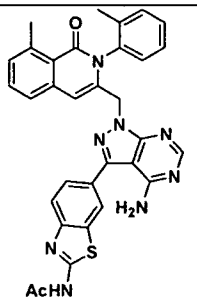
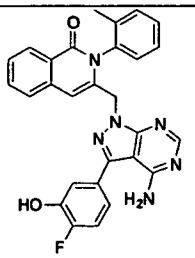
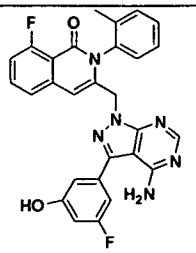
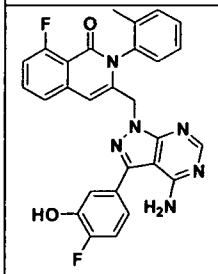
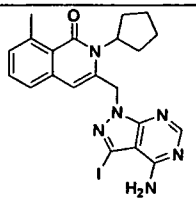
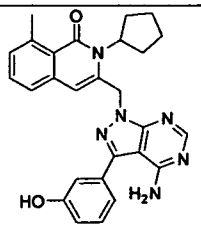
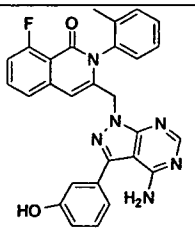
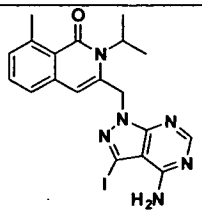
 Compound 36	 Compound 37	 Compound 38	 Compound 39	 Compound 40
 Compound 41	 Compound 42	 Compound 43	 Compound 44	 Compound 45
 Compound 46	 Compound 47	 Compound 48	 Compound 49	 Compound 50
 Compound 51	 Compound 52	 Compound 53	 Compound 54	 Compound 55
 Compound 56	 Compound 57	 Compound 58	 Compound 59	 Compound 60

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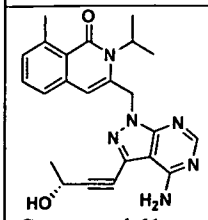
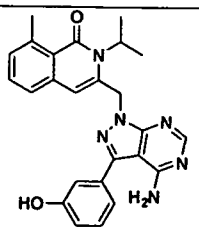
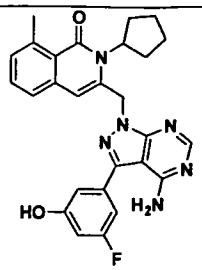
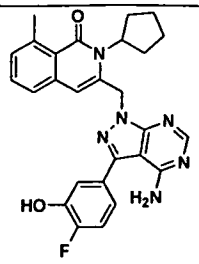
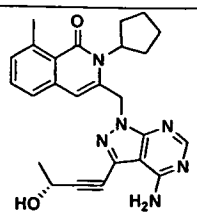
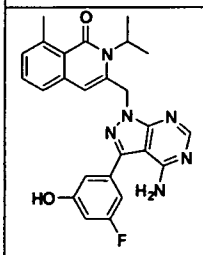
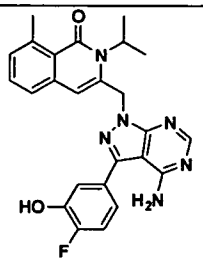
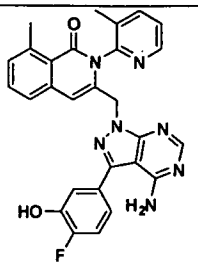
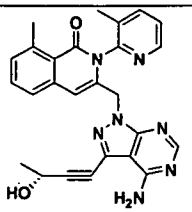
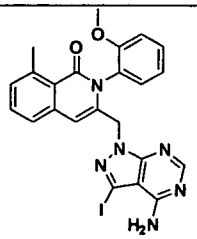
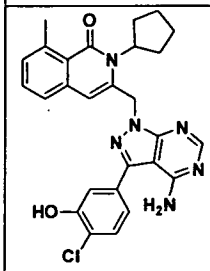
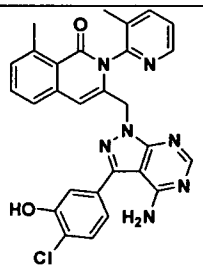
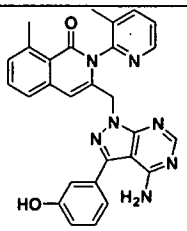
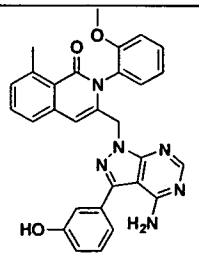
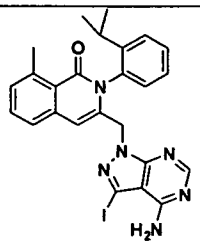
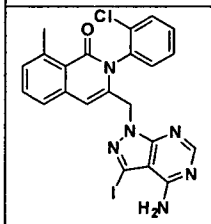
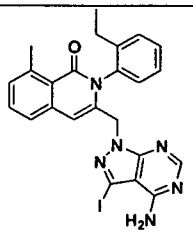
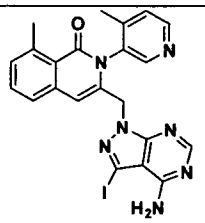
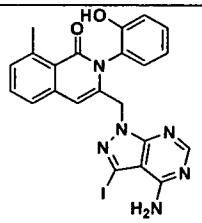
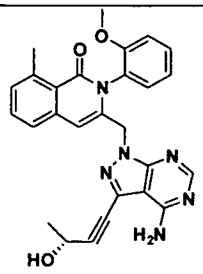
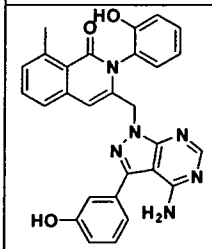
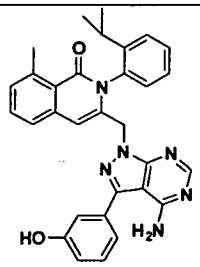
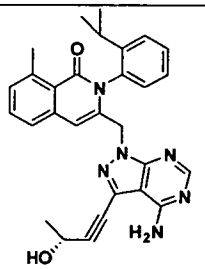
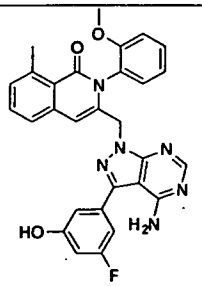
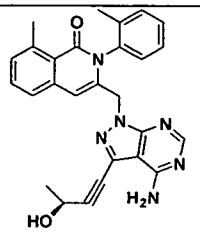
 Compound 61	 Compound 62	 Compound 63	 Compound 64	 Compound 65
 Compound 66	 Compound 67	 Compound 68	 Compound 69	 Compound 70
 Compound 71	 Compound 72	 Compound 73	 Compound 74	 Compound 75
 Compound 76	 Compound 77	 Compound 78	 Compound 79	 Compound 80
 Compound 81	 Compound 82	 Compound 83	 Compound 84	 Compound 85

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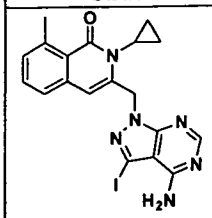
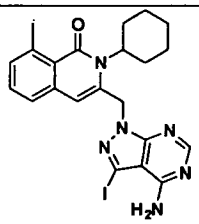
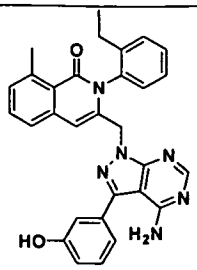
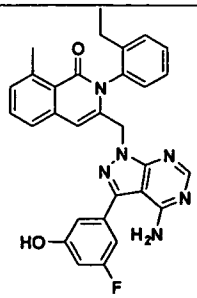
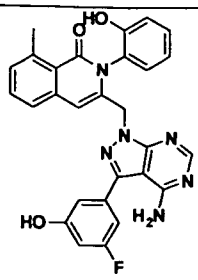
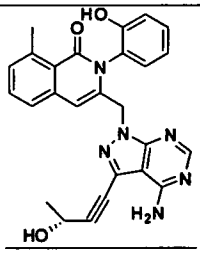
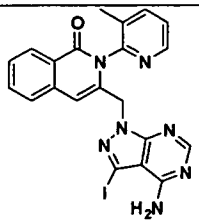
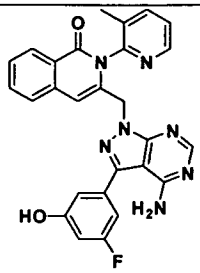
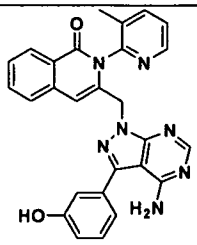
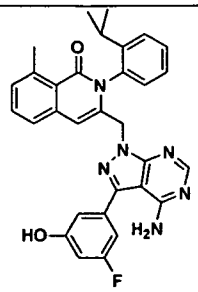
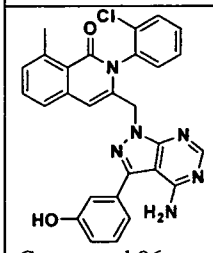
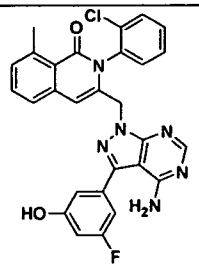
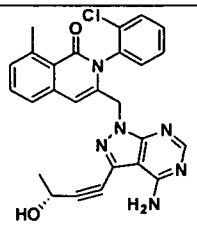
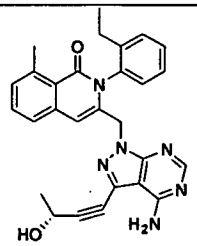
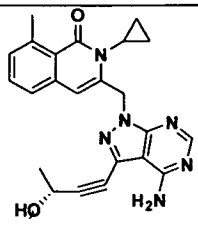
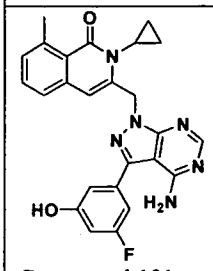
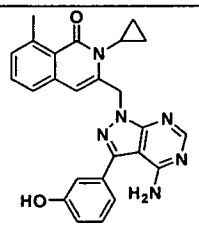
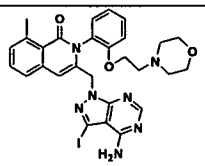
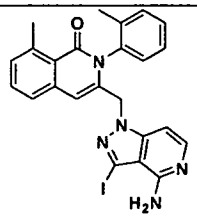
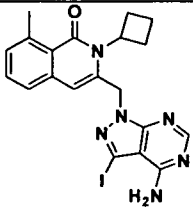
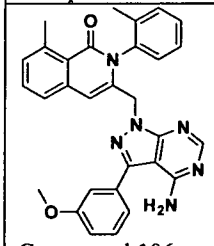
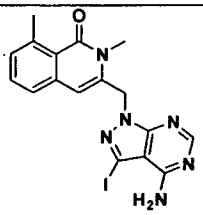
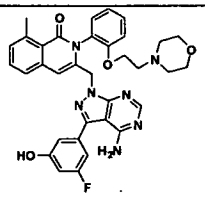
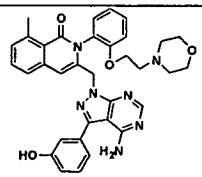
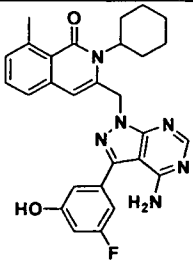
 Compound 86	 Compound 87	 Compound 88	 Compound 89	 Compound 90
 Compound 91	 Compound 92	 Compound 93	 Compound 94	 Compound 95
 Compound 96	 Compound 97	 Compound 98	 Compound 99	 Compound 100
 Compound 101	 Compound 102	 Compound 103	 Compound 104	 Compound 105
 Compound 106	 Compound 107	 Compound 108	 Compound 109	 Compound 110

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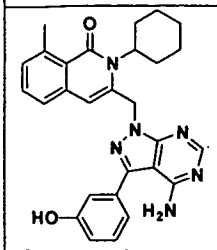
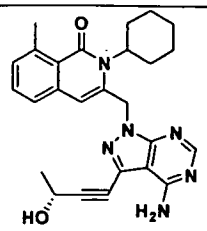
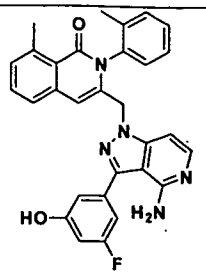
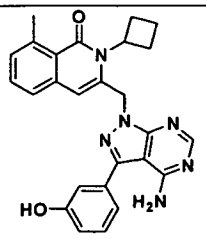
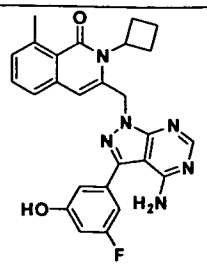
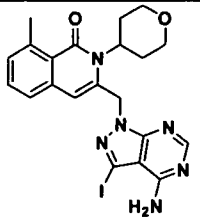
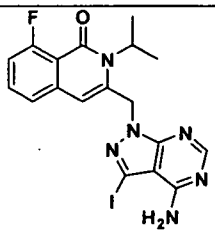
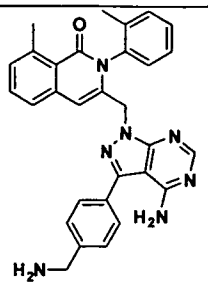
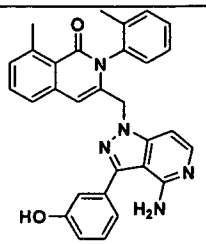
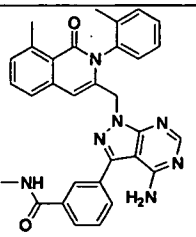
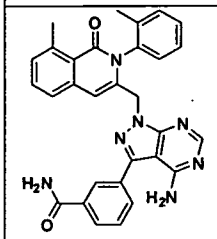
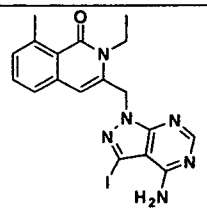
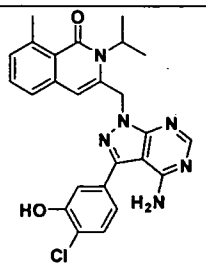
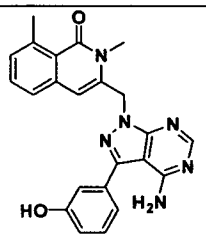
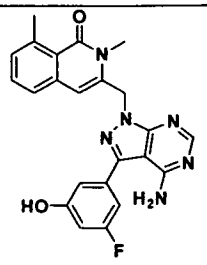
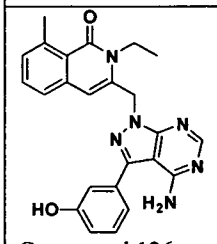
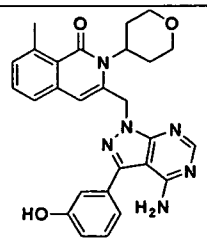
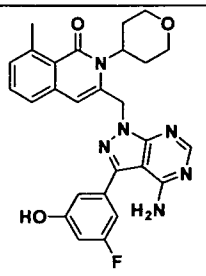
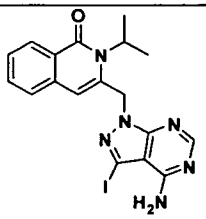
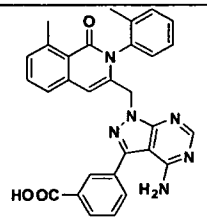
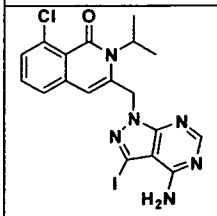
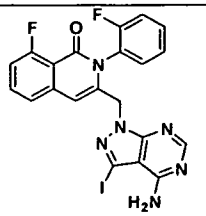
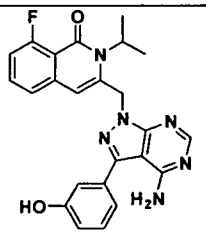
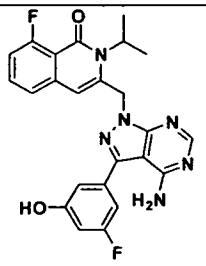
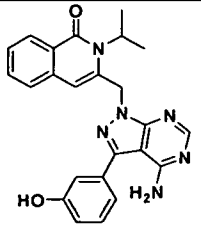
 Compound 111	 Compound 112	 Compound 113	 Compound 114	 Compound 115
 Compound 116	 Compound 117	 Compound 118	 Compound 119	 Compound 120
 Compound 121	 Compound 122	 Compound 123	 Compound 124	 Compound 125
 Compound 126	 Compound 127	 Compound 128	 Compound 129	 Compound 130
 Compound 131	 Compound 132	 Compound 133	 Compound 134	 Compound 135

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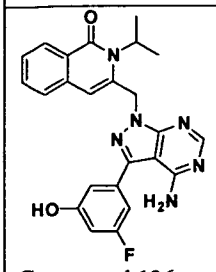
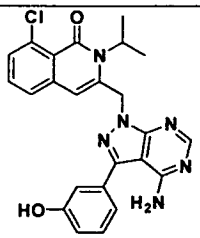
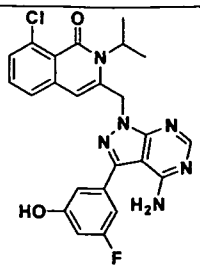
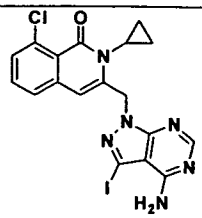
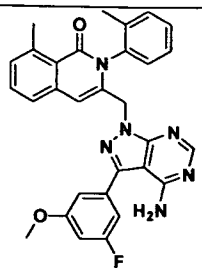
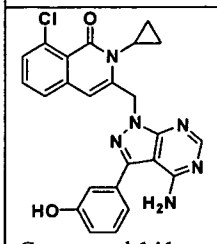
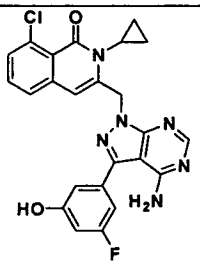
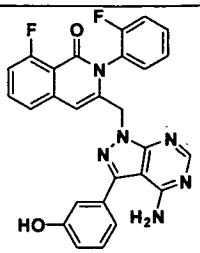
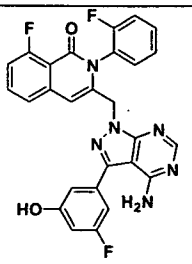
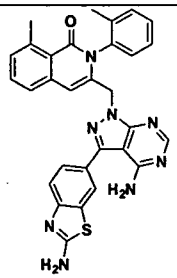
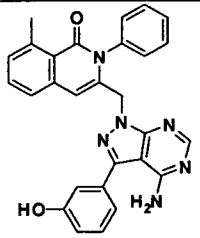
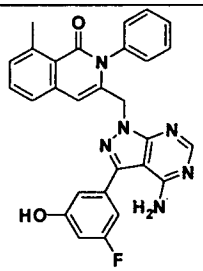
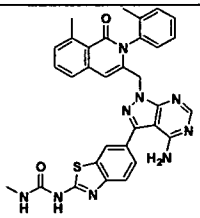
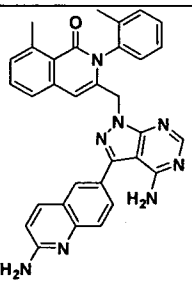
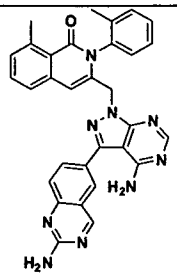
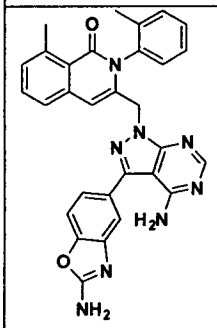
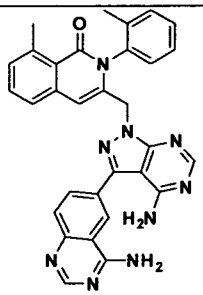
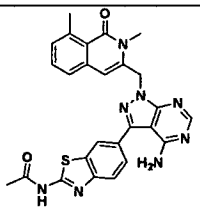
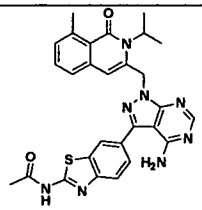
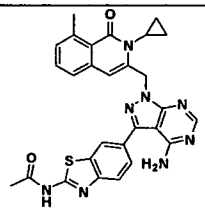
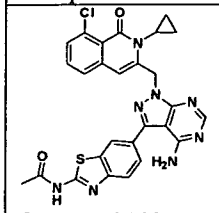
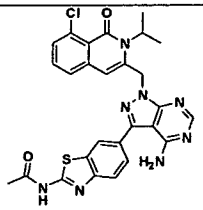
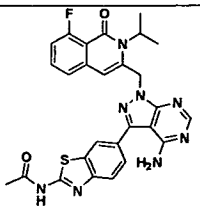
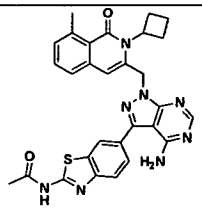
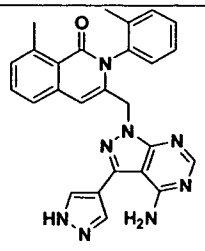
 Compound 136	 Compound 137	 Compound 138	 Compound 139	 Compound 140
 Compound 141	 Compound 142	 Compound 143	 Compound 144	 Compound 145
 Compound 146	 Compound 147	 Compound 148	 Compound 149	 Compound 150
 Compound 151	 Compound 152	 Compound 153	 Compound 154	 Compound 155
 Compound 156	 Compound 157	 Compound 158	 Compound 159	 Compound 160

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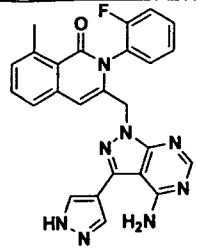
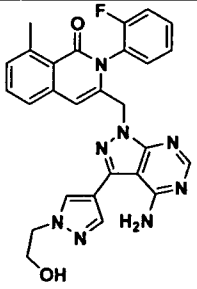
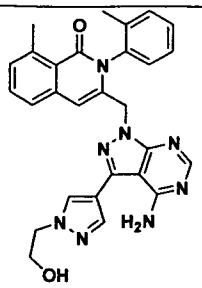
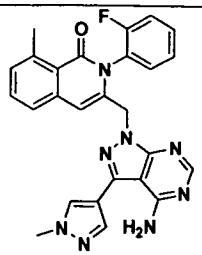
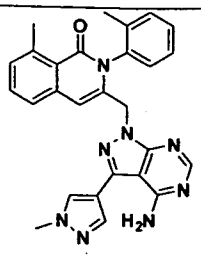
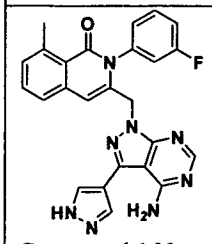
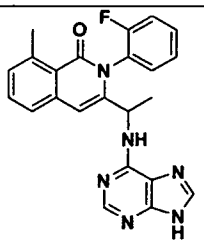
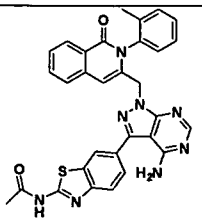
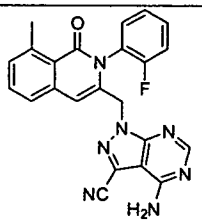
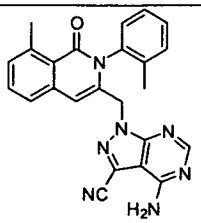
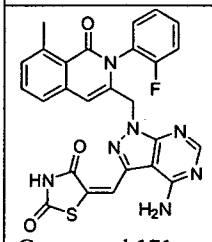
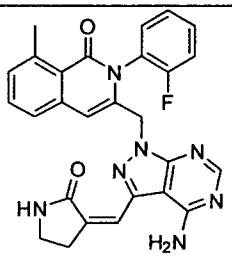
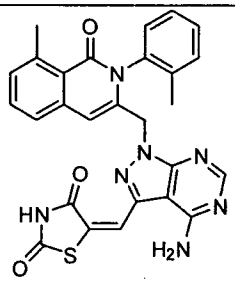
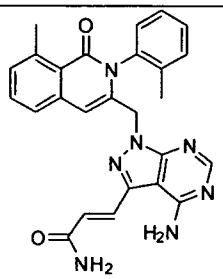
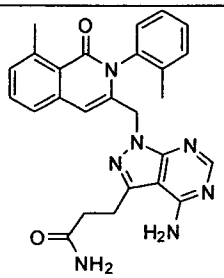
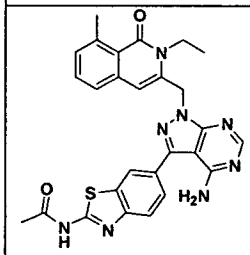
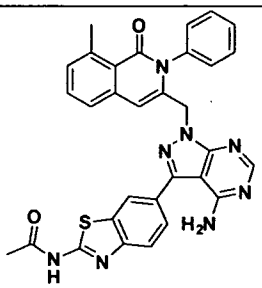
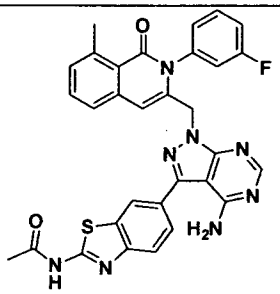
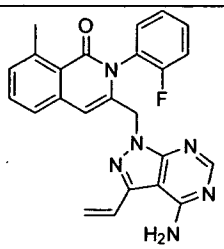
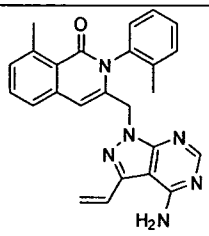
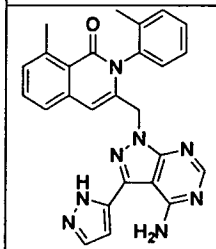
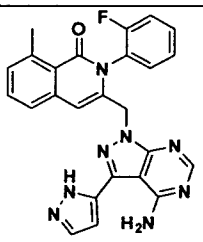
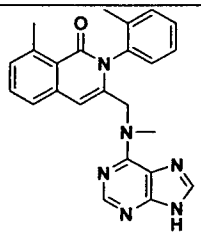
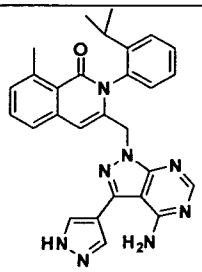
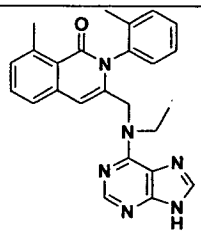
 Compound 161	 Compound 162	 Compound 163	 Compound 164	 Compound 165
 Compound 166	 Compound 167	 Compound 168	 Compound 169	 Compound 170
 Compound 171	 Compound 172	 Compound 173	 Compound 174	 Compound 175
 Compound 176	 Compound 177	 Compound 178	 Compound 179	 Compound 180
 Compound 183	 Compound 184	 Compound 188	 Compound 189	 Compound 190

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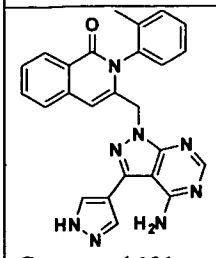
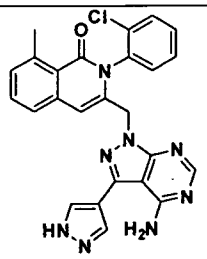
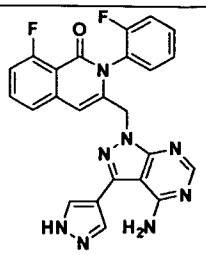
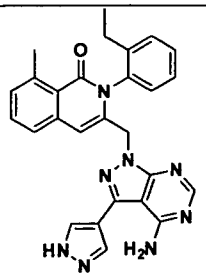
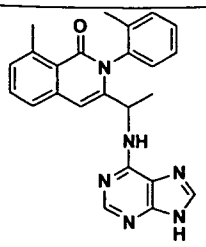
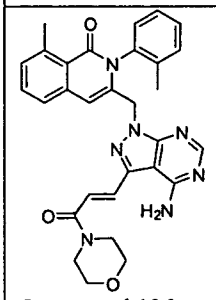
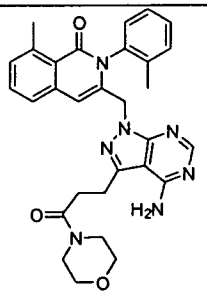
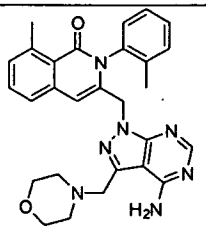
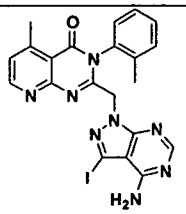
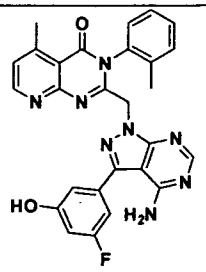
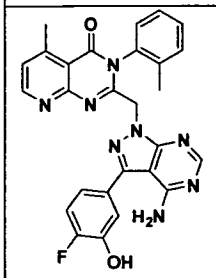
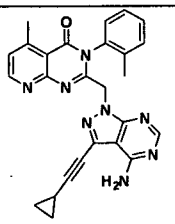
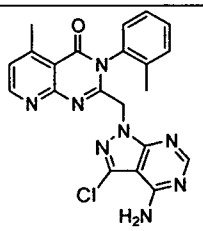
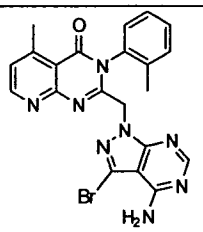
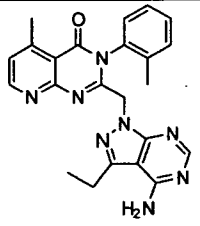
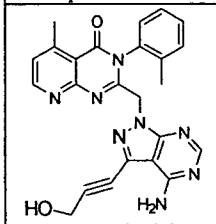
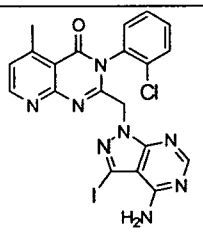
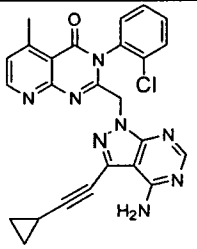
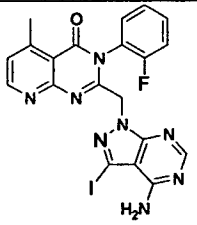
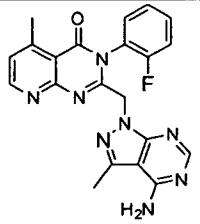
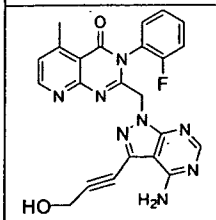
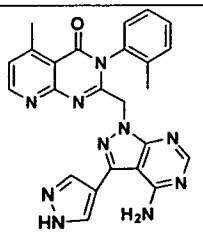
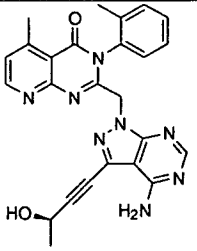
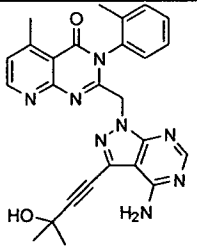
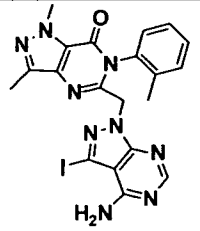
 Compound 191	 Compound 192	 Compound 193	 Compound 194	 Compound 195
 Compound 196	 Compound 197	 Compound 198	 Compound 199	 Compound 200
 Compound 201	 Compound 202	 Compound 203	 Compound 204	 Compound 205
 Compound 206	 Compound 207	 Compound 208	 Compound 209	 Compound 210
 Compound 211	 Compound 212	 Compound 213	 Compound 214	 Compound 215

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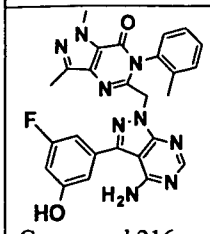
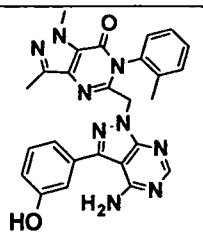
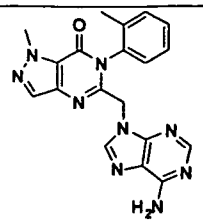
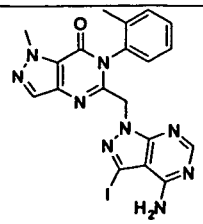
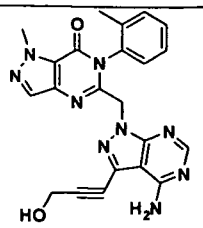
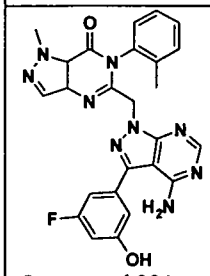
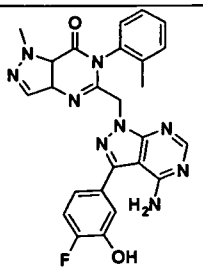
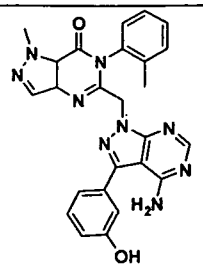
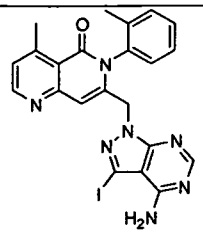
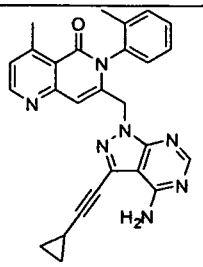
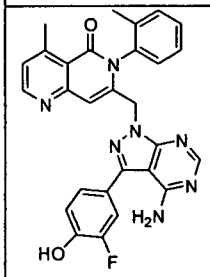
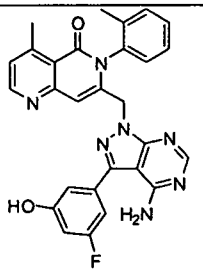
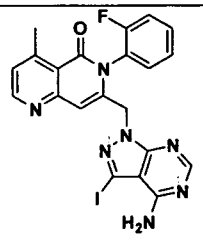
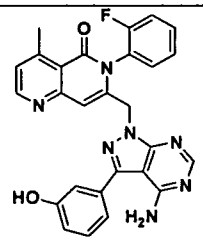
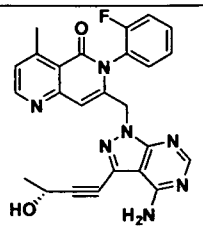
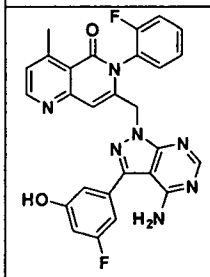
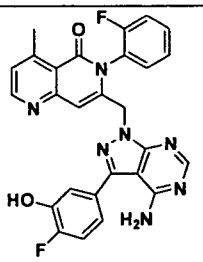
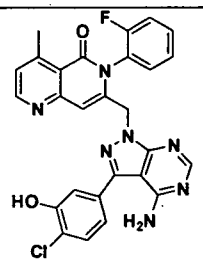
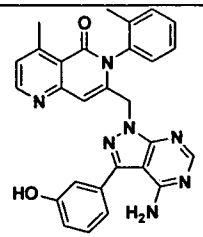
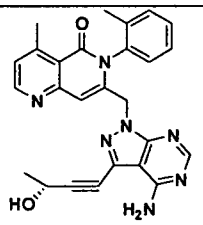
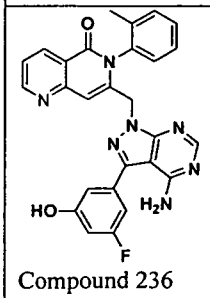
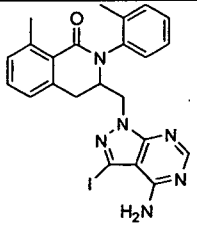
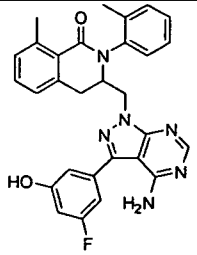
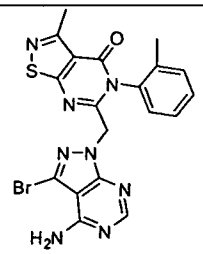
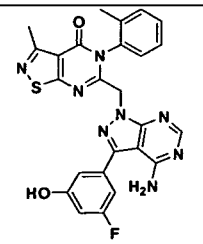
 Compound 216	 Compound 217	 Compound 218	 Compound 219	 Compound 220
 Compound 221	 Compound 222	 Compound 223	 Compound 224	 Compound 225
 Compound 226	 Compound 227	 Compound 228	 Compound 229	 Compound 230
 Compound 231	 Compound 232	 Compound 233	 Compound 234	 Compound 235
 Compound 236	 Compound 237	 Compound 238	 Compound 239	 Compound 240

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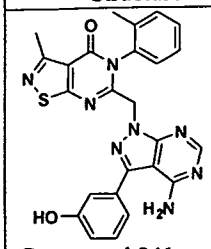
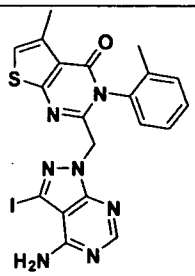
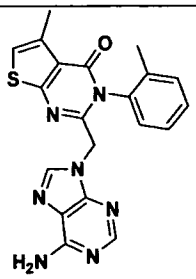
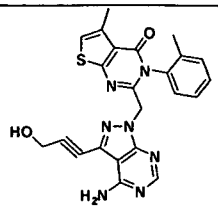
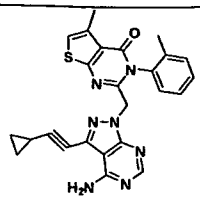
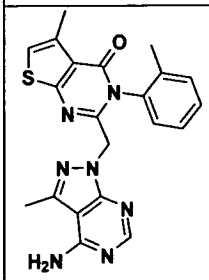
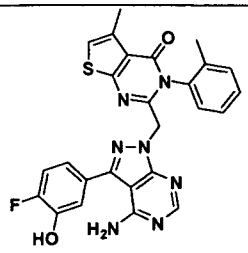
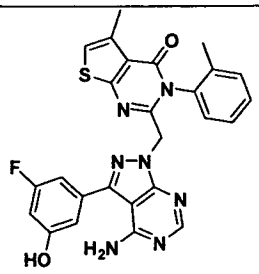
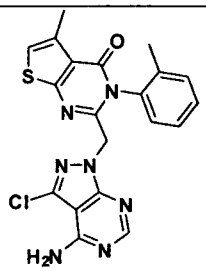
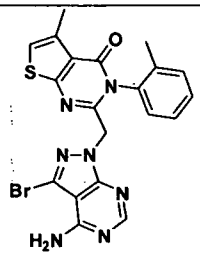
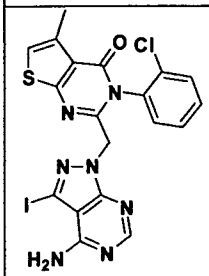
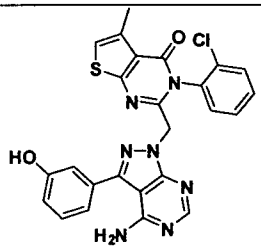
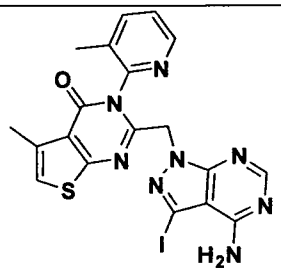
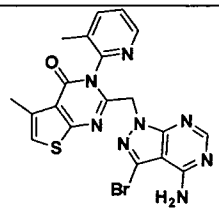
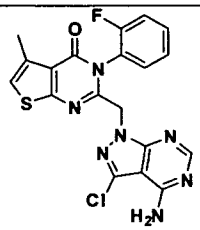
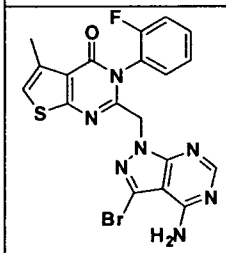
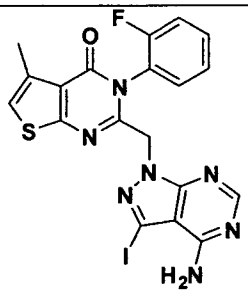
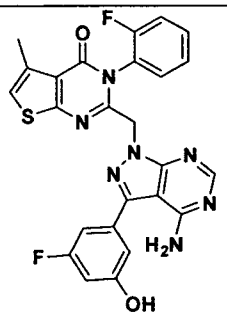
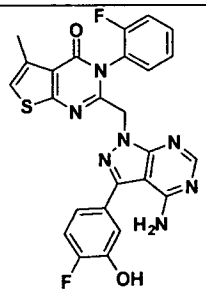
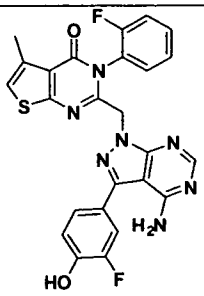
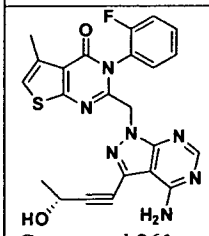
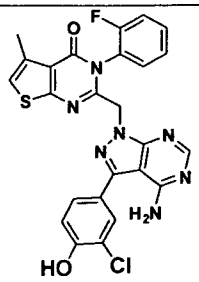
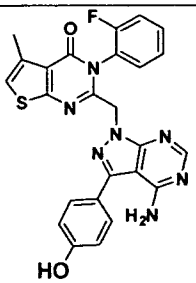
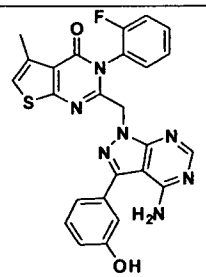
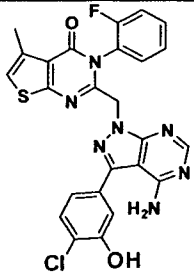
 Compound 241	 Compound 242	 Compound 243	 Compound 244	 Compound 245
 Compound 246	 Compound 247	 Compound 248	 Compound 249	 Compound 250
 Compound 251	 Compound 252	 Compound 253	 Compound 254	 Compound 255
 Compound 256	 Compound 257	 Compound 258	 Compound 259	 Compound 260
 Compound 261	 Compound 262	 Compound 263	 Compound 264	 Compound 265

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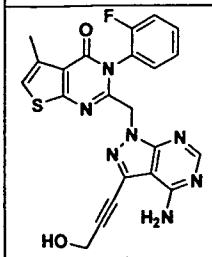
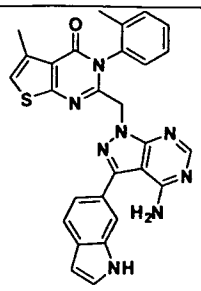
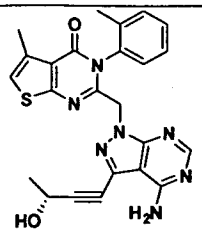
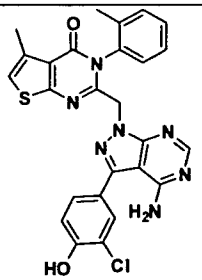
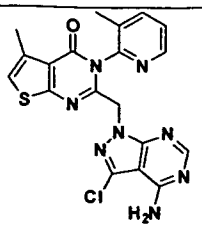
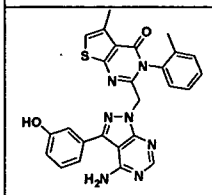
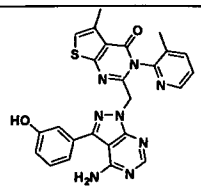
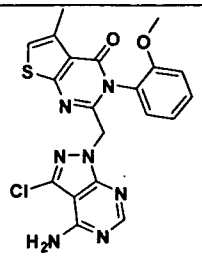
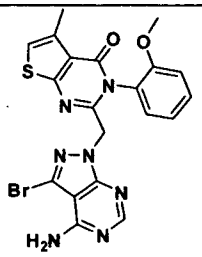
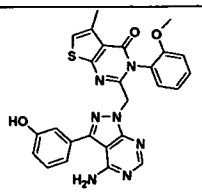
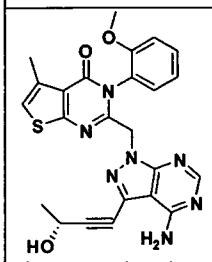
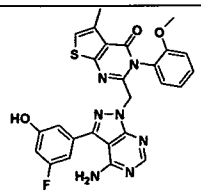
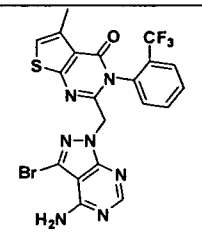
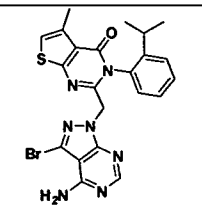
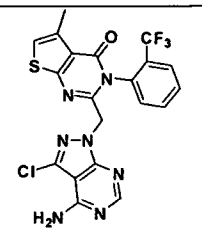
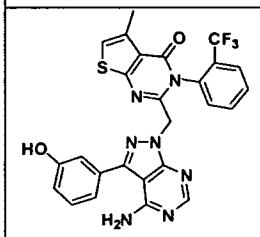
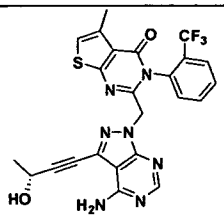
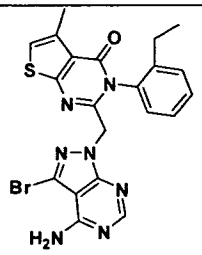
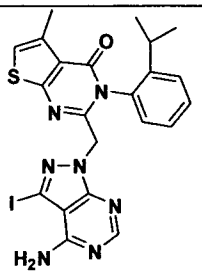
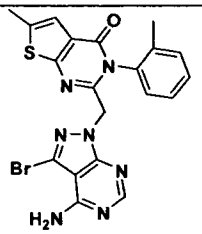
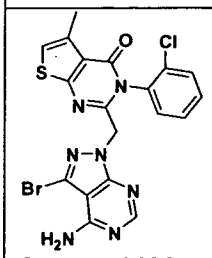
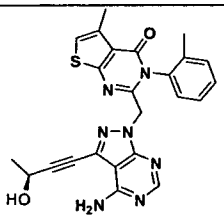
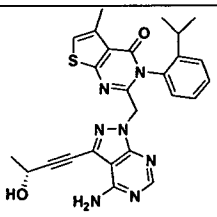
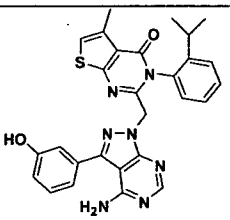
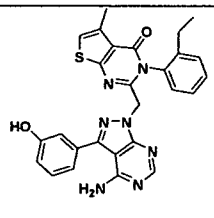
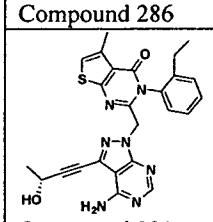
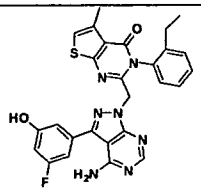
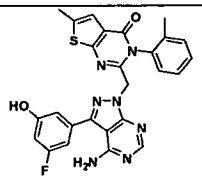
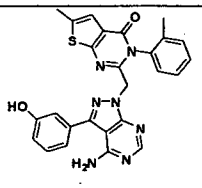
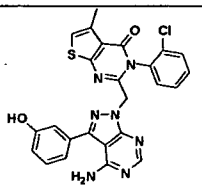
 Compound 266	 Compound 267	 Compound 268	 Compound 269	 Compound 270
 Compound 271	 Compound 272	 Compound 273	 Compound 274	 Compound 275
 Compound 276	 Compound 277	 Compound 278	 Compound 279	 Compound 280
 Compound 281	 Compound 282	 Compound 283	 Compound 284	 Compound 285
 Compound 286	 Compound 287	 Compound 288	 Compound 289	 Compound 290
 Compound 291	 Compound 292	 Compound 293	 Compound 294	 Compound 295

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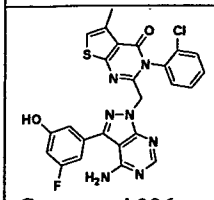
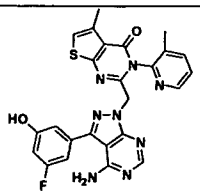
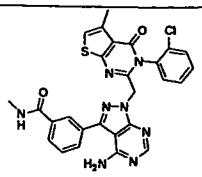
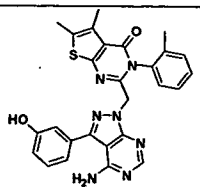
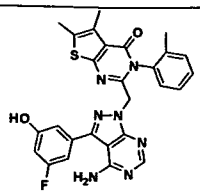
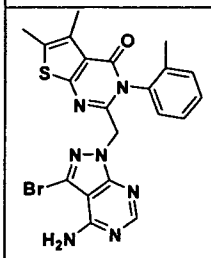
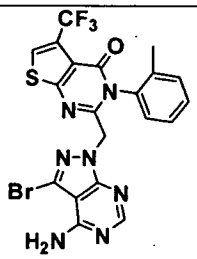
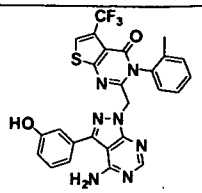
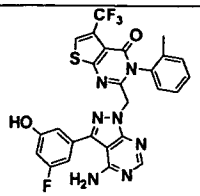
 Compound 296	 Compound 297	 Compound 298	 Compound 299	 Compound 300
 Compound 301	 Compound 302	 Compound 303	 Compound 304	

Example 16: Expression and Inhibition Assays of p110α/p85α, p110β/p85α, p110δ/p85α, and p110γ:

[00524] Class I PI3-Ks can be either purchased (p110α/p85α, p110β/p85α, p110δ/p85α from Upstate, and p110γ from Sigma) or expressed as previously described (Knight et al., 2004). IC50 values are measured using either a standard TLC assay for lipid kinase activity (described below) or a high-throughput membrane capture assay. Kinase reactions are performed by preparing a reaction mixture containing kinase, inhibitor (2% DMSO final concentration), buffer (25 mM HEPES, pH 7.4, 10 mM MgCl2), and freshly sonicated phosphatidylinositol (100 μg/ml). Reactions are initiated by the addition of ATP containing 10 μCi of γ-32P-ATP to a final concentration 10 or 100 μM and allowed to proceed for 5 minutes at room temperature. For TLC analysis, reactions are then terminated by the addition of 105 μl 1N HCl followed by 160 μl CHCl3:MeOH (1:1). The biphasic mixture is vortexed, briefly centrifuged, and the organic phase is transferred to a new tube using a gel loading pipette tip precoated with $CHCl_3$. This extract is spotted on TLC plates and developed for 3 – 4 hours in a 65:35 solution of n-propanol:1M acetic acid. The TLC plates are then dried, exposed to a phosphorimager screen (Storm, Amersham), and quantitated. For each compound, kinase activity is measured at 10 – 12 inhibitor concentrations representing two-fold dilutions from the highest concentration tested (typically, 200 μM). For compounds showing significant activity, IC50 determinations are repeated two to four times, and the reported value is the average of these independent measurements.

[00525] Other commercial kits or systems for assaying PI3-K activities are available. The commercially available kits or systems can be used to screen for inhibitors and/or agonists of PI3-Ks including but not limited to PI 3-Kinase α, β, δ, and γ. An exemplary system is PI 3-Kinase (human) HTRF™ Assay from Upstate. The assay can be carried out according to the procedures suggested by the manufacturer. Briefly, the assay is a time resolved FRET assay that indirectly measures PIP3 product formed by the activity of a PI3-K. The kinase reaction is performed in a microtiter plate (e.g., a 384 well microtiter plate). The total reaction volume is approximately 20ul per well. In the first step, each well receives 2ul of test compound in 20% dimethylsulphoxide resulting in a 2% DMSO final concentration. Next, approximately 14.5ul of a kinase/PIP2 mixture (diluted in 1X reaction buffer) is added per well for a final concentration of 0.25-0.3ug/ml kinase and 10uM PIP2. The plate is sealed and incubated for 15 minutes at room temperature. To start the reaction, 3.5ul of ATP (diluted in 1X reaction buffer) is added per well for a final concentration of 10uM ATP. The plate is sealed and incubated for 1 hour at room temperature. The reaction is stopped by adding 5ul of Stop Solution per well and then 5ul of Detection Mix is added per well. The plate is sealed,

incubated for 1 hour at room temperature, and then read on an appropriate plate reader. Data is analyzed and IC50s are generated using GraphPad Prism 5.

Example 17: Expression and Inhibition Assays of Abl

[00526] The cross-activity or lack thereof of one or more compounds of the present invention against Abl kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be assayed in triplicate against recombinant full-length Abl or Abl (T315I) (Upstate) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 200 μM ATP (2.5 μCi of γ-32P-ATP), and 0.5 mg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK is used as phosphoacceptor (200 μM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 18: Expression and Inhibition Assays of Hck

[00527] The cross-activity or lack thereof of one or more compounds of the present invention against Hck kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be assayed in triplicate against recombinant full-length Hck in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 200 μM ATP (2.5 μCi of γ-32P-ATP), and 0.5 mg/mL BSA. The optimized Src family kinase peptide substrate EIYGEFKKK is used as phosphoacceptor (200 μM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 19: Expression and Inhibition Assays of Inulsin Receptor (IR)

[00528] The cross-activity or lack thereof of one or more compounds of the present invention against IR receptor kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be assayed in triplicate against recombinant insulin receptor kinase domain (Upstate) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 10 mM MnCl2, 200 μM ATP (2.5 μCi of γ-32P-ATP), and 0.5 mg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 20: Expression and Inhibition Assays of Src

[00529] The cross-activity or lack thereof of one or more compounds of the present invention against Src kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be assayed in triplicate against recombinant full-length Src or Src (T338I) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 200 μM ATP (2.5 μCi of γ-32P-ATP), and 0.5 mg/mL BSA. The optimized Src family kinase peptide substrate EIYGEFKKK is used as phosphoacceptor (200 μM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

Example 21: Expression and Inhibition Assays of DNA-PK (DNAK)

[00530] The cross-activity or lack thereof of one or more compounds of the present invention against DNAK kinase can be measured according to any procedures known in the art. DNA-PK can be purchased from Promega and assayed using the DNA-PK Assay System (Promega) according to the manufacturer's instructions.

Example 22: Expression and Inhibition Assays mTOR

[00531] The cross-activity or lack thereof of one or more compounds of the present invention against mTor can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein

can be tested against recombinant mTOR (Invitrogen) in an assay containing 50 mM HEPES, pH 7.5, 1mM EGTA, 10 mM MgCl2, 2.5 mM, 0.01% Tween, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Rat recombinant PHAS-1/4EBP1 (Calbiochem; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

[00532] Other kits or systems for assaying mTOR activity are commercially available. For instance, one can use Invitrogen's LanthaScreen™ Kinase assay to test the inhibitors of mTOR disclosed herein. This assay is a time resolved FRET platform that measures the phosphorylation of GFP labeled 4EBP1 by mTOR kinase. The kinase reaction is performed in a white 384 well microtiter plate. The total reaction volume is 20ul per well and the reaction buffer composition is 50mM HEPES pH7.5, 0.01% Polysorbate 20, 1mM EGTA, 10mM MnCl2, and 2mM DTT. In the first step, each well receives 2ul of test compound in 20% dimethylsulphoxide resulting in a 2% DMSO final concentration. Next, 8ul of mTOR diluted in reaction buffer is added per well for a 60ng/ml final concentration. To start the reaction, 10ul of an ATP/GFP-4EBP1 mixture (diluted in reaction buffer) is added per well for a final concentration of 10uM ATP and 0.5uM GFP-4EBP1. The plate is sealed and incubated for 1 hour at room temperature. The reaction is stopped by adding 10ul per well of a Tb-anti-pT46 4EBP1 antibody/EDTA mixture (diluted in TR-FRET buffer) for a final concentration of 1.3nM antibody and 6.7mM EDTA. The plate is sealed, incubated for 1 hour at room temperature, and then read on a plate reader set up for LanthaScreen™ TR-FRET. Data is analyzed and IC50s are generated using GraphPad Prism 5.

Example 23: Expression and Inhibition Assays of Vascular endothelial growth receptor

[00533] The cross-activity or lack thereof of one or more compounds of the present invention against VEGF receptor can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant KDR receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 0.1% BME, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 24: Expression and Inhibition Assays of Ephrin receptor B4 (EphB4)

[00534] The cross-activity or lack thereof of one or more compounds of the present invention against EphB4 can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant Ephrin receptor B4 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 0.1% BME, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 25: Expression and Inhibition Assays of Epidermal growth factor receptor (EGFR)

[00535] The cross-activity or lack thereof of one or more compounds of the present invention against EGFR kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant EGF receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 0.1% BME, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed

with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 26: Expression and Inhibition Assays of KIT Assay

[00536] The cross-activity or lack thereof of one or more compounds of the present invention against KIT kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant KIT kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 1mM DTT, 10mM MnCl2, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 27: Expression and Inhibition Assays of RET

[00537] The cross-activity or lack thereof of one or more compounds of the present invention against RET kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant RET kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 2.5mM DTT,10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK is used as phosphoacceptor (200 μM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 28: Expression and Inhibition Assays of Platelet derived growth factor receptor (PDGFR)

[00538] The cross-activity or lack thereof of one or more compounds of the present invention against PDGFR kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant PDG receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 2.5mM DTT,10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK is used as phosphoacceptor (200 μM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 29: Expression and Inhibition Assays of FMS-related tyrosine kinase 3 (FLT-3)

[00539] The cross-activity or lack thereof of one or more compounds of the present invention against FLT-3 kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant FLT-3 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 2.5mM DTT,10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK is used as phosphoacceptor (200 μM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 30: Expression and Inhibition Assays of TEK receptor tyrosine kinase (TIE2)

[00540] The cross-activity or lack thereof of one or more compounds of the present invention against TIE2 kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant TIE2 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 2mM DTT, 10mM MnCl2, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed

with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 31: B Cell Activation and Proliferation Assay

[00541] The ability of one or more subject compounds to inhibit B cell activitation and proliferation is determined according to standard procedures known in the art. For example, an in vitro cellular proliferation assay is established that measures the metabolic activity of live cells. The assay is performed in a 96 well microtiter plate using Alamar Blue reduction. Balb/c splenic B cells are purified over a Ficoll-Paque™ PLUS gradient followed by magnetic cell separation using a MACS B cell Isolation Kit (Miletenyi). Cells are plated in 90ul at 50,000 cells/well in B Cell Media (RPMI + 10%FBS + Penn/Strep + 50uM bME + 5mM HEPES). A compound disclosed herein is diluted in B Cell Media and added in a 10ul volume. Plates are incubated for 30min at 37C and 5% CO_2 (0.2% DMSO final concentration). A 50ul B cell stimulation cocktail is then added containing either 10ug/ml LPS or 5ug/ml F(ab')2 Donkey anti-mouse IgM plus 2ng/ml recombinant mouse IL4 in B Cell Media. Plates are incubated for 72 hours at 37^0C and 5% CO_2. A volume of 15uL of Alamar Blue reagent is added to each well and plates are incubated for 5 hours at 37C and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC50 or EC50 values are calculated using GraphPad Prism 5.

Example 32: Tumor Cell Line Proliferation Assay

[00542] The ability of one or more subject compounds to inhibit tumor cell line proliferation is determined according to standard procedures known in the art. For instance, an in vitro cellular proliferation assay can be performed to measure the metabolic activity of live cells. The assay is performed in a 96 well microtiter plate using Alamar Blue reduction. Human tumor cell lines are obtained from ATCC (e.g., MCF7, U-87 MG, MDA-MB-468, PC-3), grown to confluency in T75 flasks, trypsinized with 0.25% trypsin, washed one time with Tumor Cell Media (DMEM + 10%FBS), and plated in 90ul at 5,000 cells/well in Tumor Cell Media. A compound disclosed herein is diluted in Tumor Cell Media and added in a 10ul volume. Plates are incubated for 72 hours at 37C and 5% CO_2. A volume of 10uL of Alamar Blue reagent is added to each well and plates are incubated for 3 hours at 37C and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC50 values are calculated using GraphPad Prism 5.

Example 33: Antitumor Activity in Vivo

[00543] The compounds described herein can be evaluated in a panel of human and murine tumor models.

[00544] Paclitaxel-refractory Tumor Models

[00545] *1. Clinically-derived Ovarian Carcinoma Model.*

[00546] This tumor model is established from a tumor biopsy of an ovarian cancer patient. Tumor biopsy is taken from the patient.

[00547] The compounds described herein are administered to nude mice bearing staged tumors using an every 2 days x 5 schedule.

[00548] 2. *A2780Tax Human Ovarian Carcinoma Xenograft (Mutated Tubulin).*

[00549] A2780Tax is a paclitaxel-resistant human ovarian carcinoma model. It is derived from the sensitive parent A2780 line by co-incubation of cells with paclitaxel and verapamil, an MDR-reversal agent. Its resistance mechanism has been shown to be non-MDR related and is attributed to a mutation in the gene encoding the beta-tubulin protein.

[00550] The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[00551] *3. HCT116/VM46 Human Colon Carcinoma Xenograft (Multi-Drug Resistant).*

[00552] HCT116/VM46 is an MDR-resistant colon carcinoma developed from the sensitive HCT116 parent line. In vivo, grown in nude mice, HCT116/VM46 has consistently demonstrated high resistance to paclitaxel.

[00553] The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[00554] *5. M5076 Murine Sarcoma Model*

[00555] M5076 is a mouse fibrosarcoma that is inherently refractory to paclitaxel in vivo.

[00556] The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[00557] One or more compounds of the invention can be used in combination other therapeutic agents in vivo in the multidrug resistant human colon carcinoma xenografts HCT/VM46 or any other model known in the art including those described herein.

Example 34: Microsome stability assay

[00558] The stability of one or more subject compounds is determined according to standard procedures known in the art. For example, stability of one or more subject compounds is established by an in vitro assay. In particular, an in vitro microsome stability assay is established that measures stability of one or more subject compounds when reacting with mouse, rat or human microsomes from liver. The microsome reaction with compounds is performed in 1.5 mL Eppendorf tube. Each tube contains 0.1 µL of 10.0 mg/ml NADPH; 75 µL of 20.0 mg/ml mouse, rat or human liver microsome; 0.4 µL of 0.2 M phosphate buffer, and 425 µL of ddH_2O. Negative control (without NADPH) tube contains 75 µL of 20.0 mg/ml mouse, rat or human liver microsome; 0.4 µL of 0.2 M phosphate buffer, and 525 µL of ddH_2O. The reaction is started by adding 1.0 µL of 10.0 mM tested compound. The reaction tubes are incubated at 37°C. 100 µL sample is collected into new Eppendorf tube containing 300 µL cold Methanol at 0, 5, 10, 15, 30 and 60 minutes of reaction. Samples are centrifuged at 15,000 rpm to remove protein. Supernatant of centrifuged sample is transferred to new tube. Concentration of stable compound after reaction with microsome in the supernatant is measured by Liquid Chromatography/Mass Spectrometry (LC-MS).

Example 35: Plasma stability assay

[00559] The stability of one or more subject compounds in plasma is determined according to standard procedures known in the art. See, e.g., *Rapid Commun. Mass Spectrom.*, **10**: 1019-1026. The following procedure is an HPLC-MS/MS assay using human plasma; other species including monkey, dog, rat, and mouse are also available. Frozen, heparinized human plasma is thawed in a cold water bath and spun for 10 minutes at 2000 rpm at 4 °C prior to use. A subject compound is added from a 400 µM stock solution to an aliquot of pre-warmed plasma to give a final assay volume of 400 µL (or 800 µL for half-life determination), containing 5 µM test compound and 0.5 % DMSO. Reactions are incubated, with shaking, for 0 minutes and 60 minutes at 37 °C, or for 0, 15, 30, 45 and 60 minutes at 37 C for half life determination. Reactions are stopped by transferring 50 µL of the incubation mixture to 200 µL of ice-cold acetonitrile and mixed by shaking for 5 minutes. The samples are centrifuged at 6000 x g for 15 minutes at 4°C and 120 µL of supernatant removed into clean tubes. The samples are then evaporated to dryness and submitted for analysis by HPLC-MS/MS.

[00560] Where desired, one or more control or reference compounds (5 µM) are tested simultaneously with the test compounds: one compound, propoxycaine, with low plasma stability and another compound, propantheline, with intermediate plasma stability.

[00561] Samples are reconstituted in acetonitrile/methanol/water (1/1/2, v/v/v) and analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 60 minutes relative to the amount remaining at time zero, expressed as percent, is reported as plasma stability. In case of half-life

determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 36: Chemical Stability

[00562] The chemical stability of one or more subject compounds is determined according to standard procedures known in the art. The following details an exemplary procedure for ascertaining chemical stability of a subject compound. The default buffer used for the chemical stability assay is phosphate-buffered saline (PBS) at pH 7.4; other suitable buffers can be used. A subject compound is added from a 100 μM stock solution to an aliquot of PBS (in duplicate) to give a final assay volume of 400 μL, containing 5 μM test compound and 1% DMSO (for half-life determination a total sample volume of 700 μL is prepared). Reactions are incubated, with shaking, for 0 minutes and 24 hours at 37°C; for half-life determination samples are incubated for 0, 2, 4, 6, and 24 hours. Reactions are stopped by adding immediately 100 μL of the incubation mixture to 100 μL of acetonitrile and vortexing for 5 minutes. The samples are then stored at -20°C until analysis by HPLC-MS/MS. Where desired, a control compound or a reference compound such as chlorambucil (5 μM) is tested simultaneously with a subject compound of interest, as this compound is largely hydrolyzed over the course of 24 hours. Samples are analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 24 hours relative to the amount remaining at time zero, expressed as percent, is reported as chemical stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 37: Akt Kinase Assay

[00563] Cells comprising components of the Akt/mTOR pathway, including but not limited to L6 myoblasts, B-ALL cells, B-cells, T-cells, leukemia cells, bone marrow cells, p190 transduced cells, philladelphia chromosome positive cells (Ph+), and mouse embryonic fibroblasts, are typically grown in cell growth media such as DMEM supplemented with fetal bovine serum and/or antibiotics, and grown to confluency.

[00564] In order to compare the effect of one or more compounds disclosed herein on Akt activation, said cells are serum starved overnight and incubated with one or more compounds disclosed herein or about 0.1% DMSO for approximately 1 minute to about 1 hour prior to stimulation with insulin (e.g. 100 nM) for about 1 minutes to about 1 hour. Cells are lysed by scraping into ice cold lysis buffer containing detergents such as sodium dodecyl sulfate and protease inhibitors (e.g., PMSF). After contacting cells with lysis buffer, the solution is briefly sonicated, cleared by centrifugation, resolved by SDS-PAGE, transferred to nitrocellulose or PVDF and immunoblotted using antibodies to phospho- Akt S473, phospho- Akt T308, Akt, and β-actin (Cell Signaling Technologies).

[00565] The results demonstrate that one or more compounds of the present disclosure inhibit insulin stimulated phosphorylation of Akt at S473. Alternatively, some compounds disclosed herein additionally inhibit insulin stimulated phosphorylation of Akt at T308. Such class of compounds can inhibit Akt more effectively than rapamycin and may be indicative of mTORC2 inhibitors or inhibitors of upstream kinases such as PI3K or Akt.

Example 38: Kinase Signaling in Blood

[00566] PI3K/ Akt /mTor signaling is measured in blood cells using the phosflow method (Methods Enzymol. 2007;434:131-54). The advantage of this method is that it is by nature a single cell assay so that cellular heterogeneity can be detected rather than population averages. This allows concurrent dinstinction of signaling states in different populations defined by other markers. Phosflow is also highly quantitative. To test the effects of one or more compounds disclosed herein, unfractionated splenocytes, or peripheral blood mononuclear cells are stimulated with

anti-CD3 to initiate T-cell receptor signaling. The cells are then fixed and stained for surface markers and intracellular phosphoproteins. It is expected that inhibitors disclosed herein inhibit anti-CD3 mediated phosphorylation of Akt - S473 and S6, whereas rapamycin inhibits S6 phosphorylation and enhances Akt phosphorylation under the conditions tested.

[00567] Similarly, aliquots of whole blood are incubated for 15 minutes with vehicle (e.g. 0.1%DMSO) or kinase inhibitors at various concentrations, before addition of stimuli to crosslink the T cell receptor (TCR) (anti-CD3 with secondary antibody) or the B cell receptor (BCR) using anti-kappa light chain antibody (Fab'2 fragments). After approximately 5 and 15 minutes, samples are fixed (e.g. with cold 4% paraformaldehyde) and used for phosflow. Surface staining is used to distinguish T and B cells using antibodies directed to cell surface markers that are known to the art. The level of phosphorylation of kinase substrates such as Akt and S6 are then measured by incubating the fixed cells with labeled antibodies specific to the phosphorylated isoforms of these proteins. The population of cells are then analyzed by flow cytometry.

Example 39: Colony Formation Assay

[00568] Murine bone marrow cells freshly transformed with a p190 BCR-Abl retrovirus (herein referred to as p190 transduced cells) are plated in the presence of various drug combinations in M3630 methylcellulose media for about 7 days with recombinant human IL-7 in about 30% serum, and the number of colonies formed is counted by visual examination under a microscope.

[00569] Alternatively, human peripheral blood mononuclear cells are obtained from Philadelphia chromosome positive (Ph+) and negative (Ph-) patients upon initial diagnosis or relapse. Live cells are isolated and enriched for CD19+ CD34+ B cell progenitors. After overnight liquid culture, cells are plated in methocult GF+ H4435, Stem Cell Tehcnologies) supplemented with cytokines (IL-3, IL-6, IL-7, G-CSF, GM-CSF, CF, Flt3 ligand, and erythropoietin) and various concentrations of known chemotherapeutic agents in combination with either compounds of the present disclosure. Colonies are counted by microscopy 12-14 days later. This method can be used to test for evidence of additive or synergistic activity.

Example 40: *In Vivo* Effect of Kinase Inhibitors on Leukemic Cells

[00570] Female recipient mice are lethally irradiated from a γ source in two doses about 4 hr apart, with approximately 5Gy each. About 1hr after the second radiation dose, mice are injected i.v. with about $1x10^6$ leukemic cells (e.g. Ph+ human or murine cells, or p190 transduced bone marrow cells). These cells are administered together with a radioprotective dose of about $5x10^6$ normal bone marrow cells from 3-5 week old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs are harvested for analysis. Kinase inhibitor treatment begins about 10 days after leukemic cell injection and continues daily until the mice become sick or a maximum of approximately 35 days post-transplant. Inhibitors are given by oral lavage.

[00571] Peripheral blood cells are collected approximately on day 10 (pre-treatment) and upon euthanization (post treatment), contacted with labeled anti-hCD4 antibodies and counted by flow cytometry. This method can be used to demonstrate that the synergistic effect of one or more compounds disclosed herein in combination with known chemotherapeutic agents significantly reduce leukemic blood cell counts as compared to treatment with known chemotherapeutic agents (e.g. Gleevec) alone under the conditions tested.

Example 41: Treatment of Lupus Disease Model Mice

[00572] Mice lacking the inhibitory receptor FcγRIIb that opposes PI3K signaling in B cells develop lupus with high penetrance. FcγRIIb knockout mice (R2KO, Jackson Labs) are considered a valid model of the human disease as some

lupus patients show decreased expression or function of FcγRIIb (S. Bolland and J.V. Ravtech 2000. *Immunity* 12:277-285).

[00573] The R2KO mice develop lupus-like disease with anti-nuclear antibodies, glomerulonephritis and proteinurea within about 4-6 months of age. For these experiments, the rapamycin analogue RAD001 (available from LC Laboratories) is used as a benchmark compound, and administered orally. This compound has been shown to ameliorate lupus symptoms in the B6.Sle1z.Sle3z model (T. Wu et al. *J. Clin Invest.* 117:2186-2196).

[00574] Lupus disease model mice such as R2KO, BXSB or MLR/lpr are treated at about 2 months old, approximately for about two months. Mice are given doses of: vehicle, RAD001 at about 10mg/kg, or compounds disclosed herein at approximately 1 mg/kg to about 500 mg/kg. Blood and urine samples are obtained at approximately throughout the testing period, and tested for antinuclear antibodies (in dilutions of serum) or protein concentration (in urine). Serum is also tested for anti-ssDNA and anti-dsDNA antibodies by ELISA. Animals are euthanized at day 60 and tissues harvested for measuring spleen weight and kidney disease. Glomerulonephritis is assessed in kidney sections stained with H&E. Other animals are studied for about two months after cessation of treatment, using the same endpoints.

[00575] This model established in the art can be employed to demonstrate that the kinase inhibitors disclosed herein can suppress or delay the onset of lupus symptoms in lupus disease model mice.

Example 42: Murine Bone Marrow Transplant Assay

[00576] Female recipient mice are lethally irradiated from a γ ray source. About 1hr after the radiation dose, mice are injected with about 1x106 leukemic cells from early passage p190 transduced cultures (e.g. as described in *Cancer Genet Cytogenet.* 2005 Aug;161(1):51-6) . These cells are administered together with a radioprotective dose of approximately 5x106 normal bone marrow cells from 3-5wk old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs harvested for flow cytometry and/or magnetic enrichment. Treatment begins on approximately day 10 and continues daily until mice become sick, or after a maximum of about 35 days post-transplant. Drugs are given by oral gavage (p.o.). In a pilot experiment a dose of chemotherapeutic that is not curative but delays leukemia onset by about one week or less is identified; controls are vehicle-treated or treated with chemotherapeutic agent, previously shown to delay but not cure leukemogenesis in this model (e.g. imatinib at about 70mg/kg twice daily). For the first phase p190 cells that express eGFP are used, and postmortem analysis is limited to enumeration of the percentage of leukemic cells in bone marrow, spleen and lymph node (LN) by flow cytometry. In the second phase, p190 cells that express a tailless form of human CD4 are used and the postmortem analysis includes magnetic sorting of hCD4+ cells from spleen followed by immunoblot analysis of key signaling endpoints: p Akt -T308 and S473; pS6 and p4EBP-1. As controls for immunoblot detection, sorted cells are incubated in the presence or absence of kinase inhibitors of the present disclosure inhibitors before lysis. Optionally, "phosflow" is used to detect p Akt -S473 and pS6-S235/236 in hCD4-gated cells without prior sorting. These signaling studies are particularly useful if, for example, drug-treated mice have not developed clinical leukemia at the 35 day time point. Kaplan-Meier plots of survival are generated and statistical analysis done according to methods known in the art. Results from p190 cells are analyzed separated as well as cumulatively.

[00577] Samples of peripheral blood (100-200μl) are obtained weekly from all mice, starting on day 10 immediately prior to commencing treatment. Plasma is used for measuring drug concentrations, and cells are analyzed for leukemia markers (eGFP or hCD4) and signaling biomarkers as described herein.

[00578] This general assay known in the art may be used to demonstrate that effective therapeutic doses of the compounds disclosed herein can be used for inhibiting the proliferation of leukemic cells.

Example 43: Cell Culture of Epithelial Cells of Ocular Origin

[00579] Ocular epithelial cells are obtained within 5 days postmortem post-mortem from corneas preserved under cold storage conditions in Optisol (Bausch and Lomb, Irvine, CA) or from corneal biopsy from living donors. The tissue is washed with phosphate-buffered saline and incubated in Dispase II (Roche Diagnostics, Basel, Switzerland) at 37°C for 30 minutes, and the epithelial surface is gently scraped to separate the epithelium from the underlying stroma. The separated epithelium is then incubated and pipetted in trypsin- ethylenediaminetetraacetic acid to obtain a single cell suspension. The trypsin is then neutralized with corneal epithelium culture medium. Corneal epithelium culture medium is composed of Dulbecco modified Eagle medium:F12 basal media in a 2:1 ratio containing 10% irradiated fetal bovine serum, hydrocortisone 0.4 μg/mL, cholera toxin 0.1 nmol, recombinant human insulin 5 μg/mL, and epidermal growth factor 10 ng/mL, and the antimicrobials penicillin (100 IU/mL), streptomycin (100 μg/mL), and amphotericin B (0.25 μg/mL). Cells are maintined by sub-culturing at a 1:4 ratio after reaching 80% confluency. Ocular epithelial cells are screened for inhibition of proliferation or toxicity by contacting a test compound with the cells and assaying for viability using the commercially available MTT assay (Promega).

Example 44: Cell Culture of Endothelial Cells of Ocular Origin

[00580] All tissues are maintained at 4°C in storage medium (Optisol; Chiron Vision, Irvine, CA) for less than 10 days before study. The tissue is rinsed three times with DMEM containing 50 mg/mL gentamicin and 1.25 mg/mL amphotericin B. The central cornea is removed by a trephine of 8-mm diameter. Afterward, the Descemet's membrane and corneal endothelial cells are stripped from the posterior surface of the peripheral corneoscleral tissue under a dissecting microscope and digested at 37°C for 1.5 to 16 hours with 2 mg/mL collagenase A in supplemented hormonal epithelial medium (SHEM), which is made of an equal volume of HEPES-buffered DMEM and Ham's F12 supplemented with 5% FBS, 0.5% dimethyl sulfoxide, 2 ng/mL mouse EGF, 5 μg/mL insulin, 5 μg/mL transferrin, 5 ng/mL selenium, 0.5 μg/mL hydrocortisone, 1 nM cholera toxin, 50 μg/mL gentamicin, and 1.25 μg/mL amphotericin B. After digestion, HCECs formed aggregates, which are collected by centrifugation at 2000 rpm for 3 minutes to remove the digestion solution. As a control, Descemet's membrane strips are also digested in 10 mg/mL Dispase II in SHEM and trypsin/EDTA for up to 3 hours.

Preservation of Isolated HCEC Aggregates

[00581] The resultant aggregates of HCECs are preserved in KSFM with complete supplement (storage medium 1), DMEM/F12 with KSFM supplements (storage medium 2), or DMEM/F12 with SHEM supplements without FBS (storage medium 3). All these media are serum free, one of the major differences among them is the calcium concentration, which is 0.09 mM in storage medium 1, but is 1.05 mM in storage media 2 and 3. HCEC aggregates are stored in a tissue culture incubator at 37°C for up to 3 weeks. Cell viability is determined (Live and Dead assay; Invitrogen) and also evaluated by subculturing them in SHEM.

Expansion of Isolated HCEC Aggregates

[00582] The resultant HCEC aggregates, either immediately after digestion or after a period of preservation in a storage medium, are then cultured in SHEM with or without additional growth factors such as 40 ng/mL bFGF, 0.1 mg/mL BPE, and 20 ng/mL NGF on a plastic dish under 37°C and 5% CO2. The media are changed every 2 to 3 days. Some HCEC aggregates are pretreated with trypsin/EDTA at 37°C for 10 minutes to dissociate endothelial cells before the aforementioned cultivation.

Immunostaining

[00583] HCEC aggregates are embedded in OCT and subjected to frozen sectioning. Cryosections of 4 μm are air-dried at room temperature (RT) for 30 minutes, and fixed in cold acetone for 10 minutes at –20°C. Sections used for immunostaining are rehydrated in PBS, and incubated in 0.2% Triton X-100 for 10 minutes. After three rinses with

PBS for 5 minutes each and preincubation with 2% BSA to block nonspecific staining, the sections are incubated with anti-laminin 5, type IV collagen, perlecan, ZO-1, and connexin 43 (all at 1:100) antibodies for 1 hour. After three washes with PBS for 15 minutes, the sections are incubated with a FITC-conjugated secondary antibody (goat anti-rabbit or anti-mouse IgG at 1:100) for 45 minutes. After three additional PBS washes, each for 10 minutes, they are counterstained with propidium iodide (1:1000) or Hoechst 33342 (10 μg/mL), then mounted with an antifade solution and analyzed with a fluorescence microscope. HCECs cultured in 24-well plates or chamber slides are fixed in 4% paraformaldehyde for 15 minutes at RT and stained with anti-ZO-1 and connexin 43 antibodies as just described. For immunohistochemical staining of Ki67, endogenous peroxidase activity is blocked by 0.6% hydrogen peroxide for 10 minutes. Nonspecific staining is blocked by 1% normal goat serum for 30 minutes. Cells are then incubated with anti-Ki67 antibody (1:100) for 1 hour. After three washes with PBS for 15 minutes, cells are incubated with biotinylated rabbit anti-mouse IgG (1:100) for 30 minutes, followed by incubation with ABC reagent for 30 minutes. The reaction product is developed with DAB for 5 minutes and examined by light microscope.

Cell-Viability and TUNEL Assays

[00584] Cell-viability and terminal deoxyribonucleotidyl transferase-mediated FITC-linked dUTP nick-end DNA labeling (TUNEL) assays are used to determine living and apoptotic cells, respectively. HCEC aggregates are incubated with cell-viability assay reagents for 15 minutes at RT. Live cells are distinguished by green fluorescence staining of the cell cytoplasm, and dead cells are stained with red fluorescence in the nuclei. The TUNEL assay is performed according to the manufacturer's instructions. Briefly, cross-sections of HCEC aggregates are fixed in 4% paraformaldehyde for 20 minutes at RT and permeabilized with 1% Triton X-100. Samples are then incubated for 60 minutes at 37°C with exogenous TdT and fluorescein-conjugated dUTP, for repair of nicked 3'-hydroxyl DNA ends. Cells are treated with DNase I as the positive control, whereas negative control cells are incubated with a buffer lacking the rTdT enzyme. The apoptotic nuclei are labeled with green fluorescence.

Example 45: Cell Culture of Retinal Cells

[00585] Eyes are cut in half along their equator and the neural retina is dissected from the anterior part of the eye in buffered saline solution, according to standard methods known in the art. Briefly, the retina, ciliary body, and vitreous are dissected away from the anterior half of the eye in one piece, and the retina is gently detached from the clear vitreous. Each retina is dissociated with papain (Worthington Biochemical Corporation, Lakewood, N.J.), followed by inactivation with fetal bovine serum (FBS) and addition of 134 Kunitz units/ml of DNaseI. The enzymatically dissociated cells are triturated and collected by centrifugation, resuspended in Dulbecco's modified Eagle's medium (DMEM)/F12 medium (Gibco BRL, Invitrogen Life Technologies, Carlsbad, Calif.) containing 25 μg/ml of insulin, 100 μg/ml of transferrin, 60 μM putrescine, 30 nM selenium, 20 nM progesterone, 100 U/ml of penicillin, 100 μg/ml of streptomycin, 0.05 M Hepes, and 10% FBS. Dissociated primary retina l cells are plated onto Poly-D-lysine- and Matrigel- (BD, Franklin Lakes, N.J.) coated glass coverslips that are placed in 24-well tissue culture plates (Falcon Tissue Culture Plates, Fisher Scientific, Pittsburgh, Pa.). Cells are maintained in culture for 5 days to one month in 0.5 ml of media (as above, except with only 1% FBS) at 37° C. and 5% CO2.

Immunocytochemistry Analysis

[00586] The retina l neuronal cells are cultured for 1, 3, 6, and 8 weeks in the presence and absence of test compounds of the present invention, and the cells are analyzed by immunohistochemistry at each time point. Immunocytochemistry analysis is performed according to standard techniques known in the art. Rod photoreceptors are identified by labeling with a rhodopsin-specific antibody (mouse monoclonal, diluted 1:500; Chemicon, Temecula, Calif.). An antibody to mid-weight neurofilament (NFM rabbit polyclonal, diluted 1:10,000, Chemicon) is used to identify ganglion cells; an antibody to β3-tubulin (G7121 mouse monoclonal, diluted 1:1000, Promega, Madison,

Wis.) is used to generally identify interneurons and ganglion cells, and antibodies to calbindin (AB1778 rabbit polyclonal, diluted 1:250, Chemicon) and calretinin (AB5054 rabbit polyclonal, diluted 1:5000, Chemicon) are used to identify subpopulations of calbindin- and calretinin-expressing interneurons in the inner nuclear layer. Briefly, the retina l cell cultures are fixed with 4% paraformaldehyde (Polysciences, Inc, Warrington, Pa.) and/or ethanol, rinsed in Dulbecco's phosphate buffered saline (DPBS), and incubated with primary antibody for 1 hour at 37° C. The cells are then rinsed with DPBS, incubated with a secondary antibody (Alexa 488- or Alexa 568-conjugated secondary antibodies (Molecular Probes, Eugene, Oreg.)), and rinsed with DPBS. Nuclei are stained with 4',6-diamidino-2-phenylindole (DAPI, Molecular Probes), and the cultures are rinsed with DPBS before removing the glass coverslips and mounting them with Fluoromount-G (Southern Biotech, Birmingham, Ala.) on glass slides for viewing and analysis.

Example 46: Matrigel Plug Angiogenesis Assay.

[00587] Matrigel containing test compounds are injected subcutaneously or intraocularly, where it solidifies to form a plug. The plug is recovered after 7–21 days in the animal and examined histologically to determine the extent to which blood vessels have entered it. Angiogenesis is measured by quantification of the vessels in histologic sections. Alternatively, fluorescence measurement of plasma volume is performed using fluorescein isothiocyanate (FITC)-labeled dextran 150. The results are expected to indicate one or more compounds disclosed herein that inhibit angiogenesis and are thus expected to be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 47: The Corneal Angiogenesis Assay

[00588] A pocket is made in the cornea, and a plug containing an angiogenesis inducing formulation (e.g. VEGF, FGF, or tumor cells), when introduced into this pocket, elicits the ingrowth of new vessels from the peripheral limbal vasculature. Slow-release materials such as ELVAX (ethylene vinyl copolymer) or Hydron are used to introduce angiogenesis inducing substances into the corneal pocket. Alternatively, a sponge material is used.

[00589] The effect of putative inhibitors on the locally induced (e.g., sponge implant) angiogenic reaction in the cornea (e.g., by FGF, VEGF, or tumor cells). The test compound is administered orally, systemically, or directly to the eye. Systemic administration is by bolus injection or, more effectively, by use of a sustained- release method such as implantation of osmotic pumps loaded with the test inhibitor. Administration to the eye is by any of the methods described herein including but not limited to eye drops, topical administration of a cream, emulsion, or gel, intravitreal injection.

[00590] The vascular response is monitored by direct observation throughout the course of the experiment using a stereomicroscope in mice. Definitive visualization of the corneal vasculature is achieved by administration of fluorochrome-labeled high-molecular weight dextran. Quantification is performed by measuring the area of vessel penetration, the progress of vessels toward the angiogenic stimulus over time, or in the case of fluorescence, histogram analysis or pixel counts above a specific (background) threshold.

[00591] The results are expected to indicate one or more compounds disclosed herein that inhibit angiogenesis and are thus expected to be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 48: Microtiter-plate Angiogenesis Assay

[00592] The assay plate is prepared by placing a collagen plug in the bottom of each well with 5-10 cell spheroids per collagen plug each spheroid containing 400-500 cells. Each collagen plug is covered with 1100µl of storage medium per well and stored for future use (1-3 days at 37°C, 5% CO2). The plate is sealed with sealing. Test compounds are dissolved in 200µl assay medium with at least one well including a VEGF positive control and at least one well without VEGF or test compound as a negative control. The assay plate is removed from the incubator and storage

medium is carefully pipeted away. Assay medium containing the test compounds are pipeted onto the collagen plug. The plug is placed in a humidified incubator for (37°C, 5% CO2) 24-48 hours. Angiogenesis is quantified by counting the number of sprouts, measuring average sprout length, or determining cumulative sprout length. The assay can be preserved for later analysis by removing the assay medium, adding 1ml of 10% paraformaldehyde in Hanks BSS per well, and storing at 4°C. The results are expected to identify compounds that inhibit angiogenesis in various cell types tested, including cells of ocular origin.

Example 49: TNP-Ficoll T-cell Independent B-cell Activation Assay

[00593] To test the effects of the compounds of the present invention in suppressing T cell independent antibody production, the TNP-Ficoll B-cell activation assay was used as described herein. Compounds of the present invention were dissolved in an appropriate vehicle (e.g. 5% 1-methyl-2-pyrrolidinone, 85% polyethylene glycol 400, 10% solutor). Compounds were administered orally approximately 1hr before TNP-Ficoll treatment to 4-10 week old mice. To study the effects of the compounds on B-cell activation, one set of mice were grouped according to the following table:

Group#	Mice/ group	Comp treated	Group	Antigen injection at day-1		Compound Administration from day-1 to day-7		
				TNP-F	Route	(mg/kg)	Route	Regimen
1	4	Vehicle	Antigen only	200 uL (0.5 mg/ml)	ip	0	Po	BID for 7 days
2	8	-	Antigen only			0		
3	8	Compound #7	reference			30		
4	8	Compound #53	Antigen + cmp			1		
5	8					3		
6	8					10		
7	8					30		
8	8					60		

[00594] Four animals in group 1, and eight animals in groups 2 to 7 were euthanized in CO2 2 hours after the last compound administration on day 7. Blood was immediately collected by cadio-puncture and kept at 37°C for 1hr to clot followed by overnight incubation at 4°C to allow the clot to contract. The following day, serum was collected by decanting and centrifugation at 3000 rpm for 10 min. The collected serum was then frozen at -80°C for future analysis.

[00595] Serum samples were analyzed for anti-TNP antibody titers by ELISA as described herein. TNP-BSA was coated onto a Nunc Maxisorb microtiter plate with 100µl/well at a concentration of 10µg/ml in phosphate buffered saline (PBS). The Maxisorb plate was incubated for 1.5 hours at room temperature and the solution was removed. 200 µl/well of blocking buffer (e.g. 1% BSA in PBS) was added to each well and incubated 1hr at room temperature. The plate was washed once with 200 µl/well of PBS 0.05% Tween-20 (wash buffer). A 1:2 dilution of serum from each mouse in blocking buffer was added to each well in the first column (1) of the microtiter plate. The serum in each well of column 1 was then diluted 3-fold in blocking buffer and added to column 2. The serum in each well of column 2 was diluted 3-fold in blocking buffer and added to column 3. The procedure was repeated across the twelve columns of the microtiter plate. The microtiter plate was incubated 1 hr at room temperature. Serum was removed from the plate and the plate was washed three times with wash buffer. 100 µl/well of goat anti-mouse IgG3-HRP diluted 1:250 in blocking buffer was added to each well and incubated 1hr at room temperature. The anti-mouse IgG3-HRP was removed from the microtiter plate and the plate was washed six times with wash buffer. HRP substrate (200 µl ABTS

solution + 30% H2O2 + 10ml citrate buffer) was added to each well at 100 µl/well, incubated 2-20 minutes in the dark and the amount of anti-TNP IgG3 was determined spectrophotometrically at 405nm. Similarly, anti-TNP IgM and total anti-TNP Ab were determined using anti-mouse IgM-HRP and anti-mouse Ig-HRP respectively.

[00596] The results as shown in Figure 2 futher show that under the conditions tested compounds #7 and #53 exhibit 3.4 and 6.5-fold reductions respectively in IgG3 levels relative to vehicle control mice at a 30mg/kg dose level. Figure 2 further shows that compound #53 exhibits 29.9-fold reduction in IgG3 levels relative to vehicle control mice at a 60mg/kg dose level under the conditions tested,

Example 50: Rat Developing Type II Collagen Induced Arthritis Assay

[00597] In order to study the effects of the compounds of the present invention on the autoimmune disease arthritis, a collagen induced developing arthritis model was used. Female Lewis rats were given collagen injections at day 0. Bovine type II collagen was prepared as a 4mg/ml solution in 0.01N acetic acid. Equal volumes of collagen and Freund's incomplete adjuvant were emulsified by hand mixing until a bead of the emulsified material held its form in water. Each rodent received a 300 µl injection of the mixture at each injection time spread over three subcutaneous sites on the back.

[00598] Oral compound administration began on day 0 and continued through day 16 with vehicle (5% NMP, 85% PEG 400, 10% Solutol) or compounds of the present invention in vehicle or control (e.g. methotrexate) at 12 hour intervals daily. Rats were weighed on days 0, 3, 6, 9-17 and caliper measurements of ankles taken on days 9-17. Final body weights were taken, and then the animals were euthanized on day 17. After euthanization, blood was drawn and hind paws and knees were removed. Blood was further processed for pharmacokinetics experiments as well as an anti-type II collagen antibody ELISA assay. Hind paws were weighed and then with the knees preserved in 10% formalin. The paws and knees were subsequently processed for microcopy. Livers, spleen and thymus were also weighed. Sciatic nerves were prepared for histopathology.

[00599] Knee and ankle joints were fixed for 1-2 days and decalcified for 4-5 days. Ankle joints were cut in half longitudinally, knees were cut in half along the frontal plane. Joints were then processed, embedded, sectioned and stained with toluidine blue. Scoring of the joints was done according to the following criteria:

Knee and Ankle Inflammation

0=Normal

1=Minimal infiltration of inflammatory cells in synovium/periarticular tissue

2=Mild infiltration

3=Moderate infiltration with moderate edema

4=Marked infiltration with marked edema

5=Severe infiltration with severe edema

Ankle Pannus

0=Normal

1=Minimal infiltration of pannus in cartilage and subchondral bone

2=Mild infiltration (<1/4 of tibia or tarsals at marginal zones)

3=Moderate infiltration (1/4 to 1/3 of tibia or small tarsals affected at marginal zones)

4=Marked infiltration (1/2-3/4 of tibia or tarsals affected at marginal zones)

5=Severe infiltration (>3/4 of tibia or tarsals affected at marginal zones, severe distortion of overall architecture)

Knee Pannus

0=Normal

1=Minimal infiltration of pannus in cartilage and subchondral bone

2=Mild infiltration (extends over up to1/4 of surface or subchondral area of tibia or femur)

3=Moderate infiltration (extends over >1/4 but < 1/2 of surface or subchondral area of tibia or femur)

4=Marked infiltration (extends over 1/2 to 3/4 of tibial or femoral surface)

5=Severe infiltration (covers > 3/4 of surface)

Cartilage Damage (Ankle, emphasis on small tarsals)

0=Normal

1=Minimal=minimal to mild loss of toluidine blue staining with no obvious chondrocyte loss or collagen disruption

2=Mild=mild loss of toluidine blue staining with focal mild (superficial) chondrocyte loss and/or collagen disruption

3=Moderate=moderate loss of toluidine blue staining with multifocal moderate (depth to middle zone) chondrocyte loss and/or collagen disruption, smaller tarsals affected to 1/2-3/4 depth

4=Marked=marked loss of toluidine blue staining with multifocal marked (depth to deep zone) chondrocyte loss and/or collagen disruption, 1 or more small tarsals have full thickness loss of cartilage

5=Severe =severe diffuse loss of toluidine blue staining with multifocal severe (depth to tide mark) chondrocyte loss and/or collagen disruption

Cartilage Damage (Knee, emphasis on femoral condyles)

0=Normal

1=Minimal=minimal to mild loss of toluidine blue staining with no obvious chondrocyte loss or collagen disruption

2=Mild=mild loss of toluidine blue staining with focal mild (superficial) chondrocyte loss and/or collagen disruption

3=Moderate=moderate loss of toluidine blue staining with multifocal to diffuse moderate (depth to middle zone) chondrocyte loss and/or collagen disruption

4=Marked=marked loss of toluidine blue staining with multifocal to diffuse marked (depth to deep zone) chondrocyte loss and/or collagen disruption or single femoral surface with total or near total loss

5=Severe =severe diffuse loss of toluidine blue staining with multifocal severe (depth to tide mark) chondrocyte loss and/or collagen disruption on both femurs and/or tibias

Bone Resorption (Ankle)

0=Normal

1=Minimal=small areas of resorption, not readily apparent on low magnification, rare osteoclasts

2=Mild=more numerous areas of resorption, not readily apparent on low magnification, osteoclasts more numerous, <1/4 of tibia or tarsals at marginal zones resorbed

3=Moderate=obvious resorption of medullary trabecular and cortical bone without full thickness defects in cortex, loss of some medullary trabeculae, lesion apparent on low magnification, osteoclasts more numerous, 1/4 to 1/3 of tibia or tarsals affected at marginal zones

4=Marked=Full thickness defects in cortical bone, often with distortion of profile of remaining cortical surface, marked loss of medullary bone, numerous osteoclasts, 1/2-3/4 of tibia or tarsals affected at marginal zones

5=Severe=Full thickness defects in cortical bone, often with distortion of profile of remaining cortical surface, marked loss of medullary bone, numerous osteoclasts, >3/4 of tibia or tarsals affected at marginal zones, severe distortion of overall architecture

Bone Resorption (Knee)

0=Normal

1=Minimal=small areas of resorption, not readily apparent on low magnification, rare osteoclasts

2=Mild=more numerous areas of resorption, definite loss of subchondral bone involving 1/4 of tibial or femoral surface (medial or lateral)

3=Moderate=obvious resorption of subchondral bone involving >1/4 but <1/2 of tibial or femoral surface (medial or lateral)

4=Marked= obvious resorption of subchondral bone involving ≥1/2 but <3/4 of tibial or femoral surface (medial or lateral)

5=Severe= distortion of entire joint due to destruction involving >3/4 of tibial or femoral surface (medial or lateral)

[00600] Statistical analysis of body/paw weights, paw AUC parameters and histopathologic parameters were evaluated using a Student's t-test or other appropriate (ANOVA with post-test) with significance set at the 5% significance level. Percent inhibition of paw weight and AUC was calculated using the following formula:

% Inhibition=A - B/A X 100

A=Mean Disease Control – Mean Normal

B=Mean Treated – Mean Normal

[00601] The results as shown in **Figure 3** demonstrate the effect of compound #53 at 10, 30, and 60 mg/kg dosages at 12 hour intervals on mean ankle diameter over time in a rat developing type II collagen induced arthritis model under the conditions tested. Relative to the vehicle alone control or to the methotrexate control, the compounds of the present invention exhibited a siginificant reduction in arthritis induced ankle diameter increase over time.

[00602] The results as shown in **Figure 4** demonstrate the effect of compounds #7 and #53 on ankle histopathology in the categories of inflammation, pannus, cartilage damage, and bone resporption as previously described under the conditions tested. The results show a significant reduction in one or more categories by one of the compounds of the present invention (i.e. compound #53) under the conditions tested. **Figure 4** further shows that at 60mg/kg, there is a statistically significant reduction in all categories of ankle histopathology for one of the compounds of the present invention (i.e. compound #53) under the conditions tested. This suggests that one or more compounds of the present invention may be useful for the treatment and reduction of arthritis disease symptoms.

[00603] The results as shown in **Figure 5** demonstrate the effect of compounds #7 and #53 on knee histopathology under the conditions tested. The results demonstrate a dose dependent reduction in knee histopathology. This suggests that one or more compounds of the present invention may be useful for the treatment and reduction of arthritis disease symptoms.

[00604] The results as shown in **Figure 6** demonstrate the effect of the compounds #7 and #53 on serum anti-type II collagen levels under the conditions tested. The results further show a singificant reduction at 10, 20, and 60mg/kg dosage levels of serum anti-type II collagen levels for compound #53, suggesting that one or more compounds of the present invention may not only be useful for the treatment and reduction of arthritis disease symptoms, but may also be useful for the inhibition of the autoimmune reaction itself.

[00605] The results as shown in **Figure 7** demonstrate the effect of compound #7 at 10, 30, and 60 mg/kg dosages at 12 hour intervals on mean ankle diameter over time under the conditions tested. Relative to the vehicle alone control or to the methotrexate control, the compound exhibited a reduction in arthritis induced ankle diameter increase over time under the conditions tested.

Example 51: Rat Established Type II Collagen Induced Arthritis Assay

[00606] In order to examine the dose responsive efficacy of the compounds of the present invention in inhibiting the inflammation, cartilage destruction and bone resporption of 7 day established type II collagen induced arthritis in rats, compounds were administered orally daily or twice daily for 6 days.

[00607] Female Lewis rats were anesthetized and given collagen injections prepared and administered as described previously on day 0. On day 6, animals were anesthetized and given a second collagen injection. Caliper measurements of normal (pre-disease) right and left ankle joints were performed on day 9. On days 10-11, arthritis typically occured and rats were randomized into treatment groups. Randomization was performed after ankle joint swelling was obviously established and there was good evidence of bilateral disease.

[00608] After an animal was selected for enrollment in the study, treatment was initiated by the oral route. Animals were given vehicle, control (Enbrel) or compound doses, twice daily or once daily(BID or QD respectively). Dosing was administered on days 1-6 using a volume of 2.5ml/kg (BID) or 5ml/kg (QD) for oral solutions. Rats were weighed on days 1-7 following establishment of arthritis and caliper measurements of ankles taken every day. Final body weights were taken on day 7 and animals were euthanized.

[00609] The results as shown in **Figure 8** shows a significant reduction in mean ankle diameter increase over time for compound #53 with a once daily dosage under the conditions tested. The results in **Figure 9** further demonstrate a significant reduction in mean ankle diameter increase over time for compound #53 with a twice daily dosage under the conditions tested. This suggests that the compounds of the present invention may be useful for the treatment of autoimmune diseases such as arthritis.

Example 52: Adjuvant Induced Arthritis Assay

Intrathecal Catheterization of Rats

[00610] Isoflurane-anesthetized Lewis rats (200–250 g) were implanted with an intrathecal (IT) catheter. After a 6 d recovery period, all animals except those that appeared to have sensory or motor abnormalities (fewer than 5% of the total number) were used for experiments. For IT administration, 10 μl of drug or saline followed by 10 μl of isotonic saline was injected through the catheter.

[00611] Adjuvant Arthritis and Drug Treatment

[00612] Lewis rats were immunized at the base of the tail with 0.1 ml of complete Freund's adjuvant (CFA) on day 0 several days after catheter implantation (n=6/group). Drug (e.g. one or more compounds of the present invention or or vehicle) treatment was generally started on day 8 and continued daily until day 20. Clinical signs of arthritis generally begin on day 10, and paw swelling was determined every second day by water displacement plethysmometry.

[00613] The results as depicted in **Figure 10** by the average change in paw volume under the dosage regimes indicated show that under the conditions tested, compound #53 shows a dose dependent reduction in the average paw volume increase as measured in this adjuvant induced arthritis model system. These results suggest that one or more of the compounds of the present invention may be useful for the treatment of one or more of the diseases or conditions described herein.

[00614] The results as depicted in **Figure 11** show that compound #53 does not exhibit toxicity or other adverse reaction under the conditions tested as measured by a lack of weight loss.

Example 53: Rodent Pharmacokinetic Assay

[00615] In order to study the pharmacokinetics of the compounds of the present invention a set of 4-10 week old mice are grouped according to the following table:

Group#	Mice/ group	Compound treated	Compound Administration from day-1 to day-7		
			(mg/kg)	Route	Regimen

1	3		1	Po	BID for 7 days
2	3		3		
3	3		10		
4	3		30		
5	3		60		

[00616] Compounds of the present invention are dissolved in an appropriate vehicle (e.g. 5% 1-methyl-2-pyrrolidinone, 85% polyethylene glycol 400, 10% Solutor) and administered orally at 12 hour intervals daily. All animals are euthanized in CO2 2 hours after the final compound is administered. Blood is collected immediately and kept on ice for plasma isolation. Plasma is isolated by centrifuging at 5000 rpm for 10 minutes. Harvested plasma is frozen for pharmacokinetic detection.

[00617] The results are expected to demonstrate the pharmacokinetic parameters such as absorption, distribution, metabolism, excretion, and toxicity for the compounds of the present invention.

[00618] Example 54: Basotest assay

[00619] The baseotest assay is performed using Orpegen Pharma Basotest reagent kit. Heparinized whole blood is pre-incubated with test compound or solvent at 37C for 20min. Blood is then incubated with assay kit stimulation buffer (to prime cells for response) followed by allergen (dust mite extract or grass extract) for 20min. The degranulation process is stopped by incubating the blood samples on ice. The cells are then labeled with anti-IgE-PE to detect basophilic granulocytes, and anti-gp53-FITC to detect gp53 (a glycoprotein expressed on activated basophils). After staining red blood cells are lysed by addition of Lysing Solution. Cells are washed, and analyzed by flow cytometry. Compounds 7 and 53 when tested in this assay inhibit allergen induced activation of basophilic granulocytes at sub micromolar range.

[00620] Example 55: Combination use of PI3Kδ inhibitors and agents that inhibit IgE production or activity

[00621] The compounds of the present invention may present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Agents that inhibit IgE production include, for example, one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (i.e. rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as Omalizumab and TNX-901.

[00622] One or more of the subject compounds capable of inhibiting PI3Kδ are efficacious in treatment of autoimmune and inflammatory disorders (AIID) for example rheumatoid arthritis. If any of the compounds causes an undesired level of IgE production, one may choose to administer it in combination with an agent that inhibits IgE production or IgE activity. Additionally, the administration of PI3Kδ or PI3Kδ/γ inhibitors of the present invention in combination with inhibitors of mTOR may also exhibit synergy through enhanced inhibition of the PI3K pathway. Various *in vivo* and *in vitro* models may be used to establish the effect of such combination treatment on AIID including but not limited to (a) *in vitro* B-cell antibody production assay, (b) *in vivo* TNP assay, and (c) rodent collagen induced arthritis model.

(a) B-cell Assay

[00623] Mice are euthanized, and the spleens are removed and dispersed through a nylon mesh to generate a single-cell suspension. The splenocytes are washed (following removal of erythrocytes by osmotic shock) and incubated with anti-CD43 and anti-Mac-1 antibody-conjugated microbeads (Miltenyi Biotec). The bead-bound cells are separated

from unbound cells using a magnetic cell sorter. The magnetized column retains the unwanted cells and the resting B cells are collected in the flow-through. Purified B-cells are stimulated with lipopolysaccharide or an anti-CD40 antibody and interleukin 4. Stimulated B-cells are treated with vehicle alone or with PI3Kδ inhibitors of the present invention such as compound 53 with and without mTOR inhibitors such as rapamycin, rapalogs, or mTORC1/C2 inhibitors. The results are expected to show that in the presence of mTOR inhibitors (e.g., rapamycin) alone, there is little to no substantial effect on IgG and IgE response. However, in the presence of PI3Kδ and mTOR inhibitors, the B-cells are expected to exhibit a decreased IgG response as compared to the B-cells treated with vehicle alone, and the B-cells are expected to exhibit a decreased IgE response as compared to the response from B-cells treated with PI3Kδ inhibitors alone.

(b) TNP Assay

[00624] Mice are immunized with TNP-Ficoll or TNP-KHL and treated with: vehicle, a PI3Kδ inhibitor, for example, compound 53 of the present invention, an mTOR inhibitor, for example rapamycin, or a PI3Kδ inhibitor in combination with an mTOR inhibitor such as rapamycin. Antigen-specific serum IgE is measured by ELISA using TNP-BSA coated plates and isotype specific labeled antibodies. It is expected that mice treated with an mTOR inhibitor alone exhibit little or no substantial effect on antigen specific IgG3 response and no statistically significant elevation in IgE response as compared to the vehicle control. It is also expected that mice treated with both PI3Kδ inhibitor and mTOR inhibitor exhibit a reduction in antigen specific IgG3 response as compared to the mice treated with vehicle alone. Additionally, the mice treated with both PI3Kδ inhibitor and mTOR inhibitor exhibit a decrease in IgE response as compared to the mice treated with PI3Kδ inhibitor alone.

(c) *Rat Collagen Induced Arthritis Model*

[00625] Female Lewis rats are anesthetized and given collagen injections prepared and administered as described previously on day 0. On day 6, animals are anesthetized and given a second collagen injection. Caliper measurements of normal (pre-disease) right and left ankle joints are performed on day 9. On days 10-11, arthritis typically occurs and rats are randomized into treatment groups. Randomization is performed after ankle joint swelling is obviously established and there is good evidence of bilateral disease.

[00626] After an animal is selected for enrollment in the study, treatment is initiated. Animals are given vehicle, PI3Kδ inhibitor, or PI3Kδ inhibitor in combination with rapamycin. Dosing is administered on days 1-6. Rats are weighed on days 1-7 following establishment of arthritis and caliper measurements of ankles taken every day. Final body weights are taken on day 7 and animals are euthanized.

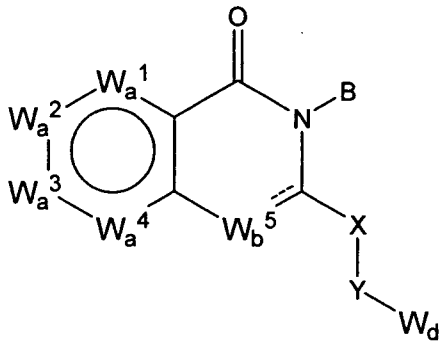
[00627] It is expected that the combination treatment using PI3Kδ inhibitor and rapamycin provides greater efficacy than treatment with PI3Kδ inhibitor alone.

[00628] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula I:



Formula 1

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;

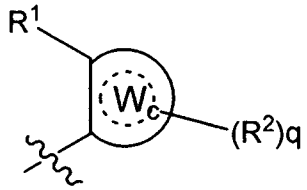
W_a^4 is N or CR^7;

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;

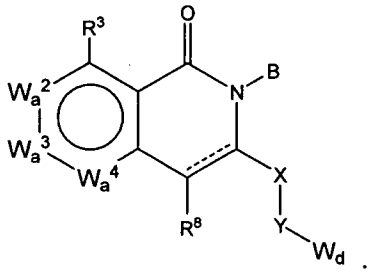
R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro;

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

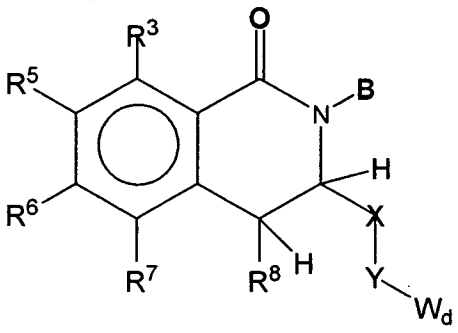
each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, or C_2-C_{10}heteroalkyl.

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



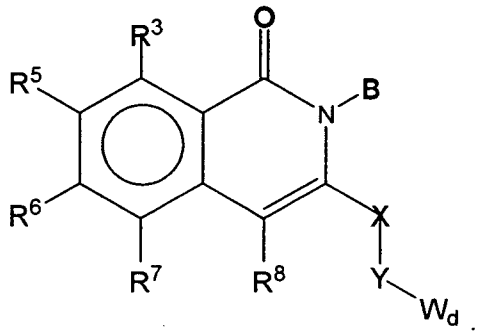
Formula IV

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



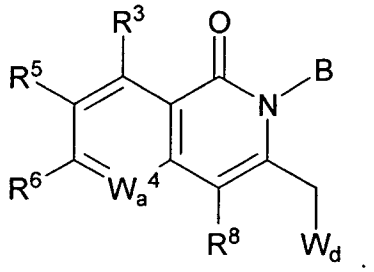
Formula V

or



Formula VI

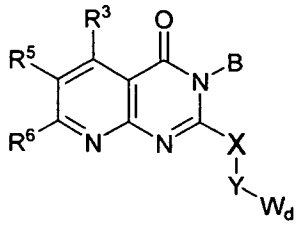
4. The compound of claim 1 of Formula VII:



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-;

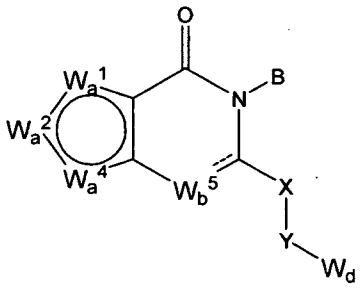
or X is –(CH(R^9))$_z$-, and Y is absent;

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:



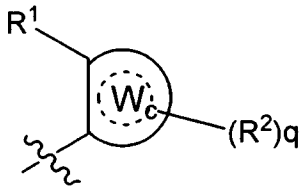
Formula IX

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;

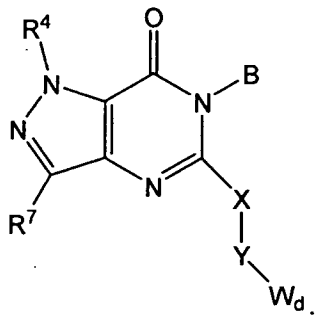
R^4 is hydrogen, acyl, C_1-C_4alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_3-C_5cycloalkyl, or C_1-C_4heteroalkyl;

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:

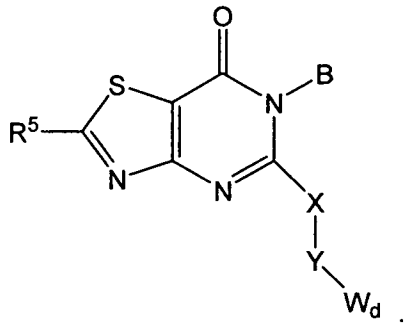


Formula X

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

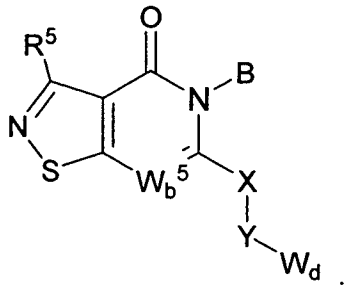
11. The compound of claim 10 wherein R^4 is methyl or ethyl.

12. A compound of claim 7 of Formula XI:



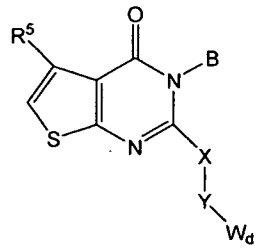
Formula XI

13. A compound of claim 7 of Formula XII:

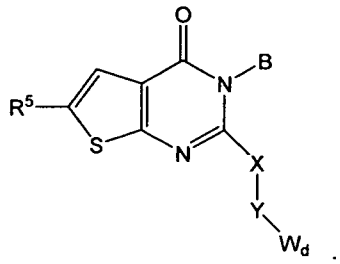


Formula XII

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 $-CH_2-N(CH_3)$.

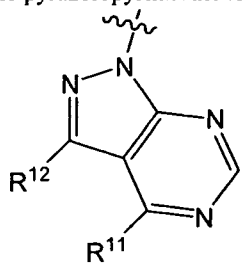
34. The compound of claim 1, 2, or 7 wherein X-Y is (S) $-CH(CH_3)-NH-$.

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:

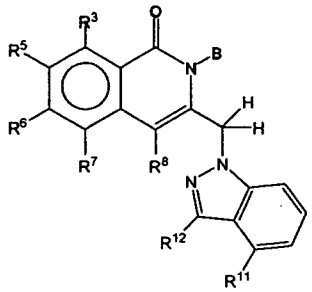


Formula III

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:

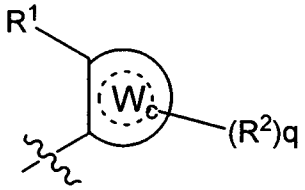


Formula VI-A

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.