CERTAIN CHEMICAL ENTITIES, COMPOSITIONS AND METHODS

[0001] This application claims the benefit of U.S. Patent Application No. 12/503,776, filed on July 15, 2009, which is a continuation in part of International Application No. PCT/US09/00038, filed on January 5, 2009 and International Application No. PCT/US09/00042, filed on January 5, 2009, each of which 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 on December 5, 2008. All of the above-referenced patent applications are are hereby incorporated by reference in their entirety for all purposes.

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).

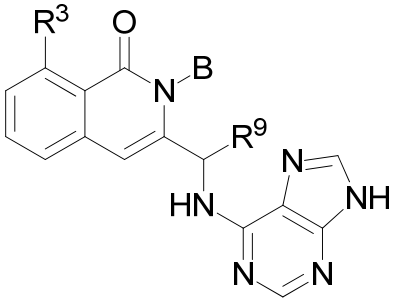
[0007] The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3K δ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3K δ is integrally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

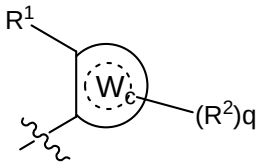
[0009a] In one aspect of the present disclosure, there is provided a compound of Formula V-A:



Formula V-A

or a pharmaceutically acceptable salt thereof, wherein

B is a moiety of Formula II:



Formula II

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

q is an integer of 0 or 1;

R^1 is hydrogen, alkyl, or halo;

R^2 is alkyl or halo;

R^3 is halo;

R^9 is hydrogen, alkyl, or heterocycloalkyl;

wherein alkyl is optionally substituted with one or more halo.

[0009b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0009c] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disorder in a subject, wherein said disorder is one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, or cardiac disease.

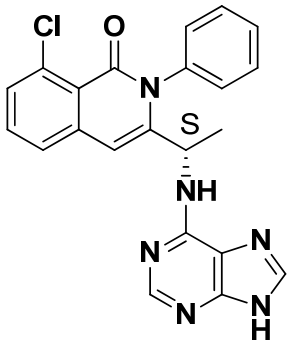
[0009d] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of one or more of asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder (COPD), psoriasis, multiple sclerosis, disorders related to diabetic complications, lupus erythematosus, scleroderma, graft versus host disease, restenosis, or atherosclerosis in a subject.

[0009e] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of medicament for the treatment of cancer in a subject.

[0009f] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder in a subject, wherein the disorder is selected from one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, and cardiac disease.

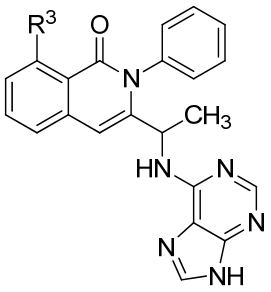
[0009g] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject.

[0009h] In a further aspect of the present disclosure, there is provided a compound of the formula:



(Compound 292).

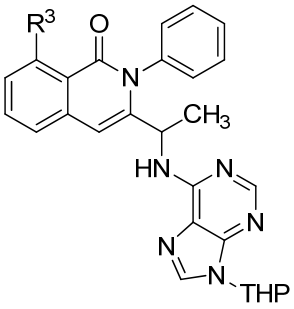
[0009i] In another aspect of the present disclosure, there is provided a process for preparing a compound of formula:



or a pharmaceutically acceptable salt thereof, wherein

R^3 is halo;

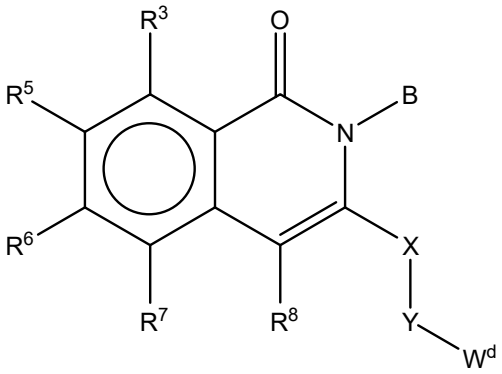
comprising deprotecting a compound of formula:



wherein the deprotection occurs in the presence of an acid.

[0009j] In a further aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutical composition disclosed herein, for use in the treatment of a disorder in a subject, wherein said disorder is one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, or cardiac disease; or for use in the treatment of asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder (COPD), psoriasis, multiple sclerosis, disorders related to diabetic complications, lupus erythematosus, scleroderma, graft versus host disease, restenosis, or atherosclerosis.

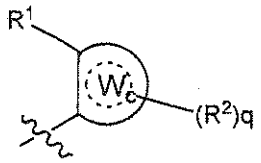
[0010] The present disclosure also provides compounds of Formula I below or pharmaceutically acceptable salts thereof, wherein



Formula I

[0011] W_d is heterocycloalkyl, aryl or heteroaryl;

[0012] B is alkyl or a moiety of Formula II;



Formula II

[0013] wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4;

[0014] X is absent or $-(CH(R^9))_z-$, and z is an integer of 1;

[0015] Y is absent, or $-N(R^9)-$;

[0016] R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

[0017] R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro;

[0018] R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl or heteroaryl

[0019] R^5, R^6, R^7, and R^8 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, hetercycloalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxy or nitro; and

[0020] each instance of R^9 is independently hydrogen, alkyl, cycloalkyl, or heterocycloalkyl.

[0021] In some of the embodiments, X is absent or $-(CH(R^9))_z-$ and z is an integer of 1. In some embodiments, X is absent. In some embodiments, X is $-(CH(R^9))_z-$, and z is an integer of 1. In some embodiments, X is $-CH_2-$, $-CH(CH_2CH_3)$, or $-CH(CH_3)-$.

[0022] In some embodiments, Y is absent, or $-N(R^9)-$. In some embodiments, Y is absent. In some embodiments, Y is $-N(R^9)-$. In some embodiments, Y is –NH-, $-N(CH_3)$, or $-N(CH_2CH_3)-$.

[0023] In some embodiments, X is absent or $-(CH(R^9))_z-$, z is an integer of 1, and Y is absent or $-N(R^9)-$. In certain embodiments, X is absent and Y is $N(R^9)-$. In certain embodiments, Y is absent and X is $-(CH(R^9))_z-$ wherein z is an integer of 1. In certain embodiments, neither X nor Y is absent.

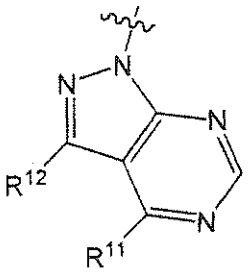
[0024] For example, in some embodiments of the compounds of Formula I, wherein both X and Y are present then Y is –NH- (e.g., X is $-(CH(R^9))_z-$ and Y is –NH-). In certain embodiments, X is $-CH_2-$, $-CH(CH_2CH_3)$, or $-CH(CH_3)-$ and Y is –NH-.

[0025] In other embodiments of the compounds of Formula I, wherein both X and Y are present then Y is $-N(CH_3)-$ (e.g., X is $-(CH(R^9))_z-$ and Y is $-N(CH_3)-$). In certain embodiments, X is $-CH_2-$, $-CH(CH_2CH_3)$, or $-CH(CH_3)-$ and Y is $-N(CH_3)-$.

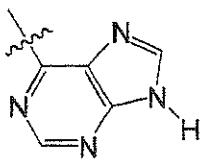
[0026] In yet other embodiments of the compounds of Formula I, wherein both X and Y are present then Y is $-N(CH_2CH_3)-$ (e.g., X is $-(CH(R^9))_z-$ and Y is $-N(CH_2CH_3)-$). In certain embodiments, X is $-CH_2-$, $-CH(CH_2CH_3)$, or $-CH(CH_3)-$ and Y is $-N(CH_2CH_3)-$.

[0027] In some embodiments, the group X-Y is $-CH_2-N(CH_3)$, $-CH_2-N(CH_2CH_3)$, $-CH(CH_2CH_3)-NH-$ or $-CH(CH_3)-NH-$.

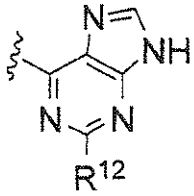
[0028] In some embodiments, W_d is a pyrazolopyrimidine of Formula III(a), or purine of Formula III(b), Formula III(c) or Formula III(d) below:



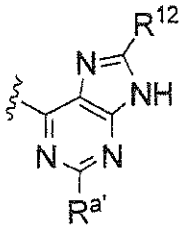
Formula III(a)



Formula III(b)



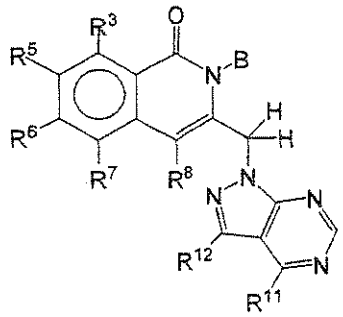
Formula III(c)



Formula III(d)

[0029] wherein $R^{a'}$ of Formula III(d) is hydrogen, halo, phosphate, urea, a carbonate, amino, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl; R^{11} of Formula III(a) is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} of Formula III(a), Formula III(c) or Formula III(d) is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In some embodiments, W_d is a pyrazolopyrimidine of Formula III(a), wherein R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} is cyano, amino, carboxylic acid, or amido.

[0030] In some embodiments, the compound of Formula I has the structure of Formula IV:

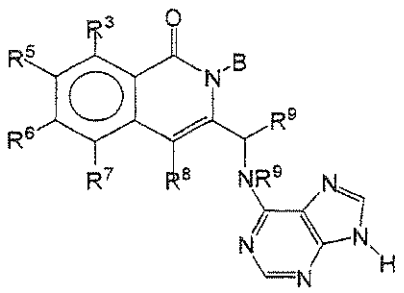


Formula IV

[0031] 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, the compound of Formula I has the structure of Formula IV wherein R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} is cyano, amino, carboxylic acid, or amido.

[0032] In some embodiments of the compound of Formula IV, R^{11} is amino. In some embodiments of the compound of Formula IV, R^{12} is alkyl, alkenyl, alkynyl, heteroaryl, aryl, or heterocycloalkyl. In some embodiments of the compound of Formula IV, R^{12} is cyano, amino, carboxylic acid, amido, monocyclic heteroaryl, or bicyclic heteroaryl.

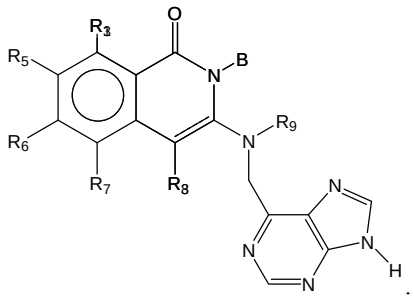
[0033] In some embodiments of the compound of Formula I, the compound has the structure of Formula V:



Formula V

[0034] In some of the embodiments of Formula V, NR^9 is $-N(CH_2CH_3)CH_2-$ or $N(CH_3)CH_2-$.

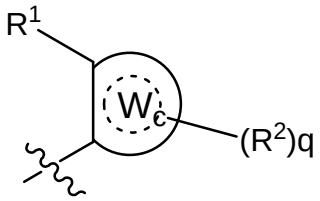
[0035] In some of the embodiments of Formula I, the compound has a structure of Formula VI:



Formula VI

[0036] In some of the embodiments of the compound of Formula VI, R^3 is-H, -CH_3, -Cl, or –F, and R^5, R^6, R^7, and R^8 are independently hydrogen.

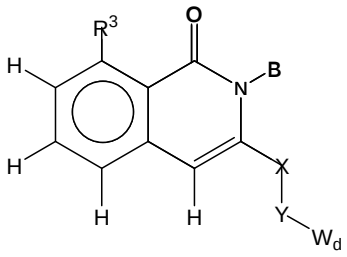
[0037] In some of the embodiments of Formula VI, B is a moiety of Formula II;



Formula II

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

[0038] In the present disclosure a compound and its pharmaceutically acceptable salts having the structure of Formula I-1 is also provided, wherein:



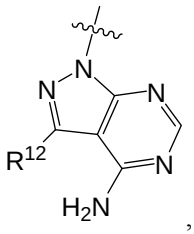
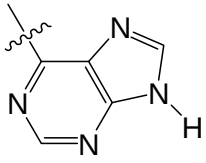
Formula I-1

[0039] B is a moiety of Formula II;

[0040] wherein W_c in B is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4;

[0041] X is absent or $–(CH(R^9))_z$-, and z is an integer of 1;

[0042] Y is absent, or -$N(R^9)$-;

[0043] when Y is absent, Wd is:  , or when Y is present, Wd is: 

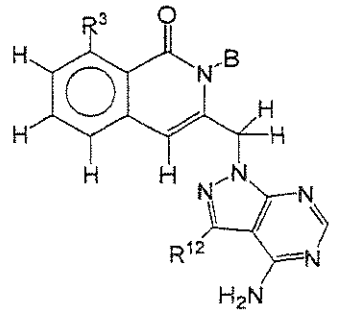
[0044] R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

[0045] R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro;

[0046] R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl or heteroaryl;

[0047] each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, cycloalkyl, or hetercyclooalkyl; and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

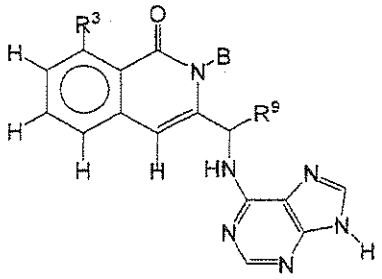
[0048] In some embodiments, a compound of Formula I or Formula I-1 has the structure of Formula IV-A:



Formula IV-A

In some embodiments of the compound of Formula IV-A, R^{12} is substituted benzoxazole.

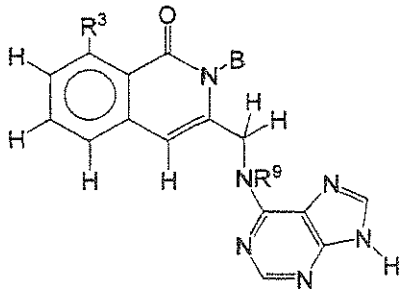
[0049] In some embodiments, a compound of Formula I or Formula I-1 has the structure of Formula V-A:



Formula V-A

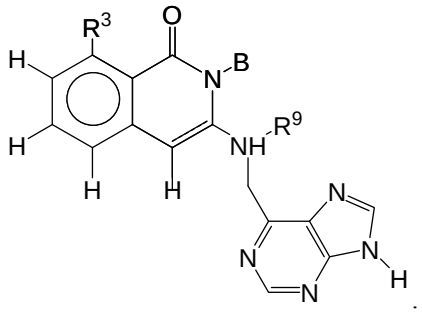
[0050] In some embodiments, a compound of Formula I or Formula I-1 has the structure of Formula IV-A or Formula V-A.

[0051] In some embodiments, a compound of Formula I or Formula I-1 has the structure of Formula V-B:



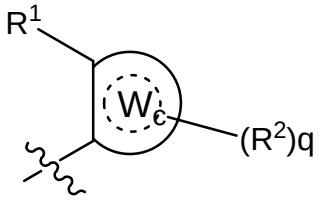
Formula V-B

[0052] In some embodiments, a compound of Formula I or Formula I-1 has the structure of Formula VI-A:



Formula VI-A

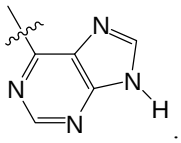
[0053] In some embodiments, a compound of Formula I or Formula I-1 is the compound wherein B is a moiety of Formula II;



Formula II

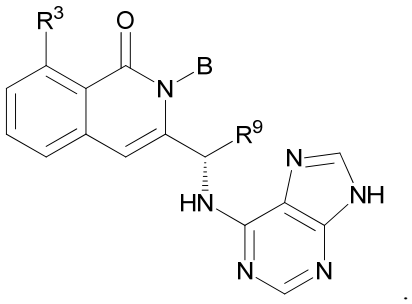
wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; q is an integer of 0 or 1; R^1 is hydrogen, alkyl, or halo; R^2 is alkyl or halo; andR^3 is hydrogen, alkyl, or halo. In some embodiments, when both X and Y are present then Y is –NH-. In other embodiments, R^3 is -H, -CH_3, -CH_2CH_3, -CF_3, -Cl or –F. In further embodiments, R^3 is methyl or chloro. In other embodiments, R^3 is haloalkyl. For example, R^3 is -CF_3, -CH_2F or –CHF_2.

[0054] In some embodiments of the compound of Formula I or Formula I-1 , X is –$(CH(R^9))_z$-, wherein R^9 is methyl and z = 1; and

Wd is .

[0055] In other embodiments of the compound of Formula I or Formula I-1, the compound is predominately in an (S)-stereochemical configuration.

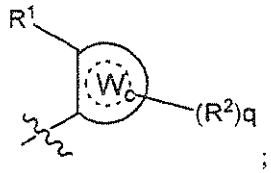
[0056] In further embodiments of the compound of the present disclosure, the compound has a structure of Formula V-A2:



Formula V-A2

or its pharmaceutically acceptable salt thereof, wherein

B is a moiety of Formula II:



;

Formula II

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

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

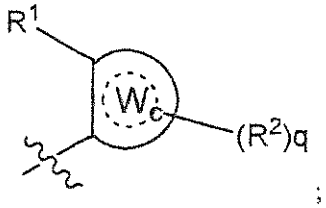
R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro;

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

each instance of R^9 is independently hydrogen, alkyl, or heterocycloalkyl.

[0057] In some embodiments of the compound of Formula V-A2, B is a moiety of Formula II:



;

Formula II

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

q is an integer of 0 or 1;

R^1 is hydrogen, alkyl, or halo;

R^2 is alkyl or halo; and

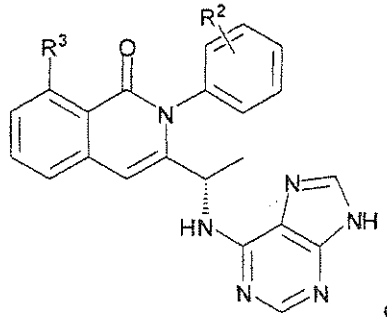
R^3 is hydrogen, alkyl, or halo.

[0058] For example, W_c is aryl, such as phenyl. Alternatively, W_c is cyclopropyl. Optionally, W_c is substituted by at least one of $-CH_3$, $-CH_2CH_3$, $-CF_3$, -Cl or –F.

[0059] In some embodiments of the compound of Formula V-A2, R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxycarbonyl sulfonamido, halo, cyano, hydroxy or nitro. For example, R^3 is -H, $-CH_3$, $-CH_2CH_3$, $-CF_3$, -Cl or –F. In some embodiments, R^3 is $-CH_3$ or -Cl. In other embodiments, R^3 is haloalkyl. For example, R^3 is $-CF_3$, $-CH_2F$ or $-CHF_2$.

[0060] In some embodiments of the compound of Formula V-A2, R^9 is $-CH_3$. In other embodiments, R^9 is $-CH_2-CH_3$.

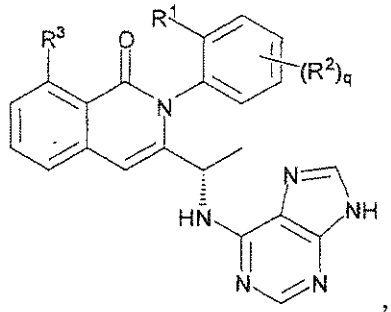
[0061] In some embodiments of the compound of Formula V-A2, the compound has the Formula:



or pharmaceutically acceptable salts thereof.

[0062] In some embodiments, R^2 is –H.

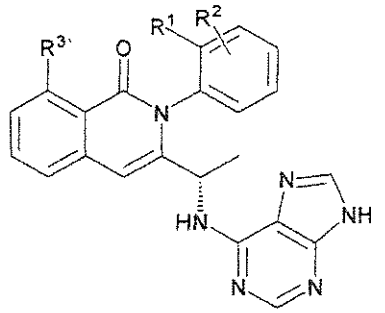
[0063] In some embodiments of the compound of Formula V-A2, the compound has the Formula:



, and stereoisomers and pharmaceutically acceptable salts thereof.

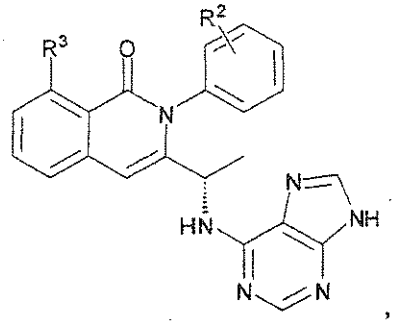
[0064] In certain embodiments, R^1 and R^2 are independently selected from the group of hydrogen and halo.

[0065] In certain embodiments, the compound is of the formula:



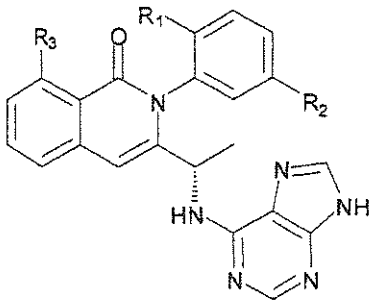
, or pharmaceutically acceptable salts thereof.

[0066] In some embodiments, R^1 is –H, e.g., of the formula:



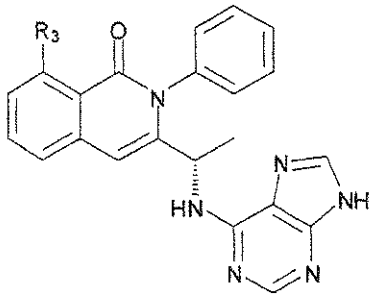
, or pharmaceutically acceptable salts thereof.

[0067] In certain embodiments, q is 1 and R^2 is provided in the meta position, e.g., of the formula:



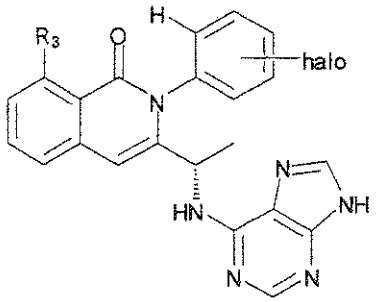
, or pharmaceutically acceptable salts thereof.

[0068] In certain embodiments, R^1 is H and R^2 is H, e.g. of the formula:



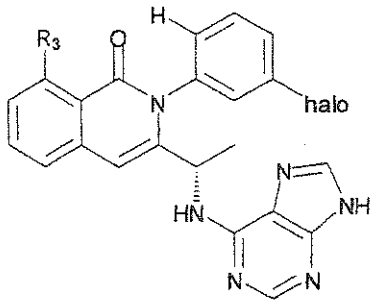
or pharmaceutically acceptable salts thereof.

[0069] In certain embodiments, R^1 is H, q is 1 and R^2 is halo (e.g., fluoro) of the formula:



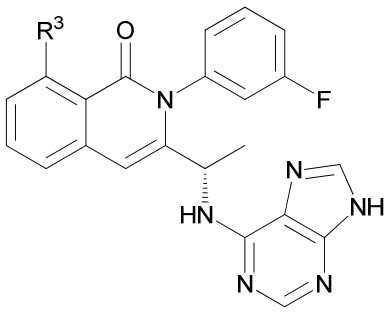
or pharmaceutically acceptable salts thereof.

[0070] In certain embodiments, R^1 is H, q is 1 and R^2 is halo (e.g., fluoro) in the meta position, e.g., of the formula:

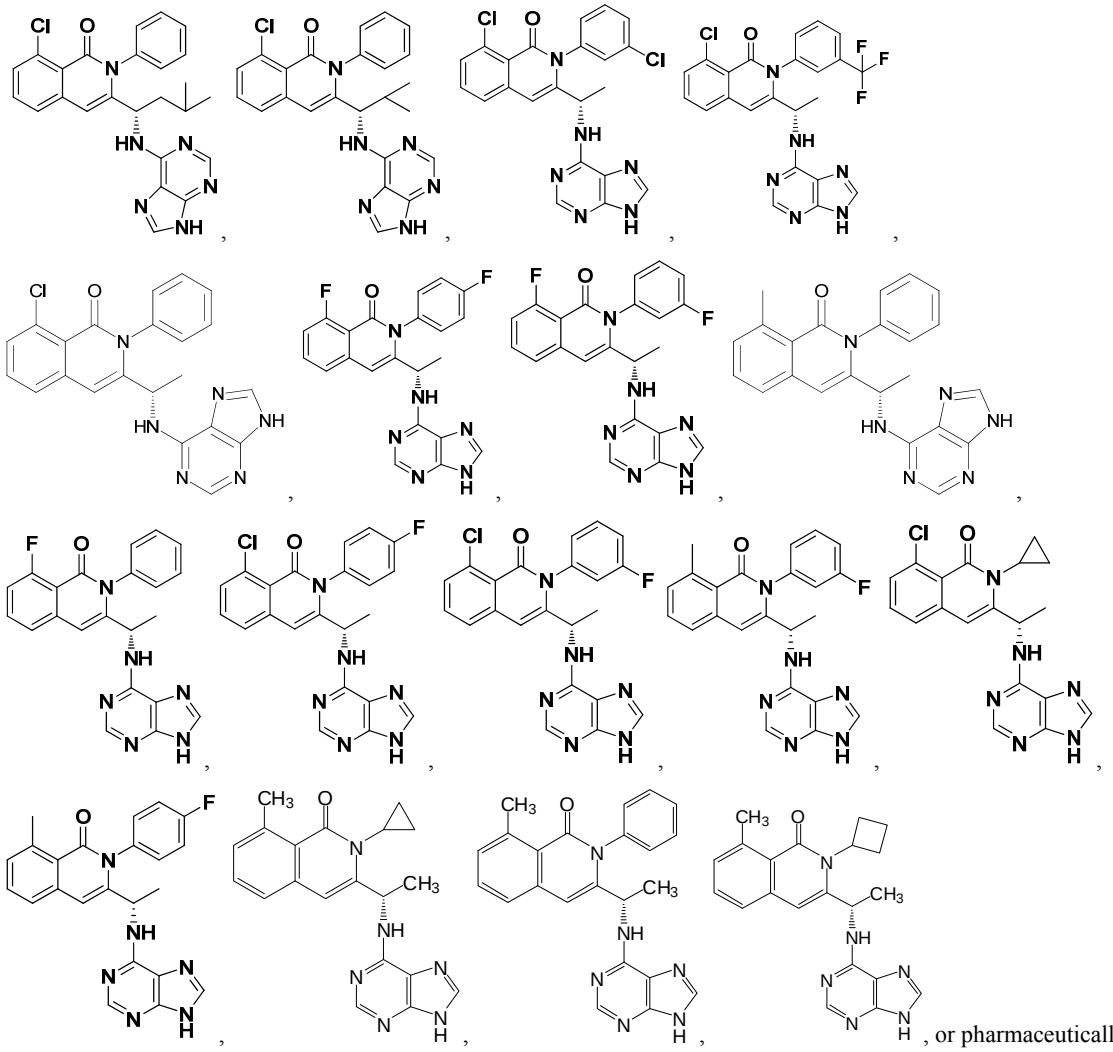


or pharmaceutically acceptable salts thereof.

[0071] In other embodiments, the compound of the Formula V-A2 has the Formula:



[0072] In some embodiments, the compound has the Formula:



acceptable salts thereof.

[0073] In the present disclosure, a pharmaceutical composition is also provided which comprises a pharmaceutically acceptable excipient and one or more compounds of any formulae provided herein, including but not limited to Formula I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI, and VI-A. In some embodiments, the composition is a liquid, solid, semi-solid, gel, or an aerosol form.

[0074] In the present disclosure, a method of inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase), is also 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 any formulae provided herien including but not limited to Formula I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI, and VI-A. 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 associated with malfunctioning of one or more types of PI3 kinase. Some exemplary diseases involving malfunctioning of one or more types of PI3 kinases are selected from the group consisting of autoimmune diseases, rheumatoid arthritis, respiratory disease, allergic reactions, and various types of cancers. Where desired, the compound used in the method has the structure of Formula IV, wherein R^{11} is amino and R^{12} is substituted phenyl.

[0075] 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 IV, and wherein R^{11} is amino and R^{12} is bicyclic heteroaryl.

[0076] In some embodiments, the method comprises administering a second therapeutic agent to the subject.

[0077] The present disclosure also 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, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI, and/or VI-A, 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.

[0078] 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.

INCORPORATION BY REFERENCE

[0079] 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

[0080] 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:

[0081] FIG. 1 depicts an exemplary protocol for measuring T-cell independent production of TNP specific antibodies *in vivo*.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] FIG. 12 depicts the effect of compound 292 ("Cpd-A") of formula V-A2 on reducing the increase in ankle diameter over time in a collagen-induced developing arthritis model in rats.

[0093] FIG. 13 depicts the effect of compound 292 ("Cpd-A") of formula V-A2 ankle histopathology in a collagen-induced established arthritis model in rats.

[0094] FIG. 14 depicts the effect of compound 292 ("Cpd-A") of formula V-A2 on reducing the increase in ankle diameter over time in a rat adjuvant induced arthritis model in rats.

[0095] FIG. 15 depicts the effect of compound 292 ("Cpd-A") of formula V-A2 of inhibiting LPS-induced total leukocyte neutrophil influx in a LPS-induced lung inflammation model in rats.

[0096] FIG. 16 depicts the effect of compound 292 ("Cpd-A") of formula V-A2 of inhibiting eosinophil influx in a OVA-induced allergic lung inflammation model in rats.

[0097] FIG. 17 depicts the effect of compound 200 ("Cpd-B") of formula V-A2 on reducing the increase in ankle diameter over time in a collagen-induced developing arthritis model in rats.

[0098] FIG. 18 depicts the effect of compound 270 ("Cpd-C") of formula V-A2 on reducing the increase in ankle diameter over time in a collagen-induced developing arthritis model in rats.

[0099] FIG. 19 depicts the effect of compound 196 ("Cpd-D") of formula V-A2 on reducing the increase in ankle diameter over time in a collagen-induced developing arthritis model in rats.

DETAILED DESCRIPTION OF THE INVENTION

[00100] 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.

[00101] 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.

[00102] As used in the specification and claims, the singular form "a", "an" and "the" includes plural references unless the context clearly dictates otherwise.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] The terms "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompass 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.

[00109] 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.

[00110] As used herein, "treatment" or "treating," or "palliating" or "ameliorating" is used interchangeably herein. These terms refer 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.

[00111] 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.

[00112] 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.

[00113] "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.

[00114] "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.

[00115] 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.

[00116] The term "B-ALL" as used herein refers to B-cell Acute Lymphoblastic Leukemia.

[00117] "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.

[00118] "Radiation therapy" means exposing a patient, using routine methods and compositions known to the practitioner, to radiation emitters such as alpha-particle emitting radionucleotides (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.

[00119] "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.

[00120] The term "*in vivo*" refers to an event that takes place in a subject's body.

[00121] 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.

[00122] 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 wherein hydrogen is replaced by deuterium or tritium, or wherein carbon atom is replaced by ^{13}C- or ^{14}C-enriched carbon, are within the scope of this invention.

[00123] 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.

[00124] 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.

[00125] 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.

[00126] Abbreviations used herein have their conventional meaning within the chemical and biological arts.

[00127] "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.

[00128] "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 subsituents described as suitable substituents for aryl and alkyl respectively.

[00129] "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 subsituents described as suitable substituents for aryl and alkyl respectively.

[00130] "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 subsituents described as suitable substituents for heterocycloalkyl and alkyl respectively.

[00131] 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.

[00132] "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 (ie. 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.

[00133] "Alkenyl-cycloalkyl" 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 subsituents described as suitable substituents for alkenyl and cycloalkyl respectively.

[00134] "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 (ie. 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.

[00135] "Alkynyl-cycloalkyl" refers to an -(alkynyl)cycloalkyl radical where alkynyl and cyclo alkyl are as disclosed herein and which are optionally substituted by one or more of the subsituents described as suitable substituents for alkynyl and cycloalkyl respectively.

[00136] "Carboxaldehyde" refers to a –(C=O)H radical.

[00137] "Carboxyl" refers to a –(C=O)OH radical.

[00138] "Cyano" refers to a –CN radical.

[00139] "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 (ie. 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.

[00140] "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 subsituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively.

[00141] "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 subsituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively.

[00142] "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 subsituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively.

[00143] 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.

[00144] 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.

[00145] 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.

[00146] 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.

[00147] "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.

[00148] "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.

[00149] "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.

[00150] 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.

[00151] "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.

[00152] "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.

[00153] "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 subsituents described as suitable substituents for aryl and alkyl respectively.

[00154] "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.

[00155] "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.

[00156] "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.

[00157] "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.

[00158] "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 subsituents described as suitable substituents for heteroalkyl and aryl respectively.

[00159] "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 subsituents described as suitable substituents for heteroalkyl and heteroaryl respectively.

[00160] "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 subsituents described as suitable substituents for heteroalkyl and heterocycloalkyl respectively

[00161] "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 subsituents described as suitable substituents for heteroalkyl and cycloalkyl respectively.

[00162] "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.

[00163] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as pyridinyl N-oxides.

[00164] "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.

[00165] "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.

[00166] "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.

[00167] "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, i.e. having a different stereochemical configuration. "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.

[00168] "Enantiomeric purity" as used herein refers to the relative amounts, expressed as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For example, if a compound, which may potentially have an (R)- or an (S)- isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (R)- or (S)- isomer. If that compound has one isomeric form predominant over the other, for example, 80% (S)- and 20% (R)-, the enantiomeric purity of the compound with respect to the (S)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways known in the art, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or the Pirkle alcohol, or derivatization of a compounds using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

[00169] "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.

[00170] "Nitro" refers to the $-NO_2$ radical.

[00171] "Oxa" refers to the -O- radical.

[00172] "Oxo" refers to the =O radical.

[00173] "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.

[00174] The terms "enantiomerically enriched," "enantiomerically pure" and "non-racemic," as used interchangeably herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (S)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (S)-enantiomer relative to the (R)-enantiomer, more preferably at least 75% by weight, and even more preferably at least 80% by weight. In some embodiments, the enrichment can be much greater than 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, more preferably at least 90% by weight, and even more preferably at least 95% by weight.
[00175] In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen, S.H., et al., Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).
[00176] 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.
[00177] 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.
[00178] "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.
[00179] "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.
[00180] "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 cycloakyl 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.

[00181] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl), and -S-(optionally substituted heterocycloalkyl).

[00182] "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).

[00183] "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).

[00184] "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 subsituents described for alkyl, cycloalkyl, aryl, heteroaryl respectively

[00185] "Sulfoxyl" refers to a $-S(=O)_2OH$ radical.

[00186] "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.

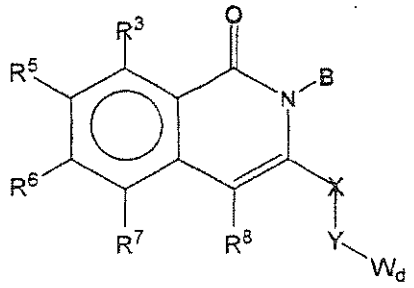
[00187] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O$- is equivalent to $-OCH_2$-.

[00188] 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.

[00189] Chemical entities include, but are not limited to, compounds of Formula I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI or VI-A, 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.

[00190] In addition, if the compound of Formula I 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.

[00191] In one aspect, the present invention provides a compound of Formula I:

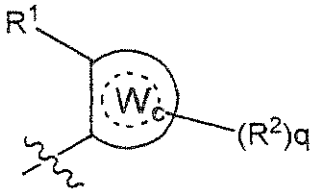


Formula I

[00192] or its stereoisomers or pharmaceutically acceptable salt thereof, wherein

[00193] W_d is heterocycloalkyl, aryl or heteroaryl;

[00194] B is alkyl, amino, heteroalkyl, or a moiety of Formula II;



Formula II

[00195] wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

[00196] q is an integer of 0, 1, 2, 3, or 4;

[00197] X is absent or is $-(CH(R^9))_z$-and z is an integer of 1, 2, 3, or 4;

[00198] 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 $-C(=O)-(CHR^9)_z$-;

[00199] 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;

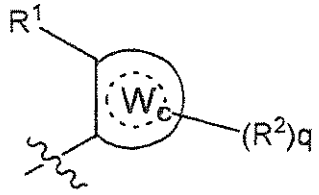
[00200] R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

[00201] R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl, or heteroaryl;

[00202] 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

[00203] each instance of R^9 is independently hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, or C_2-C_{10}heteroalkyl.

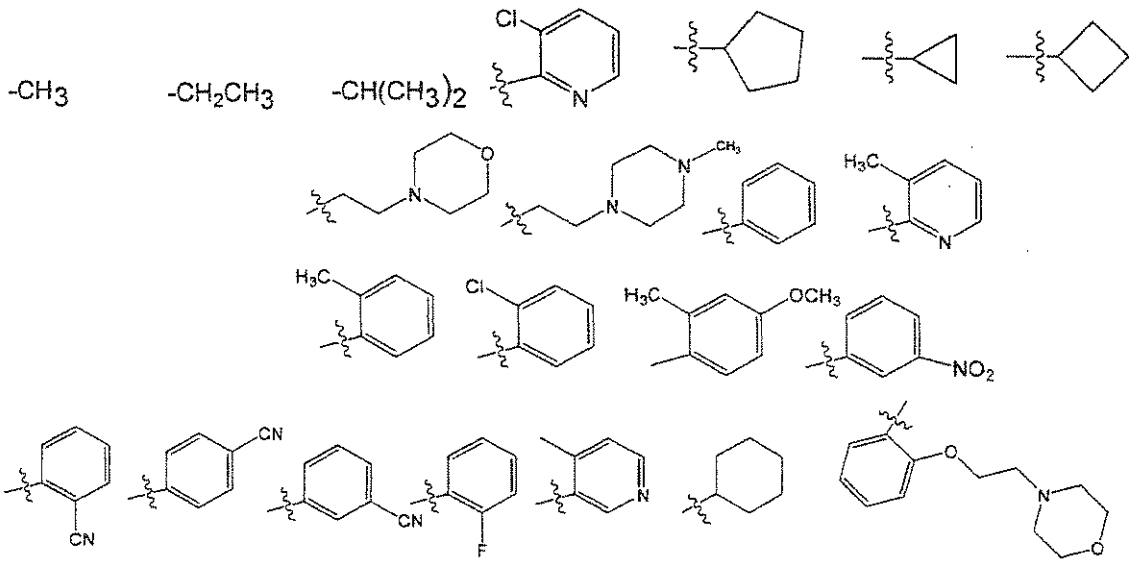
[00204] In some embodiments, B is unsubstituted or substituted alkyl, including but not limited to $-(CH_2)_2$-NR^aR^a ,wherein each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, 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.

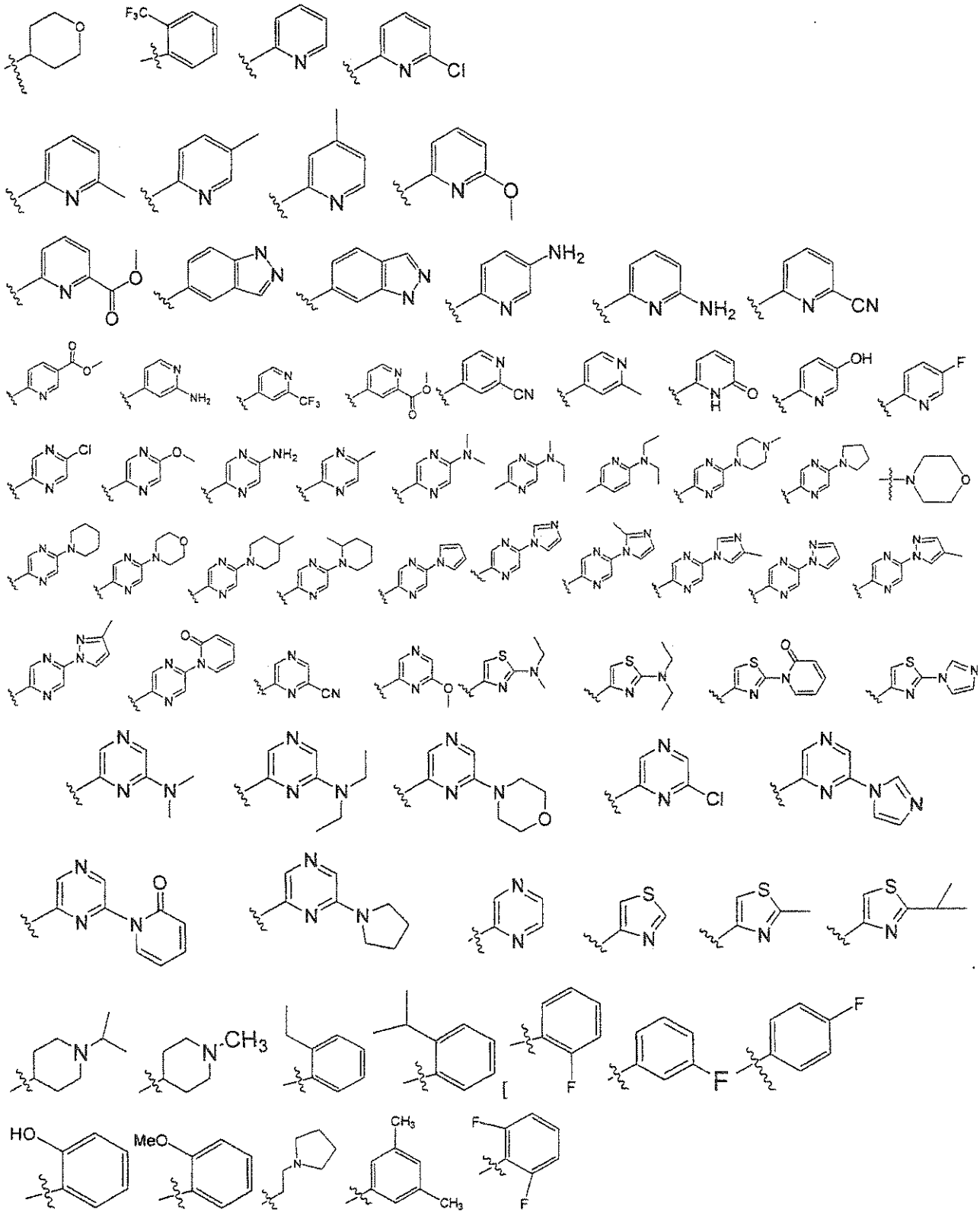


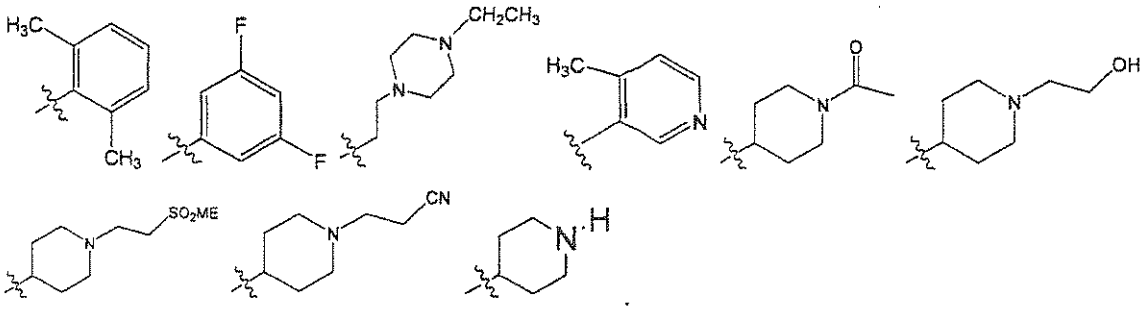
Formula II

[00205] In some embodiments, B is a moiety of Formula II and wherein W_e 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 limted to cyclopentyl and cyclohexyl.

[00206] In some embodiments, B is one of the following moieties:







[00207] 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.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] 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.

[00212] 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.

[00213] 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.

[00214] 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.

[00215] 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.

[00216] In some embodiments of the compound of Formula I, 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 is –I, -F, -Cl, or -Br.

[00217] 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 $-CF_3$, $-CH_2F$ or $-CHF_2$.

[00218] 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.

[00219] In some embodiments of the compound of Formula I, 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 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 $-CF_3$.

[00220] 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.

[00221] In some embodiments of the compound of Formula I, 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 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 $-CF_3$.

[00222] 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.

[00223] In some embodiments of the compound of Formula I, 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-

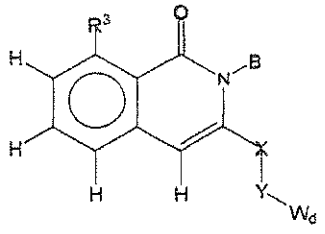
C_4sulfonamido. In some embodiments, R^7 is halo, which is is –I, -F, -Cl, or -Br. In some embodiments, R^7 is selected from the group consisting of cyano, hydroxy, and nitro. In some other embodiments, R^7 is $-CH_3$, $-CH_2CH_3$, n-propyl, isopropyl, $-OCH_3$, $-OCH_2CH_3$, or $-CF_3$.

[00224] 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.

[00225] In some embodiments of the compound of Formula I, 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 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 $-CF_3$.

[00226] 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.

[00227] In some embodiments of the compound of Formula I, R^5, R^6, R^7, and R^8 are H and the compound has a structure of Formula I-1:



Formula I-1.

[00228] In some embodiments of the compound of Formula I, X is absent. In some embodiments, X is $-(CH(R^9))_z$, and z is an integer of 1, 2, 3 or 4.

[00229] 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 ethyl, 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.

[00230] The invention also provides a compound of Formula I wherein R^9 is hydrogen, and X is -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH(CH_3)$-, or -$CH(CH_2CH_3)$-. In other embodiments, X is $-(CH(R^9))_z$, R^9 is not hydrogen, and z is an integer of 1. When X is-$CH(R^9)$- and R^9 is not hydrogen, then the compound can adopt either an (S)- or (R)-stereochemical configuration with respect to carbon X. In some embodiments, the compound is a racemic mixture of (S)- and (R) isomers with respect to carbon X. In other embodiments, the present invention provides a mixture of compounds of Formula I wherein individual compounds of the mixture exist predominately in an (S)- or (R)- isomeric configuration. For example, the compound mixture has an (S)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more at the X carbon. In other embodiments, the compound mixture has an (S)-enantiomeric purity of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[00231] In other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more at the X carbon. In some other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[00232] In other embodiments, the compound mixture contains identical chemical entities except for their stereochemical orientations, namely (S)- or (R)- isomers. For instance, in the compounds of Formula I, when X is -$CH(R^9)$-, and R^9 is not hydrogen, then the -$CH(R^9)$- is in an (S)- or (R)- sterochemical orientation for each of the identical chemical entities. In some embodiments, the mixture of identical chemical entities of Formula I is a racemic mixture of (S)- and (R)- isomers at the carbon represented by X. In another embodiment, the mixture of the identical chemical entities (except for their stereochemical orientations),contain predominately (S)-isomers or predominately (R)- isomers. For example, the (S)-isomers in the mixture of identical chemical entities are present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5% ,or more, relative to the (R)- isomers. In some embodiments, the (S)- isomers in the mixture of identical chemical entities are present at an (S)-enantiomeric purity of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[00233] In another embodiment, the (R)- isomers in the mixture of identical chemical entities (except for their stereochemical orientations),are present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more, relative to the (S)-isomers. In some embodiments, the (R)- isomers in the mixture of identical chemical entities (except for their stereochemical orientations), are present at a (R)- enantiomeric purity greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[00234] In some embodiments, the compound of Formula I, X is $-CH(R^9)-$, R^9 is methyl or ethyl, and the compound is the (S)- isomer.

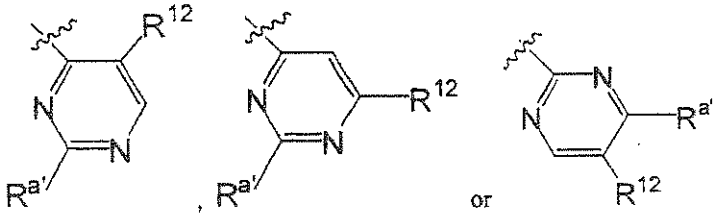
[00235] In some embodiments of the compound of Formula I, Y is absent. In some embodiments, Y is -O-, -S-, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-N(R^9)(C=O)-$, $-N(R^9)(C=O)NH-$, $-N(R^9)C(R^9)_2-$ (such as $-N(R^9)CH_2-$, specifically $-N(CH_3)CH_2-$, $N(CH(CH_3)_2)CH_2-$ or $N(CH_2CH_3)CH_2-$), $-N(R^9)-$, $-N(CH_3)-$, $-N(CH_2CH_3)-$, 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.

[00236] In some embodiments, at least one of X and Y is present. In some embodiments of the compound of Formula I, -XY- is $-CH_2-$, $-CH_2-N(CH_3)$, $-CH_2-N(CH_2CH_3)$, $-CH(CH_3)-NH-$, (S) $-CH(CH_3)-NH-$, or (R) $-CH(CH_3)-NH-$. In other embodiments, X-Y is $-N(CH_3).CH_2-$, $N(CH_2CH_3)\ CH_2-$, $-N(CH(CH_3)_2)CH_2-$, or $-NHCH_2-$. The invention provides other compounds of Formula I wherein when X-Y is X is $-(CH(R^9))_zN(R^9)-$, z is an integer of 1, 2, 3 or 4, and $-N(R^9)-$ is not –NH-, then -XY- is not connected to purinyl.

[00237] In some embodiments, W_d in a formula disclosed herein (including but not limited to I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI and VI-A), is a member selected from the group consisting of unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl.

[00238] In various embodiments, W_d is unsubstituted or substituted monocyclic heteroaryl (including but not limited to pyrimidinyl, pyrrolyl, pyrazinyl, triazinyl, or pyridazinyl) or unsubstituted or substituted bicyclic heteroaryl.

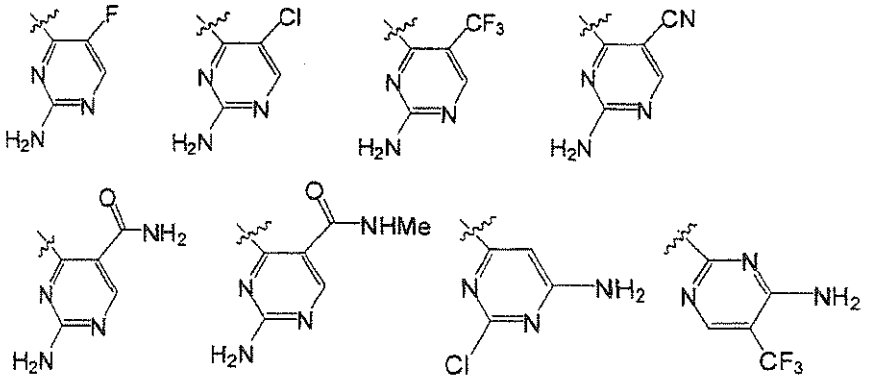
[00239] In some embodiments, W_d is a monocyclic heteroaryl of the following formula:



wherein $R^{a'}$ is hydrogen, halo, phosphate, urea, a carbonate, unsubstituted or substituted amino, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heteroalkyl, or unsubstituted or substituted heterocycloalkyl; and

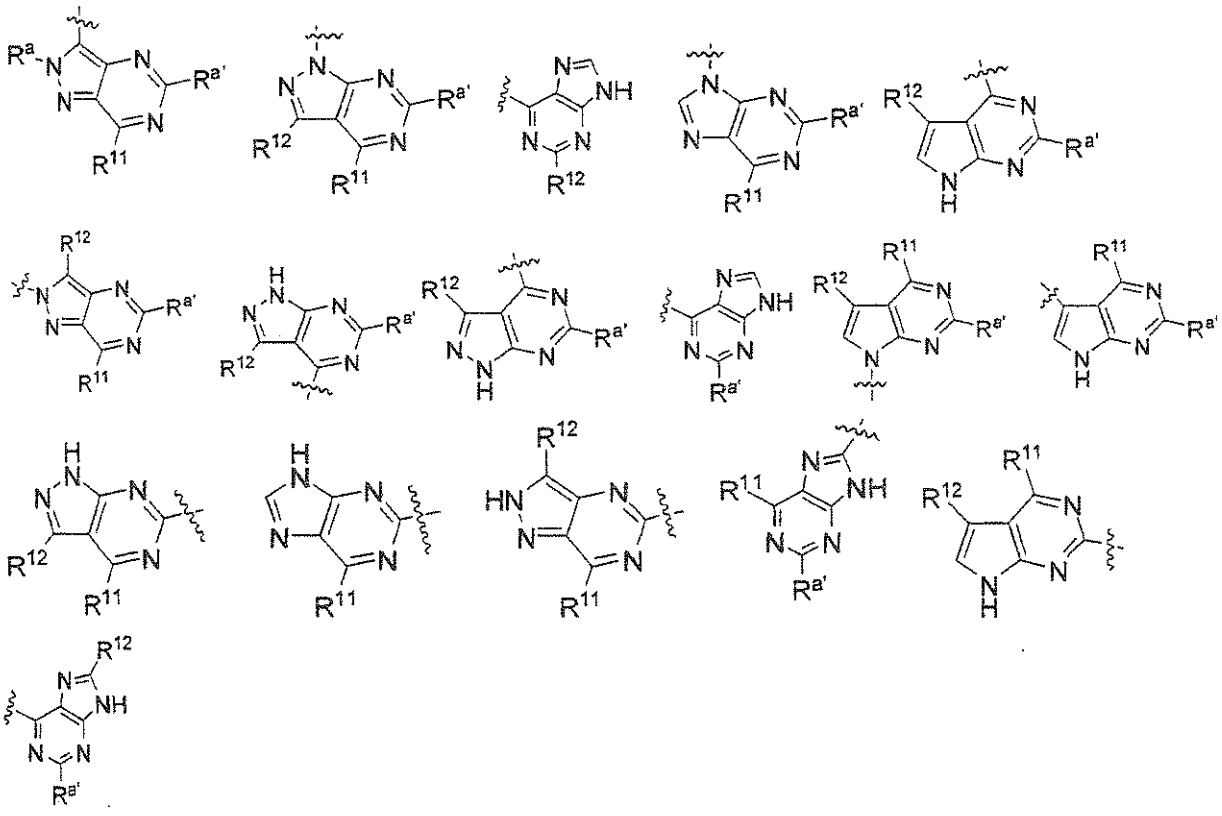
R^{12} is H, unsubstituted or substituted alkyl, unsubstituted or substituted cyano, unsubstituted or substituted alkynyl, unsubstituted or substituted alkenyl, halo, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocycloalkyl, unsubstituted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

The invention provides monocyclic heteroaryl W_d including but not limited to one of the following formulae:



[00240] In some embodiments, W_d in a formula disclosed herein (including but not limited to I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI and VI-A), 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.

[00241] In some embodiments W_d is one of the following:



wherein $R^{8'}$ is hydrogen, halo, phosphate, urea, a carbonate, unsubstituted or substituted amino, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heteroalkyl, or unsubstituted or substituted heterocycloalkyl;

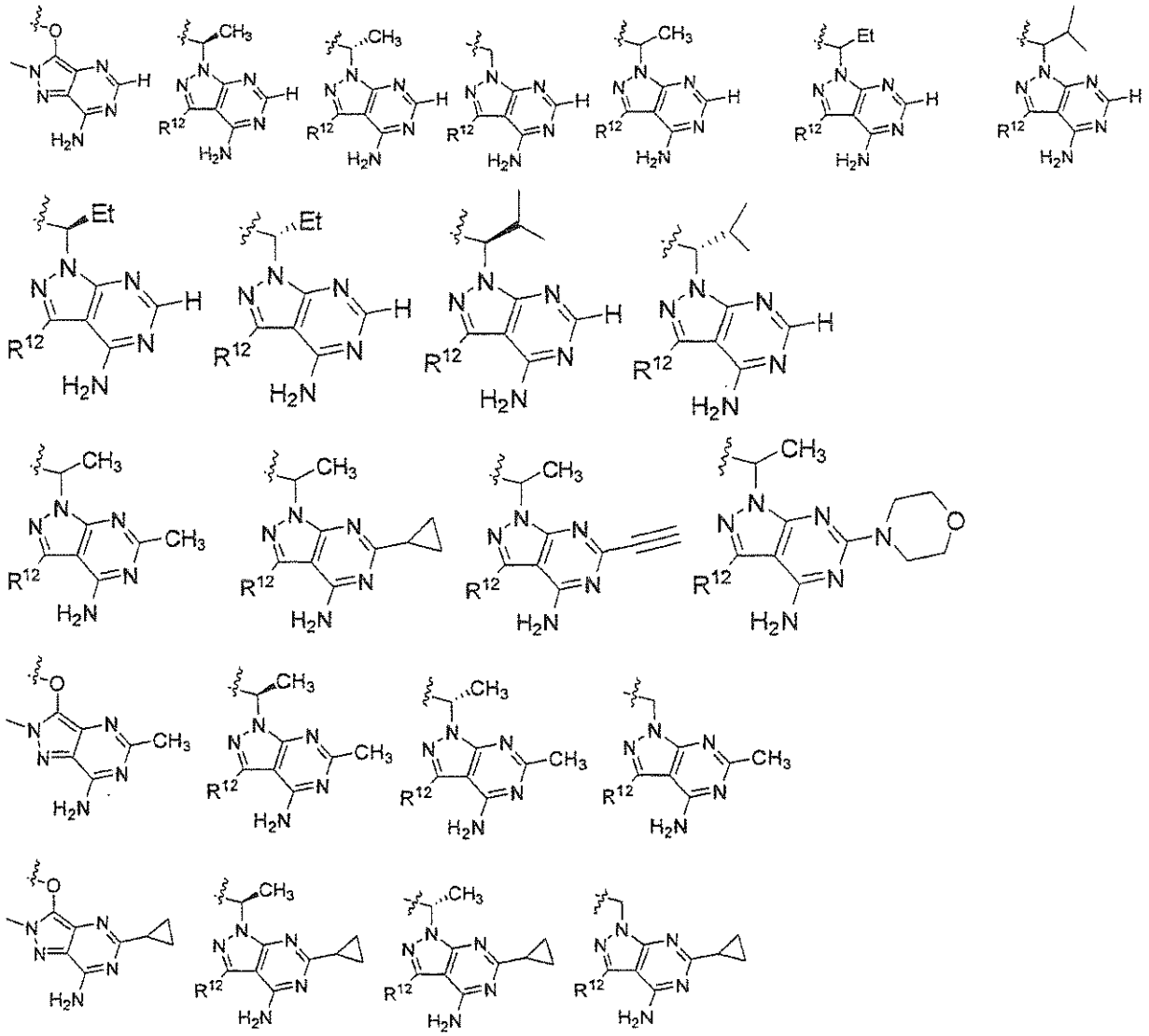
R^{11} is hydrogen, unsubstituted or substituted alkyl, halo (which includes –I, -F, -Cl, or –Br), unsubstituted or substituted amino, unsubstituted or substituted amido, hydroxy, or unsubstituted or substituted alkoxy, phosphate, unsubstituted or substituted urea, or carbonate; and

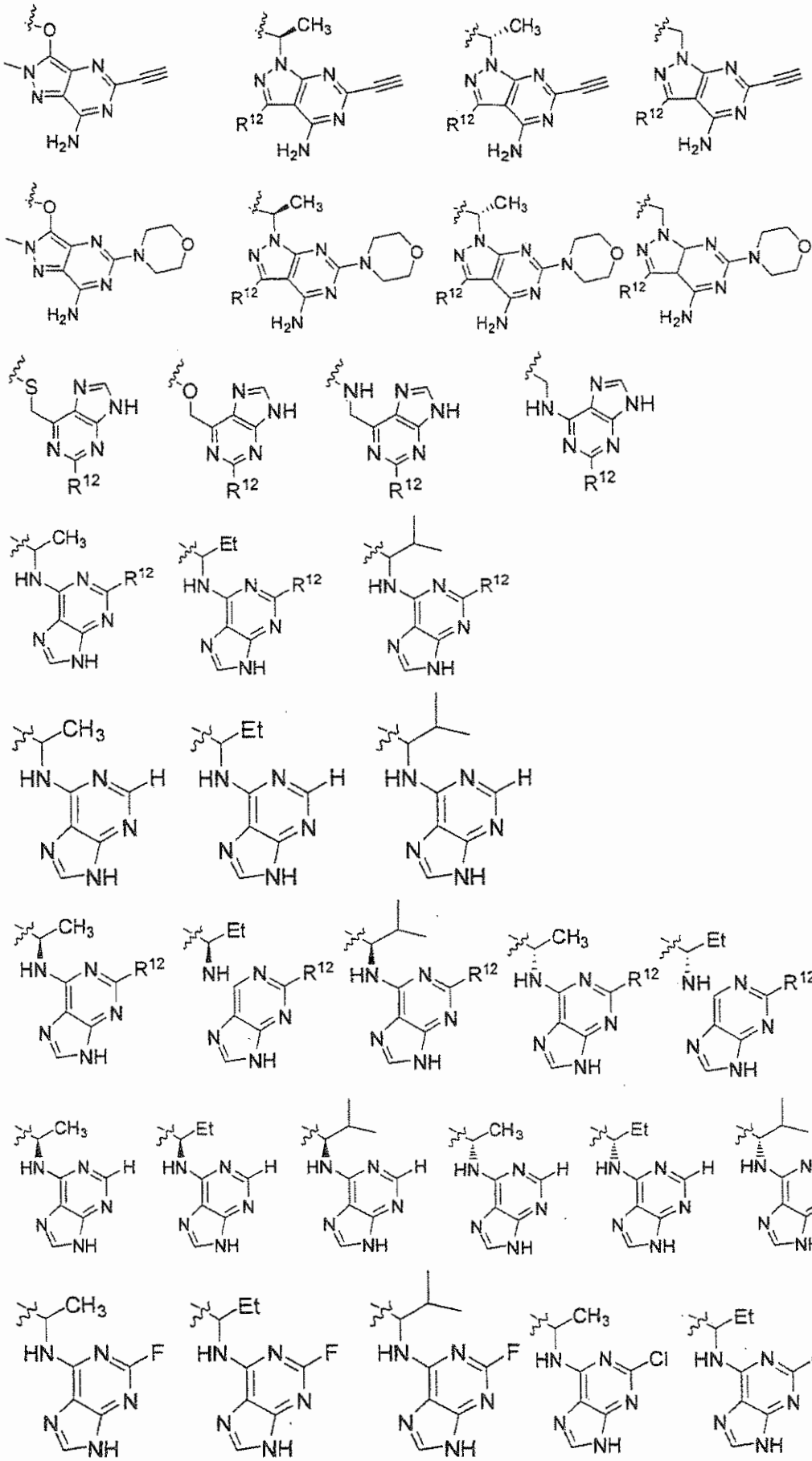
R^{12} is H, unsubstituted or substituted alkyl, unsubstituted or substituted cyano, unsubstituted or substituted alkynyl, unsubstituted or substituted alkenyl, halo, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocycloalkyl, unsubstituted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

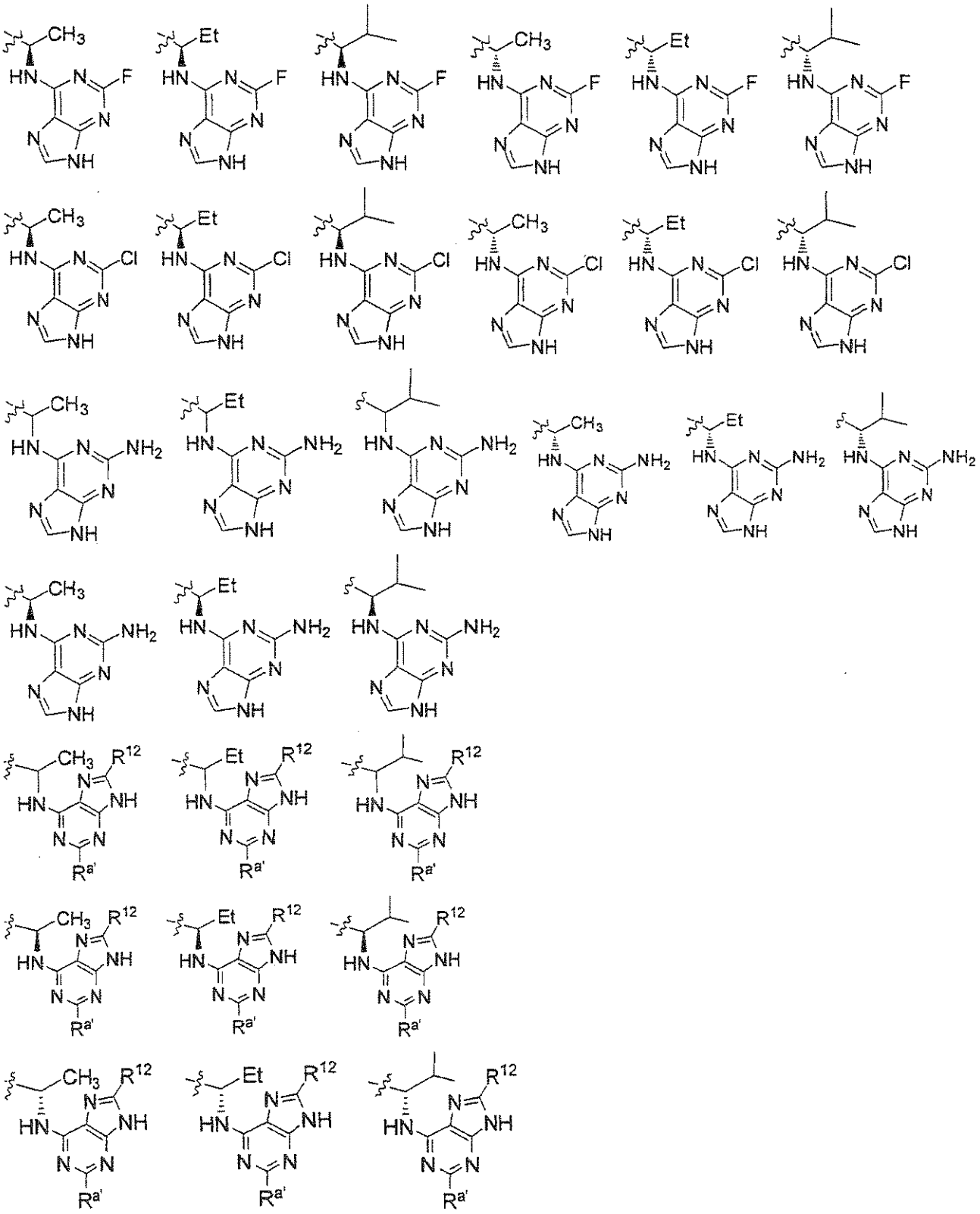
[00242] In some embodiments of W_d of the compounds of Formula I, when $R^{8'}$ is alkyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl, it is substituted by phosphate, urea, or carbonate.

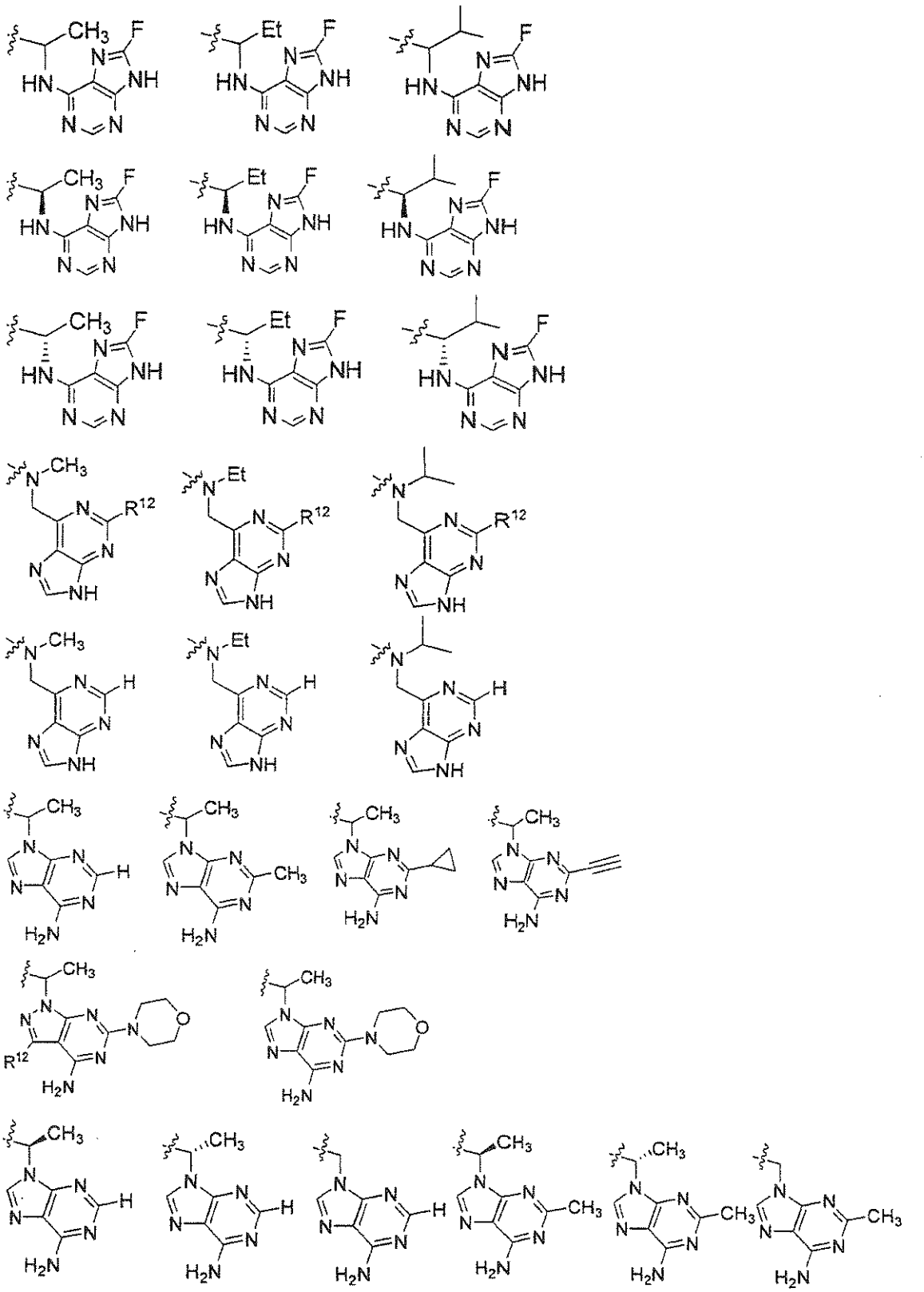
[00243] In some embodiments of W_d of the compounds of Formula I, when R^{11} is alkyl, amino, amido, hydroxy, or alkoxy, it is substituted by phosphate, urea, or carbonate.

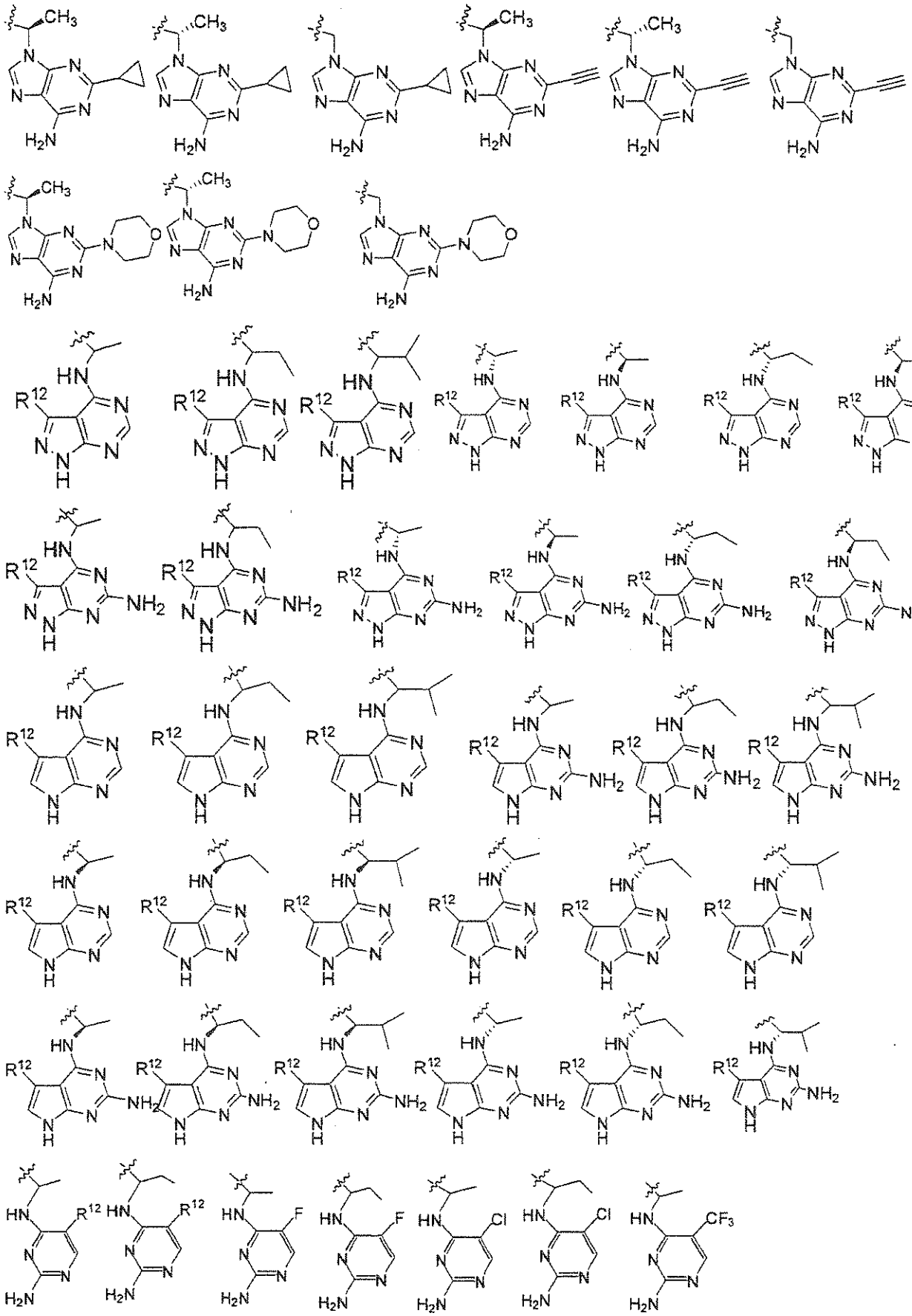
[00244] In some embodiments of the compound of Formula I,-X-Y-W_d is one of the following moieties:

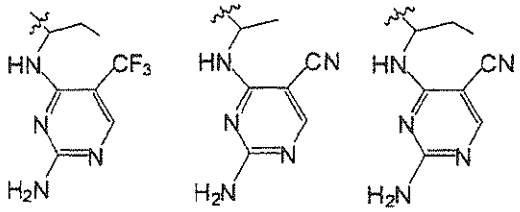


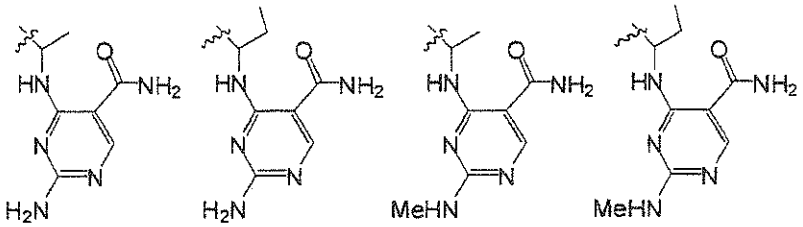


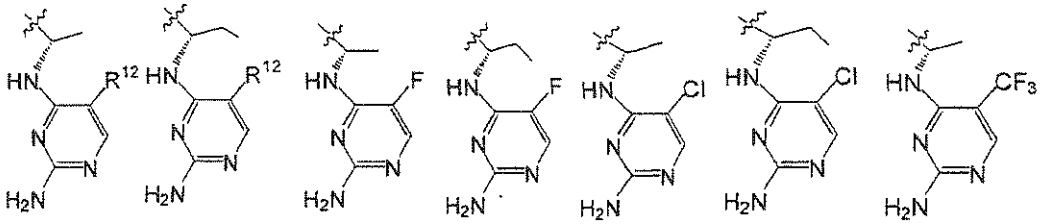


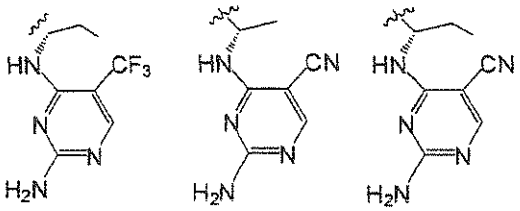


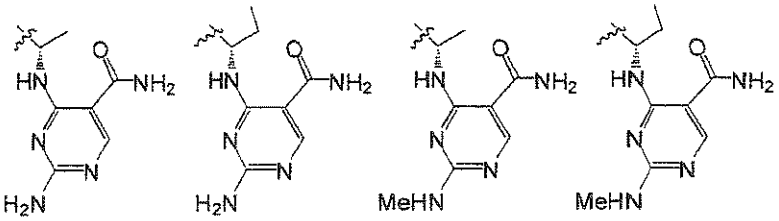


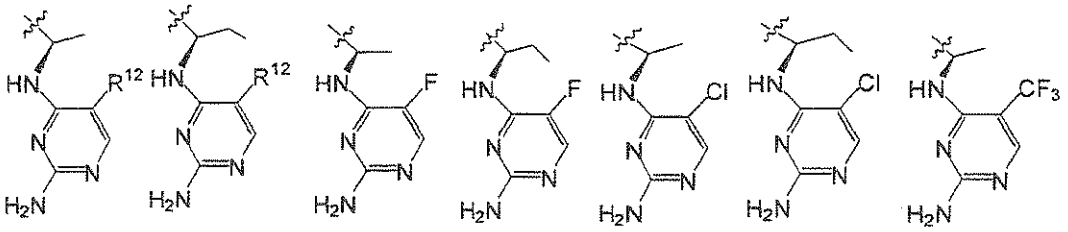


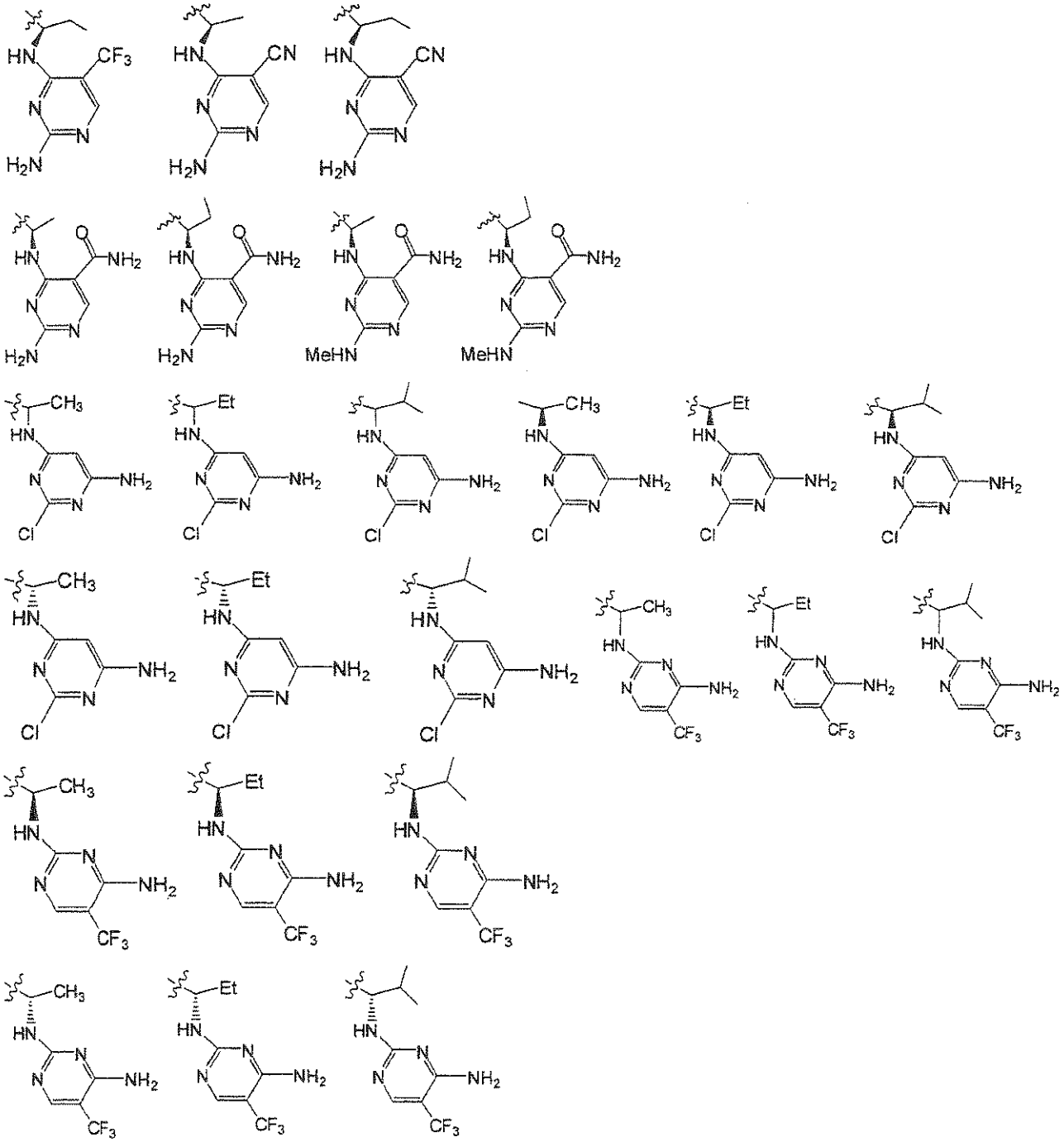












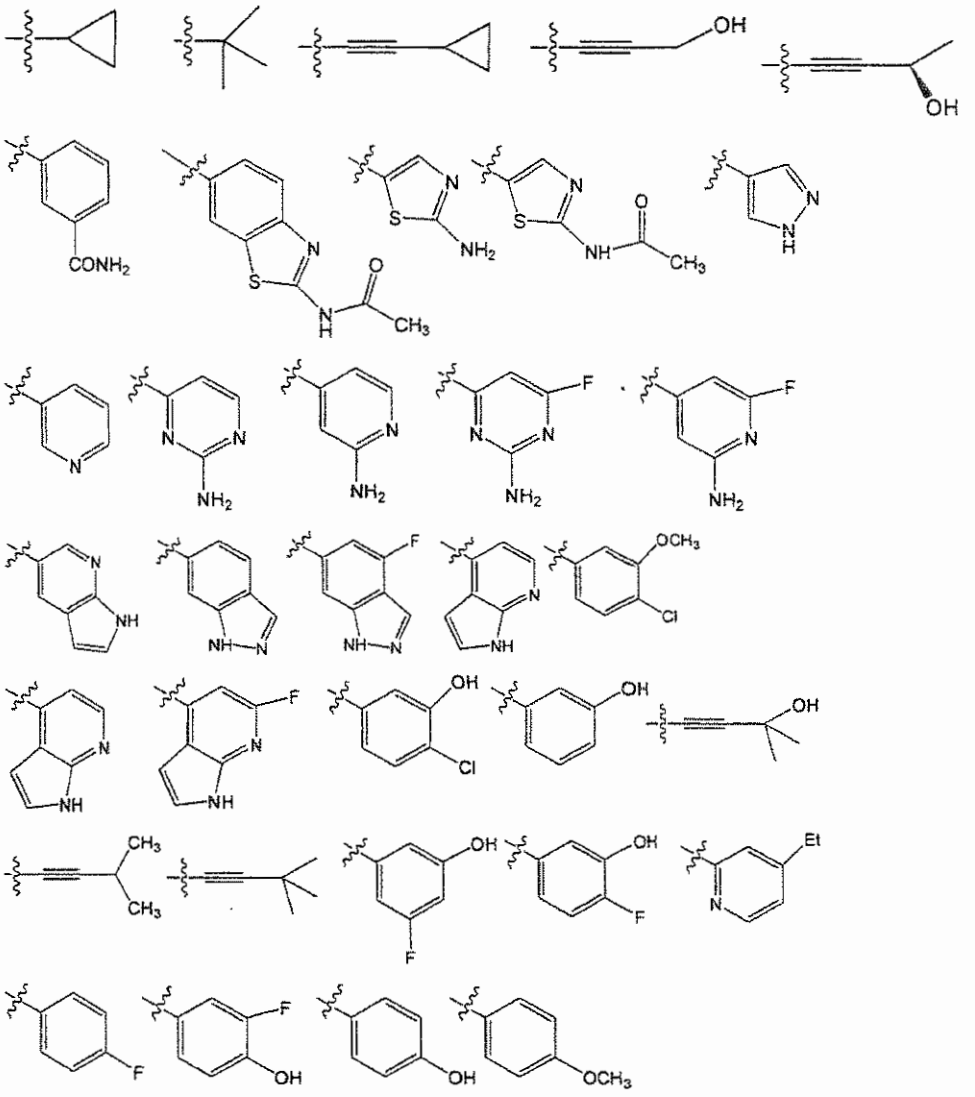
[00245] In some embodiments of the compound of Formula I, R^{12} is a member of the group consisting of hydrogen, cyano, halo, unsubstituted or substituted alkyl, unsubstituted or substituted alkynyl, and unsubstituted or substituted alkenyl. In some embodiments, R^{12} is unsubstituted or substituted 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 bicylic 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

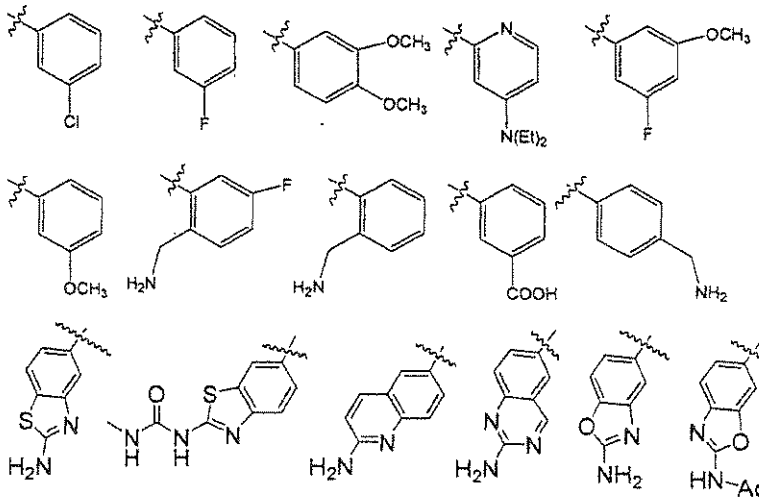
embodiments, R^{12} is unsubstituted or substituted cycloalkyl, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkyl substituted by one oxo, cycloalkyl having an unsaturated moiety connected to the cycloalkyl ring. In some embodiments, R^{12} is unsubstituted or substituted amido, carboxylic acid, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted acyl, or unsubstituted or substituted sulfonamido.

[00246] 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.

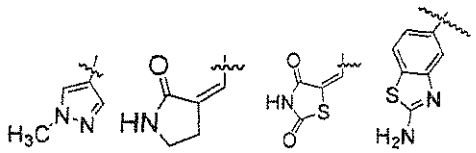
[00247] In some embodiments, when R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkoxycarbonyl, amido, acyloxy, acyl, or sulfonamido, it is substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, 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, aloxycarbonyl, or sulfonamido may itself be substituted.

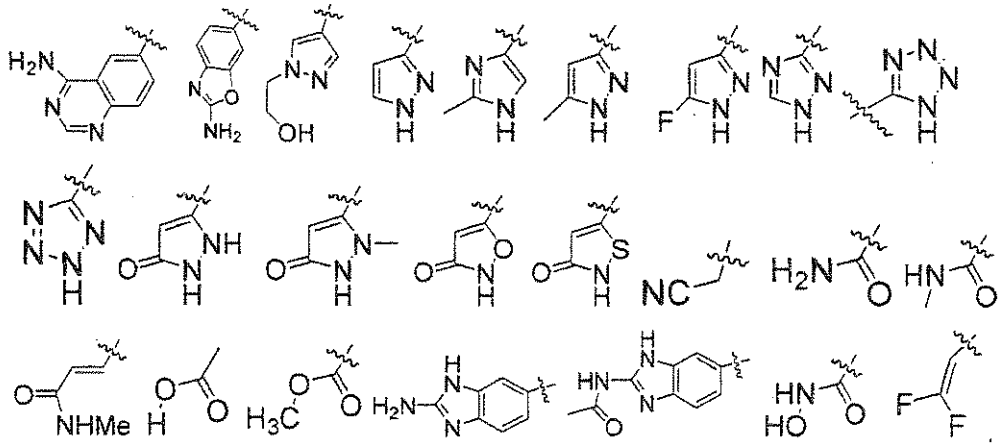
[00248] In some embodiments of the compound of Formula I, R^{12} of W_d is one of the following moieties:



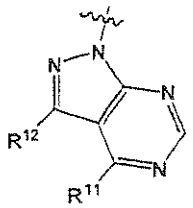


-CN, -Br, -Cl, -I, -H, -Me, -Et, -*i*-Pr,





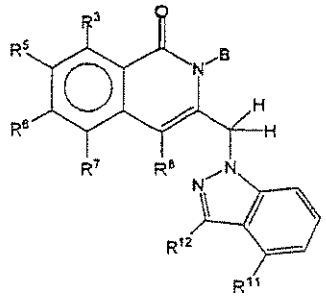
[00249] In some embodiments of the compound of Formula I, W_d is a pyrazolopyrimidine of Formula III:



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 and R^{12} is cyano, amino, carboxylic acid, acyloxy, alkoxycarbonyl,or amido.

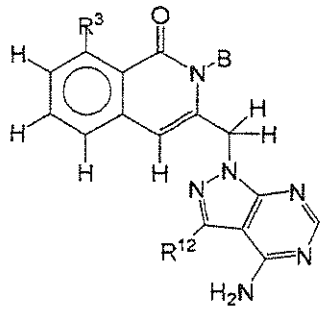
[00250] In some embodiments of the invention, the compound of Formula I is a compound having a structure of Formula IV:



Formula IV

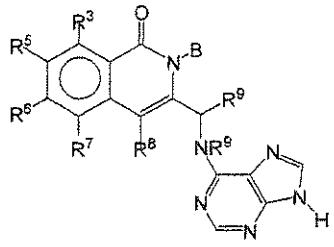
In some embodiments of the compound of Formula IV, R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In another embodiment, R^{11} is amino and R^{12} is alkyl, alkenyl, heteroaryl, aryl, or heterocycloalkyl. In some embodiments, R^{11} is amino and and R^{12} is cyano, amino, carboxylic acid, alkoxycarbonyl, or amido.

In some embodiments, the compound of Formula IV is a compound of Formula IV-A:

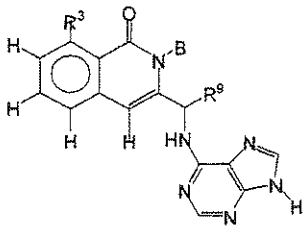


Formula IV-A

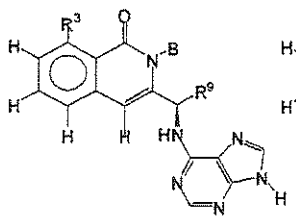
[00251] The invention also provides compounds of Formula I having a structure of any of Formulae V, V-A1, V-A2, V-B, VI, VI-A, VII-A1, VII-A2, VIII-A1, VIII-A2, IX-A1, IX-A2, X-A1, X-A2, XI-A1, XI-A2, XII-A, XII-A1, XII-A2, XIII-A, XIII-A1, XIII-A2, XIV-A, XIV-A1, XIV-A2, XV-A, XV-A1, XV-A2, XVI-A, XVI-A1, XVI-A2, XVII-A, XVII-A1, XVII-A2, XVIII-A, XVIII-A1, or XVIII-A2:



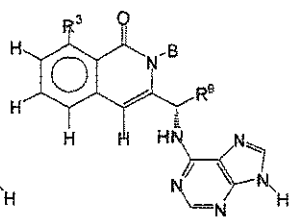
Formula V



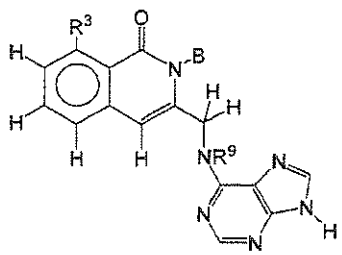
Formula V-A



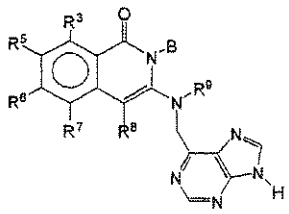
Formula V-A1



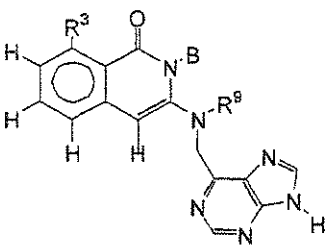
Formula V-A2



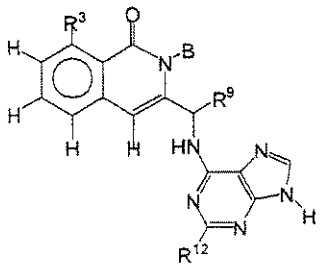
Formula V-B



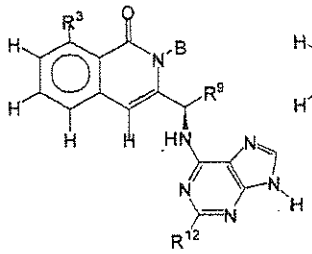
Formula VI



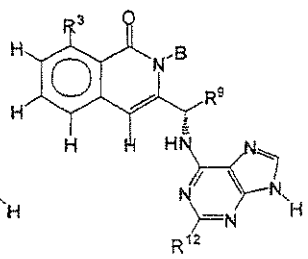
Formula VI-A



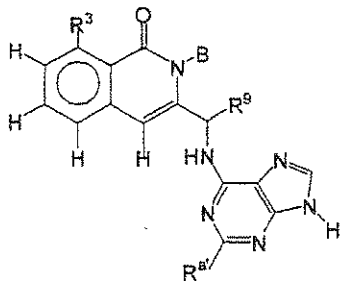
Formula VII-A



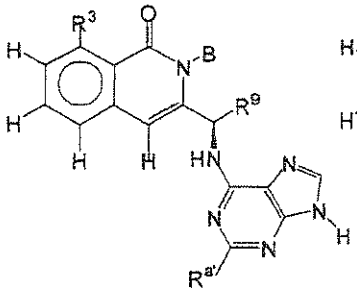
Formula VII-A1



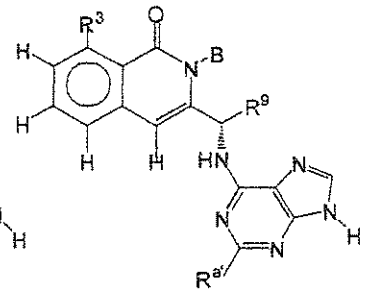
Formula VII-A2



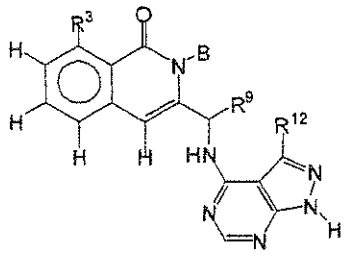
Formula VIII-A



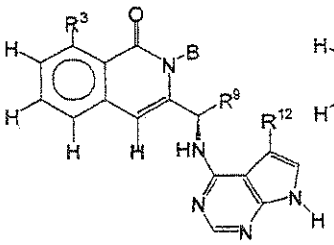
Formula VIII-A1



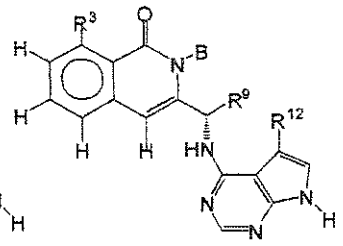
Formula VIII-A2



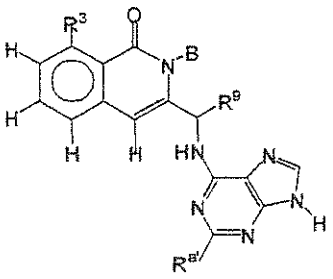
Formula IX-A



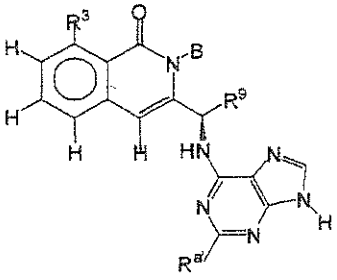
Formula IX-A1



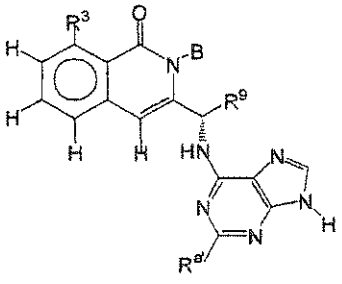
Formula IX-A2



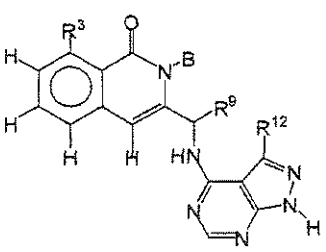
Formula X-A

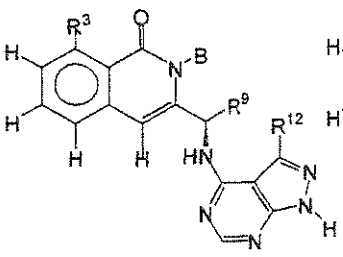


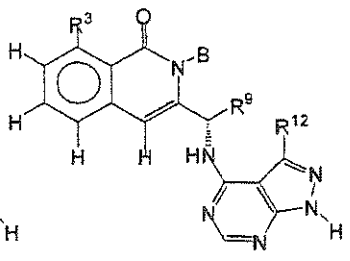
Formula X-A1



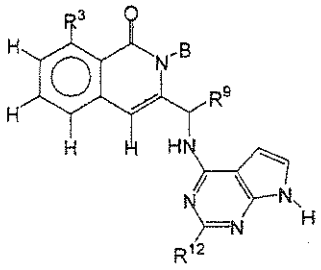
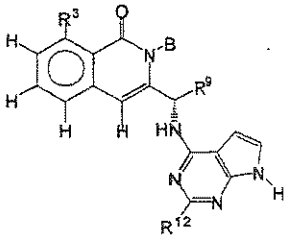
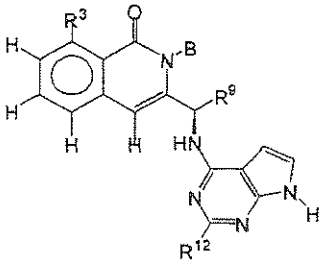
Formula X-A2



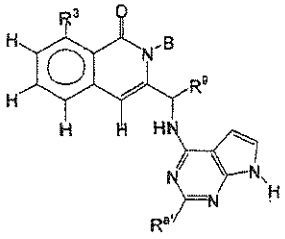
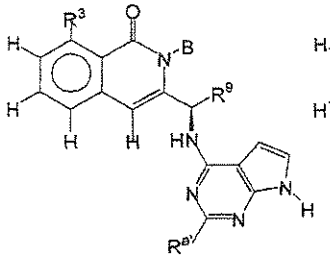
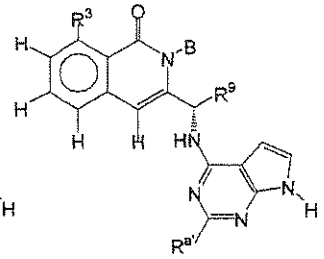




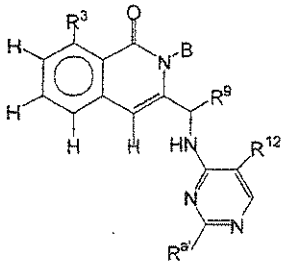
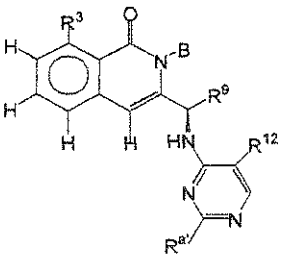
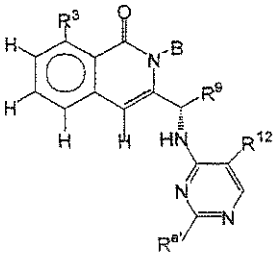
Formula XI-A Formula XI-A1 Formula XI-A2

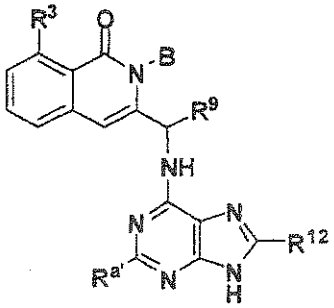
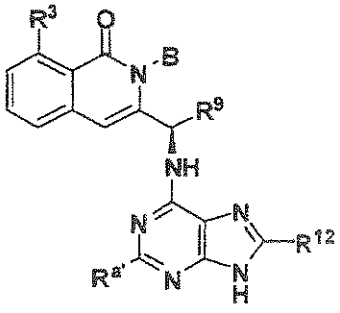
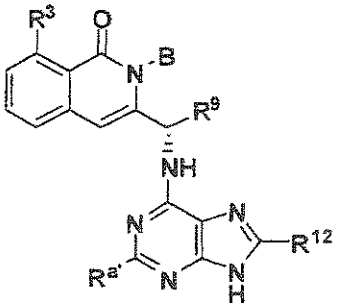
Formula XII-A Formula XII-A1 Formula XII-A2

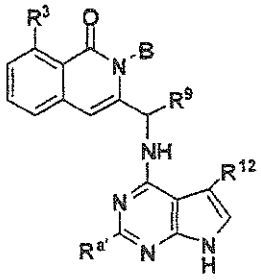
Formula XIII-A Formula XIII-A1 Formula XIII-A2

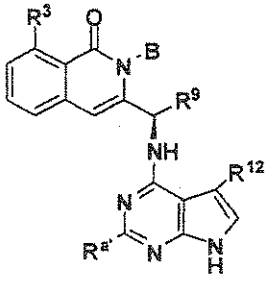
Formula XIV-A Formula XIV-A1 Formula XIV-A2

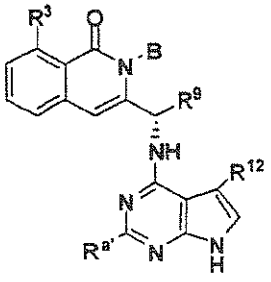
Formula XV-A Formula XV-A1 Formula XV-A2



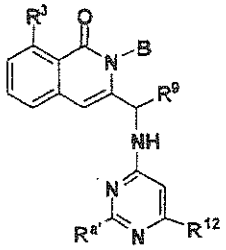
Formula XVI-A



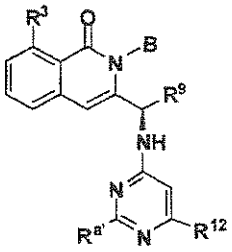
Formula XVI-A1



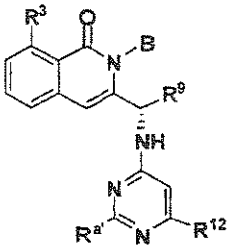
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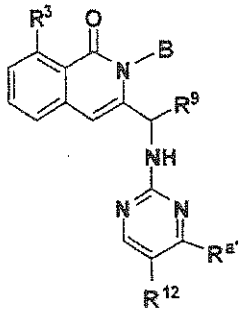
Formula XVII-A



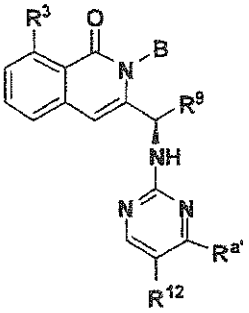
Formula XVII-A1



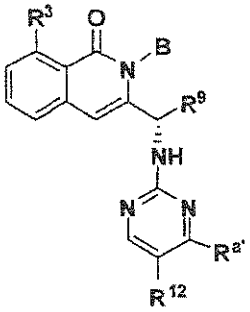
Formula XVII-A2



Formula XVIII-A



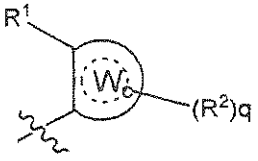
Formula XVIII-A1



Formula XVIII-A2

[00252] Any of the disclosed elements and their substituents for the compounds of Formula I can be used in any combination.

[00253] In one aspect, for the compounds of Formula I, R_3 is H, CH_3, CF_3, Cl, or F; and B is a moiety of Formula II:

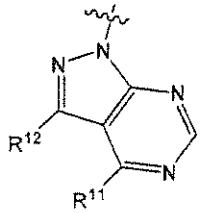


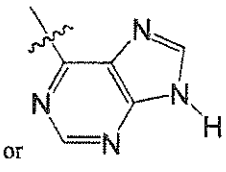
Formula II

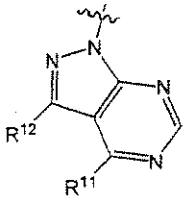
wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, or nitro; q is an integer of 0, 1, 2, 3, or 4; R^5, R^6, R^7, and R^8 are H; X is absent or $(CH_2)_z$; z is 1; Y is absent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

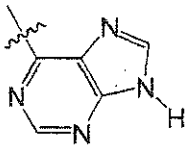
[00254] In another aspect, for the compounds of Formula I, R_3 is H, CH_3, CF_3, Cl, or F; B is a moiety of Formula II which is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or

phosphate; R^2 is halo, hydroxy, cyano, or nitro; 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 or $-N(R^9)-$; R^9 is hydrogen, methyl, or ethyl; at least one of X and Y is present; W_d is:



or ; R^{11} is amino; and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In some embodiments, when X and Y are present and W_d is purine, then $-N(R^9)-$ is –NH-.

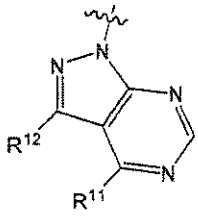
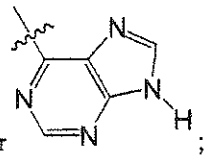
[00255] In another aspect, for the compounds of Formula I, R_3 is H, CH_3, CF_3, Cl, or F; B is a moiety of Formula II, which is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, or nitro; q is 0, 1 or 2; X is $(CH_2)_z$; z is 1; R^5, R^6, R^7, and R^8 are H; 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.

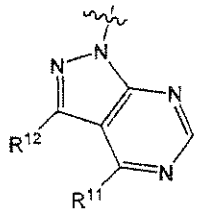
[00256] In another aspect, R_3 is H, CH_3, CF_3, Cl, or F; B is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, or nitro; q is 0, 1 or 2; R^5, R^6, R^7, and R^8 are H; X is $(CH_2)_z$; z is 1; X is $(CH_2)_z$; z is 1; Y is $-N(R^9)-$; R^9 is hydrogen, methyl, or ethyl; and W_d is . In some embodiments, Y is –NH-.

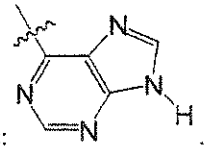
[00257] In another aspect, for the compounds of Formula I R_3 is aryl, heteroaryl, H, CH_3, CF_3, Cl, or F; B is alkyl or a moiety of Formula II;

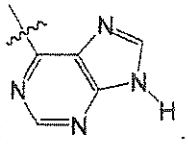
[00258] wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4; R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is 0, 1 or 2; R^5, R^6, R^7, and R^8 are H; X is absent or $(CH(R^9))_z$; z is an integer of 1, 2, 3, or 4; Y is absent, $-N(R^9)-$, or $-N(R^9)\,CH(R^9)-$; R^9 is hydrogen, alkyl, cycloalkyl, or heteroalkyl; at least one of X and Y is present; and W_d is pyrazolopyrimidine or purine. In some embodiments, when X is present, Y is $-N(R^9)-$, and W_d is purine, then Y is –NH-.

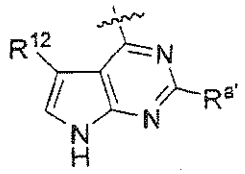
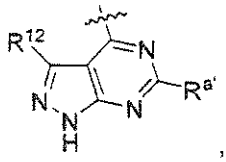
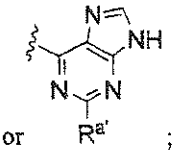
[00259] In another aspect, for the compounds of Formula I, R_3 is aryl, heteroaryl, H, CH_3, CF_3, Cl, or F; B is alkyl or a moiety of Formula II which is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, R^1 is H, –F, -Cl, -CN, $-CH_3$, isopropyl, $-CF_3$, $-OCH_3$, nitro, or phosphate; R^2 is halo, 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 $(CH(R^9))_z$; z is an integer of 1, 2, 3, or 4; Y is absent, $-N(R^9)-$, or $-N(R^9)\,CH(R^9)-$; R^9 is hydrogen, methyl, or

ethyl; at least one of X and Y is present; 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, aloxycarbonyl, or amido . In some embodiments, when X is present, Y is –N(R^9)-, and W_d is purine, then Y is –NH-.

[00260] In another aspect, for the compounds of Formula I, 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 ($CH(R^9)$)$_z$; z is an integer of 1; Y is absent–; R^9 is hydrogen, methyl, or ethyl; 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.

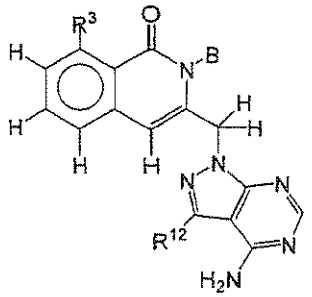
[00261] In another aspect, for the compounds of Formula I, R_3 is aryl, heteroaryl, H, CH_3, CF_3, Cl, or F; B is a moiety of Formula II which is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, R^1 is H, –F, -Cl, -CN, -CH_3, isopropyl, -CF_3, -OCH_3, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is 0, 1 or 2; R^5, R^6, R^7, and R^8 are H; X is absent or ($CH(R^9)$)$_z$; z is an integer of 1; Y is absent, –N(R^9)-, or –N(R^9) $CH(R^9)$-; R^9 is hydrogen, methyl, or ethyl; at least one of X and Y is present, and W_d is: . In some embodiments, when X is present, Y is –N(R^9)-, and W_d is purine, then Y is –NH-.

[00262] In another aspect, for the compounds of Formula I, R_3 is aryl, heteroaryl, H, CH_3, CF_3, Cl, or F; B is 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: .

[00263] In another aspect, for the compounds of Formula I, R_3 is aryl, heteroaryl, 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 ($CH(R^9)$)$_z$; z is an integer of 1, 2, 3, or 4; Y is absent, –N(R^9)-, or –N(R^9) $CH(R^9)$-; R^9 is hydrogen, methyl, or ethyl; at least one of X and Y is present; W_d is: , , or ; $R^{a'}$ is

hydrogen, halo, or amino; and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, cyano, amino, carboxylic acid, aloxycarbonyl, or amido . In some embodiments, when X is present, Y is $-N(R^9)-$, and W_d is purine, then Y is –NH-.

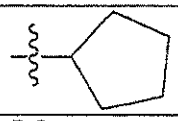
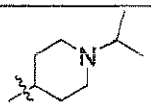
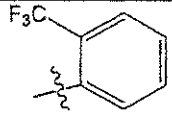
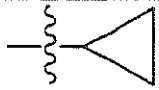
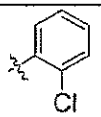
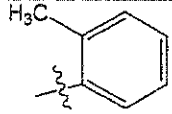
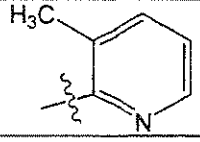
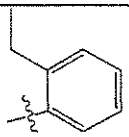
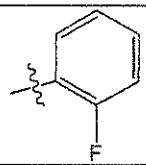
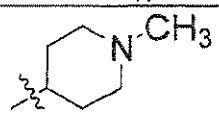
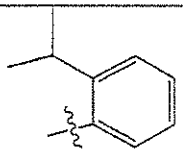
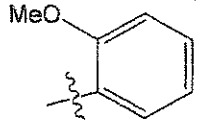
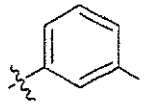
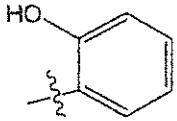
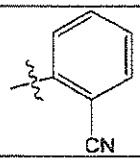
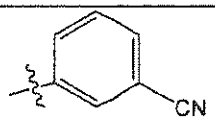
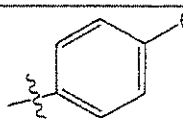
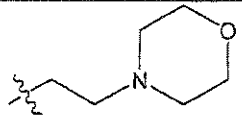
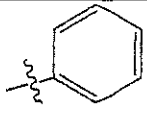
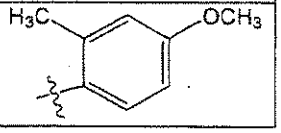
[00264] Additional exemplary compounds of the present invention are disclosed having a sub-structure of Formula IV-A.

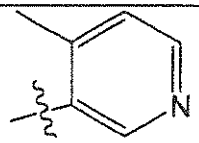
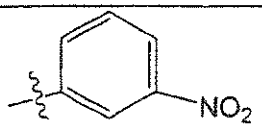
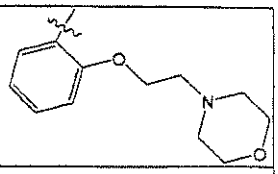
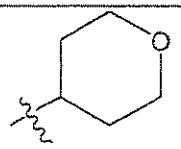
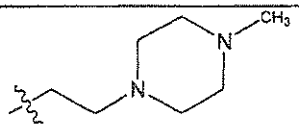
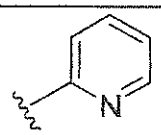
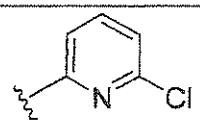
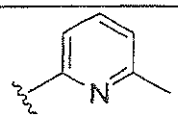
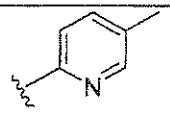
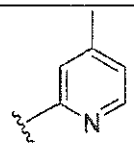
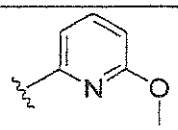
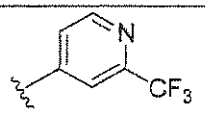
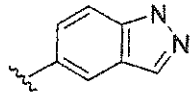
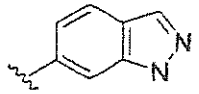
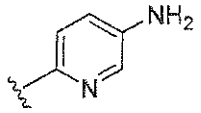
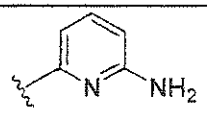
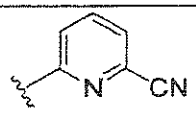
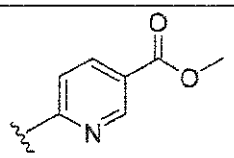
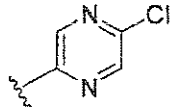
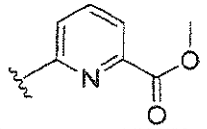
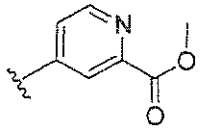
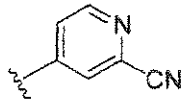
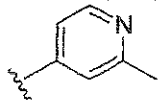
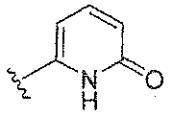
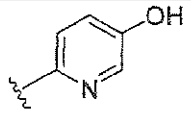
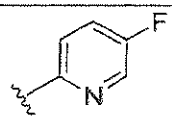
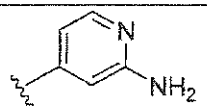
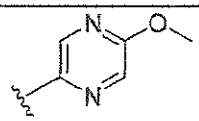
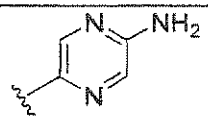
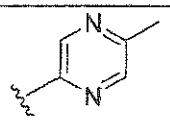
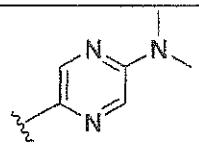
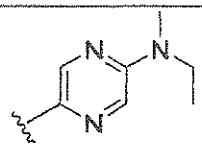
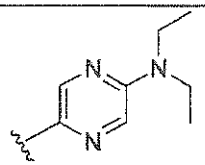
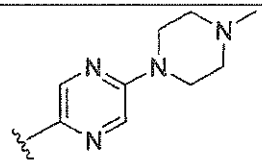
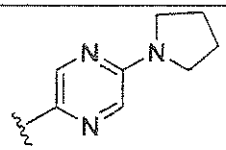
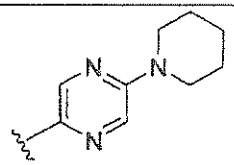
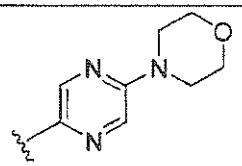
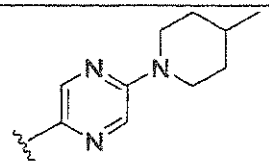
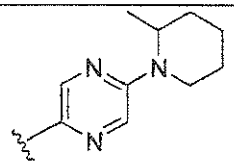


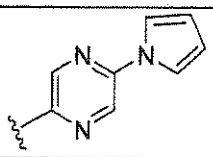
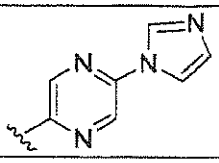
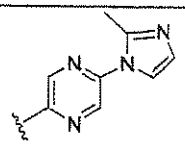
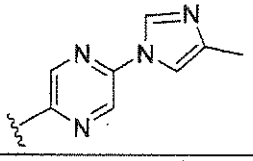
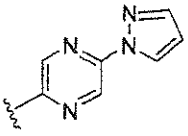
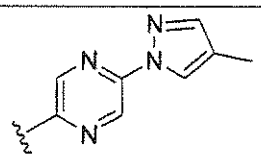
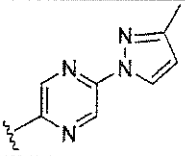
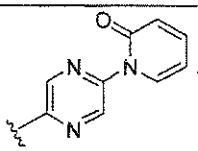
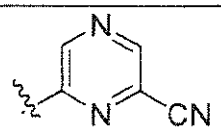
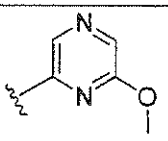
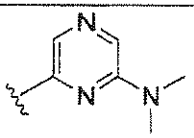
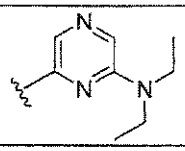
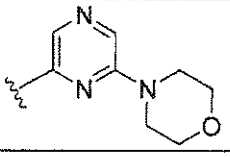
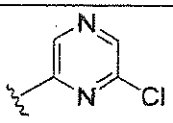
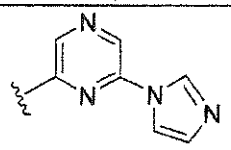
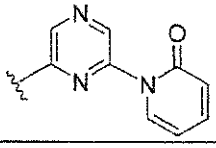
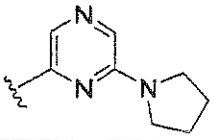
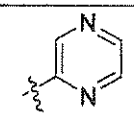
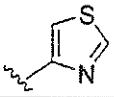
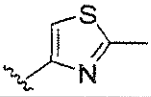
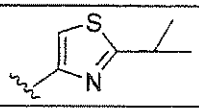
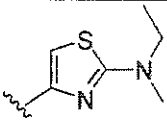
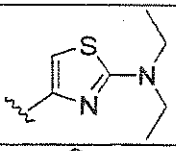
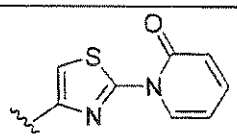
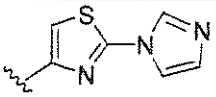
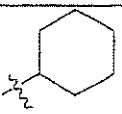
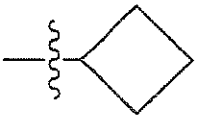
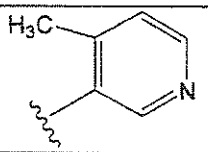
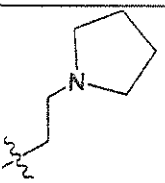
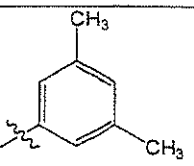
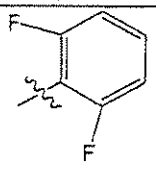
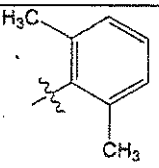
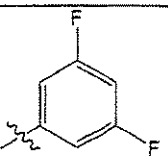
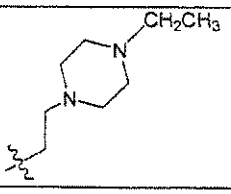
Formula IV-A

[00265] Some illustrative compounds of the present invention having a structure of Formula IV-A include those in which R^3 is –H, -Cl, -F, or $-CH_3$ in combination with any B moiety described in Table 1, and any R^{12} as described in Table 2. A compound of Formula IV-A includes any combination of R^3, B, and R^{12}. Additional exemplary compounds of Formula IV-A are illustrated in Table 4.

Table 1. Illustrative B moieties of the compounds of Formula I.

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	

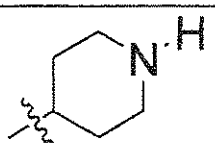
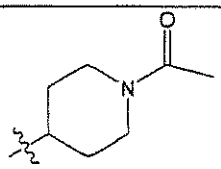
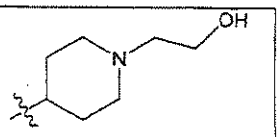
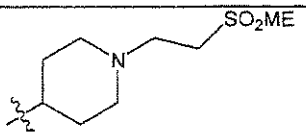
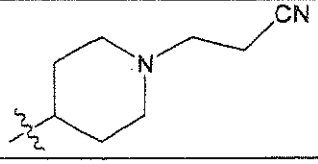
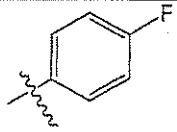
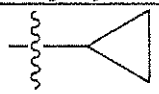
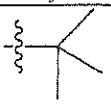
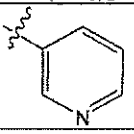
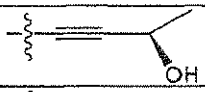
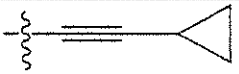
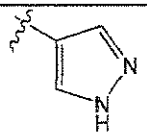
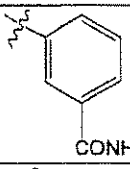
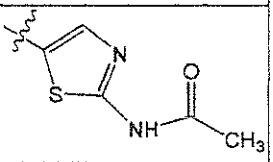
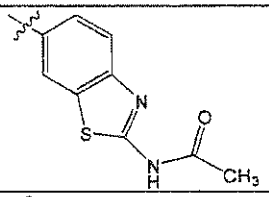
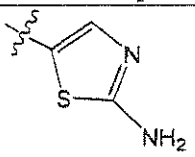
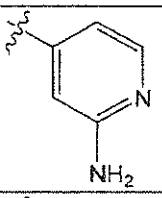
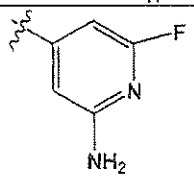
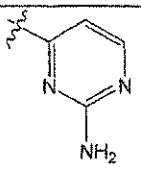
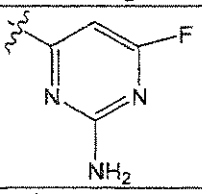
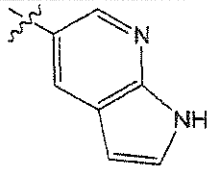
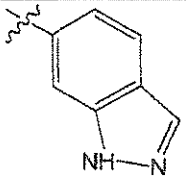
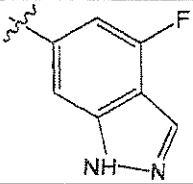
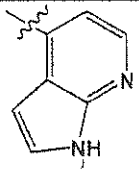
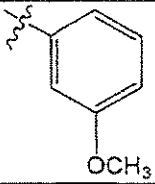
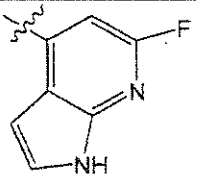
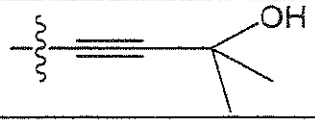
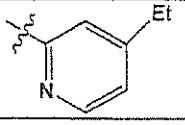
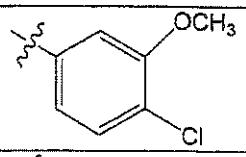
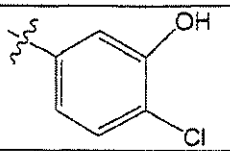
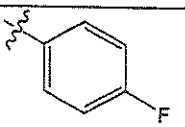
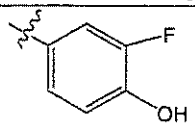
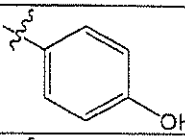
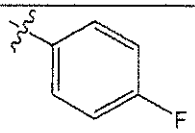
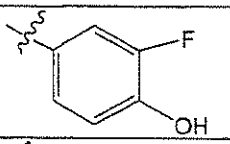
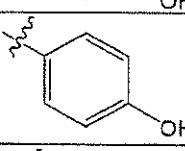
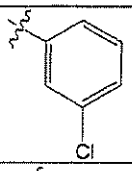
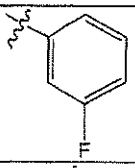
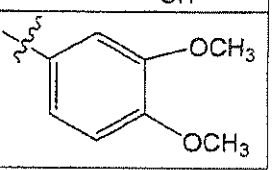
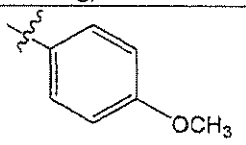
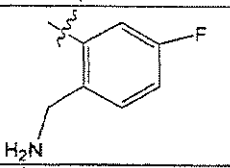
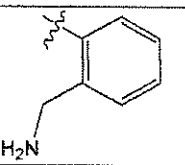
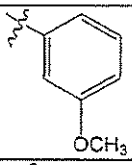
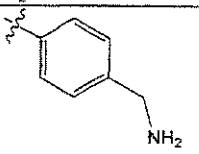
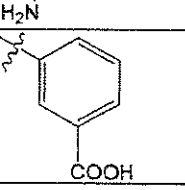
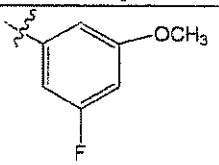
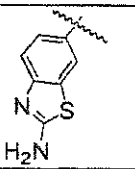
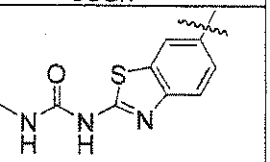
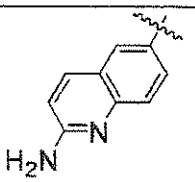
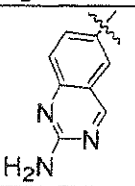
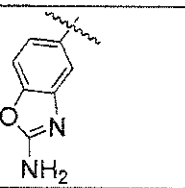
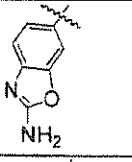
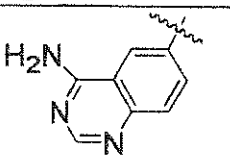
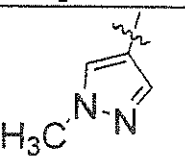
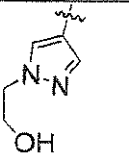
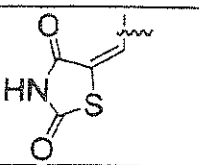
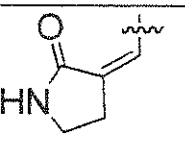
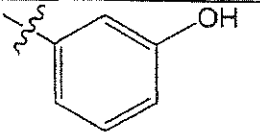
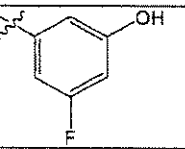
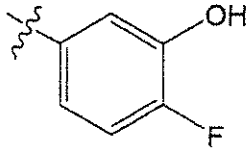
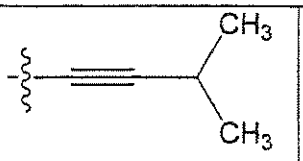
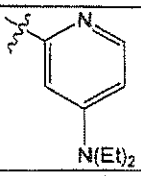
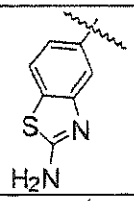
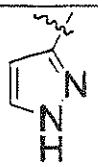
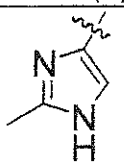
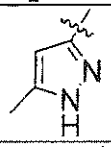
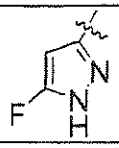
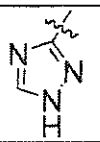
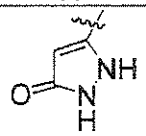
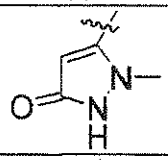
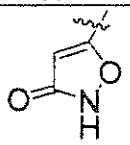
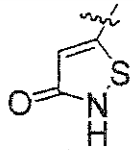
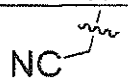
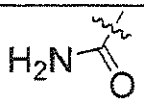
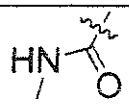
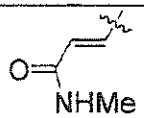
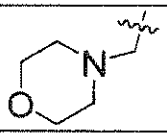
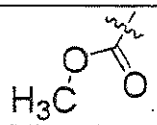
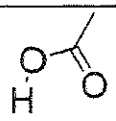
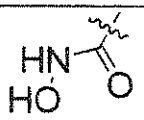
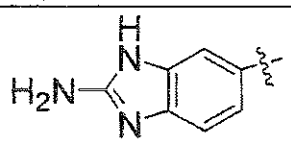
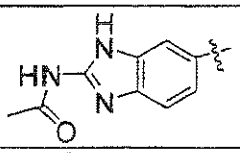
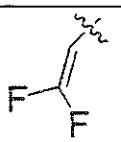
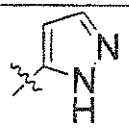
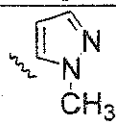
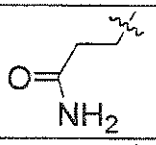
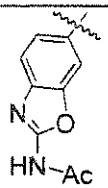
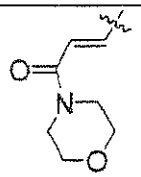
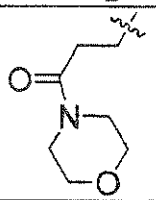
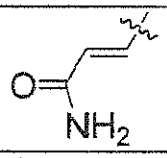
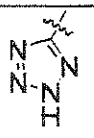
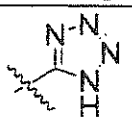
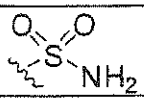
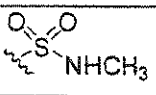
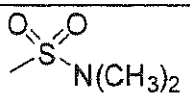
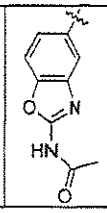
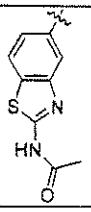
B-97		B-98		B-99	
B-100		B-101		B-102	

Table 2. Illustrative R^{12} of compounds of Formula I.

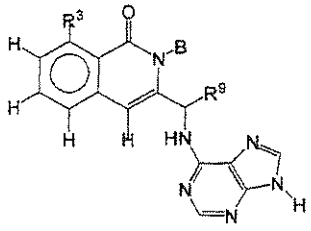
Sub-class #	R^{12}	Sub-class #	R^{12}	Sub-class #	R^{12}
12-1	-CN	12-2	-Br	12-3	-Cl
12-4	$-CH_2CH_3$	12-5	$-CH_3$	12-6	$-CH(CH_3)_2$
12-7		12-8		12-9	
12-10		12-11		12-12	
12-13		12-14		12-15	
12-16		12-17		12-18	
12-19		12-20		12-21	
12-22		12-23		12-24	
12-25		12-26		12-27	
12-28		12-29		12-30	

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	

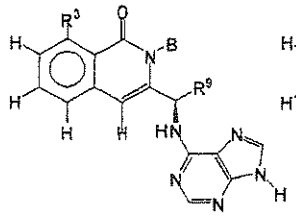
12-64		12-65		12-66	
12-67		12-68		12-69	
12-70		12-71		12-72	
12-73		12-74		12-75	
12-76		12-77		12-78	
12-79		12-80		12-81	
12-82		12-83		12-84	
12-85		12-86		12-87	
12-88		12-89		12-90	
12-91		12-92		12-93	
12-94		12-95		12-96	
12-97	-F	12-98		12-99	

12-100		12-101		12-102	

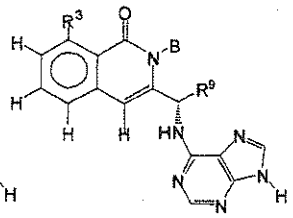
[00266] Other illustrative compounds of the present invention have a structure of Formula V-A, V-A1, or V-A2, wherein B is a moiety described in Table 1, in combination with R^3, which is –H, -Cl, -F, or CH_3,and R^9, which is –H, -CH_3, or -CH_2CH_3. A compound of Formula V-A, V-A1, or V-A2 includes any combination of R^3, B, and R^9.



Formula V-A

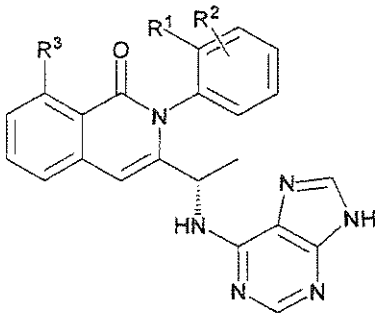


Formula V-A1



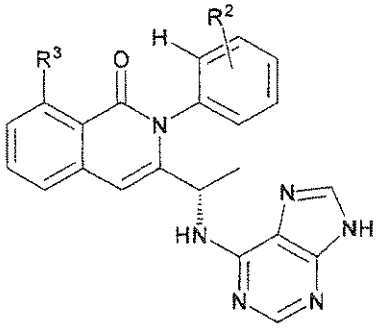
Formula V-A2

[00267] In certain embodiments, the compound of Formula V-A2 is:



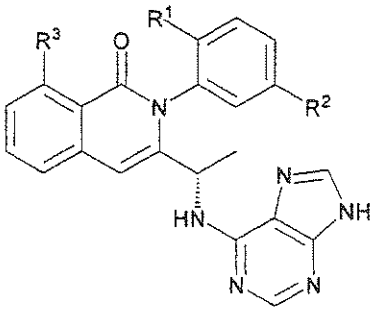
, or pharmaceutically acceptable salts thereof.

[00268] In some embodiments, R^1 is –H, e.g., of the formula:



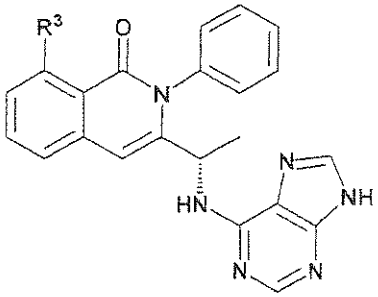
, or pharmaceutically acceptable salts thereof.

[00269] In certain embodiments, q is 1 and R^2 is provided as in the formula:



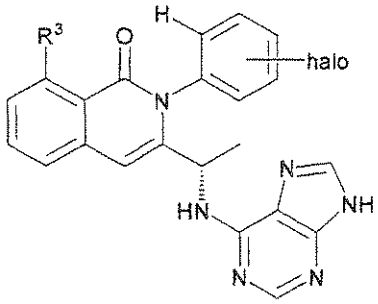
, or pharmaceutically acceptable salts thereof.

[00270] In certain embodiments, R1 is H and R2 is H, e.g. of the formula:



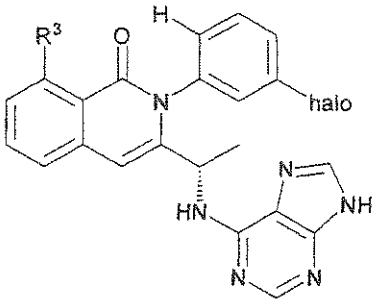
or pharmaceutically acceptable salts thereof.

[00271] In certain embodiments, R1 is H, q is 1 and R2 is halo (e.g., fluoro) of the formula:



or pharmaceutically acceptable salts thereof.

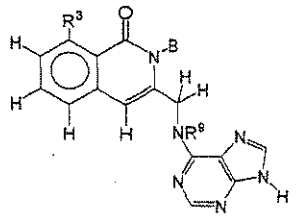
[00272] In certain embodiments, R^1 is H, q is 1 and R^2 is halo (e.g., fluoro) in the meta position, e.g., of the formula:



or pharmaceutically acceptable salts thereof.

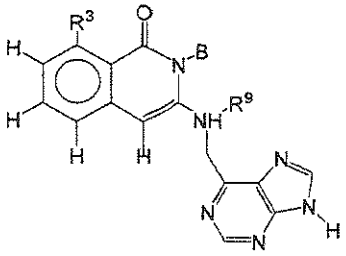
[00273] In some embodiments of Formula VA-2, R^3 is haloalkyl. For example, R^3 is $-CF_3$, $-CH_2F$ or $-CHF_2$.

[00274] Yet other illustrative compounds of the present invention have a structure of Formula V-B, wherein B is a moiety described in Table 1, in combination with R^3, which is –H, -Cl, -F, or CH_3, and R^9, which is –H, $-CH_3$, or $-CH_2CH_3$. A compound of Formula V-B includes any combination of R^3, B, and R^9.



Formula V-B

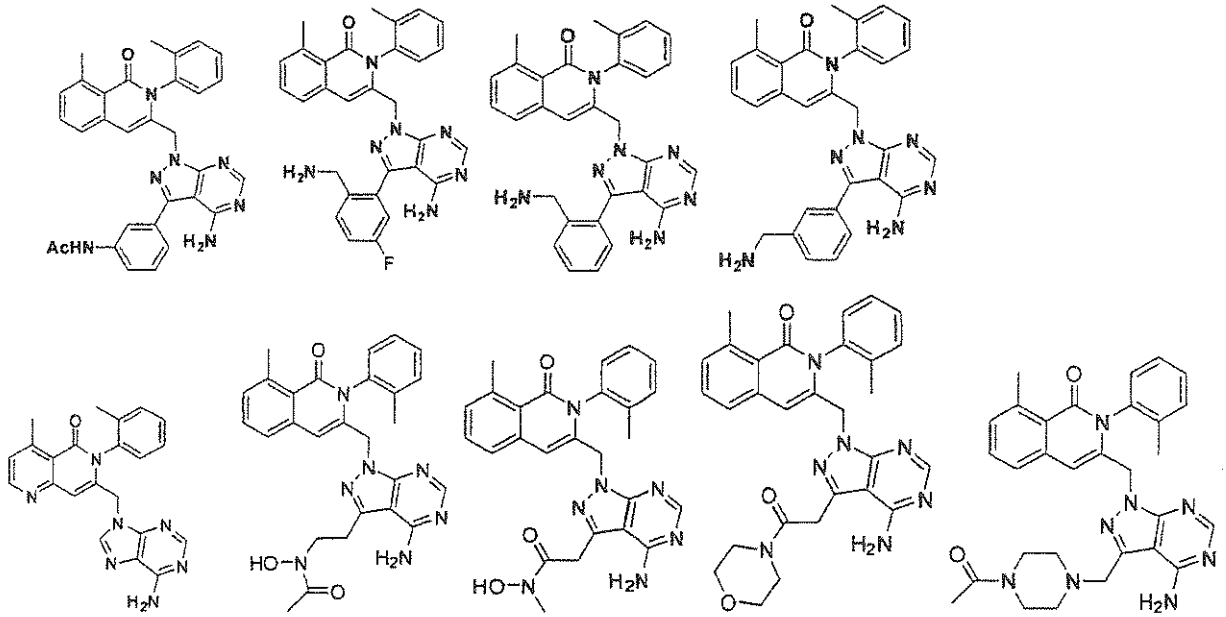
[00275] Some other illustrative compounds of the present invention have a structure of Formula VI-A, wherein B is a moiety described in Table 1, in combination with R^3, which is –H, -Cl, -F, or CH_3,and R^9, which is –H, $-CH_3$, or $-CH_2CH_3$. A compound of Formula VI-A includes any combination of R^3, B, and R^9.

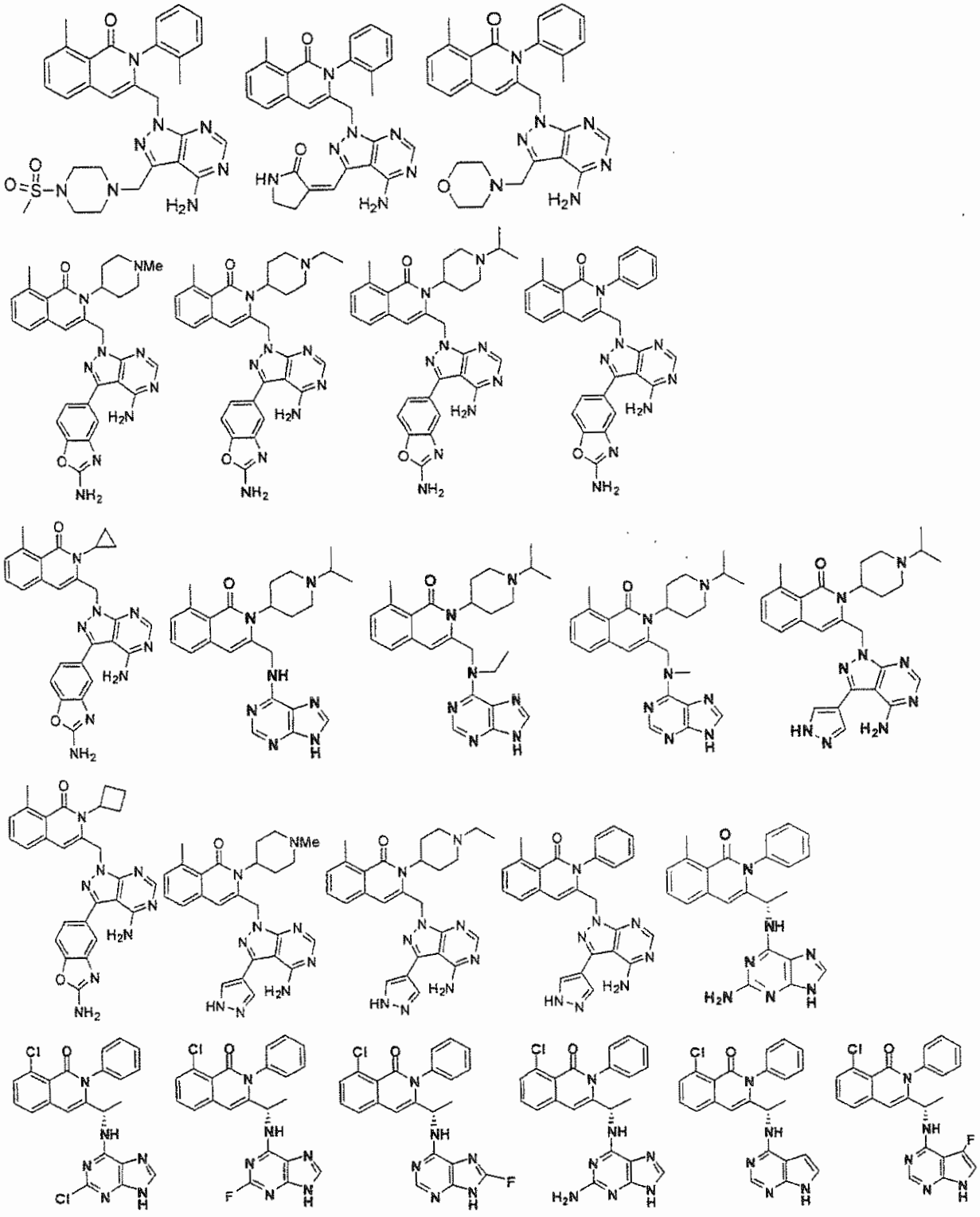


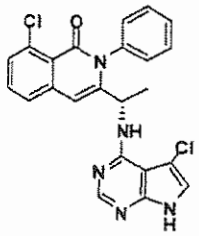
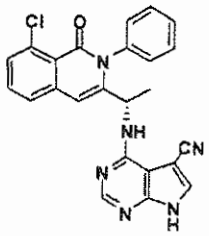
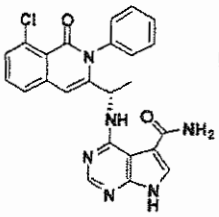
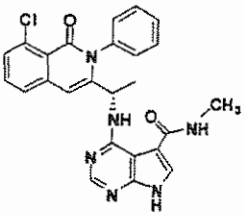
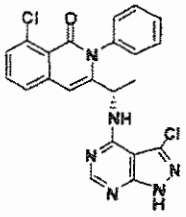
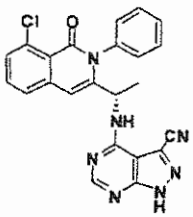
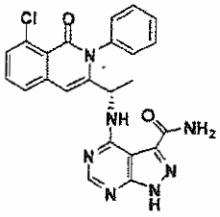
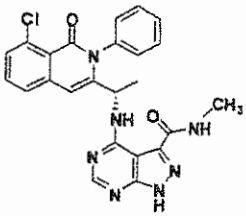
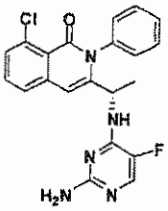
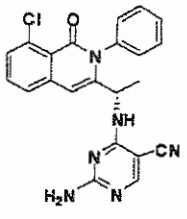
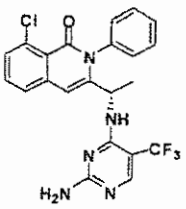
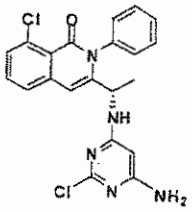
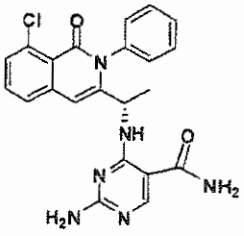
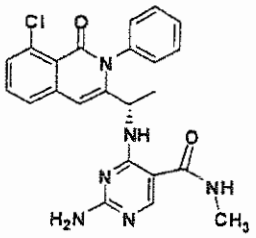
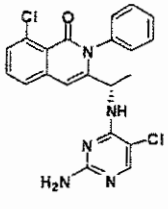
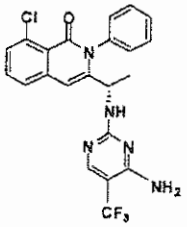
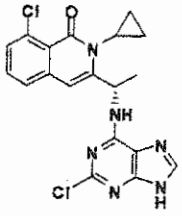
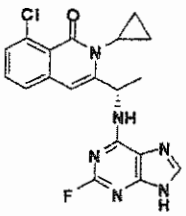
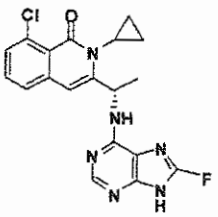
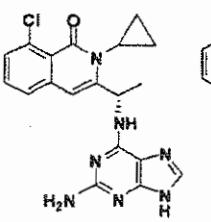
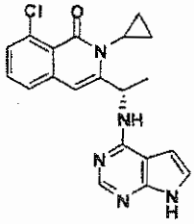
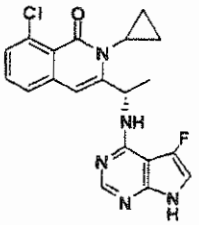
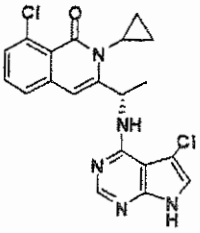
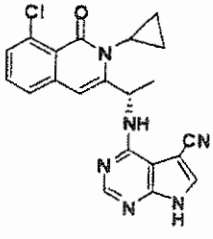
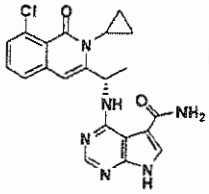
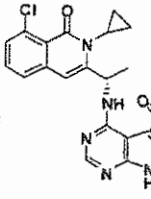
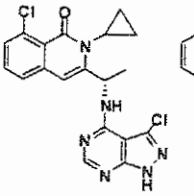
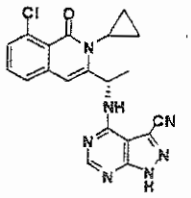
Formula VI-A

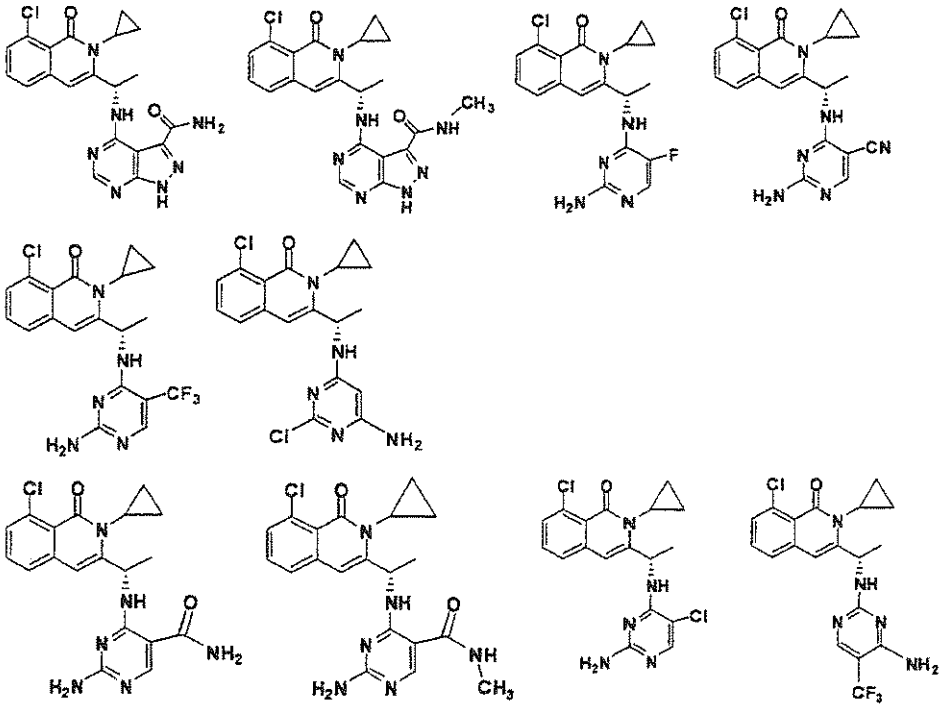
[00276] Further illustrative compounds of the invention have a structure of one of Formulae VII-A1, VII-A2, VIII-A1, VIII-A2, IX-A1, IX-A2, X-A1, X-A2, XI-A1, XI-A2, XII-A, XII-A1, XII-A2, XIII-A, XIII-A1, XIII-A2, XIV-A, XIV-A1, or XIV-A2: wherein B is a moiety described in Table 1, any R^{12} as described in Table 2, in combination with R^3, which is –H, -Cl, -F, or CH_3, R^9 which is –H, $-CH_3$, or $-CH_2CH_3$, and $R^{8'}$ which is –H, -Cl, -F, or $–NH_2$. A compound of Formulae VII-A1, VII-A2, VIII-A1, VIII-A2, IX-A1, IX-A2, X-A1, X-A2, XI-A1, XI-A2, XII-A, XII-A1, XII-A2, XIII-A, XIII-A1, XIII-A2, XIV-A, XIV-A1, or XIV-A2: includes any combination of R^a, R^3, B, $R^9$and R^{12}.

[00277] Additional exemplary compounds of the present invention include but are not limited to the following:







or stereoisomers and pharmaceutically acceptable salts thereof.

[00278] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/ or techniques well known in the art.

[00279] 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.

[00280] The terms "solvent," "organic solvent," and "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.

[00281] 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.

[00282] 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.

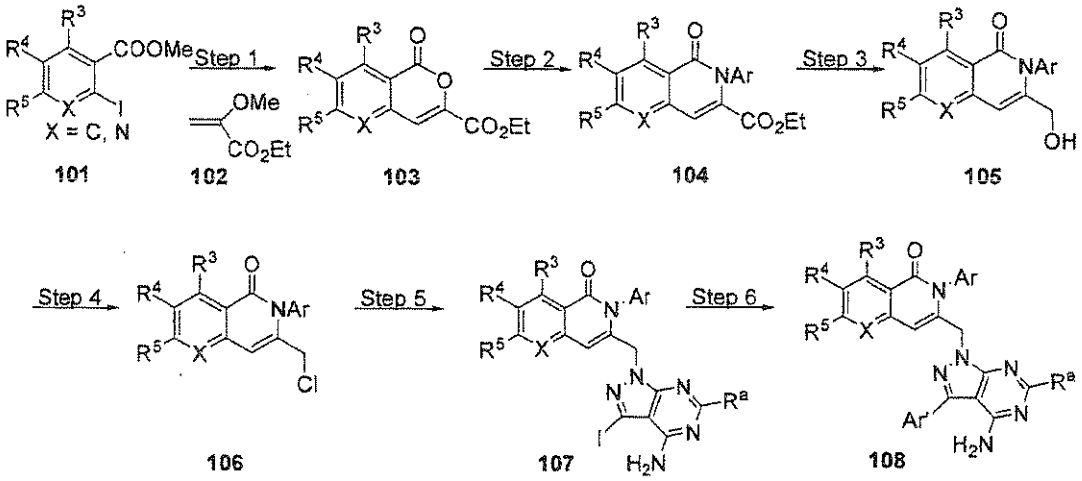
[00283] The compounds described herein can be optionally contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salts.

[00284] 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.

[00285] 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.

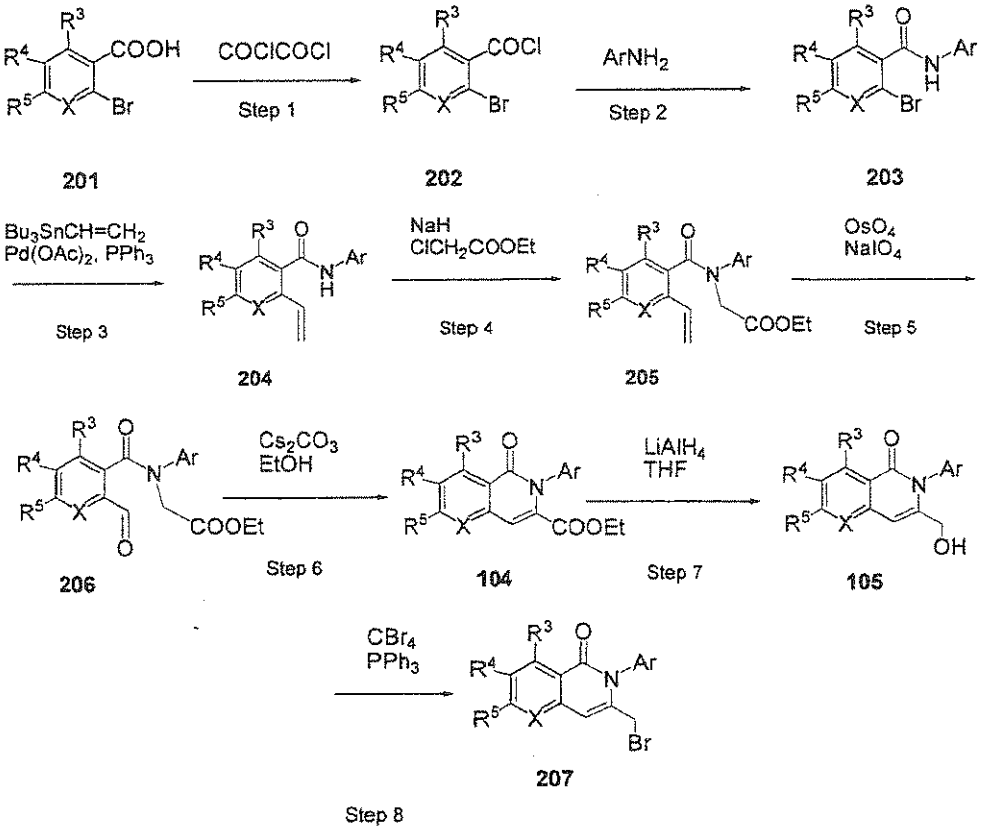
[00286] The compounds of the invention can be synthesized by an appropriate combination of known synthetic methods in the art. The discussion below is offered to illustrate certain of the diverse methods available for use in making the compounds of the invention and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds of the present invention.

Reaction Scheme 1



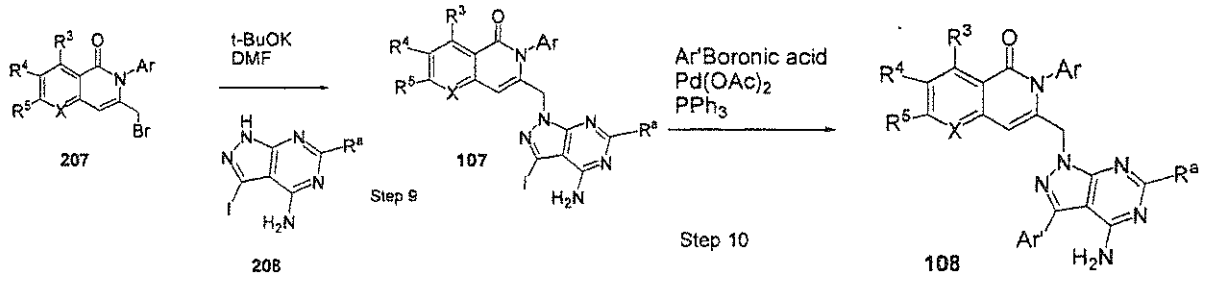
[00287] Referring to Scheme 1, Step 1, a compound of Formula **101**, wherein X is N or CR^7, is converted to a compound of Formula **103**, for example, via a two step process of Heck coupling with a compound of Formula **102**, followed by acid catalyzed cyclization in methanol. The product, a compound of Formula **103**, is isolated. Referring to Scheme 1, Step 2, a compound of Formula **103** is converted to a compound of Formula **404**, for example, via reaction with an appropriately substituted aniline. The product, a compound of Formula **104**, is isolated. Referring to Scheme 1, Step 3, a compound of Formula **104** is converted to a compound of Formula **105**, for example, though reduction with lithium aluminum hydride. The product, a compound of Formula **105**, is isolated. Referring to Scheme 1, Step 4, a compound of Formula **105** is converted to a compound of Formula **106**, for example, via reaction with thionyl chloride. The product, a compound of Formula **106**, is isolated. Referring to Scheme 1, Step 5, a compound of Formula **106** is converted to a compound of Formula **107**, for example, via alkylation with a pyrrazolopyrimidine using a base such as potassium carbonate. The product, a compound of Formula **107**, is isolated. Referring to Scheme 1, Step 6, a compound of Formula **107** is converted to a compound of Formula **108**, for example, via a Suzuki reaction. The product, a compound of Formula **108**, is isolated and optionally purified.

Reaction Scheme 2:



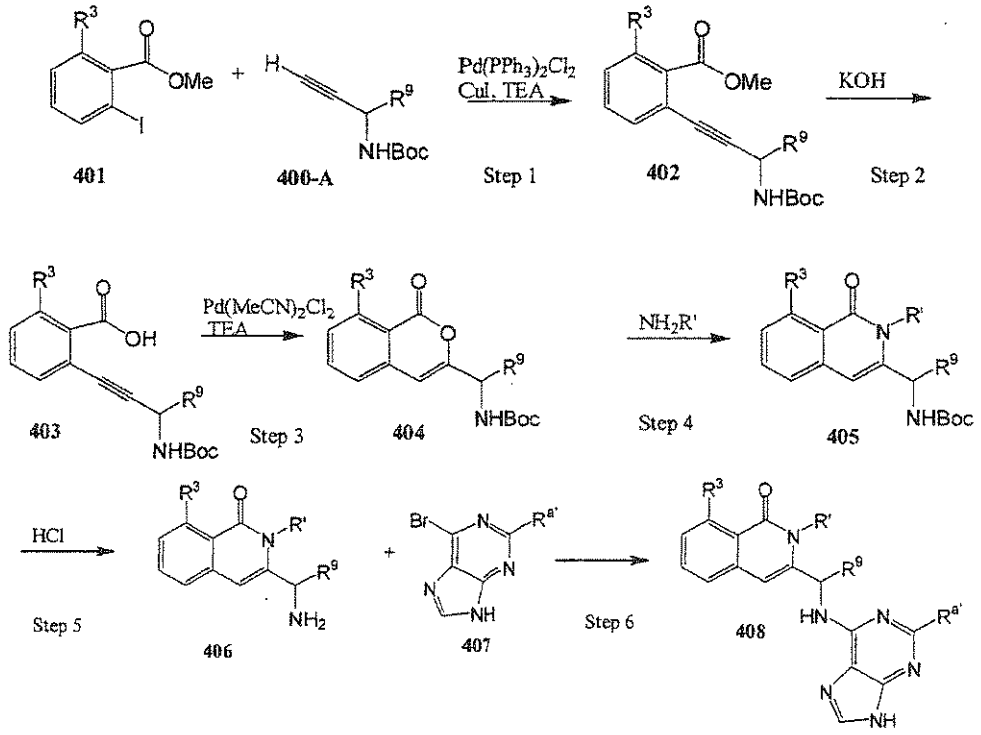
[00288] Referring to Scheme 2, Step 1, a compound of Formula **201**, wherein X is N or CR^7, is converted to a compound of Formula **202**, for example, with a reagent suitable for introduction of an acid chloride, for example, oxalyl chloride. The product, a compound of Formula **202**, is optionally isolated. Referring to Scheme 2, Step 2, a compound of Formula **202** is converted to a compound of Formula **503** for example, reaction with, for example, an an aryl amine . The product, a compound of Formula **203**, is isolated. Referring to Scheme 2, Step 3, a compound of Formula **203** is converted to a compound of Formula **204**, for example, via a Stille coupling using an appropriate vinyl-stannane. The product, a compound of Formula **204**, is isolated. Referring to Scheme 2, Step 4, a compound of Formula **204** is converted to a tertiary amide, a compoundof Formula **205**, via reaction with chloroethyl acetate and sodium hydride base. The compound of Formula **205** is isolated. Referring to Scheme 2, Step 5, a compound of Formula **205** is oxidized to an aldehyde, using, for example, osmonium tetraoxide and sodium periodinate. The product, a compound of Formula **206**, is isolated. Referring to Scheme 2, Step 6, a compound of Formula **206** is converted to a compound of Formula **104**, for example, though aldol reaction in ethanol with a base, such as cesium carbonate. The product, a compound of Formula **104**, is isolated. Referring to Scheme 2, Step 7, a compound of Formula **104** is reduced to a primary alcohol via reduction with, for example, lithium aluminum hydride, to produce a compound of Formula **105**, which is isolated. Referring to Scheme 2, Step 8, a compound of Formula **105** is converted to a compound of Formula **207** via reaction with carbon tetrabromide and triphenylphosphine. The compound of Formula **207** is isolated. This compound can be a central intermediate in the synthesis of the compounds of the invention.

Reaction Scheme 3:

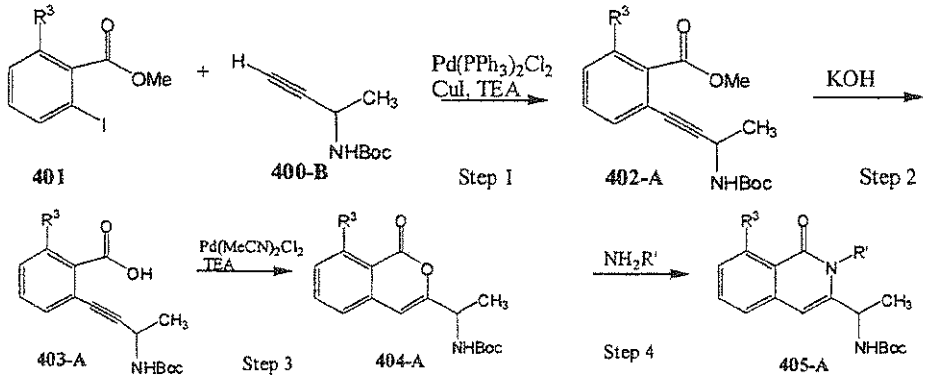


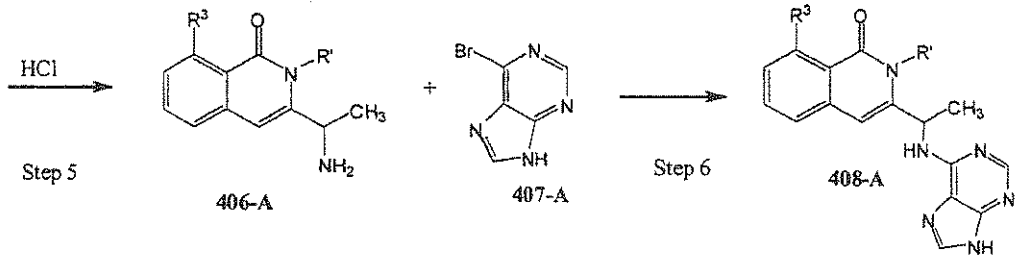
[00289] Referring to Scheme 3, Step 9, a compound of Formula **207**, wherein X is N or CR^7, is synthesized as described in Reaction Scheme 2 and is converted to a compound of Formula **107** via coupling with the compound of Formula **208** in the presence of base, for example, potassium *t*- butoxide. The compound of Formula **107** is isolated. Referring to Scheme 3, Step 10, a compound of Formula **107** is converted to a compound of Formula **108** 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 **108** is isolated.

Reaction Scheme 4A:



Reaction Scheme 4B:

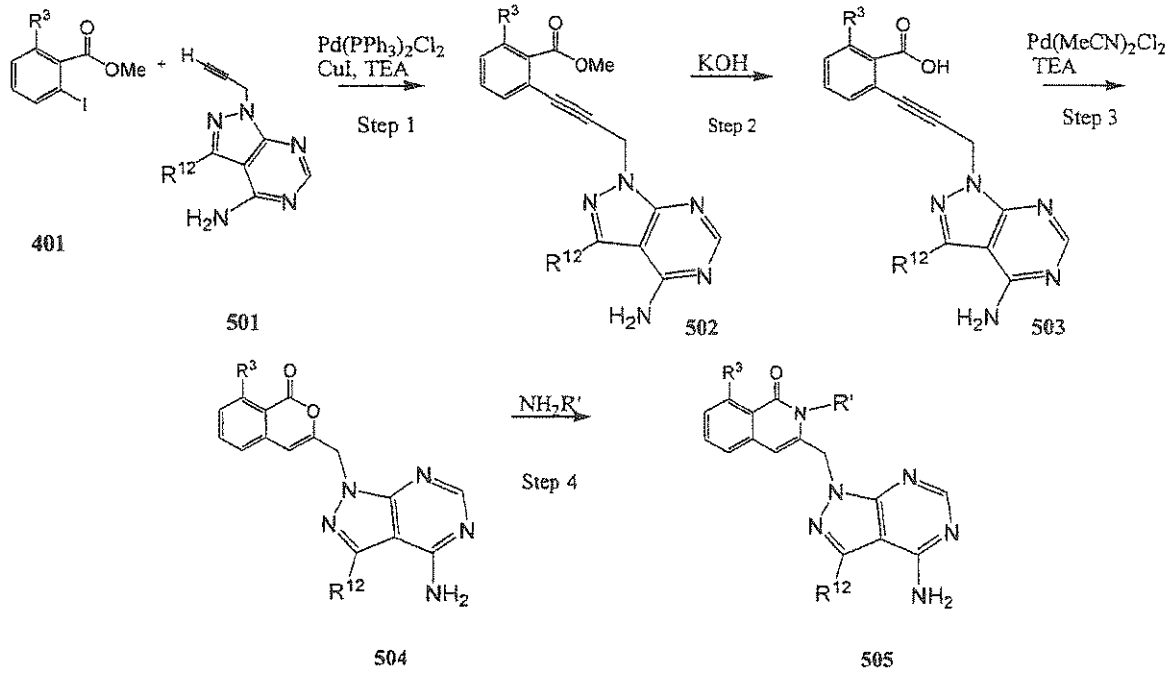




[00290] Referring to Reaction Scheme 4A, which illustrates synthesis of a general class of purinyl substituted isoquinolones, Step 1, iodo ester **401**, is reacted with an alkyne of Formula 400-A in the presence of a palladium catalyst, copper iodide and triethylamine (TEA) to couple the alkyne to the aryl core of compound **401** to produce a compound of Formula **402**. The compound of Formula **402** is optionally isolated. Referring to Reaction Scheme 4, Step 2, a compound of Formula **402** is treated with potassium hydroxide base to obtain the carboxylic acid, a compound of Formula **403**, if the reaction product is acidified, or its salt. The compound of Formula **403** is optionally isolated. Referring to Reaction Scheme 4, Step 3, a compound of Formula **403** is treated with bis (acetonitrile)dichoropalladium (II) and TEA to effect intramolecular ring closure to produce a compound of Formula **404**. The compound of Formula **404** is isolated. Referring to Reaction Scheme 4, Step 4, a compound of Formula **404** is reacted with a primary amine to produce a compound of Formula **405**. The compound of Formula **405** is optionally isolated. Referring to Reaction Scheme 4, Step 5, a compound of Formula **405** is treated with hydrochoric acid, removing the protecting group on nitrogen, and to obtain a compound of Formula **406**. The compound of Formula **406** is optionally isolated. Referring to Reaction Scheme 4, Step 6, a compound of Formula **406** is reacted with a compound of Formula **407**, to produce a compound of Formula **408**. The compound of Formula **408** is isolated.

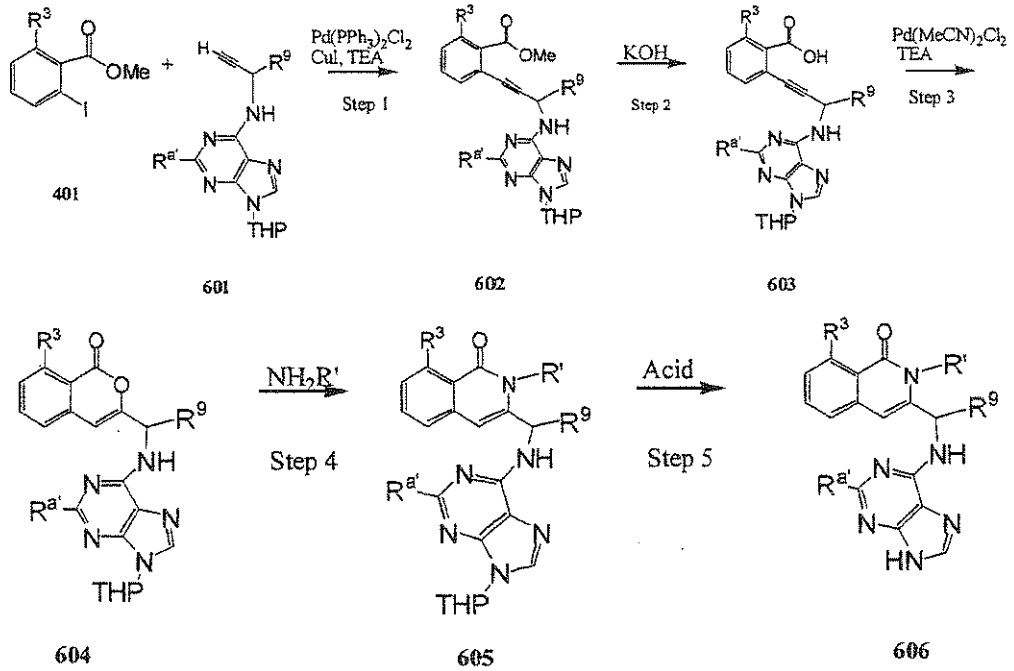
[00291] In Reaction Scheme 4B, the synthesis of one subset of purinyl substituted isoquinolones, wherein R^9 is methyl and R^8 is hydrogen, is illustrated using the synthetic transformations described for Reaction Scheme 4A.

Reaction Scheme 5:

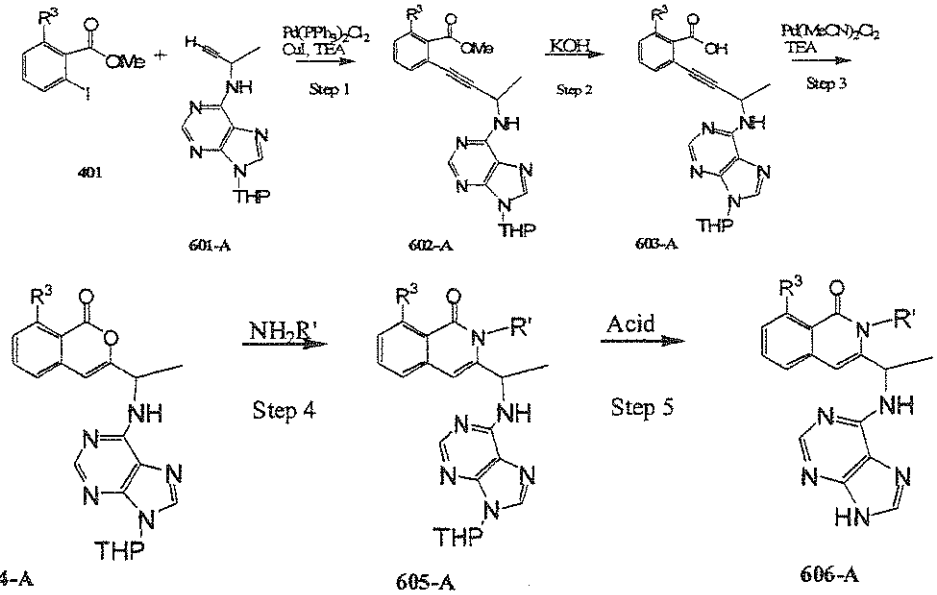


[00292] Referring to Reaction Scheme 5, Step 1, iodo ester **401** is reacted with alkyne **501** in the presence of palladium coupling catalyst, copper iodide, and TEA, to obtain a compound of Formula **502**. The compound of Formula **502** is optionally isolated. Referring to Reaction Scheme 5, Step 2, the compound of Formula **502** is treated with potassium hydroxide base to obtain the carboxylate or free acid of a compound of Formula **503**. Referring to Reaction Scheme 5, Step 3, the compound of Formula **503** is treated with bis (acetonitrile)dichoropalladium (II) and TEA to effect intramolecular ring closure to produce a compound of Formula **504**. The compound of Formula **504** is optionally isolated. Referring to Reaction Scheme 5, Step 4, the compound of Formula 504 is treated with a primary amine to produce a compound of Formula **505**. The compound of Formula **505** is isolated.

Reaction Scheme 6A:



Reaction Scheme 6B:

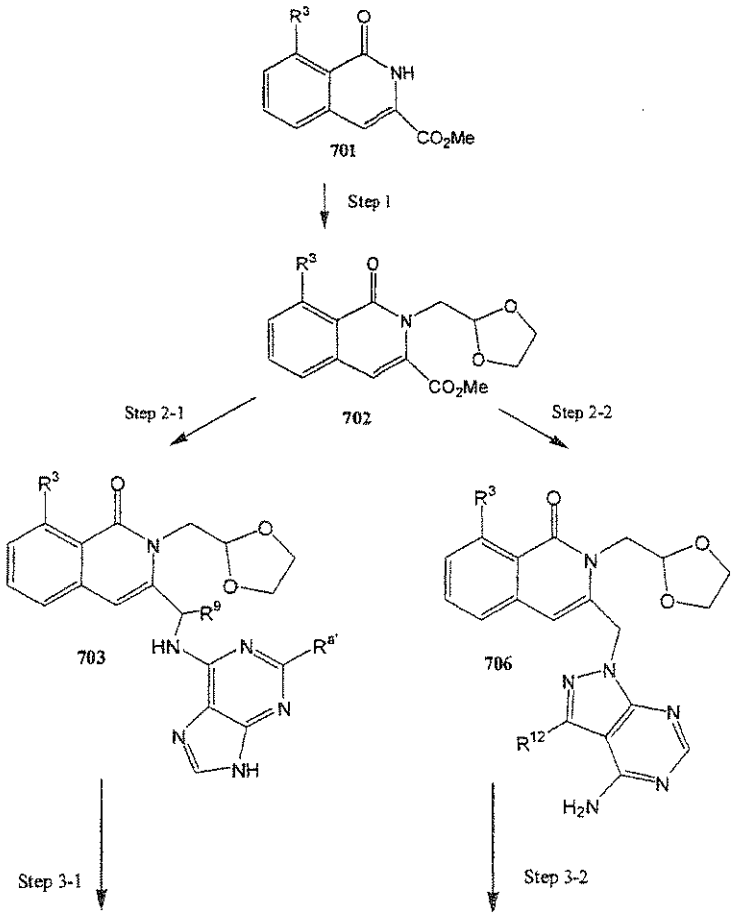


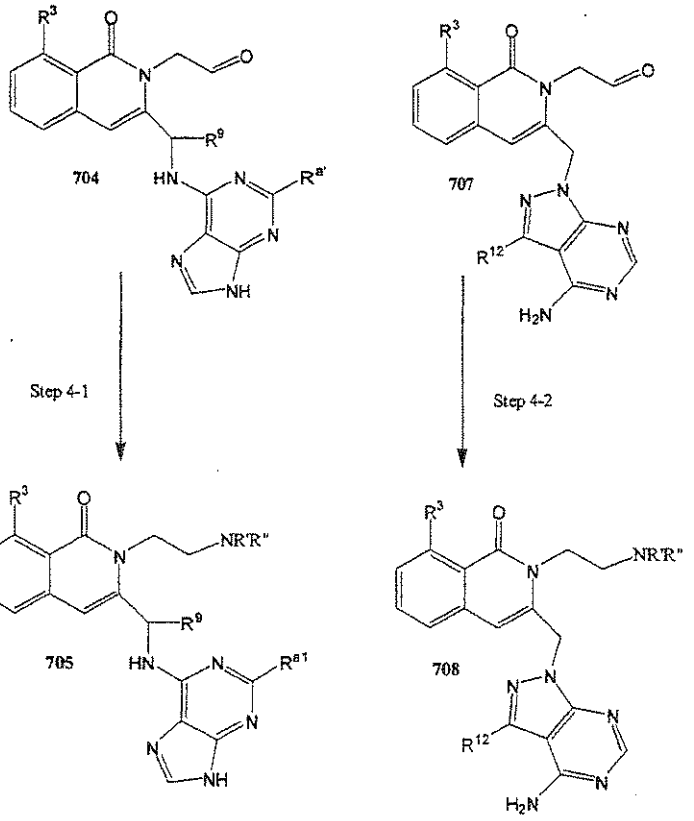
[00293] Referring to Reaction Scheme 6A, which illustrates synthesis of a general class of purinyl substituted isoquinolones,, Step 1, iodo ester **401** is reacted with alkyne **601** in the presence of palladium coupling catalyst, copper

iodide, and TEA, to obtain a compound of Formula **602**. The compound of Formula **602** is optionally isolated. Referring to Reaction Scheme 6, Step 2, the compound of Formula **602** is treated with potassium hydroxide base to obtain the carboxylate or free acid of a compound of Formula **603**. Referring to Reaction Scheme 6, Step 3, the compound of Formula **603** is treated with bis (acetonitrile)dichloropalladium (II) and TEA to effect intramolecular ring closure to produce a compound of Formula **604**. The compound of Formula **604** is optionally isolated. Referring to Reaction Scheme 6, Step 4, the compound of Formula **604** is treated with a primary amine to produce a compound of Formula **605**. The compound of Formula **605** is isolated. Referring to Reaction Scheme 6, Step 5, the compound of Formula **605** is treated with acid to remove the THP protecting group to obtain a compound of Formula **606**. The compound of Formula **606** is isolated.

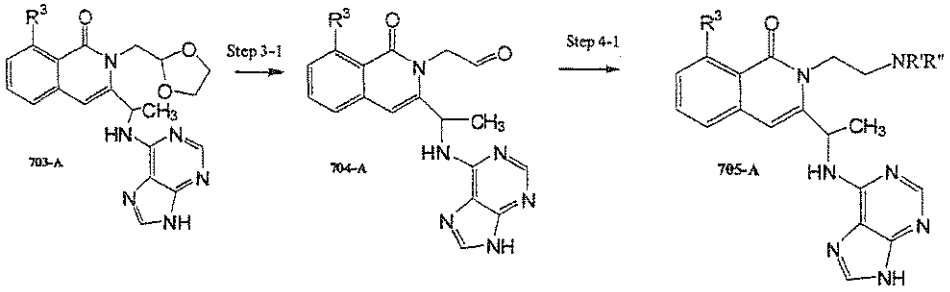
[00294] In Reaction Scheme 6B, the synthesis of purinyl substituted isoquinolones, wherein R^9 is methyl and R^a is hydrogen, is illustrated using the synthetic transformations described for Reaction Scheme 6A.

Reaction Scheme 7A:





Reaction Scheme 7B:



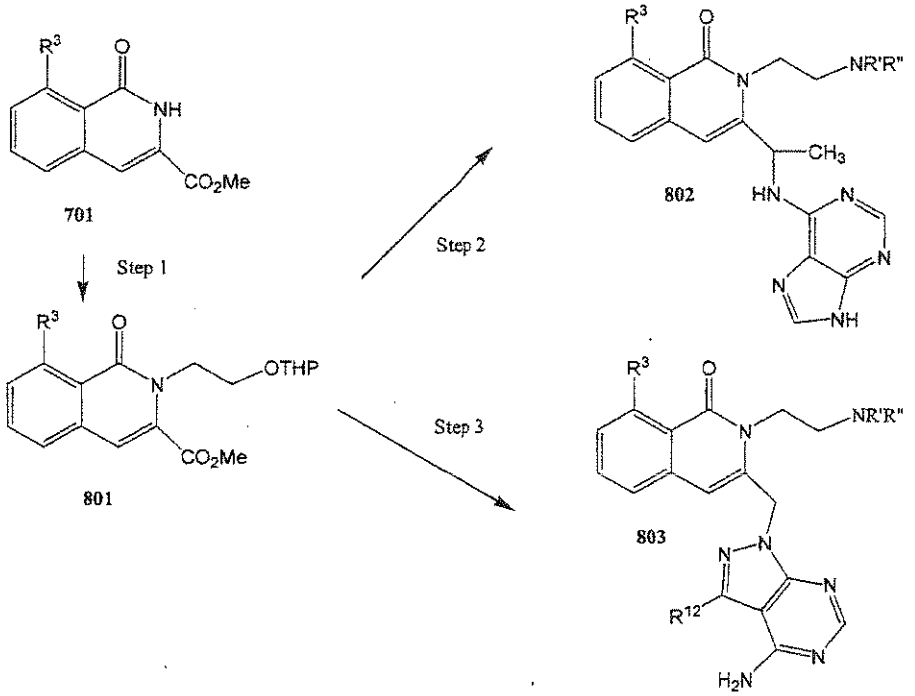
[00295] Referring to Reaction Scheme 7A, which illustrates the synthesis of purinyl or pyrazolopyrimidinyl substituted isoquinoliones comprising an alkyl amine subsituent at the position represented by B in Formula I, Step 1 the compound of Formula **701** is synthesized by a variety of synthetic routes, including variations of Schemes 1 or 2 where, for example, a benzyl amine is used in the step of converting a compound of Formula **103** to a compound of Formula **104**. The benzyl protecting group of the amine may be removed by standard deprotection chemistry to produce a compound of **701**. Another example of a conversion of a compound of Formula **103** to a compoound of Formula **701**, treatment of the compound of Formula **103** with ammonia produces the compound of Formula **701**. The compound of Formula **701** is converted to a compound of Formula **702** 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 **702**. Referring to Reaction Scheme 7, Step 2-1, the compound of Formula **702** is transformed by, for example, reductive amination of the ester moiety to introduce the purinyl moiety of a compound of Formula **703**, or alternatively, is alkylated to so introduce a purinyl moiety and obtain a compound of Formula **703**. Referring to Reaction Scheme 7, Step 3-1, the compound of Formula **703** is treated with acid to remove the ketal protecting group to produce a compound of Formula **704**. The compound of Formula **704** is isolated. Referring to Reaction Scheme 7, Step 4-1, the compound of Formula **704** is reductively aminated with an amine to produce a compound of Formula **705**. The compound of Formula **705** is isolated.

Referring to Reaction Scheme 7, Step 2-2, the compound of Formula **702** is transformed by, steps 7 and 8 of Scheme 2 and step 9 of Scheme 3 to introduce the pyrazolopyrimidine moiety of a compound of Formula **706.** The compound of Formula **706** is isolated. Referring to Reaction Scheme 7, Step 3-2, the compound of Formula **706** is treated with acid to remove the ketal protecting group to produce a compound of Formula **707**. The compound of Formula **707** is isolated.

[00296] Referring to Reaction Scheme 7, Step 4-2, the compound of Formula **707** is reductively aminated with an amine to produce a compound of Formula **708**. The compound of Formula **708** is isolated.

[00297] In Reaction Scheme 7B, the synthesis of compounds wherein R^9 is methyl and R^8 is hydrogen is illustrated, using the steps described in Scheme 7A.

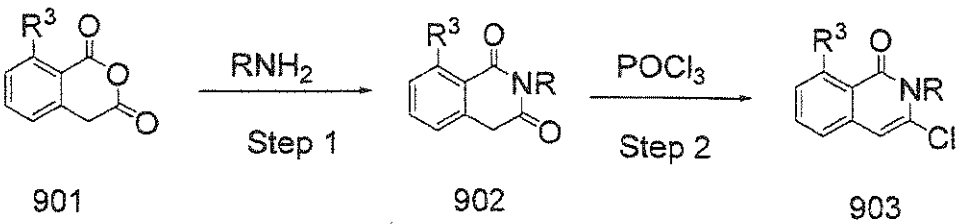
Reaction Scheme 8:

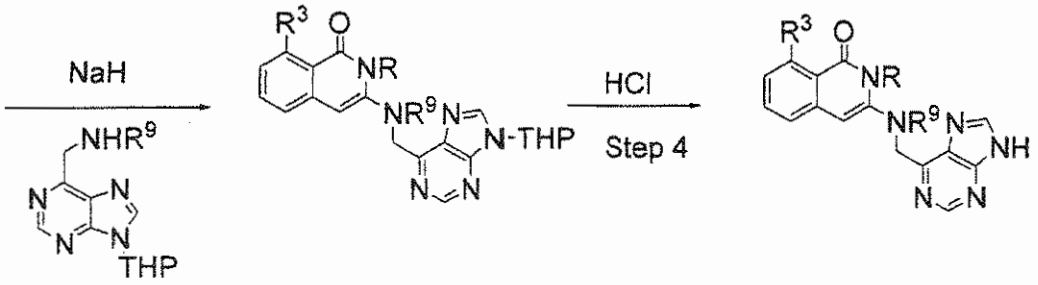


[00298] Referring to Reaction Scheme 8, Step 1, the compound of Formula **701** is synthesized as described in Scheme 7 or any other generally known chemistry. The compound of Formula **701** is tranformed by alkylation of the amide nitrogen with a number of 2-carbon containing synthons which can be deprotected, and converted to the alkoxy protected species as shown in the compond of Formula **801**, which can be isolated. Referring to Reaction Scheme 8, Step 2, the compound of Formula **801** is converted via chemistry described in Step 2-1 of Scheme 7 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 **802**, which is isolated.

[00299] Referring to Reaction Scheme 8, Step 3, the compound of Formula 801 is converted via chemistry described in Step 2-2 of Scheme 7 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 803, which is isolated.

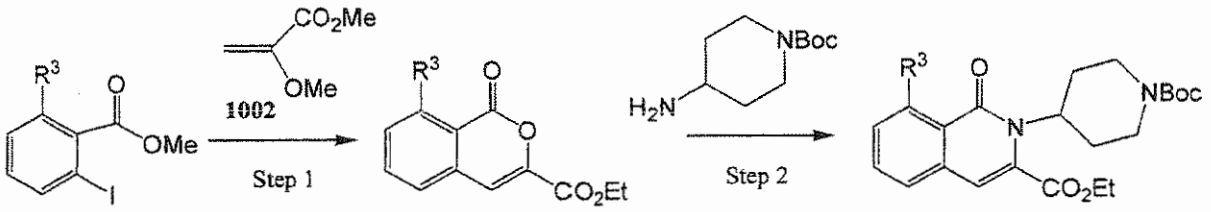
Reaction Scheme 9:





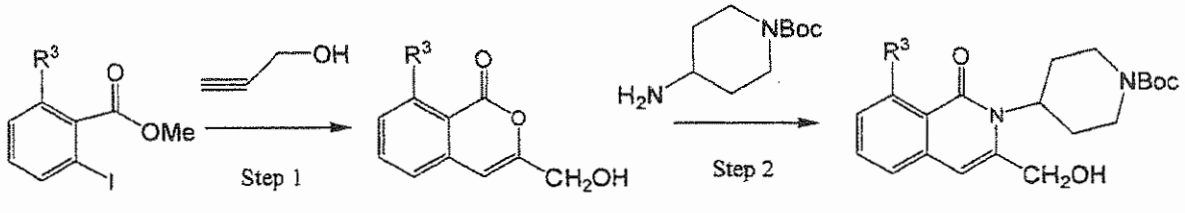
[00300] Referring to Reaction Scheme 9, Step 1, the compound of Formula **901** is treated with an amine to produce a compound of Formula **902**. The compound of Formula **902** is isolated. Referring to Reaction Scheme 9, Step 2, the compound of Formula **902** is treated with phosphorus oxychloride to generate a compound of Formula **903**. The compound of Formula **903** is isolated. Referring to Reaction Scheme 9, Step 3, the compound of Formula **903** is reacted with an amino purine of Formula **904** to obtain a compound of Formula **905**. The compound of Formula **905** is isolated. Referring to Reaction Scheme 9, Step 4, the compound of Formula **905** is treated with hydrochloric acid to remove the protecting group at nitrogen on the purine moiety to produce a compound of Formula **906**. The compound of **906** is isolated.

Reaction Scheme 10:



[00301] Referring to Reaction Scheme 10, Step 1, the compound of Formula **1001** is treated with vinylogous ester **1002** using, for example a Heck reaction with subsequent cyclization, to produce a compound of Formula **1003**. The compound of Formula **1003** is isolated. Referring to Reaction Scheme 10, Step 2, the compound of Formula **1003** is reacted with 4-amino N-Boc piperidine to produce a compound of Formula **1004**. The compound of Formula **1004** is isolated. The compound of Formula **1004** can be used as an intermediate in the synthesis of the compounds of the invention.

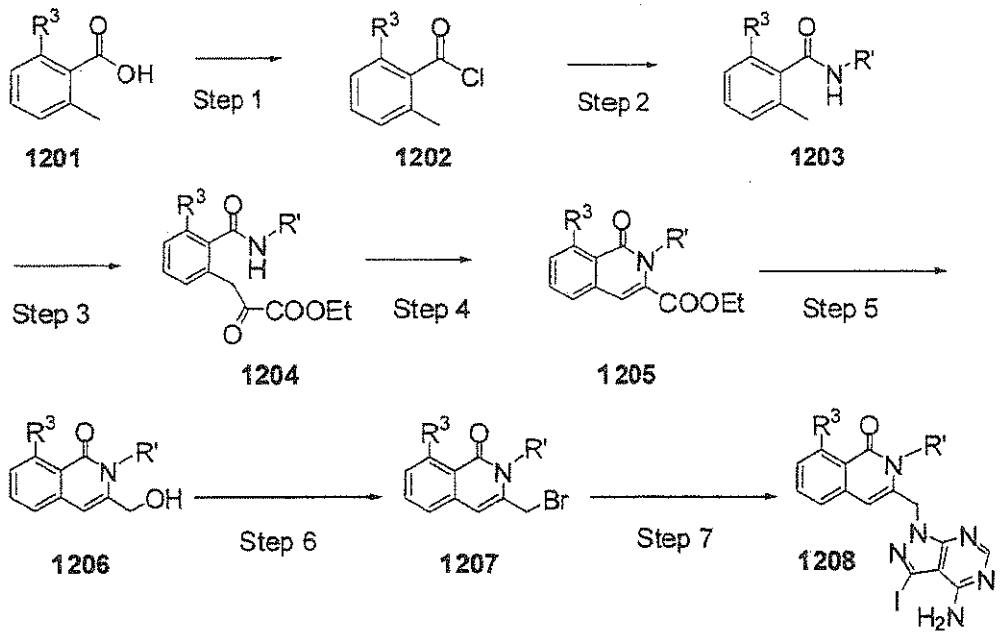
Reaction Scheme 11:



[00302] Referring to Reaction Scheme 11, Step 1, the compound of Formula **1101** is treated with an alkynyl alcohol, for example, of Formula **1102**, in the presence of copper iodide and palladium on carbon catalyst, to produce a compound of Formula **1103**. The compound of Formula **1103** is isolated. Referring to Reaction Scheme 11, Step 1, the compound of Formula **1102** is reacted with 4- amino N-Boc piperidine to produce a compound of Formula **1103**. The compound of

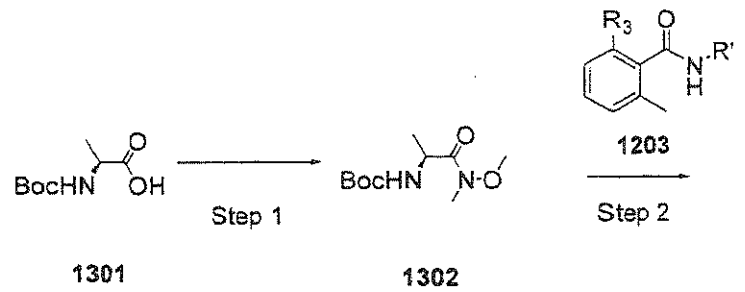
Formula **1103** is isolated. The compound of Formula **1103** can be used as an intermediate in the synthesis of the compounds of the invention.

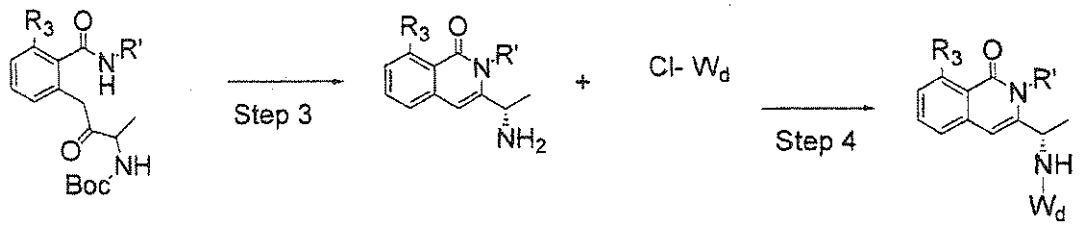
Reaction Scheme 12:



[00303] Another approach to synthesis of compounds of Formula I is illustrated in Scheme 12. Referring to Step 1, the compound of Formula **1201** is treated with a chlorinating agent such as oxalyl chloride to produce an acid chloride of Formula **1202**. In Step 2, the compound of Formula **1202** is reacted with a compound of Formula $R'NH_2$ in the presence of a base such as triethylamine, to produce a compound of Formula **1203**. In some embodiments, the chlorinating agent used for the conversion of compound **1201** is thionyl chloride, for example thionyl chloride in toluene. When thionyl chloride is used, step 1 and 2 may be combined to form a one-pot reaction. In Step 3, the compound of Formula **1203** is treated with n-butyllithium and then reacted with an dialkyl oxalate such as diethyl oxalate to produce a compound of Formula **1204**. In Step 4, the compound of Formula **1204** is refluxed in an acidic solution, for example, hydrochloric acid in methanol to produce a compound of Formula **1205**. In Step 5, the compound of Formula **1205** is treated with a reducing agent such as lithium aluminum hydride to produce a compound of Formula **1206**. In Step 6, the compound of Formula **1206** is reacted with a brominating agent such as phosphorus tribromide, in the presence of dimethylformamide in acetonitrile to produce a bromo compound of Formula **1207**. In Step 7, the compound of Formula **1207** is reacted with a heteroaryl compound, for example 3-iodo 1H-pyrazolo[3,4-d]pyrimidin-4-amine, in the presence of a base such as potasssium tert-butoxide in dimethylformamide to produce a compound of Formula **1208**.

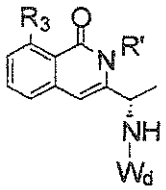
Reaction Scheme 13:





1303 **1304** **1305** **1306**

[00304] In Scheme 13, an approach is described for synthesizing compounds of Formula I having a XY linker wherein X is predominately or solely (S)- $C(CH_3)H$- and Y is –NH-. Wd is a monocyclic or bicyclic heteroaryl, including but not limited to purinyl, pyrimidinyl, pyrrolopyrimidinyl, or pyrazolopyrimidinyl. Referring to Step 1 of Scheme 13, the compound of Formula **1301**, (the S-isomer) is coupled to N, O- dimethylhydroxylamine using hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDCI) in the presence of triethylamine to produce a compound of Formula **1302**. In Step 2, a compound of Formula **1203**, which may be synthesized as described in Scheme 12, is deprotonated with n-butyllithium in THF and hexamethylphosphoramide at -78°C under an argon atmosphere. The compound of Formula **1302** is added and the reaction mixture is allowed to warm to -50°C, quenched with the addition of water and a compound of Formula **1303** is isolated. In some embodiments, a weakly nucleophilic organomagnesium species such as iPrMgCl can be used to generate the magnesium anion of compound **1302** before its addition to the dianion. In Step 3 the compound of Formula **1303** is treated with hydrochloric acid in methanol at reflux, and then the reaction mixture is basified with the addition of sodium carbonate solution to a pH of about 7- about 8, to produce a compound of Formula **1304.** The compound of formula **1304** may be partly epimerized as a result of the preceding reaction steps. Highly enantiopure **1304** may be isolated by preparing the tartaric acid salt by dissolving the compound of Formula **1304** in methanol and adding D-tartaric acid. The resulting reaction mixture is refluxed for one hour, then stirred at room temperature for 16 hours, and permits isolation of the salt of the compound of Formula **1304** wherein the enantiomeric purity is greater than 90% of the (S)- isomer. The free amine of the compound of Formula **1304** is regenerated before its use in the next synthesis step. The compound of Formula **1304**, which is substantially the (S)-enantiomer is coupled to a chloro substituted heteroaryl W_d, a compound of Formula **1305**, including but not limited to 6-chloro- 9(tetrahydro-2H-pyran-2-yl)-9H-purine, 2, 4, 5, -trichloropyrimidine, 4-chloro -7H-pyrrolo[2, 3-d] primidine, and 4-chloro-1H-pyrazolo[3,4-d]pyrimidine in the presence of base such as diisopropylethylamine or ammonia, to produce a compound of Formula **1306**, and where the compound of Formula **1306** is the (S)- isomer.

[00305] Synthesis of R^3- halo analogs, e.g. chloro substituted isoquinolone analogs. The same reaction scheme 13 applies to the generation of a compound having the formula:  , wherein R^3 is chloro.

[00306] Compounds disclosed herein can be synthesized using the reaction schemes as disclosed herein, variants thereof, or other synthetic methods known in the art.

[00307] 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.

[00308] In some embodiments, one or more of the subject compounds 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.

[00309] Additionally, a compound of Formula having an (S)-enantiomeric configuration with respect to carbon X may exhibit greater potency against one or more target PI3-kinases than the corresponding compound having an (R)-enantiomeric configuration with respect to carbon X. For example, the compound of the invention having an (S)-enantiomeric configuration with respect to carbon X may have a PI3-kinase IC50 value which is 1, 2, 3, or 4 orders of magnitude lower than the PI3-kinase IC50 value of the corresponding compound having an (R)-configuration. In some embodiments, the compound of the invention is a compound of Formula V-A2 in an (S)-configuration with respect to carbon X which has a PI3-kinase IC50 value which is 1, 2, 3, or 4 orders of magnitude lower than the PI3-kinase IC50 value of the corresponding compound having an (R)-configuration. For example, the compound of the invention is a compound of Formula V-A2 in an (S)-configuration with respect to carbon X which has a PI3-kinase IC50 value which is 4 orders of magnitude lower than a PI3-kinase IC50 value of the corresponding compound having an (R)-configuration. In some embodiments, the compound of the invention is a compound of Formula V-A2 wherein R^3 is C_1-C_3 alkyl and B is phenyl, and where the compound is in an (S)-configuration with respect to carbon X and has a PI3-kinase IC50 value which is at least 3 orders of magnitude lower than the PI3-kinase IC50 value of the corresponding compound having an (R)-configuration. In other embodiments, the compound of the invention is a compound of Formula V-A2 wherein R^3 is halo and B is phenyl, and where the compound is in an (S)-configuration with respect to carbon X and has a PI3-kinase IC50 value which is at least 3 orders of magnitude lower than the PI3-kinase IC50 value of the corresponding compound having an (R)-configuration. In yet other embodiments, the compound of the invention is a compound of Formula V-A2 wherein R^3 is C_1-C_3 alkyl and B is cycloalkyl, and where the compound is in an (S)-configuration with respect to carbon X and has a PI3-kinase IC50 value which is 3 orders of magnitude lower than the PI3-kinase IC50 value of the corresponding compound having an (R)-configuration.

[00310] In some embodiments, one or more of the subject compounds 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.

[00311] In some embodiments, one or more 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 some aspects, a compound of the invention exhibits an IC50 for PI3-kinase δ which is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, 10 or 5 times lower than the IC50 for PI3-kinase γ. In other aspects, a compound of the invention exhibits an IC50 for PI3-kinase δ which is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, 10 or 5 times higher than the IC50 for PI3-kinase γ. In some embodiments, the compound of the invention exhibits an

IC50 for PI3-kinase δ which is less than 10 times lower than the IC50 for PI3-kinase γ. In other embodiments, the compound of the invention exhibits an IC50 for PI3-kinase δ which is less than 10 times higher than the IC50 for PI3-kinase γ. For example, the compound of the invention exhibits an IC50 for PI3-kinase δ which is less than 5 times higher or lower than the IC50 for PI3-kinase γ. In some aspects, a subject compound has an IC50 for PI3-kinase δ which is lower than the IC50 for PI3-kinase γ by a factor of less than 20, 10, 5, or 2. For example, a subject compound has an IC50 for PI3-kinase δ which is lower than the IC50 for PI3-kinase γ by a factor of less than 5.

[00312] 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.

[00313] In some embodiments, one or more of the subject compounds inhibits p110α, p110β, DNAPK or mTor with an IC50 value of greater than 30 nM, and inhibits p110δ and/or p110γ with an IC50 value of less than 1 μM. In some embodiments, the compound additionally shows selective inhibition of p110δ and/or p110γ relative to p110α, p110β, DNAPK and/or mTor by a factor of at least 3, 10, 100, 1000 or higher. For example, a subject compound shows selective inhibition of p110δ or p110γ relative to p110α, p110β, DNAPK and/or mTor by a factor of at least 3. Exemplary compounds showing selective inhibition of p110δ or p110γ relative to p110α, p110β, DNAPK and/or mTor by a factor of at least 3 include, but are not limited to, compounds 328, 329, 330, 331, 332, 333, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 352, 354, 357 and 361 of Table 4.

Pharmaceutical Compositions

[00314] The invention provides pharmaceutical compositions comprising one or more compounds of the present invention.

[00315] 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.

[00316] 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)).

[00317] 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.

[00318] The invention further provides a composition for the prevention of blastocyte implantation in a mammal.

[00319] 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.

[00320] 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.

[00321] 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.

[00322] 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.

[00323] 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.

[00324] 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.

[00325] 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.

[00326] 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.

[00327] 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.

[00328] 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.

[00329] 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.

[00330] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

[00331] 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.

[00332] 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.

[00333] 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.

[00334] 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.

[00335] 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.

[00336] 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.

[00337] 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.

[00338] 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.

[00339] 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.

[00340] 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.

[00341] 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.

[00342] 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.

[00343] 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.

[00344] 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.

[00345] 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.

[00346] 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.

[00347] 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.

[00348] 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.

[00349] 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.

[00350] 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.

[00351] 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.

[00352] 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.

[00353] 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.

[00354] 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.

[00355] 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.

[00356] 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.

[00357] 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.

[00358] 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.

[00359] 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.

[00360] 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.

[00361] 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.

[00362] 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.

[00363] 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.

[00364] 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.

[00365] 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.

[00366] 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.

[00367] 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.

[00368] 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.

[00369] 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.

[00370] 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.

[00371] 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.

[00372] 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.

[00373] 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.

[00374] 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.

[00375] 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.

[00376] 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.

[00377] 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.

[00378] 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.

[00379] 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.

[00380] 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.

[00381] 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

[00382] 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.

[00383] 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.

[00384] 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.

[00385] 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.

[00386] 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.

[00387] 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.

[00388] 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)).

[00389] 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.

[00390] 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.

[00391] 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 conditions including, but not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (e.g., lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), benign monoclonal gammopathy, biliary cancer (e.g., cholangiocarcinoma), bladder cancer, breast cancer (e.g., adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (e.g., meningioma; glioma, e.g., astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, cervical cancer (e.g., cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (e.g., colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endotheliosarcoma (e.g., Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer, esophageal cancer (e.g., adenocarcinoma of the esophagus, Barrett's adenocarinoma), Ewing sarcoma, familiar hypereosinophilia, gastric cancer (e.g., stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (e.g., head and neck squamous cell carcinoma, oral cancer (e.g., oral squamous cell carcinoma (OSCC)), heavy chain disease (e.g., alpha chain disease, gamma chain disease, mu chain disease), hemangioblastoma, inflammatory myofibroblastic tumors, immunocytic amyloidosis, kidney cancer (e.g., nephroblastoma a.k.a. Wilms' tumor, renal cell carcinoma), liver cancer (e.g., hepatocellular cancer (HCC), malignant hepatoma), lung cancer (e.g., bronchogenic carcinoma, small cell lung cancer (SCLC), non–small cell lung cancer (NSCLC), adenocarcinoma of the lung), leukemia (e.g., acute lymphocytic leukemia (ALL), which includes B-lineage ALL and T-lineage ALL, chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HLL) and Waldenstrom's macroglobulinemia (WM); peripheral T cell lymphomas (PTCL), adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGF), Hodgkin's disease and Reed-Stemberg disease; acute myelocytic leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL)), lymphoma (e.g., Hodgkin lymphoma (HL), non–Hodgkin lymphoma (NHL), follicular lymphoma, diffuse large B–cell lymphoma (DLBCL), mantle cell lymphoma (MCL)), leiomyosarcoma (LMS), mastocytosis (e.g., systemic mastocytosis), multiple myeloma (MM), myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorder (MPD) (e.g., polycythemia Vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) a.k.a. myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (e.g., neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (e.g., gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (e.g., cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), Paget's disease of the vulva, Paget's disease of the penis, papillary adenocarcinoma, pancreatic cancer (e.g., pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN)), pinealoma, primitive neuroectodermal tumor (PNT), prostate cancer (e.g., prostate adenocarcinoma), rhabdomyosarcoma,

retinoblastoma, salivary gland cancer, skin cancer (e.g., squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (e.g., appendix cancer), soft tissue sarcoma (e.g., malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, sweat gland carcinoma, synovioma, testicular cancer (e.g., seminoma, testicular embryonal carcinoma), thyroid cancer (e.g., papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), and Waldenström's macroglobulinemia.

[00392] 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.

[00393] In addition, the compounds described herein may be used to treat acne.

[00394] 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.

[00395] 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.

[00396] 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.

[00397] Further, the compounds of the invention may be used for the treatment of Perennial allergic rhinitis, Mesenteritis, Peritonitis, Acrodermatitis, Angiodermatitis, Atopic dermatitis, Contact dermatitis, Eczema, Erythema multiforme, Intertrigo, Stevens Johnson syndrome, Toxic epidermal necrolysis, Skin allergy, Severe allergic reaction/anaphylaxis, Allergic granulomatosis, Wegener granulomatosis, Allergic conjunctivitis , Chorioretinitis, Conjunctivitis, Infectious keratoconjunctivitis, Keratoconjunctivitis, Ophthalmia neonatorum, Trachoma, Uveitis, Ocular inflammation, Blepharoconjunctivitis, Mastitis, Gingivitis, Pericoronitis, Pharyngitis, Rhinopharyngitis, Sialadenitis, Musculoskeletal system inflammation, Adult onset Stills disease, Behcets disease, Bursitis, Chondrocalcinosis, Dactylitis, Felty syndrome, Gout, Infectious arthritis, Lyme disease, Inflammatory osteoarthritis, Periarthritis, Reiter syndrome, Ross River virus

infection, Acute Respiratory, Distress Syndrome, Acute bronchitis, Acute sinusitis, Allergic rhinitis, Asthma, Severe refractory asthma, Pharyngitis, Pleurisy, Rhinopharyngitis, Seasonal allergic rhinitis, Sinusitis, Status asthmaticus, Tracheobronchitis, Rhinitis, Serositis, Meningitis, Neuromyelitis optica, Poliovirus infection, Alport syndrome, Balanitis, Epididymitis, Epididymo orchitis, Focal segmental, Glomerulosclerosis, Glomerulonephritis, IgA Nephropathy (Berger's Disease), Orchitis, Parametritis, Pelvic inflammatory disease, Prostatitis, Pyelitis, Pyelocystitis, Pyelonephritis, Wegener granulomatosis, Hyperuricemia, Aortitis, Arteritis, Chylopericarditis, Dressler syndrome, Endarteritis, Endocarditis, Extracranial temporal arteritis, HIV associated arteritis, Intracranial temporal arteritis, Kawasaki disease, Lymphangiophlebitis, Mondor disease, Periarteritis, or Pericarditis.

[00398] In other aspects, the compounds of the invention are used for the treatment of Autoimmune hepatitis, Jejunitis, Mesenteritis, Mucositis, Non alcoholic steatohepatitis, Non viral hepatitis, Autoimmune pancreatitis, Perihepatitis, Peritonitis, Pouchitis, Proctitis, Pseudomembranous colitis, Rectosigmoiditis, Salpingoperitonitis, Sigmoiditis, Steatohepatitis, Ulcerative colitis, Churg Strauss syndrome, Ulcerative proctitis, Irritable bowel syndrome, Gastrointestinal inflammation, Acute enterocolitis, Anusitis, Balser necrosis, Cholecystitis, Colitis, Crohns disease, Diverticulitis, Enteritis, Enterocolitis, Enterohepatitis, Eosinophilic esophagitis, Esophagitis, Gastritis, Hemorrhagic enteritis, Hepatitis, Hepatitis virus infection, Hepatocholangitis, Hypertrophic gastritis, Ileitis, Ileocecitis, Sarcoidosis, Inflammatory bowel disease, Ankylosing spondylitis, Rheumatoid arthritis, Juvenile rheumatoid arthritis, Psoriasis, Psoriatic arthritis, Lupus (cutaneous/systemic/ nephritis), AIDS, Agammaglobulinemia, AIDS related complex, Brutons disease , Chediak Higashi syndrome, Common variable immunodeficiency, DiGeorge syndrome, Dysgammaglobulinemia, Immunoglobulindeficiency, Job syndrome, Nezelof syndrome, Phagocyte bactericidal disorder, Wiskott Aldrich syndrome, Asplenia, Elephantiasis, Hypersplenism, Kawasaki disease, Lymphadenopathy, Lymphedema, Lymphocele, Nonne Milroy Meige syndrome, Spleen disease, Splenomegaly, Thymoma, Thymus disease, Perivasculitis, Phlebitis, Pleuropericarditis, Polyarteritis nodosa, Vasculitis, Takayasus arteritis, Temporal arteritis, Thromboangiitis, Thromboangiitis obliterans, Thromboendocarditis, Thrombophlebitis, or COPD.

[00399] 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.

[00400] 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.

[00401] 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.

[00402] 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.

[00403] 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.

[00404] 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.

[00405] 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.

[00406] 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

[00407] 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.

[00408] 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.

[00409] 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 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.

[00410] 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.

[00411] 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®.

[00412] 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. Other compounds used in the treatment of lupus include belimumab (Benlysta®).

[00413] 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 biotherapeutic chemotherapeutic agent). Many chemotherapeutics are presently known in the art and can be used in combination with the compounds of the invention. Other cancer therapies can also be used in combination with the compounds of the invention and include, but are not limited to, surgery and surgical treatments, and radiation therapy.

[00414] 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®.

[00415] Other chemotherapeutic agents include, but are not limited to, anti-estrogens (e.g. tamoxifen, raloxifene, and megestrol), LHRH agonists (e.g. goscrclin and leuprolide), anti-androgens (e.g. flutamide and bicalutamide), photodynamic therapies (e.g. vertoporfin (BPD-MA), phthalocyanine, photosensitizer Pc4, and demethoxy-hypocrellin A (2BA-2-DMHA)), nitrogen mustards (e.g. cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, estramustine, and melphalan), nitrosoureas (e.g. carmustine (BCNU) and lomustine (CCNU)), alkylsulphonates (e.g. busulfan and treosulfan), triazenes (e.g. dacarbazine, temozolomide), platinum containing compounds (e.g. cisplatin, carboplatin, oxaliplatin), vinca alkaloids (e.g. vincristine, vinblastine, vindesine, and vinorelbine), taxoids (e.g. paclitaxel or a paclitaxel equivalent such as nanoparticle albumin-bound paclitaxel (Abraxane), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX), the tumor-activated prodrug (TAP) ANG1005 (Angiopep-2 bound to three molecules of paclitaxel), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1), and glucose-conjugated paclitaxel, e.g., 2'-paclitaxel methyl 2-glucopyranosyl succinate; docetaxel, taxol), epipodophyllins (e.g. etoposide, etoposide phosphate, teniposide, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomycin C), anti-metabolites, DHFR inhibitors (e.g. methotrexate, dichloromethotrexate, trimetrexate, edatrexate), IMP dehydrogenase inhibitors (e.g. mycophenolic acid, tiazofurin, ribavirin, and EICAR), ribonuclotide reductase inhibitors (e.g. hydroxyurea and deferoxamine), uracil analogs (e.g. 5-fluorouracil (5-FU), floxuridine, doxifluridine, ratitrexed, tegafur-uracil, capecitabine), cytosine analogs (e.g. cytarabine (ara C), cytosine arabinoside, and fludarabine), purine analogs (e.g. mercaptopurine and Thioguanine), Vitamin D3 analogs (e.g. EB 1089, CB 1093, and KH 1060), isoprenylation inhibitors (e.g. lovastatin), dopaminergic neurotoxins (e.g. 1-methyl-4-phenylpyridinium ion), cell cycle inhibitors (e.g. staurosporine), actinomycin (e.g. actinomycin D, dactinomycin), bleomycin (e.g. bleomycin A2, bleomycin B2, peplomycin), anthracycline (e.g. daunorubicin, doxorubicin, pegylated liposomal doxorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, mitoxantrone), MDR inhibitors (e.g. verapamil), Ca2+ ATPase inhibitors (e.g. thapsigargin), imatinib, thalidomide, lenalidomide, tyrosine kinase inhibitors (e.g., axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTINTM, AZD2171), dasatinib (SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib (IRESSA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN®), bevacizumab (AVASTIN®), rituximab (RITUXAN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), nilotinib (TASIGNA®), sorafenib (NEXAVAR®), everolimus (AFINITOR®), alemtuzumab (CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), temsirolimus (TORISEL®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOKTM), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, and/or XL228), proteasome inhibitors (e.g., bortezomib (Velcade)), mTOR inhibitors (e.g., rapamycin, temsirolimus (CCI-779),

everolimus (RAD-001), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Norvartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe) and OSI-027 (OSI)), oblimersen, gemcitabine, carminomycin, leucovorin, pemetrexed, cyclophosphamide, dacarbazine, procarbizine, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, aminopterin, methopterin, porfiromycin, melphalan, leurosidine, leurosine, chlorambucil, trabectedin, procarbazine, discodermolide, carminomycin,, aminopterin, and hexamethyl melamine.

[00416] Exemplary biotherapeutic agents include, but are not limited to, interferons, cytokines (e.g., tumor necrosis factor, interferon α, interferon γ), vaccines, hematopoietic growth factors, monoclonal serotherapy, immunostimulants and/or immunodulatory agents (e.g., IL-1, 2, 4, 6, or 12), immune cell growth factors (e.g., GM-CSF) and antibodies (e.g. Herceptin (trastuzumab), T-DM1, AVASTIN (bevacizumab), ERBITUX (cetuximab), Vectibix (panitumumab), Rituxan (rituximab), Bexxar (tositumomab)).

[00417] 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.

[00418] 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.

[00419] 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.

[00420] 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.

[00421] 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.

[00422] 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.

[00423] 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.

[00424] 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.

[00425] 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.

[00426] 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.

[00427] 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.

[00428] 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.

[00429] 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.

[00430] 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.

[00431] 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.

[00432] 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.

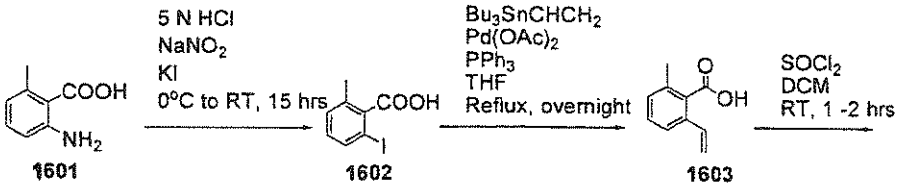
[00433] The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the compounds of the invention will be co-administer with other agents as described above. When used in combination 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.

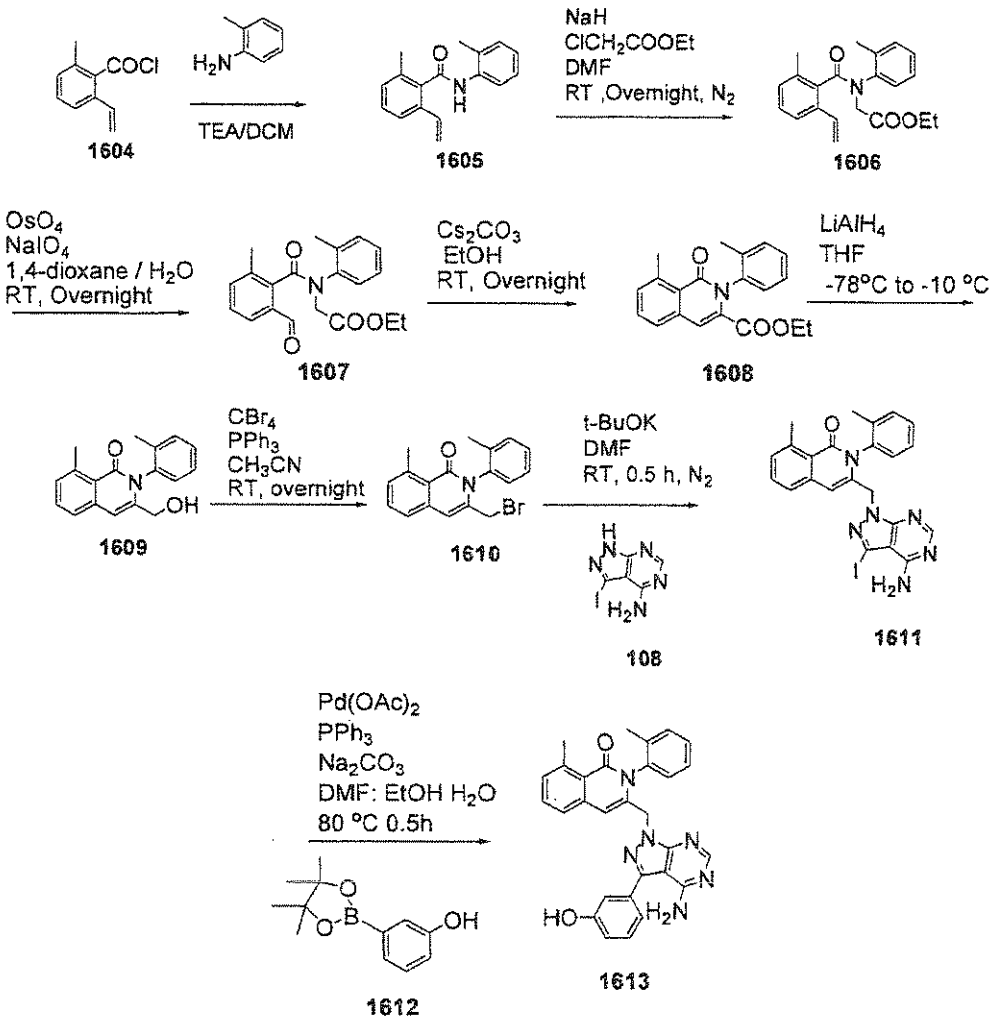
[00434] The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. 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

Example 1: 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 1613), (method A).

Scheme 14. 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 1613).





[00435] A solution of 2-amino-6-methylbenzoic acid (**1601**) (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 (**1602**) (145 g, 79% yield) as a yellow solid

[00436] To a stirred mixture of 2-iodo-6-methylbenzoic acid (**1602**) (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 (**1603**) (61 g, 95% yield) as a yellow solid.

[00437] A mixture of 2-methyl-6-vinylbenzoic acid (**1603**) (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 (**1604**) (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 (**1604**) (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 (**1605**) (81 g, 80% yield) as a yellow solid.

[00439] To a solution of 2-methyl-N-o-tolyl-6-vinylbenzamide (**1605**) (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 (**1606**) (67 g, 62% yield) as a white solid.

[00440] To a stirred mixture of ethyl 2-(2-methyl-N-o-tolyl-6-vinylbenzamido) acetate (**1606**) (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 (**1607**) (38 g, 57% yield) as a yellow solid.

[00441] To a stirred solution of ethyl 2-(2-formyl-6-methyl-N-o-tolylbenzamido) acetate (**1607**) (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 (**1608**) (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 (**1608**) (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 (**1609**) (22 g, 92% yield) as a white solid.

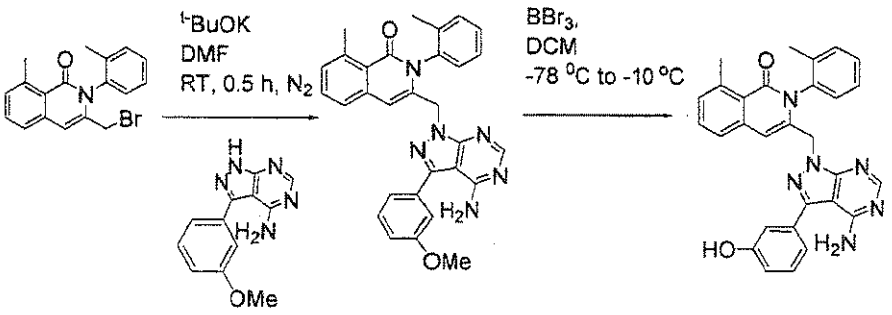
[00443] PBr_3 (25.6 g, 95 mmol) was slowly added to a stirred solution of DMF (11.5 g, 158 mol) in acetonitrile (200 mL) at 0° C, and the resulting mixture was stirred at 0C for 30 min. 3-(Hydroxymethyl)-8-methyl-2-o-tolylisoquinolin -1-(2H)-one (**1609**) (22 g, 78.8 mmol) was slowly added. Then the reaction mixture was allowed to warm to RTand 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 (**1610**) (21 g, 80% yield) as a white solid.

[00444] 3-Iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**108**) (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 (**1610**) (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 (**1611**) (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 (**1611**) (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 (**1611**) (13 g, 24.9 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**1612**)(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 (**1613, compound 13 of Table 4**) (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 (**1613**)(8.4 g, 69% yield) as a white solid.

Example 2: 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 1613) (method B).

Scheme 15. 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 1613) via method B is described.

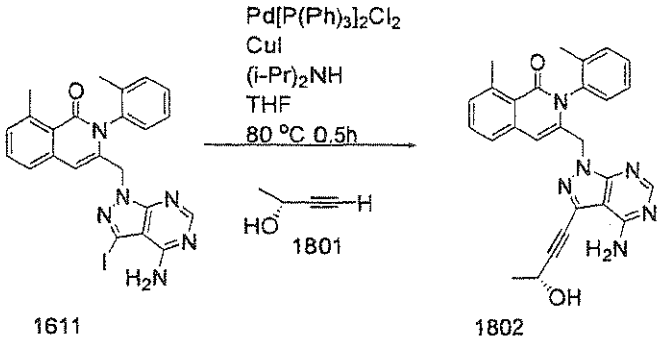


[00446] 3-(3-Methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**1701**)(964 mg, 4 mmol) and potassium tert - butoxide (0.44 g, 4 mmol) were dissolved in anhydrous DMF (150 mL) and stirred at RT for 30 min. 3-(Bromomethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1610**) (1.37 g, 4.0 mmol) was added. 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.

[00447] 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 fro 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 (**1613**)(87 mg, 91% yield) as a white solid.

Example 3: 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 16. 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.

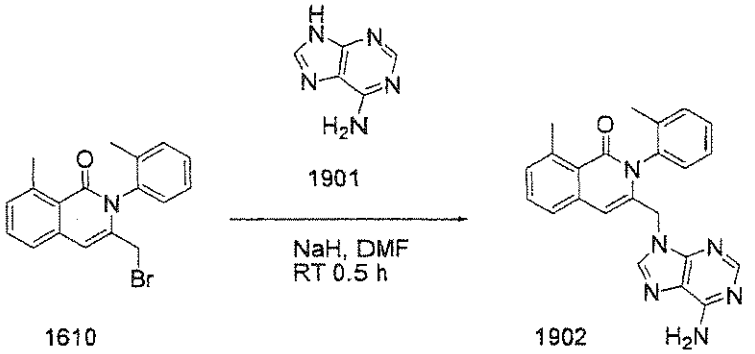


[00448] 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o- tolylisoquinolin-1(2H)-one (**1611**) (522 mg, 1 mmol) and (R)-but-3-yn-2-ol (84 mg, 1.2 mmol) were dissolved in anhydrous THF (40 mL). The mixture was degassed and back-filled with nitrogen three times. $Pd(PPh_3)_2Cl_2$ (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 compound 37 of Table 4**) (324 mg, 70% yield) as a slightly yellow solid.

Example 4: Synthesis of 3-((6-amino-9H-purin-9-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound 1902).

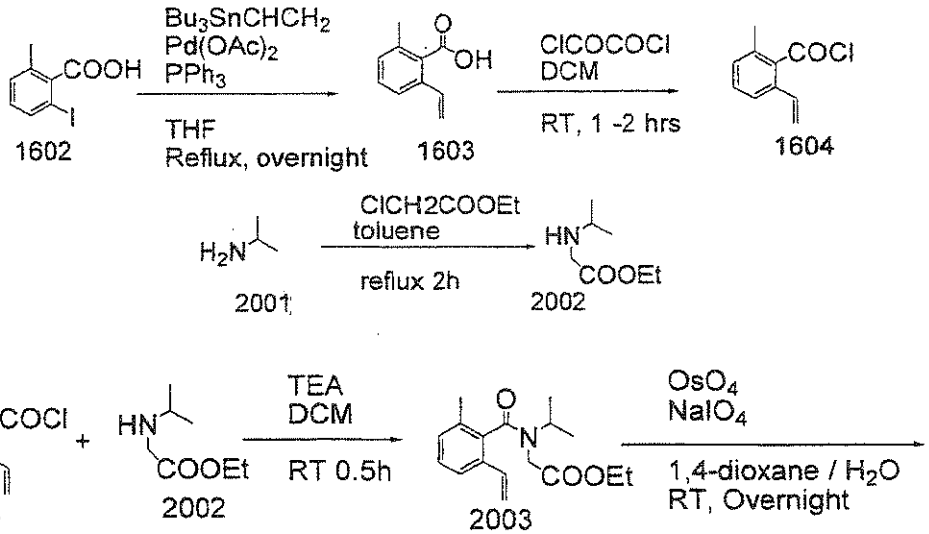
Scheme 17. Synthesis of 3-((6-amino-9H-purin-9-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound 1902) is described.

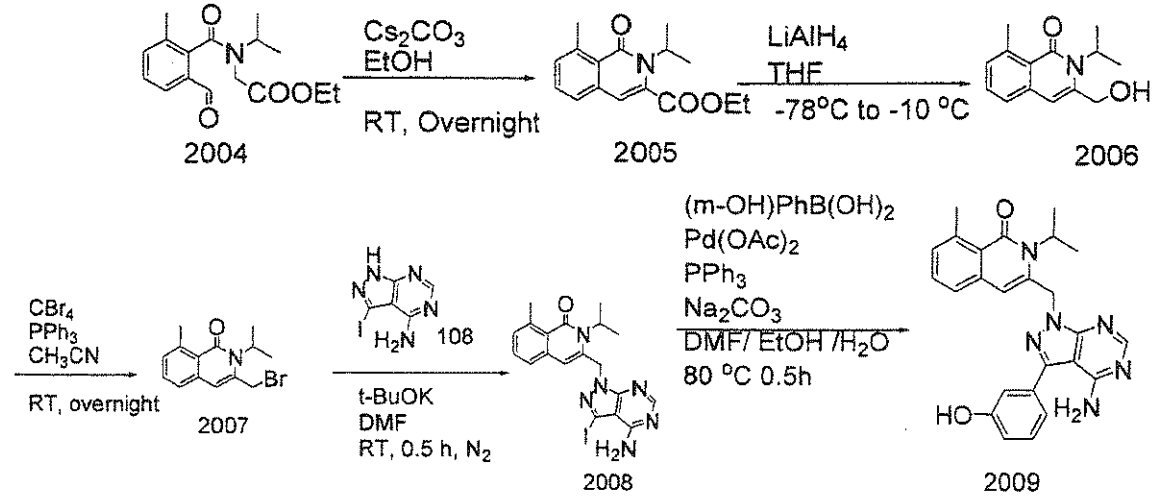


[00449] 9H-Purin-6-amine (**1901**)(540 mg, 4.0 mmol) was dissolved in anhydrous DMF (20 mL). NaH (60% in mineral oil, 160 mg, 4.0 mmol) was added and the resulting mixture was stirred at RT for 30 min. 3-(Bromomethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**1610**)(1.37 g, 4.0 mmol) was added. The 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, compound 5 of Table 4**)(1.1 g, 70% yield) as a white solid.

Example 5: 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 18. 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.





[00450] To a stirred mixture of 2-iodo-6-methylbenzoic acid (**1602**) (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 (**1603**) (61 g, 95% yield) as a yellow solid.

[00451] A mixture of 2-methyl-6-vinylbenzoic acid (**1603**) (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 (**1604**) (63 g, 95% yield) as a yellow oil. The product obtained was used directly in the next step without purification.

[00452] 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.

[00453] 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 (**1604**) (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.

[00454] 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.

[00455] 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.

[00456] 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.

[00457] 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.

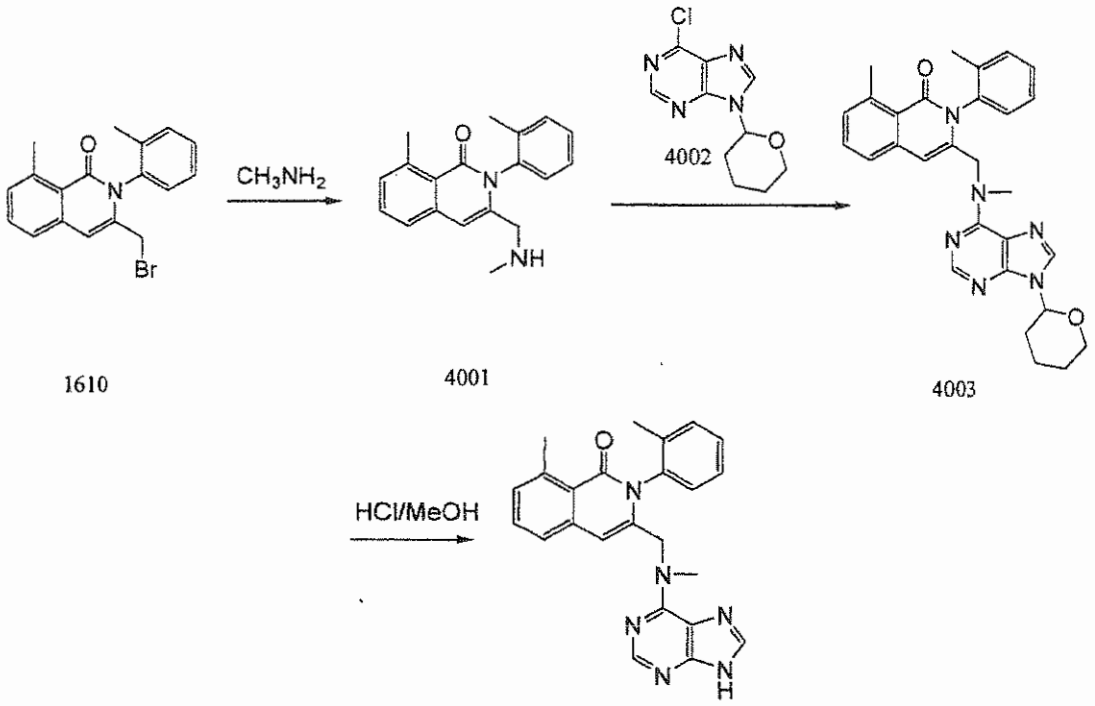
[00458] A mixture of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**108**) (1.3 g, 5 mmol) and potassium tert-butoxide (0.55 g, 5 mmol) in anhydrous DMF (20 mL) was stirred at RT for 30 min and then 3-(bromomethyl)-2-isopropyl-8-methylisoquinolin-1(2H)-one (**2007**) (1.47 g, 5 mmol) was added. The resulting 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.

[00459] 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, compound 62 in Table 4**) (53 mg, 61% yield) as a slightly yellow solid.

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

Scheme 19. The synthesis of 8-methyl-3-((methyl(9H-purin-6-yl)amino)methyl)-2-o-tolylisoquinolin-1(2H)-one (Compound **4004**) is described.



1610 4001 4003

4004

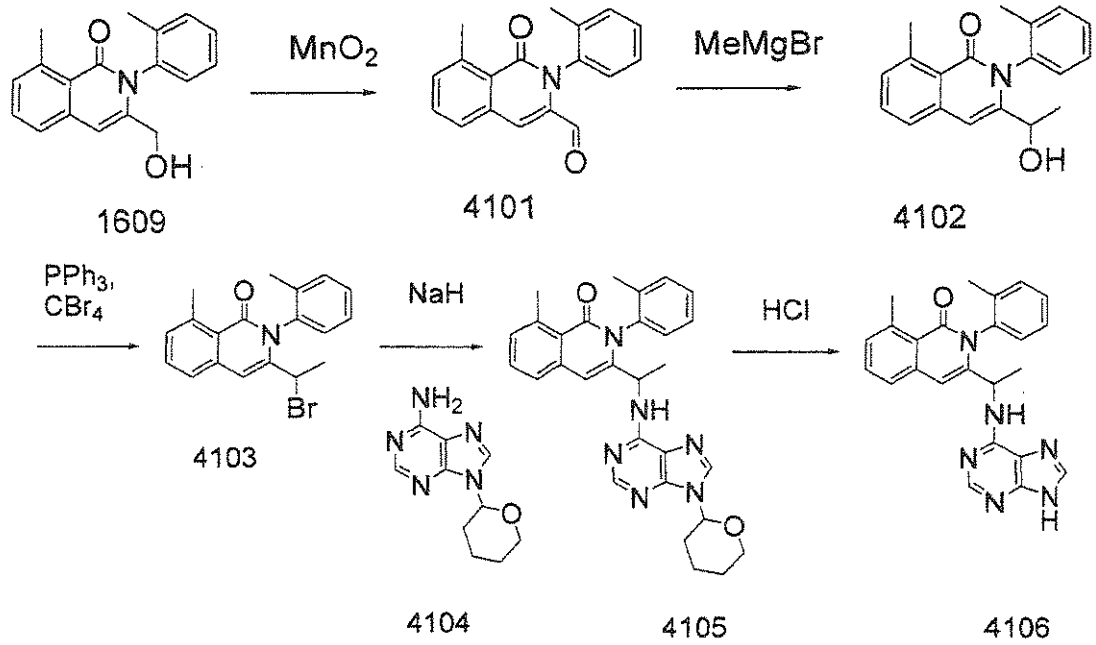
[00460] 3-(Bromomethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (342 mg, 1.0 mmol) **1610** was dissolved in methylamine solution (100 mL) and stirred for 2 h. The mixturen was poured into ice-water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (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.

[00461] 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.

[00462] 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 value 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, compound 184 in Table 4**) (80 mg, 54% yield) as a yellow solid.

Example 7: Synthesis of 3-(1-(9H-purin-6-ylamino)ethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one.

Scheme 20. The synthesis of 3-(1-(9H-purin-6-ylamino)ethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (Compound **4106**) is described.



[00463] To a stirred solution of 3-(hydroxymethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **1609** (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.

[00464] 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.

[00465] 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.

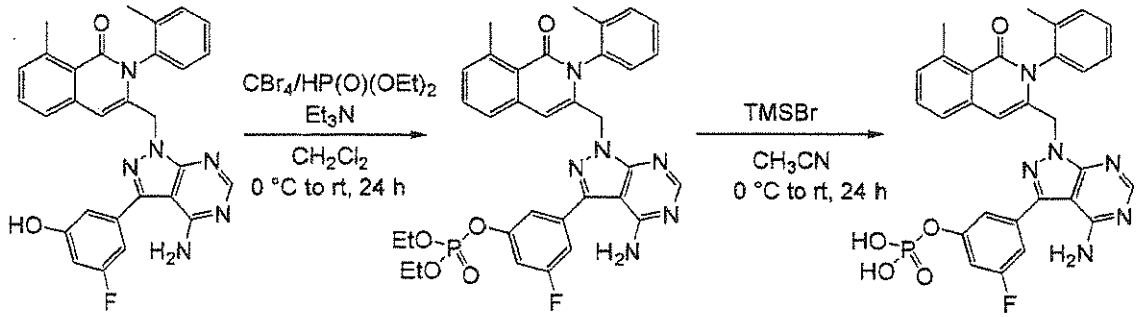
[00466] To a stirred solution of 9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine **4103** (436 mg 2mmol) in anhydrous DMF (10 mL), NaH (60% in mineral oil, 77 mg, 2 mmol) was added and the mixture was stirred for 30 min. 3-(1-Bromoethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one **4104** (700 mg, 2 mmol) 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.

[00467] 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, compound 191 in Table 4**) (80 mg, 54% yield) as a yellow solid.

Example 8: 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.

Scheme 21. 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 **4303**) is described.



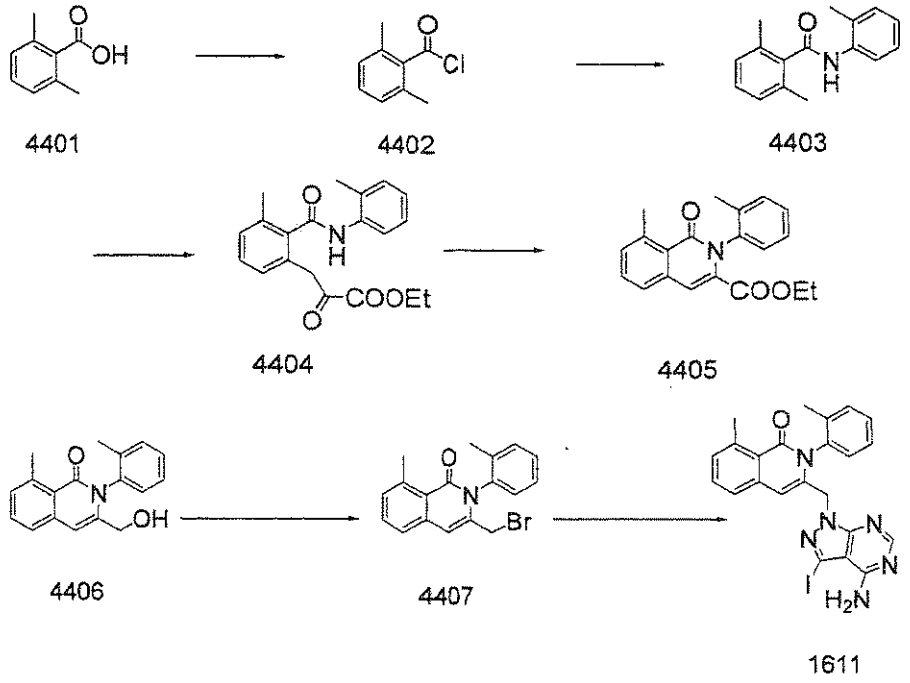
4301 4302 4303

[00468] 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.

[00469] 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 staRT ing 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 **4303** (140 mg, 91% yield).

Example 9: Synthesis of 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (compound 1611).

Scheme 22. The synthesis of 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (compound 1611) is described.



[00470] A mixture of 2,6-dimethylbenzoic acid (**compound 4401**) (60 g, 400 mmol) and oxalyl chloride (101 g, 800 mmol) in CH_2Cl_2 (400 mL) was stirred at room temperature for 2h. The mixture was concentrated *in vacuo* to afford the desired product, 2,6-dimethylbenzoyl chloride (**compound 4402**) (64 g, 95% yield) as a yellow oil. The material obtained was used directly in the next step without purification.

[00471] A mixture of o-toluidine (45 g, 420 mmol) and triethylamine (71 g, 700 mmol) in CH_2Cl_2 (300 mL) was stirred at room temperature for 10 min. To this mixture, 2,6-dimethylbenzoyl chloride (**compound 4402**) (64 g, 400 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water (300 mL), extracted with CH_2Cl_2 (3 x 200 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the crude product. The crude product was suspended in isopropyl ether (300 mL), stirred at reflux for 30 min and then was cooled to 0 - 5°C. The solid was collected by filtration and further dried *in vacuo* to afford the desired product, 2,6-dimethyl-N-o-tolylbenzamide (**compound 4403**) (81 g, 80% yield) as a yellow solid.

[00472] To a stirred solution of 2,6-dimethyl-N-o-tolylbenzamide (**compound 4403**) (23.9 g, 0.1 mol, 1eq) and HMPA (17.9 g, 0.1 mol, 1eq) in anhydrous THF (250 mL) at -78 °C under an argon atmosphere, n-butyllithium (100 mL, 2.5 M, 0.25 mol, 2.5 eq) was carefully added over 1 h and the reaction temperature was kept below -60°C during the addition. The resulting mixture was stirred at -78°C for 1h, and then diethyl oxalate (17.6 g, 0.12 mol, 1.2 eq) was quickly added (the reaction temperature rose to -20 °C upon addition). The mixture was stirred at -50 °C for 10 min, and then quenched with water (100 mL). The inorganic salt was removed by filtration, and the filtrate was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to afford the crude product as a semi-solid oil. The crude product was slurried in isopropyl ether (100 mL) at room temperature for 10 min. The solid was collected by filtration and further dried *in vacuo* to afford the desired product, ethyl 3-(3-methyl-2-(o-tolylcarbamoyl)phenyl)-2-oxopropanoate (**compound 4404**) (16.1 g, 47.4% yield) as a white solid.

[00473] 3-(3-Methyl-2-(o-tolylcarbamoyl)phenyl)-2-oxopropanoate (**compound 4404**) (11.0 g, 32.4 mmol, 1eq) was dissolved in HCl/MeOH (10 M, 100 mL, 10 mL/ 1 g of **4404**) and stirred at reflux for 1h. The reaction mixture was concentrated *in vacuo*, and the residue was slurried in ethyl acetate (10 mL) at room temperature for 30 min. The solid 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 (**compound 4405**) (7.52g, 72.5% yield) as a white solid.

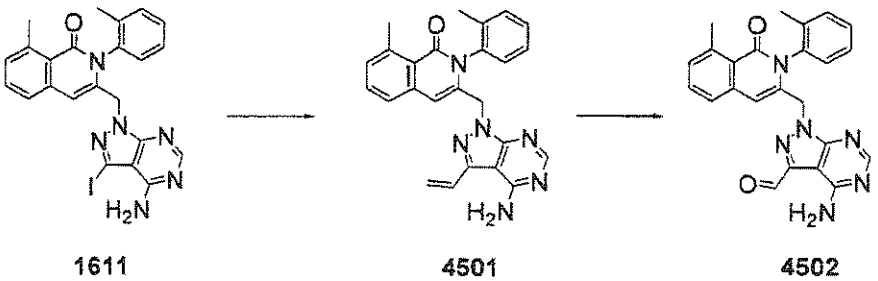
[00474] To a stirred solution of lithium aluminum hydride (8.28 g, 218 mol) in anhydrous THF (500 mL) at -78°C under a nitrogen atmosphere, ethyl 8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinoline-3-carboxylate (**compound 4405**) (28 g, 87 mmol) was slowly added over a 10 min period of time. The resulting mixture was allowed to warm to -30°C, stirred for 30min and analysis by thin layer chromatography showed 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 room temperature, 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 (**compound 4406**) (22 g, 92% yield) as a white solid.

[00475] Phosphorus tribromide (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 0°C for 30 min. 3-(Hydroxymethyl)-8-methyl-2-o-tolylisoquinolin -1-(2H)-one (**compound 4406**) (22 g, 78.8 mmol) was slowly added. Then the reaction mixture was allowed to warm to room temperature 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 isopropyl ether (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 (**compound 4407**) (21 g, 80% yield) as a white solid.

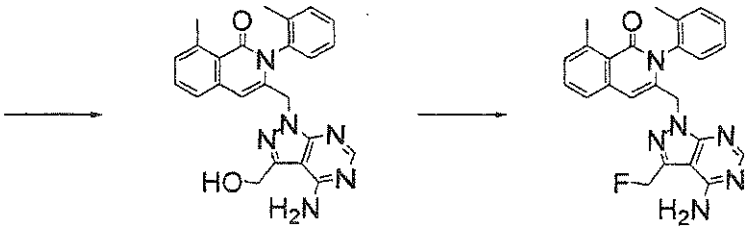
[00476] 3-Iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (10.8 g, 41.4 mmol) and potassium tert -butoxide (4.4 g, 40 mmol) were dissolved in anhydrous DMF (150 mL) and stirred at room temperature for 30 min. 3-(Bromomethyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**compound 4407**) (13.7 g, 40 mmol) was added. The resulting mixture was stirred at room temperature 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 (**compound 1611**) (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 (**1611, compound 6 in Table 4**) (6 g, 30% yield) as a white solid.

Example 10: Synthesis of 3-((4-amino-3-(fluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (compound 4504).

Scheme 23. The synthesis of 3-((4-amino-3-(fluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (compound 4504) is described.



1611 4501 4502



4503 4504

[00477] To a stirred mixture of 3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**compound 1611**) (1.50 g, 2.87 mmol) and tetrakis(triphenylphosphine)palladium (166 mg, 0.14 mmol) in anhydrous DMF (15 mL) under an argon atmosphere, tributyl vinyl tin (1.26 mL, 4.31 mmol) was added and the resulting mixture was stirred at 80 °C for 3h. The reaction mixture was allowed to cool to room temperature, and then partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was triturated with a minimal amount of anhydrous ethyl ether and filtered to afford the desired product, 3-((4-amino-3-vinyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**compound 4501**) (853 mg, 70% yield) as an off-white solid.

[00478] To a stirred solution of 3-((4-amino-3-vinyl-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**compound 4501**) (853 mg, 2.0 mmol) in 1,4-dioxane-H_2O (3:1, 30 mL) under an argon atmosphere, osmium tetroxide (2.5 wt% in t-BuOH, 252 µL, 0.020 mmol) was added and the resulting mixture was stirred at RT for 30 min. To this mixture, sodium periodate (863 mg, 4.0 mmol) was added and the resulting mixture was stirred for 3h. The reaction mixture partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the desired product, 4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carbaldehyde as a tan/brown solid (**compound 4502**) (716 mg, 84% yield).

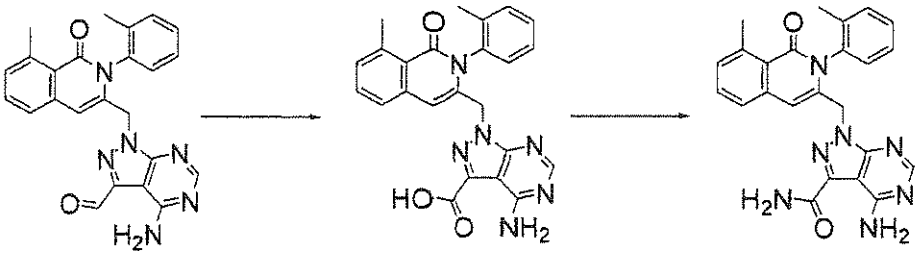
[00479] To a stirred mixture of 4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carbaldehyde as a tan/brown solid (**compound 4502**) (841 mg, 1.98 mmol) in anhydrous MeOH (35 mL) at 0 °C under an argon atmosphere, $NaBH_4$ (89 mg, 2.38 mmol) was added in portions. The mixture was stirred from 0°C to RT for 2h, and then was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the desired product, 3-((4-amino-3-(hydroxymethyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**compound 4503**) (626 mg, 74% yield) as dark brown solid.

[00480] To a stirred suspension of 3-((4-amino-3-(hydroxymethyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**compound 4503**) (50 mg, 0.12 mmol) in anhydrous DCM (2 mL) at 0°C under an argon atmosphere, diethylaminosulfur trifluoride (DAST, 77 µL, 0.59 mmol) was slowly added and the resulting mixture was stirred from 0°C to room termperature for 5h. The reaction was quenched with water and extracted with ethyl acetate. The combined 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 prep-TLC plate (7% MeOH/DCM) to afford the desired product, 3-((4-amino-3-(fluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-8-methyl-2-o-tolylisoquinolin-1(2H)-one (**4504, compound 310 in Table 4**) (10.3 mg, 20% yield) as a white solid.

Example 11: Synthesis of 4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carboxamide (compound 4602).

Scheme 24. The synthesis of 4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carboxamide (compound 4602) is described.



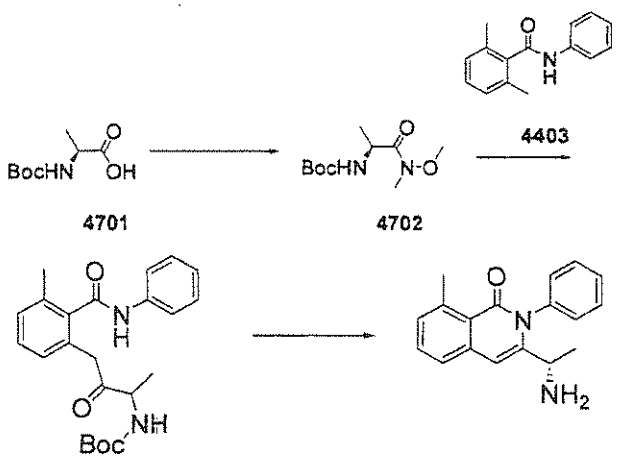
4502 **4601** **4602**

[00481] To a stirred solution of 4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carbaldehyde (**compound 4502**) (400 mg, 0.94 mmol) in *t*-BuOH (1.8 mL), a solution of NaH_2PO_4 (3.90 g, 28.27 mmol) in water (4.8 mL), methyl-2-butene (1.0 mL) and (dropwise) a solution of $NaClO_2$ (767 mg, 6.78 mmol) in water (4.8 mL) were added sequentially. The mixture was stirred at RT for 3h under an argon atmosphere. The pale yellow solution was acidified with aqueous HCl solution (2 M, 4 mL) to PH = 2 and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was triturated with anhydrous ethyl ether and ethyl acetate. The solid was collected by filtration to afford the desired product, 4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carboxylic acid (**compound 4601**) (200 mg, 47% yield) as a yellow solid.

[00482] To a stirred solution of 4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carboxylic acid (**compound 4601**) (150 mg, 0.34 mmol) in anhydrous DCM (10 mL), oxalyl chloride (2.0 M in DCM, 0.22 mL) was slowly added followed by a catalytic amount of anhydrous DMF (1 drop). The resulting mixture was stirred at room temperature for 30 min and then concentrated *in vacuo*. The residue was re-dissolved in DCM (6 mL) and an excess amount of ammonium hydroxide was added (0.35 mL). The mixture was stirred at room temperature for 2h, and then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (eluting with 5% MeOH/DCM) to afford the desired product, 4-amino-1-((8-methyl-1-oxo-2-o-tolyl-1,2-dihydroisoquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carboxamide (**4602, compound 298 in Table 4**) (22 mg, 15% yield) as a white solid.

Example 12: Synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 4704) (Method A)

Scheme 25. The synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 4704) via Method A is described.



[00483] To a stirred mixture of (S)-2-(tert-butoxycarbonylamino)propanoic acid (**compound 4701**) (189.1 g, 1 mol, 1 eq), triethylamine (404.8 g, 4 mol, 4 eq) and HOBt (135 g, 1.0 mol, 1 eq) in anhydrous dichloromethane (1.8 L) at 0 °C, EDCI (384.3 g, 2 mol, 2 eq) was added in portions over 30 min. The resulting mixture was stirred at RT for 30 min, and then N,O-dimethylhydroxylamine hydrochloride (107.3 g, 1.1 mol, 1.1 eq) was added. The reaction mixture was stirred at RT for 20 h, and then quenched with water (1 L). The organic layer was washed with water (2 x 1 L) and brine (500 mL), dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*. The crude product was slurried in petroleum ether (1 L) and stirred at RT for 10 min. The solid was collected by filtration and further dried *in vacuo* to afford the desired product, (S)-tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (**compound 4702**) (218 g, 93.9% yield) as a white solid.

[00484] To a stirred mixture of 2,6-dimethyl-N-phenylbenzamide (**compound 4403**, which may be synthesized as described in Example 9) (30 g, 0.13 mol, 1 eq) and HMPA (26 g, 0.16 mol, 1.2 eq) in anhydrous THF (300 mL) at -78 °C under an argon atmosphere, n-butyllithium (2.5 M, 100 mL, 0.25 mol, 2.5 eq) was carefully added (dropwise) over a 1h and the reaction temperature was kept below -60 °C during the addition. The resulting mixture was stirred at -78 °C for 1h. To this mixture, tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-yl carbamate (**compound 4702**) (40 g, 0.173 mol, 1.3 eq) was quickly added (the reaction temperature rose to -50 °C upon addition). The mixture was stirred at -50 °C for 10 min, quenched with water (300 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with water (500 mL x 2) and brine (50 mL), dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to give the crude product as a semi-solid oil. The crude product was slurried in EA and stirred for 10 min. The white solid was removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was stirred in a mixture of ethyl acetate (30 mL) and isopropyl alcohol (200 mL) at RT for 10 min. The solid was collected by filtration and further dried *in vacuo* to afford the desired product, tert-butyl4-(3-methyl-2-(phenylcarbamoyl)pheny)-3-oxobutan-2-yl carbamate (**compound 4703**) (9.23 g, 17.5% yield) as a white solid.

[00485] Tert-Butyl-4-(3-methyl-2-(phenylcarbamoyl) pheny)-3-oxobutan-2-yl carbamate (**compound 4703**) (9.23 g, 23 mmol) was dissolved in HCl/MeOH (100 mL) and stirred at reflux for 30 min. The mixture was allowed to cool to RT, concentrated *in vacuo*, and then saturated Na_2CO_3 solution was added to adjust the PH to 7-8. The solid was collected by filtration and further dried *in vacuo* to afford the desired product, 3-(1-aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 4704**) (5.8 g, 90% yield, S:R isomers = 7:1) as a white solid.

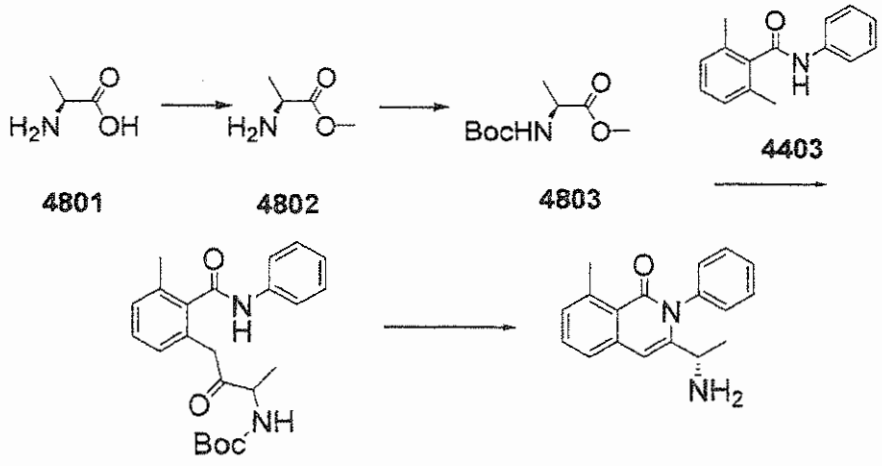


S;R=(7:1) S;R=(41:1)

[00486] Resolution of isomers to increase the enantiomeric purity: 3-(1-Aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 4704**) (where the ratio of isomers is S:R = 7:1) (5 g, 18 mmol) was dissoved in MeOH (100 mL), (D)-tartaric-acid (2.7 g, 18 mmol) was added. The mixture was stirred at RT for 30 min and the solid was precipitated. The resulting mixture was stirred at reflux for 1h, and then stirred at RT for 16h. The solid was collected by filtration and rinsed with methanol (10 mL). The solid was then dissolved in H_2O (15 mL) and saturated $NaHCO_3$ (5 mL) was added to adjust the PH to 8. The solid was collected by filtration , rinsed with water (5 mL), and then dried *in vacuo* to afford the enantiomerically enriched product (**compound 4704**) (2.7 g, 58% yield,) where the ratio of isomers, S:R > 41:1.This is an enantiomeric purity of greater than about 97.6% of the (S)- enantiomer. The ratio of two enantiomers was confirmed by coupling with (R)-(-)-alpha- methoxyphenylacetic acid and detection of the resultant diastereomers by Nuclear Magnetic Resonance Spectroscopy.

Example 13: Synthesis of (S)-3-(1-aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (Method B) (compound 4704.

Scheme 26. The synthesis of (S)-3-(1-aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 4704) via Method B is described..



4801 **4802** **4803** **4403**

4703 **4704**

[00487] Thionyl chloride (320.8 g, 2.7 mol, 1.2 eq) was added dropwise to stirred anhydrous MeOH (2 L) at 0 °C over 50 min and the reaction temperature was kept below 25 °C during the addition. The mixture was allowed to warm to room temperature and then (S)-2-aminopropanoic acid (**compound 4801**) (200 g, 2.24 mol, 1 eq) was added. The resulting mixture was stirred at room temperature for 20h, and concentrated *in vacuo* to afford the desired product, (S)-methyl 2-aminopropanoate hydrochloride (**compound 4802**) as a white solid.

[00488] To a stirred solution of above obtained (S)-methyl 2-aminopropanoate hydrochloride (**compound 4802**) in water (1.6 L) at room temperature, $NaHCO_3$ (566.2 g, 6.741 mol, 3 eq) and a solution of di-tert-butyl dicarbonate (490.4 g, 2.247 g, 1 eq) in THF (1.6 L) were added sequentially. The resulting mixture was stirred at room temperature for 20h. The inorganic salt was removed by filtration, and the filtrate was extracted with ethyl acetate (2 x 500 mL). The combined organic layer was washed with brine (500 mL), dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in*

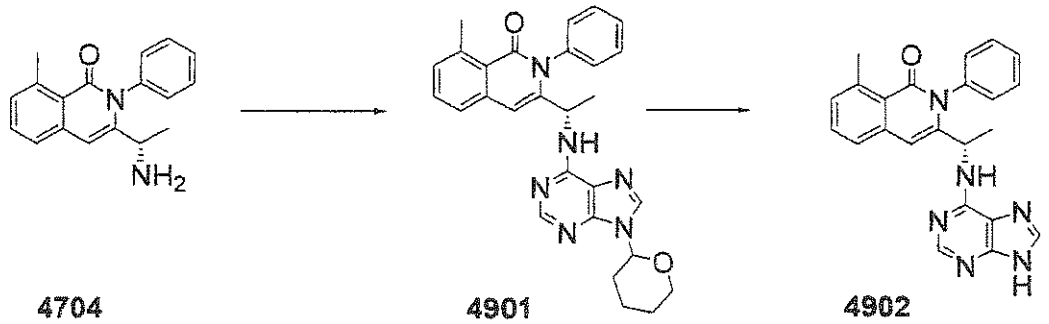
vacuo to afford the desired product, (S)-methyl 2-(tert-butoxycarbonylamino)propanoate (**compound 4803**) (448 g, 98.2% yield) as a colorless crystal.

[00489] To a stirred solution of 2,6-dimethyl-N-phenylbenzamide (**compound 4403**), which may be synthesized as described in Example 9) (30 g, 0.13 mol, 1 eq) and HMPA (26 g, 0.16 mol, 1.2 eq) in anhydrous THF (300 mL) at -78 °C under an argon atmosphere, n-butyllithium (100 mL, 2.5 M, 0.25 mol, 2.5 eq) was added carefully over 1 h and the reaction temperature was kept below -60 °C during addition. The resulting mixture was stirred at -78 °C for 1h, and then (S)-methyl 2-(tert-butoxycarbonylamino)-propanoate (**compound 4803**) (35 g, 0.173 mol, 1.3 eq) was quickly added (the reaction temperature rose to -50 °C during addition). The mixture was stirred at -50 °C for 10 min, quenched with water (300 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with water (500 mL x 2), dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to afford the crude product as a semi-solid oil. The crude product was slurried in ethyl acetate (500 mL) and stirred for 10 min. The solid was removed by filtration, and the filtrate was concentrated *in vacuo*. The oil residue was stirred in a mixture of ethyl acetate (30 mL) and isopropyl alcohol (200 mL) at room temperature for 10 min. The solid was collected by filtration and further dried *in vacuo* to afford the desired product, tert-butyl4-(3-methyl-2-(phenylcarbamoyl)pheny)-3-oxobutan-2-ylcarbamate (**compound 4703**) (4.61 g, 9 % yield) as a white solid.

[00490] Tert-Butyl 4-(3-methyl-2-(phenylcarbamoyl)phenyl)-3-oxobutan-2-ylcarbamate (**compound 4703**) (4.61 g, 0.012 mol) was dissolved in HCl/MeOH (50 mL) and stirred at reflux for 30 min. The mixture was concentrated *in vacuo* and then saturated Na_2CO_3 solution was added to adjust PH to about 7-8. The resulting solid was collected by filtration and further dried *in vacuo* to afford the desired product, 3-(1-aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 4704**) (2.9g, 90% yield, where the ratio of isomers is S:R = 5:1) as a white solid.

Example 14a: Synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (9) (compound 4902)

Scheme 27a. The synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (9) (compound 4902) is described.



4704 4901 4902

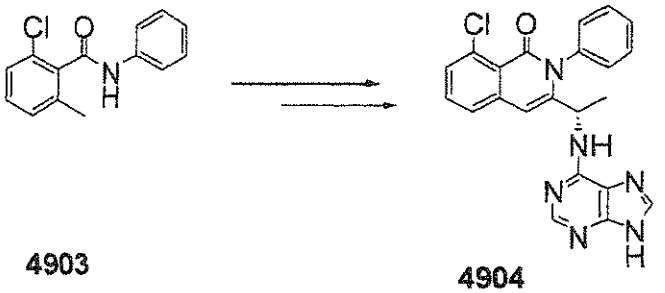
[00491] 3-(1-Aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 4704**) (200 mg, 0.72 mmol), 6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (344 mg, 1.44 mmol) and DIPEA (279 mg, 2.16 mmol) were dissolved in *n*-BuOH (20 ml) , and the resulting mixture was stirred at reflux for 16h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (eluting with 30% to 50% Hex/EA) to afford the desired product, 8-methyl-2-phenyl-3-((1S)-1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)isoquinolin-1(2H)-one (**compound 4901**) (207 mg, 60% yield) as a white solid.

[00492] 8-Methyl-2-phenyl-3-((1S)-1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)-isoquinolin-1(2H)-one (**compound 4901**) (200 mg, 0.42 mmol) was dissolved in HCl/EtOH (3 M, 5 mL) and the resulting mixture was stirred at room temperature for 1h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution and the PH was

adjusted to about 7-8. The mixture was extracted with CH_2Cl_2 (50 mL × 3), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was recrystallized from ethyl acetate and hexanes (1 : 1). The solid was collected by filtration and dried *in vacuo* to afford the desired product, (S)-3-(1-(9H-purin-6-ylamino) ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 4902**) (150 mg, 90% yield) as a white solid.

Example 14b: Synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (9) (compound 4904)

Scheme 27b. The synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (9) (compound 4904) is described.

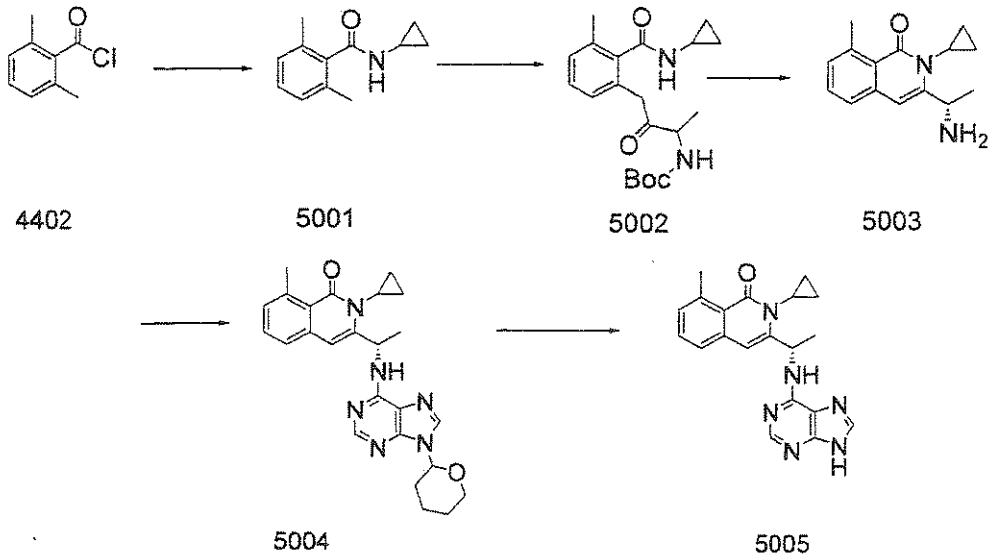


4903 4904

[00493] The compound of Formula **4904** (compound 292 in Table 4) was synthesized using the synthetic transformations as described in Examples 12 and 14a, but 2-chloro-6-methyl benzoic acid (compound **4903**) was used instead of 2, 6 ,dimethyl benzoic acid (compound **4403**). By a similar method, compound 328 in Table 4 was synthesized using the synthetic transformations as described starting from the 2-chloro-6-methyl m-fluorobenzoic acid.

Example 15a: Synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-2-cyclopropyl-8-methylisoquinolin-1(2H)-one (compound 5005).

Scheme 28a. The synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-2-cyclopropyl-8-methylisoquinolin-1(2H)-one is described.



4402 5001 5002 5003

5004 5005

[00494] A mixture of cyclopropanamine (24 g, 420 mmol) and triethylamine (71 g, 700 mmol) in CH_2Cl_2 (300 mL) was stirred at RT for 10min. To this mixture, 2,6-dimethylbenzoyl chloride (**compound 4402**) (64 g, 400 mmol) was added dropwise, and the resulting mixture was stirred at room temperature for 30min. The raction mixture was poured into water (300 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the crude product. The crude product was suspended in isopropyl

ether (IPE) (300 mL), stirred at reflux for 30min and then was allowed to cool to 0 - 5°C. The precipitate was collected by filtration and further dried *in vacuo* to afford the desired product, N-cyclopropyl-2,6-dimethylbenzamide (**compound 5001**) (61 g, 80% yield) as a yellow solid.

[00495] To a stirred solution of N-cyclopropyl-2,6-dimethylbenzamide (**compound 5001**) (25 g, 0.13 mol, 1 eq) and HMPA (26 g, 0.16 mol, 1.2 eq) in anhydrous THF (300 mL) at -78 °C under an argon atmosphere, n-butyllithium (2.5M, 100 mL, 0.25 mol, 2.5 eq) was added carefully over 1 h and the temperature was kept below -60 °C during addition. The resulting mixture was stirred at -78 °C for 1h, and then tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (40 g, 0.173 mol, 1.3 eq) was quickly added (the reaction temperature rose to -50 °C during addition). The mixture was stirred at -50 °C for 10 min, quenched with water (300 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with water (500mL x 2) and brine (100 mL), dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to afford the desired product, tert-butyl 4-(2-(cyclopropylcarbamoyl)-3-methylphenyl)-3-oxobutan-2-ylcarbamate (**compound 5002**) (32 g, 70 % yield) as a yellow oil.

[00496] Tert-Butyl 4-(2-(cyclopropylcarbamoyl)-3-methylphenyl)-3-oxobutan-2-ylcarbamate (**compound 5002**) (32 g, 88 mmol) was dissolved in HCl/MeOH (300 mL) and stirred at room temperature for 16h. The mixture was concentrated *in vacuo*, and then saturated Na_2CO_3 aqueous solution was added to adjust the pH to about 7-8. The resulting solid was collected by filtration and further dried *in vacuo* to afford the desired product, 3-(1-aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 5003**) (17 g, 80% yield, S:R = 7:1) as a white solid.



S;R=(7:1) S

[00497] To a stirred solution of 3-(1-aminoethyl)-2-cyclopropyl-8-methylisoquinolin-1(2H)-one (S:R = 7:1) (4.84 g, 20 mmol) (**compound 5003**) in MeOH (96.8 mL), (L) tartaric-acid (3.0 g, 20 mmol) was added and the resulting mixture was stirred at room temperature for 16h. The precipitate was collected by filtration and rinsed with MeOH (10 mL). The solid was dissolved in H_2O (15 mL) and statured $NaHCO_3$ (5 mL) was added to adjust the pH to about 8. The resulting solid was collected by filtration, rinsed with water (5 mL), and dried *in vacuo* to afford the desired product (**compound 5003**) (1.94 g. 40% yield) as a single enantiomer (S configuration). The enantiomeric purity was confirmed by coupling with (R)-(-)-alpha-methoxyphenylacetic acid and performing Nuclear Magnetic Resonance Spectroscopy on the resulting diastereomeric mixture.

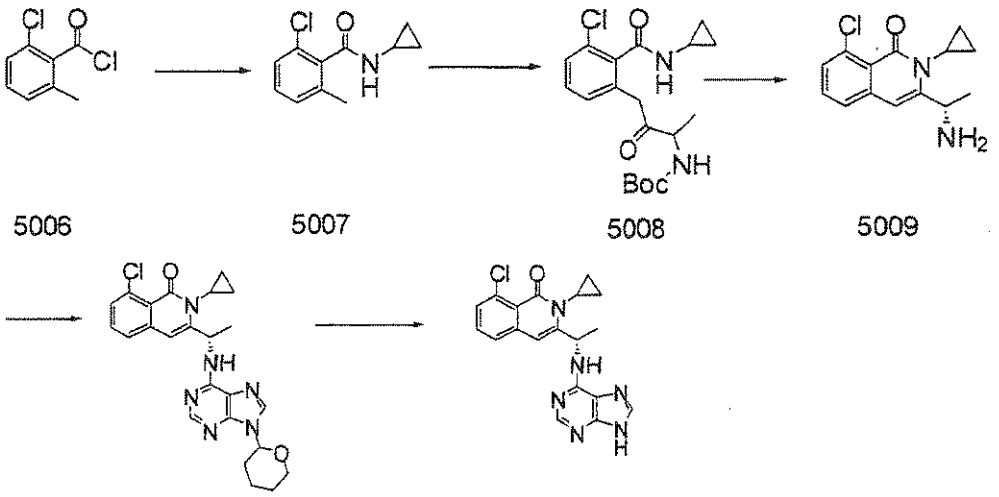
[00498] (S)-3-(1-Aminoethyl)-2-cyclopropyl-8-methylisoquinolin-1(2H)-one (242 mg, 1 mmol) (**compound 5003**), 6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (344 mg, 1.44 mmol) and DIPEA (279 mg, 2.16 mmol) were dissolved in n-BuOH (20 mL), and the resulting mixture was stirred at reflux for 16h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluting with 30% to 50% Hex/EA) to afford the desired product, 2-cyclopropyl-8-methyl-3-((1S)-1-(9-(tetrahydro-2H-Pyran-2-yl)-9H-purin-6-ylamino)ethyl)isoquinolin-1(2H)-one (**compound 5004**) (288 mg, 65% yield) as a white solid.

[00499] 2-Cyclopropyl-8-methyl-3-((1S)-1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)isoquinolin-1(2H)-one (**compound 5004**) (222 mg, 0.5 mmol) was dissolved in HCl/EtOH (3 M, 5 mL) and the resulting mixture was stirred at room temperature for 1h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution to pH = 7-8, and then extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and

filtered. The filtrate was concentrated *in vacuo* and the residue was recrystallized from ethyl acetate and hexanes (1 : 1). The solid was collected by filtration and dried *in vacuo* to afford the desired product, (S)-3-(1-(9H-purin-6-ylamino)ethyl)-2-cyclopropyl-8-methylisoquinolin-1(2H)-one (**5005, compound 200 in Table 4**) (150 mg, 83% yield) as a white solid.

Example 15b. Synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-2-cyclopropyl-8-chloro-isoquinolin-1(2H)-one (compound 5011).

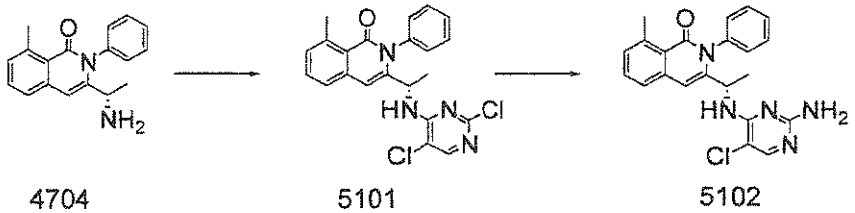
Scheme 28b. The synthesis of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-2-cyclopropyl-8- chloro-isoquinolin-1(2H)-one is described:



[00500] The compound of Formula **5011 (compound 270 in Table 4)** was synthesized using the synthetic transformations as desribed in Example 15a, but 2-chloro-6-methyl benzoyl chloride (**compound 5006**) was used instead of 2, 6 ,dimethyl benzoyl chloride (**compound 4402**).

Example 16: Synthesis of (S)-3-(1-(2-amino-5-chloropyrimidin-4-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 5102).

Scheme 29. The synthesis of (S)-3-(1-(2-amino-5-chloropyrimidin-4-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 5102) is described.



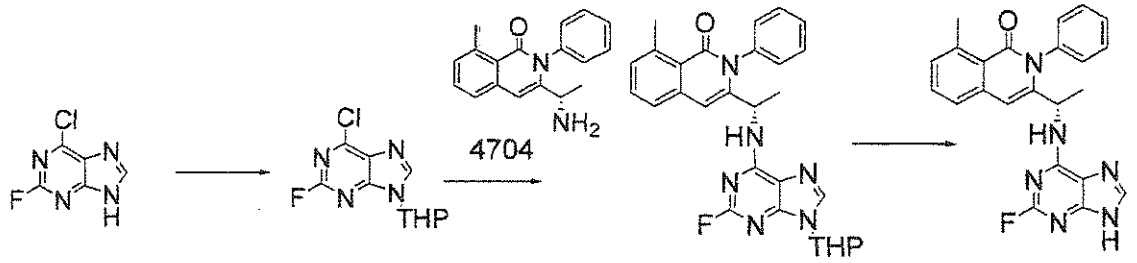
[00501] A mixture of 3-(1-aminoethyl)-8-methyl-2-phenylisoquinolin- 1(2H)-one (**compound 4704**) (150 mg, 0.54 mmol), 2,4,5-trichloropyrimidine (119 mg, 0.65 mmol) and triethylamine (137 mg, 1.35 mmol) in n-BuOH (10 mL) was stirred at reflux for 2h. The mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH:CH_2Cl_2 = 1:100) to afford the desired product, (S)-3-(1-(2,5-dichloropyrimidin-4-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (2H)-one (**compound 5101**) (170 mg, 74% yield) as a white solid.

[00502] A mixture of (S)-3-(1-(2,5-dichloropyrimidin-4-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 5101**) (85 mg, 0.20 mmol) in ammonia water (15 mL) in a sealed tube was stirred at 150 °C for 16h. The solution was allowed to cool to room temperature and then partitioned between water (30 mL) and ethyl acetate (3 ×

30mL). The combined organic layer was washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the desired product, (S)-3-(1-(2-amino-5-chloropyrimidin-4-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**5102, compound 249 in Table 4**) (40 mg, 49.6% yield) as a white solid.

Example 17: Synthesis of (S)-3-(1-(2-fluoro-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 5204).

Scheme 30. The synthesis of (S)-3-(1-(2-fluoro-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 5204) is described.



5201 **5202** **5203** **5204**

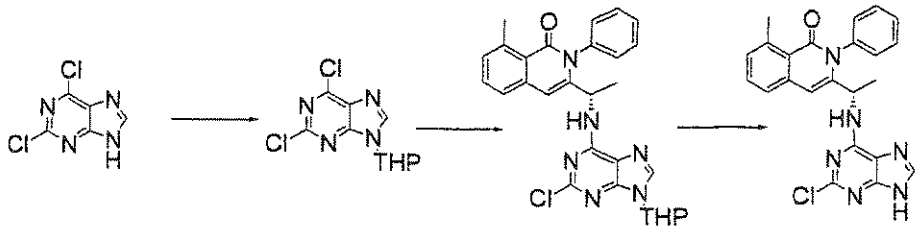
[00503] To a stirred mixture of 6-chloro-2-fluoro-9H-purine (**compound 5201**) (2.07 g, 12.0 mmol) and p-toluenesulfonic acid monohydrate (34 mg, 0.18 mmol) in ethyl acetate (50 mL) under an argon atmosphere, 3,4-dihydropyran (3.03 g, 36.0 mmol) was added and the resulting mixture was stirred at reflux for 16h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluting with 10% Hex/EA) to afford the desired product, 6-chloro-2-fluoro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (**compound 5202**) (1.82 g, 59% yield) as a white solid.

[00504] 3-(1-Aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (200 mg, 0.72 mol), 6-chloro-2-fluoro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (**compound 5202**) (369 mg, 1.44 mmol) and DIPEA (279 mg, 2.16 mmol) were dissolved in n-BuOH (20 mL) in a sealed tube, and the resulting mixture was stirred at 120 °C for 16h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluting with 30% to 50% Hex/EA) to afford the desired product, 3-(1-(2-fluoro-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 5203**) (167 mg, 47% yield) as a white solid.

[00505] 3-(1-(2-Fluoro-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 5203**) (160 mg, 0.32 mmol) was dissolved in HCl/EtOH (3 M, 5 mL) and the resulting mixture was stirred at room temperature for 1h. The mixture was neutralized with saturated $NaHCO_3$ aqueous solution to pH = 7-8, and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was recrystallized from ethyl acetate and hexanes. The solid was collected by filtration and dried *in vacuo* to afford the desired product, 3-(1-(2-fluoro-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin -1(2H)-one (**5204, compound 245 in Table 4**) (125 mg, 94% yield) as a white solid.

Example 18: : Synthesis of (S)-3-(1-(2-chloro-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 5304).

Scheme 31. The synthesis of (S)-3-(1-(2-chloro-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 5304) is described.



5301 5302 5303 5304

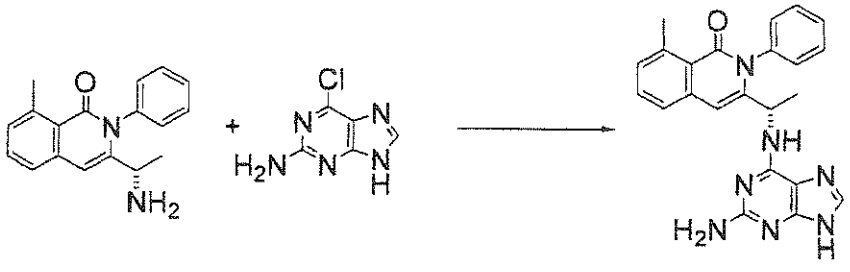
[00506] To a stirred mixture of 2,6-dichloro-9H-purine (**compound 5301**) (2.27 g, 12.0 mmol) and p-toluenesulfonic acid monohydrate (34 mg, 0.18 mmol) in ethyl acetate (50 mL) under an argon atmosphere, 3,4-dihydropyran (3.03 g, 36.0 mmol) was added and the resulting mixture was stirred at reflux for 16h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluting with 10% Hex/EA) to afford the desired product, 2,6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (**compound 5302**) (2.04 g, 62% yield) as a white solid.

[00507] 3-(1-Aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 4704**) (200 mg, 0.72 mol), 2,6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (**compound 5302**) (393 mg, 1.44 mmol) and DIPEA (279 mg, 2.16 mmol) were dissolved in n-BuOH (20 mL) in a sealed tube, and the resulting mixture was stirred at 120 °C for 16h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluting with 30% to 50% Hex/EA) to afford the desired product, 3-(1-(2-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 5303**) (172 mg, 46% yield) as a white solid.

[00508] 3-(1-(2-Chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 5303**) (172 mg, 0.33 mmol) was dissolved in HCl/EtOH (3 M, 5 mL) and the resulting mixture was stirred at room temperature for 1h. The mixture was neutralized with saturated $NaHCO_3$ aqueous solution to pH = 7-8, and then extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and recrystallized from ethyl acetate and hexanes. The solid was collected by filtration and dried *in vacuo* to afford the desired product, 3-(1-(2-chloro-9H- purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**5304, compound 244 in Table 4**) (128 mg, 90% yield) as a white solid.

Example 19: Synthesis of (S)-3-(1-(2-amino-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 5402).

Scheme 32. The synthesis of (S)-3-(1-(2-amino-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (compound 5402) is described.



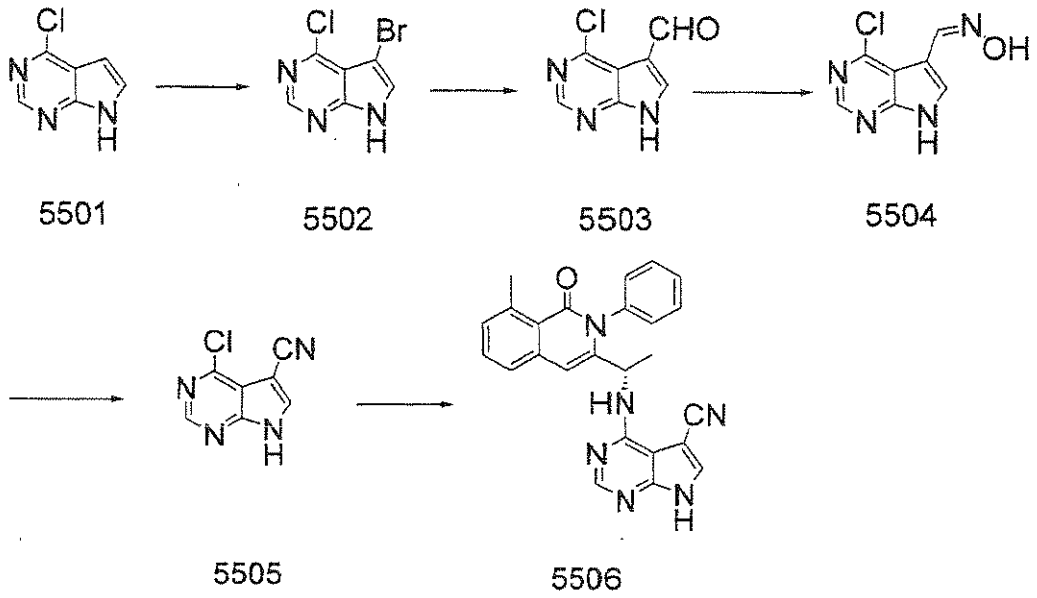
4704 5401 5402

[00509] (S)-3-(1-Aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 4704**) (100 mg, 0.36 mmol), 2-Amino-6-chloropurine (**compound 5401**) (60.9 mg, 0.36 mmol) and N,N-diisopropylethyl amine (69 μL, 0.40 mmol) were suspended in n-BuOH (4 mL) in a sealed tube, and the resulting mixture was stirred at 100 °C for 48h and then at

120 °C for 24 h. The mixture was allowed to cool to room temperature and concentrate *in vacuo* to remove n-BuOH. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The residue was triturated with anhydrous ethyl ether and further purified by flash column chromatography on silica gel (eluting with 0–8% MeOH/DCM) to afford the desired product, (S)-3-(1-(2-amino-9H-purin-6-ylamino)ethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one as a off white/yellow solid (**5402, compound 323 in Table 4**), (28 mg, 20%).

Example 20: Synthesis of (S)-4-(1-(8-methyl-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (compound 5506).

Scheme 33. The synthesis of (S)-4-(1-(8-methyl-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (compound 5506) is described.



[00510] To a stirred mixture of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**compound 5501**) (3.99 g, 26.0 mmol) in dry CH_2Cl_2 (150 mL) under an argon atmosphere, N-bromosuccinimide (6.02 g, 33.8 mmol) was added. The reaction mixture was stirred at room temperature for 3h, diluted with MeOH (30 mL), and then concentrated *in vacuo* to yield a slight brown solid. The residue was triturated with H_2O (150 mL) and then recrystallized from MeOH (120 mL). The solid was collected by filtration and dried *in vacuo* to afford the desired product, 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**compound 5502**) (4.0 g, 66% yield) as a white solid.

[00511] To a stirred solution of 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**compound 5502**) (2.33 g, 10.0 mmol) in anhydrous THF (100 mL) at -78 °C under an argon atmosphere, a solution of n-BuLi (8.8 mL, 22.0 mmol) in THF (50 mL) was added dropwise over 10 min. The reaction mixture was stirred at -78 °C for 1h and then DMF (2.00 g, 11.0 mmol) was added dropwise over 10 min. The reaction mixture was stirred at -78 °C for 30 min, and then was allowed to slowly warm to room temperature and stirred at room temperature for 16h. The mixture was diluted with H_2O (50 mL), and then concentrated *in vacuo* to remove THF. The resulting slurry was treated with saturated NH_4Cl aqueous solution (50 mL), filtered, washed with ethyl acetate (100 mL), and dried *in vacuo* to afford the desired product, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde (**compound 5503**) (1.17 g, 65% yield) as a white solid.

[00512] To a stirred mixture of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde (**compound 5503**) (1.17 g, 6.47 mmol) in EtOH (25 mL), hydroxylamine hydrochloride solid (0.54 g, 7.77 mmol) and a solution of NaOH (0.311 g, 7.77 mmol) in H_2O (4 mL) were added sequentially. The reaction mixture was stirred at room temperature for 30 min and

diluted with a sufficient amount of EtOH (30 mL) and stirring was continued for 30 min. The solid was collected by filtration, rinsed with H_2O (100 mL) and dried *in vacuo* to afford the desired product, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde oxime (**compound 5504**) (0.89 g, 70% yield) as a mixture of isomers.

[00513] To a stirred mixture of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde oxime (**compound 5504**) (865 mg, 4.40 mmol) in CH_2Cl_2 (20 mL), $SOCl_2$ (3.1 mL, 43.7 mmol) was added and the resulting mixture was stirred at room temperature for 16h. The reaction mixture was concentrated *in vacuo*. The residue was treated with ethyl acetate (20 mL), H_2O (20 mL) and then saturated $NaHCO_3$ aqueous solution (50 mL) to adjust pH to about 3-4. The mixture was stirred at room temperature for 15 min and the solid was collected by filtration. The filtrate was extracted with ethyl acetate (80 mL × 3), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the second batch of product. The combined solid was recrystallized from ethyl acetate and hexanes (1 : 1, 20 mL). The solid was collected by filtration and dried *in vacuo* to afford the desired product, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (**compound 5505**) (763 mg, 97% yield).

[00514] (S)-3-(1-Aminoethyl)-8-methyl-2-phenylisoquinolin-1(2H)-one (**compound 4704**) (208 mg, 0.75 mol), 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (**compound 5505**) (160 mg, 0.90 mmol) and Et_3N (228 mg, 2.25 mmol) were dissolved in n-BuOH (20 mL) in a sealed tube, and the resulting mixture stirred at 150 °C for 16h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (eluting with 50% Hex/EA) to afford the desired product, (S)-4-(1-(8-methyl-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (**5506, compound 264 in Table 4**) (90 mg, 28% yield) as a white solid.

Example 21: IC50 Values for Selected Compounds.

Table 3. *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. 197, 199, 241, 259, 261, 263, 280, 282, 283, 314, 315, 318, 321, 322, 326, 333, 334, 351, 360	Compound No. 1, 5, 22, 27, 38, 39, 40, 41, 46, 92, 117, 118, 120, 129, 132, 164, 165, 172, 188, 186, 193, 194, 195, 217, 242, 246, 281, 284, 305, 317, 325, 327, 347, 353, 356, 359	Compound No. 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, 143, 175, 179, 181, 182, 183, 187, 189, 192, 225, 226, 228, 235, 236, 239, 248, 250, 258, 269, 274, 275, 285, 286, 297,298, 299, 300, 307, 309, 313, 319, 332, 340, 355, 358, 362	Compound No. 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,

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PI3K γ	Compound No. 1, 4, 5, 18, 38, 43, 60, 69, 169, 172, 192, 193, 194, 199, 227, 228, 233, 259, 263, 280, 281, 282, 283, 314, 315, 317, 318, 321, 322, 325, 326, 327, 351	Compound No. 17, 34, 35, 37, 38, 40, 42, 57, 61, 65, 91, 92, 94, 105, 107, 164, 170, 175, 179, 181, 183, 184, 186, 187, 189, 195, 197, 219, 221, 224, 232, 239, 241, 242, 246, 248, 258, 261, 274, 284, 285, 294, 299, 303, 305, 307, 309, 312, 313, 319, 334, 337,	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, 188, 202, 206, 209, 212, 214, 216, 218, 220, 222, 229, 234, 236, 238, 250, 267, 268, 269, 271, 275, 279,	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. 182, 185, 190, 191, 196, 198, 200, 201, 203, 204, 205,

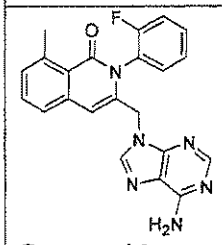
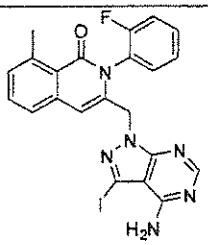
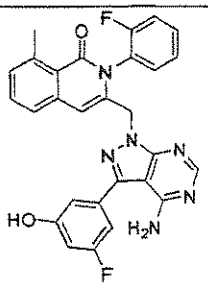
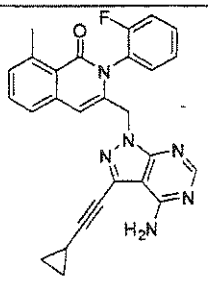
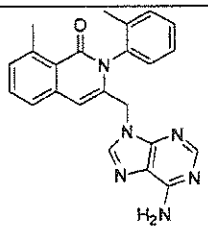
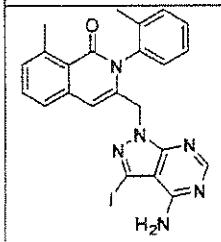
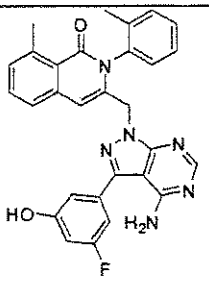
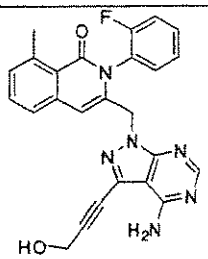
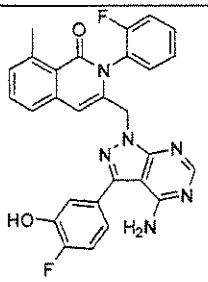
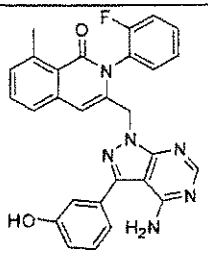
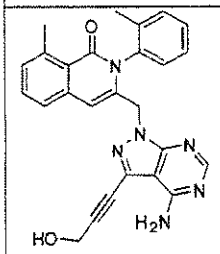
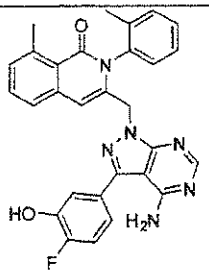
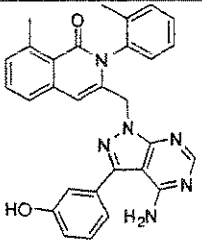
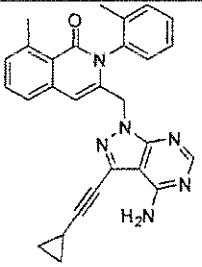
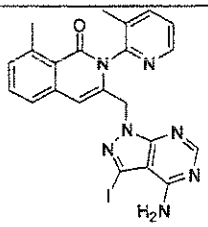
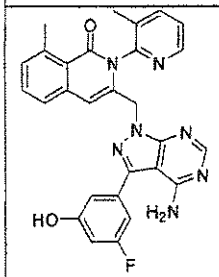
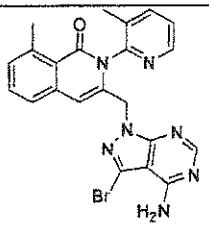
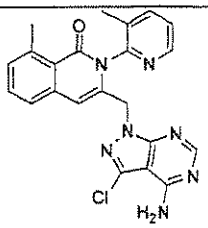
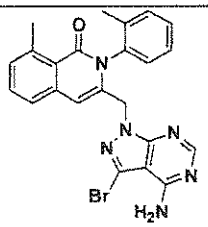
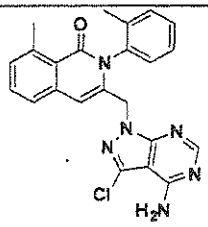
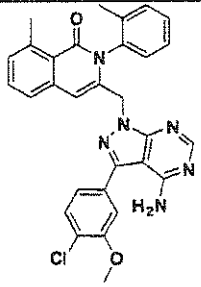
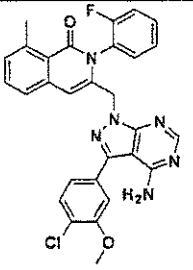
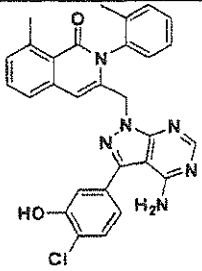
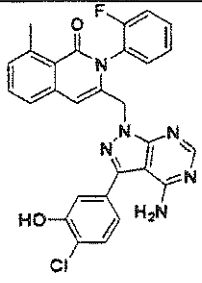
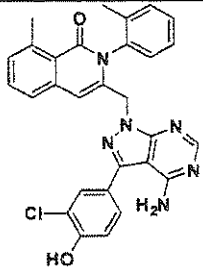
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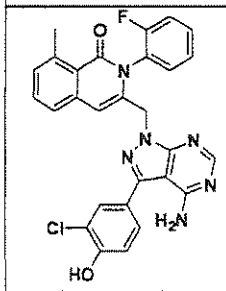
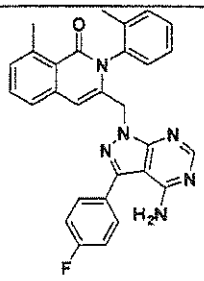
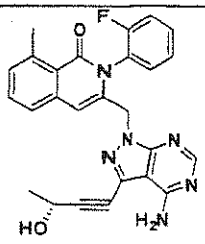
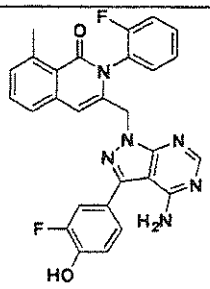
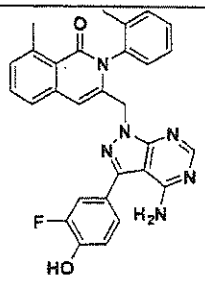
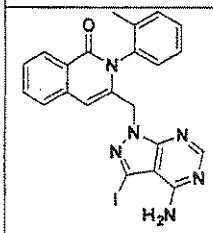
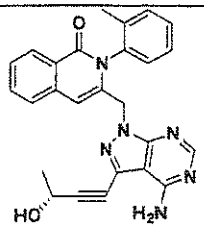
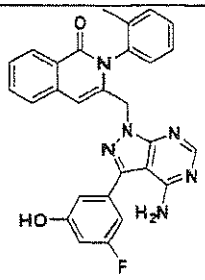
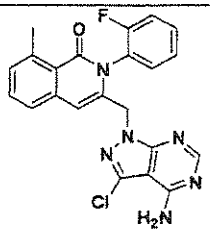
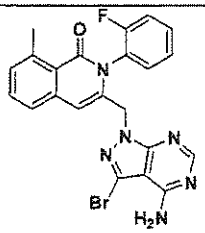
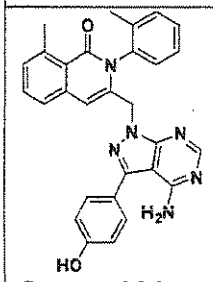
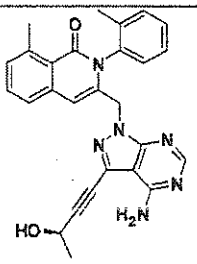
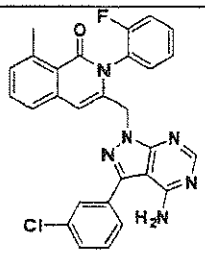
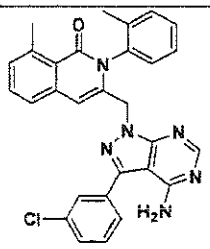
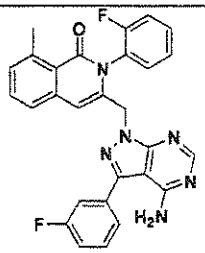
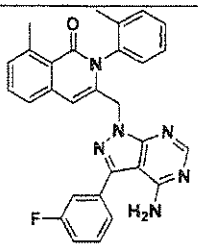
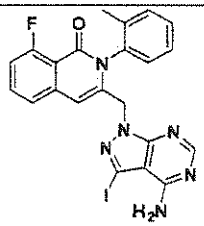
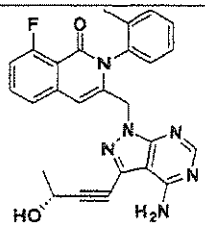
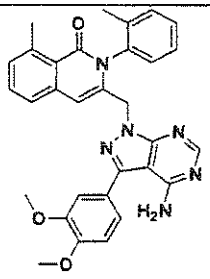
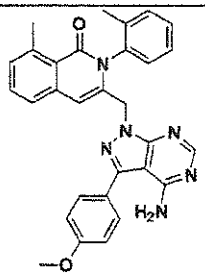
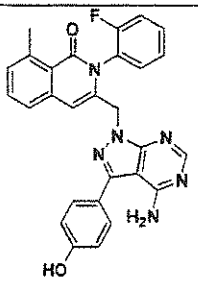
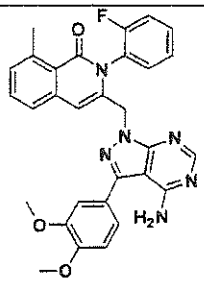
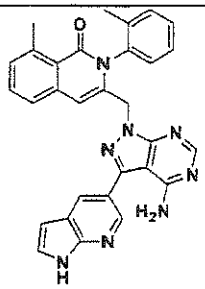
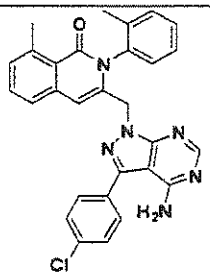
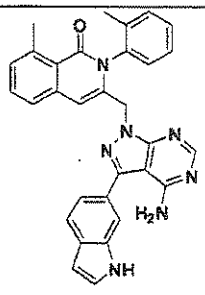
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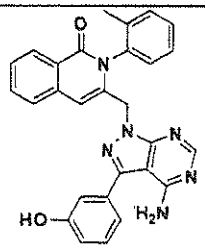
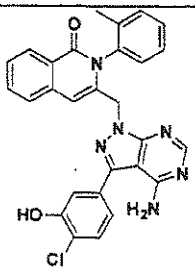
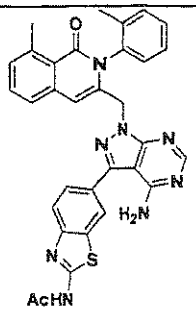
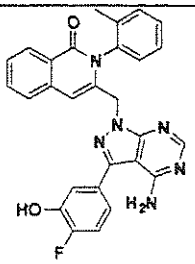
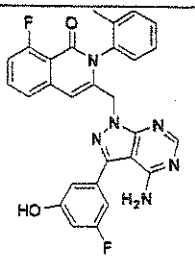
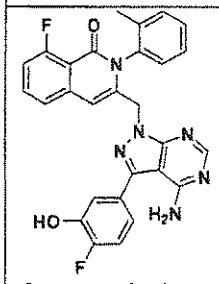
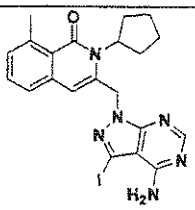
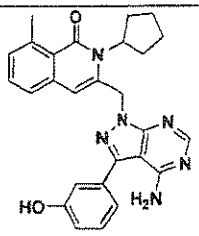
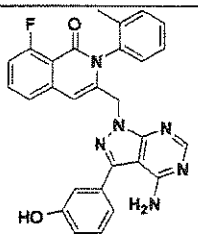
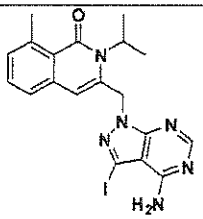
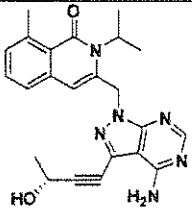
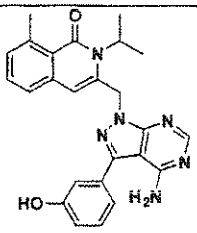
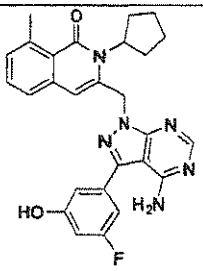
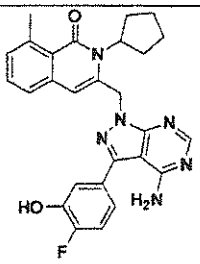
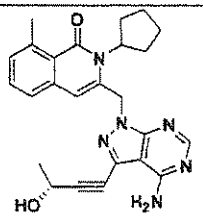
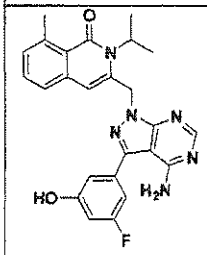
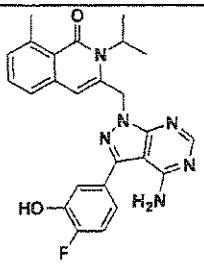
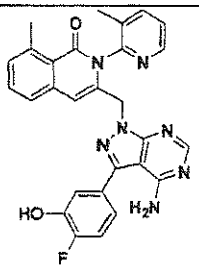
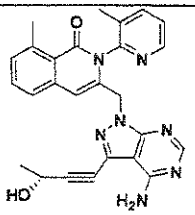
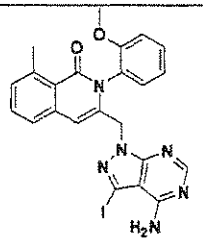
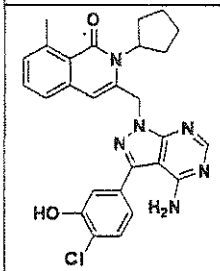
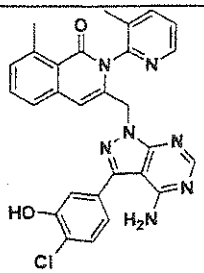
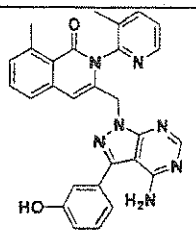
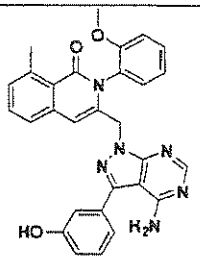
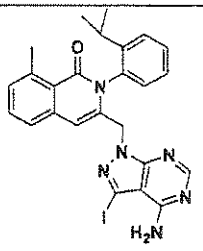
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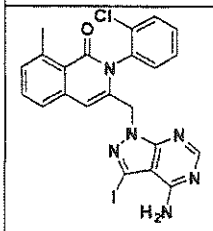
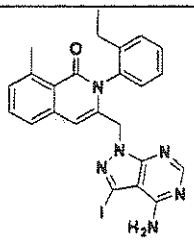
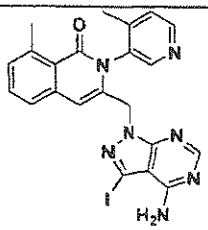
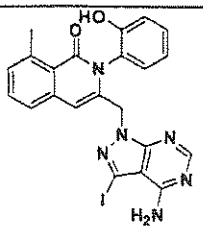
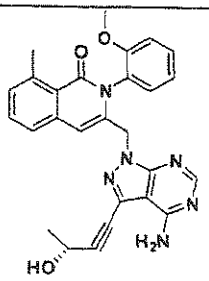
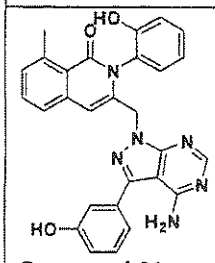
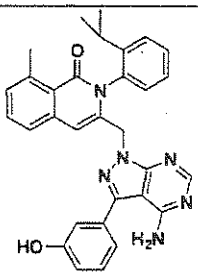
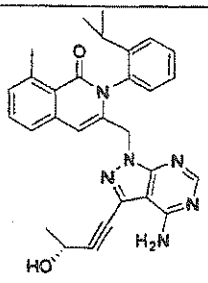
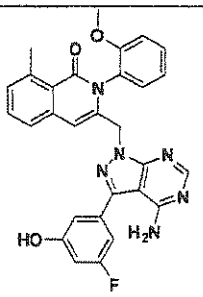
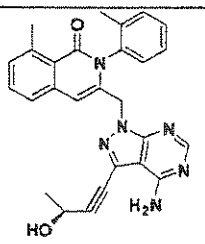
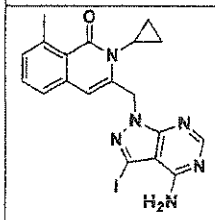
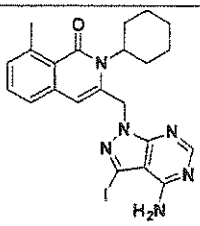
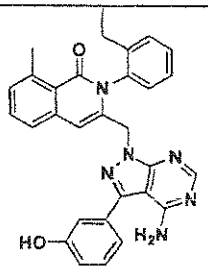
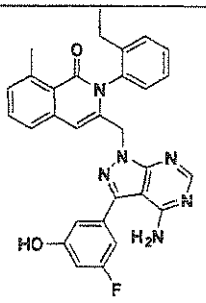
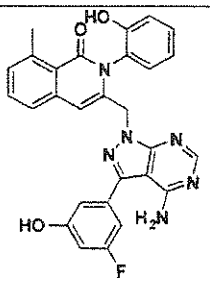
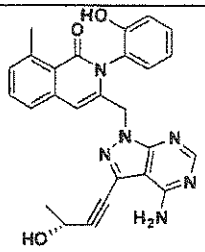
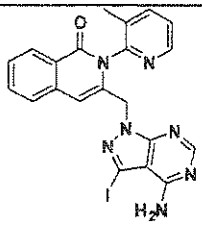
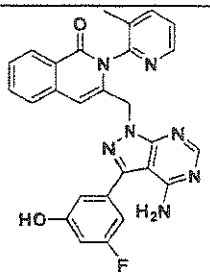
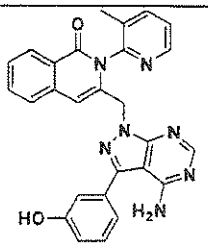
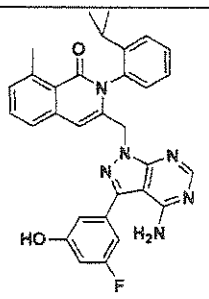
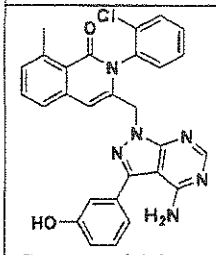
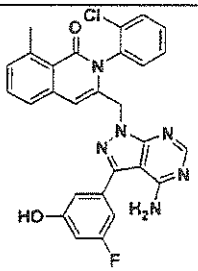
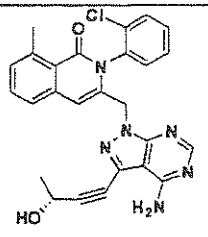
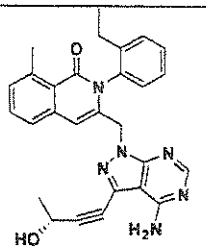
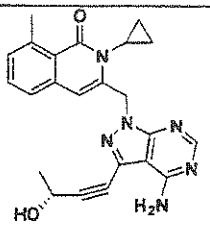
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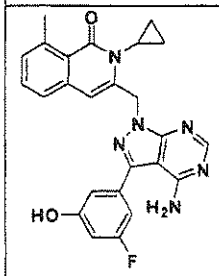
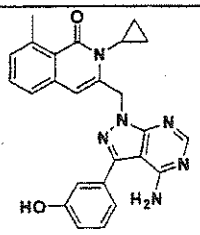
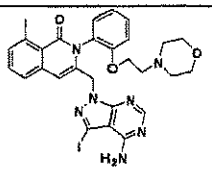
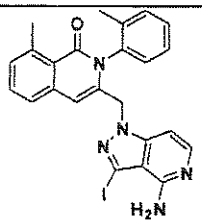
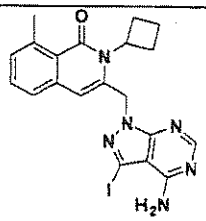
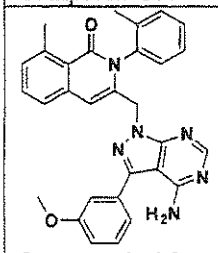
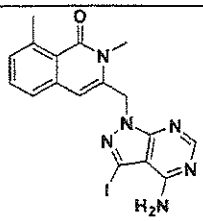
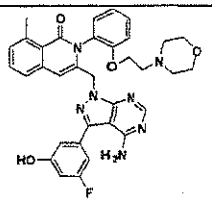
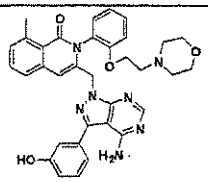
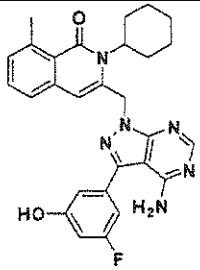
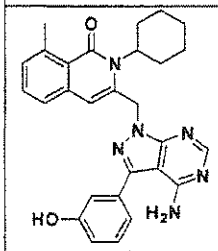
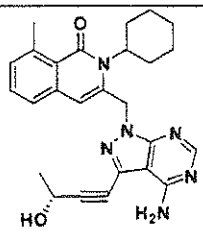
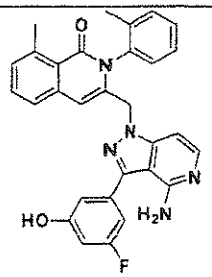
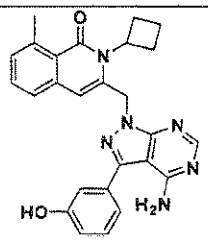
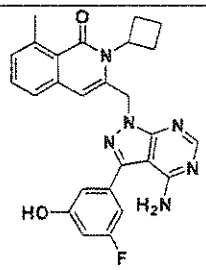
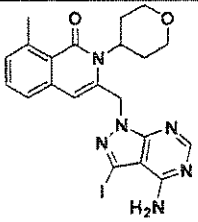
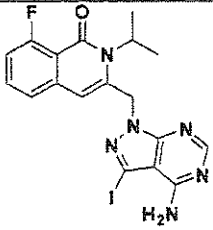
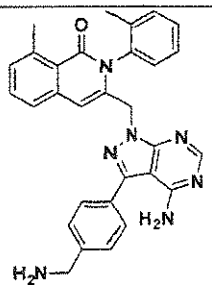
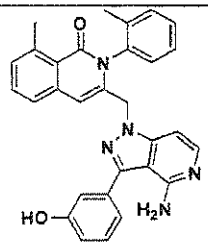
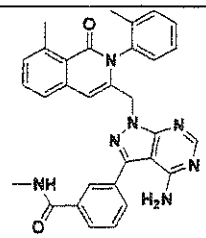
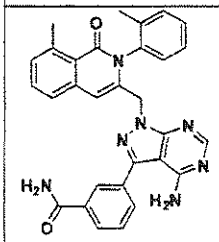
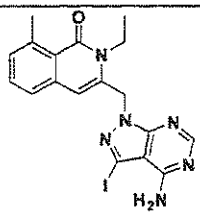
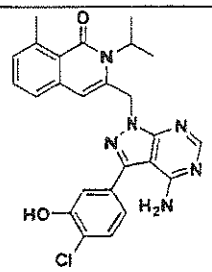
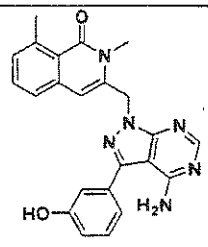
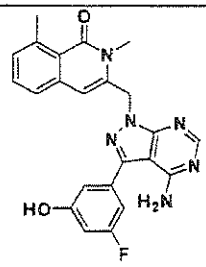
Table 4. Structures of the Compounds for the IC50 results described in Table 3.

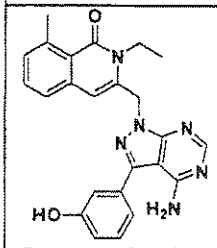
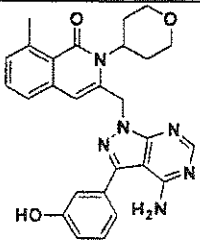
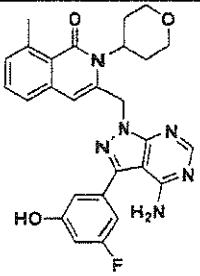
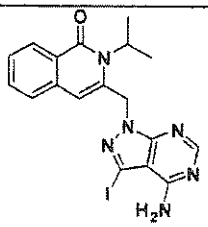
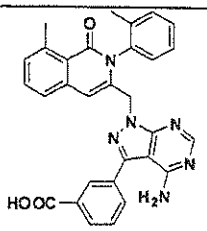
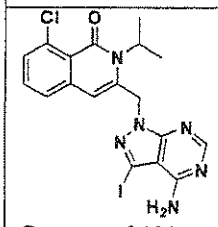
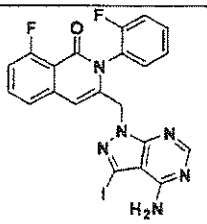
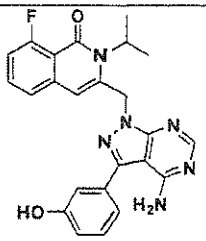
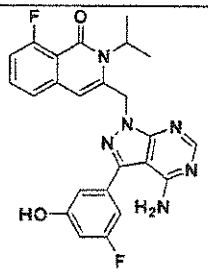
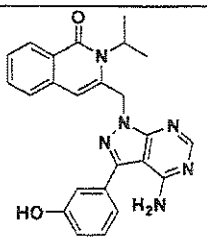
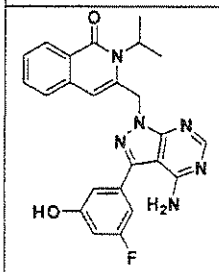
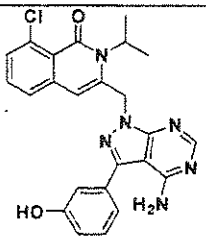
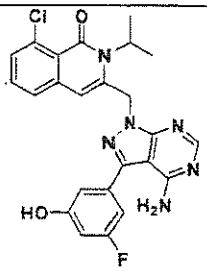
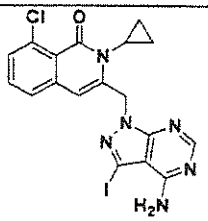
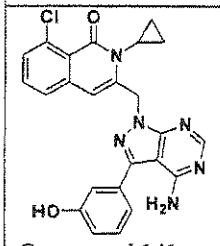
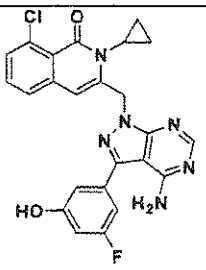
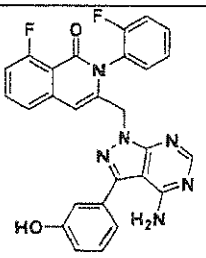
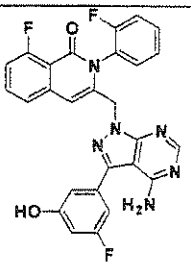
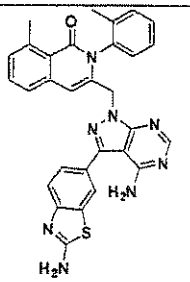
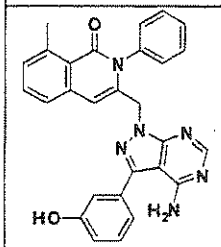
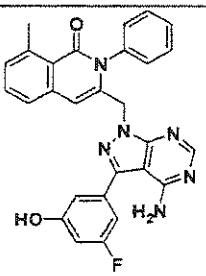
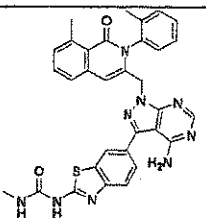
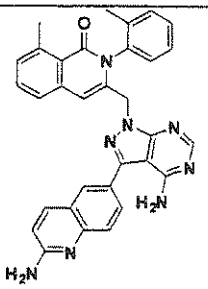
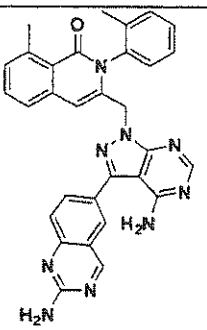
Structure				
 Compound 1	 Compound 2	 Compound 3	 Compound 4	 Compound 5
 Compound 6	 Compound 7	 Compound 8	 Compound 9	 Compound 10
 Compound 11	 Compound 12	 Compound 13	 Compound 14	 Compound 15
 Compound 16	 Compound 17	 Compound 18	 Compound 19	 Compound 20
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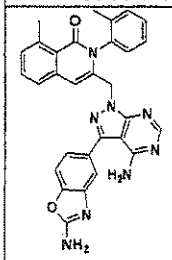
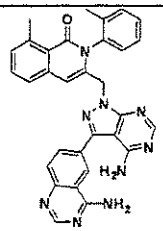
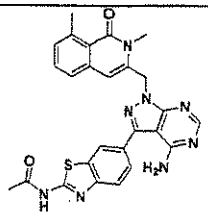
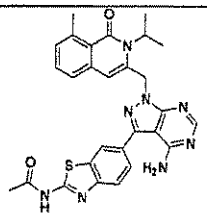
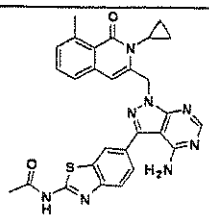
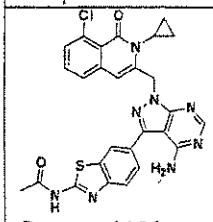
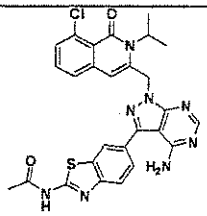
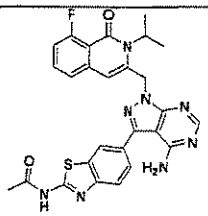
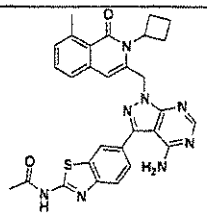
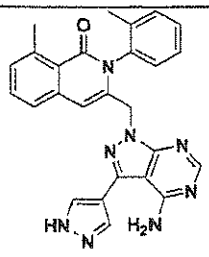
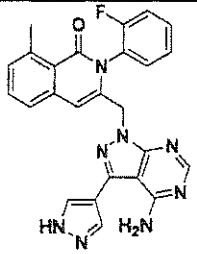
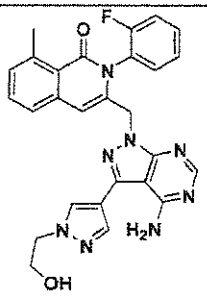
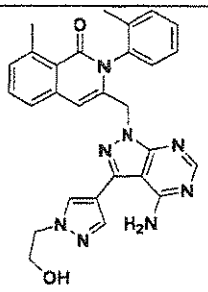
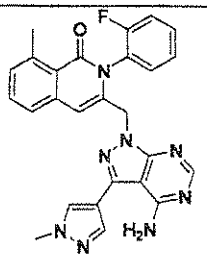
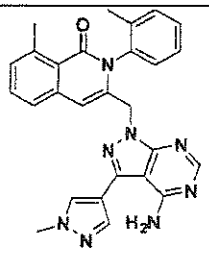
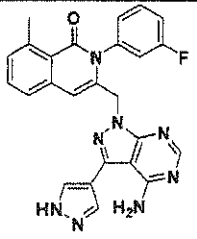
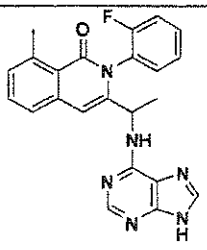
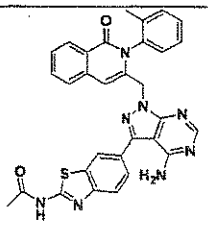
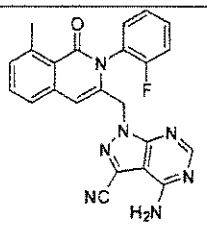
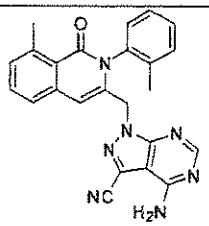
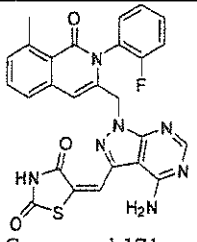
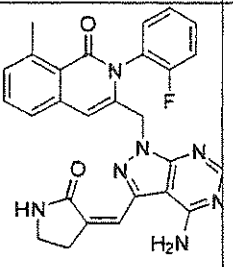
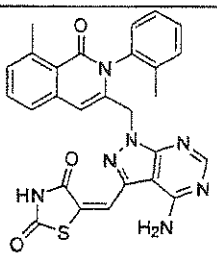
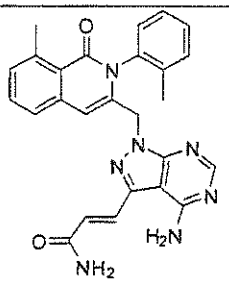
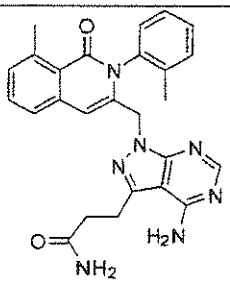
Structure				
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 Compound 31	 Compound 32	 Compound 33	 Compound 34	 Compound 35
 Compound 36	 Compound 37	 Compound 38	 Compound 39	 Compound 40
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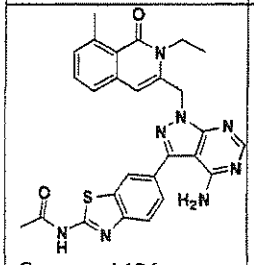
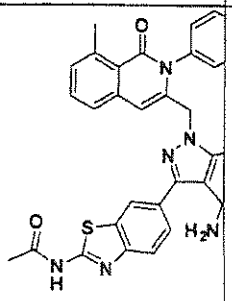
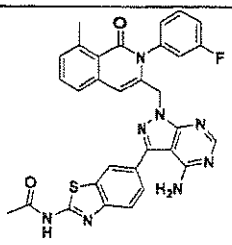
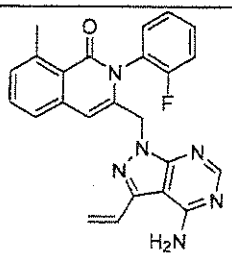
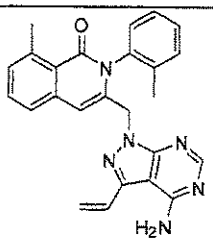
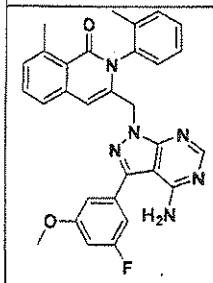
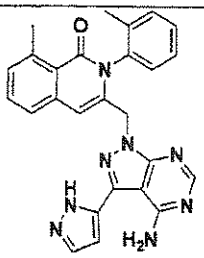
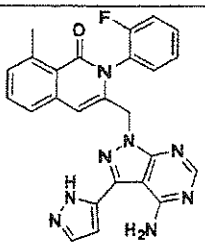
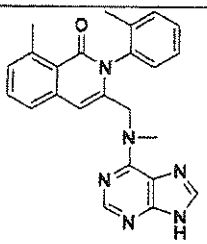
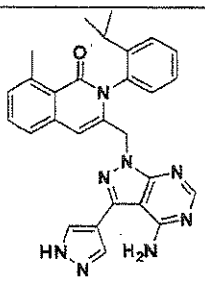
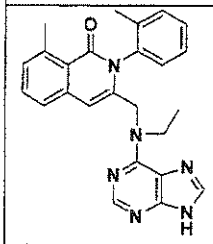
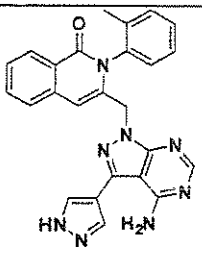
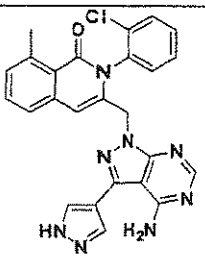
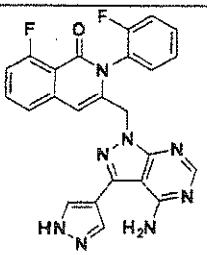
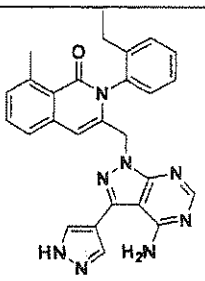
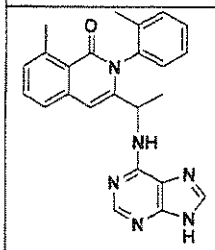
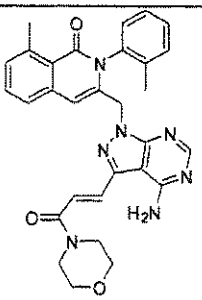
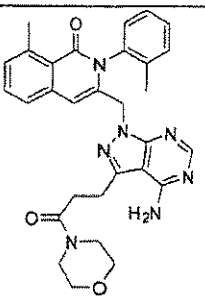
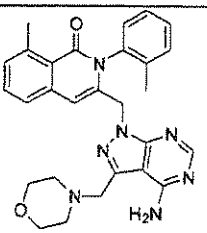
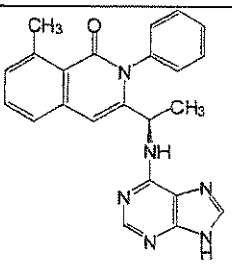
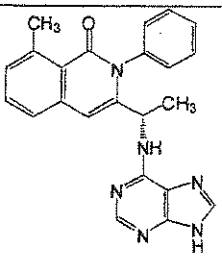
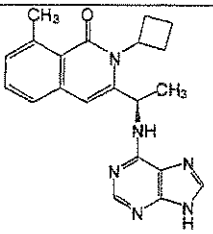
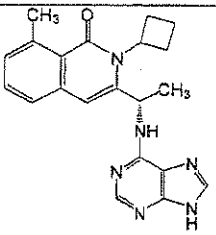
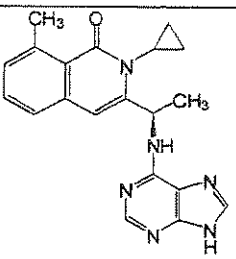
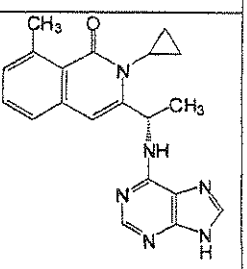
Structure				
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 Compound 56	 Compound 57	 Compound 58	 Compound 59	 Compound 60
 Compound 61	 Compound 62	 Compound 63	 Compound 64	 Compound 65
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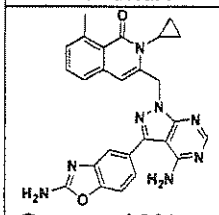
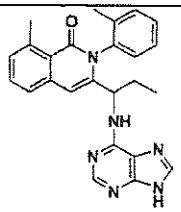
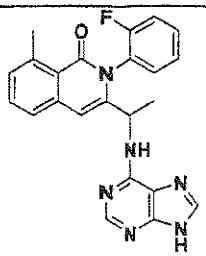
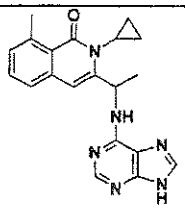
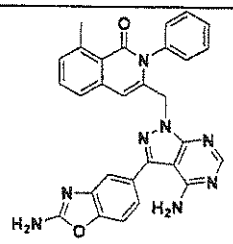
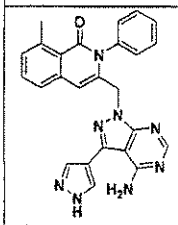
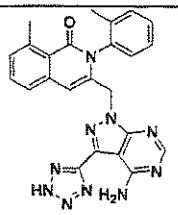
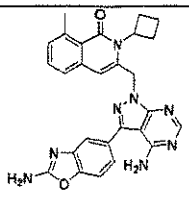
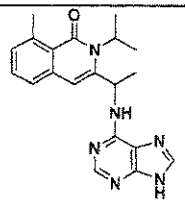
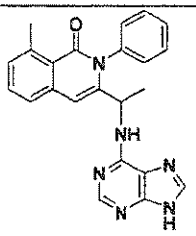
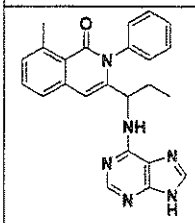
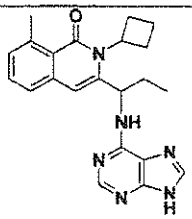
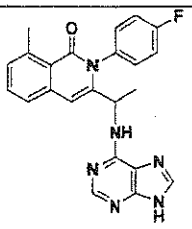
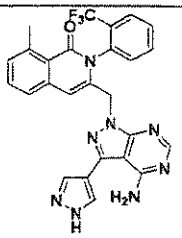
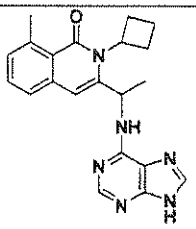
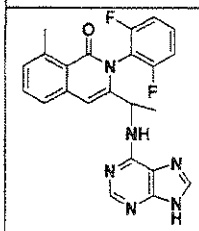
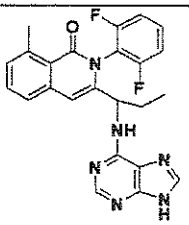
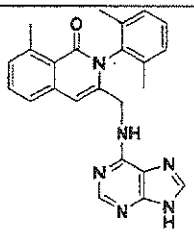
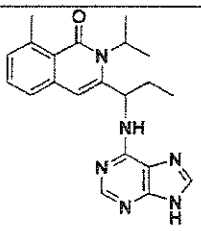
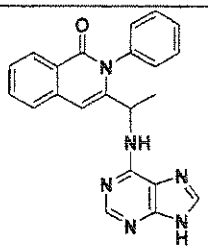
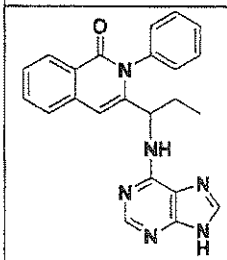
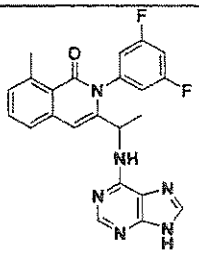
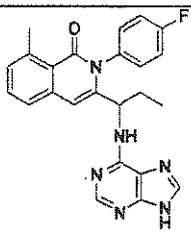
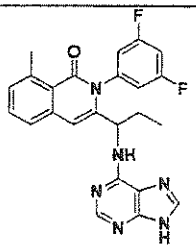
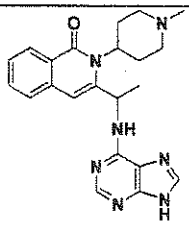
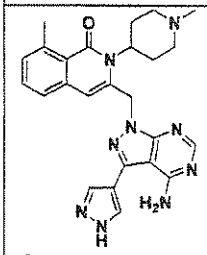
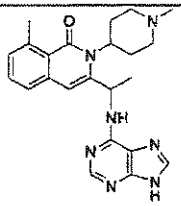
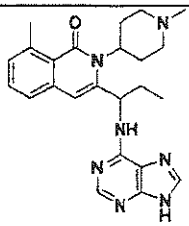
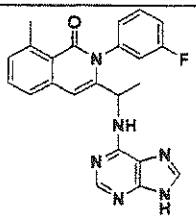
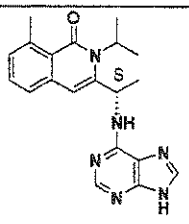
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 Compound 76	 Compound 77	 Compound 78	 Compound 79	 Compound 80
 Compound 81	 Compound 82	 Compound 83	 Compound 84	 Compound 85
 Compound 86	 Comopund 87	 Compound 88	 Compound 89	 Compound 90
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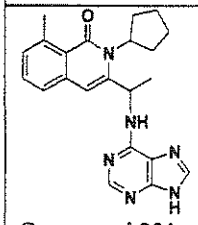
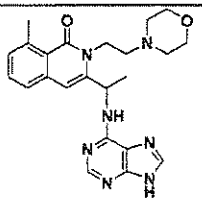
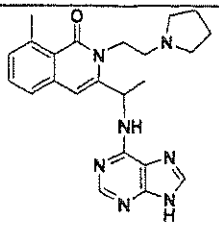
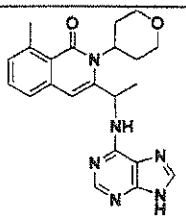
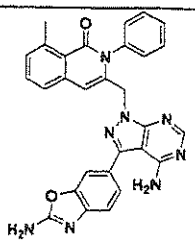
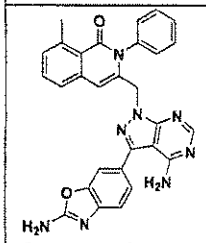
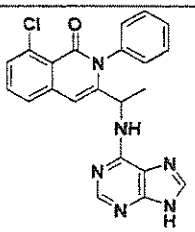
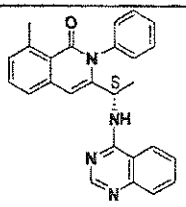
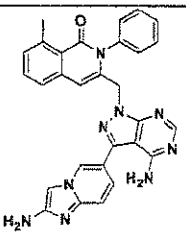
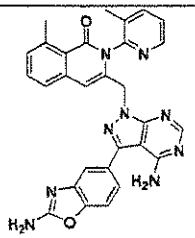
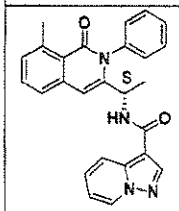
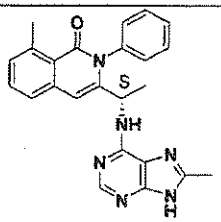
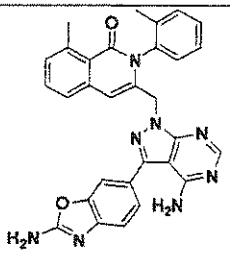
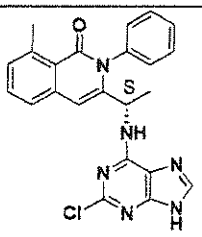
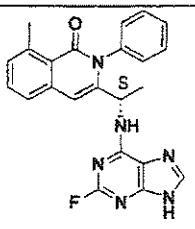
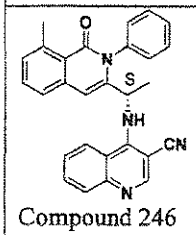
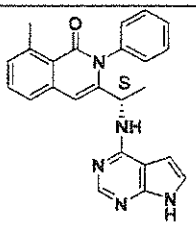
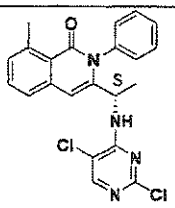
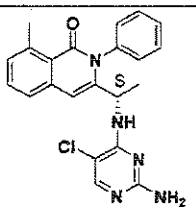
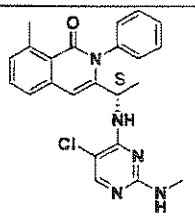
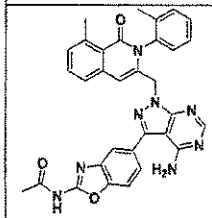
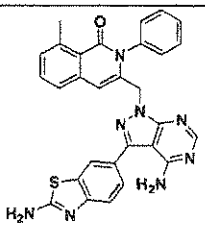
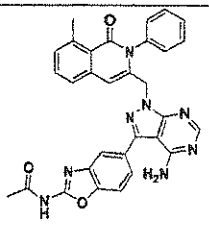
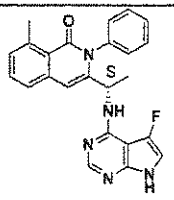
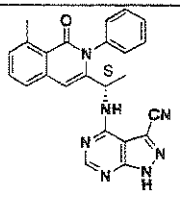
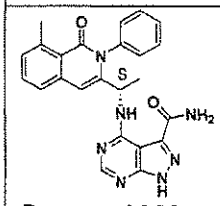
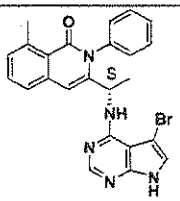
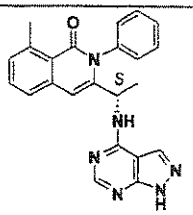
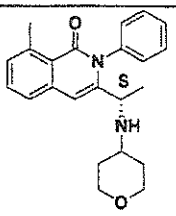
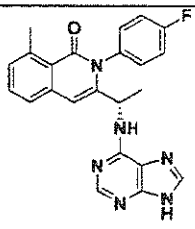
Structure				
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 Compound 106	 Compound 107	 Compound 108	 Compound 109	 Compound 110
 Compound 111	 Compound 112	 Compound 113	 Compound 114	 Compound 115
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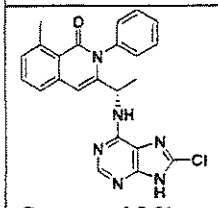
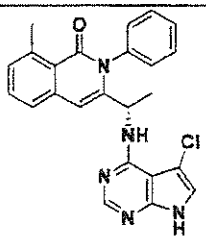
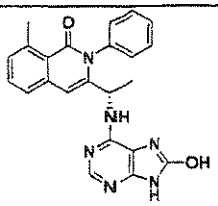
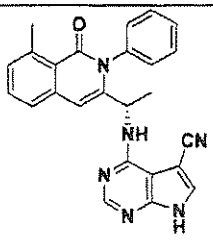
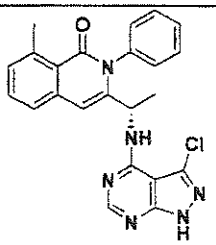
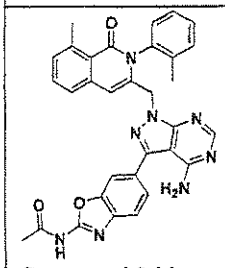
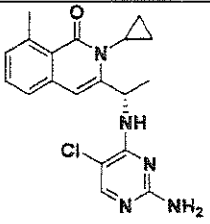
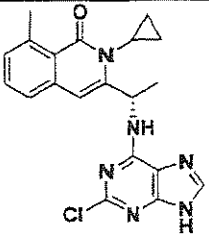
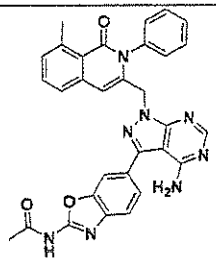
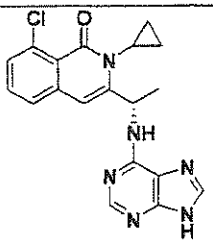
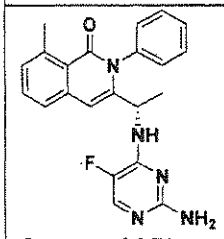
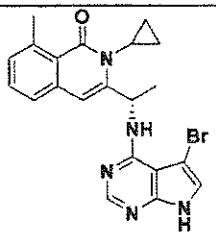
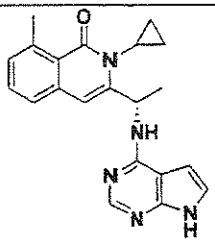
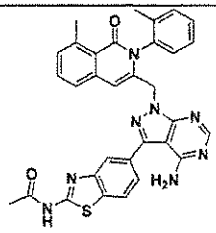
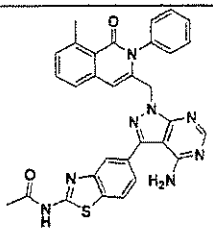
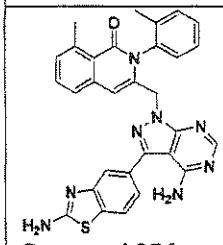
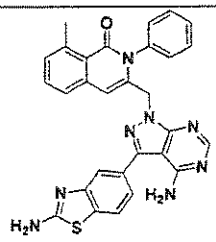
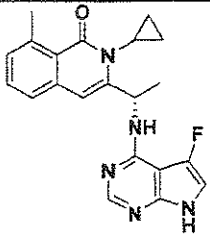
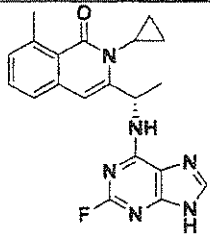
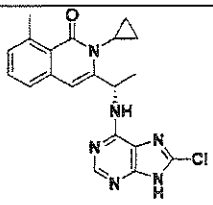
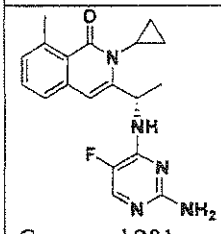
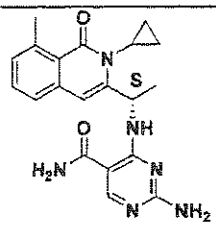
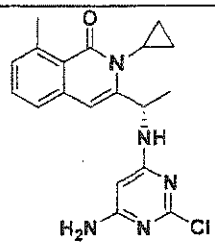
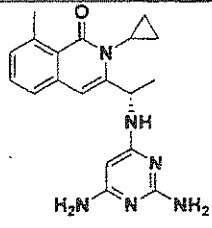
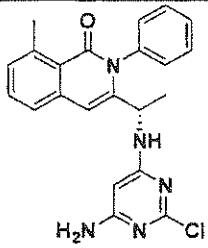
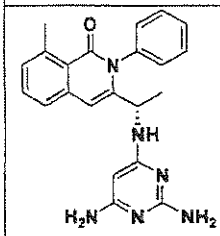
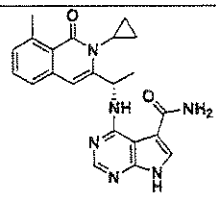
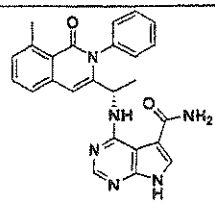
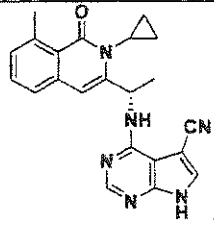
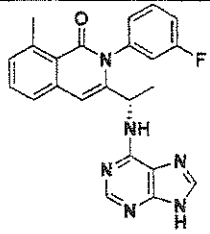
Structure				
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 Compound 131	 Compound 132	 Compound 133	 Compound 134	 Compound 135
 Compound 136	 Compound 137	 Compound 138	 Compound 139	
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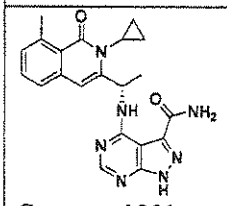
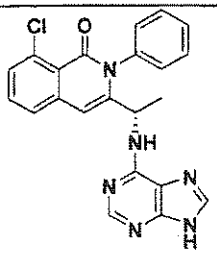
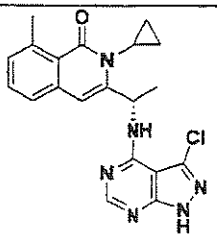
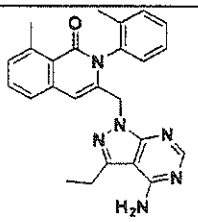
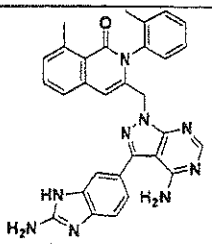
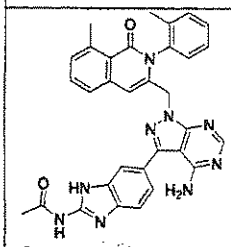
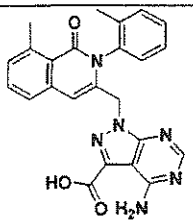
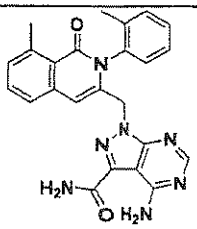
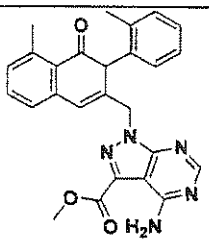
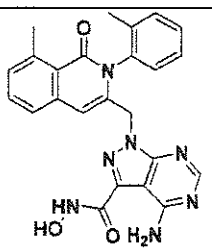
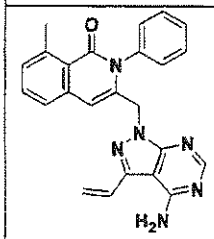
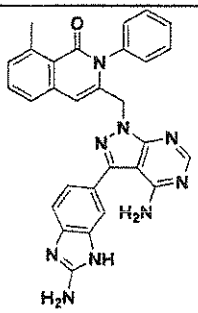
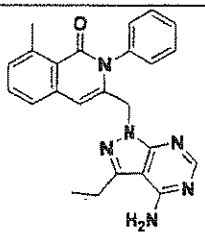
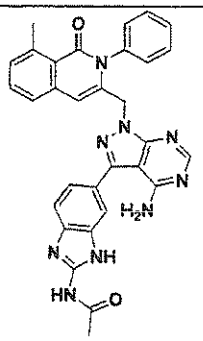
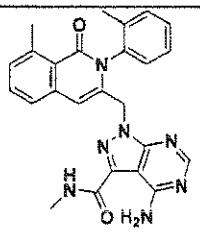
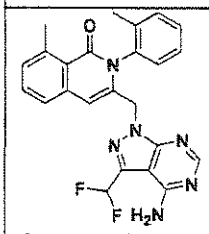
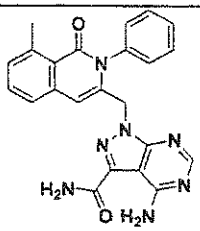
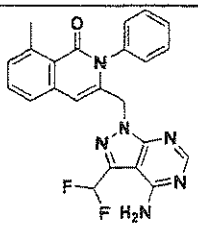
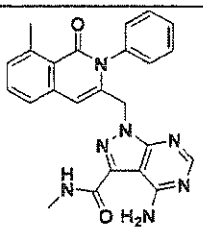
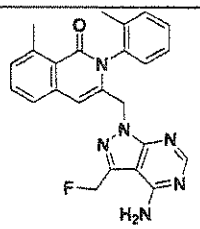
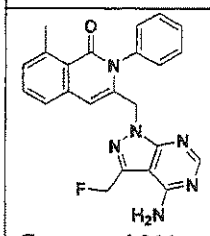
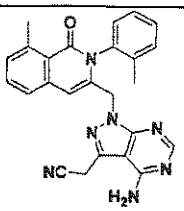
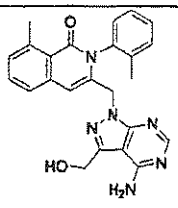
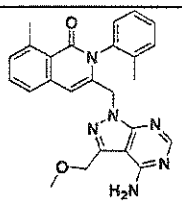
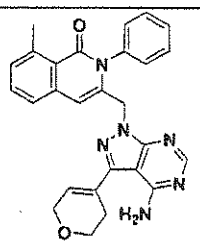
Structure				
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 Compound 156	 Compound 157	 Compound 158	 Compound 159	 Compound 160
 Compound 161	 Compound 162	 Compound 163	 Compound 164	 Compound 165
 Compound 166	 Compound 167	 Compound 168	 Compound 169	 Compound 170
 Compound 171	 Compound 172	 Compound 173	 Compound 174	 Compound 175

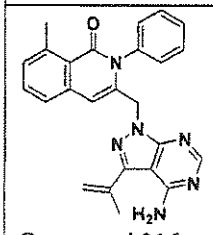
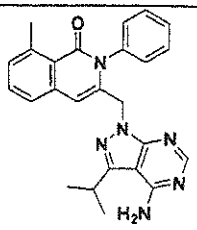
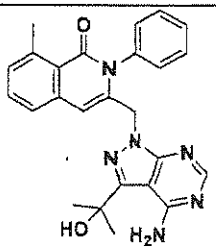
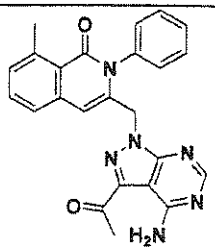
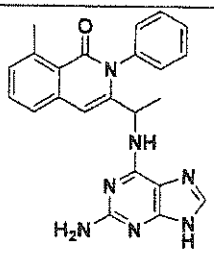
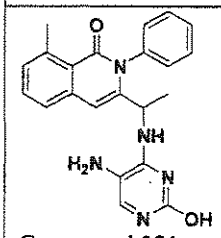
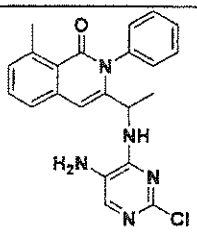
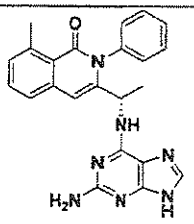
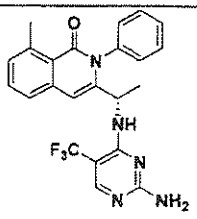
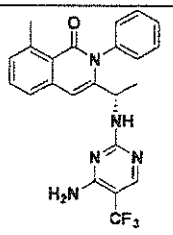
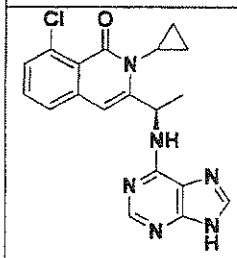
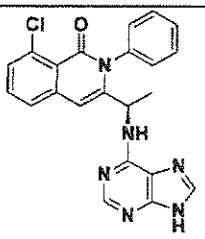
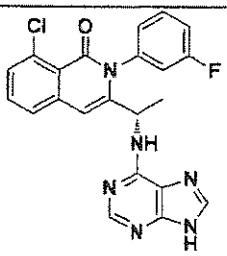
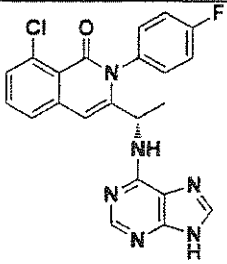
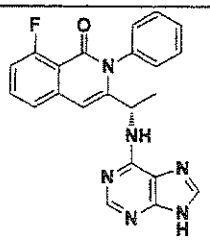
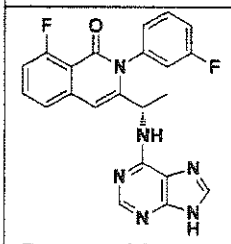
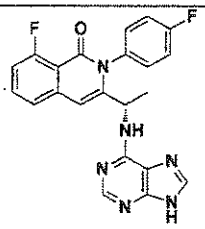
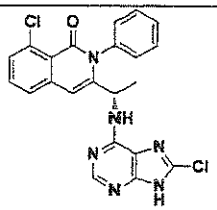
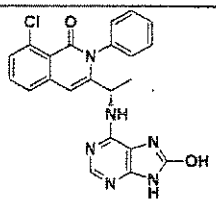
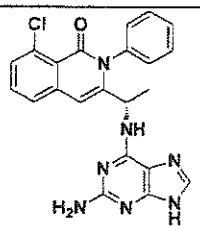
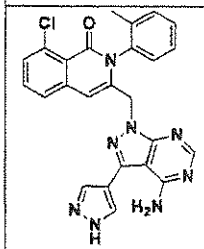
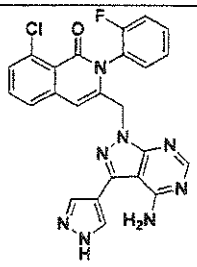
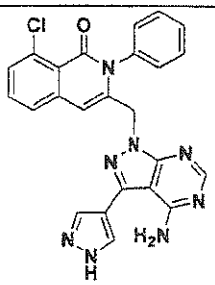
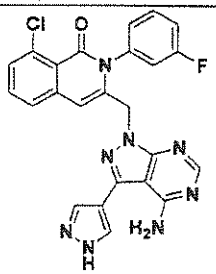
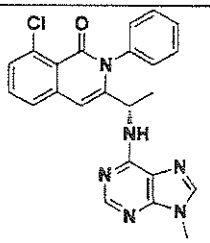
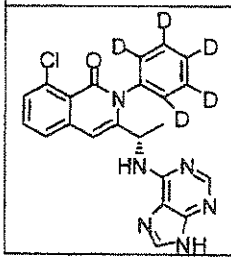
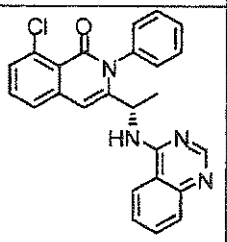
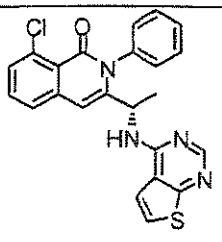
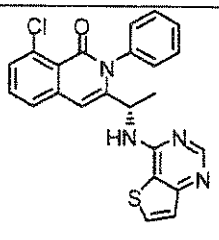
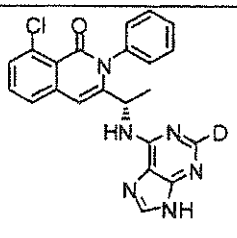
Structure				
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 Compound 181	 Compound 182	 Compound 183	 Compound 184	 Compound 185
 Compound 186	 Compound 187	 Compound 188	 Compound 189	 Compound 190
 Compound 191	 Compound 192	 Compound 193	 Compound 194	 Compound 195
 Compound 196	 Compound 197	 Compound 198	 Compound 199	 Compound 200

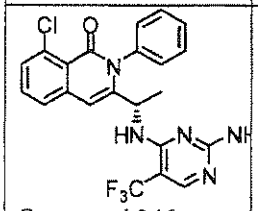
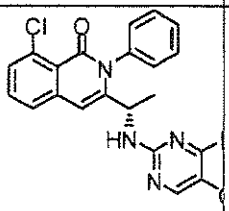
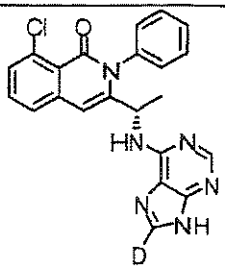
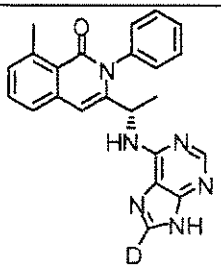
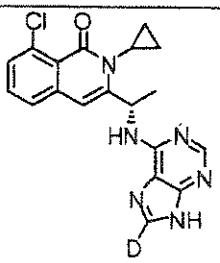
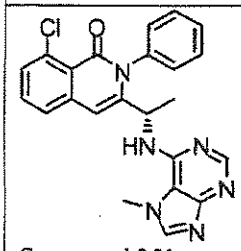
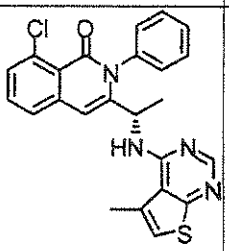
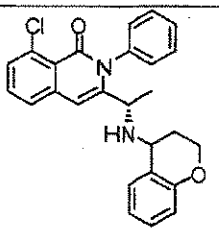
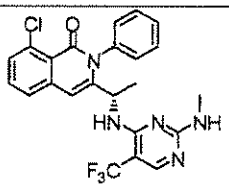
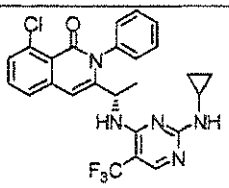
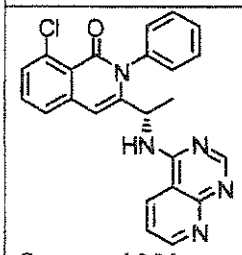
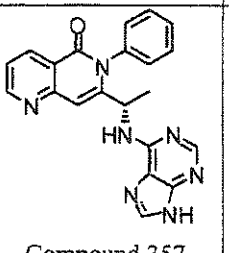
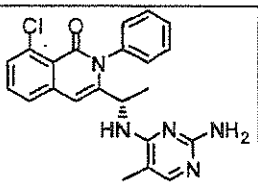
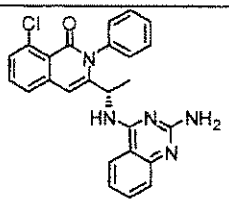
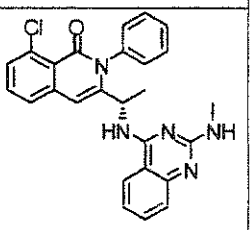
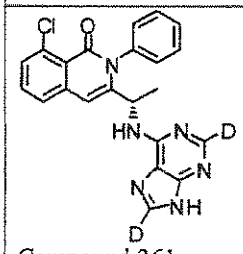
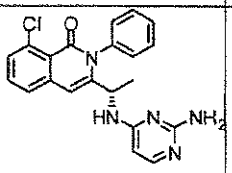
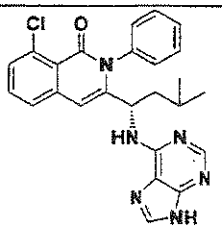
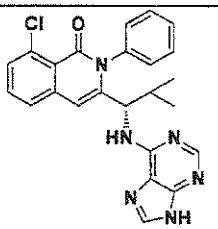
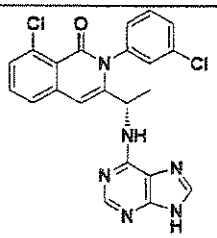
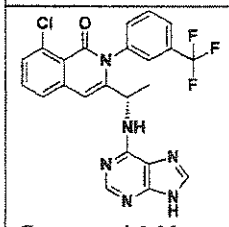
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 Compound 206	 Compound 207	 Compound 208	 Compound 209	 Compound 210
 Compound 211	 Compound 212	 Compound 213	 Compound 214	 Compound 215
 Compound 216	 Compound 217	 Compound 218	 Compound 219	 Compound 220
 Compound 221	 Compound 222	 Compound 223	 Compound 224	 Compound 225
 Compound 226	 Compound 227	 Compound 228	 Compound 229	 Compound 230

Structure				
 Compound 231	 Compound 232	 Compound 233	 Compound 234	 Compound 235
 Compound 236	 Compound 237	 Compound 238	 Compound 239	 Compound 240
 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

Structure				
 Compound 261	 Compound 262	 Compound 263	 Compound 264	 Compound 265
 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	

Structure				
				Compound 290
 Compound 291	 Compound 292	 Compound 293	 Compound 294	 Compound 295
 Compound 296	 Compound 297	 Compound 298	 Compound 299	 Compound 300
 Compound 301	 Compound 302	 Compound 303	 Compound 304	 Compound 305
 Compound 306	 Compound 307	 Compound 308	 Compound 309	 Compound 310
 Compound 311	 Compound 312	 Compound 313	 Compound 314	 Compound 315

Structure				
 Compound 316	 Compound 317	 Compound 318	 Compound 319	 Compound 320
 Compound 321	 Compound 322	 Compound 323	 Compound 324	 Compound 325
 Compound 326	 Compound 327	 Compound 328	 Compound 329	 Compound 330
 Compound 331	 Compound 332	 Compound 333	 Compound 334	 Compound 335
 Compound 336	 Compound 337	 Compound 338	 Compound 339	 Compound 340
				

Structure				
Compound 341	Compound 342	Compound 343	Compound 344	Compound 345
 Compound 346	 Compound 347	 Compound 348	 Compound 349	 Compound 350
 Compound 351	 Compound 352	 Compound 353	 Compound 354	 Compound 355
 Compound 356	 Compound 357	 Compound 358	 Compound 359	 Compound 360
 Compound 361	 Compound 362	 Compound 363	 Compound 364	 Compound 365
 Compound 366				

Example 22: Expression and Inhibition Assays of p110α/p85α, p110β/p85α, p110δ/p85α, and p110γ:

[00515] 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.

[00516] Other commercial kits or systems for assaying PI3-K activities are avaiable. 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. Anr 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 microtitre plate (e.g., a 384 well microtitre 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 23: Expression and Inhibition Assays of Abl

[00517] 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. For example, 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 24: Expression and Inhibition Assays of Hck

[00518] 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 25: Expression and Inhibition Assays of Inulsin Receptor (IR)

[00519] 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 26: Expression and Inhibition Assays of Src

[00520] 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 27: Expression and Inhibition Assays of DNA-PK (DNAK)

[00521] 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 28: Expression and Inhibition Assays of mTOR

[00522] 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.

[00523] Other kits or systems for assaying mTOR activity are commercially avaiable. 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 microtitre 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 29: Expression and Inhibition Assays of Vascular endothelial growth receptor

[00524] 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 30: Expression and Inhibition Assays of Ephrin receptor B4 (EphB4)

[00525] 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 31: Expression and Inhibition Assays of Epidermal growth factor receptor (EGFR)

[00526] 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 32: Expression and Inhibition Assays of KIT Assay

[00527] 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 33: Expression and Inhibition Assays of RET

[00528] 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 34: Expression and Inhibition Assays of Platelet derived growth factor receptor (PDGFR)

[00529] 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 35: Expression and Inhibition Assays of FMS-related tyrosine kinase 3 (FLT-3)

[00530] 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 36: Expression and Inhibition Assays of TEK receptor tyrosine kinase (TIE2)

[00531] 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 37: B Cell Activation and Proliferation Assay

[00532] 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 38: Tumor Cell Line Proliferation Assay

[00533] 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 39: Antitumor Activity in Vivo

[00534] The compounds described herein can be evaluated in a panel of human and murine tumor models.

[00535] Paclitaxel-refractory Tumor Models

[00536] *1. Clinically-derived Ovarian Carcinoma Model.*

[00537] This tumor model is established from a tumor biopsy of an ovarian cancer patient. Tumor biopsy is taken from the patient.

[00538] The compounds described herein are administered to nude mice bearing staged tumors using an every 2 days x 5 schedule.

[00539] *2. A2780Tax Human Ovarian Carcinoma Xenograft (Mutated Tubulin).*

[00540] 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.

[00541] The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[00542] *3. HCT116/VM46 Human Colon Carcinoma Xenograft (Multi-Drug Resistant).*

[00543] 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.

[00544] The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[00545] *5. M5076 Murine Sarcoma Model*

[00546] M5076 is a mouse fibrosarcoma that is inherently refractory to paclitaxel in vivo.

[00547] The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[00548] 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 40: Microsome stability assay

[00549] 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 41: Plasma stability assay

[00550] 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.

[00551] 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.

[00552] 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 42: Chemical Stability

[00553] 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 43: Akt Kinase Assay

[00554] 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.

[00555] 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).

[00556] 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 44: Kinase Signaling in Blood

[00557] 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.

[00558] 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 phosphrylation 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 45: Colony Formation Assay

[00559] 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.

[00560] 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) suplemented 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 46: *In Vivo* Effect of Kinase Inhibitors on Leukemic Cells

[00561] 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.

[00562] Peripheral blood cells are collected approximately on day 10 (pre-treatment) and upon euthanization (post treatment), contacted with labled 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 47: Treatment of Lupus Disease Model Mice

[00563] 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).

[00564] 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).

[00565] 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.

[00566] 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 48: Murine Bone Marrow Transplant Assay

[00567] 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.

[00568] 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.

[00569] 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 49: TNP-Ficoll T-cell Independent B-cell Activation Assay

[00570] 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		

[00571] Four animals in group 1, and eight animals in groups 2 to 7 were euthanized in CO_2 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.

[00572] 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% H_2O_2 + 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.

[00573] 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

[00574] 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.

[00575] 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.

[00576] 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)

[00577] 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

[00578] 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.

[00579] 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.

[00580] 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.

[00581] 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.

[00582] 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. When tested in the same model, at least five other compounds of the present invention exhibit comparable or even higher efficacy.

Example 51: Rat Established Type II Collagen Induced Arthritis Assay

[00583] 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 10 day established type II collagen induced arthritis in rats, compounds were administered orally daily or twice daily for 6 days.

[00584] 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.

[00585] 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 f ankles taken every day. Final body weights were taken on day 7 and animals were euthanized.

[00586] The results as shown in **Figure 8** shows a significant reduction in mean ankle diamter increase over time for compound #53 with a once daily dosage under the conditions tested. The results in **Figure 9** futher demonstrate a significant reduction in mean ankle diamter increase over time for compound #53 with a twice daily dosage under the conditions tested. This suggests that the compounds of the present invention can be useful for the treatment of autoimmune diseases such as arthritis. When tested in the same model, at least five other compounds of the present invention exhibit comparable or even higher efficacy as compared to compound #53.

Example 52: Adjuvant Induced Arthritis Assay

Intrathecal Catheterization of Rats

[00587] 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.

Adjuvant Arthritis and Drug Treatment

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.

[00588] 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.

[00589] 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

[00590] 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 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		

[00591] 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 CO_2 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.

[00592] The results are expected to demonstrate the pharmacokinetic parameters such as absorption, distribution, metabolism, excretion, and toxicity for the compounds of the present invention.

[00593] Example 54: Basotest assay

[00594] 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.

[00595] Example 55: Combination use of PI3Kδ inhibitors and agents that inhibit IgE production or activity

[00596] 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.

[00597] 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

[00598] 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

[00599] 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*

[00600] 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.

[00601] 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.

[00602] It is expected that the combination treatment using PI3Kδ inhibitor and rapamycin provides greater efficacy than treatment with PI3Kδ inhibitor alone.

Example 54:Lung inflammation assay

[00603] Compounds of the invention were tested using one or both of the LPS-induced lung inflammation assay and the ovalbumin-induced lung inflammation assay.

[00604] To perform the LPS-induced lung inflammation assay, compounds were dosed orally. A group was dosed with vehicle only and dexamethasone (5 mg/kg) was used in another group as positive control. Pulmonary inflammation was determined 6 h after intranasal instillation of LPS (10 μg). The following parameters were evaluated: total number of leukocytes and number of neutrophils in bronchoalveolar lavage (BAL).

[00605] In the ovalbumin-induced lung inflammation assay, compounds were dosed orally. A group was dosed with vehicle only and dexamethasone (5 mg/kg) was used in another group as positive control. Pulmonary inflammation was determined 4 days after 4 consecutive daily intranasal instillation of ovalbumin. Compounds were given by gavage 30 min before each challenge (4 challenges) at the indicated doses. The following parameters were evaluated: Total number of leukocytes and number of eosinophils in bronchoalveolar lavage (BAL).

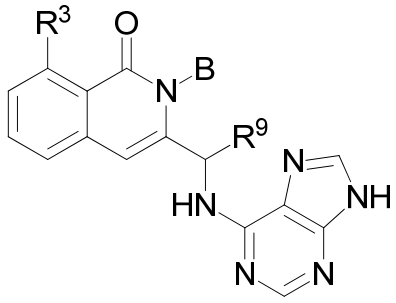
[00606] Exemplary results are shown in FIG. 15 (LPS-induced assay) and FIG. 16 (OVA-induced assay).

[00607] 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:

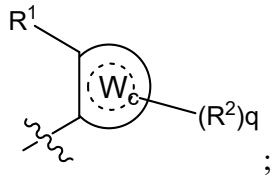
1. A compound of Formula V-A:



Formula V-A

or a pharmaceutically acceptable salt thereof, wherein

B is a moiety of Formula II:



;

Formula II

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

q is an integer of 0 or 1;

R^1 is hydrogen, alkyl, or halo;

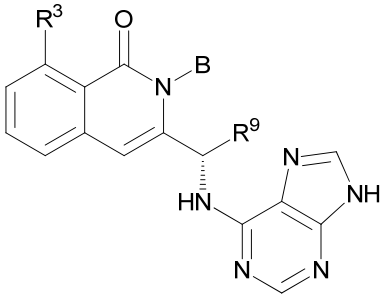
R^2 is alkyl or halo;

R^3 is halo;

R^9 is hydrogen, alkyl, or heterocycloalkyl;

wherein alkyl is optionally substituted with one or more halo.

2. The compound of claim 1 of the Formula V-A2:



Formula V-A2

or a pharmaceutically acceptable salt thereof.

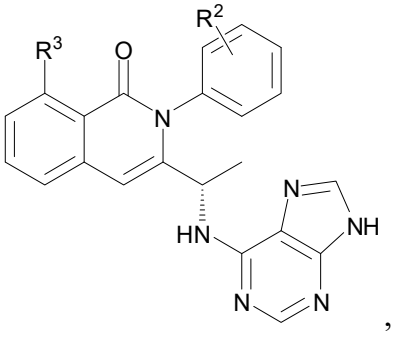
3. The compound of claim 1 or 2, wherein R^3 is -F.

4. The compound of claim 1 or 2, wherein R^3 is -Cl.

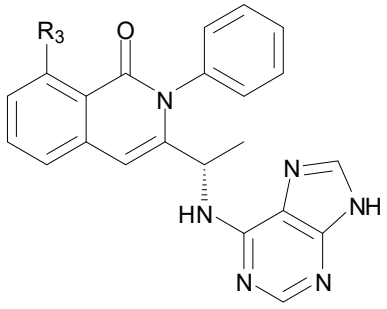
5. The compound of any one of claims 1-4, wherein R^9 is $-CH_3$ or $-CH_2CH_3$.

6. The compound of any one of claims 1-5, wherein W_c is phenyl or cyclopropyl, which is optionally substituted with at least one of $-CH_3$, $-CH_2CH_3$, $-CF_3$, -Cl, or -F.

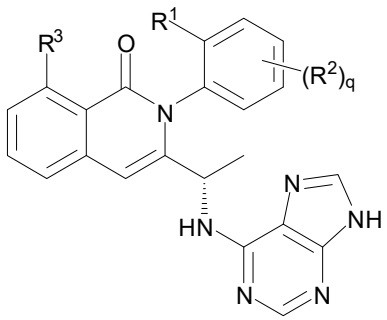
7. The compound of any one of claims 1-6, wherein the compound is a compound of formula:



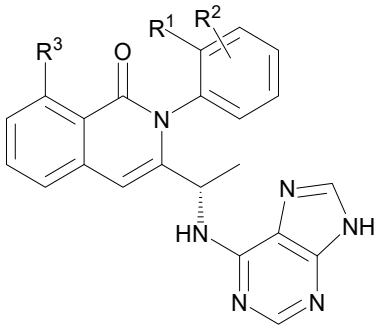
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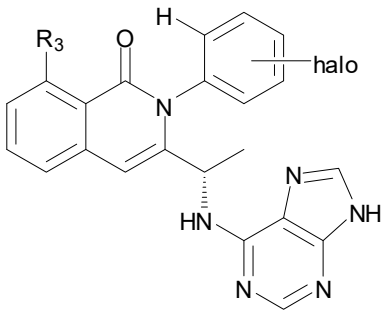
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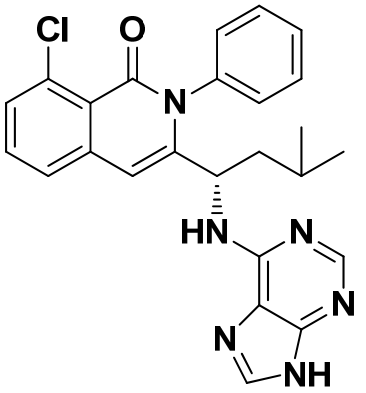
, or



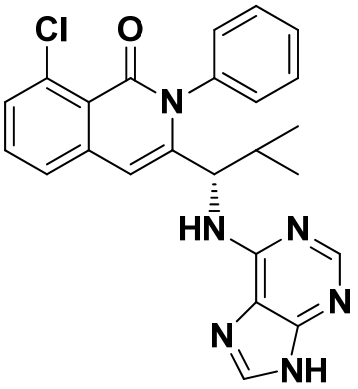
,

or a pharmaceutically acceptable salt thereof.

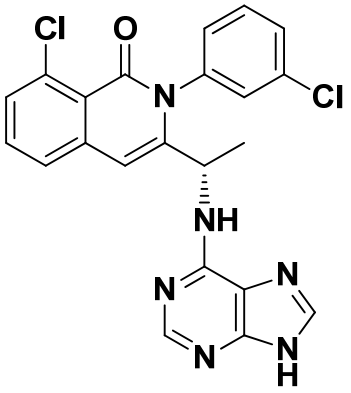
8. The compound of claim 1, wherein the compound is selected from:



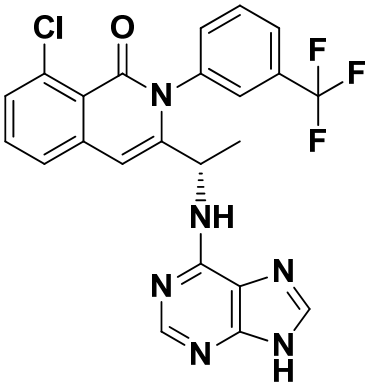
Compound 363,



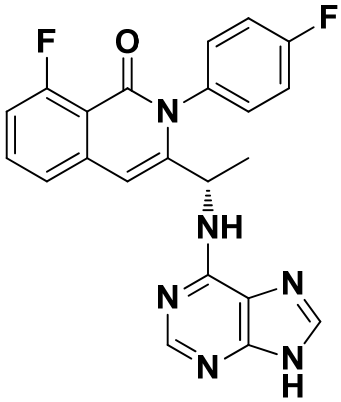
Compound 364,



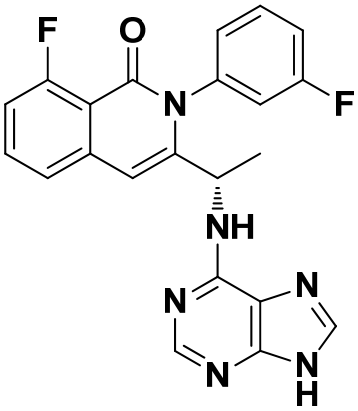
Compound 365



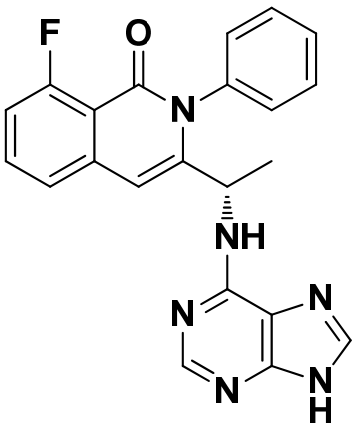
Compound 366,



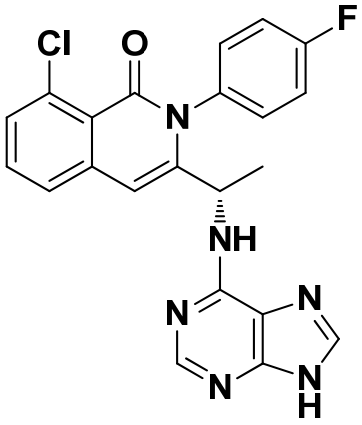
Compound 332,



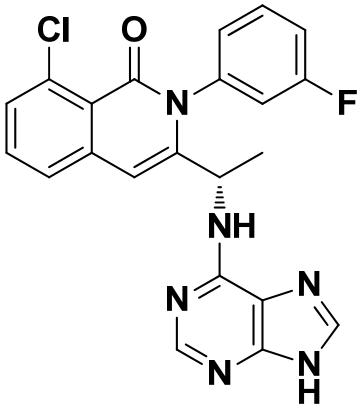
Compound 331



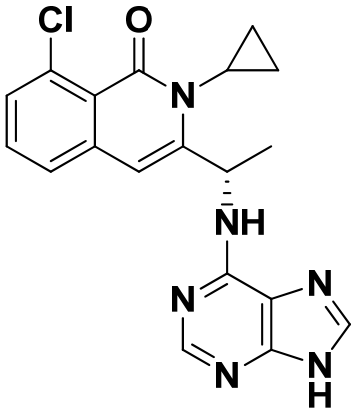
Compound 330,

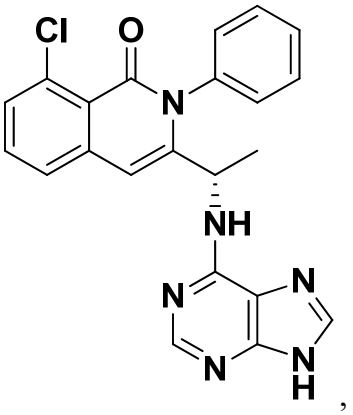


Compound 329,



Compound 328,



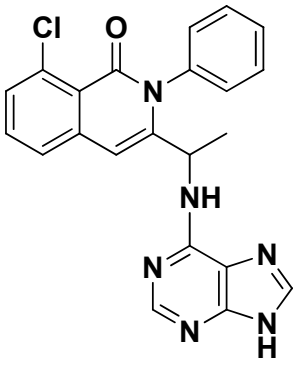


,

Compound 270, and Compound 292,

or a pharmaceutically acceptable salt thereof.

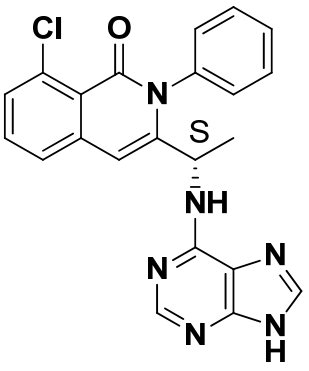
9. The compound of claim 1, wherein the compound is:



(Compound 237),

or a pharmaceutically acceptable salt thereof.

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



(Compound 292),

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 or 9, wherein the compound is the S-enantiomer having an enantiomeric purity greater than 55%, greater than 80%, greater than 90%, or greater than 95%.

12. A pharmaceutical composition comprising the compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

13. A pharmaceutical composition comprising the compound of claim 10, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

14. Use of a compound of any one of claims 1-11 or a pharmaceutical composition of claim 12 or 13 in the manufacture of a medicament for the treatment of a disorder in a subject, wherein said disorder is one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, or cardiac disease.

15. Use of a compound of any one of claims 1-11 or a pharmaceutical composition of claim 12 or 13 in the manufacture of a medicament for the treatment of one or more of asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder (COPD), psoriasis, multiple sclerosis, disorders related to diabetic complications, lupus erythematosus, scleroderma, graft versus host disease, restenosis, or atherosclerosis in a subject.

16. Use of a compound of any one of claims 1-11 or a pharmaceutical composition of claim 12 or 13 in the manufacture of a medicament for the treatment of cancer in a subject.

17. The use of claim 16, wherein the cancer is a leukemia or a lymphoma.

18. The use of claim 16, wherein the cancer is selected from 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 cancer, Kaposi's Sarcoma, mastocytosis, and viral-induced cancer.

19. The use of claim 16, wherein the cancer is selected from acute myelogenous leukemia (AML), acute lymphocytic leukemia, T-cell acute lymphocytic leukemia, chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplasia, myeloproliferative disorders, chronic myelogenous leukemia (CML), multiple myeloma (MM), myelodysplastic syndrome (MDS), human lymphotropic virus-type 1 (HTLV-1) leukemia, and B-cell acute lymphoblastic leukemia.

20. The use of claim 16, wherein the cancer is selected from diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, small non-cleaved cell lymphoma, human lymphotropic virus-type 1 (HTLV-1) leukemia/lymphoma, adult T-cell lymphoma, mantle cell lymphoma (MCL), Hodgkin disease, non-Hodgkin lymphomas, AIDS-related lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, multiple myeloma, and follicular lymphoma.

21. The use of claim 14, wherein the inflammatory or immune disease is one or more of:

(i) 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, and vulvitis;

(ii) perennial allergic rhinitis, mesenteritis, acrodermatitis, angiodermatitis, atopic dermatitis, contact dermatitis, eczema, erythema multiforme, intertrigo, Stevens Johnson syndrome, toxic epidermal necrolysis, skin allergy, severe allergic reaction/anaphylaxis, allergic granulomatosis, allergic conjunctivitis, chorioretinitis, infectious keratoconjunctivitis, keratoconjunctivitis, ophthalmia neonatorum, trachoma, ocular inflammation, blepharoconjunctivitis, pericoronitis, rhinopharyngitis, sialadenitis, musculoskeletal system inflammation, adult onset Stills disease, Behcets disease, chondrocalcinosis, dactylitis, Felty syndrome, gout, infectious arthritis, Lyme disease, inflammatory osteoarthritis, periarthritis, Ross River virus infection, acute respiratory distress syndrome, acute bronchitis, acute sinusitis, allergic rhinitis, asthma, severe refractory asthma, pleurisy, seasonal allergic rhinitis, status asthmaticus, tracheobronchitis, serositis, neuromyelitis optica, poliovirus infection, Alport syndrome, balanitis, epididymo orchitis, focal segmental, glomerulosclerosis, glomerulonephritis, IgA nephropathy (Berger's Disease), orchitis, parametritis, pelvic inflammatory disease, pyelitis, pyelocystitis, hyperuricemia, aortitis, chylopericarditis, Dressler syndrome, endarteritis, extracranial temporal arteritis, HIV associated arteritis, intracranial temporal arteritis, Kawasaki disease, lymphangiophlebitis, Mondor disease, and periarteritis; and

(iii) jejunitis, mucositis, non alcoholic steatohepatitis, non viral hepatitis, autoimmune pancreatitis, perihepatitis, pouchitis, pseudomembranous colitis, rectosigmoiditis, salpingoperitonitis, sigmoiditis, steatohepatitis, Churg Strauss syndrome, ulcerative proctitis, irritable bowel syndrome, gastrointestinal inflammation, acute enterocolitis, anusitis, Balser necrosis, diverticulitis, enterohepatitis, eosinophilic esophagitis, esophagitis, hemorrhagic enteritis, hepatitis virus infection, hepatocholangitis, hypertrophic gastritis, ileocecitis, ankylosing spondylitis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic

arthritis, cutaneous lupus, systemic lupus, lupus nephritis, AIDS, agammaglobulinemia, AIDS related complex, Brutons disease, Chediak Higashi syndrome, common variable immunodeficiency, DiGeorge syndrome, dysgammaglobulinemia, immunoglobulindeficiency, Job syndrome, Nezelof syndrome, phagocyte bactericidal disorder, Wiskott Aldrich syndrome, asplenia, elephantiasis, hypersplenism, lymphadenopathy, lymphedema, lymphocele, Nonne Milroy Meige syndrome, spleen disease, splenomegaly, thymoma, thymus disease, perivasculitis, pleuropericarditis, polyarteritis nodosa, thromboangiitis, thromboangiitis obliterans, thromboendocarditis, thrombophlebitis, and chronic obstructive pulmonary disease (COPD).

22. The use of claim 14, wherein the inflammatory or immune disease is asthma.

23. The use of claim 14, wherein the inflammatory or immune disease is rheumatoid arthritis.

24. The use of claim 23, wherein the compound is used in an amount effective to ameliorate one or more symptoms associated with rheumatoid arthritis selected from one or more of a reduction in the swelling of the joints, a reduction in serum anti-collagen levels, a reduction in bone resorption, a reduction in cartilage damage, a reduction in pannus, and a reduction in inflammation.

25. The use of any one of claims 14-24, further comprises use of one or more second therapeutic agents.

26. The use of claim 25, wherein the second therapeutic agent is a chemotherapeutic agent, optionally
wherein the chemotherapeutic agent is selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, anti-androgens, alkyl sulfonates, aziridines, ethylenimines, methylamelamines, nitrogen mustards, nitrosureas, folic acid analogues, purine analogues, folic acid replenishers, taxanes, anti-estrogens, LHRH agonists, photodynamic therapies, triazenes, platinum containing

compounds, vinca alkaloids, taxoids, epipodophyllins, DHFR inhibitors, IMP dehydrogenase inhibitors, ribonucleotide reductase inhibitors, uracil analogues, cytocine analogues, Vitamin D analogues, isoprenylation inhibitors, dopaminergic neurotoxins, MDR inhibitors, Ca2+ ATPase inhibitors, tyrosine kinase inhibitors, proteasome inhibitors, and mTOR inhibitors; optionally wherein the chemotherapeutic agent is selected from the group consisting of imatinib, bortezomib, bicalutamide, adriamycin, thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide, trimethylolomelamine, chlorambucil, chlornaphazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, chlorozotocin, fotemustine, nimustine, ranimustine; aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, 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, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfomithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidamine, mitoguazone, mopidamol, nitracrine, pentostatin, phenamet; pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofiran, spirogermanium; tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside (“Ara-C”), paclitaxel, docetaxel, retinoic acid, esperamicins, capecitabine, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, toremifene, flutamide, nilutamide, leuprolide, goserelin, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin,

carboplatin, vinblastine, platinum, mitomycin C, mitoxantrone, vincristine, vinorelbine, navelbine, novantrone, teniposide, daunomycin, aminopterin, xeloda, ibandronate, camptothecin-11 (CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), tamoxifen, raloxifene, megestrol, vertoporfin(BPD-MA), phthalocyanine, photosensitizer Pc4, demethoxy-hypocrellin A (2BA-2-DMHA), carmustine (BCNU), lomustine (CCNU), treosulfan, temozolomide, oxaliplatin, DHA-paclitaxel, Taxoprexin, PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX, ANG1005, paclitaxel-EC-1, glucose-conjugated paclitaxel, etoposide, etoposide phosphate, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomycin C, methotrexate, dichloromethotrexate, edatrexate, tiazofurin, ribavirin, EICAR, deferoxamine, ratitrexed, tegafur-uracil, cytosine arabinoside, fludarabine, EB 1089, CB 1093, KH 1060, lovastatin, 1-methyl-4-phenylpyridinium ion, staurosporine, actinomycin D, bleomycin A2, bleomycin B2, peplomycin, pegylated liposomal doxorubicin, pirarubicin, zorubicin, verapamil, thapsigargin, thalidomide, lenalidomide, axitinib (AG013736), bosutinib (SKI-606), cediranib (AZD2171), dasatinib (BMS-354825), erlotinib, gefitinib, lapatinib, lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib, semaxanib (semaxinib, SU5416), sunitinib (SU11248), toceranib, vandetanib (ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab, bevacizumab, rituximab, cetuximab, panitumumab, ranibizumab, sorafenib, everolimus, alemtuzumab, gemtuzumab, ozogamicin, temsirolimus, ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992, SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120, AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, XL228, rapamycin, temsirolimus (CCI-779), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Norvartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe), OSI-027 (OSI), oblimersen, leucovorin, pemetrexed, cyclophosphamide, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, methopterin, porfiromycin, melphalan, leurosidine, leurosine, trabectedin, discodermolide, and hexamethylmelamine, or a pharmaceutically acceptable salt thereof.

27. The use of claim 25, wherein the second therapeutic agent is selected from

(i) an agent that inhibits IgE production or activity,

(ii) an anti-inflammatory drug,

(iii) anticoagulants,

(iv) a biotherapeutic agent,

(v) an anti-angiogenesis agents,

(vi) a diuretic agent,

(vii) a hormone or therapeutic peptide or protein, and

(viii) radiation therapy; optionally

wherein

(i) the agent that inhibits IgE production or activity is selected from TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs, TORC1 inhibitors, TORC2 inhibitors, anti-IgE antibodies, omalizumab, and TNX-901;

(ii) the anti-inflammatory drug is selected from acetylsalicylic acid, ibuprofen, naproxen, indomethacin, nabumetone, tolmetin, a corticosteroid, prednisone, chloroquine, and hydroxychloroquine;

(iii) the anticoagulant is selected from aspirin™, heparin, and coumadin;

(iv) the biotherapeutic agent is selected from tumor necrosis factor, interferon α, interferon γ, IL-1, IL-2, IL-4, IL-6, IL-12, GM-CSF, Herceptin™ (trastuzumab), T-DM1, bevacizumab, cetuximab, panitumumab, rituximab, and tositumomab;

(v) the anti-angiogenic agent is selected from 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;

(vi) the diuretic agent is selected from amiloride, anticholinergics, ipratropium, atropine and oxitropium;

(vii) the hormone or therapeutic peptide or protein is selected from cortisone, hydrocortisone, prednisolone, xanthines, aminophylline, choline theophyllinate, lysine theophyllinate, theophylline, insulin and glucagon; or
(viii) the radiation therapy is selected from external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy.

28. The use of claim 25, wherein the second therapeutic agent is a therapeutic antibody.

29. The use of claim 28, wherein the therapeutic antibody is anti-CD20 antibody.

30. The use of claim 28, wherein the therapeutic antibody is selected from cetuximab, panitumumab, trastuzumab, rituximab, tositumomab, alemtuzumab, bevacizumab, and gemtuzumab.

31. Use of a compound of claim 9 or claim 10, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of claim 9 or claim 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder in a subject, wherein the disorder is selected from one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, and cardiac disease.

32. Use of a compound of claim 9 or 10, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of claim 9 or 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject.

33. The use of claim 32, wherein the cancer is a leukemia or a lymphoma.

34. The use of claim 32, wherein the cancer is selected from 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 cancer, Kaposi's Sarcoma, mastocytosis, and viral-induced cancer.

35. The use of claim 32, wherein the cancer is selected from acute myelogenous leukemia (AML), acute lymphocytic leukemia, T-cell acute lymphocytic leukemia, chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplasia, myeloproliferative disorders, chronic myelogenous leukemia (CML), multiple myeloma (MM), myelodysplastic syndrome (MDS), human lymphotropic virus-type 1 (HTLV-1) leukemia, and B-cell acute lymphoblastic leukemia.

36. The use of claim 32, wherein the cancer is selected from diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, small non-cleaved cell lymphoma, human lymphotropic virus-type 1 (HTLV-1) leukemia/lymphoma, adult T-cell lymphoma, mantle cell lymphoma (MCL), Hodgkin disease, non-Hodgkin lymphomas, AIDS-related lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, multiple myeloma, and follicular lymphoma.

37. The use of claim 33, wherein the leukemia is chronic lymphocytic leukemia.

38. The use of claim 33, wherein the lymphoma is non-Hodgkin lymphoma.

39. The use of claim 33, wherein the lymphoma is diffuse large B-cell lymphoma.

40. The use of claim 33, wherein the lymphoma is mantle cell lymphoma.

41. The use of claim 33, wherein the lymphoma is adult T-cell lymphoma.

42 The use of any one of claims 31-41, further comprises use of one or more second therapeutic agents.

43. The use of claim 42, wherein the second therapeutic agent is a chemotherapeutic agent; optionally
wherein the chemotherapeutic agent is selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes,

topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, anti-androgens, alkyl sulfonates, aziridines, ethylenimines, methylamelamines, nitrogen mustards, nitrosureas, folic acid analogues, purine analogues, folic acid replenishers, taxanes, anti-estrogens, LHRH agonists, photodynamic therapies, triazenes, platinum containing compounds, vinca alkaloids, taxoids, epipodophyllins, DHFR inhibitors, IMP dehydrogenase inhibitors, ribonucleotide reductase inhibitors, uracil analogues, cytocine analogues, Vitamin D analogues, isoprenylation inhibitors, dopaminergic neurotoxins, MDR inhibitors, Ca2+ ATPase inhibitors, tyrosine kinase inhibitors, proteasome inhibitors, and mTOR inhibitors; optionally wherein the chemotherapeutic agent is selected from the group consisting of imatinib, bortezomib, bicalutamide, adriamycin, thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide, trimethylolomelamine, chlorambucil, chlornaphazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, chlorozotocin, fotemustine, nimustine, ranimustine; aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, 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, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfomithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidamine, mitoguazone, mopidamol, nitracrine, pentostatin, phenamet; pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofiran, spirogermanium; tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, urethane,

vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), paclitaxel, docetaxel, retinoic acid, esperamicins, capecitabine, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, toremifene, flutamide, nilutamide, leuprolide, goserelin, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin, carboplatin, vinblastine, platinum, mitomycin C, mitoxantrone, vincristine, vinorelbine, navelbine, novantrone, teniposide, daunomycin, aminopterin, xeloda, ibandronate, camptothecin-11 (CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), tamoxifen, raloxifene, megestrol, vertoporfin(BPD-MA), phthalocyanine, photosensitizer Pc4, demethoxy-hypocrellin A (2BA-2-DMHA), carmustine (BCNU), lomustine (CCNU), treosulfan, temozolomide, oxaliplatin, DHA-paclitaxel, Taxoprexin, PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX, ANG1005, paclitaxel-EC-1, glucose-conjugated paclitaxel, etoposide, etoposide phosphate, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomycin C, methotrexate, dichloromethotrexate, edatrexate, tiazofurin, ribavirin, EICAR, deferoxamine, ratitrexed, tegafur-uracil, cytosine arabinoside, fludarabine, EB 1089, CB 1093, KH 1060, lovastatin, 1-methyl-4-phenylpyridinium ion, staurosporine, actinomycin D, bleomycin A2, bleomycin B2, peplomycin, pegylated liposomal doxorubicin, pirarubicin, zorubicin, verapamil, thapsigargin, thalidomide, lenalidomide, axitinib (AG013736), bosutinib (SKI-606), cediranib (AZD2171), dasatinib (BMS-354825), erlotinib, gefitinib, lapatinib, lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib, semaxanib (semaxinib, SU5416), sunitinib (SU11248), toceranib, vandetanib (ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab, bevacizumab, rituximab, cetuximab, panitumumab, ranibizumab, sorafenib, everolimus, alemtuzumab, gemtuzumab, ozogamicin, temsirolimus, ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992, SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120, AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, XL228, rapamycin, temsirolimus (CCI-779), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Norvartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe), OSI-027 (OSI), oblimersen,

leucovorin, pemetrexed, cyclophosphamide, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, methopterin, porfiromycin, melphalan, leurosidine, leurosine, trabectedin, discodermolide, and hexamethylmelamine, or a pharmaceutically acceptable salt thereof.

44. The use of claim 42 wherein the second therapeutic agent is selected from
(i) an agent that inhibits IgE production or activity,
(ii) an anti-inflammatory drug,
(iii) anticoagulants,
(iv) a biotherapeutic agent,
(v) an anti-angiogenesis agents,
(vi) a diuretic agent,
(vii) a hormone or therapeutic peptide or protein, and
(viii) radiation therapy; optionally
wherein
(i) the agent that inhibits IgE production or activity is selected from TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs, TORC1 inhibitors, TORC2 inhibitors, anti-IgE antibodies, omalizumab, and TNX-901;
(ii) the anti-inflammatory drug is selected from acetylsalicylic acid, ibuprofen, naproxen, indomethacin, nabumetone, tolmetin, a corticosteroid, prednisone, chloroquine, and hydroxychloroquine;
(iii) the anticoagulant is selected from aspirin™, heparin, and coumadin;
(iv) the biotherapeutic agent is selected from tumor necrosis factor, interferon α, interferon γ, IL-1, IL-2, IL-4, IL-6, IL-12, GM-CSF, Herceptin™ (trastuzumab), T-DM1, bevacizumab, cetuximab, panitumumab, rituximab, and tositumomab;
(v) the anti-angiogenic agent is selected from 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;
(vi) the diuretic agent is selected from amiloride, anticholinergics, ipratropium, atropine and oxitropium;
(vii) the hormone or therapeutic peptide or protein is selected from cortisone, hydrocortisone, prednisolone, xanthines, aminophylline, choline theophyllinate, lysine theophyllinate, theophylline, insulin and glucagon; or
(viii) the radiation therapy is selected from external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy.

45. The use of claim 42, wherein the second therapeutic agent is a therapeutic antibody.

46. The use of claim 45, wherein the therapeutic antibody is anti-CD20 antibody.

47. The use of claim 45, wherein the therapeutic antibody is selected from cetuximab, panitumumab, trastuzumab, rituximab, tositumomab, alemtuzumab, bevacizumab, and gemtuzumab.

48. The use of claim 47, wherein the therapeutic antibody is rituximab.

49. The use of claim 43, wherein the chemotherapeutic agent is nitrogen mustard.

50. The use of claim 43, wherein the chemotherapeutic agent is chlorambucil.

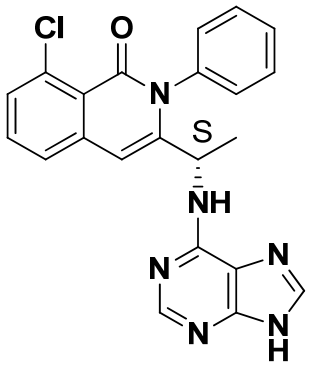
51. The use of claim 31, wherein the disorder is an inflammatory disease or immune disease.

52 The use of claim 51, wherein the inflammatory disease or immune disease is rheumatoid arthritis.

53 The use of claim 31, wherein the disorder is a respiratory disease.

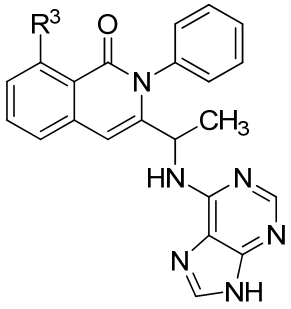
54. The use of claim 53, wherein the respiratory disease is asthma.

55. A compound of the formula:



(Compound 292).

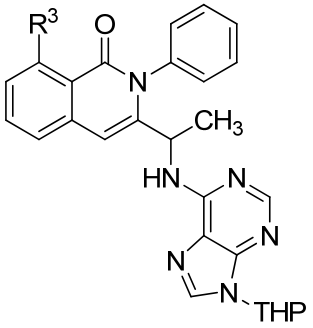
56. A process for preparing a compound of formula:



or a pharmaceutically acceptable salt thereof, wherein

R^3 is halo;

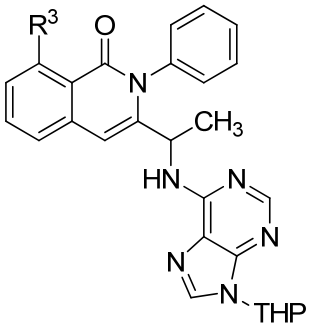
comprising deprotecting a compound of formula:



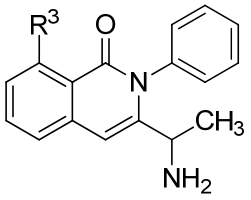
wherein the deprotection occurs in the presence of an acid.

57. The process of claim 56, wherein the acid is HCl.

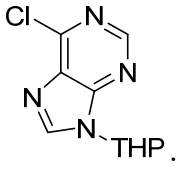
58. The process of claim 56 or claim 57, wherein the compound of formula:



is prepared by a process comprising reacting a compound of formula:

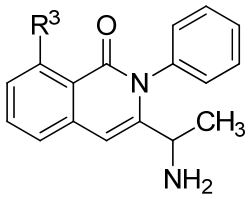


with a compound of formula:

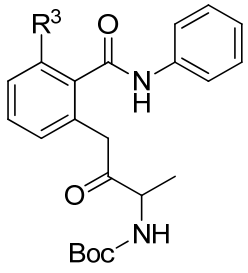


59. The process of claim 58, wherein the reaction occurs in the presence of N,N-diisopropylethylamine and n-butanol.

60. The process of claim 58 or claim 59, wherein the compound of formula:



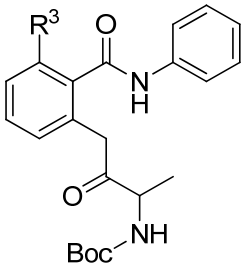
is prepared by a process comprising an intramolecular ring closure of a compound of formula:



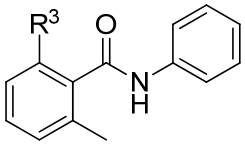
.

61. The process of claim 60, wherein the intramolecular ring closure occurs in the presence of hydrochloric acid and methanol.

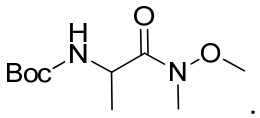
62. The process of claim 60 or claim 61, wherein the compound of formula:



is prepared by a process comprising reacting a compound of formula:

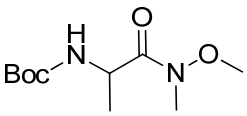


with a compound of formula:

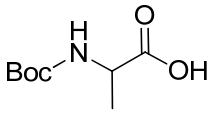


63. The process of claim 62, wherein the reaction occurs in the presence of hexamethylphosphoramide and n-butyllithium.

64. The process of claim 62 or claim 63, wherein the compound of formula:



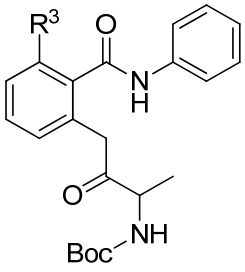
is prepared by a process comprising reacting a compound of formula:



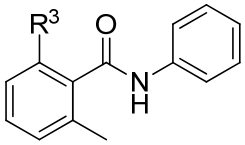
with N,O-dimethylhydroxylamine hydrochloride.

65. The process of claim 64, wherein the reaction occurs in the presence of triethylamine, hydroxybenzotriazole, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

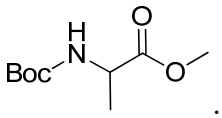
66. The process of claim 60 or claim 61, wherein the compound of formula:



is prepared by a process comprising reacting a compound of formula:

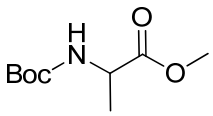


with a compound of formula:

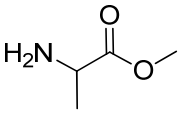


67. The process of claim 66, wherein the reaction occurs in the presence of hexamethylphosphoramide and n-butyllithium.

68. The process of claim 66 or claim 67, wherein the compound of formula:



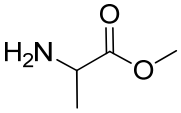
is prepared by a process comprising reacting a compound of formula:



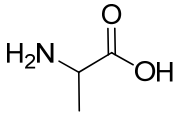
with di-tert-butyl dicarbonate.

69. The process of claim 68, wherein the reaction occurs in the presence of $NaHCO_3$.

70. The process of claim 68 or claim 69, wherein the compound of formula:



is prepared by a process comprising reacting a compound of formula:



with methanol.

71. The process of claim 70, wherein the reaction occurs in the presence of thionyl chloride.

72. The process of any one of claims 56–71, wherein R^3 is Cl.

73. A compound of any one of claims 1-11 or a pharmaceutical composition of claim 12 or 13, for use in the treatment of a disorder in a subject, wherein said disorder is one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, or cardiac disease; or for use in the treatment of asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder (COPD), psoriasis, multiple sclerosis, disorders related to diabetic complications, lupus erythematosus, scleroderma, graft versus host disease, restenosis, or atherosclerosis.

CERTAIN CHEMICAL ENTITIES, COMPOSITIONS AND METHODS

ABSTRACT

Chemical entities that modulate PI3 kinase activity, pharmaceutical compositions containing the chemical entities, and methods of using these chemical entities for treating diseases and conditions associated with PO kinase activity are described herein.

[No suitable figure]