Certain Imidazo[1,2-a]pyrazin-8-ylamines, Method of Making, and Method of Use Thereof

[0001] This application claims priority to U.S. Application No.10/985,023, filed November 10, 2004; Application No. 60/630,860, filed November 24, 2004; Application No. 60/630,645, filed November 24, 2004; and Application No. 60/630,861, filed November 24, 2004, each of which is incorporated herein by reference.

[0002] Provided herein are certain imidazo[1,2-a]pyrazinylamines and related compounds, compositions comprising such compounds, and methods of their use.

[0003] Protein kinases, the largest family of human enzymes, encompass well over 500 proteins. Bruton's Tyrosine Kinase (Btk) is a member of the Tec family of tyrosine kinases, and is a regulator of early B-cell development as well as mature B-cell activation, signaling and survival.

[0004] B-cell signaling through the B-cell receptor (BCR) leads to a wide range of biological outputs, which in turn depend on the developmental stage of the B-cell. The magnitude and duration of BCR signals must be precisely regulated. Aberrant BCR-mediated signaling can cause disregulated B-cell activation and/or the formation of pathogenic auto-antibodies leading to multiple autoimmune and/or inflammatory diseases. Mutation of Btk in humans results in X-linked agammaglobulinaemia (XLA). This disease is associated with the impaired maturation of B-cells, diminished immunoglobulin production, compromised T-cell-independent immune responses and marked attenuation of the sustained calcium sign upon BCR stimulation.

[0005] Evidence for the role of Btk in allergic disorders and/or autoimmune disease and/or inflammatory disease has been established in Btk-deficient mouse models. For example, in standard murine preclinical models of systemic lupus erythematosus (SLE), Btk deficiency has been shown to result in a marked amelioration of disease progression. Moreover, Btk deficient mice are also resistant to developing collagen-induced arthritis and are less susceptible to Staphylococcus-induced arthritis.

[0006] A large body of evidence supports the role of B-cells and the humoral immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Protein-based therapeutics (such as Rituxan) developed to deplete B-cells, represent an important approach to the treatment of a number of autoimmune and/or inflammatory diseases. Because of Btk's role in B-cell activation, inhibitors of Btk can be useful as inhibitors of B-cell mediated pathogenic activity (such as autoantibody production).

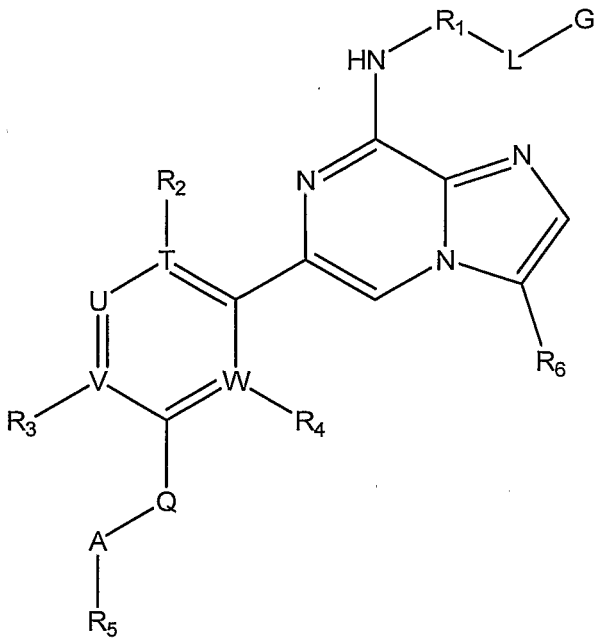
[0007] Btk is also expressed in mast cells and monocytes and has been shown to be important for the function of these cells. For example, Btk deficiency in mice is associated with impaired IgE-mediated mast cell activation (marked diminution of TNF-alpha and other inflammatory cytokine release), and Btk deficiency in humans is associated with greatly reduced TNF-alpha production by activated monocytes.

[0008] Thus, inhibition of Btk activity can be useful for the treatment of allergic disorders and/or autoimmune and/or inflammatory diseases including, but not limited to: SLE, rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, multiple sclerosis (MS), transplant rejection, Type I diabetes, membranous nephritis, inflammatory bowel disease, autoimmune hemolytic anemia, autoimmune thyroiditis, cold and warm agglutinin diseases, Evan's syndrome, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), sarcoidosis, Sjogren's syndrome, peripheral neuropathies (e.g. Guillain-Barre syndrome), pemphigus vulgaris, and asthma.

[0009] In addition, Btk has been reported to play a role in controlling B-cell survival in certain B-cell cancers. For example, Btk has been shown to be important for the survival of BCR-Abl-positive B-cell acute lymphoblastic leukemia cells. Thus inhibition of Btk activity can be useful for the treatment of B-cell lymphoma and leukemia.

[0010] Modulators of kinase activity which may generally be described as imidazo[1,2-a]pyrazinylamines are provided herein.

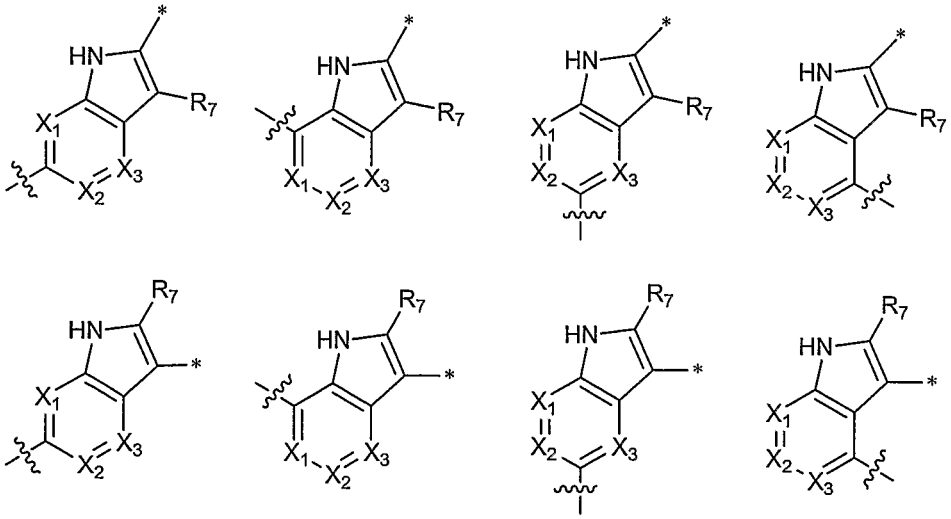
[0011] Provided is at least one chemical entity chosen from compounds of Formula 1:

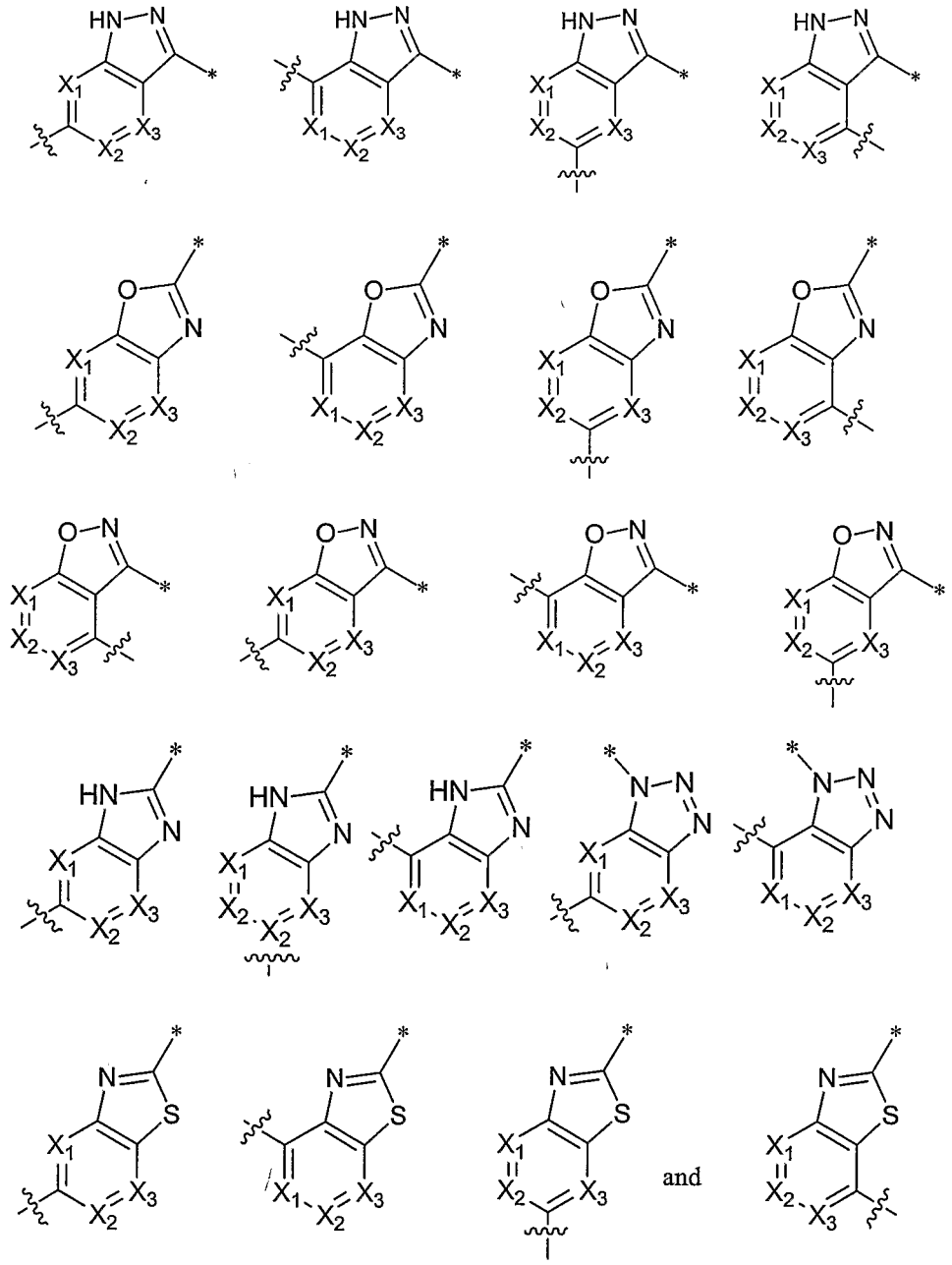


(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein

R_1 is chosen from optionally substituted phenylene, optionally substituted pyridylidene, optionally 2-oxo-1,2-dihydropyridinyl,





and

wherein * indicates the point of attachment to the group –L-G and the broken bond indicates the point of attachment to the amino group; and wherein X_1 is chosen from N and CR_7; X_2 is chosen from N and CR_7; and X_3 is chosen from N and CR_7; wherein no more than one of X_1, X_2, and X_3 is N and wherein R_7 is chosen from hydrogen, hydroxy, cyano, halo, optionally substituted lower alkyl, and optionally substituted lower alkoxy;

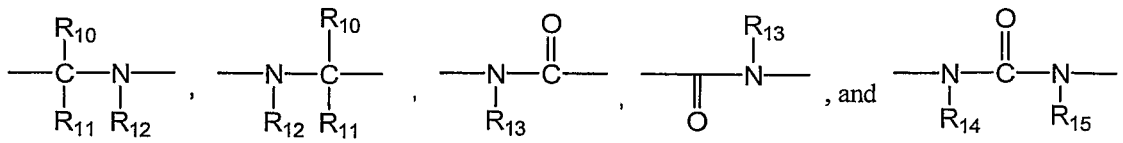
L is chosen from a covalent bond, optionally substituted C_1-C_4alkylene, -O-, -O-(optionally substituted C_1-C_4alkylene)-, -(C=O)-, -(optionally substituted C_1-C_4alkylene)(C=O)-, (SO)-, -(optionally substituted C_1-C_4alkylene)(SO)-; (SO_2)-, -(optionally substituted C_1-C_4alkylene)(SO_2)-; -(C=NR_9)-, and -(optionally substituted C_1-C_4alkylene)(C=NR_9)- wherein R_9 is chosen from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

G is chosen from hydrogen, halo, hydroxy, alkoxy, nitro, optionally substituted alkyl, -$NR_{16}R_{17}$, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl wherein R_{16} and R_{17} are independently chosen from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl; or when L is chosen from -(C=NR_9)- and -(optionally substituted C_1-C_4alkylene)(C=NR_9) then-R_9 and R_{16}, together with the nitrogen to which they are bound, form an optionally substituted 5- to 7-membered nitrogen containing heterocycloalkyl which optionally further includes one or two additional heteroatoms chosen from N, O, and S and R_{17} is chosen from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

T, V, and W are chosen from C and N and U is chosen from –CH and N, provided that at most one of T, U, V and W is N;

R_2, R_3, and R_4 are independently chosen from hydrogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, halo, and hydroxy, provided that at least one of R_2, R_3, and R_4 is not hydrogen when A is a covalent bond, G is -$NR_{16}R_{17}$ and L is not chosen from -(C=NR_9)- and -(optionally substituted C_1-C_4alkylene)(C=NR_9)-, and R_2, R_3, or R_4 is absent when the respective T, V, or W to which it is bound, is N;

Q is chosen from



;

wherein

R_{10} and R_{11} are independently chosen from hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

R_{12}, R_{13}, R_{14}, and R_{15} are each independently chosen from hydrogen,

C_1-C_6 alkyl,

C_1-C_6 haloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

A is chosen from a covalent bond and -(CH=CH)-;

R_5 is chosen from optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl; and

R_6 is chosen from hydrogen, optionally substituted alkyl, cycloalkyl, and heterocycloalkyl.

[0012] Also provided is a pharmaceutical composition comprising at least one chemical entity described herein, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients.

[0013] Also provided is a packaged pharmaceutical composition, comprising

a pharmaceutical composition comprising at least one chemical entity described herein, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients; and

instructions for using the composition to treat a patient suffering from a disease responsive to inhibition of Btk activity.

[0014] Also provided is a method for treating a patient having a disease responsive to inhibition of Btk activity, comprising administering to the patient an effective amount of at least one chemical entity described herein.

[0015] Also provided is a method for treating a patient having a disease chosen from cancer, autoimmune diseases, inflammatory diseases, acute inflammatory reactions, and allergic disorders comprising administering to the patient an effective amount of at least one chemical entity described herein.

[0016] Also provided is a method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient undergoing chemotherapy with a chemotherapeutic agent an amount of at least one chemical entity described herein, sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent.

[0017] Also provided is a method of reducing medication error and enhancing therapeutic compliance of a patient being treated for a disease responsive to inhibition of Btk activity, the method comprising providing a packaged pharmaceutical preparation described herein wherein the instructions additionally include contraindication and adverse reaction information pertaining to the packaged pharmaceutical composition.

[0018] Also provided is a method for inhibiting ATP hydrolysis, the method comprising contacting cells expressing Btk with at least one chemical entity described herein in an amount sufficient to detectably decrease the level of ATP hydrolysis *in vitro*.

[0019] Also provided is a method for determining the presence of Btk in a sample, comprising contacting the sample with at least one chemical entity described

herein under conditions that permit detection of Btk activity, detecting a level of Btk activity in the sample, and therefrom determining the presence or absence of Btk in the sample.

[0020] Also provided is a method for inhibiting B-cell activity comprising contacting cells expressing Btk with at least one chemical entity described herein, in an amount sufficient to detectably decrease B-cell activity *in vitro*.

[0021] Also provided is the use of at least one chemical entity described herein for the manufacture of a medicament for the treatment of a patient having a disease responsive to inhibition of Btk activity.

[0022] Also provided is a method for the manufacture of a medicament for the treatment of a patient having a disease responsive to inhibition of Btk activity, comprising including in said medicament at least one chemical entity described herein.

[0023] As used herein, when any variable occurs more than one time in a chemical formula, its definition on each occurrence is independent of its definition at every other occurrence. In accordance with the usual meaning of "a" and "the" in patents, reference, for example, to "a" kinase or "the" kinase is inclusive of one or more kinases.

[0024] Formula 1 includes all subformulae thereof. For example Formula 1 includes compounds of Formulae 1 to 4.

[0025] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom.

[0026] By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

[0027] "Alkyl" encompasses straight chain and branched chain having the indicated number of carbon atoms, usually from 1 to 20 carbon atoms, for example 1 to 8 carbon atoms, such as 1 to 6 carbon atoms. For example C_1-C_6alkyl encompasses both straight and branched chain alkyl of from 1 to 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl, and the like. Alkylene is another subset of alkyl, referring to the same residues as alkyl, but having two points of attachment. Alkylene groups will usually have from 2 to 20 carbon atoms, for example 2 to 8 carbon atoms, such as from 2 to 6 carbon atoms. For example, C_0 alkylene indicates a covalent bond and C_1 alkylene is a methylene group. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, "butyl" is meant to include n-butyl, sec-butyl, isobutyl and t-butyl; "propyl" includes n-propyl and isopropyl. "Lower alkyl" refers to alkyl groups having one to four carbons.

[0028] "Alkenyl" refers to an unsaturated branched or straight-chain alkyl group having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl; and the like. In certain embodiments, an alkenyl group has from 2 to 20 carbon atoms and in other embodiments, from 2 to 6 carbon atoms.

[0029] "Alkynyl" refers to an unsaturated branched or straight-chain alkyl group having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl; and the

like. In certain embodiments, an alkynyl group has from 2 to 20 carbon atoms and in other embodiments, from 3 to 6 carbon atoms.

[0030] "Cycloalkyl" indicates a non-aromatic carbocyclic ring, usually having from 3 to 7 ring carbon atoms. The ring may be saturated or have one or more carbon-carbon double bonds. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, and cyclohexenyl, as well as bridged and caged saturated ring groups such as norbornane.

[0031] By "alkoxy" is meant an alkyl group of the indicated number of carbon atoms attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. Alkoxy groups will usually have from 1 to 6 carbon atoms attached through the oxygen bridge. "Lower alkoxy" refers to alkoxy groups having one to four carbons.

[0032] "Mono- and di-alkylcarboxamide" encompasses a group of the formula $-(C=O)NR_aR_b$ where R_a and R_b are independently chosen from hydrogen and alkyl groups of the indicated number of carbon atoms, provided that R_a and R_b are not both hydrogen.

[0033] By "alkylthio" is meant an alkyl group of the indicated number of carbon atoms attached through a sulfur bridge.

[0034] "Acyl" refers to the groups (alkyl)-C(O)-; (cycloalkyl)-C(O)-; (aryl)-C(O)-; (heteroaryl)-C(O)-; and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality and wherein alkyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl are as described herein. Acyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C_2 acyl group is an acetyl group having the formula $CH_3(C=O)$-.

[0035] By "alkoxycarbonyl" is meant an ester 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_6alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker.

[0036] By "amino" is meant the group $-NH_2$.

[0037] "Mono- and di-(alkyl)amino" encompasses secondary and tertiary alkyl amino groups, wherein the alkyl groups are as defined above and have the indicated number of carbon atoms. The point of attachment of the alkylamino group is on the nitrogen. Examples of mono- and di-alkylamino groups include ethylamino, dimethylamino, and methyl-propyl-amino.

[0038] "Mono- and di-(alkyl)aminoalkyl" encompasses mono- and di-(alkyl)amino as defined above linked to an alkyl group.

[0039] By "amino(alkyl)" is meant an amino group linked to an alkyl group having the indicated number of carbons. Similarly "hydroxyalkyl" is a hydroxy group linked to an alkyl group.

[0040] The term "aminocarbonyl" refers to the group $-CONR^bR^c$, where

R^b is chosen from H, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C_1-C_4 alkyl; or

R^b and R^c taken together with the nitrogen to which they are bound, form an optionally substituted 5- to 7-membered nitrogen-containing heterocycloalkyl which optionally includes 1 or 2 additional heteroatoms selected from O, N, and S in the heterocycloalkyl ring;

where each substituted group is independently substituted with one or more substituents independently selected from C_1-C_4 alkyl, aryl, heteroaryl, aryl-C_1-C_4 alkyl-, heteroaryl-C_1-C_4 alkyl-, C_1-C_4 haloalkyl-, $-OC_1$-C_4 alkyl, $-OC_1$-C_4 alkylphenyl, $-C_1$-C_4 alkyl-OH, $-OC_1$-C_4 haloalkyl, halo, -OH, $-NH_2$, $-C_1$-C_4 alkyl-NH_2, $-N(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)(C_1$-C_4 alkylphenyl), $-NH(C_1$-C_4 alkylphenyl), cyano, nitro, oxo (as a substitutent for cycloalkyl, heterocycloalkyl, or heteroaryl), $-CO_2H$, $-C(O)OC_1$-C_4 alkyl, $-CON(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CONH_2$, $-NHC(O)(C_1$-C_4 alkyl), -NHC(O)(phenyl), $-N(C_1$-C_4 alkyl$)C(O)(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)C(O)$(phenyl), $-C(O)C_1$-C_4 alkyl, $-C(O)C_1$-C_4 phenyl, $-C(O)C_1$-C_4 haloalkyl, $-OC(O)C_1$-C_4 alkyl, $-SO_2(C_1$-C_4 alkyl), $-SO_2$(phenyl), $-SO_2(C_1$-C_4 haloalkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-C_4 alkyl), $-SO_2NH$(phenyl), $-NHSO_2(C_1$-C_4 alkyl), $-NHSO_2$(phenyl), and $-NHSO_2(C_1$-C_4 haloalkyl).

[0041] "Aryl" encompasses:

5- and 6-membered carbocyclic aromatic rings, for example, benzene;

bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and tetralin; and

tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

For example, aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered cycloalkyl ring or a 5- to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms chosen from N, O, and S. For such fused, bicyclic ring systems wherein only one of the rings is a carbocyclic aromatic ring, the point of attachment may be at the carbocyclic aromatic ring or the other ring. 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. Aryl, however, does not encompass or overlap in any way with heteroaryl, separately defined below. Hence, if one or more carbocyclic aromatic rings is fused with a heterocycloalkyl aromatic ring, the resulting ring system is heteroaryl, not aryl, as defined herein.

[0042] The term "aryloxy" refers to the group -O-aryl.

[0043] The term "halo" includes fluoro, chloro, bromo, and iodo, and the term "halogen" includes fluorine, chlorine, bromine, and iodine.

[0044] "Haloalkyl" indicates alkyl as defined above having the specified number of carbon atoms, substituted with 1 or more halogen atoms, up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0045] "Heteroaryl" encompasses:

5- to 7-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3,

heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and

bicyclic heterocycloalkyl rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring.

For example, heteroaryl includes a 5- to 7-membered heterocycloalkyl, aromatic ring fused to a 5- to 7-membered cycloalkyl or heterocycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings contains one or more heteroatoms, the point of attachment may be at either ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In certain embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In certain embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, (as numbered from the linkage position assigned priority 1), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2,3-pyrazinyl, 3,4-pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,3-pyrazolinyl, 2,4-imidazolinyl, isoxazolinyl, oxazolinyl, thiazolinyl, thiadiazolinyl, tetrazolyl, thienyl, benzothiophenyl, furanyl, benzofuranyl, benzoimidazolinyl, indolinyl, pyridizinyl, triazolyl, quinolinyl, pyrazolyl, and 5,6,7,8-tetrahydroisoquinoline. 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. Heteroaryl does not encompass or overlap with aryl, cycloalkyl, or heterocycloalkyl, as defined herein

[0046] Substituted heteroaryl also includes ring systems substituted with one or more oxide ($-O^-$) substituents, such as pyridinyl N-oxides.

[0047] In the term "heteroaralkyl," heteroaryl and alkyl are as defined herein, and the point of attachment is on the alkyl group. This term encompasses, but is not limited to, pyridylmethyl, thiophenylmethyl, and (pyrrolyl)1-ethyl.

[0048] By "heterocycloalkyl" is meant a single, non-aromatic ring, usually with 3 to 7 ring atoms, containing 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. The ring may be saturated or have one or more carbon-carbon double bonds. Suitable heterocycloalkyl groups include, for example (as numbered from the linkage position assigned priority 1), 2-pyrrolinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 2-piperidyl, 3-piperidyl, 4-piperdyl, and 2,5-piperzinyl. Morpholinyl groups are also contemplated, including 2-morpholinyl and 3-morpholinyl (numbered wherein the oxygen is assigned priority 1). Substituted heterocycloalkyl also includes ring systems substituted with one or more oxo (=0) or oxide ($-O^-$) substituents, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1,1-dioxo-1-thiomorpholinyl.

[0049] "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 heteratoms independently selected from oxygen, sulfur, and nitrogen and is not-aromatic.

[0050] As used herein, "modulation" refers to a change in kinase activity as a direct or indirect response to the presence of compounds of Formula 1, relative to the activity of the kinase in the absence of the compound. The change may be an increase in activity or a decrease in activity, and may be due to the direct interaction of the compound with the kinase, or due to the interaction of the compound with one or more other factors that in turn affect kinase activity. For example, the presence of the compound may, for example, increase or decrease kinase activity by directly binding to the kinase, by causing (directly or indirectly) another factor to increase or decrease the kinase activity, or by (directly or indirectly) increasing or decreasing the amount of kinase present in the cell or organism.

[0051] The term "sulfanyl" includes the groups: -S-(optionally substituted (C_1-C_6)alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl), and -S-(optionally substituted heterocycloalkyl). Hence, sulfanyl includes the group C_1-C_6 alkylsulfanyl.

[0052] The term "sulfinyl" includes the groups: -S(O)-(optionally substituted (C_1-C_6)alkyl), -S(O)-optionally substituted aryl), -S(O)-optionally substituted

heteroaryl), -S(O)-(optionally substituted heterocycloalkyl); and -S(O)-(optionally substituted amino).

[0053] The term "sulfonyl" includes the groups: -S(O_2)-(optionally substituted (C_1-C_6)alkyl), -S(O_2)-optionally substituted aryl), -S(O_2)-optionally substituted heteroaryl), -S(O_2)-(optionally substituted heterocycloalkyl) ,-S(O_2)-(optionally substituted alkoxy), -S(O_2)-optionally substituted aryloxy), -S(O_2)-optionally substituted heteroaryloxy), -S(O_2)-(optionally substituted heterocyclyloxy); and -S(O_2)-(optionally substituted amino).

[0054] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo (i.e., =O) then 2 hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation as an agent having at least practical utility. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion.

[0055] The terms "substituted" alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, unless otherwise expressly defined, refer respectively to alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

$-R^a$, $-OR^b$, -O(C_1-C_2 alkyl)O- (e.g., methylenedioxy-), $-SR^b$, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, $-NR^bR^c$, halo, cyano, nitro, oxo (as a substitutent for cycloalkyl, heterocycloalkyl, and heteroaryl), $-COR^b$, $-CO_2R^b$, $-CONR^bR^c$, $-OCOR^b$, $-OCO_2R^a$, $-OCONR^bR^c$, $-NR^cCOR^b$, $-NR^cCO_2R^a$, $-NR^cCONR^bR^c$, $-CO_2R^b$, $-CONR^bR^c$, $-NR^cCOR^b$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^bR^c$, and $-NR^cSO_2R^a$,

where R^a is chosen from optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C_1-C_4 alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C_1-C_4 alkyl, aryl, heteroaryl, aryl-C_1-C_4 alkyl-, heteroaryl-C_1-C_4 alkyl-, C_1-C_4 haloalkyl-, -OC_1-C_4 alkyl, -OC_1-C_4 alkylphenyl, -C_1-C_4 alkyl-OH, -OC_1-C_4 haloalkyl, halo, -OH, -NH_2, -C_1-C_4 alkyl-NH_2, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkylphenyl), -NH(C_1-C_4 alkylphenyl), cyano, nitro, oxo (as a substitutent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -$CONH_2$, -NHC(O)(C_1-C_4 alkyl), -NHC(O)(phenyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(phenyl), -C(O)C_1-C_4 alkyl, -C(O)C_1-C_4 phenyl, -C(O)C_1-C_4 haloalkyl, -OC(O)C_1-C_4 alkyl, -SO_2(C_1-C_4 alkyl), -SO_2(phenyl), -SO_2(C_1-C_4 haloalkyl), -SO_2NH_2, -SO_2NH(C_1-C_4 alkyl), -SO_2NH(phenyl), -NHSO_2(C_1-C_4 alkyl), -NHSO_2(phenyl), and -NHSO_2(C_1-C_4 haloalkyl).

[0056] The term "substituted acyl" refers to the groups (substituted alkyl)-C(O)-; (substituted cycloalkyl)-C(O)-; (substituted aryl)-C(O)-; (substituted heteroaryl)-C(O)-; and (substituted heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality and wherein substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl, refer respectively to alkyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

$-R^a$, $-OR^b$, $-O(C_1-C_2$ alkyl$)O-$ (e.g., methylenedioxy-), $-SR^b$, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, $-NR^bR^c$, halo, cyano, nitro, $-COR^b$, $-CO_2R^b$, $-CONR^bR^c$, $-OCOR^b$, $-OCO_2R^a$, $-OCONR^bR^c$, $-NR^cCOR^b$, $-NR^cCO_2R^a$, $-NR^cCONR^bR^c$, $-CO_2R^b$, $-CONR^bR^c$, $-NR^cCOR^b$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^bR^c$, and $-NR^cSO_2R^a$,

where R^a is chosen from optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C_1-C_4 alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C_1-C_4 alkyl, aryl, heteroaryl, aryl-C_1-C_4 alkyl-, heteroaryl-C_1-C_4 alkyl-, C_1-C_4 haloalkyl-, $-OC_1-C_4$ alkyl, $-OC_1-C_4$ alkylphenyl, $-C_1-C_4$ alkyl-OH, $-OC_1-C_4$ haloalkyl, halo, -OH, $-NH_2$, $-C_1-C_4$ alkyl-NH_2, $-N(C_1-C_4$ alkyl$)(C_1-C_4$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)(C_1-C_4$ alkylphenyl), $-NH(C_1-C_4$ alkylphenyl), cyano, nitro, oxo (as a substitutent for cycloalkyl, heterocycloalkyl, or heteroaryl), $-CO_2H$, $-C(O)OC_1-C_4$ alkyl, $-CON(C_1-C_4$ alkyl$)(C_1-C_4$ alkyl), $-CONH(C_1-C_4$ alkyl), $-CONH_2$, $-NHC(O)(C_1-C_4$ alkyl), -NHC(O)(phenyl), $-N(C_1-C_4$ alkyl$)C(O)(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)C(O)$(phenyl), $-C(O)C_1-C_4$ alkyl, $-C(O)C_1-C_4$ phenyl, $-C(O)C_1-C_4$ haloalkyl, $-OC(O)C_1-C_4$ alkyl, $-SO_2(C_1-C_4$ alkyl), $-SO_2$(phenyl), $-SO_2(C_1-C_4$ haloalkyl), $-SO_2NH_2$, $-SO_2NH(C_1-C_4$ alkyl), $-SO_2NH$(phenyl), $-NHSO_2(C_1-C_4$ alkyl), $-NHSO_2$(phenyl), and $-NHSO_2(C_1-C_4$ haloalkyl).

[0057] The term "substituted alkoxy" refers to alkoxy wherein the alkyl constituent is substituted (i.e., -O-(substituted alkyl)) wherein "substituted alkyl" refers to alkyl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

-R^a, -OR^b, -O(C_1-C_2 alkyl)O- (e.g., methylenedioxy-), -SR^b, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, -NR^bR^c, halo, cyano, nitro, -COR^b, -CO_2R^b, -$CONR^bR^c$, -$OCOR^b$, -OCO_2R^a, -$OCONR^bR^c$, -NR^cCOR^b, -$NR^cCO_2R^a$, -$NR^cCONR^bR^c$, -CO_2R^b, -$CONR^bR^c$, -NR^cCOR^b, -SOR^a, -SO_2R^a, -$SO_2NR^bR^c$, and -$NR^cSO_2R^a$,

where R^a is chosen from optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C_1-C_4 alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C_1-C_4 alkyl, aryl, heteroaryl, aryl-C_1-C_4 alkyl-, heteroaryl-C_1-C_4 alkyl-, C_1-C_4 haloalkyl-, -OC_1-C_4 alkyl, -OC_1-C_4 alkylphenyl, -C_1-C_4 alkyl-OH, -OC_1-C_4 haloalkyl, halo, -OH, -NH_2, -C_1-C_4 alkyl-NH_2, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkylphenyl), -NH(C_1-C_4 alkylphenyl), cyano, nitro, oxo (as a substitutent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -$CONH_2$, -NHC(O)(C_1-C_4 alkyl), -NHC(O)(phenyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(phenyl), -C(O)C_1-C_4 alkyl, -C(O)C_1-C_4 phenyl, -C(O)C_1-C_4 haloalkyl, -OC(O)C_1-C_4 alkyl, -SO_2(C_1-C_4 alkyl), -SO_2(phenyl), -SO_2(C_1-C_4 haloalkyl), -SO_2NH_2, -SO_2NH(C_1-C_4 alkyl), -SO_2NH(phenyl), -$NHSO_2$(C_1-C_4 alkyl), -$NHSO_2$(phenyl), and -$NHSO_2$(C_1-C_4 haloalkyl). In some embodiments, a substituted alkoxy group is "polyalkoxy" or -O-(optionally substituted alkylene)-(optionally substituted alkoxy), and includes groups such as -$OCH_2CH_2OCH_3$, and residues of glycol ethers such as polyethyleneglycol, and -$O(CH_2CH_2O)_xCH_3$, where x is an integer of 2-20, such as 2-10, and for example, 2-5. Another substituted alkoxy group is hydroxyalkoxy or

$-OCH_2(CH_2)_yOH$, where y is an integer of 1-10, such as 1-4.

[0058] 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 and wherein substituted refers to alkyl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

$-R^a$, $-OR^b$, $-O(C_1-C_2$ alkyl$)O-$ (e.g., methylenedioxy-), $-SR^b$, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, $-NR^bR^c$, halo, cyano, nitro, $-COR^b$, $-CO_2R^b$, $-CONR^bR^c$, $-OCOR^b$, $-OCO_2R^a$, $-OCONR^bR^c$, $-NR^cCOR^b$, $-NR^cCO_2R^a$, $-NR^cCONR^bR^c$, $-CO_2R^b$, $-CONR^bR^c$, $-NR^cCOR^b$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^bR^c$, and $-NR^cSO_2R^a$,

where R^a is chosen from optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C_1-C_4 alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C_1-C_4 alkyl, aryl, heteroaryl, aryl-C_1-C_4 alkyl-, heteroaryl-C_1-C_4 alkyl-, C_1-C_4 haloalkyl-, $-OC_1-C_4$ alkyl, $-OC_1-C_4$ alkylphenyl, $-C_1-C_4$ alkyl-OH, $-OC_1-C_4$ haloalkyl, halo, -OH, $-NH_2$, $-C_1-C_4$ alkyl-NH_2, $-N(C_1-C_4$ alkyl$)(C_1-C_4$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)(C_1-C_4$ alkylphenyl), $-NH(C_1-C_4$ alkylphenyl), cyano, nitro, oxo (as a substitutent for cycloalkyl, heterocycloalkyl, or heteroaryl), $-CO_2H$, $-C(O)OC_1-C_4$ alkyl, $-CON(C_1-C_4$ alkyl$)(C_1-C_4$ alkyl), $-CONH(C_1-C_4$ alkyl), $-CONH_2$, $-NHC(O)(C_1-C_4$ alkyl), -NHC(O)(phenyl), $-N(C_1-C_4$ alkyl$)C(O)(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)C(O)$(phenyl), $-C(O)C_1-C_4$ alkyl, $-C(O)C_1-C_4$ phenyl, $-C(O)C_1-C_4$ haloalkyl, $-OC(O)C_1-C_4$ alkyl, $-SO_2(C_1-C_4$ alkyl), $-SO_2$(phenyl), $-SO_2(C_1-C_4$ haloalkyl), $-SO_2NH_2$, $-SO_2NH(C_1-C_4$ alkyl),

-SO_2NH(phenyl), -$NHSO_2$(C_1-C_4 alkyl), -$NHSO_2$(phenyl), and -$NHSO_2$(C_1-C_4 haloalkyl).

[0059] The term "substituted amino" refers to the group $-NHR^d$ or $-NR^dR^e$ wherein R^d is chosen from: hydroxy, optionally substitued alkoxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, alkoxycarbonyl, sulfinyl and sulfonyl, and wherein R^e is chosen from: optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, alkoxycarbonyl, sulfinyl and sulfonyl, and wherein substituted alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl refer respectively to alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

-R^a, -OR^b, -O(C_1-C_2 alkyl)O- (e.g., methylenedioxy-), -SR^b, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, -NR^bR^c, halo, cyano, nitro, -COR^b, -CO_2R^b, -$CONR^bR^c$, -$OCOR^b$, -OCO_2R^a, -$OCONR^bR^c$, -NR^cCOR^b, -$NR^cCO_2R^a$, -$NR^cCONR^bR^c$, -CO_2R^b, -$CONR^bR^c$, -NR^cCOR^b, -SOR^a, -SO_2R^a, -$SO_2NR^bR^c$, and -$NR^cSO_2R^a$,

where R^a is chosen from optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C_1-C_4 alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C_1-C_4 alkyl, aryl, heteroaryl, aryl-C_1-C_4 alkyl-, heteroaryl-C_1-C_4 alkyl-, C_1-C_4 haloalkyl-, -OC_1-C_4 alkyl, -OC_1-C_4 alkylphenyl, -C_1-C_4 alkyl-OH,

-OC_1-C_4 haloalkyl, halo, -OH, -NH_2, -C_1-C_4 alkyl-NH_2, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkylphenyl), -NH(C_1-C_4 alkylphenyl), cyano, nitro, oxo (as a substitutent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -$CONH_2$, -NHC(O)(C_1-C_4 alkyl), -NHC(O)(phenyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(phenyl), -C(O)C_1-C_4 alkyl, -C(O)C_1-C_4 phenyl, -C(O)C_1-C_4 haloalkyl, -OC(O)C_1-C_4 alkyl, -SO_2(C_1-C_4 alkyl), -SO_2(phenyl), -SO_2(C_1-C_4 haloalkyl), -SO_2NH_2, -SO_2NH(C_1-C_4 alkyl), -SO_2NH(phenyl), -NHSO_2(C_1-C_4 alkyl), -NHSO_2(phenyl), and -NHSO_2(C_1-C_4 haloalkyl); and

wherein optionally substituted acyl, alkoxycarbonyl, sulfinyl and sulfonyl are as defined herein.

[0060] 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.

[0061] "Carbamimidoyl" refers to the group -C(=NH)-NH_2.

[0062] "Substituted carbamimidoyl" refers to the group -$C(=NR^e)$-NR^fR^g where R^e, R^f, and R^g is independently chosen from: hydrogen optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl, provided that at least one of R^e, R^f, and R^g is not hydrogen and wherein substituted alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl refer respectively to alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

-R^a, -OR^b, -O(C_1-C_2 alkyl)O- (e.g., methylenedioxy-), -SR^b, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, -NR^bR^c, halo, cyano, nitro, -COR^b, -CO_2R^b, -$CONR^bR^c$, -$OCOR^b$, -OCO_2R^a, -$OCONR^bR^c$, -NR^cCOR^b, -$NR^cCO_2R^a$, -$NR^cCONR^bR^c$, -CO_2R^b, -$CONR^bR^c$, -NR^cCOR^b, -SOR^a, -SO_2R^a, -$SO_2NR^bR^c$, and -$NR^cSO_2R^a$,

where R^a is chosen from optionally substituted C_1-C_6 alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C_1-C_4 alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C_1-C_4 alkyl, aryl, heteroaryl, aryl-C_1-C_4 alkyl-, heteroaryl-C_1-C_4 alkyl-, C_1-C_4 haloalkyl-, -OC_1-C_4 alkyl, -OC_1-C_4 alkylphenyl, -C_1-C_4 alkyl-OH, -OC_1-C_4 haloalkyl, halo, -OH, -NH_2, -C_1-C_4 alkyl-NH_2, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkylphenyl), -NH(C_1-C_4 alkylphenyl), cyano, nitro, oxo (as a substitutent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -$CONH_2$, -NHC(O)(C_1-C_4 alkyl), -NHC(O)(phenyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(phenyl), -C(O)C_1-C_4 alkyl, -C(O)C_1-C_4 phenyl, -C(O)C_1-C_4 haloalkyl, -OC(O)C_1-C_4 alkyl, -SO_2(C_1-C_4 alkyl), -SO_2(phenyl), -SO_2(C_1-C_4 haloalkyl), -SO_2NH_2, -SO_2NH(C_1-C_4 alkyl), -SO_2NH(phenyl), -NHSO_2(C_1-C_4 alkyl), -NHSO_2(phenyl), and -NHSO_2(C_1-C_4 haloalkyl).

[0063] Compounds of Formula 1 include, but are not limited to, optical isomers of compounds of Formula 1, racemates, and other mixtures thereof. In those situations, the single enantiomers or diastereomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high-pressure liquid chromatography (HPLC) column. In addition, compounds of Formula 1 include Z- and E- forms (or *cis-* and *trans-* forms) of compounds with carbon-carbon double bonds. Where compounds of Formula 1 exists

in various tautomeric forms, chemical entities of the present invention include all tautomeric forms of the compound.

[0064] Chemical entities of the present invention include, but are not limited to compounds of Formula 1 and all pharmaceutically acceptable forms thereof. Pharmaceutically acceptable forms of the compounds recited herein include pharmaceutically acceptable salts, solvates, crystal forms (including polymorphs and clathrates), 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, solvates, chelates, non-covalent complexes, prodrugs, and mixtures.

[0065] "Pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, such as hydrochlorate, phosphate, diphosphate, hydrobromate, sulfate, sulfinate, nitrate, and like salts; as well as salts with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate such as acetate, HOOC-$(CH_2)_n$-COOH where n is 0-4, and like salts. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium, and ammonium.

[0066] In addition, if the compound of Formula 1 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.

[0067] As noted above, prodrugs also fall within the scope of chemical entities, for example ester or amide derivatives of the compounds of Formula 1. The term "prodrugs" includes any compounds that become compounds of Formula 1 when administered to a patient, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate and like

derivatives of functional groups (such as alcohol or amine groups) in the compounds of Formula 1.

[0068] The term "solvate" refers to the chemical entity formed by the interaction of a solvent and a compound. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates.

[0069] The term "chelate" refers to the chemical entity formed by the coordination of a compound to a metal ion at two (or more) points.

[0070] The term "non-covalent complex" refers to the chemical entity formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding).

[0071] The term "active agent" is used to indicate a chemical entity which has biological activity. In certain embodiments, an "active agent" is a compound having pharmaceutical utility. For example an active agent may be an anti-cancer therapeutic.

[0072] The term "therapeutically effective amount" of a chemical entity of this invention means an amount effective, when administered to a human or non-human patient, to provide a therapeutic benefit such as amelioration of symptoms, slowing of disease progression, or prevention of disease e.g., a therapeutically effective amount may be an amount sufficient to decrease the symptoms of a disease responsive to Btk inhibition. In some embodiments, a therapeutically effective amount is an amount sufficient to reduce cancer symptoms, the symptoms of an allergic disorder, the symptoms of an autoimmune and/or inflammatory disease, or the symptoms of an acute inflammatory reaction. In some embodiments a therapeutically effective amount is an amount sufficient to decrease the number of detectable cancerous cells in an organism, detectably slow, or stop the growth of a cancerous tumor. In some embodiments, a therapeutically effective amount is an amount sufficient to shrink a cancerous tumor. In certain circumstances a patient suffering from cancer may not present symptoms of being affected. In some embodiments, a therapeutically effective amount of a chemical entity is an amount sufficient to prevent a significant increase or significantly reduce the detectable level of cancerous cells or cancer

markers in the patient's blood, serum, or tissues. In methods described herein for treating allergic disorders and/or autoimmune and/or inflammatory diseases and/or acute inflammatory reactions, a therapeutically effective amount may also be an amount sufficient, when administered to a patient, to detectably slow progression of the disease, or prevent the patient to whom the chemical entity is given from presenting symptoms of the allergic disorders and/or autoimmune and/or inflammatory disease, and/or acute inflammatory response. In certain methods described herein for treating allergic disorders and/or autoimmune and/or inflammatory diseases and/or acute inflammatory reactions, a therapeutically effective amount may also be an amount sufficient to produce a detectable decrease in the amount of a marker protein or cell type in the patient's blood or serum. For example, in some embodiments a therapeutically effective amount is an amount of a chemical entity described herein sufficient to significantly decrease the activity of B-cells. In another example, in some embodiments a therapeutically effective amount is an amount of a chemical entity described herein sufficient to significantly decrease the number of B-cells. In another example, in some embodiments a therapeutically effective amount is an amount of a chemical entity described herein sufficient to decrease the level of anti- acetylcholine receptor antibody in a patient's blood with the disease myasthenia gravis.

[0073] The term "inhibition" indicates a significant decrease in the baseline activity of a biological activity or process. "Inhibition of Btk activity" refers to a decrease in Btk activity as a direct or indirect response to the presence of at least one chemical entity described herein, relative to the activity of Btk in the absence of the at least one chemical entity. The decrease in activity may be due to the direct interaction of the compound with Btk, or due to the interaction of the chemical entity(ies) described herein with one or more other factors that in turn affect Btk activity. For example, the presence of the chemical entity(ies) may decrease Btk activity by directly binding to the Btk, by causing (directly or indirectly) another factor to decrease Btk activity, or by (directly or indirectly) decreasing the amount of Btk present in the cell or organism.

[0074] Inhibition of Btk activity also refers to observable inhibition of Btk activity in a standard biochemical assay for Btk activity, such as the ATP hydrolysis

assay described below. In some embodiments, the chemical entity described herein has an IC_{50} value less than or equal to 10 micromolar. In some embodiments, the chemical entity has an IC_{50} value less than or equal to less than 1 micromolar. In some embodiments, the chemical entity has an IC_{50} value less than or equal to 0.1 micromolar.

[0075] "Inhibition of B-cell activity" refers to a decrease in B-cell activity as a direct or indirect response to the presence of at least one chemical entity described herein, relative to the activity of B-cells in the absence of the at least one chemical entity. The decrease in activity may be due to the direct interaction of the compound with Btk or with one or more other factors that in turn affect B-cell activity.

[0076] Inhibition of B-cell activity also refers to observable inhibition of CD86 expression in a standard assay such as the assay described below. In some embodiments, the chemical entity described herein has an IC_{50} value less than or equal to 10 micromolar. In some embodiments, the chemical entity has an IC_{50} value less than or equal to less than 1 micromolar. In some embodiments, the chemical entity has an IC_{50} value less than or equal to 500 nanomolar.

[0077] "B cell activity" also includes activation, redistribution, reorganization, or capping of one or more various B cell membrane receptors, or membrane-bound immunoglobulins, e.g, IgM, IgG, and IgD. Most B cells also have membrane receptors for Fc portion of IgG in the form of either antigen-antibody complexes or aggregated IgG. B cells also carry membrane receptors for the activated components of complement, e.g., C3b, C3d, C4, and Clq. These various membrane receptors and membrane-bound immunoglobulins have membrane mobility and can undergo redistribution and capping that can initiate signal transduction.

[0078] B cell activity also includes the synthesis or production of antibodies or immunoglobulins. Immunoglobulins are synthesized by the B cell series and have common structural features and structural units. Five immunoglobulin classes, i.e., IgG, IgA, IgM, IgD, and IgE, are recognized on the basis of structural differences of their heavy chains including the amino acid sequence and length of the polypeptide chain. Antibodies to a given antigen may be detected in all or several classes of immunoglobulins or may be restricted to a single class or subclass of immunoglobulin. Autoantibodies or autoimmune antibodies may likewise belong to

one or several classes of immunoglobulins. For example, rheumatoid factors (antibodies to IgG) are most often recognized as an IgM imnnunoglobulin, but can also consist of IgG or IgA.

[0079] In addition, B cell activity also is intended to include a series of events leading to B cell clonal expansion (proliferation) from precursor B lymphocytes and differentiation into antibody-synthesizing plasma cells which takes place in conjunction with antigen-binding and with cytokine signals from other cells.

[0080] "Inhibition of B-cell proliferation" refers to inhibition of proliferation of abnormal B-cells, such as cancerous B-cells, e.g. lymphoma B-cells and/ or inhibition of normal, non-diseased B-cells. The term "inhibition of B-cell proliferation" indicates any significant decrease in the number of B-cells, either *in vitro* or *in vivo*. Thus an inhibition of B-cell proliferation *in vitro* would be any significant decrease in the number of B-cells in an *in vitro* sample contacted with at least one chemical entity described herein as compared to a matched sample not contacted with the chemical entity(ies).

[0081] Inhibition of B-cell proliferation also refers to observable inhibition of B-cell proliferation in a standard thymidine incorporation assay for B-cell proliferation, such as the assay described herein. In some embodiments, the chemical entity has an IC_{50} value less than or equal to 10 micromolar. In some embodiments, the chemical entity has an IC_{50} value less than or equal to less than 1 micromolar. In some embodiments, the chemical entity has an IC_{50} value less than or equal to 500 nanomolar.

[0082] An "allergy" or "allergic disorder" refers to acquired hypersensitivity to a substance (allergen). Allergic conditions include eczema, allergic rhinitis or coryza, hay fever, bronchial asthma, urticaria (hives) and food allergies, and other atopic conditions.

[0083] "Asthma" refers to a disorder of the respiratory system characterized by inflammation, narrowing of the airways and increased reactivity of the airways to inhaled agents. Asthma is frequently, although not exclusively associated with atopic or allergic symptoms.

[0084] By "significant" is meant any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student's T-

test, where $p < 0.05$.

[0085] A "disease responsive to inhibition of Btk activity" is a disease in which inhibiting Btk kinase provides a therapeutic benefit such as an amelioration of symptoms, decrease in disease progression, prevention or delay of disease onset, or inhibition of aberrant activity of certain cell-types (monocytes, B-cells, and mast cells).

[0086] "Treatment or treating means any treatment of a disease in a patient, including:

a) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;

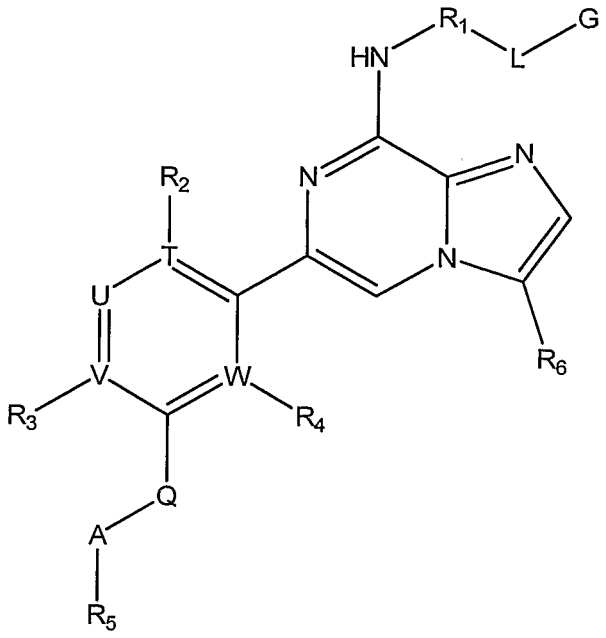
b) inhibiting the disease;

c) slowing or arresting the development of clinical symptoms; and/or

d) relieving the disease, that is, causing the regression of clinical symptoms.

[0087] "Patient" refers to an animal, such as a mammal, that has been or will be the object of treatment, observation or experiment. The methods of the invention can be useful in both human therapy and veterinary applications. In some embodiments, the patient is a mammal; in some embodiments the patient is human; and in some embodiments the patient is chosen from cats and dogs.

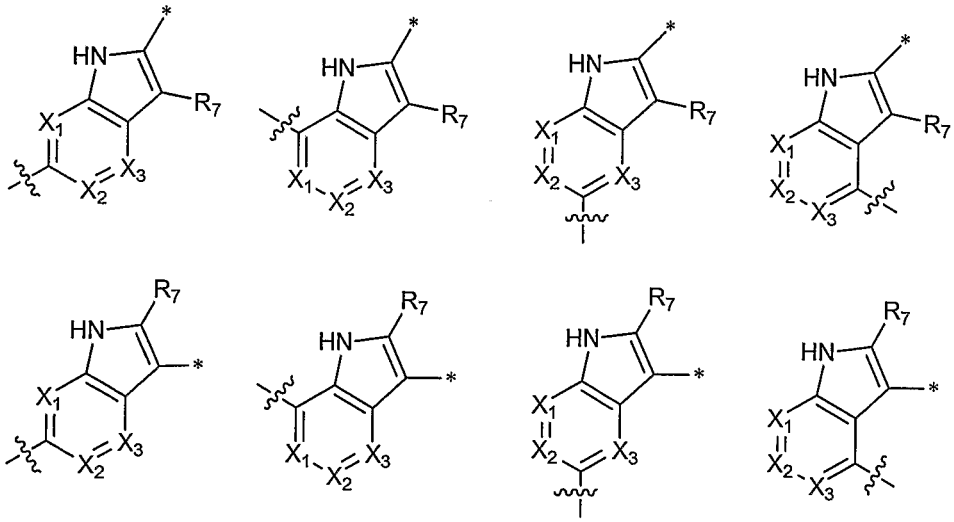
[0088] In certain embodiments, the invention provides at least one chemical entity chosen from compounds of Formula 1:

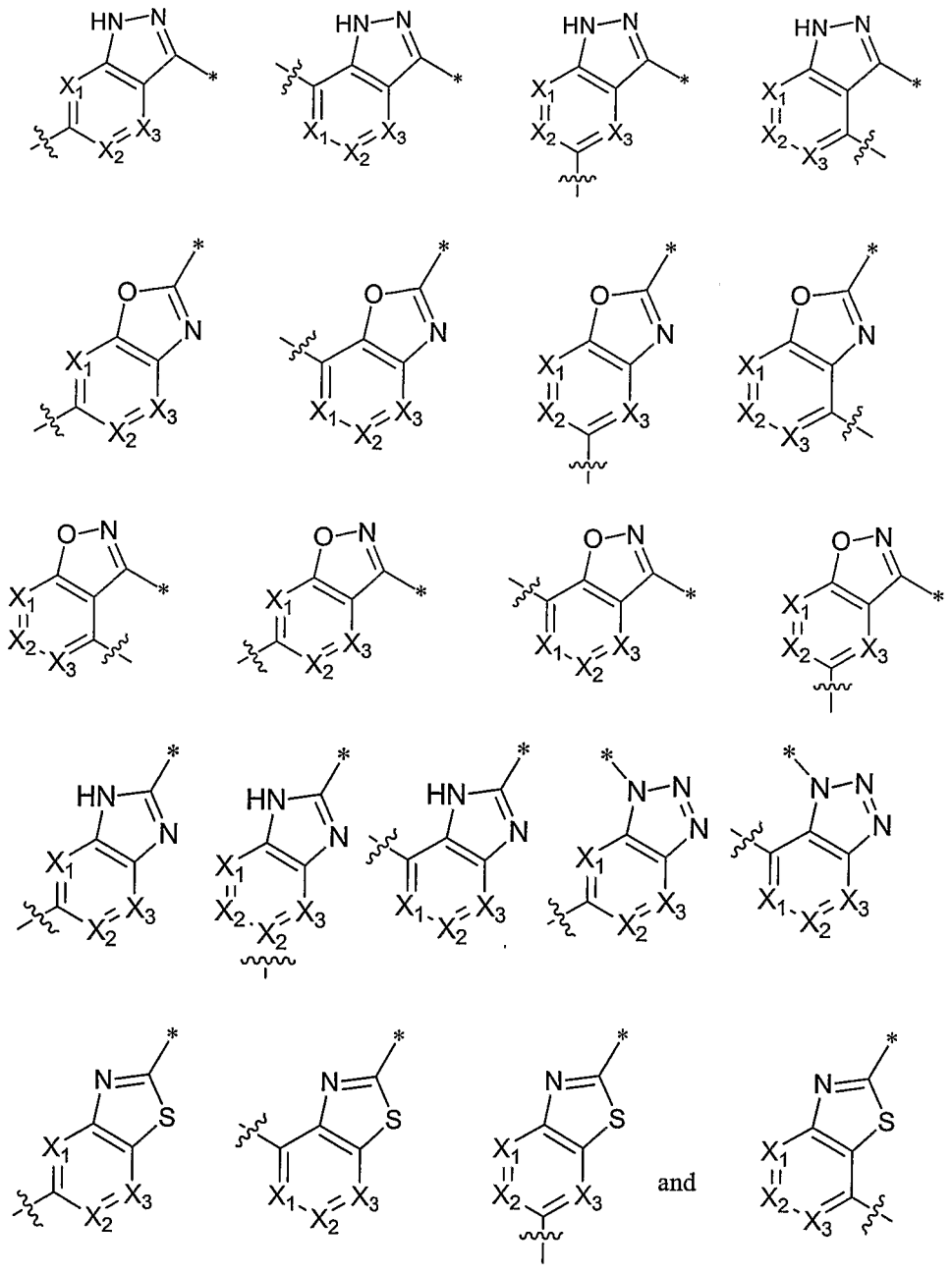


(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein

R_1 is chosen from optionally substituted phenylene, optionally substituted pyridylidene, optionally 2-oxo-1,2-dihydropyridinyl,





and

wherein * indicates the point of attachment to the group –L-G and the broken bond indicates the point of attachment to the amino group; and wherein X_1 is chosen from N and CR_7; X_2 is chosen from N and CR_7; and X_3 is chosen from N and CR_7; wherein no more than one of X_1, X_2, and X_3 is N and wherein R_7 is chosen from hydrogen, hydroxy, cyano, halo, optionally substituted lower alkyl, and optionally substituted lower alkoxy;

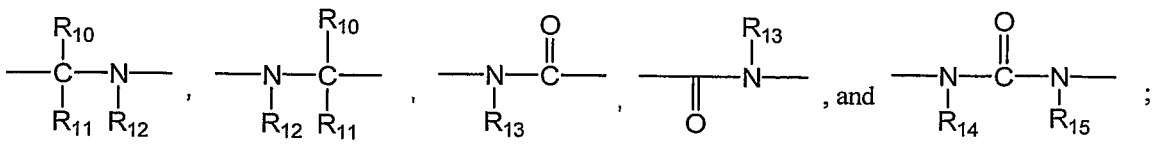
L is chosen from a covalent bond, optionally substituted C_1-C_4alkylene, -O-, -O-(optionally substituted C_1-C_4alkylene)-, -(C=O)-, -(optionally substituted C_1-C_4alkylene)(C=O)-, (SO)-, -(optionally substituted C_1-C_4alkylene)(SO)-; (SO_2)-, -(optionally substituted C_1-C_4alkylene)(SO_2)-; -(C=NR_9)-, and -(optionally substituted C_1-C_4alkylene)(C=NR_9)- wherein R_9 is chosen from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

G is chosen from hydrogen, halo, hydroxy, alkoxy, nitro, optionally substituted alkyl, -$NR_{16}R_{17}$, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl wherein R_{16} and R_{17} are independently chosen from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl; or when L is chosen from -(C=NR_9)- and -(optionally substituted C_1-C_4alkylene)(C=NR_9) then-R_9 and R_{16}, together with the nitrogen to which they are bound, form an optionally substituted 5- to 7-membered nitrogen containing heterocycloalkyl which optionally further includes one or two additional heteroatoms chosen from N, O, and S and R_{17} is chosen from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

T, V, and W are chosen from C and N and U is chosen from –CH and N, provided that at most one of T, U, V and W is N;

R_2, R_3, and R_4 are independently chosen from hydrogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, halo, and hydroxy, provided that at least one of R_2, R_3, and R_4 is not hydrogen when A is a covalent bond, G is -$NR_{16}R_{17}$ and L is not chosen from -(C=NR_9)- and -(optionally substituted C_1-C_4alkylene)(C=NR_9)-, and R_2, R_3, or R_4 is absent when the respective T, V, or W to which it is bound, is N;

Q is chosen from



;

wherein

R_{10} and R_{11} are independently chosen from hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

R_{12}, R_{13}, R_{14}, and R_{15} are each independently chosen from hydrogen,

C_1-C_6 alkyl,

C_1-C_6 haloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

A is chosen from a covalent bond and -(CH=CH)-;

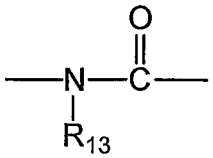
R_5 is chosen from optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl; and

R_6 is chosen from hydrogen, optionally substituted alkyl, cycloalkyl, and heterocycloalkyl.

[0089] In some embodiments, A is a covalent bond. In some embodiments, A

is -(CH=CH)-.

[0090] In some embodiments, R_{12}, R_{13}, R_{14}, and R_{15} are independently chosen from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and phenyl. In some embodiments, R_{13} is chosen from hydrogen and C_1-C_6 alkyl.

[0091] In some embodiments, Q is  wherein R_{13} is chosen from hydrogen and C_1-C_6 alkyl.

[0092] In some embodiments, R_5 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfanyl, sulfonyl, optionally substituted amino, lower alkoxy, lower alkyl substituted with one or more halo, lower alkoxy substituted with one or more halo, lower alkyl substituted with hydroxy, and heteroaryl,

pyridyl,

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

pyrimidinyl,

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

pyrazinyl,

substituted pyrazinyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

pyridazinyl,

substituted pyridazinyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

oxazol-2-yl,

substituted oxazol-2-yl l chosen from mono-, di-, and tri-substituted oxazol-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

2H-pyrazol-3-yl,

substituted 2H-pyrazol-3-yl chosen from mono-, di-, and tri-substituted 2H-pyrazol-3-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

[1,2,3]thiadiazol-4-yl,

substituted [1,2,3]thiadiazol-4-yl chosen from mono-, di-, and tri-substituted [1,2,3]thiadiazol-4-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

isoxazol-5-yl,

substituted isoxazol-5-yl chosen from mono-, di-, and tri-substituted isoxazol-5-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl,

substituted 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl chosen from mono-, di-, and tri-substituted 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

4,5,6,7-tetrahydrobenzofuran-2-yl,

substituted 4,5,6,7-tetrahydrobenzofuran-2-yl chosen from mono-, di-, and tri-substituted 4,5,6,7-tetrahydrobenzofuran-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

4,5,6,7-tetrahydro-1H-indol-2-yl,

substituted 4,5,6,7-tetrahydro-1H-indol-2-yl chosen from mono-, di-, and tri-substituted 4,5,6,7-tetrahydro-1H-indol-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl and wherein the amine nitrogen of the

indole ring is optionally substituted with an optionally substituted lower alkyl group,

1H-indol-2-yl,

substituted 1H-indol-2-yl chosen from mono-, di-, and tri-substituted 1H-indol-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl and wherein the amine nitrogen of the indole ring is optionally substituted with an optionally substituted lower alkyl group,

1H-indol-3-yl,

substituted 1H-indol-3-yl chosen from mono-, di-, and tri-substituted 1H-indol-3-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl and wherein the amine nitrogen of the indole ring is optionally substituted with an optionally substituted lower alkyl group,

benzofuran-2-yl,

substituted benzofuran-2-yl chosen from mono-, di-, and tri-substituted benzofuran-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

benzo[b]thiophen-2-yl,

substituted benzo[b]thiophen-2-yl chosen from mono-, di-, and tri-substituted benzo[b]thiophen-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl;

quinolin-3-yl, and

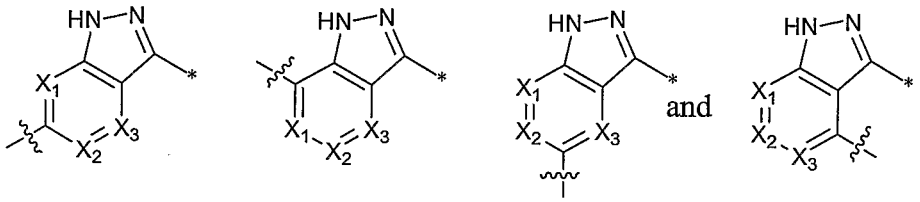
substituted quinolin-3-yl chosen from mono-, di-, and tri-substituted quinolin-3-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl.

[0093] In some embodiments, R_5 is chosen from phenyl and substituted phenyl wherein substituted phenyl is chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfanyl, sulfonyl, optionally substituted amino, lower alkoxy, lower alkyl substituted

with one or more halo, lower alkoxy substituted with one or more halo, lower alkyl substituted with hydroxy, and heteroaryl.

[0094] In some embodiments, R_5 is substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl. In some embodiments, R_5 is 4-lower alkyl-phenyl-. In some embodiments, R_5 is 4-*tert*-butyl-phenyl.

[0095] In some embodiments, R_1 is chosen from ortho-phenylene, meta-phenylene, para-phenylene, ortho-pyridylidene, meta-pyridylidene, para-pyridylidene,



In some embodiments, R_1 is chosen from ortho-phenylene, meta-phenylene, para-phenylene, ortho-pyridylidene, meta-pyridylidene, and para-pyridylidene. In some embodiments, R_1 is chosen from para-phenylene and meta-phenylene. In some embodiments, R_1 is para-phenylene.

[0096] In some embodiments, L is chosen from a covalent bond, -(C=O)-, -CH_2-, -SO_2-, -CH_2(C=O)-, -$CH(CH_3)$(C=O)-, -CH_2CH_2(C=O)-, -(C=NR_9)-, and -(optionally substituted C_1-C_4alkylene)(C=NR_9)-. In some embodiments, L is chosen from -(C=O)-, -CH_2-, -SO_2-, -CH_2(C=O)-, and -$CH(CH_3)$(C=O)-. In some embodiments, L is -(C=O)-.

[0097] In some embodiments, G is chosen from

hydrogen,

hydroxy,

-$NR_{16}R_{17}$,

optionally substituted heterocycloalkyl,

optionally substituted 5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl,

lower alkoxy, and

1H-tetrazol-5-yl.

[0098] In some embodiments, G is chosen from

hydrogen,

hydroxy,

N-methylethanolamino,

optionally substituted 4,5-dihydro-1H-imidazol-2-yl;

optionally substituted morpholin-4-yl,

optionally substituted piperazin-1-yl, and

optionally substituted homopiperazin1-yl.

[0099] In some embodiments, G is chosen from

hydrogen,

morpholin-4-yl,

4-acyl-piperazin-1-yl,

4-lower alkyl-piperazin-1-yl,

3-oxo-piperazin-1-yl,

homopiperazin-1-yl, and

4-lower alkyl-homopiperazin-1-yl.

[00100] In certain embodiments, G is chosen from $-NR_{16}R_{17}$, and optionally substituted heterocycloalkyl. In certain embodiments, G is chosen from optionally substituted morpholin-4-yl and optionally substituted piperazin-1-yl. In certain embodiments, G is morpholin-4-yl.

[00101] In some embodiments, L is chosen from $-(C=NR_9)-$, and -(optionally substituted C_1-C_4alkylene)$(C=NR_9)-$ and G is $-NR_{16}R_{17}$.

[00102] In certain embodiments, R_{16} and R_{17} are independently chosen from hydrogen and optionally substituted alkyl. In certaine mbodiments, when L is chosen from $-(C=NR_9)-$ and -(optionally substituted C_1-C_4alkylene)$(C=NR_9)$ then-R_9 and R_{16}, together with the nitrogen to which they are bound, form an optionally substituted 5- to 7-membered nitrogen containing heterocycloalkyl which optionally further includes one or two additional heteroatoms chosen from N, O, and S and R_{17} is chosen from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

[00103] In some embodiments, R_9 is chosen from hydrogen and lower alkyl. In some embodiments, R_9 is chosen from hydrogen and methyl.

[00104] In some embodiments, R_6 is hydrogen.

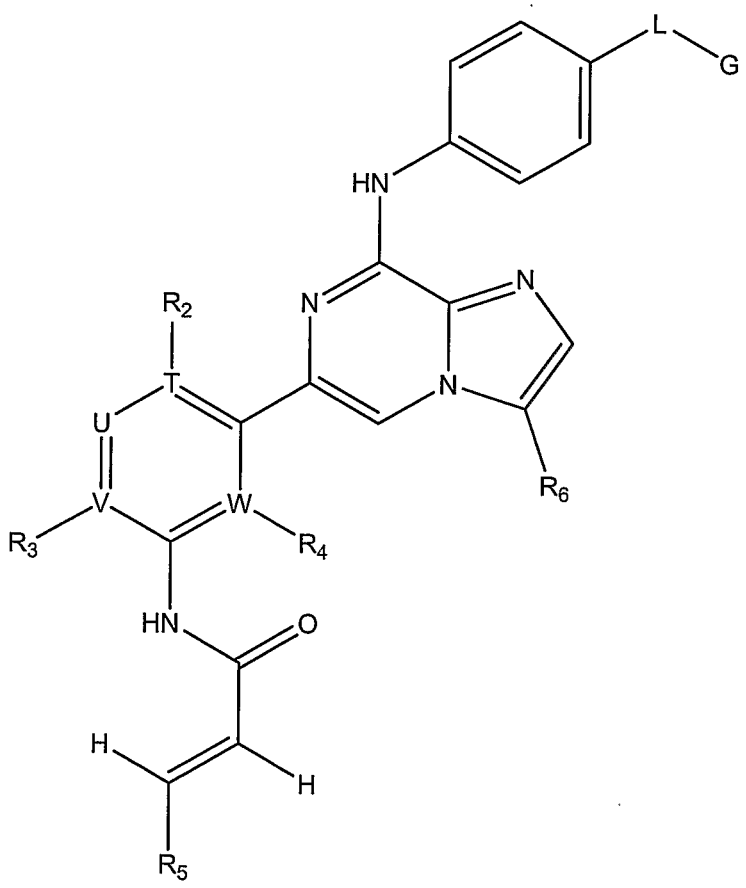
[00105] In some embodiments, R_2 is chosen from methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, and fluoro. In some embodiments, R_2 is methyl. In some embodiments, R_3 and R_4 are hydrogen.

[00106] In some embodiments, R_3 is chosen from methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, and fluoro. In some embodiments, R_3 is methyl. In some embodiments, R_2 and R_4 are hydrogen.

[00107] In some embodiments, R_4 is chosen from methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, and fluoro. In some embodiments, R_4 is methyl. In some embodiments, R_2 and R_3 are hydrogen.

[00108] In some embodiments, T, V, and W are C and U is -CH.

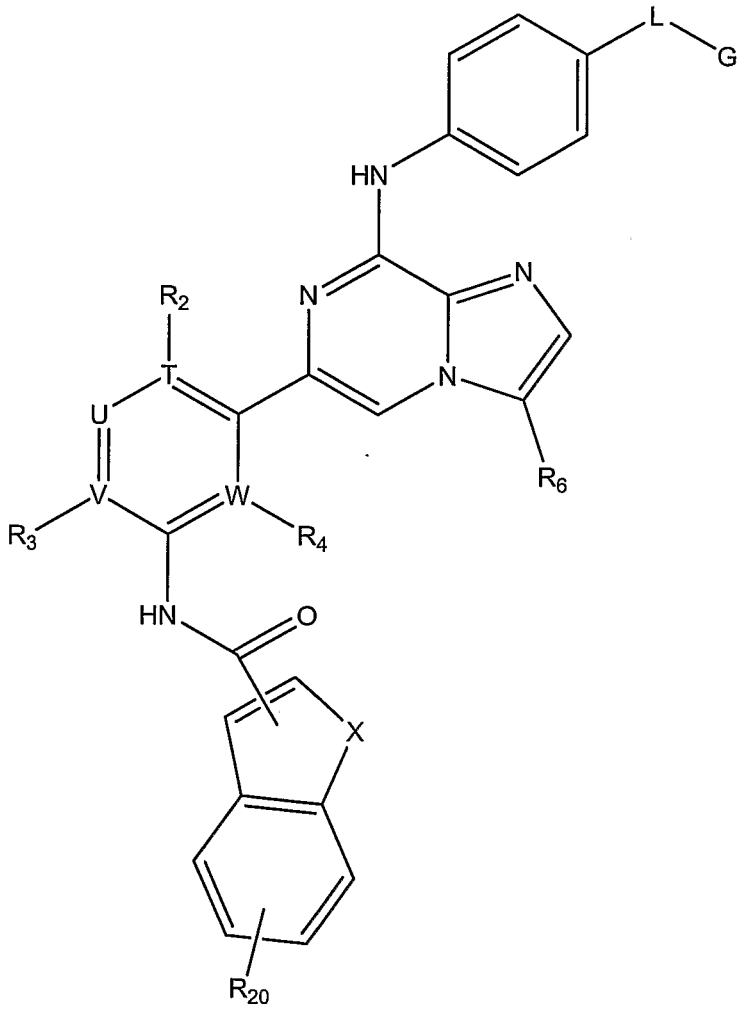
[00109] Also provided is at least one chemical entity chosen from compounds of Formula 2:



(Formula 2).

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein R_5, R_2, R_3, R_4, T, U, V, W, R_6, L, and G are as described for compounds of Formula 1.

[00110] Also provided is at least one chemical entity chosen from compounds of Formula 3:



(Formula 3)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein R_2, R_3, R_4, T, U, V, W, R_6, L, and G are as described for compounds of Formula 1; and wherein

X is chosen from O, S, NR_{18}, -CH=N-, and –N=CH-;

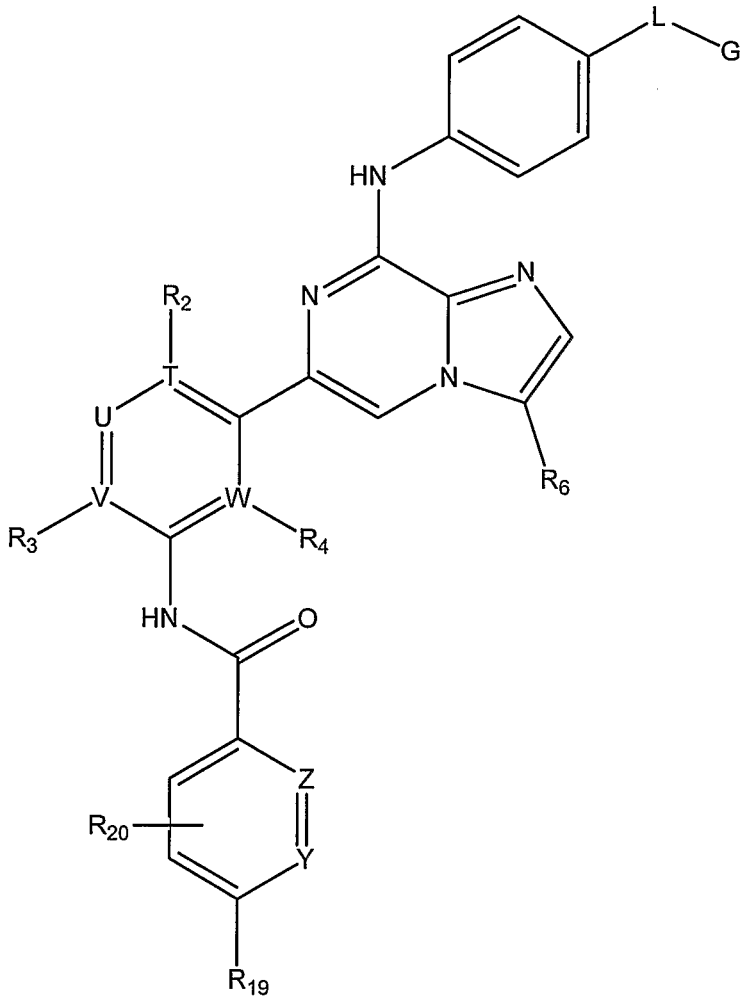
R_{18} is chosen from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

[00111] In some embodiments, X is chosen from O, NR_{18}, -CH=N-, and –N=CH. In some embodiments, X is chosen from O and NR_{18}.

[00112] In some embodiments, R_{20} is absent.

[00113] Also provided is at least one chemical entity chosen from compounds of Formula 4:



(Formula 4)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein R_2, R_3, R_4, T, U, V, W, R_6, L, and G are as described for compounds of Formula 1; and wherein

Y and Z are independently chosen from CH and N;

R_{19} is chosen from hydrogen, hydroxy, lower alkyl, sulfonyl, optionally substituted amino, lower alkoxy, lower alkyl substituted with one or more halo, lower alkoxy substituted with one or more halo, lower alkyl substituted with hydroxy, and heteroaryl; and

R_{20} is chosen from hydrogen, lower alkyl, halo, lower alkoxy, and hydroxy.

[00114] In some embodiments, Y and Z are CH.

[00115] In some embodiments, R_{19} is chosen from hydrogen and lower alkyl. In some embodiments, R_{19} is chosen from hydrogen, *iso*-propyl, and *tert*-butyl. In some embodiments, R_{19} is *tert*-butyl.

[00116] In some embodiments, R_{20} is absent.

[00117] In some embodiments, at least one chemical entity is chosen from 4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(5-{8-[4-(4-Acetyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-4-tert-butyl-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(N-methyl-hydroxyethyl-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(NNdimethyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(N-methyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(amide)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(5-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-4-tert-butyl-benzamide;

4-tert-Butyl-N-(2-fluoro-5-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-{2-methyl-5-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(3-oxo-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(5-{8-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-4-tert-butyl-benzamide;

4-tert-Butyl-N-(5-{8-[4-(5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

(4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-{5-[8-(4-{[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide;

4-tert-Butyl-N-[2-methyl-5-(8-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

(3-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid;

4-tert-Butyl-N-(2-methyl-5-{8-[3-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-[2-methyl-5-(8-{3-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

4-tert-Butyl-N-{5-[8-(3-dimethylcarbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide;

2-(3-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-propionic acid;

4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methoxy-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-{6-[3-(4-tert-Butyl-benzoylamino)-4-fluoro-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylhydroxyethyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylethyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-{6-[5-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-tert-Butyl-N-(4-methyl-3-{8-[4-(Nmethylhydroxyethyl-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester;

4-tert-Butyl-N-(2-fluoro-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

6-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

[1,2,3]Thiadiazole-4-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

Isoxazole-5-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

Pyridine-2-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

6-tert-Butyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-nicotinamide;

4-tert-Butyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-Isopropyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

6-Hydroxy-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

5-tert-Butyl-oxazole-2-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-methylsulfanyl-benzamide;

4-(1H-Imidazol-2-yl)-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(1H-tetrazol-5-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-Methanesulfonyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

2-Hydroxy-6-methyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(1H-tetrazol-5-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

2,5-Dimethyl-2H-pyrazole-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

4-tert-Butyl-N-{2-methyl-5-[8-(4-sulfamoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

4-tert-Butyl-N-{3-[8-(4-carbamimidoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N'-dimethyl-carbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(imino-morpholin-4-yl-methyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N-dimethyl-carbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(2-imino-2-morpholin-4-yl-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylcarbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N'-dimethyl-carbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(4,5-dihydro-1H-imidazol-2-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

4-tert-Butyl-N-{3-[8-(4-carbamimidoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide;

4-tert-Butyl-N-{3-[8-(4-carbamimidoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylcarbamimidoylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N'-dimethyl-carbamimidoylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N-dimethyl-carbamimidoylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

Benzofuran-2-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-3-pyridin-3-yl-acrylamide;

Quinoline-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

1-Methyl-1H-indole-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

1H-Indole-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide,

6-tert-Butyl-N-(2-methyl-3-{8-[4-(1-oxo-1l4-thiomorpholin-4-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

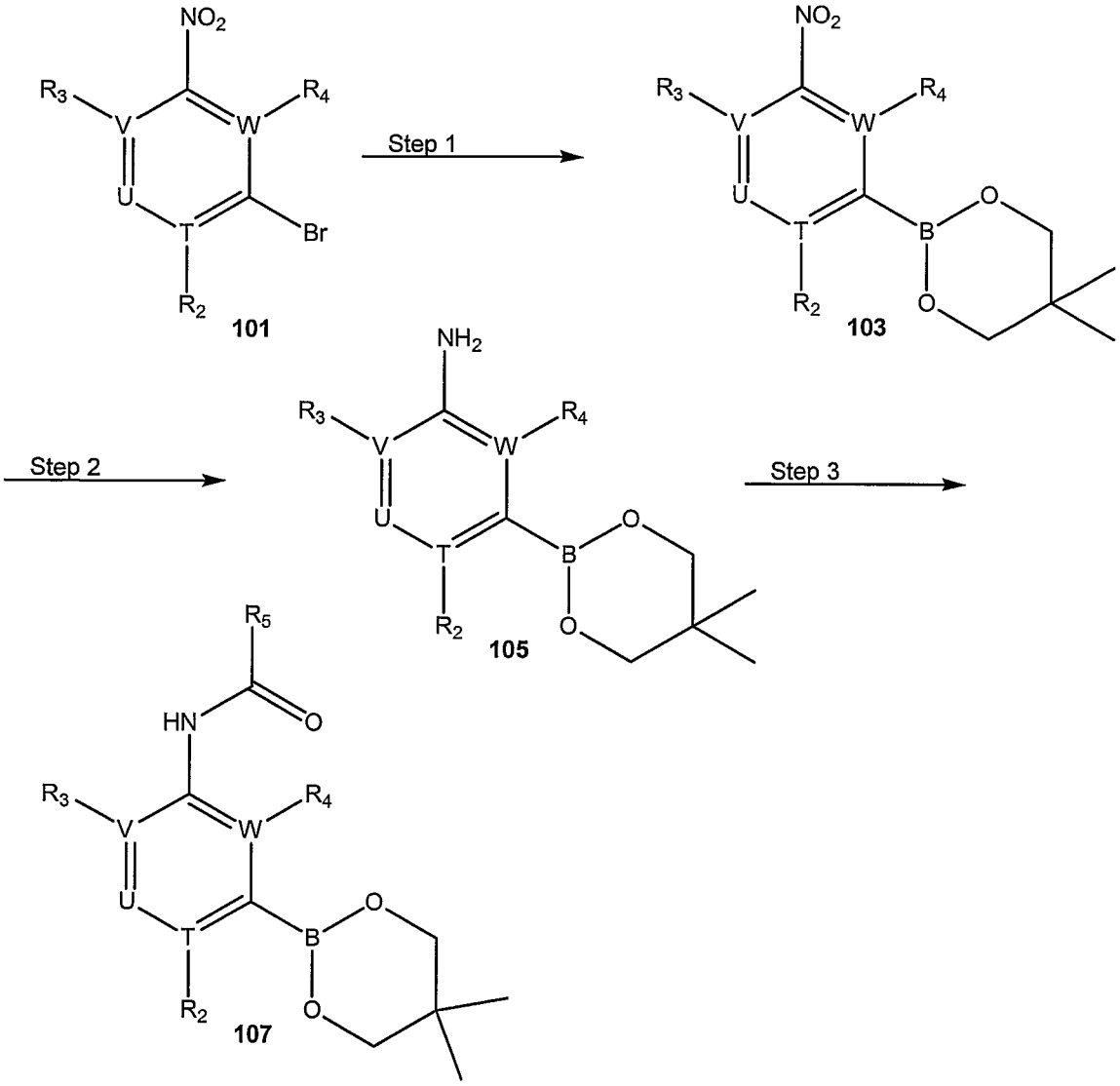
N-{3-[8-(3-Amino-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-4-tert-butyl-benzamide; and

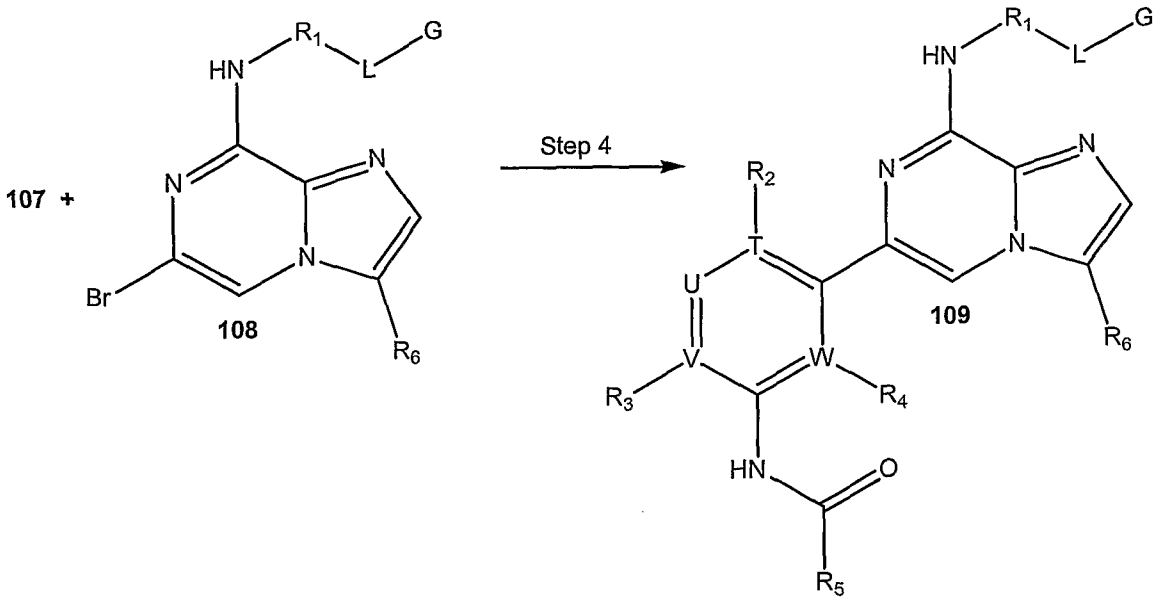
Tetrahydro-furan-2-carboxylic acid (3-{6-[3-(4-tert-butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-amide,

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[00118] Methods for obtaining the novel compounds described herein will be apparent to those of ordinary skill in the art, suitable procedures being described, for example, in the reaction schemes and examples below, and in the references cited herein. See, also, PCT/US04/18227; and PCT/US04/025884.

Reaction Scheme 1


NO2
R3
R4
V
W
U
T
Br
R2
101
Step 1
NO2
R3
R4
V
W
U
T
B
O
O
R2
103
Step 2
NH2
R3
R4
V
W
U
T
B
O
O
R2
105
Step 3
R5
HN
O
R3
R4
V
W
U
T
B
O
O
R2
107



[00119] Referring to Reaction Scheme 1, Step 1, a mixture of a compound of Formula 101; an excess (such as about 1.2 equivalents) of bis(neopentyl glycolato)diboron; and about 0.3 equivalent of [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium, 1:1 complex with dichloromethane; and a base such as potassium acetate in an inert solvent such as dioxane is heated at reflux for about 3h. The product, a compound of Formula 103, is isolated and optionally purified.

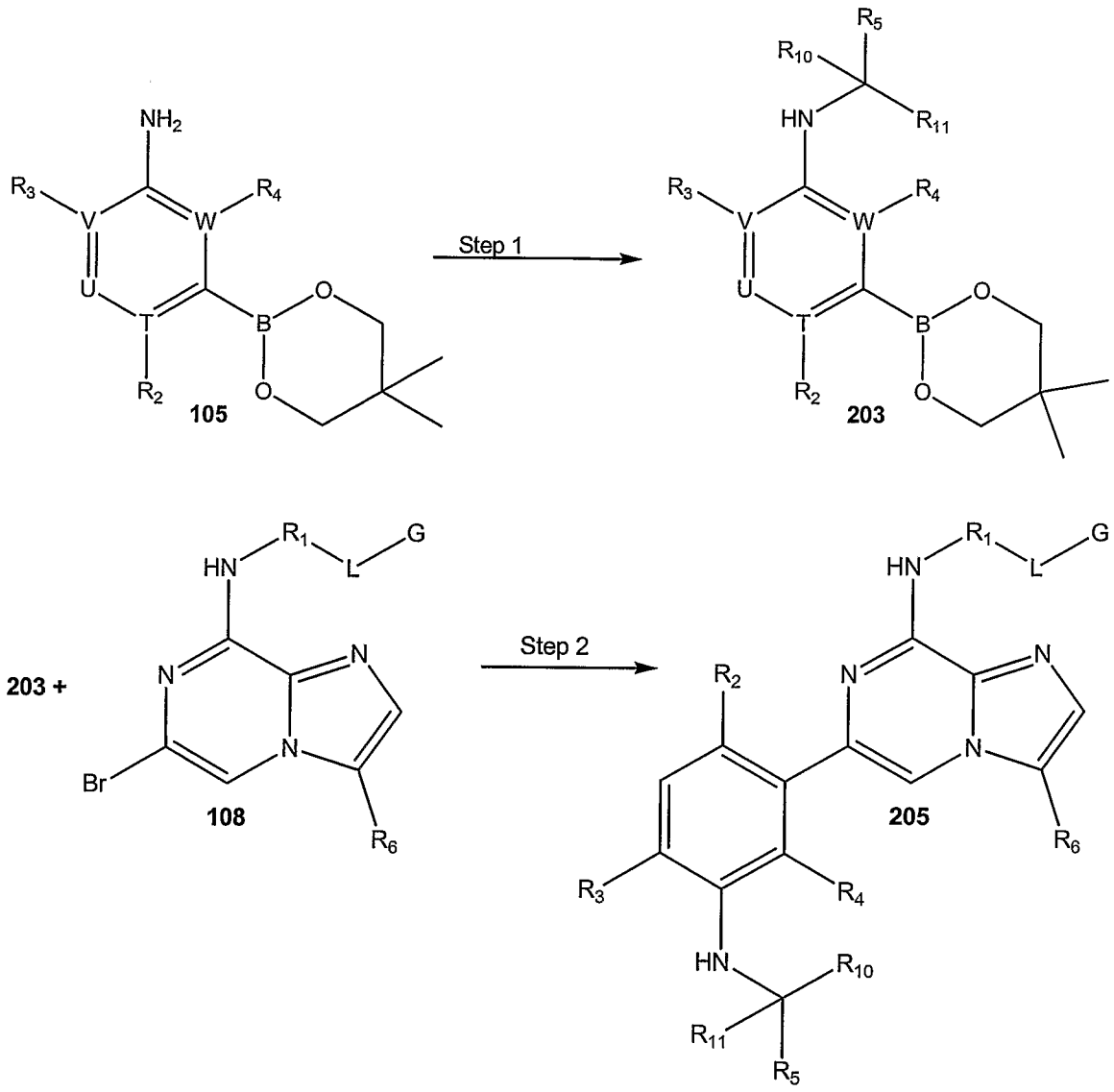
[00120] Referring to Reaction Scheme 1, Step 2, a mixture of a compound of Formula 103 and 10% palladium-on-carbon in an inert solvent such as ethyl acetate methanol is treated with 40psi of hydrogen for about 2h at room temperature. The product, a compound of Formula 105, is isolated and optionally purified.

[00121] Referring to Reaction Scheme 1, Step 3, a solution of a compound of Formula 105 and a base, such as triethylamine in an inert solvent such as THF is treated dropwise with about an equivalent of an acid chloride of the formula $R_5C(O)Cl$ and the mixture is stirred at room temperature for about 15 min. The product, a compound of Formula 107, is isolated and optionally purified.

[00122] Referring to Reaction Scheme 1, Step 4, a mixture of a compound of Formula 108, an excess (such as about 1.2 equivalents) of a compound of Formula 107, and a catalyst such as palladium tetrakis(triphenylphosphine) in aqueous base (such as 1N aqueous sodium carbonate and an inert solvent such as DME is heated at about 95 °C in a sealed tube for about 16h. The product, a compound of formula 109,

is isolated and purified.

Reaction Scheme 2

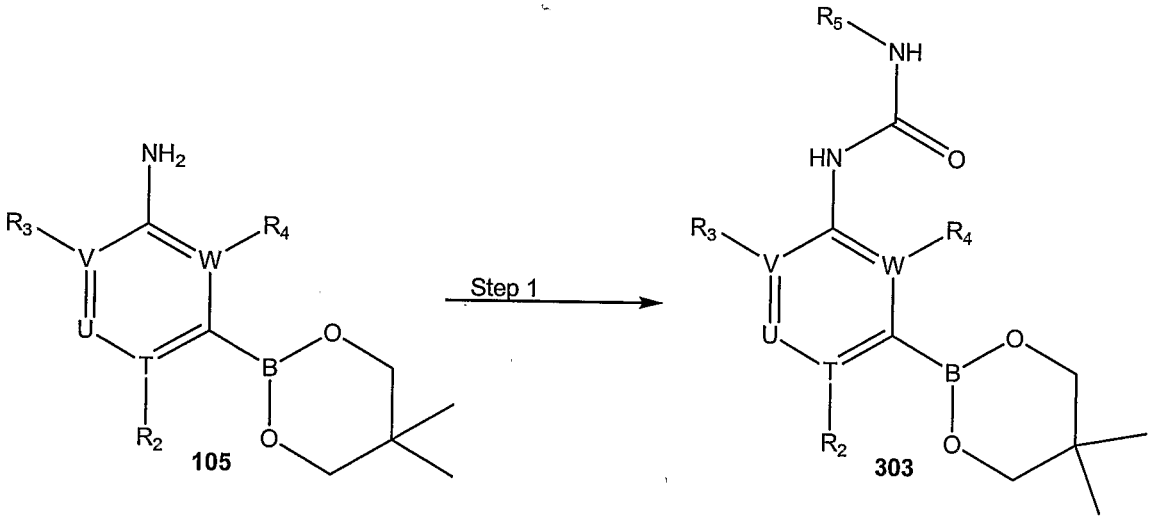


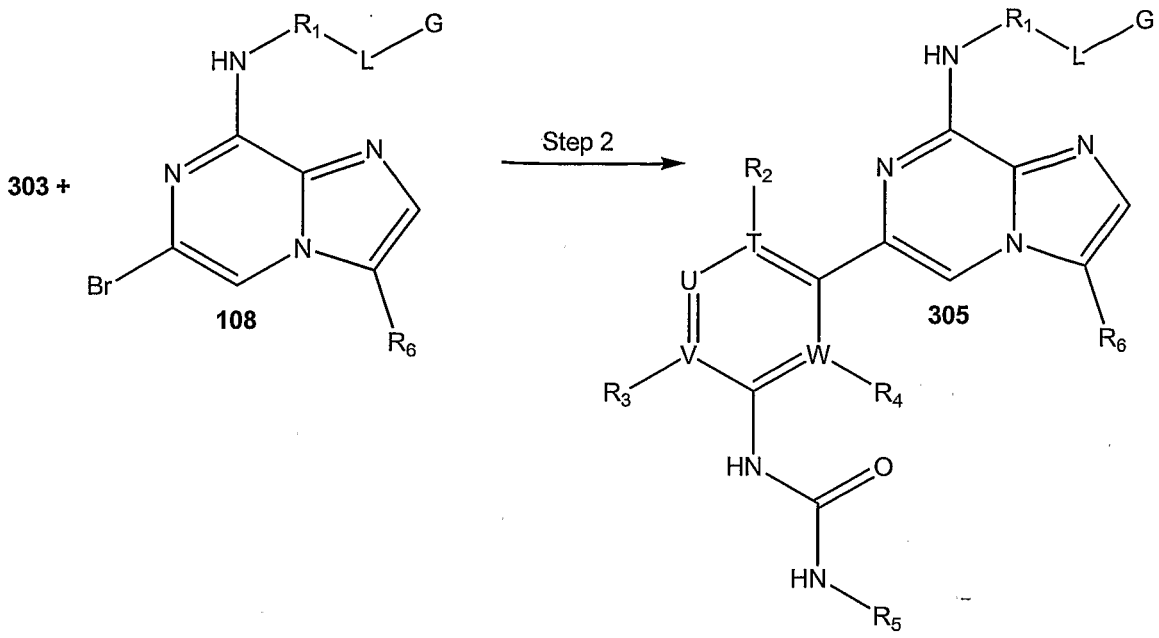
[00123] Referring to Reaction Scheme 2 to a solution of a compound of Formula 105 and an amine base such as diisopropylethylamine in a polar, aprotic solvent such as dichloromethane is added a compound having the formula X-$C(R_{10})(R_{11})$-R_5 where R_5 is as described above and X is a leaving group (such as a halide). The resulting solution is stirred under nitrogen at room temperature or with heat for several hours. The product, a compound of Formula 203, is isolated and purified.

[00124] Alternatively, to a solution of a compound of Formula 105 in an inert solvent (such as toluene) is added an excess (such as about 1.2 equivalents) of an aldehyde of formula X-C(O)-R_5 where R_5 is as described above, and an excess of a reducing agent such as sodium triacetoxyborohydride. The resulting mixture is stirred under nitrogen with heat (such as at about 65°C) for several hours. The product, a compound of Formula 203, is isolated and purified.

[00125] Referring to Reaction Scheme 2 Step 2, a mixture of a compound of Formula 108, an excess (such as about 1.2 equivalents) of a compound of Formula 203, and a catalyst such as palladium tetrakis(triphenylphosphine) in aqueous base (such as 1N aqueous sodium carbonate and an inert solvent such as DME is heated at about 95 °C in a sealed tube for about 16h. The product, a compound of Formula 205, is isolated and purified.

Reaction Scheme 3

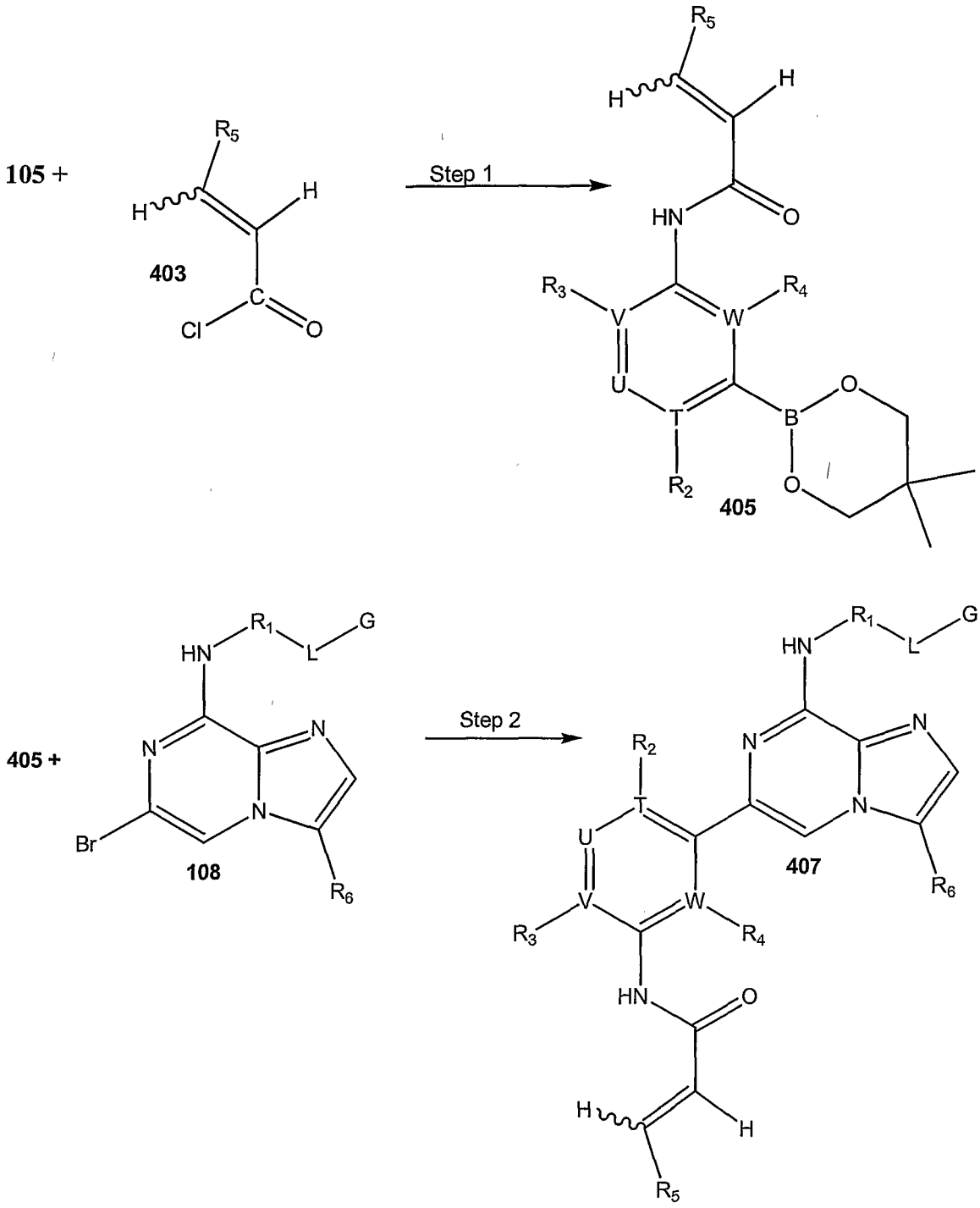




[00126] Referring to Reaction Scheme 3, Step 1, a compound of Formula 105 is treated with a slight excess of an isocyanate R_5-N=C=O in the presence of a base, such as triethylamine, in a nonpolar, aprotic solvent, such as dichloromethane. The product, a compound of Formula 303, is isolated and purified.

[00127] Referring to Reaction Scheme 3, Step 2, a mixture of a compound of Formula 108, an excess (such as about 1.2 equivalents) of a compound of Formula 303, and a catalyst such as palladium tetrakis(triphenylphosphine) in aqueous base (such as 1N aqueous sodium carbonate and an inert solvent such as DME is heated at about 95 °C in a sealed tube for about 16h. The product, a compound of Formula 305, is isolated and purified.

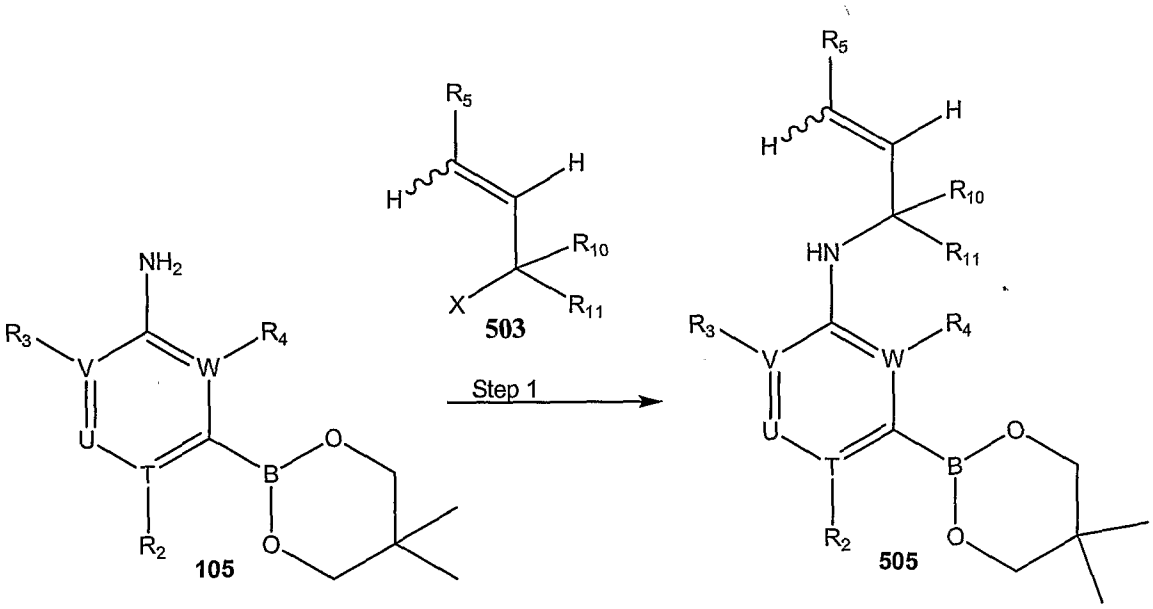
Reaction Scheme 4

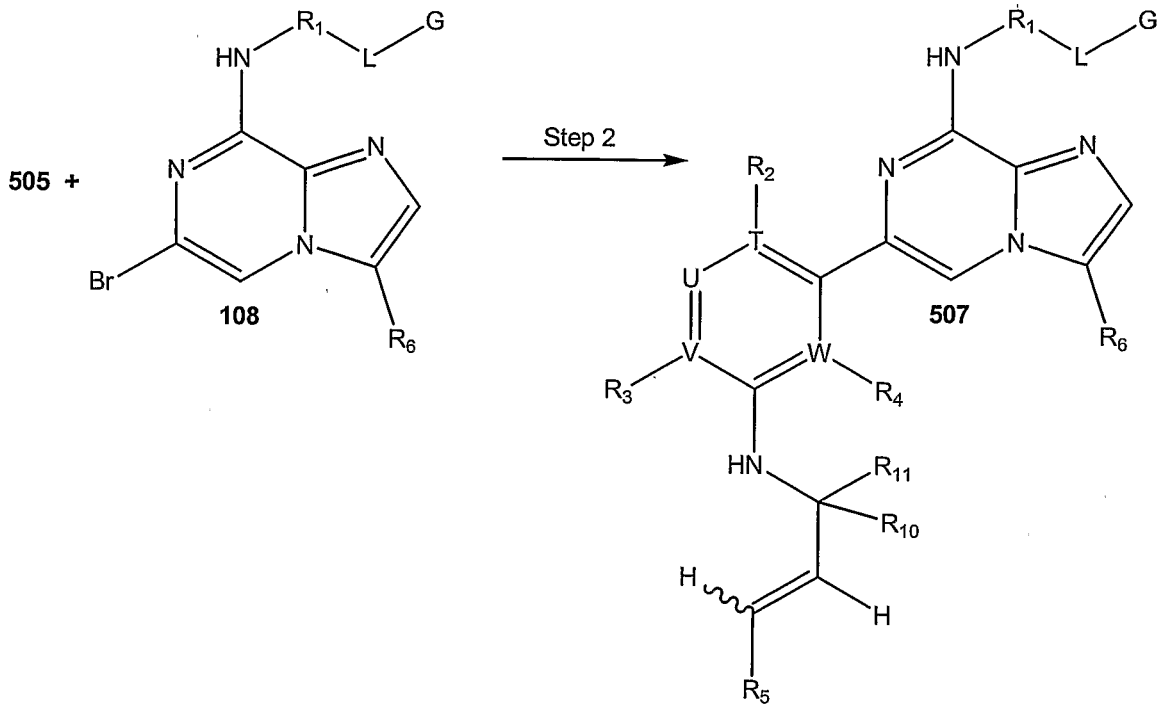


[00128] Referring to Reaction Scheme 4, Step 1, a solution of a compound of Formula 105 and a base, such as triethylamine in an inert solvent such as THF is treated dropwise with about an equivalent of an acid chloride of the formula 403 and the mixture is stirred at room temperature for about 15 min. The product, a compound of Formula 405, is isolated and optionally purified.

[00129] Referring to Reaction Scheme 4, Step 2, a mixture of a compound of Formula 108, an excess (such as about 1.2 equivalents) of a compound of Formula 405, and a catalyst such as palladium tetrakis(triphenylphosphine) in aqueous base (such as 1N aqueous sodium carbonate and an inert solvent such as DME is heated at about 95 °C in a sealed tube for about 16h. The product, a compound of formula 407, is isolated and purified.

Reaction Scheme 5



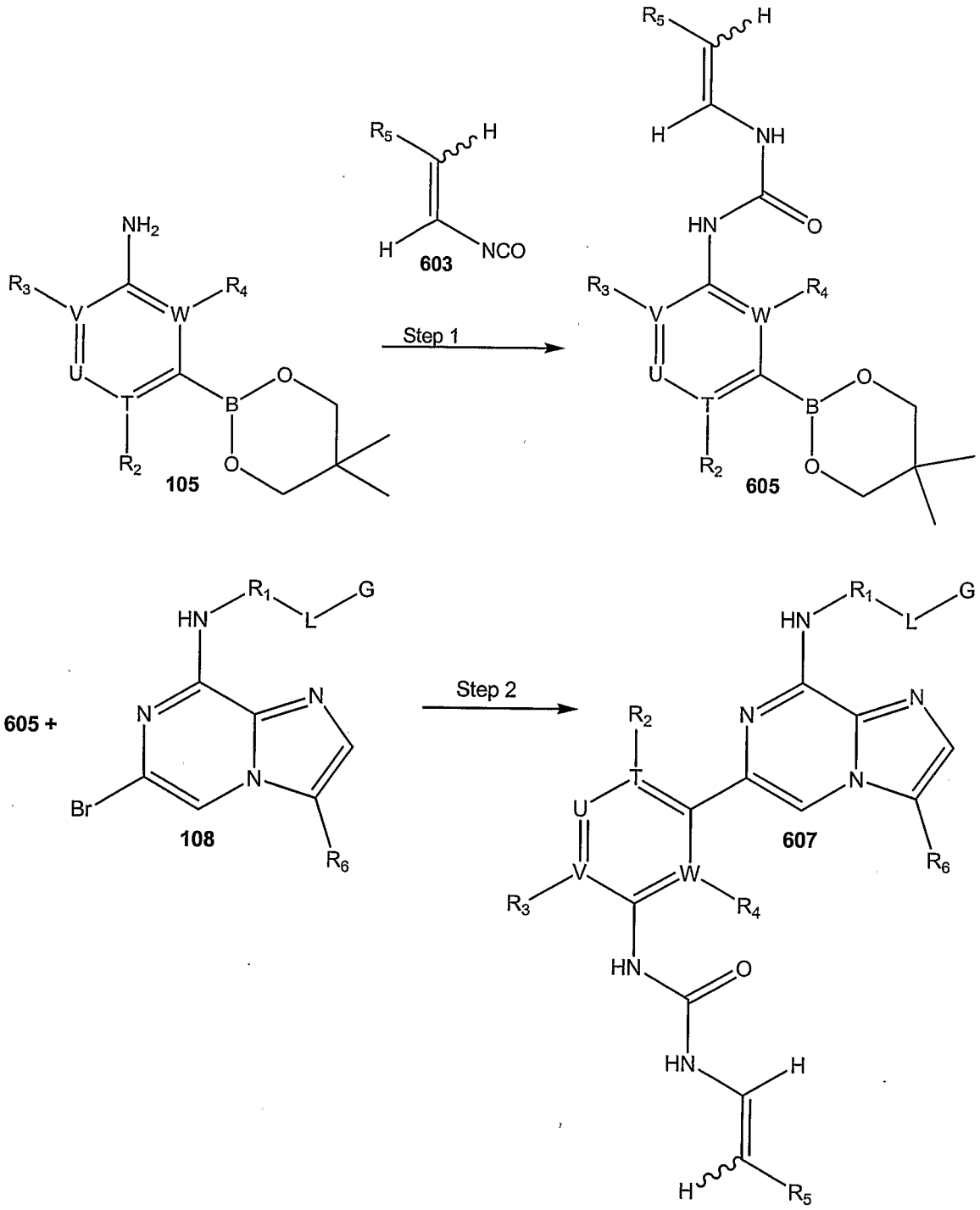


[00130] Referring to Reaction Scheme 5 to a solution of a compound of Formula 105 and an amine base such as diisopropylethylamine in a polar, aprotic solvent such as dichloromethane is added a compound of Formula 503 where X is a leaving group (such as a halide). The resulting solution is stirred under nitrogen at room temperature or with heat for several hours. The product, a compound of Formula 505, is isolated and purified.

[00131] Alternatively, to a solution of a compound of Formula 105 in an inert solvent (such as toluene) is added an excess (such as about 1.2 equivalents) of an aldehyde of formula H-C(O)-C(H)=CH(R_5) is as described above, and an excess of a reducing agent such as sodium triacetoxyborohydride. The resulting mixture is stirred under nitrogen with heat (such as at about 65°C) for several hours. The product, a compound of Formula 505, is isolated and purified.

[00132] Referring to Reaction Scheme 5 Step 2, a mixture of a compound of Formula 108, an excess (such as about 1.2 equivalents) of a compound of Formula 505, and a catalyst such as palladium tetrakis(triphenylphosphine) in aqueous base (such as 1N aqueous sodium carbonate and an inert solvent such as DME is heated at about 95 °C in a sealed tube for about 16h. The product, a compound of Formula 507, is isolated and purified.

Reaction Scheme 6



[00133] Referring to Reaction Scheme 6, Step 1, a compound of Formula 105 is treated with a slight excess of an isocyanate of Formula 603 in the presence of a base, such as triethylamine, in a nonpolar, aprotic solvent, such as dichloromethane.

The product, a compound of Formula 605, is isolated and purified.

[00134] Referring to Reaction Scheme 6, Step 2, a mixture of a compound of Formula 108, an excess (such as about 1.2 equivalents) of a compound of Formula 605, and a catalyst such as palladium tetrakis(triphenylphosphine) in aqueous base (such as 1N aqueous sodium carbonate and an inert solvent such as DME is heated at about 95 °C in a sealed tube for about 16h. The product, a compound of Formula 607, is isolated and purified.

[00135] In some embodiments, a compound of Formula 109, 205, 305, 407, 507, or 607 is further transformed to yield other compounds of Formula 1. For example, a compound of Formula 109 wherein G is alkoxy can be converted to a compound of Formula 1 wherein G is hydroxy by treatment with aqueous base. Likewise, a compound of Formula 109 wherein G is hydroxy can be converted to a compound of Formula 1 wherein G is optionally substituted amino by treatment with the appropriate amine, optionally, in the presence of a catalyst. Other transformations, for example, reductions, alkylations, acylations, and the like, are well known and within the skill of those in the art.

[00136] In some embodiments, the chemical entities described herein are administered as a pharmaceutical composition or formulation. Accordingly, the invention provides pharmaceutical formulations comprising at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients.

[00137] Pharmaceutically acceptable vehicles must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal being treated. The vehicle can be inert or it can possess pharmaceutical benefits. The amount of vehicle employed in conjunction with the chemical entity is sufficient to provide a practical quantity of material for administration per unit dose of the chemical entity.

[00138] Exemplary pharmaceutically acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose,

ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; synthetic oils; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, and corn oil; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; phosphate buffer solutions; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[00139] Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the chemical entity of the present invention.

[00140] Effective concentrations of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, are mixed with a suitable pharmaceutical acceptable vehicle. In instances in which the chemical entity exhibits insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN, or dissolution in aqueous sodium bicarbonate.

[00141] Upon mixing or addition of the chemical entity described herein, the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the chemical entity in the chosen vehicle. The effective concentration sufficient for ameliorating the symptoms of the disease treated may be empirically determined.

[00142] Chemical entities described herein may be administered orally, topically, parenterally, intravenously, by intramuscular injection, by inhalation or spray, sublingually, transdermally, via buccal administration, rectally, as an ophthalmic solution, or by other means, in dosage unit formulations.

[00143] Dosage formulations suitable for oral use, include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions

intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents, such as sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide pharmaceutically elegant and palatable preparations. In some embodiments, oral formulations contain from 0.1 to 99% of at least one chemical entity described herein. In some embodiments, oral formulations contain at least 5% (weight %) of at least one chemical entity described herein. Some embodiments contain from 25% to 50% or from 5% to 75 % of at least one chemical entity described herein.

[00144] Orally administered compositions also include liquid solutions, emulsions, suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The pharmaceutically acceptable carriers suitable for preparation of such compositions are well known in the art. Oral formulations may contain preservatives, flavoring agents, sweetening agents, such as sucrose or saccharin, taste-masking agents, and coloring agents.

[00145] Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent.

[00146] Chemical entities described herein can be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, for example. Moreover, formulations containing these chemical entities can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can contain conventional additives, such as suspending agents (e.g., sorbitol syrup, methyl cellulose, glucose/sugar, syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats), emulsifying agents (e.g., lecithin, sorbitan monsoleate, or acacia), non-aqueous vehicles, which can include edible oils (e.g., almond oil, fractionated coconut oil, silyl esters, propylene glycol and ethyl alcohol), and preservatives (e.g., methyl or propyl p-hydroxybenzoate and sorbic acid).

[00147] For a suspension, typical suspending agents include methylcellulose,

sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate.

[00148] Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents; may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol substitute, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan substitute. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n- propyl p-hydroxybenzoate.

[00149] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example peanut oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[00150] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or peanut oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate.

[00151] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

[00152] Tablets typically comprise conventional pharmaceutically acceptable adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, can be useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components often depends on secondary considerations like taste, cost, and shelf stability.

[00153] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the chemical entity is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methylcellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[00154] Formulations for oral use may 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.

[00155] Pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents

that have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable vehicle, for example as a solution in 1,3-butanediol. Among the acceptable vehicles that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be useful in the preparation of injectables.

[00156] Chemical entities described herein may be administered parenterally in a sterile medium. Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intrathecal injection or infusion techniques. Chemical entities described herein, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle. In many compositions for parenteral administration the carrier comprises at least 90% by weight of the total composition. In some embodiments, the carrier for parenteral administration is chosen from propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil.

[00157] Chemical entites described herein may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[00158] Chemical entities described herein may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye. Topical compositions may be in any form including, for example, solutions, creams, ointments, gels, lotions, milks, cleansers, moisturizers, sprays, skin patches, and the like.

[00159] Such solutions may be formulated as 0.01% -10% isotonic solutions, pH 5-7, with appropriate salts. Chemical entities described herein may also be

formulated for transdermal administration as a transdermal patch.

[00160] Topical compositions comprising at least one chemical entity described herein can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

[00161] Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

[00162] Representative emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, iso-propyl isostearate, stearic acid, iso-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, iso-propyl myristate, iso-propyl palmitate, iso-propyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, iso-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, iso-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

[00163] Chemical entities described herein may also be topically administered in the form of liposome delivery systems, such as small unilamellar vesicles, large

unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

[00164] Other compositions useful for attaining systemic delivery of the chemical entity include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol, and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[00165] Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (e.g., dichlorodifluoromethane or trichlorofluoromethane).

[00166] The compositions of the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules that function in different ways to enhance or be independent of therapeutic effects of the chemical entities described herein. Particular classes of activity enhancers include skin penetration enhancers and absorption enhancers.

[00167] Pharmaceutical compositions of the invention may also contain additional active agents that can be chosen from a wide variety of molecules, which can function in different ways to enhance the therapeutic effects of at least one chemical entity described herein. These optional other active agents, when present, are typically employed in the compositions of the invention at a level ranging from 0.01% to 15%. Some embodiments contain from 0.1% to 10% by weight of the composition. Other embodiments contain from 0.5% to 5% by weight of the composition.

[00168] The invention includes packaged pharmaceutical formulations. Such packaged formulations include a pharmaceutical composition comprising at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, and instructions for using the composition to treat a mammal (typically a human patient). In some embodiments, the instructions are for using the

pharmaceutical composition to treat a patient suffering from a disease responsive to inhibition of Btk activity and/ or inhibition of B-cell proliferation. The invention can include providing prescribing information; for example, to a patient or health care provider, or as a label in a packaged pharmaceutical formulation. Prescribing information may include for example efficacy, dosage and administration, contraindication and adverse reaction information pertaining to the pharmaceutical formulation.

[00169] In all of the foregoing the chemical entities can be administered alone, as mixtures, or in combination with other active agents.

[00170] Accordingly, the invention includes a method of treating a mammal, for example, a human, having a disease responsive to inhibition of Btk activity, comprising administrating to the mammal having such a disease, an effective amount of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[00171] To the extent that Btk is implicated in any of the following, alleviation of the disease, disease symptoms, preventative, and prophylactic treatment is within the scope of this invention. In some embodies, the chemical entities described herein may also inhibit other kinases, such that alleviation of disease, disease symptoms, preventative, and prophylactic treatment of conditions associated with these kinases is also within the scope of this invention.

[00172] Methods of treatment also include inhibiting Btk activity and/ or inhibiting B-cell proliferation, by inhibiting ATP binding or hydrolysis by Btk or by some other mechanism, *in vivo*, in a patient suffering from a disease responsive to inhibition of Btk activity, by administering an effective concentration of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, to inhibit Btk activity *in vitro*. An effective concentration may be ascertained experimentally, for example by assaying blood concentration of the chemical entity, or theoretically, by calculating bioavailability.

[00173] The invention includes a method of treating a patient having cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction, by

administering an effective amount of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[00174] In some embodiments, the condition responsive to inhibition of Btk activity and/ or B-cell proliferation is cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction.

[00175] In some embodiments, the conditions and diseases that can be affected using chemical entities described herein, include, but are not limited to:

_autoimmune and/or inflammatory diseases, including but not limited to psoriasis, allergy, Crohn's disease, irritable bowel syndrome, Sjogren's disease, tissue graft rejection, and hyperacute rejection of transplanted organs, asthma, systemic lupus erythematosus (and associated glomerulonephritis), dermatomyositis, multiple sclerosis, scleroderma, vasculitis (ANCA-associated and other vasculitides), autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), atherosclerosis, rheumatoid arthritis, chronic Idiopathic thrombocytopenic purpura (ITP), Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, septic shock, myasthenia gravis, and the like,

acute inflammatory reactions, including but not limited to skin sunburn, inflammatory pelvic disease, inflammatory bowel disease, urethritis, uvitis, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, and cholocystitis, and

cancer, including but not limited to, B-cell lymphoma, lymphoma (including Hodgkin's and non-Hodgkins lymphoma), hairy cell leukemia, multiple myeloma, chronic and acute myelogenous leukemia, and chronic and acute lymphocytic leukemia.

[00176] Btk is a known inhibitor of apoptosis in lymphoma B-cells. Defective apoptosis contributes to the pathogenesis and drug resistance of human leukemias and lymphomas. Thus, further provided is a method of promoting or inducing apoptosis in cells expressing Btk comprising contacting the cell with at least one chemical entity chosen from compounds of Formula 1 pharmaceutically acceptable salts, solvates,

crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[00177] The invention provides methods of treatment in which at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, is the only active agent given to a patient and also includes methods of treatment in which at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, is given to a patient in combination with one or more additional active agents.

[00178] Thus in one embodiment the invention provides a method of treating cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction, which comprises administering to a mammal in need thereof an effective amount of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, together with a second active agent, which can be useful for treating a cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction. For example the second agent may be an anti-inflammatory agent. Treatment with the second active agent may be prior to, concomitant with, or following treatment with at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof. In certain embodiments, at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, is combined with another active agent in a single dosage form. Suitable antitumor therapeutics that may be used in combination with at least one chemical entity described herein include, but are not limited to chemotherapeutic agents, for example mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, doxorubicin, or a combination comprising at least one of the foregoing chemotherapeutic agents. Radiotherapeutic antitumor agents may also be used, alone or in combination with chemotherapeutic agents.

[00179] Chemical entities described herein can be useful as chemosensitizing agents, and, thus, can be useful in combination with other chemotherapeutic drugs, in

particular, drugs that induce apoptosis.

[00180] A method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient undergoing chemotherapy a chemotherapeutic agent together with at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, in an amount sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent is also provided herein.

[00181] Examples of other chemotherapeutic drugs that can be used in combination with chemical entities described herein include topoisomerase I inhibitors (camptothesin or topotecan), topoisomerase II inhibitors (e.g. daunomycin and etoposide), alkylating agents (e.g. cyclophosphamide, melphalan and BCNU), tubulin directed agents (e.g. taxol and vinblastine), and biological agents (e.g. antibodies such as anti CD20 antibody, IDEC 8, immunotoxins, and cytokines).

[00182] Included herein are methods of treatment in which at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, is administered in combination with an anti-inflammatory agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX- 2 specific cyclooxgenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor receptor (TNF) receptors antagonists, immunosuppressants and methotrexate.

[00183] Examples of NSAIDs include, but are not limited to ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. Examples of NSAIDs also include COX-2 specific inhibitors (i.e., a compound that inhibits COX-2 with an IC_{50} that is at least 50-fold lower than the IC_{50} for COX-1) such as celecoxib, valdecoxib, lumiracoxib, etoricoxib and/or rofecoxib.

[00184] In a further embodiment, the anti-inflammatory agent is a salicylate. Salicylates include by are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

[00185] The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be chosen from cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone.

[00186] In additional embodiments the anti-inflammatory therapeutic agent is a gold compound such as gold sodium thiomalate or auranofin.

[00187] The invention also includes embodiments in which the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

[00188] Other embodiments of the invention pertain to combinations in which at least one anti-inflammatory compound is an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as entanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody.

[00189] Still other embodiments of the invention pertain to combinations in which at least one active agent is an immunosuppressant compound such as methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, or mycophenolate mofetil.

[00190] Dosage levels of the order, for example, of from 0.1 mg to 140 mg per kilogram of body weight per day can be useful in the treatment of the above-indicated conditions (0.5 mg to 7 g per patient per day). The amount of active ingredient that may be combined with the vehicle to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain from 1 mg to 500 mg of an active ingredient. Frequency of dosage may also vary depending on the compound used and the particular disease treated. In some embodiments, for example, for the treatment of autoimmune and/or inflammatory, a dosage regimen of 4 times daily or less is used. In some embodiments, a dosage regimen of 1 or 2 times daily is used. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the patient undergoing therapy.

[00191] A labeled form of a compound of the invention can be used as a diagnostic for identifying and/or obtaining compounds that have the function of modulating an activity of a kinase as described herein. The compounds of the invention may additionally be used for validating, optimizing, and standardizing bioassays.

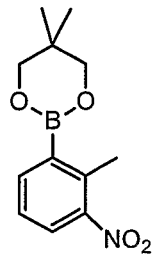
[00192] By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g., radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, etc. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

[00193] The invention is further illustrated by the following non-limiting examples.

Example 1

Synthesis of 4-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide

STEP 1: **2-(2-Methyl-3-nitrophenyl)-5,5-dimethyl[1,3,2]dioxaborinane**

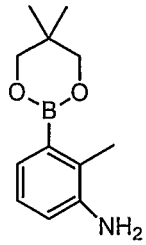


[00194] A mixture of 2-bromo-6-nitrotoluene (3.2g; 14.8mmol), bis(neopentyl glycolato)diboron (4g; 17.7mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichlropalladium, 1:1 complex with dichloromethane (362mg; 0.44mmol), potassium acetate (7.3g; 73.8mmol), and dioxane (75mL) is heated at reflux for 3h.

[00195] The mixture is then cooled to room temperature, treated with water

(100mL), and extracted with ethyl acetate (3 x 80mL). The extracts are washed with water (2 x 50mL) and brine (1 x 50mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified by flash chromatography over silica gel (elution with hexane/EtOAc 95/5 – 6/1, gradient) to afford 2-(2-methyl-3-nitrophenyl)-5,5-dimethyl[1,3,2]dioxaborinane as a white solid (3.3g)

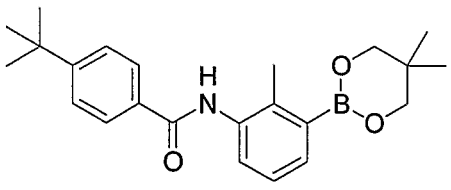
STEP 2: 3-(5,5-Dimethyl[1,3,2]dioxaborinan-2-yl)-2-methylaniline



[00196] A mixture of 2-(2-methyl-3-nitrophenyl)-5,5-dimethyl[1,3,2]dioxaborinan (6.7g; 27.7mmol), 10% palladium-on-carbon (670mg), ethyl acetate (75mL) and methanol (75mL) is treated with 40psi of hydrogen for 2h at room temperature.

[00197] The mixture is filtered through celite, washing with DCM (2 x 100mL), and the filtrate is concentrated in vacuo to afford 3-(5,5-dimethyl[1,3,2]dioxaborinan-2-yl)-2-methylaniline as a white solid (6.0g)

STEP 3: 4-t-Butyl-N-[3-(5,5-dimethyl[1,3,2]dioxaborinan-2-yl)-2-methylphenyl]-benzamide

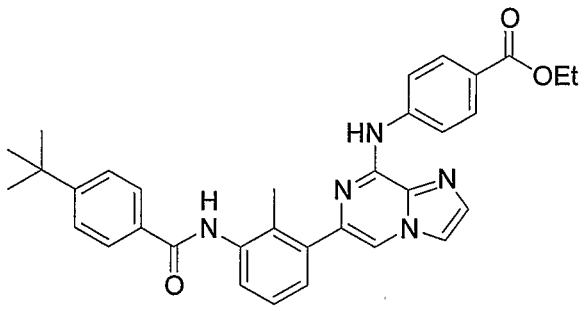


[00198] A solution of 3-(5,5-dimethyl[1,3,2]dioxaborinan-2-yl)-2-methylaniline (3.1g; 14.2mmol) and triethylamine (3.0mL; 21.2mmol) in THF

(110mL) is treated dropwise with 4-(t-butyl)benzoyl chloride (2.6mL; 14.2mmol) and the mixture is stirred at room temperature for 15min.

[00199] The mixture is then filtered through Celite, and washed with EtOAc, the filtrate is concentrated in vacuo to afford 4-t-butyl-N-[3-(5,5-dimethyl[1,3,2]dioxaborinan-2-yl)-2-methylphenyl]-benzamide as a white solid (4.0g).

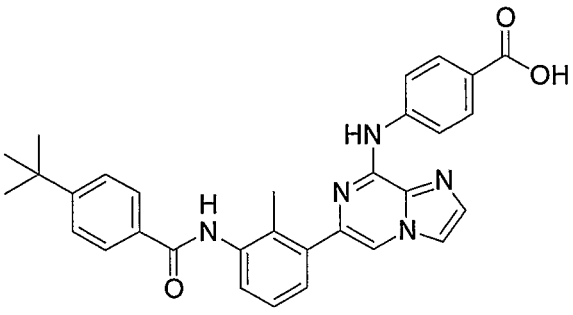
STEP 4: 4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methylphenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester



[00200] A mixture of 4-(6-bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester (687mg; 1.9mmol), 4-t-butyl-N-[3-(5,5-dimethyl[1,3,2]dioxaborinan-2-yl)-2-methylphenyl]-benzamide (866mg; 2.3mmol), palladium tetrakis(triphenylphosphine) (220mg; 0.19mmol), 1N aqueous sodium carbonate (3mL), and DME (13mL) is heated at 95 °C in a sealed tube for 16h.

[00201] The mixture is then cooled to room temperature, treated with water (30mL) and extracted with ethyl acetate (3 x 40mL). The extracts are washed with brine (1 x 50mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue is triturated with hexane and filtered to afford 4-{6-[3-(4-tert-butyl-benzoylamino)-2-methylphenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester as a dark yellow solid (600mg).

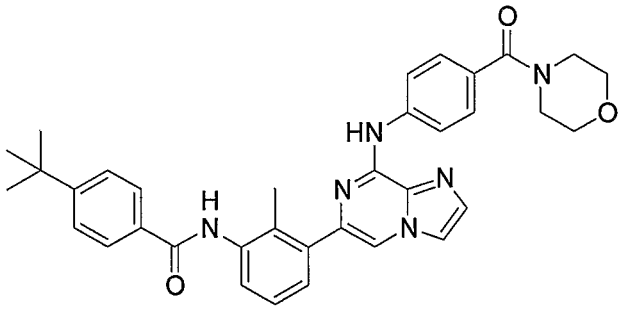
STEP 5: 4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methylphenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid



[00202] A mixture of 4-{6-[3-(4-tert-butyl-benzoylamino)-2-methylphenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester (600mg; 1.1mmol), ethanol (50mL) and 1N aqueous sodium hydroxide (50mL) is heated at reflux for 1h.

[00203] The mixture is then cooled to room temperature, adjusted to pH 6 with 1N HCl and extracted with ethyl actetate (3 x 100ml). The extracts are washed with brine (1 x 50mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is triturated with ethyl acetate to afford 4-{6-[3-(4-tert-butyl-benzoylamino)-2-methylphenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid as a white solid (300mg).

STEP 6: 4-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide



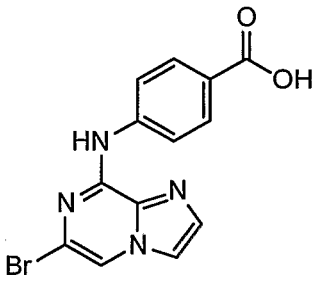
[00204] A mixture of 4-{6-[3-(4-tert-butyl-benzoylamino)-2-methylphenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid (52mg; 0.1mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (49mg; 0.11mmol), diisopropylethylamine (0.05mL; 0.3mmol), and DMF (1.7mL) is stirred at room temperature for 20min. Morpholine (0.04mL) is added and the mixture is stirred at

room temperature for 2h.

[00205] Water (10mL) is then added and the mixture filtered to afford 4-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide as a white solid (40mg).

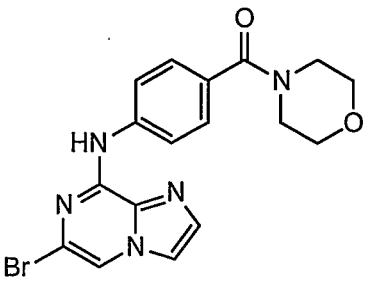
Example 2

Synthesis of 6-*tert*-Butyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-nicotinamide



STEP 1: 4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid

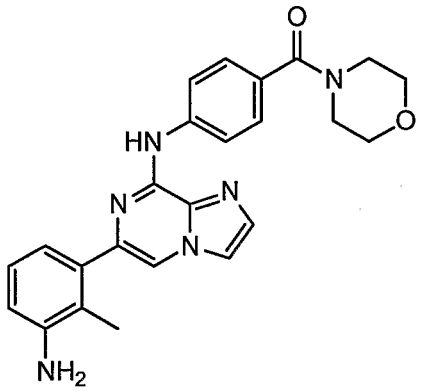
[00206] 4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester (10.0g; 27.7mmol) is dissolved in 200mL ethanol (200 proof) and 100mL 1 N NaOH is added. The reaction is refluxed for 2 hours and then cooled to rt. The resulting solid is filtered and collected, then slurried up in 0.1 N HCl (75mL) and extracted with CH_2Cl_2 (2 x 75mL). The pooled CH_2Cl_2 layers is washed with brine, then dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide 4-(6-bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid as a white solid (8g).



STEP 2: [4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-phenyl]-morpholin-4-yl-methanone

[00207] A mixture of 4-(6-bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid (4.0g, 12.0mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (6.0g; 13.6mmol), and diisopropylethylamine (6mL; 34.4mmol) is dissolved in dimethylacetamide (50mL) and stirred at room temperature for 20min. Morpholine (5mL; 57mmol) is added and the mixture is stirred at room temperature for 16hr.

[00208] Water (100mL) is added and the mixture is filtered to give [4-(6-bromo-imidazo[1,2-a]pyrazin-8-ylamino)-phenyl]-morpholin-4-yl-methanone as a cream solid (2.65g)

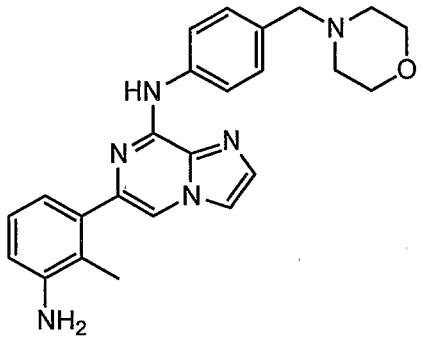


STEP 3: {4-[6-(3-Amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-phenyl}-morpholin-4-yl-methanone

[00209] A mixture of [4-(6-bromo-imidazo[1,2-a]pyrazin-8-ylamino)-phenyl]-morpholin-4-yl-methanone (500mg; 1.24mmol), 3-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-2-methyl-phenylamine (340mg; 1.6mmol), palladium tetrakis(triphenylphosphine) (200mg; 0.17mmol), 1M sodium carbonate (10mL), and DME (25mL) is heated at 95° in a sealed tube for 16hr.

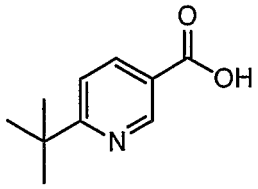
[00210] The mixture is cooled to room temperature, treated with water (75mL) and extracted with ethyl acetate (3 x 80mL). The extracts are washed with water (2 x

100mL) and brine (1 x 100mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue is triturated with ether and filtered to give {4-[6-(3-amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-phenyl}-morpholin-4-yl-methanone as a tan solid (540mg).



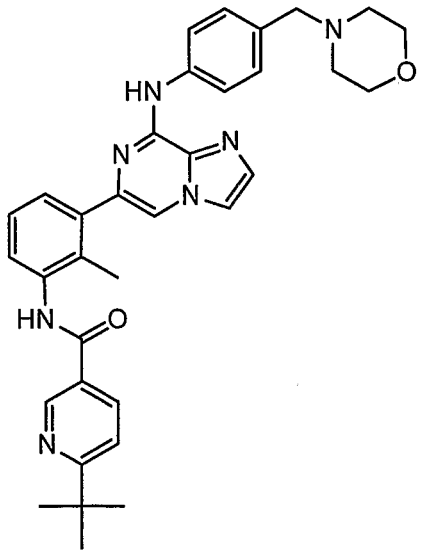
STEP 4: [6-(3-Amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-(4-morpholin-4-ylmethyl-phenyl)-amine

[00211] {4-[6-(3-Amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-phenyl}-morpholin-4-yl-methanone (350mg; 0.82mmol) is dissolved in anhydrous THF (50mL) under nitrogen at rt. Solid lithium aluminum hydride (0.5g) is added portion-wise to the stirring reaction, and the reaction refluxed under nitrogen for 2 hr. The reaction is cooled to 0°C in an ice bath and quenched carefully by the dropwise addition of water (0.5 mL), then 15% $NaOH_{(aq)}$ (0.5mL), and finally by more water (5mL). The reaction is stirred at 0°C for 15 minutes then the slurry is filtered through celite to remove the aluminum salts. The filtrate is partitioned between water and ethyl acetate, and the ethyl acetate layer is washed with water (1 x 50mL), and brine (1 x 50 mL), then dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide [6-(3-amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-(4-morpholin-4-ylmethyl-phenyl)-amine as a tan solid (300mg), which is pure enough to use in further steps.



STEP 5: 6-*tert*-Butyl-nicotinic acid

[00212] Nicotinic acid (1.0g; 7.3mmol) is dissolved in a mixture of water (10mL) and conc. H_2SO_4 (0.5mL) with stirring. *tert*-Butyl carboxylic acid is added, and the resulting crystalline slurry stirred under nitrogen. Catalytic $AgNO_3$ and ammonium persulfate (140mg; 0.61mmol) are then added, the flask wrapped in aluminum foil to shield from light and the reaction heated to 90°C for 3 hr. The reaction is cooled to 0°C, basified to pH 10 and extracted with EtOAc (4 x 50mL). The pooled organic layers are washed with saturated sodium carbonate (2 x 50mL) and brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting oil is purified by flash chromatography over silica gel to provide 6-*tert*-butyl-nicotinic acid (1.1g) as a white solid.



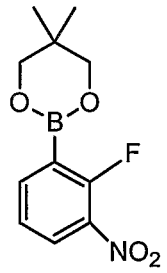
STEP 6: 6-*tert*-Butyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-nicotinamide

[00213] A mixture of [6-(3-amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-(4-morpholin-4-ylmethyl-phenyl)-amine (150mg; 0.36mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (450mg; 1.0mmol), and diisopropylethylamine (0.3mL; 1.7mmol) is dissolved in dimethylacetamide (1mL) and stirred at room temperature for 20min. 6-*tert*-butyl-nicotinic acid (200mg; 1.1mmol) is added and the mixture is stirred at room temperature for 16hr.

[00214] Water (10mL) is added and the mixture is filtered to give 6-*tert*-Butyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-nicotinamide as a crude tan solid (120mg). The crude solid is purified by flash chromatography over silica gel to provide the final compound as a pale cream solid (100mg)

Example 3

Synthesis of 3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-2-fluoro-phenylamine

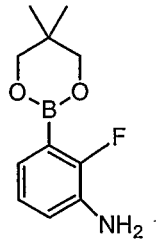


STEP 1: 2-(2-Fluoro-3-nitro-phenyl)-5,5-dimethyl-[1,3,2]dioxaborinane

[00215] A mixture of 1-bromo-2-fluoro-3-nitrobenzene (800mg; 3.63mmol), bis(neopentyl glycolato)diboron (900mg; 3.98mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichlropalladium, 1:1 complex with dichloromethane (100mg; 0.12mmol), potassium acetate (1.0 g; 10.2mmol), and dioxane (20mL) was heated at reflux for 16hr.

[00216] The mixture is cooled to room temperature, treated with water (100mL), and extracted with ethyl acetate (3 x 25mL). The extracts are washed with water (2 x 25mL) and brine (1 x 25mL), dried over sodium sulfate, and concentrated *in vacuo*. The residue is purified by flash chromatography over silica gel (elution with

ether/hexane 1/2) to give 2-(2-fluoro-3-nitro-phenyl)-5,5-dimethyl-[1,3,2]dioxaborinane as a pale yellow solid (350mg)



STEP 2: 3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-2-fluoro-phenylamine

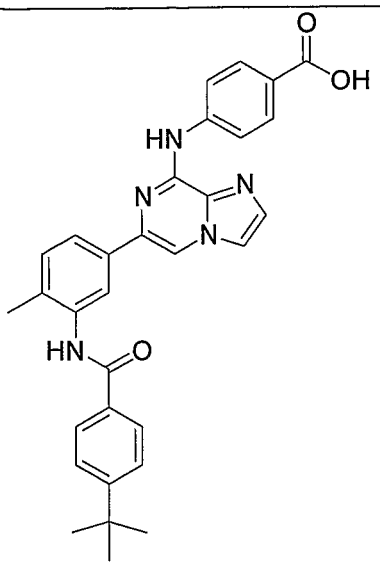
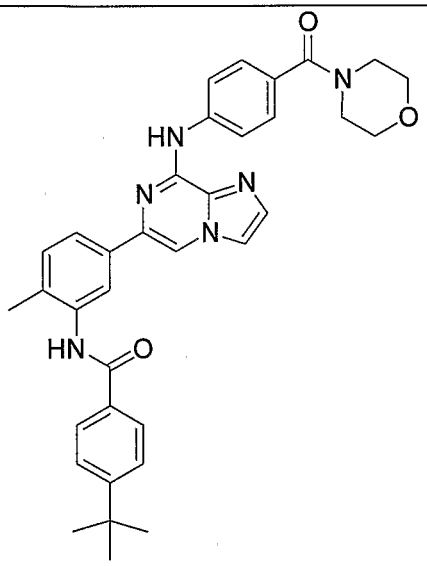
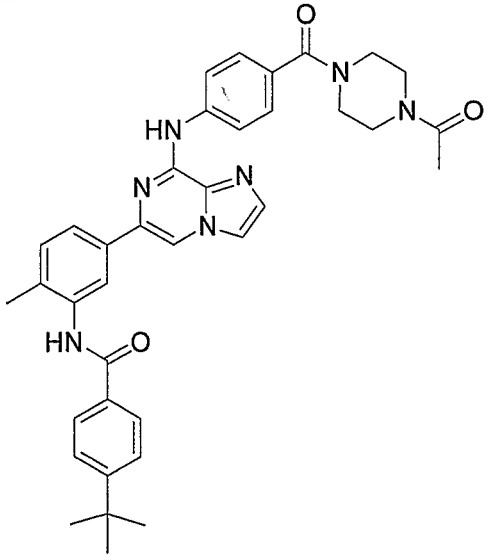
[00217] A mixture of 2-(2-fluoro-3-nitro-phenyl)-5,5-dimethyl-[1,3,2]dioxaborinane (240mg; 1.1mmol), 10% palladium-on-carbon (100mg) and ethyl acetate (75mL) is hydrogenated at room temperature and 40psi hydrogen for 2hr.

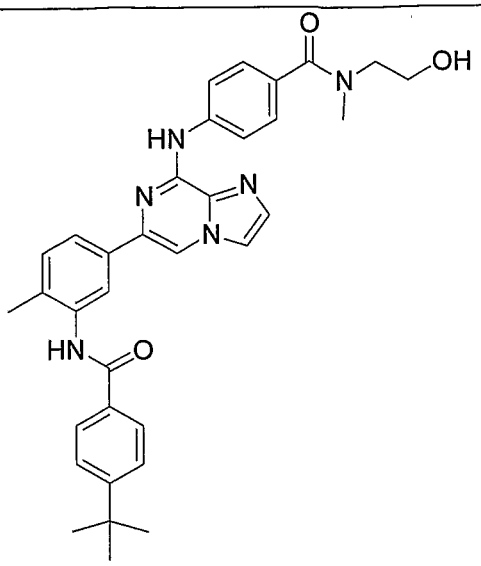
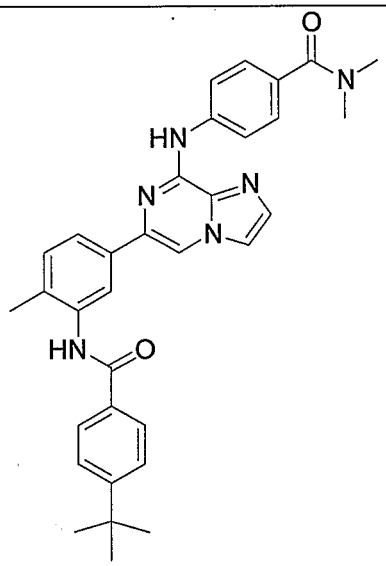
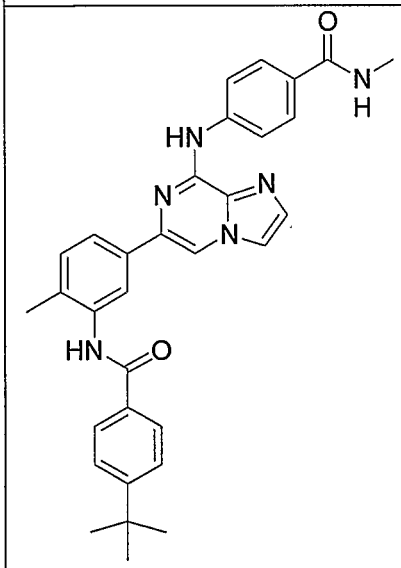
[00218] The mixture is filtered through celite, washed with CH_2Cl_2 (2 x 100mL), and the filtrate is evaporated to give 3-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-2-fluoro-phenylamine as an tan solid (200mg)

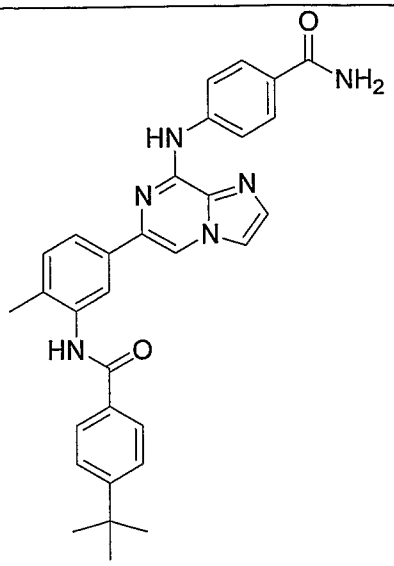
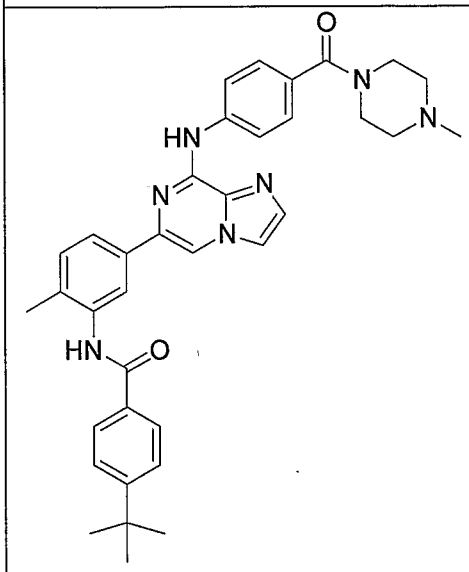
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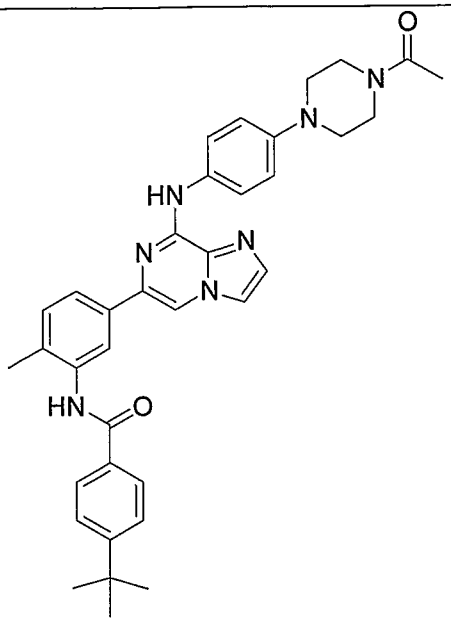
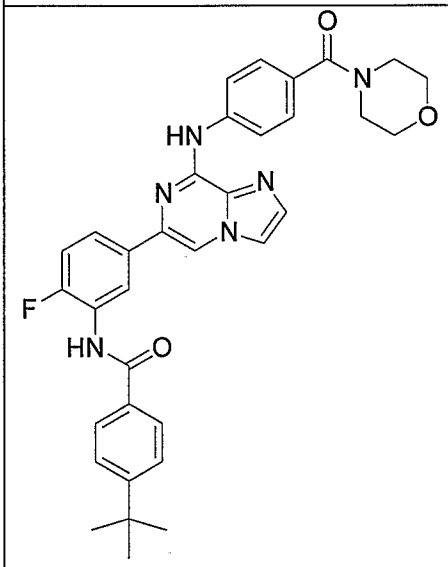
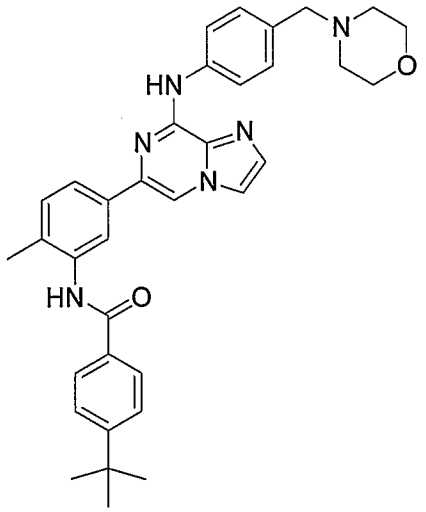
The following compounds were prepared using procedures similar to those described above in Examples 1 to 3.

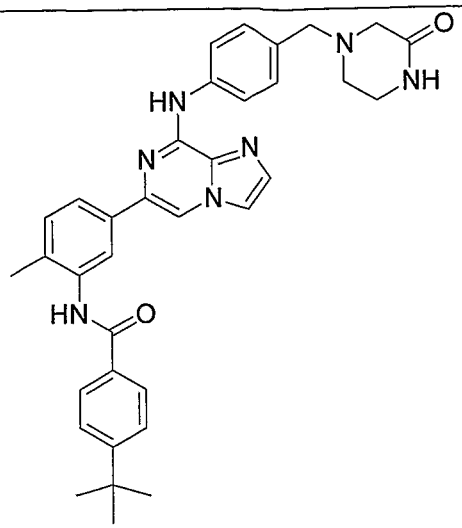
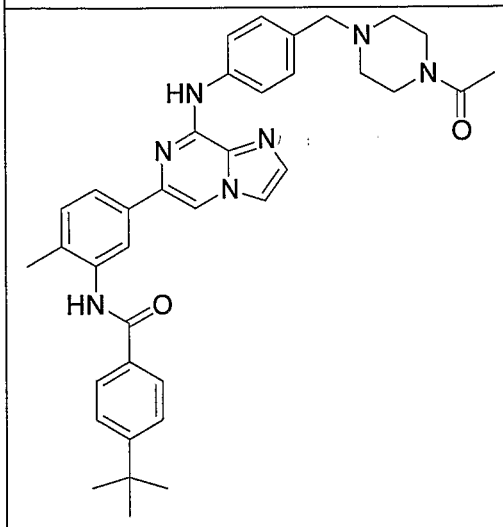
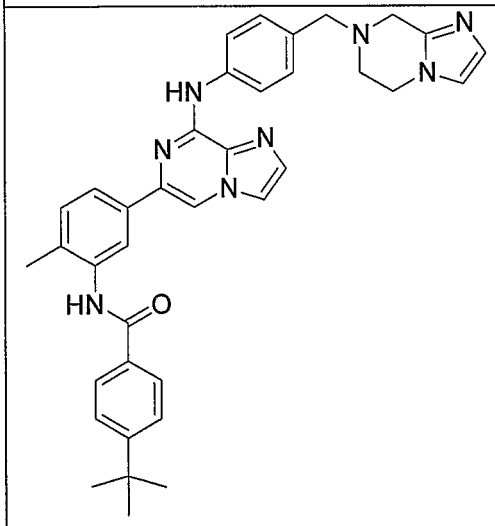
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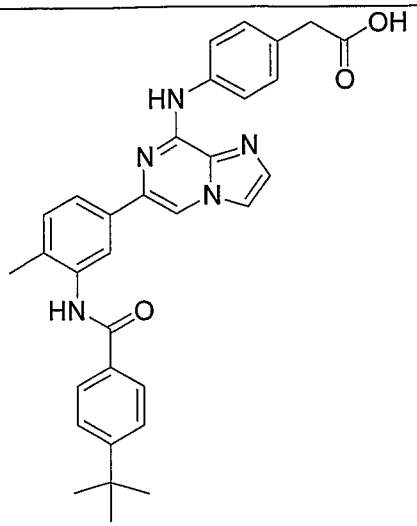
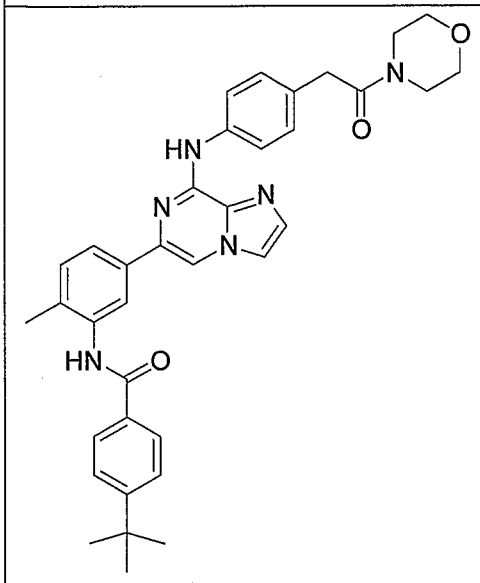
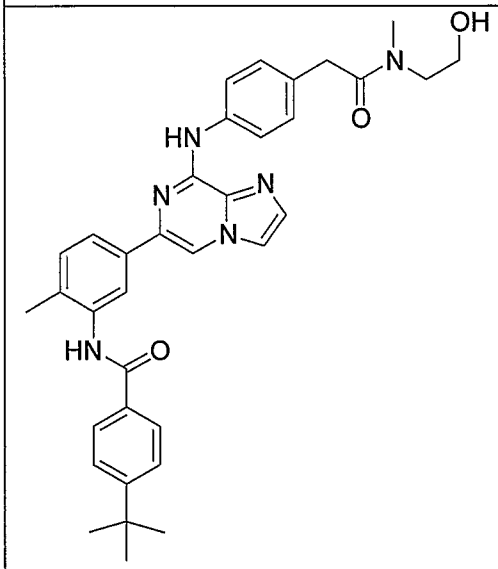
	4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid $C_{31}H_{29}N_5O_3$ Mol. Wt.: 519.59	520.4
	4-tert-Butyl-N-(2-methyl-5-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{35}H_{36}N_6O_3$ Mol. Wt.: 588.70	589.3
	N-(5-{8-[4-(4-Acetyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-4-tert-butyl-benzamide $C_{37}H_{39}N_7O_3$ Mol. Wt.: 629.75	630.3

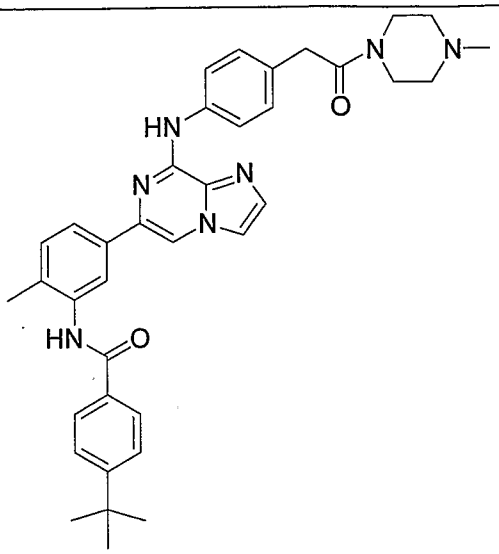
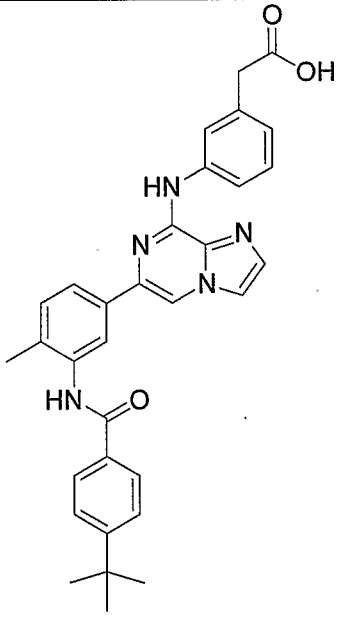
	4-tert-Butyl-N-(2-methyl-5-{8-[4-(N-methyl-hydroxyethyl-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{34}H_{36}N_6O_3$ Mol. Wt.: 576.69	577.4
	4-tert-Butyl-N-(2-methyl-5-{8-[4-(NNdimethyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{33}H_{34}N_6O_2$ Mol. Wt.: 546.66	547.3
	4-tert-Butyl-N-(2-methyl-5-{8-[4-(N-methyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{32}H_{32}N_6O_2$ Mol. Wt.: 532.64	533.3

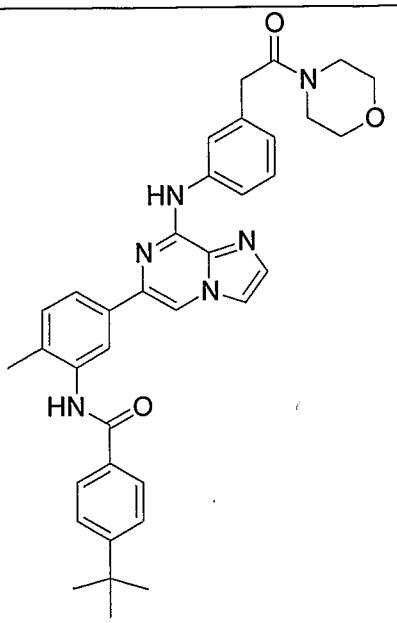
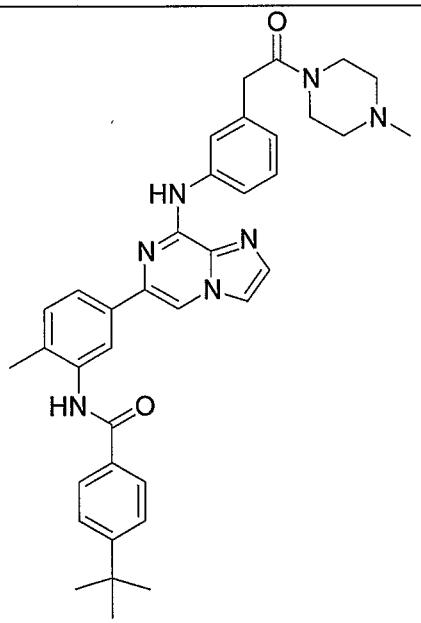
	4-tert-Butyl-N-(2-methyl-5-{8-[4-(amide)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{31}H_{30}N_6O_2$ Mol. Wt.: 518.61	519.3
	4-tert-Butyl-N-(2-methyl-5-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{36}H_{39}N_7O_2$ Mol. Wt.: 601.74	602.4

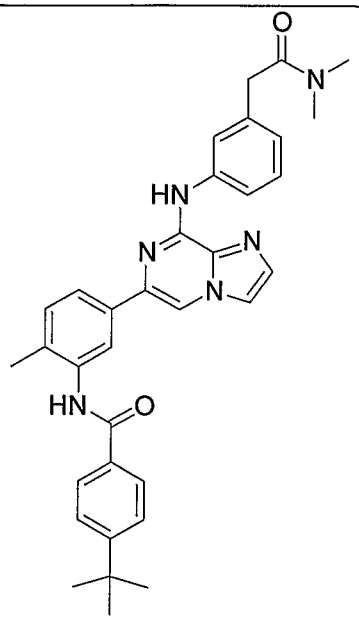
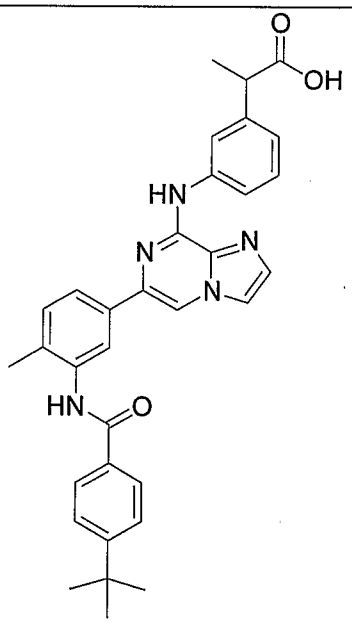
	N-(5-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-4-tert-butyl-benzamide $C_{36}H_{39}N_7O_2$ Mol. Wt.: 601.74	602.2
	4-tert-Butyl-N-(2-fluoro-5-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{34}H_{33}FN_6O_3$ Mol. Wt.: 592.66	593.3
	4-tert-Butyl-N-{2-methyl-5-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $C_{35}H_{38}N_6O_2$ Mol. Wt.: 574.72	575.2

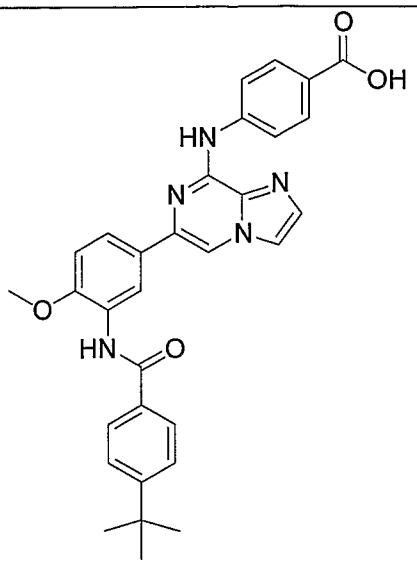
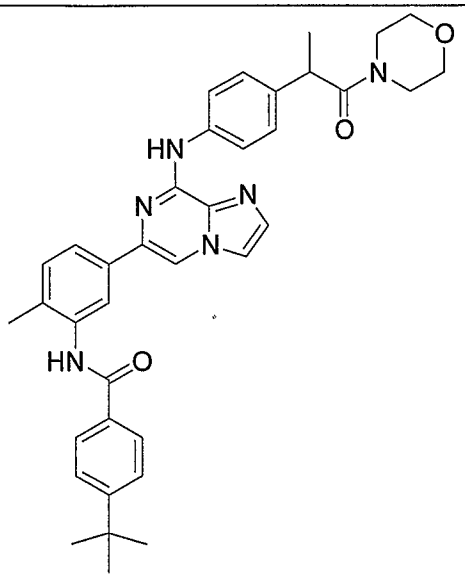
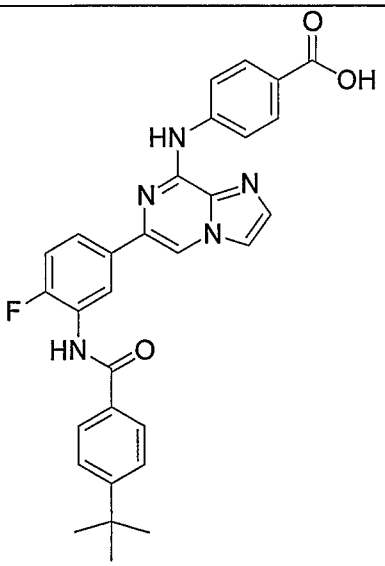
	4-tert-Butyl-N-(2-methyl-5-{8-[4-(3-oxo-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{35}H_{37}N_7O_2$ Mol. Wt.: 587.71	588.2
	N-(5-{8-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-4-tert-butyl-benzamide $C_{37}H_{41}N_7O_2$ Mol. Wt.: 615.77	616.3
	4-tert-Butyl-N-(5-{8-[4-(5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide $C_{37}H_{38}N_8O$ Mol. Wt.: 610.75	611.3

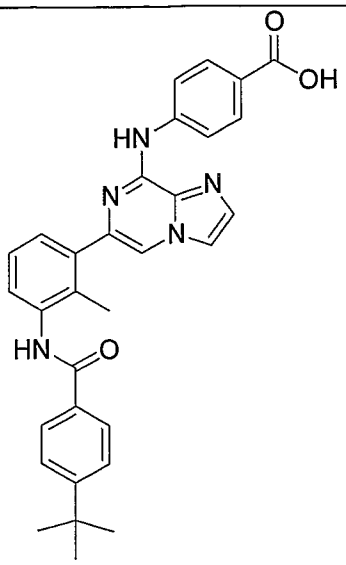
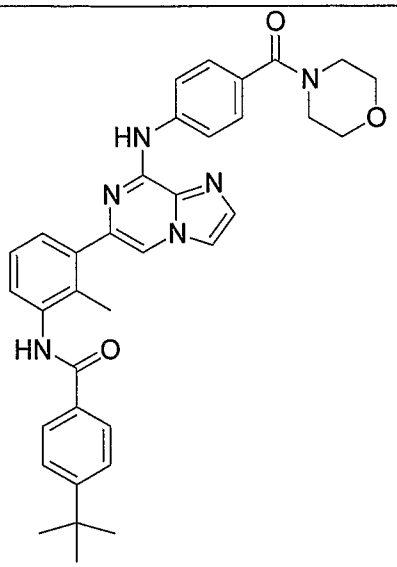
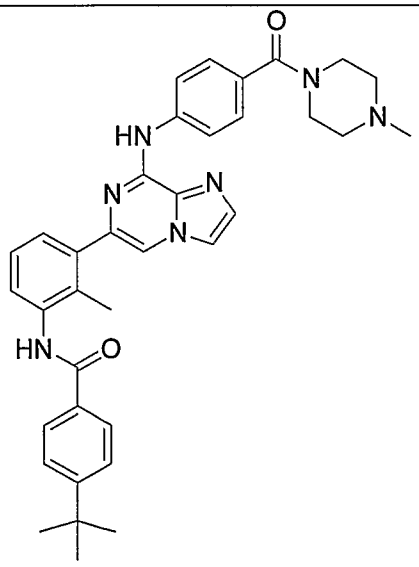
	(4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid $C_{32}H_{31}N_5O_3$ Mol. Wt.: 533.62	534.2
	4-tert-Butyl-N-(2-methyl-5-{8-[4-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{36}H_{38}N_6O_3$ Mol. Wt.: 602.73	602.9
	4-tert-Butyl-N-{5-[8-(4-{[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide $C_{35}H_{38}N_6O_3$ Mol. Wt.: 590.71	591.2

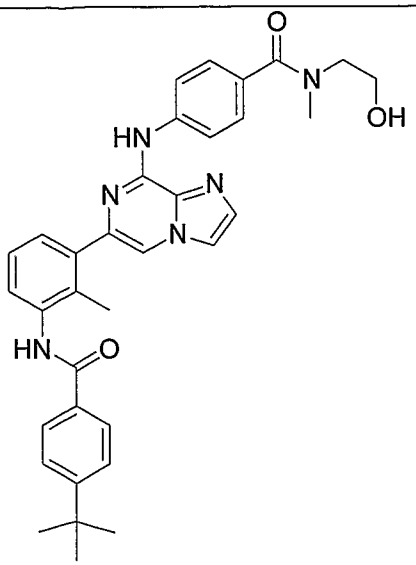
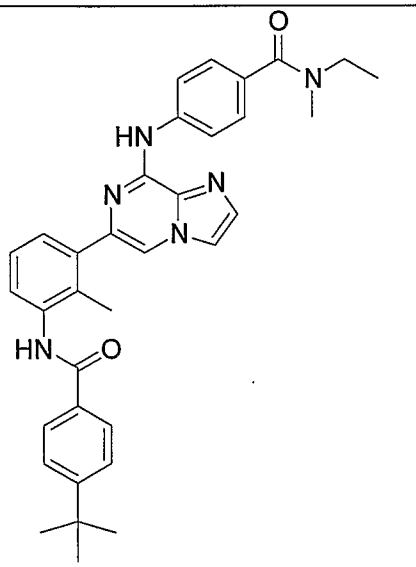
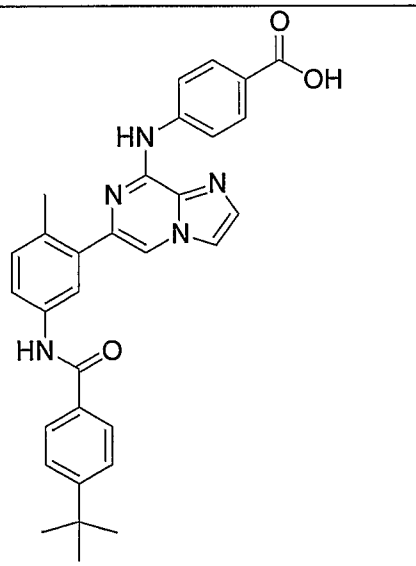
	4-tert-Butyl-N-[2-methyl-5-(8-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide $C_{37}H_{41}N_7O_2$ Mol. Wt.: 615.77	616.3
	(3-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid $C_{32}H_{31}N_5O_3$ Mol. Wt.: 533.62	534.2

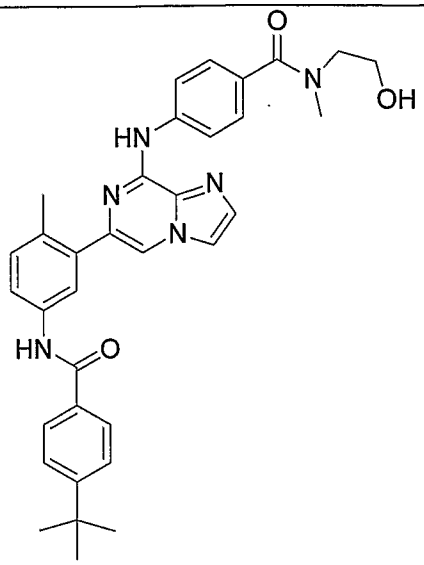
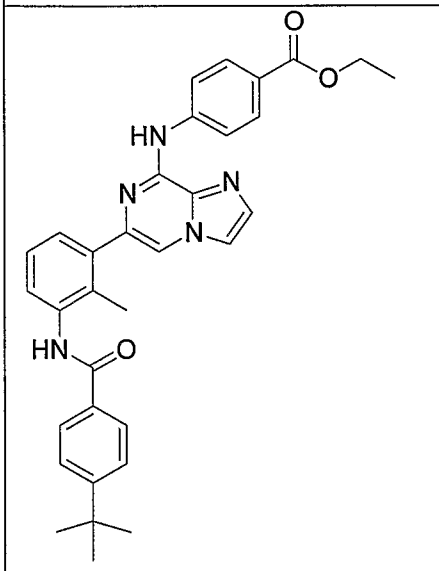
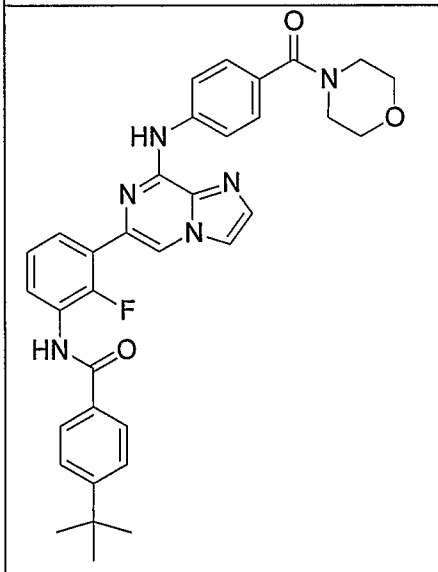
	4-tert-Butyl-N-(2-methyl-5-{8-[3-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{36}H_{38}N_6O_3$ Mol. Wt.: 602.73	603.3
	4-tert-Butyl-N-[2-methyl-5-(8-{3-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide $C_{37}H_{41}N_7O_2$ Mol. Wt.: 615.77	616.3

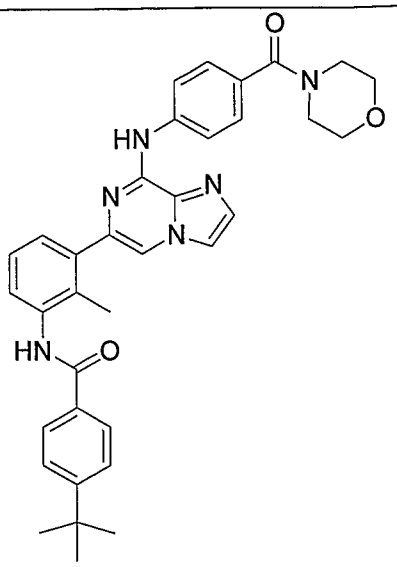
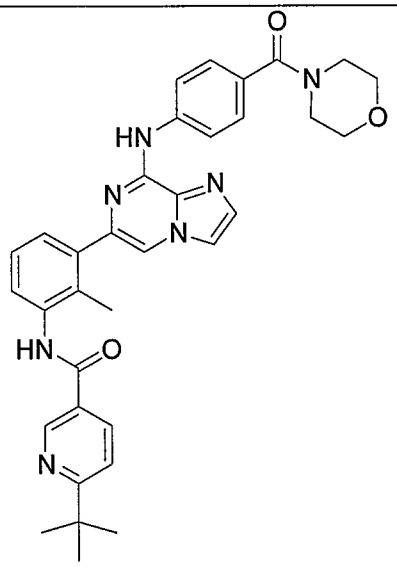
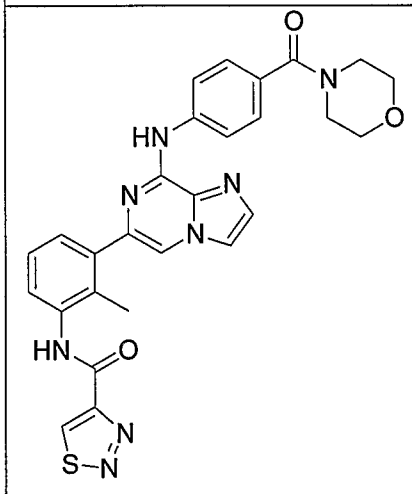
	4-tert-Butyl-N-{5-[8-(3-dimethylcarbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide $C_{34}H_{36}N_6O_2$ Mol. Wt.: 560.69	561.3
	2-(3-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-propionic acid $C_{33}H_{33}N_5O_3$ Mol. Wt.: 547.65	548.2

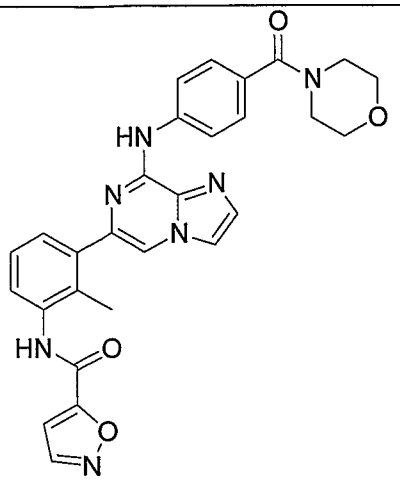
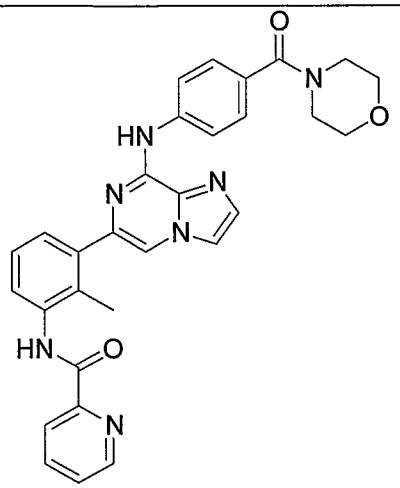
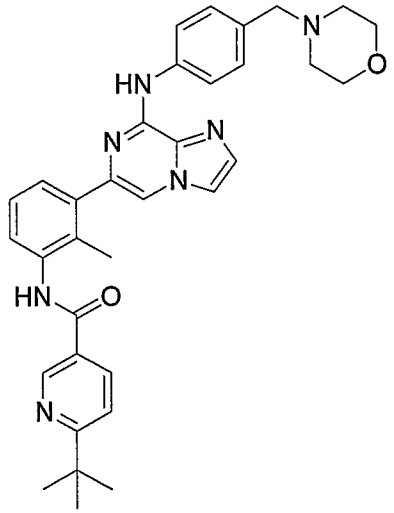
	4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methoxy-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid $C_{31}H_{29}N_5O_4$ Mol. Wt.: 535.59	536.1
	4-tert-Butyl-N-(2-methyl-5-{8-[4-(1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{37}H_{40}N_6O_3$ Mol. Wt.: 616.75	617.4
	4-{6-[3-(4-tert-Butyl-benzoylamino)-4-fluoro-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid $C_{30}H_{26}FN_5O_3$ Mol. Wt.: 523.56	522.2

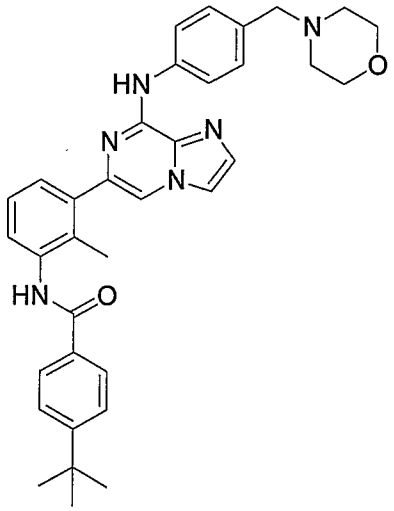
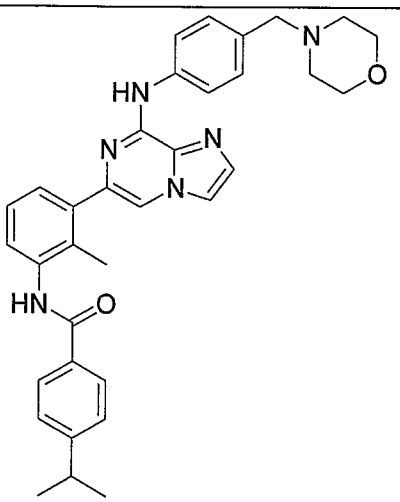
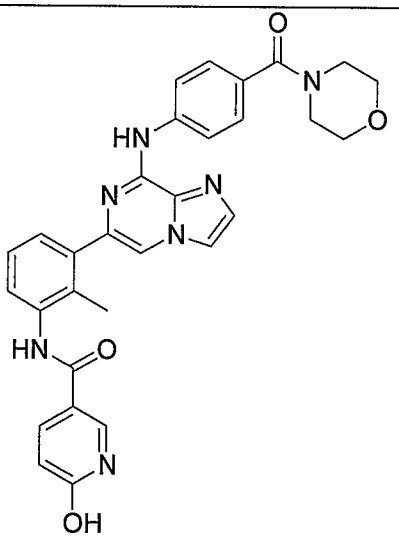
	4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid $C_{31}H_{29}N_5O_3$ Mol. Wt.: 519.59	520.2
	4-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{35}H_{36}N_6O_3$ Mol. Wt.: 588.70	589.2
	4-tert-Butyl-N-(2-methyl-3-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{36}H_{39}N_7O_2$ Mol. Wt.: 601.74	602.3

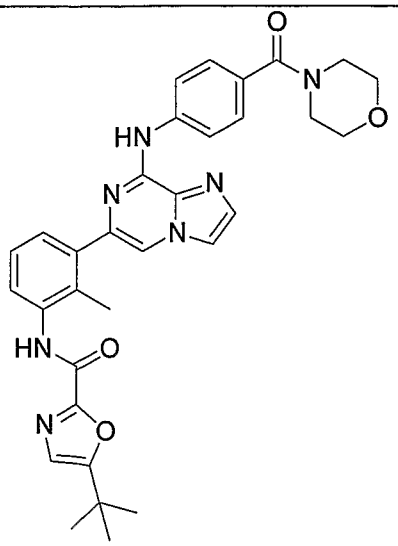
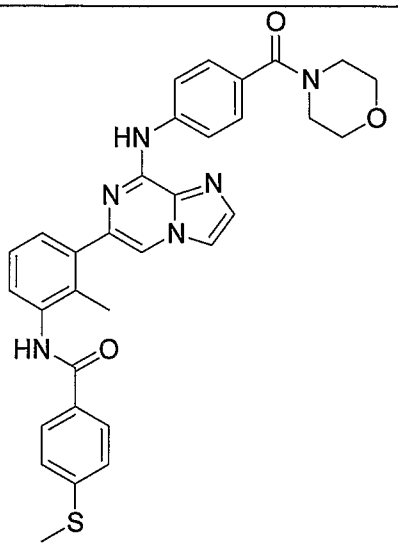
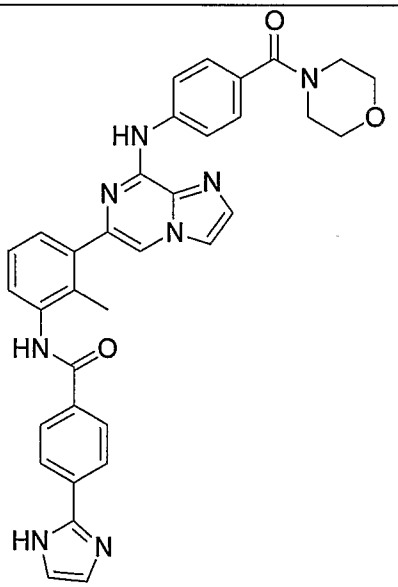
	4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylhydroxyethyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{34}H_{36}N_6O_3$ Mol. Wt.: 576.69	577.1
	4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylethyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{34}H_{36}N_6O_2$ Mol. Wt.: 560.69	561.3
	4-{6-[5-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid $C_{31}H_{29}N_5O_3$ Mol. Wt.: 519.59	520.1

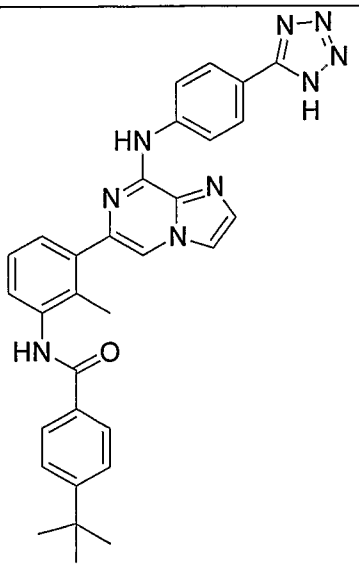
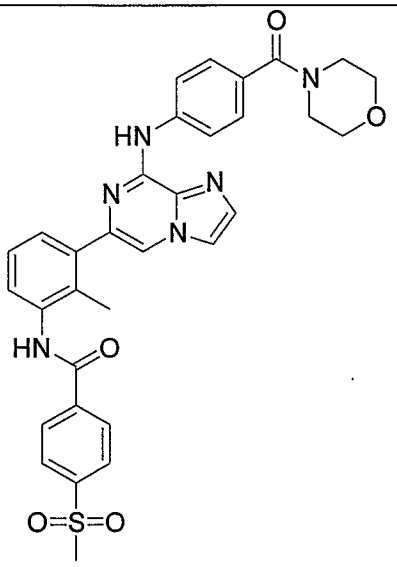
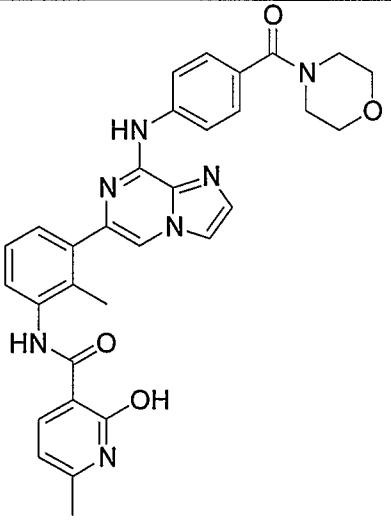
	4-tert-Butyl-N-(4-methyl-3-{8-[4-(Nmethylhydroxyethyl-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{34}H_{36}N_6O_3$ Mol. Wt.: 576.69	577.3
	4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester $C_{33}H_{33}N_5O_3$ Mol. Wt.: 547.65	548.3
	4-tert-Butyl-N-(2-fluoro-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{34}H_{33}FN_6O_3$ Mol. Wt.: 592.66	593.3

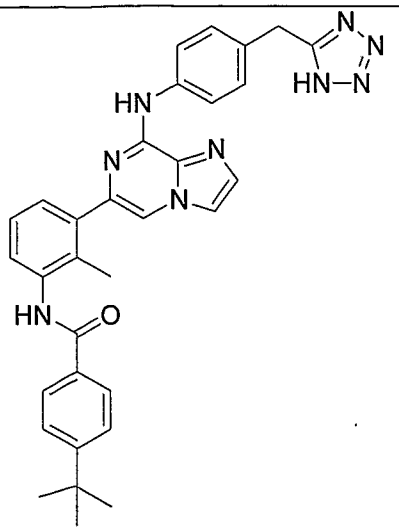
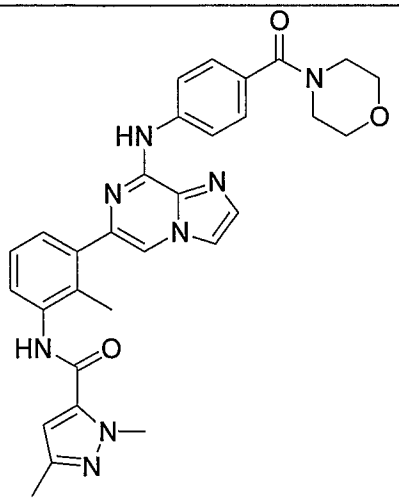
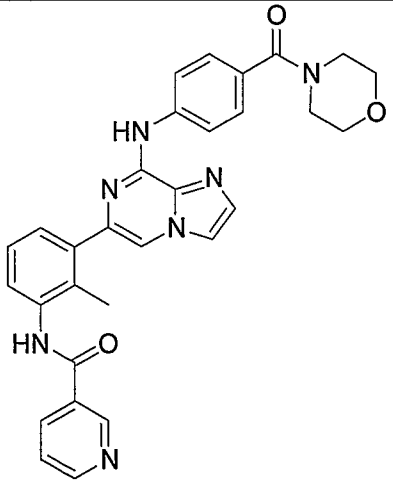
	4-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{35}H_{36}N_6O_3$ Mol. Wt.: 588.70	534.5
	6-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide $C_{34}H_{35}N_7O_3$ Mol. Wt.: 589.69	590.6
	[1,2,3]Thiadiazole-4-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide $C_{27}H_{24}N_8O_3S$ Mol. Wt.: 540.60	541.2

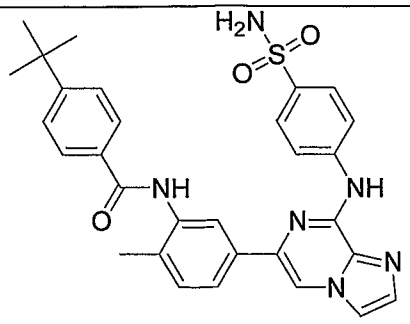
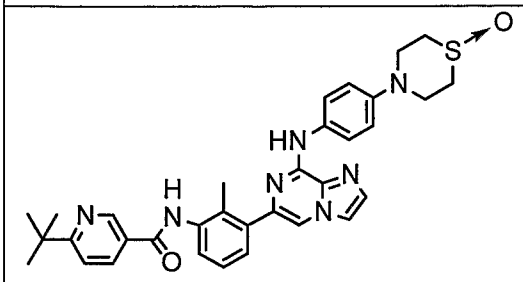
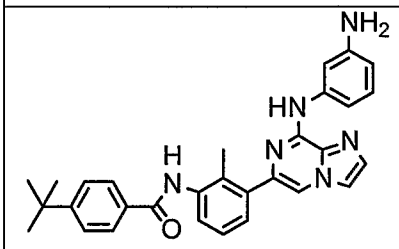
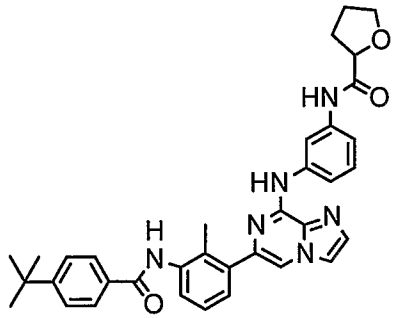
	Isoxazole-5-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide $C_{28}H_{25}N_7O_4$ Mol. Wt.: 523.54	524.2
	Pyridine-2-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide $C_{30}H_{27}N_7O_3$ Mol. Wt.: 533.58	534.3
	6-tert-Butyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-nicotinamide $C_{34}H_{37}N_7O_2$ Mol. Wt.: 575.70	576.4

	4-tert-Butyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $C_{35}H_{38}N_6O_2$ Mol. Wt.: 574.72	575.3
	4-Isopropyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $C_{34}H_{36}N_6O_2$ Mol. Wt.: 560.69	561.2
	6-Hydroxy-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide $C_{30}H_{27}N_7O_4$ Mol. Wt.: 549.58	550.5

	5-tert-Butyl-oxazole-2-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide $C_{32}H_{33}N_7O_4$ Mol. Wt.: 579.65	580.5
	N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-methylsulfanyl-benzamide $C_{32}H_{30}N_6O_3S$ Mol. Wt.: 578.69	579.5
	4-(1H-Imidazol-2-yl)-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{34}H_{30}N_8O_3$ Mol. Wt.: 598.65	599.2

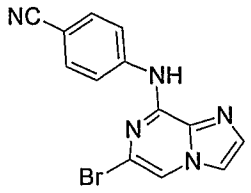
	4-tert-Butyl-N-(2-methyl-3-{8-[4-(1H-tetrazol-5-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{31}H_{29}N_9O$ Mol. Wt.: 543.62	544.2
	4-Methanesulfonyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{32}H_{30}N_6O_5S$ Mol. Wt.: 610.68	611.1
	2-Hydroxy-6-methyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide $C_{31}H_{29}N_7O_4$ Mol. Wt.: 563.61	564.3

	4-tert-Butyl-N-(2-methyl-3-{8-[4-(1H-tetrazol-5-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{32}H_{31}N_9O$ Mol. Wt.: 557.65	558.4
	2,5-Dimethyl-2H-pyrazole-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide $C_{30}H_{30}N_8O_3$ Mol. Wt.: 550.61	551.3
	N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide $C_{30}H_{27}N_7O_3$ Mol. Wt.: 533.58	

	4-tert-Butyl-N-{2-methyl-5-[8-(4-sulfamoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $C_{30}H_{30}N_6O_3S$ Mol. Wt.: 554.66	
	6-tert-Butyl-N-(2-methyl-3-{8-[4-(1-oxo-114-thiomorpholin-4-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide 593.26	594.30 (MH+)
	N-{3-[8-(3-Amino-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-4-tert-butyl-benzamide 490.25	490.35
	Tetrahydro-furan-2-carboxylic acid (3-{6-[3-(4-tert-butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-amide 588.28	588.28

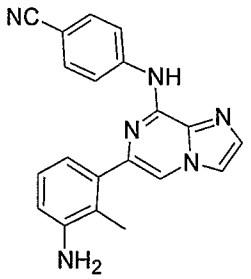
Example 5

Synthesis of 4-*tert*-Butyl-N-(2-methyl-3-{8-[4-(N-methylcarbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide



STEP 1 4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzonitrile

[00219] A mixture of 4-aminobenzonitrile (220mg; 1.89mmol) and 6,8-dibromo-imidazo[1,2-a]pyrazine (500mg; 1.81mmol) is slurried in DMF (1mL) and heated to 140°C for 20 minutes. The reaction is allowed to cool, and when the bath reaches 75°C, ethyl acetate (40mL) is added and the slurry is stirred to break up large solid lumps into fine powder. The powdered 4-(6-bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzonitrile is filtered, washed with diethyl ether (2 x 50mL) and dried under vacuum to a fine orange/tan solid (600mg).

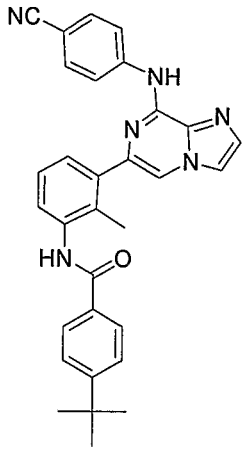


STEP 2 4-[6-(3-Amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-benzonitrile

[00220] A solution of 4-(6-bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzonitrile (1.02g; 3.27mmol) is slurried in ethylene glycol, dimethyl ether (DME; 60mL) and nitrogen gas bubbled through the reaction for 15 minutes with stirring at rt.

[00221] 3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-2-methyl-phenylamine (950mg; 3.63mmol) and palladium tetrakis(triphenylphosphine) (500mg; 0.43mmol) are added and nitrogen is bubbled through the reaction slurry for an additional 10 minutes at rt. 20 mL of a 1.0N solution of sodium carbonate is added and the biphasic

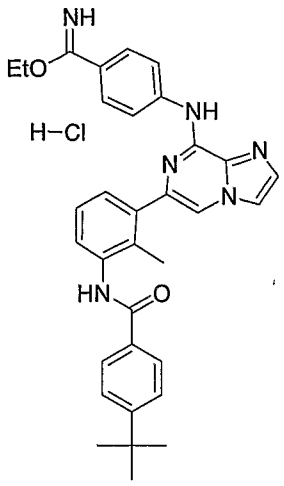
mixture is heated to 95°C for 16hrs with vigorous stirring under nitrogen. The mixture is partitioned between ethyl acetate (100mL) and water (100mL) and the water layer extracted with ethyl acetate (2 x 50mL). The organic layers are pooled, washed with brine and dried over anhydrous sodium sulfate. The filtrate is then concentrated *in vacuo* and the crude oil dissolved in a minimum volume of CH_2Cl_2. Diethyl ether is added and the resulting precipitate is filtered and washed with diethyl ether to provide 4-[6-(3-amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-benzonitrile as a pale tan solid (650mg).



STEP 3 4-*tert*-Butyl-N-{3-[8-(4-cyano-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide

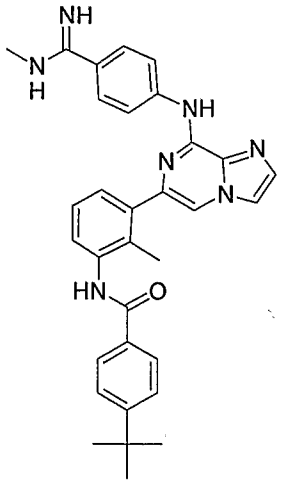
[00222] A solution of 4-[6-(3-amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-benzonitrile (380mg; 1.12 mmol) and diisopropylethylamine (187mg; 1.45mmol) in anhydrous THF (25mL) is stirred under nitrogen at rt. A solution of 4-*tert*-Butyl-benzoyl chloride (230mg; 1.17mmol) in 5mL anhydrous THF is then added dropwise to the stirring reaction solution. After 30 minutes, the mixture is partitioned between ethyl acetate (75mL) and water (75mL) and the water layer extracted with ethyl acetate (2 x 50mL). The organic layers are pooled, washed with brine and dried over anhydrous sodium sulfate. The filtrate is then concentrated *in vacuo* and the crude oil dissolved in a minimum volume of CH_2Cl_2. Diethyl ether is added and the resulting precipitate is filtered and washed with diethyl ether to provide 4-*tert*-butyl-

N-{3-[8-(4-cyano-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide as a light orange solid (450mg)



STEP 4 4-{6-[3-(4-*tert*-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzimidic acid ethyl ester hydrochloride

[00223] 4-*tert*-Butyl-N-{3-[8-(4-cyano-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide is slurried in 200mL ethanol (200 proof) and the reaction cooled to 0°C in an ice bath. The reaction is then saturated with hydrogen chloride gas and allowed to gradually warm to room temperature over 16hrs with stirring. The solvent is removed *in vacuo* and the resulting tan solid 4-{6-[3-(4-*tert*-butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzimidic acid ethyl ester hydrochloride (500mg) is used without further purification.



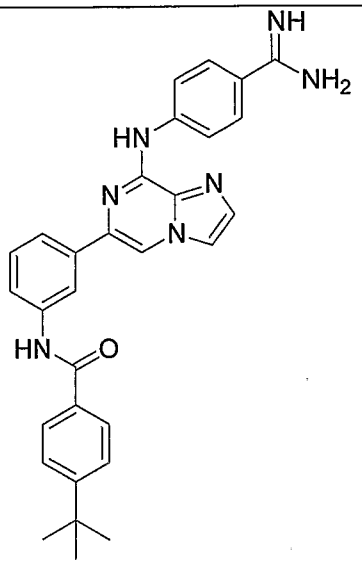
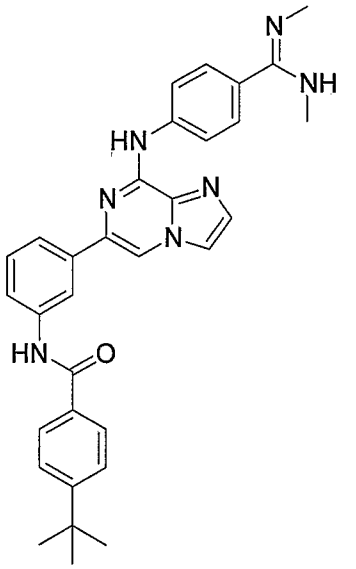
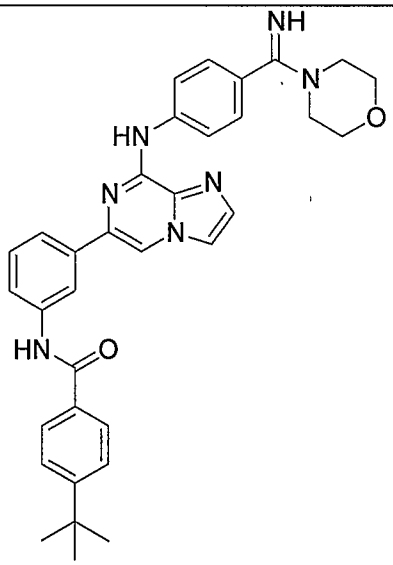
STEP 5 4-*tert*-Butyl-N-(2-methyl-3-{8-[4-(N-methylcarbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide

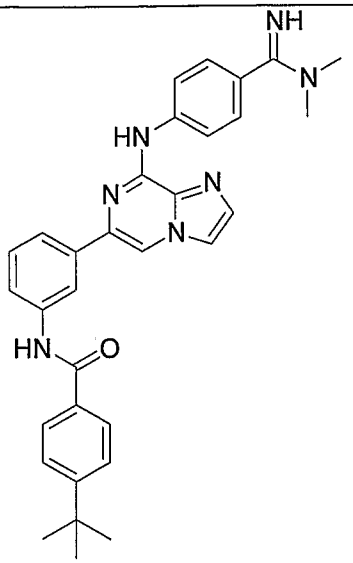
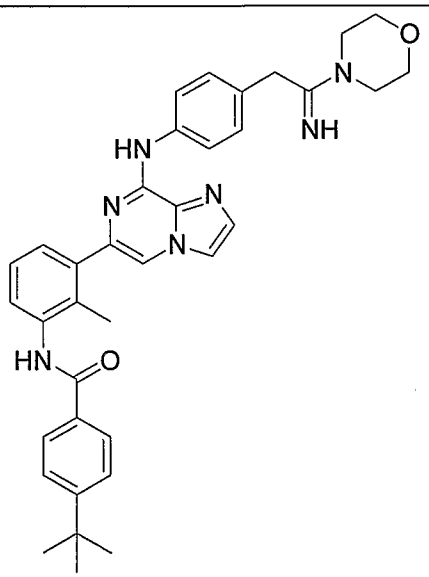
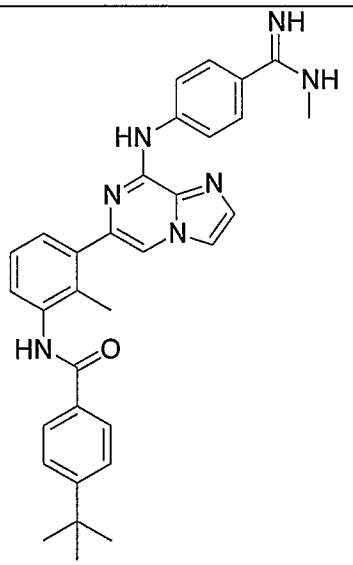
[00224] 4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzimidic acid ethyl ester hydrochloride (150mg; 0.26mmol) is dissolved in methanol (1mL) in a glass pressure reaction vessel, and a solution of methylamine in THF added (2.0N; 2mL). The reaction is heated to 50°C for 2hr then concentrated *in vacuo*. The oil is dissolved in 2 mL CH_2Cl_2 and diethyl ether (20mL) is added to precipitate out 4-*tert*-butyl-N-(2-methyl-3-{8-[4-(N-methylcarbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide as a clean light tan solid (140mg).

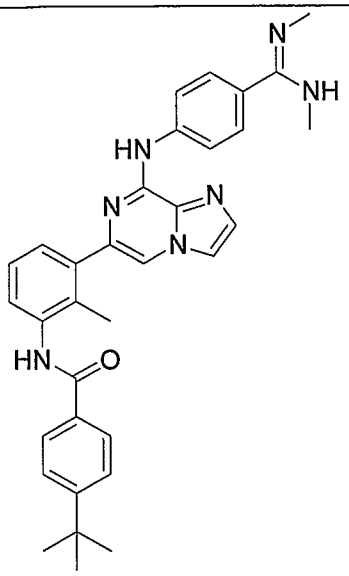
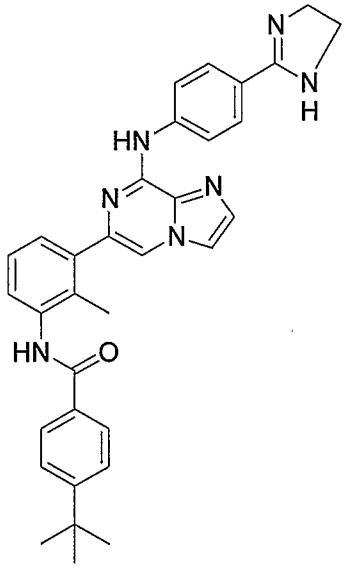
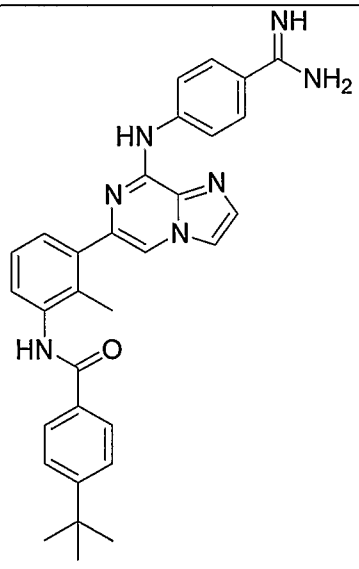
Example 6

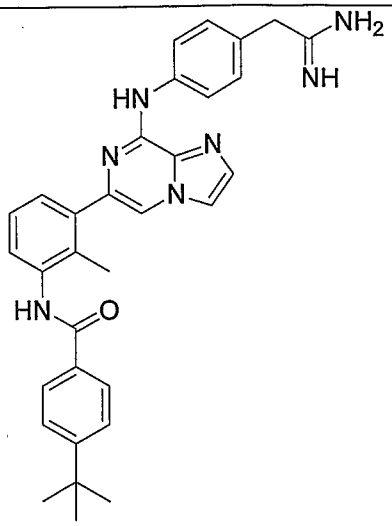
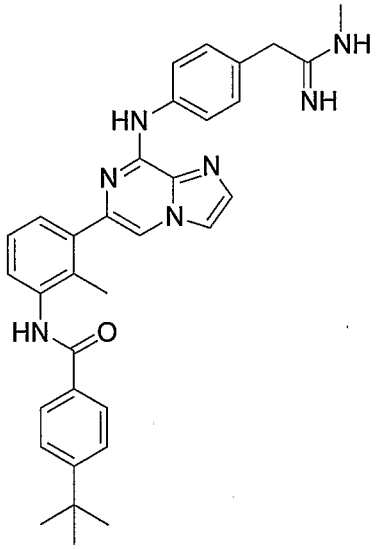
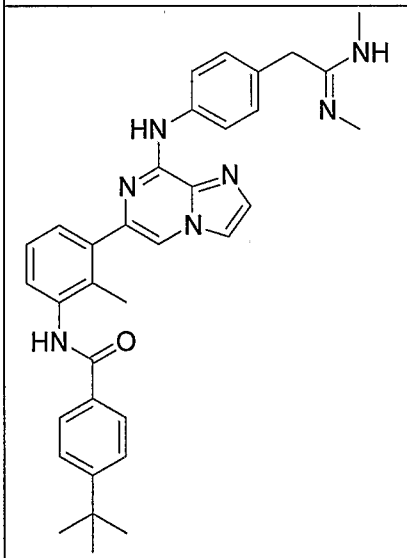
The following compounds were prepared using procedures similar to those described above in Example 5.

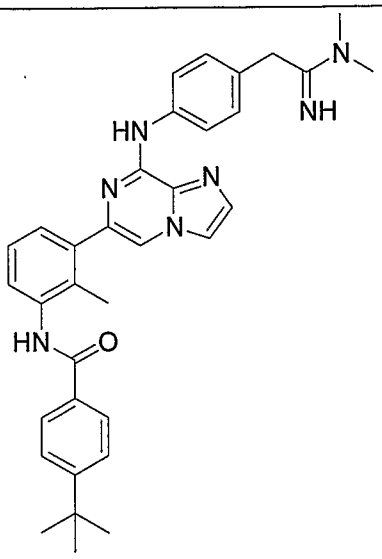
Structure	Name MW	M+

	4-tert-Butyl-N-{3-[8-(4-carbamimidoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $C_{30}H_{29}N_7O$ Mol. Wt.: 503.60	504.3
	4-tert-Butyl-N-(3-{8-[4-(N,N'-dimethyl-carbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{32}H_{33}N_7O$ Mol. Wt.: 531.65	532.31
	4-tert-Butyl-N-(3-{8-[4-(imino-morpholin-4-yl-methyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{34}H_{35}N_7O_2$ Mol. Wt.: 573.69	574.35

	4-tert-Butyl-N-(3-{8-[4-(N,N-dimethyl-carbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{32}H_{33}N_7O$ Mol. Wt.: 531.65	533.34
	4-tert-Butyl-N-(3-{8-[4-(2-imino-2-morpholin-4-yl-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide $C_{36}H_{39}N_7O_2$ Mol. Wt.: 601.74	602.22
	4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylcarbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{32}H_{33}N_7O$ Mol. Wt.: 531.65	532.23

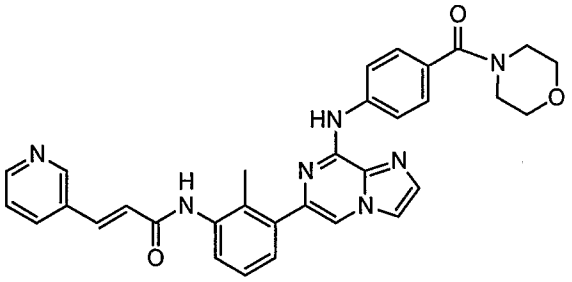
	4-tert-Butyl-N-(3-{8-[4-(N,N'-dimethyl-carbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide $C_{33}H_{35}N_7O$ Mol. Wt.: 545.68	546.19
	4-tert-Butyl-N-(3-{8-[4-(4,5-dihydro-1H-imidazol-2-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide $C_{33}H_{33}N_7O$ Mol. Wt.: 543.66	544.22
	4-tert-Butyl-N-{3-[8-(4-carbamimidoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide $C_{31}H_{31}N_7O$ Mol. Wt.: 517.62	518.06

	4-tert-Butyl-N-{3-[8-(4-carbamimidoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide $C_{32}H_{33}N_7O$ Mol. Wt.: 531.65	532.1
	4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylcarbamimidoylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide $C_{33}H_{35}N_7O$ Mol. Wt.: 545.68	546.1
	4-tert-Butyl-N-(3-{8-[4-(N,N'-dimethyl-carbamimidoylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide $C_{34}H_{37}N_7O$ Mol. Wt.: 559.70	560.05

	4-tert-Butyl-N-(3-{8-[4-(N,N-dimethyl-carbamimidoylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide $C_{34}H_{37}N_7O$ Mol. Wt.: 559.70	560.05

Example 7

Synthesis of N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-3-pyridin-3-yl-acrylamide

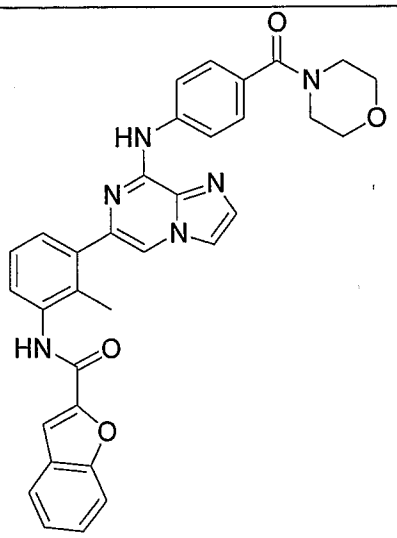
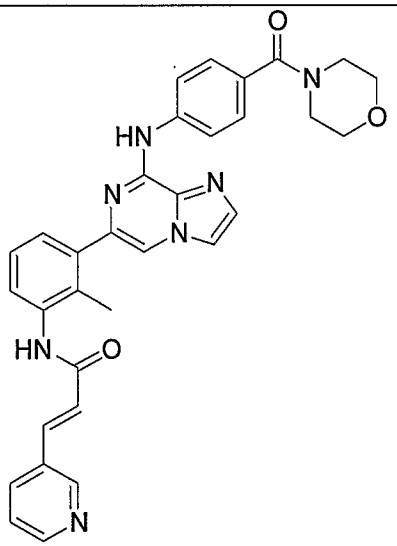


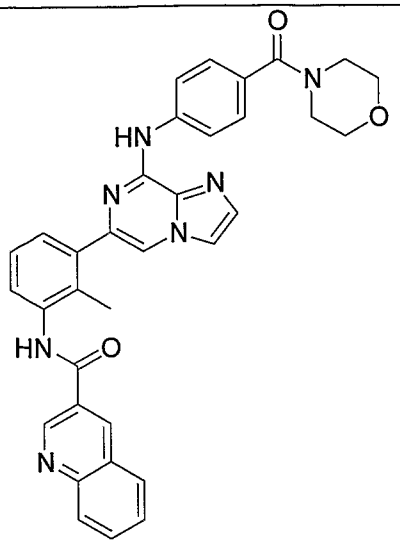
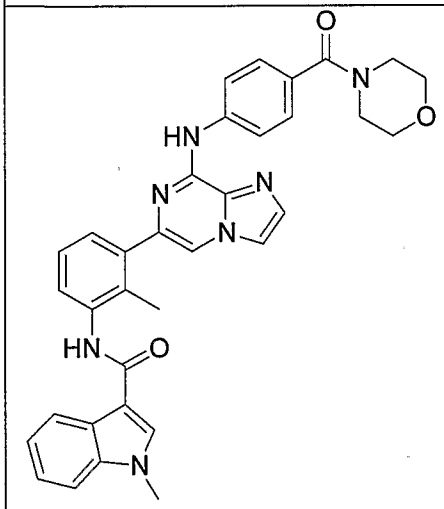
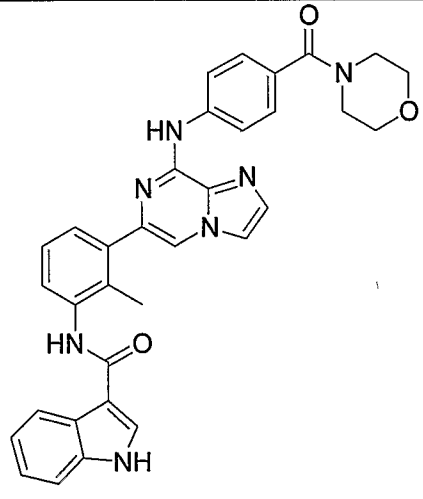
[00225] A mixture of 3-pyridin-3-ylacrylic acid (31mg; 0.21mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (100mg; 0.23mmol), diisopropylethylamine (0.11mL; 0.63mmol), and DMF (3mL) is stirred at room temperature for 30min. {4-[6-(3-amino-2-methyl-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-phenyl}-morpholin-4-yl-methanone (90mg; 0.21mmol) is added and the mixture is stirred at room temperature for 16hr.

[00226] Water (10mL) is added and the mixture is filtered to give N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-3-pyridin-3-yl-acrylamide as a pale brown solid (50mg)

Example 8

The following compounds were prepared using procedures similar to those described above in Example 7.

Structure	Name MW	M+
	Benzofuran-2-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide $C_{33}H_{28}N_6O_4$ Mol. Wt.: 572.61	573.33
	N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-3-pyridin-3-yl-acrylamide $C_{32}H_{29}N_7O_3$ Mol. Wt.: 559.62	560.3

	Quinoline-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide $C_{34}H_{29}N_7O_3$ Mol. Wt.: 583.64	584.34
	1-Methyl-1H-indole-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide $C_{34}H_{31}N_7O_3$ Mol. Wt.: 585.66	586.28
	1H-Indole-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide $C_{33}H_{29}N_7O_3$ Mol. Wt.: 571.63	572.24

Example 9

Biochemical Btk Assay

[00227] A generalized procedure for one standard biochemical Btk Kinase Assay that can be used to test compounds disclosed in this application is as follows.

[00228] A master mix minus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer (25 mM Tris-HCl, pH 7.5, 5 mM beta-glycerophosphate, 2 mM dithiothreitol, 0.1 mM Na_3VO_4, 10 mM $MgCl_2$), 0.5 μM Promega PTK Biotinylated peptide substrate 2, and 0.01% BSA. A master mix plus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer, 0.5 μM PTK Biotinylated peptide substrate 2, 0.01% BSA, and 50 ng/well Btk enzyme. Btk enzyme is prepared as follows: full length human wildtype Btk (accession number NM-000061) with a C-terminal V5 and 6x His tag was subcloned into pFastBac vector for making baculovirus carrying this epitope-tagged Btk. Generation of baculovirus was done based on Invitrogen's instructions detailed in its published protocol "Bac-toBac Baculovirus Expression Systems" (Cat. Nos. 10359-016 and 10608-016). Passage 3 virus was used to infect Sf9 cells to overexpress the recombinant Btk protein. The Btk protein was then purified to homogeneity using Ni-NTA column. The purity of the final protein preparation was greater than 95% based on the sensitive Sypro-Ruby staining. A solution of 5 mM ATP is prepared in water from a 50 mM Stock that was adjusted to pH7.4 with 1N NaOH. A quantity of 1.25 μL of compounds in 5%DMSO is transferred to a 96-well ½ area Costar polystyrene plate. Compounds are tested singly and with an 11-point dose-responsive curve (starting concentration is 10 μM; 1:2 dilution). A quantity of 18.75 μL of master mix minus enzyme (as a negative control) and master mix plus enzyme is transferred to appropriate wells in 96-well ½ area costar polystyrene plate. 5 μL of 5 mM ATP is added to that mixture in the 96-well ½ area Costar polystyrene plate for final ATP concentration of 1 mM. The reaction is allowed to incubate for 1 hour at room temperature. The reaction is stopped with Perkin Elmer 1X detection buffer containing 30 mM EDTA, 20 nM SA-APC, and 1 nM PT66 Ab. The plate is read using time-resolved fluorescence with a Perkin Elmer Envision using excitation filter 330 nm, emission filter 665 nm, and 2nd emission filter 615 nm. IC_{50} values are subsequently calculated.

Example 10

Ramos Cell Btk Assay

[00229] A generalized procedure for a standard cellular Btk Kinase Assay that can be used to test compounds disclosed in this application is as follows.

[00230] Ramos cells are incubated at a density of $0.5x10^7$ cells/ml in the presence of test compound for 1 hr at 37 °C. Cells are then stimulated by incubating with 10 μg/ml anti-human IgM $F(ab)_2$ for 5 minutes at 37 °C. Cells are pelleted, lysed, and a protein assay is performed on the cleared lysate. Equal protein amounts of each sample are subject to SDS-PAGE and western blotting with either anti-phosphoBtk(Tyr223) antibody (Cell Signaling Technology #3531) to assess Btk autophosphorylation or an anti-Btk antibody (BD Transduction Labs #611116) to control for total amounts of Btk in each lysate.

Example 11

B-Cell Proliferation Assay

[00231] A generalized procedure for a standard cellular B-cell proliferation assay that can be used to test compounds disclosed in this application is as follows.

[00232] B-cells are purified from spleens of 8-16 week old Balb/c mice using a B-cell isolation kit (Miltenyi Biotech, Cat # 130-090-862). Testing compounds are diluted in 0.25% DMSO and incubated with 2.5×10^5 purified mouse splenic B-cells for 30 min prior to addition of 10μg/ml of an anti-mouse IgM antibody (Southern Biotechnology Associates Cat # 1022-01) in a final volume of 100 μl. Following 24 hr incubation, 1 μCi ^{3}H-thymidine is added and plates are incubated an additional 36 hr prior to harvest using the manufacturer's protocol for SPA[^{3}H] thymidine uptake assay system (Amersham Biosciences # RPNQ 0130). SPA-bead based fluorescence is counted in a microbeta counter (Wallace Triplex 1450, Perkin Elmer).

Example 12

T Cell Proliferation Assay

[00233] A generalized procedure for a standard T cell proliferation assay that can be used to test compounds disclosed in this application is as follows.

[00234] T cells are purified from spleens of 8-16 week old Balb/c mice using a Pan T cell isolation kit (Miltenyi Biotech, Cat # 130-090-861). Testing compounds

are diluted in 0.25% DMSO and incubated with 2.5 x 10^5 purified mouse splenic T cells in a final volume of 100 µl in flat clear bottom plates precoated for 90 min at 37°C with 10 µg/ml each of anti-CD3 (BD # 553057) and anti-CD28 (BD # 553294) antibodies. Following 24 hr incubation, 1 µCi ^{3}H-thymidine is added and plates incubated an additional 36 hr prior to harvest using the manufacturer's protocol for SPA[^{3}H] thymidine uptake assay system (Amersham Biosciences # RPNQ 0130). SPA-bead based fluorescence was counted in a microbeta counter (Wallace Triplex 1450, Perkin Elmer).

Example 13

CD86 Inhibition Assay

[00235] A generalized procedure for a standard assay for the inhibition of B cell activity that can be used to test compounds disclosed in this application is as follows.

[00236] Total mouse splenocytes are purified from spleens of 8-16 week old Balb/c mice by red blood cell lysis (BD Pharmingen #555899). Testing compounds are diluted to 0.5% DMSO and incubated with 1.25 x 10^6 splenocytes in a final volume of 200 µl in flat clear bottom plates (Falcon 353072) for 60 min at 37°C. Cells are then stimulated with the addition of 15 µg/ml IgM (Jackson ImmunoResearch 115-006-020), and incubated for 24 hr at 37°C, 5% CO_2. Following the 24 hr incubation, cells are transferred to conical bottom clear 96-well plates and pelleted by centrifugation at 1200 x g x 5 min. Cells are preblocked by CD16/CD32 (BD Pharmingen #553142), followed by triple staining with CD19-FITC (BD Pharmingen #553785), CD86-PE (BD Pharmingen #553692), and 7AAD (BD Pharmingen #51-68981E). Cells are sorted on a BD FACSCalibur and gated on the $CD19^+/7AAD^-$ population. The levels of CD86 surface expression on the gated population is measured versus test compound concentration.

Example 14

B-ALL Cell Survival Assay

[00237] The following is a procedure for a standard B-ALL cell survival study using an XTT readout to measure the number of viable cells. This assay can be used

to test compounds disclosed in this applicationfor their ability to inhibit the survival of B-ALL cells in culture. One human B-cell acute lymphoblastic leukemia line that can be used is SUP-B15, a human Pre-B-cell ALL line that is available from the ATCC.

[00238] SUP-B15 pre-B-ALL cells are plated in multiple 96-well microtiter plates in 100 µl of Iscove's media + 20% FBS at a concentration of 5 x 10^5 cells/ml. Test compounds are then added with a final conc. of 0.4% DMSO. Cells are incubated at 37°C with 5% CO_2 for up to 3 days. After 3 days cells are split 1:3 into fresh 96-well plates containing the test compound and allowed to grow up to an additional 3 days. After each 24h period, 50 ul of an XTT solution (Roche) is added to one of the replicate 96-well plates and absorbance readings are taken at 2, 4 and 20 hours following manufacturer's directions. The reading taken with an OD for DMSO only treated cells within the linear range of the assay (0.5- 1.5) is then taken and the percentage of viable cells in the compound treated wells are measured versus the DMSO only treated cells.

Example 15

[00239] The compounds disclosed in synthetic Examples 1 to 8 are tested in the Btk biochemical assay described herein (Example 9) and exhibit an IC_{50} value less than or equal to 10 micromolar. Certain of those compounds exhibit an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibit an IC_{50} value less than or equal to 0.1 micromolar.

[00240] Some of the compounds disclosed in synthetic Examples 1 to 8 are tested in the B-cell proliferation assay (as described in Example 11) and exhibit an IC_{50} value less than or equal to 10 micromolar. Certain of those compounds exhibit an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibit an IC_{50} value less than or equal to 500 nM in this assay.

[00241] Certain of those compounds exhibiting an IC_{50} value less than or equal to 10 micromolar do not inhibit T-cell proliferation and have IC_{50} values greater than or equal to 5 micromolar when assayed under conditions described herein (as described in Example 12).

[00242] Certain compounds disclosed in Examples 1 to 8 exhibit IC_{50} values for

inhibition of T-cell proliferation that were at least 3-fold, and in some instances 5-fold, or even 10-fold greater than the IC_{50} values of those compounds for inhibition of B-cell proliferation.

[00243] Some of the compounds disclosed in Examples 1 to 8 are tested in an assay for inhibition of B cell activity (under the conditions described in Example 13), and exhibit an IC_{50} value less than or equal to 10 micromolar. Certain of those compounds exhibit an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibit an IC_{50} value less than or equal to 500 nM in this assay.

[00244] Some of the compounds disclosed in Examples 1 to 8 are tested in a B-cell leukemia cell survival assay (under the conditions described in Example 14), and exhibit an IC_{50} value less than or equal to 10 micromolar.

[00245] Some of the compounds disclosed in Examples 1 to 8 exhibit both biochemical and cell-based activity. For example, some of the compounds disclosed in Examples 1 to 8 exhibit an IC_{50} value less than or equal to 10 micromolar in the Btk biochemical assay described herein (Example 9) and an IC_{50} value less than or equal to 10 micromolar in at least one of the cell-based assays (other than the T-cell assay) described herein (Example 10, 11, 13, or 14). Certain of those compounds exhibit an IC_{50} value less than or equal to 1 micromolar in the Btk biochemical assay described herein (Example 9) and an IC_{50} value less than or equal to 10 micromolar in at least one of the cell-based assays (other than the T-cell assay) described herein (Example 10, 11, 13, or 14). Certain of those compounds exhibit an IC_{50} value less than or equal to 0.1 micromolar and an IC_{50} value less than or equal to 10 micromolar in at least one of the cell-based assays (other than the T-cell assay) described herein (Example 10, 11, 13, or 14).

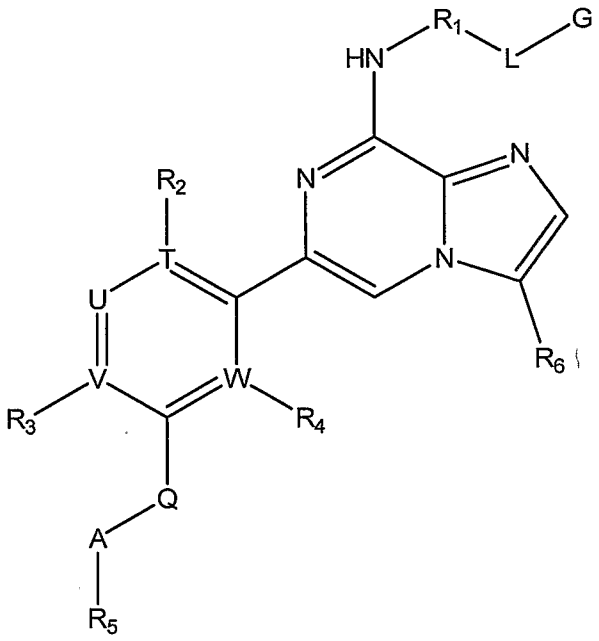
[00246] Certain of those compounds exhibiting both biochemical and cell-based activity do not inhibit T-cell proliferation. For example, some of the compounds disclosed in Examples 1 to 8 exhibit an IC_{50} value less than or equal to 10 micromolar in the Btk biochemical assay described herein (Example 9), an IC_{50} value less than or equal to 10 micromolar in at least one of the cell-based assays (other than the T-cell assay) described herein (Example 10, 11, 13, or 14) and an IC_{50} value for inhibition of T-cell proliferation at least 3-fold greater than the IC_{50} value for inhibition of B-cell proliferation. Certain of those compounds exhibit an IC_{50} value

less than or equal to 1 micromolar in the Btk biochemical assay described herein (Example 9), an IC_{50} value less than or equal to 10 micromolar in at least one of the cell-based assays (other than the T-cell assay) described herein (Example 10, 11, 13, or 14), and an IC_{50} value for inhibition of T-cell proliferation at least 5-fold greater than the IC_{50} value for inhibition of B-cell proliferation. Certain of those compounds exhibit an IC_{50} value less than or equal to 0.1 micromolar, an IC_{50} value less than or equal to 10 micromolar in at least one of the cell-based assays (other than the T-cell assay) described herein (Example 10, 11, 13, or 14), and an IC_{50} value for inhibition of T-cell proliferation at least 10-fold greater than the IC_{50} value for inhibition of B-cell proliferation.

[00247] While some embodiments have been shown and described, various modifications and substitutions may be made thereto without departing from the spirit and scope of the invention. For example, for claim construction purposes, it is not intended that the claims set forth hereinafter be construed in any way narrower than the literal language thereof, and it is thus not intended that exemplary embodiments from the specification be read into the claims. Accordingly, it is to be understood that the present invention has been described by way of illustration and not limitations on the scope of the claims.

What is claimed is:

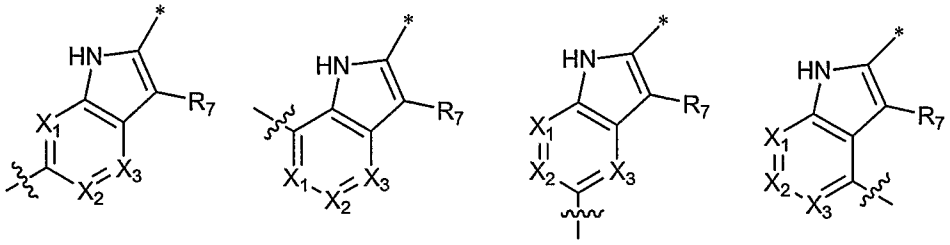
1. At least one chemical entity chosen from compounds of Formula 1:

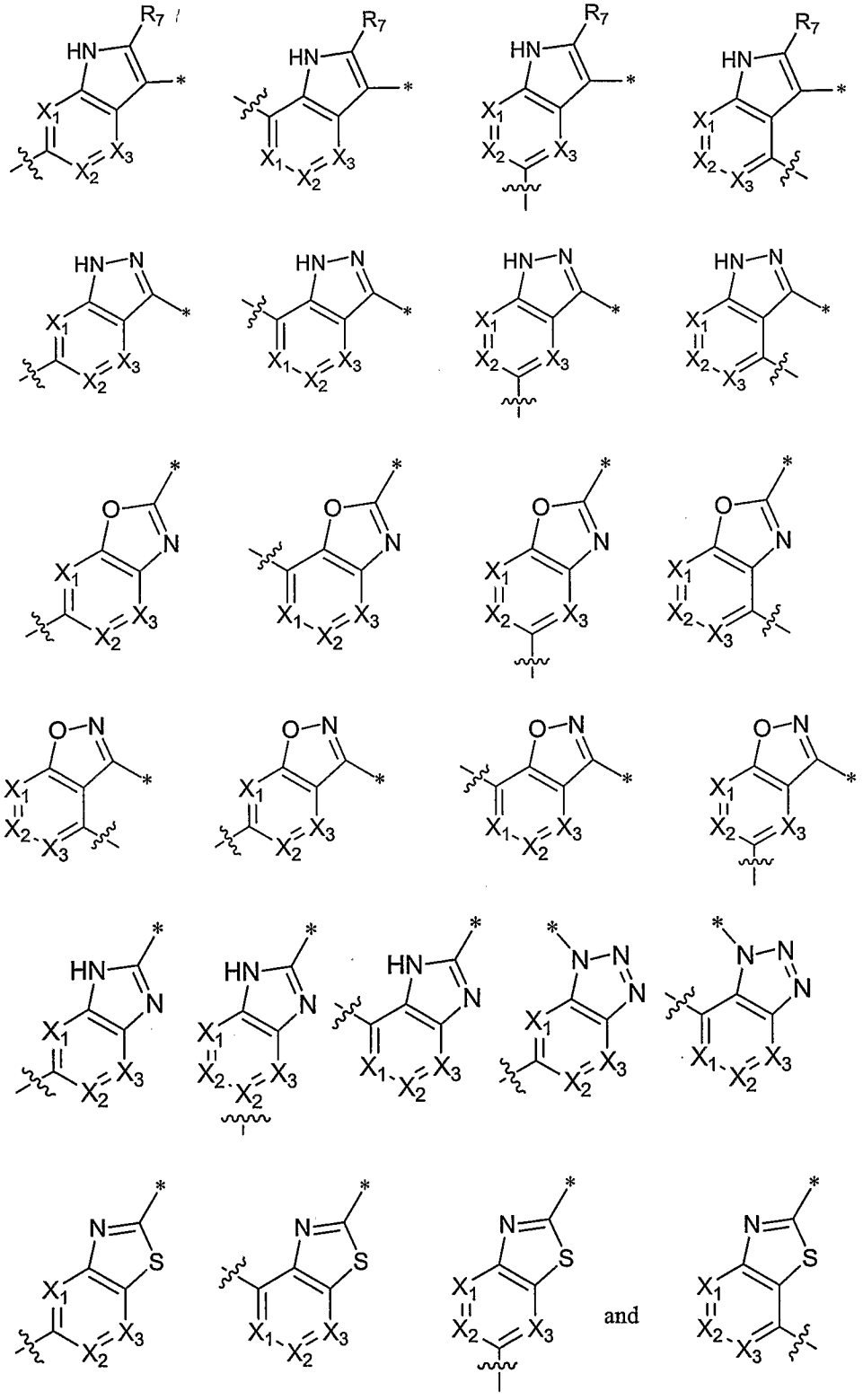


(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein

R_1 is chosen from optionally substituted phenylene, optionally substituted pyridylidene, optionally 2-oxo-1,2-dihydropyridinyl,





and

wherein * indicates the point of attachment to the group –L-G and the broken bond indicates the point of attachment to the amino group; and wherein

X_1 is chosen from N and CR_7; X_2 is chosen from N and CR_7; and X_3 is chosen from N and CR_7; wherein no more than one of X_1, X_2, and X_3 is N and wherein R_7 is chosen from hydrogen, hydroxy, cyano, halo, optionally substituted lower alkyl, and optionally substituted lower alkoxy;

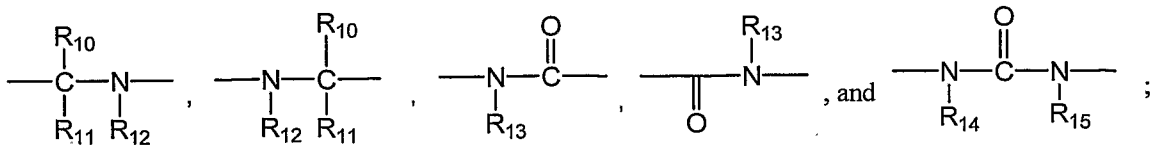
L is chosen from a covalent bond, optionally substituted C_1-C_4alkylene, -O-, -O-(optionally substituted C_1-C_4alkylene)-, -(C=O)-, -(optionally substituted C_1-C_4alkylene)(C=O)-, (SO)-, -(optionally substituted C_1-C_4alkylene)(SO)-; (SO_2)-, -(optionally substituted C_1-C_4alkylene)(SO_2)-; -(C=NR_9)-, and -(optionally substituted C_1-C_4alkylene)(C=NR_9)- wherein R_9 is chosen from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

G is chosen from hydrogen, halo, hydroxy, alkoxy, nitro, optionally substituted alkyl, -$NR_{16}R_{17}$, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl wherein R_{16} and R_{17} are independently chosen from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl; or when L is chosen from -(C=NR_9)- and -(optionally substituted C_1-C_4alkylene)(C=NR_9) then -R_9 and R_{16}, together with the nitrogen to which they are bound, form an optionally substituted 5- to 7-membered nitrogen containing heterocycloalkyl which optionally further includes one or two additional heteroatoms chosen from N, O, and S and R_{17} is chosen from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

T, V, and W are chosen from C and N and U is chosen from –CH and N, provided that at most one of T, U, V and W is N;

R_2, R_3, and R_4 are independently chosen from hydrogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, halo, and hydroxy, provided that at least one of R_2, R_3, and R_4 is not hydrogen when A is a covalent bond, G is -$NR_{16}R_{17}$ and L is not chosen from -(C=NR_9)- and -(optionally substituted C_1-C_4alkylene)(C=NR_9)-, and R_2, R_3, or R_4 is absent when the respective T, V, or W to which it is bound, is N;

Q is chosen from



wherein

R_{10} and R_{11} are independently chosen from hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

R_{12}, R_{13}, R_{14}, and R_{15} are each independently chosen from

hydrogen,

C_1-C_6 alkyl,

C_1-C_6 haloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

A is chosen from a covalent bond and -(CH=CH)-;

R_5 is chosen from optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl; and

R_6 is chosen from hydrogen, optionally substituted alkyl, cycloalkyl, and heterocycloalkyl.

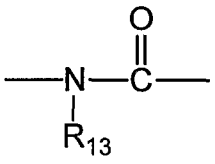
2. At least one chemical entity of claim 1 wherein A is a covalent bond.

3. At least one chemical entity of claim 1 wherein A is -(CH=CH)-.

4. At least one chemical entity of any one of claims 1 to 3 wherein R_{12}, R_{13}, R_{14}, and R_{15} are independently chosen from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and phenyl.

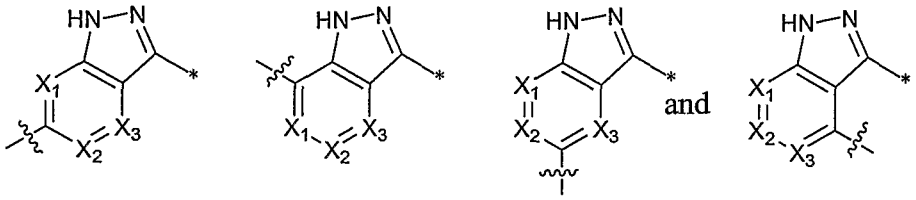
5. At least one chemical entity of claim 4 wherein R_{13} is chosen from hydrogen and C_1-C_6 alkyl.

6. At least one chemical entity of any one of claims 1 to 3 wherein Q is



wherein R_{13} is chosen from hydrogen and C_1-C_6 alkyl.

7. At least one chemical entity of any one of claims 1 to 6 wherein R_1 is chosen from ortho-phenylene, meta-phenylene, para-phenylene, ortho-pyridylidene, meta-pyridylidene, para-pyridylidene,

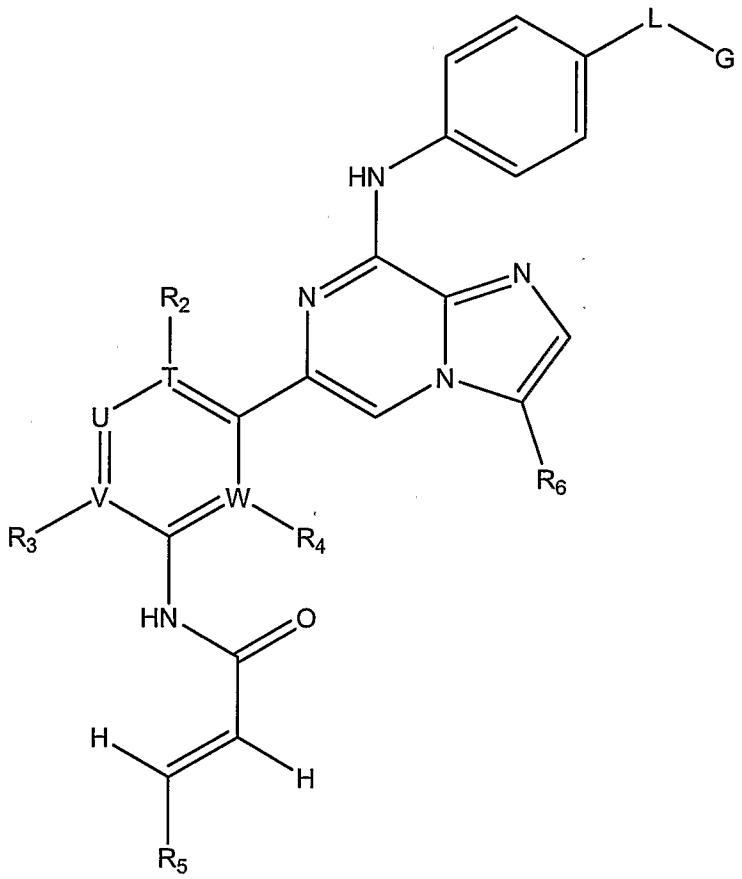


8. At least one chemical entity of claim 7 wherein R_1 is chosen from ortho-phenylene, meta-phenylene, para-phenylene, ortho-pyridylidene, meta-pyridylidene, and para-pyridylidene.

9. At least one chemical entity of claim 8 wherein R_1 is chosen from para-phenylene and meta-phenylene.

10. At least one chemical entity of claim 9 wherein R_1 is para-phenylene.

11. At least one chemical entity of claim 1 wherein the compounds of Formula 1 are chosen from compounds of Formula 2:



(Formula 2).

12. At least one chemical entity of any one of claims 1 to 11 wherein R_5 is chosen

from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfanyl, sulfonyl, optionally substituted amino, lower alkoxy, lower alkyl substituted with one or more halo, lower alkoxy substituted with one or more halo, lower alkyl substituted with hydroxy, and heteroaryl,

pyridyl,

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

pyrimidinyl,

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

pyrazinyl,

substituted pyrazinyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

pyridazinyl,

substituted pyridazinyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

oxazol-2-yl,

substituted oxazol-2-yl l chosen from mono-, di-, and tri-substituted oxazol-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

2H-pyrazol-3-yl,

substituted 2H-pyrazol-3-yl chosen from mono-, di-, and tri-substituted 2H-pyrazol-3-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

[1,2,3]thiadiazol-4-yl,

substituted [1,2,3]thiadiazol-4-yl chosen from mono-, di-, and tri-substituted [1,2,3]thiadiazol-4-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

isoxazol-5-yl,

substituted isoxazol-5-yl chosen from mono-, di-, and tri-substituted isoxazol-5-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl,

substituted 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl chosen from mono-, di-, and tri-substituted 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

4,5,6,7-tetrahydrobenzofuran-2-yl,

substituted 4,5,6,7-tetrahydrobenzofuran-2-yl chosen from mono-, di-, and tri-substituted 4,5,6,7-tetrahydrobenzofuran-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

4,5,6,7-tetrahydro-1H-indol-2-yl,

substituted 4,5,6,7-tetrahydro-1H-indol-2-yl chosen from mono-, di-, and tri-substituted 4,5,6,7-tetrahydro-1H-indol-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl and wherein the amine nitrogen of the indole ring is optionally substituted with an optionally substituted lower alkyl group,

1H-indol-2-yl,

substituted 1H-indol-2-yl chosen from mono-, di-, and tri-substituted 1H-indol-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl and wherein the amine nitrogen of the indole ring is optionally substituted with an optionally substituted lower alkyl group,

1H-indol-3-yl,

substituted 1H-indol-3-yl chosen from mono-, di-, and tri-substituted 1H-indol-3-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl and wherein the amine nitrogen of the indole ring is optionally substituted with an optionally substituted lower alkyl group,

benzofuran-2-yl,

substituted benzofuran-2-yl chosen from mono-, di-, and tri-substituted benzofuran-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl,

benzo[b]thiophen-2-yl,

substituted benzo[b]thiophen-2-yl chosen from mono-, di-, and tri-substituted benzo[b]thiophen-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl;

quinolin-3-yl, and

substituted quinolin-3-yl chosen from mono-, di-, and tri-substituted quinolin-3-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl.

13. At least one chemical entity of claim 12 wherein R_5 is chosen from phenyl and substituted phenyl wherein substituted phenyl is chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfanyl, sulfonyl, optionally substituted amino, lower alkoxy, lower alkyl substituted with one or more halo, lower alkoxy substituted with one or more halo, lower alkyl substituted with hydroxy, and heteroaryl.

14. At least one chemical entity of claim 13 wherein R_5 is substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl.

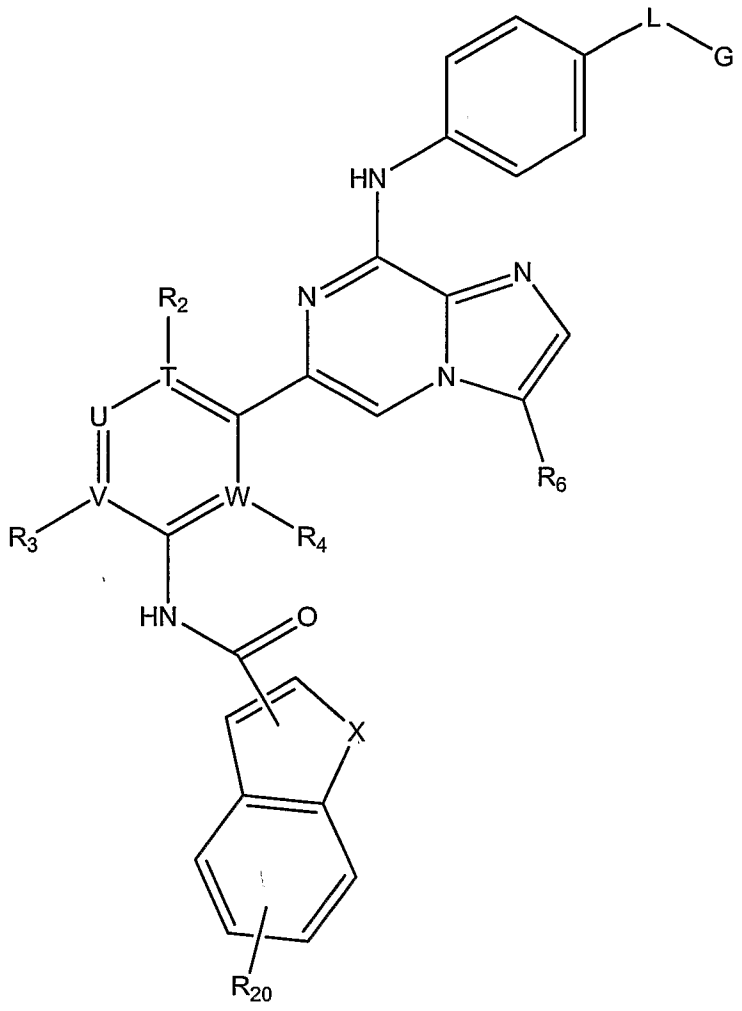
15. At least one chemical entity of claim 14 wherein R_5 is 4-lower alkyl-phenyl-.

16. At least one chemical entity of claim 15 wherein R_5 is 4-*tert*-butyl-phenyl.

17. At least one chemical entity of claim 12 wherein R_5 is chosen from pyridyl and substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, lower alkoxy, and heteroaryl.

18. At least one chemical entity of claim 17 wherein R_5 is pyrid-3-yl.

19. At least one chemical entity of claim 1 wherein the compounds of Formula 1 are chosen from compounds of Formula 3



(Formula 3)

wherein

X is chosen from O, S, NR_{18}, -CH=N-, and –N=CH-;

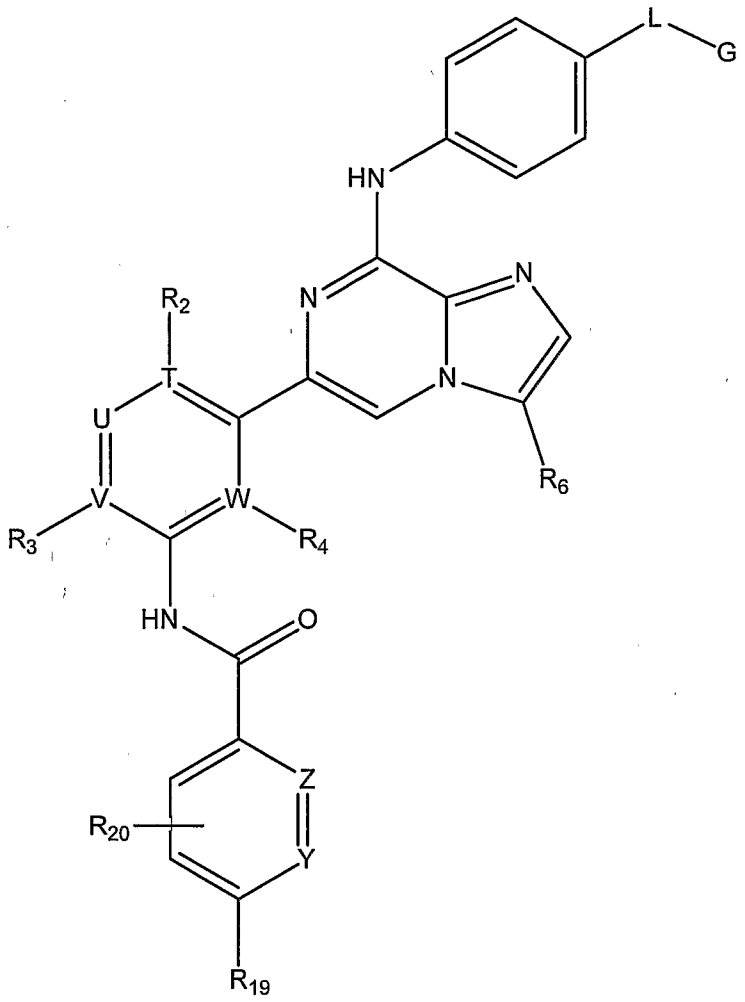
R_{18} is chosen from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

20. At least one chemical entity of claim 19 wherein X is chosen from O, NR_{18}, -CH=N-, and –N=CH.

21. At least one chemical entity of claim 20 wherein X is chosen from O and NR_{18}.

22. At least one chemical entity of claim 1 wherein the compounds of Formula 1 are chosen from compounds of Formula 4:



(Formula 4)

wherein

Y and Z are independently chosen from CH and N;

R_{19} is chosen from hydrogen, hydroxy, lower alkyl, sulfonyl, optionally substituted amino, lower alkoxy, lower alkyl substituted with one or more halo, lower

alkoxy substituted with one or more halo, lower alkyl substituted with hydroxy, and heteroaryl; and

R_{20} is chosen from hydrogen, lower alkyl, halo, lower alkoxy, and hydroxy.

23. At least one chemical entity of any one of claims 1 to 22 wherein L is chosen from a covalent bond, -(C=O)-, -CH_2-, -SO_2-, -CH_2(C=O)-, -$CH(CH_3)$(C=O)-, -CH_2CH_2(C=O)-, -(C=NR_9)-, and -(optionally substituted C_1-C_4alkylene)(C=NR_9)-.

24. At least one chemical entity of claim 23 wherein L is chosen from -(C=O)-, -CH_2-, -SO_2-, -CH_2(C=O)-, and -$CH(CH_3)$(C=O)-.

25. At least one chemical entity of claim 24 wherein L is -(C=O)-.

26. At least one chemical entity of any one of claims 1 to 25 wherein G is chosen from

hydrogen,
hydroxy,
-$NR_{16}R_{17}$,
optionally substituted heterocycloalkyl,
optionally substituted 5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl,
lower alkoxy, and
1H-tetrazol-5-yl.

27. At least one chemical entity of claim 26 wherein G is chosen from

hydrogen,
hydroxy,
N-methylethanolamino,
optionally substituted 4,5-dihydro-1H-imidazol-2-yl,
optionally substituted morpholin-4-yl,
optionally substituted piperazin-1-yl, and
optionally substituted homopiperazin1-yl.

28. At least one chemical entity of claim 27 wherein G is chosen from
hydrogen,
morpholin-4-yl,
4-acyl-piperazin-1-yl,
4-lower alkyl-piperazin-1-yl,
3-oxo-piperazin-1-yl,
homopiperazin-1-yl, and
4-lower alkyl-homopiperazin-1-yl.

29. At least one chemical entity of any one of claims 1 to 25 wherein G is chosen from $-NR_{16}R_{17}$, and optionally substituted heterocycloalkyl.

30. At least one chemical entity of claim 29 wherein G is chosen from optionally substituted morpholin-4-yl and optionally substituted piperazin-1-yl.

31. At least one chemical entity of claim 30 wherein G is morpholin-4-yl.

32. At least one chemical entity of any one of claims 1 to 22 wherein L is chosen from $-(C=NR_9)-$, and -(optionally substituted C_1-C_4alkylene)$(C=NR_9)-$ and G is $-NR_{16}R_{17}$.

33. At least one chemical entity of claim 32 wherein R_9 is chosen from hydrogen and lower alkyl.

34. At least one chemical entity of claim 33 wherein R_9 is chosen from hydrogen and methyl.

35. At least one chemical entity of any one of claims 1 to 34 wherein R_6 is hydrogen.

36. At least one chemical entity of any one of claims 1 to 35 wherein R_2 is chosen from methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy,

difluoromethoxy, and fluoro.

37. At least one chemical entity of claim 36 wherein R_2 is methyl.

38. At least one chemical entity of claim 36 or 37 wherein R_3 and R_4 are hydrogen.

39. At least one chemical entity of any one of claims 1 to 35 wherein R_3 is chosen from methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, and fluoro.

40. At least one chemical entity of claim 39 wherein R_3 is methyl.

41. At least one chemical entity of claim 39 or 40 wherein R_2 and R_4 are hydrogen.

42. At least one chemical entity of any one of claims 1 to 35 wherein R_4 is chosen from methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, and fluoro.

43. At least one chemical entity of claim 42 wherein R_4 is methyl.

44. At least one chemical entity of claim 42 or 43 wherein R_2 and R_3 are hydrogen.

45. At least one chemical entity of any one of claims 22 to 44 wherein Y and Z are CH.

46. At least one chemical entity of any of claims 22 to 45 wherein R_{19} is chosen from hydrogen and lower alkyl.

47. At least one chemical entity of claim 46 wherein R_{19} is chosen from hydrogen,

iso-propyl, and *tert*-butyl.

48. At least one chemical entity of claim 47 wherein R_{19} is *tert*-butyl.

49. At least one chemical entity of any one of claims 19 to 48 wherein R_{20} is absent.

50. At leat one chemical entity of any one of claims 1 to 49 wherein T, V, and W are C and U is -CH.

51. At least one chemical entity of any one of claims 1 to 50, wherein the at least one chemical entity exhibits an IC_{50} of 10 micromolar or less in an in vitro biochemical assay of Btk activity.

52. At least one chemical entity of claim 51, wherein the at least one chemical entity exhibits an IC_{50} of 1 micromolar or less in an in vitro biochemical assay of Btk activity.

53. At least one chemical entity of claim 52, wherein the at least one chemical entity exhibits an IC_{50} of 0.1 micromolar or less in an in vitro biochemical assay of Btk activity.

54. At least one chemical entity of any one of claims 1 to 53 wherein the at least one chemical entity exhibits an IC_{50} of 10 micromolar or less in an assay for inhibition of B-cell activity.

55. At least one chemical entity of claim 54 wherein the at least one chemical entity exhibits an IC_{50} of 1 micromolar or less in an assay for inhibition of B-cell activity.

56. At least one chemical entity of claim 55 wherein the at least one chemical entity exhibits an IC_{50} of 500 nanomolar or less in an assay for inhibition of B-cell activity.

57. At least one chemical entity of any one of claims 1 to 56, wherein the at least one chemical entity exhibits an IC_{50} value in an assay for inhibition of T-cell proliferation that is at least 3-fold greater than an IC_{50} value that the at least one chemical entity exhibits in an assay for inhibition of B-cell proliferation.

58. At least one chemical entity of claim 57, wherein the at least one chemical entity exhibits an IC_{50} value in an assay for inhibition of T-cell proliferation that is at least 5-fold greater than an IC_{50} value that the at least one chemical entity exhibits in an assay for inhibition of B-cell proliferation.

59. At least one chemical entity of claim 58, wherein the at least one chemical entity exhibits an IC_{50} value in an assay for inhibition of T-cell proliferation that is at least 10-fold greater than an IC_{50} value that the at least one chemical entity exhibits in an assay for inhibition of B-cell proliferation.

60. At least one chemical entity of any one of claims 1 to 59 wherein the at least one chemical entity exhibits an IC_{50} of 10 micromolar or less in a B-ALL cell survival assay.

61. At least one chemical entity of claim 1 wherein the compound of Formula 1 is chosen from

4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(5-{8-[4-(4-Acetyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-4-tert-butyl-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(N-methyl-hydroxyethyl-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(NNdimethyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(N-methyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(amide)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(5-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-4-tert-butyl-benzamide;

4-tert-Butyl-N-(2-fluoro-5-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-{2-methyl-5-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(3-oxo-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(5-{8-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-4-tert-butyl-benzamide;

4-tert-Butyl-N-(5-{8-[4-(5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

(4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-{5-[8-(4-{[(2-hydroxy-ethyl)-methyl-carbamoyl]-methyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide;

4-tert-Butyl-N-[2-methyl-5-(8-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

(3-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid;

4-tert-Butyl-N-(2-methyl-5-{8-[3-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-[2-methyl-5-(8-{3-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

4-tert-Butyl-N-{5-[8-(3-dimethylcarbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide;

2-(3-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-propionic acid;

4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methoxy-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-tert-Butyl-N-(2-methyl-5-{8-[4-(1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-{6-[3-(4-tert-Butyl-benzoylamino)-4-fluoro-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylhydroxyethyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylethyl-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-{6-[5-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-tert-Butyl-N-(4-methyl-3-{8-[4-(Nmethylhydroxyethyl-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester;

4-tert-Butyl-N-(2-fluoro-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

6-tert-Butyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

[1,2,3]Thiadiazole-4-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

Isoxazole-5-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

Pyridine-2-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

6-tert-Butyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-nicotinamide;

4-tert-Butyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-Isopropyl-N-{2-methyl-3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

6-Hydroxy-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

5-tert-Butyl-oxazole-2-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-methylsulfanyl-benzamide;

4-(1H-Imidazol-2-yl)-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(1H-tetrazol-5-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-Methanesulfonyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

2-Hydroxy-6-methyl-N-(2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(1H-tetrazol-5-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

2,5-Dimethyl-2H-pyrazole-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

4-tert-Butyl-N-{2-methyl-5-[8-(4-sulfamoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

4-tert-Butyl-N-{3-[8-(4-carbamimidoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N'-dimethyl-carbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(imino-morpholin-4-yl-methyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N-dimethyl-carbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(2-imino-2-morpholin-4-yl-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylcarbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N'-dimethyl-carbamimidoyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(4,5-dihydro-1H-imidazol-2-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

4-tert-Butyl-N-{3-[8-(4-carbamimidoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide;

4-tert-Butyl-N-{3-[8-(4-carbamimidoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-benzamide;

4-tert-Butyl-N-(2-methyl-3-{8-[4-(N-methylcarbamimidoylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N'-dimethyl-carbamimidoylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

4-tert-Butyl-N-(3-{8-[4-(N,N-dimethyl-carbamimidoylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-2-methyl-phenyl)-benzamide;

Benzofuran-2-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

N-(2-Methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-3-pyridin-3-yl-acrylamide;

Quinoline-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

1-Methyl-1H-indole-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

1H-Indole-3-carboxylic acid (2-methyl-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-amide;

6-tert-Butyl-N-(2-methyl-3-{8-[4-(1-oxo-1l4-thiomorpholin-4-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

N-{3-[8-(3-Amino-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-2-methyl-phenyl}-4-tert-butyl-benzamide; and

Tetrahydro-furan-2-carboxylic acid (3-{6-[3-(4-tert-butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-amide.

62. A pharmaceutical composition, comprising at least one chemical entity of any one of claims 1 to 61, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients.

63. A pharmaceutical composition of claim 62 wherein the composition is formulated in a form chosen from injectable fluids, aerosols, creams, gels, tablets, pills, capsules, syrups, ophthalmic solutions, and transdermal patches.

64. A packaged pharmaceutical composition, comprising
a pharmaceutical composition of claim 62 or 63; and
instructions for using the composition to treat a patient suffering from a disease responsive to inhibition of Btk activity.

65. The packaged pharmaceutical composition of claim 64 wherein the disease responsive to inhibition of Btk activity is cancer.

66. The packaged pharmaceutical composition of claim 65 wherein the disease responsive to inhibition of Btk activity is chosen from allergic disorders, autoimmune diseases, inflammatory diseases, and acute inflammatory reactions.

67. A method for treating a patient having a disease responsive to inhibition of Btk activity, comprising administering to the patient an effective amount of at least one chemical entity of any of claims 1 to 61 or a pharmaceutical composition of claim 62 or 63.

68. The method of claim 67 wherein the patient is a human.

69. The method of claim 67 wherein the patient is chosen from cats and dogs.

70. The method of any one of claims 67 to 69 wherein the disease responsive to inhibition of Btk activity is cancer.

71. The method of claim 70 wherein the disease responsive to inhibition of Btk activity is B-cell lymphoma and leukemia.

72. The method of any one of claims 67 to 71 wherein an effective amount of said at least one chemical entity is administered by a method chosen from intravenously, intramuscularly, and parenterally.

73. The method of any of claims 67 to 71 wherein an effective amount of said at least one chemical entity is administered orally.

74. A method for treating a patient having a disease chosen from cancer, autoimmune diseases, inflammatory diseases, acute inflammatory reactions, and allergic disorders comprising administering to the patient an effective amount of at least one chemical entity of any of claims 1 to 61 or a pharmaceutical composition of claim 62 or 63.

75. The method of claim 74 wherein the patient is a human.

76. The method of claim 74 wherein the patient is chosen from cats and dogs.

77. The method of any one of claims 74 to 76 wherein an effective amount of said at least one chemical entity is administered by a method chosen from intravenously, intramuscularly, and parenterally.

78. The method of any of claims 74 to 76 wherein an effective amount of said at least one chemical entity is administered orally.

79. A method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient undergoing chemotherapy with a chemotherapeutic agent an amount of at least one chemical entity of any of claims 1 to 61 or a pharmaceutical composition of claim 62 or 63, sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent.

80. A method of reducing medication error and enhancing therapeutic compliance of a patient being treated for a disease responsive to inhibition of Btk activity, the method comprising providing a packaged pharmaceutical preparation of claim 64 wherein the instructions additionally include contraindication and adverse reaction information pertaining to the packaged pharmaceutical composition.

81. A method for inhibiting ATP hydrolysis, the method comprising contacting cells expressing Btk with at least one chemical entity of any one of claims 1 to 61 in an amount sufficient to detectably decrease the level of ATP hydrolysis *in vitro*.

82. The method of claim 81 wherein the cells are present in a mammal.

83. The method of claim 82 wherein the mammal is a human.

84. The method of claim 82 wherein the mammal is chosen from cats and dogs.

85. A method for determining the presence of Btk in a sample, comprising contacting the sample with at least one chemical entity of any one of claims 1 to 61 under conditions that permit detection of Btk activity, detecting a level of Btk activity in the sample, and therefrom determining the presence or absence of Btk in the sample.

86. A method for inhibiting B-cell activity comprising contacting cells expressing Btk with at least one chemical entity, of any one of claims 1 to 61, in an amount sufficient to detectably decrease B-cell activity *in vitro*.

87. At least one chemical entity of any one of claims 1 to 61 wherein the at least one chemical entity is either directly or indirectly labeled with a label which provides a detectable signal.

88. At least one chemical entity of claim 87 wherein the label is chosen from radioisotopes, fluorescent tags, enzymes, antibodies, particles, chemiluminescent tags, and specific binding molecules.

89. The use of at least one chemical entity for the manufacture of a medicament for the treatment of a patient having a disease responsive to inhibition of Btk activity, wherein the at least one chemical entity is a chemical entity of any one of claims 1 to 61.

90. The use of claim 89, wherein the disease responsive to inhibition of Btk activity is chosen from cancer, autoimmune diseases, inflammatory diseases, acute inflammatory reactions, and allergic disorders.

91. A method for the manufacture of a medicament for the treatment of a patient having a disease responsive to inhibition of Btk activity, comprising including in said medicament at least one chemical entity of any one of claims 1 to 61.

92. The method of claim91 wherein the disease responsive to inhibition of Btk activity is chosen from cancer, autoimmune diseases, inflammatory diseases, acute inflammatory reactions, and allergic disorders.