Certain Substituted Amides, Method of Making, and Method of Use Thereof

This application claims the benefit of the filing date of U.S. Provisional Application Serial No. 60/843,959 filed September 11, 2006.

[0001] Provided herein are certain substituted amides and related compounds, compositions comprising such compounds, and methods of their use.

[0002] 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.

[0003] B-cell signaling through the B-cell receptor (BCR) can lead 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.

[0004] 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 can also be resistant to developing collagen-induced arthritis and can be less susceptible to Staphylococcus-induced arthritis.

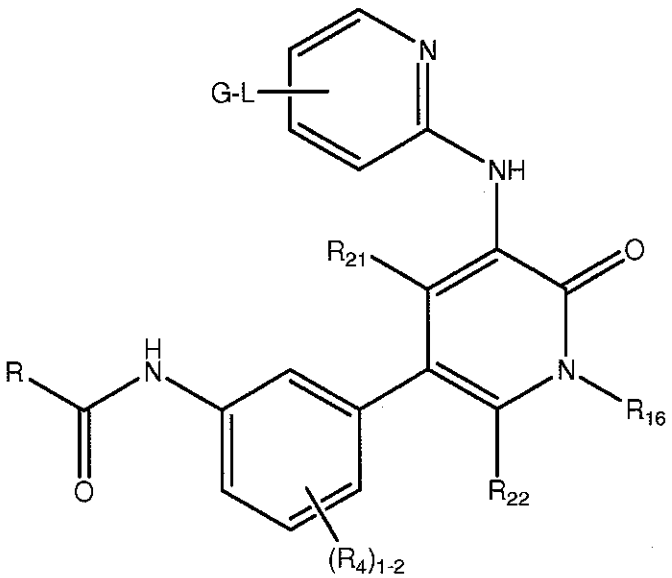
[0005] A large body of evidence supports the role of B-cells and the humoral immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Protein-based therapeutics (such as Rituxan) developed to deplete B-cells, represent

an 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).

[0006] Btk is also expressed in osteoclasts, 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.

[0007] Thus, inhibition of Btk activity can be useful for the treatment of allergic disorders and/or autoimmune and/or inflammatory diseases such as: SLE, rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, and asthma. In addition, Btk has been reported to play a role in apoptosis; thus, inhibition of Btk activity can be useful for cancer, as well as the treatment of B-cell lymphoma and leukemia. Moreover, given the role of Btk in osteoclast function, the inhibition of Btk activity can be useful for the treatment of bone disorders such as osteoporosis.

[0008] Provided is at least one chemical entity chosen from compounds of Formula 1:



(Formula 1)

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

R is chosen from optionally substituted aryl and optionally substituted heteroaryl;

R_4 is chosen from hydrogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, halo, and hydroxy.

R_{21} and R_{22} are independently chosen from hydrogen and optionally substituted lower alkyl;

R_{16} is chosen from hydrogen, cyano, optionally substituted cycloalkyl, and optionally substituted lower alkyl;

L is chosen from optionally substituted C_0-C_4alkylene, -O-optionally substituted C_0-C_4alkylene, -(C_0-C_4alkylene)(SO)-, -(C_0-C_4alkylene)(SO_2)-; and -(C_0-C_4alkylene)(C=O)-; and

G is chosen from hydrogen, halo, hydroxy, alkoxy, nitro, optionally substituted alkyl, optionally substituted amino, optionally substituted carbamimidoyl, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl.

[0009] 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.

[0010] Provided is a packaged pharmaceutical composition, comprising

a pharmaceutical composition described herein; and

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

[0011] 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.

[0012] Provided is a method for treating a patient having a disease chosen from cancer, bone disorders, 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.

[0013] 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.

[0014] 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.

[0015] 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*.

[0016] 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.

[0017] 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*.

[0018] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise. The following abbreviations and terms have the indicated meanings throughout:

[0019] 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.

[0020] 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.

[0021] As used herein, the term "at least one chemical entity" is interchangeable with the term "a compound."

[0022] 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.

[0023] "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.

[0024] "Cycloalkyl" indicates a saturated hydrocarbon ring group, having the specified number of carbon atoms, usually from 3 to 7 ring carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl as well as bridged and caged saturated ring groups such as norbornane.

[0025] 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.

[0026] "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 $CH_3(C=O)$-.

[0027] 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.

[0028] By "amino" is meant the group $-NH_2$.

[0029] 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 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 or heterocycloalkyl), $-CO_2H$, -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).

[0030] "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 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 heterocycloalkyl 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.

[0031] The term "aryloxy" refers to the group -O-aryl.

[0032] The term "halo" includes fluoro, chloro, bromo, and iodo, and the term "halogen" includes fluorine, chlorine, bromine, and iodine.

[0033] "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.

[0034] "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 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 the heteroaromatic ring or the cycloalkyl 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 as defined above.

[0035] Substituted heteroaryl also includes ring systems substituted with one or more oxide ($-O^-$) substituents, such as pyridinyl N-oxides.

[0036] By "heterocycloalkyl" is meant a single aliphatic 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. 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 moieties, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1,1-dioxo-1-thiomorpholinyl, and ring systems comprising one or more -SO- or -SO_2- groups.

[0037] "Carbamimidoyl" refers to the group -C(=NH)-NH_2.

[0038] "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 cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C_1-C_6 alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl,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 or heterocycloalkyl), -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).

[0039] 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.

[0040] 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.

[0041] The term "sulfinyl" includes the groups: -S(O)-H, -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).

[0042] The term "sulfonyl" includes the groups: -$S(O_2)$-H, -$S(O_2)$-(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).

[0043] 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. Heteroatoms present in heteroaryls or heterocycloalkyls described herein include the oxidized forms of such heteroatoms such as $N^+ \rightarrow O^-$, S(O), and $S(O)_2$.

[0044] 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, oxo, 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 cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

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

R^c is 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 or heterocycloalky), $-CO_2H$, -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), $-SO_2NH_2$, $-SO_2$NH(C_1-C_4 alkyl), $-SO_2$NH(phenyl), $-NHSO_2$(C_1-C_4 alkyl), $-NHSO_2$(phenyl), and $-NHSO_2$(C_1-C_4 haloalkyl).

[0045] 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 cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

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

R^c is 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 or heterocycloalkyl), $-CO_2H$, $-C(O)OC_1-C_4$ 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).

[0046] 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 cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

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

R^c is 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 or heterocycloalkyl), $-CO_2H$, $-C(O)OC_1-C_4$ 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.

[0047] The term "substituted amino" refers to the group $-NHR^d$ or $-NR^dR^d$ where each R^d is independently chosen from: hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted acyl, aminocarbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, alkoxycarbonyl, sulfinyl and sulfonyl, provided that only one R^d may be hydroxyl and two R^ds of $-NR^dR^d$ are optionally 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; 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 cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

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

R^c is 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 or heterocycloalkyl), -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, aminocarbonyl, alkoxycarbonyl, sulfinyl and sulfonyl are as defined herein.

[0048] 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.

[0049] 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. Compounds of Formula 1 also include crystal forms including polymorphs and clathrates.

[0050] 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, 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.

[0051] "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.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] The term "chelate" refers to the chemical entity formed by the coordination of a compound to a metal ion at two (or more) points.

[0056] 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).

[0057] The term "hydrogen bond" refers to a form of association between an electronegative atom (also known as a hydrogen bond acceptor) and a hydrogen atom attached to a second, relatively electronegative atom (also known as a hydrogen bond donor). Suitable hydrogen bond donor and acceptors are well understood in medicinal chemistry (G. C. Pimentel and A. L. McClellan, The Hydrogen Bond, Freeman, San Francisco, 1960; R. Taylor and O. Kennard, "Hydrogen Bond Geometry in Organic Crystals", Accounts of Chemical Research, 17, pp. 320-326 (1984)).

[0058] As used herein the terms "group", "radical" or "fragment" are synonymous and are intended to indicate functional groups or fragments of molecules attachable to a bond or other fragments of molecules.

[0059] 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.

[0060] 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 inhibition of Btk activity. In some embodiments, a therapeutically effective amount is an amount sufficient to reduce cancer symptoms, the symptoms of bone disorders, 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.

[0061] 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.

[0062] 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 1 micromolar. In some embodiments, the chemical entity has an IC_{50} value less than or equal to less than 100 nanomolar. In some embodiments, the chemical entity has an IC_{50} value less than or equal to 10 nanomolar.

[0063] "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.

[0064] 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.

[0065] "B cell activity" also includes activation, redistribution, reorganization, or capping of one or more various B cell membrane receptors, e.g., CD40, CD86 and Toll-like receptors TLRs (in particular TLR4), 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.

[0066] 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.

[0067] 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.

[0068] "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 no increase or 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).

[0069] 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.

[0070] 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.

[0071] "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.

[0072] 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 $p < 0.05$.

[0073] 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, osteoclasts, B-cells, mast cells, myeloid cells, basophils, macrophages, neutrophils, and dendritic cells).

[0074] "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;

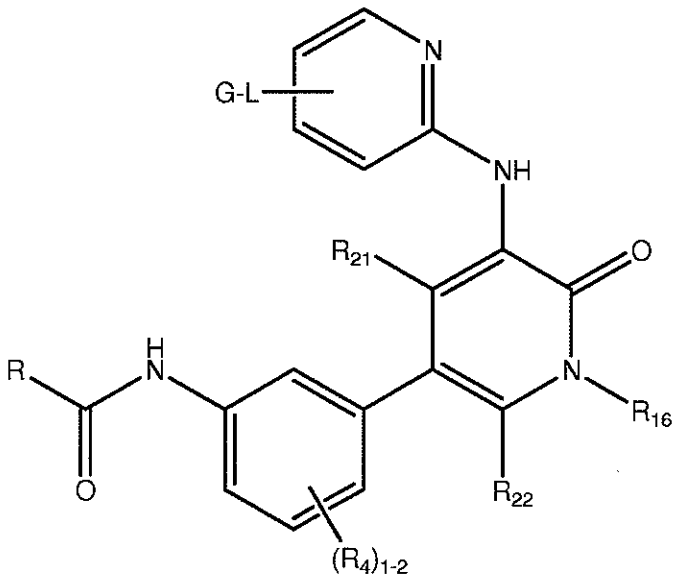
b) inhibiting the disease;

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

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

[0075] "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.

[0076] Provided is at least one chemical entity chosen from compounds of Formula 1:



(Formula 1)

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

R is chosen from optionally substituted aryl and optionally substituted heteroaryl;

R_4 is chosen from hydrogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, halo, and hydroxy.

R_{21} and R_{22} are independently chosen from hydrogen and optionally substituted lower alkyl;

R_{16} is chosen from hydrogen, cyano, optionally substituted cycloalkyl, and optionally substituted lower alkyl;

L is chosen from optionally substituted C_0-C_4alkylene, -O-optionally substituted C_0-C_4alkylene, -(C_0-C_4alkylene)(SO)-, -(C_0-C_4alkylene)(SO_2)-; and -(C_0-C_4alkylene)(C=O)-; and

G is chosen from hydrogen, halo, hydroxy, alkoxy, nitro, optionally substituted alkyl, optionally substituted amino, optionally substituted carbamimidoyl, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl.

[0077] In certain embodiments, R is chosen from 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl and 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.

[0078] In certain embodiments, R is chosen from 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl and 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 lower alkyl.

[0079] In certain embodiments, R is chosen from 4,5,6,7-tetrahydrobenzo[b] thiophen-2-yl.

[0080] In certain embodiments, R is chosen from 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl and substituted 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl chosen from mono-, di-, and tri-substituted 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl wherein the substituents are independently chosen from lower alkyl.

[0081] In certain embodiments, R is chosen from 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl.

[0082] In certain embodiments, R is chosen from pyrazin-2-yl and substituted pyrazin-2-yl chosen from mono-, di-, and tri-substituted pyrazin-2-yl wherein the substituents are independently chosen from lower alkyl.

[0083] In certain embodiments, R is chosen from 5-tert-butyl-pyrazin-2-yl.

[0084] In certain embodiments, R is 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, lower alkyl substituted with lower alkoxy, and heteroaryl.

[0085] In certain embodiments, R is substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from heterocycloalkyl (e.g., piperidin-1-yl), and lower alkyl substituted with cycloalkyl (e.g., cyclopropyl).

[0086] In certain embodiments, R 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.

[0087] In certain embodiments, R is 4-lower alkyl-phenyl-. In certain

embodiments, R is 4-*tert*-butyl-phenyl.

[0088] In certain embodiments, R_4 is chosen from hydrogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, cyano, halo, and hydroxy. In certain embodiments, R_4 is chosen from hydrogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, halo, and hydroxy. In certain embodiments, R_4 is chosen from methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, and fluoro. In certain embodiments, R_4 is methyl.

[0089] In certain embodiments, R_{22} is chosen from hydrogen and lower alkyl. In certain embodiments, R_{22} is chosen from hydrogen and methyl. In certain embodiments, R_{22} is hydrogen.

[0090] In certain embodiments, R_{21} is chosen from hydrogen and lower alkyl. In certain embodiments, R_{21} is chosen from hydrogen and methyl. In certain embodiments, R_{21} is hydrogen.

[0091] In certain embodiments, R_{16} is chosen from hydrogen, lower alkyl, and lower alkyl substituted with a group chosen from optionally substituted alkoxy, optionally substituted amino, and optionally substituted acyl. In certain embodiments, R_{16} is chosen from hydrogen and lower alkyl. In certain embodiments, R_{16} is lower alkyl. In certain embodiments, R_{16} is chosen from hydrogen, methyl, and ethyl. In certain embodiments, R_{16} is chosen from methyl and ethyl. In certain embodiments, R_{16} is methyl. In certain embodiments, R_{16} is hydrogen.

[0092] In certain embodiments, L is chosen from optionally substituted C_0-C_4alkylene, -O-optionally substituted C_0-C_4alkylene, -(C_0-C_4alkylene)(SO_2)-; and -(C_0-C_4alkylene)(C=O)-. In certain embodiments, L is chosen from optionally substituted C_0-C_4alkylene and -(C_0-C_4alkylene)(C=O)-. In certain embodiments, L is a covalent bond. In certain embodiments, L is -(C=O)-.

[0093] In certain embodiments, G is chosen from

hydrogen,

hydroxy,

-NR_7R_8 wherein R_7 and R_8 are independently chosen from hydrogen, optionally substituted acyl, and optionally substituted (C_1-C_6)alkyl; or wherein R_7 and R_8, 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;

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

lower alkoxy, and

1H-tetrazol-5-yl.

[0094] In certain embodiments, G is chosen from

hydrogen,

amino;

hydroxy,

N-methylethanolamino,

optionally substituted morpholin-4-yl,

optionally substituted piperazin-1-yl,

optionally substituted piperidin-1-yl, and

optionally substituted homopiperazin-1-yl.

[0095] In certain embodiments, G is chosen from

hydrogen,

amino,

morpholin-4-yl,

4-acyl-piperazin-1-yl,

4-lower alkyl-piperazin-1-yl,

4-lower alkyl-piperidin-1-yl,

4-hydroxy-4-lower alkyl-piperidin-1-yl,

3-oxo-piperazin-1-yl,

homopiperazin-1-yl, and

4-lower alkyl-homopiperazin-1-yl.

[0096] In certain embodiments, G is chosen from

4-lower alkyl-piperazin-1-yl wherein said alkyl is substituted with one or more substituents chosen from CN, lower alkoxy, halo, and SO_2-lower alkyl, and

4-lower alkoxy-piperidin-1-yl.

[0097] In certain embodiments, G is chosen from

hydrogen,

amino,

morpholin-4-yl,

4-methyl-piperazin-1-yl,

4-methyl-piperidin-1-yl, and

4-hydroxy-4-methyl-piperidin-1-yl.

[0098] In certain embodiments, G is chosen from

4-CN-piperidin-1-yl,

4-cyclopropyl-piperazin-1-yl,

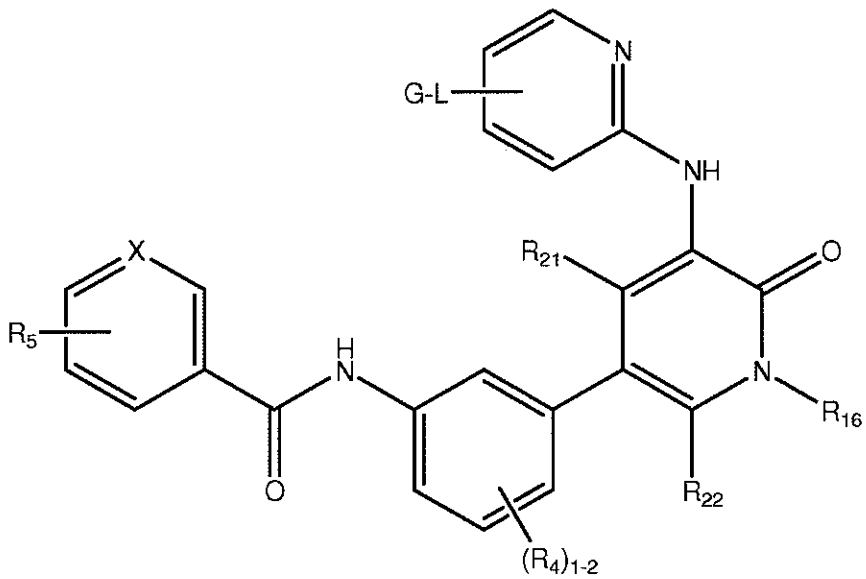
4-(4-methylpiperazin-1-yl)-piperidin-1-yl,

4-morpholinopiperidin-1-yl,

oxazepan-4-yl, and

1,1-dioxo-thiomorpholin-4-yl.

[0099] Also provided is at least one chemical entity chosen from compounds of Formula 2:



(Formula 2)

and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein R_4, R_{16}, R_{21}, R_{22}, L, and G are as described for compounds of Formula 1 or as defined in any one of the preceding embodiments, and wherein

R_5 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

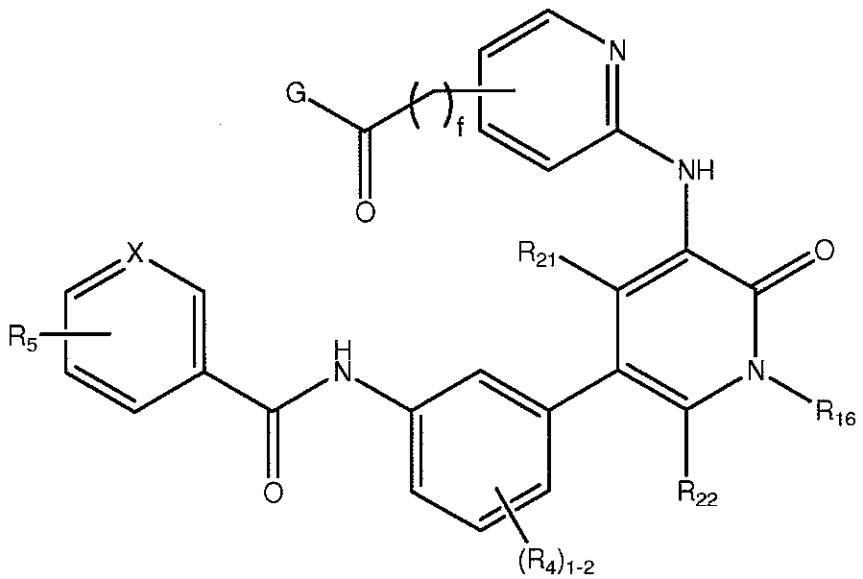
hydroxy, optionally substituted heterocycloalkyl, and optionally substituted heteroaryl; and

X is chosen from N and CH.

[00100] In certain embodiments, X is CH. In certain embodiments, X is N.

[00101] In certain embodiments, R_5 is chosen from hydrogen, optionally substituted piperidinyl, and lower alkyl. In certain embodiments, R_5 is chosen from hydrogen, optionally substituted piperidinyl, *iso*-propyl, and *tert*-butyl. In certain embodiments, R_5 is *tert*-butyl.

[00102] Also provided is at least one chemical entity chosen from compounds of Formula 3:



(Formula 3)

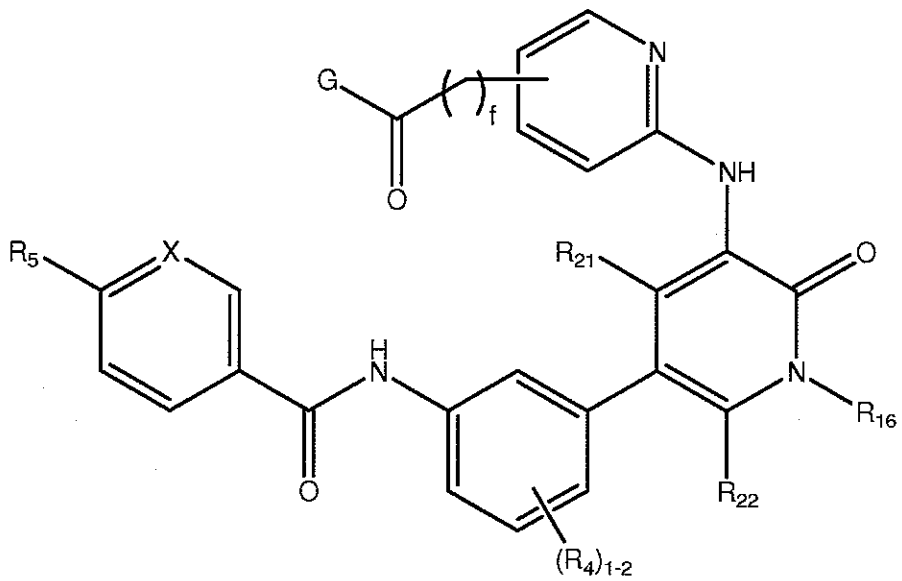
and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein R_4, R_{16}, R_{21}, R_{22}, and G are as described for compounds of Formula 1 or as defined in any one of the preceding embodiments; X and R_5 are as described for compounds of Formula 2 or as defined in any one of the preceding embodiments; and wherein f is chosen from 0, 1 and 2.

[00103] In certain embodiments, the group G-C(O)-$(CH_2)_f$- is attached to the 3 position of the ring. In certain embodiments, the group G-C(O)-$(CH_2)_f$- is attached to the 4 position of the ring.

[00104] In certain embodiments, *f* is 0.

[00105] Also provided is at least one chemical entity chosen from compounds

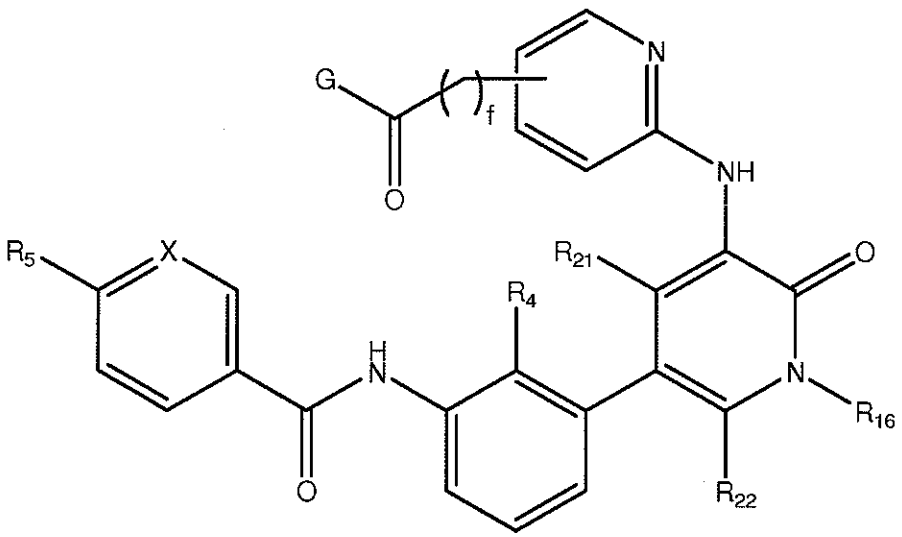
of Formula 4:



(Formula 4)

and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein R_4, R_{16}, R_{21}, R_{22}, and G are as described for compounds of Formula 1 or as defined in any one of the preceding embodiments; X and R_5 are as described for compounds of Formula 2 or as defined in any one of the preceding embodiments; and f is as described for compounds of Formula 3 or as defined in any one of the preceding embodiments.

[00106] Also provided is at least one chemical entity chosen from compounds of Formula 5:



(Formula 5)

and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein R_4, R_{16}, R_{21}, R_{22}, and G are as described for compounds of Formula 1 or as defined in any one of the preceding embodiments; X and R_5 are as described for compounds of Formula 2 or as defined in any one of the preceding embodiments; and f is as described for compounds of Formula 3 or as defined in any one of the preceding embodiments.

[00107] In certain embodiments, the compound of Formula 1 is chosen from

N-{3-[5-(6-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-tert-butyl-benzamide;

4-tert-Butyl-N-(2-methyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-benzamide;

N-{3-[5-(4-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-tert-butyl-benzamide;

4-tert-Butyl-N-{2-methyl-3-[1-methyl-6-oxo-5-(pyridin-2-ylamino)-1,6-dihydro-pyridin-3-yl]-phenyl}-benzamide;

4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;

4-tert-Butyl-N-(2-methyl-3-{5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-benzamide;

4-tert-Butyl-N-{2-methyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl}-benzamide;

4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-{5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;

4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid {2-methyl-3-[1-methyl-6-oxo-5-(pyridin-2-ylamino)-1,6-dihydro-pyridin-3-yl]-phenyl}-amide;

4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid {2-methyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl}-amide;

4-tert-Butyl-N-{3-[5-(4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-benzamide;

4-tert-Butyl-N-(2-fluoro-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-benzamide;

4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid {3-[5-(4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-amide;

4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-{1-methyl-5-[5-(4-methyl-piperazine-1-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;

4-tert-Butyl-N-[3-(5-{5-[1-hydroxy-2-(isopropyl-methyl-amino)-ethyl]-pyridin-2-ylamino}-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-2-methyl-phenyl]-benzamide;

N-{3-[5-(6-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-*tert*-butyl-benzamide;

N-(2-Methyl-3-(5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxamide;

4-*tert*-Butyl-N-(2-methyl-3-(1-methyl-5-(5-(4-methyl piperazine-1-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

N-(3-(5-(4-Amino-5-(4-hydroxy-4-methyl piperidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl) -2-methylphenyl)-4-tert-butyl benzamide;

4-*tert*-Butyl-N-(2-methyl-3-(1-methyl-6-oxo-5-(5-(piperidine-1-carbonyl) pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)benzamide;

4-*tert*-Butyl-N-(2-methyl-3-(1-methyl-6-oxo-5-(5-(2-(pyrrolidin-1-ylmethyl) morpholine-4-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl) benzamide;

N-(2-Methyl-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4-(piperidin-1-yl)benzamide;

N-(3-(5-(5-(1-Hydroxy-2-(isopropyl(methyl)amino)ethyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydro benzo[b]thiophene-2-carboxamide;

6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-N,N-dimethylnicotinamide;

N-(2-Methyl-3-(1-methyl-6-oxo-5-(5-(piperidine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-methyl-1,4-diazepane-1-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo [b]thiophene-2-carboxamide;

4-tert-Butyl-N-(5-fluoro-2-methyl-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

4-tert-Butyl-N-(3-(5-(5-(4-hydroxypiperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-(4-Hydroxypiperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-Hydroxypiperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(2-methyl-3-(1-methyl-5-(5-(morpholinomethyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

N-(2-Hydroxyethyl)-N-methyl-6-(1-methyl-5-(2-methyl-3-(5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-methylpiperazine-1-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-N-(2-hydroxyethyl)-N-methylnicotinamide;

N-(2-Methyl-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(3-(5-(5-(1,4-Oxazepane-4-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4-tert-butylbenzamide;

4-tert-Butyl-N-(2-methyl-3-(1-methyl-6-oxo-5-(5-((tetrahydro-2H-pyran-4-ylamino) methyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)benzamide;

6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-N,N-bis(2-methoxyethyl)nicotinamide;

N,N-bis(2-Methoxyethyl)-6-(1-methyl-5-(2-methyl-3-(4,5,6,7-tetrahydrobenzo[b] thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;

N,N-bis(2-Methoxyethyl)-6-(1-methyl-5-(2-methyl-3-(5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;

4-tert-Butyl-N-(2-chloro-5-fluoro-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

4-tert-Butyl-N-(3-(5-(5-(4-isopropylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-(4-Isopropylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-2-carboxamide;

N-(3-(5-(5-(4-Isopropylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta [b]thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-5-(5-(morpholinomethyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(3-(5-(5-(hydroxymethyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-(Hydroxymethyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(3-(5-(5-((isopropyl(methyl)amino)methyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-((Isopropyl(methyl)amino)methyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(3-(5-(5-((Isopropyl(methyl)amino)methyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

4-tert-Butyl-N-(3-(5-(5-(4-(2-hydroxyethyl)piperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-(4-(2-Hydroxyethyl)piperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-2-carboxamide;

N-(3-(5-(5-(4-(2-Hydroxyethyl)piperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

5-Methyl-N-(2-methyl-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(2-Chloro-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;

N-(3-(5-(5-(4-Acetylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4-tert-butylbenzamide;

N-(3-(5-(5-(4-Acetylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-Acetylpiperazine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

4-tert-Butyl-N-(2-methyl-3-(1-methyl-6-oxo-5-(5-(3-oxopiperazine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)benzamide;

N-(2-Methyl-3-(1-methyl-6-oxo-5-(5-(3-oxopiperazine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-6-oxo-5-(5-(3-oxopiperazine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-N-(2-methoxyethyl)-N-methylnicotinamide;

N-(2-Methoxyethyl)-N-methyl-6-(1-methyl-5-(2-methyl-3-(4,5,6,7-tetrahydrobenzo [b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-ylamino) nicotinamide;

N-(2-Methoxyethyl)-N-methyl-6-(1-methyl-5-(2-methyl-3-(5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;

6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-N-ethyl-N-methylnicotinamide;

N-Ethyl-N-methyl-6-(1-methyl-5-(2-methyl-3-(4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;

N-Ethyl-N-methyl-6-(1-methyl-5-(2-methyl-3-(5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinamide;

N-(5-Fluoro-2-methyl-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

N-(5-Fluoro-2-methyl-3-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-N-ethylnicotinamide;

6-(5-(3-(4-tert-Butylbenzamido)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinic acid;

6-(1-Methyl-5-(2-methyl-3-(4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinic acid;

6-(1-Methyl-5-(2-methyl-3-(5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamido)phenyl)-2-oxo-1,2-dihydropyridin-3-ylamino)nicotinic acid;

4-tert-Butyl-N-(2-methyl-3-(1-methyl-6-oxo-5-(5-(4-oxopiperidine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)benzamide;

N-(2-Methyl-3-(1-methyl-6-oxo-5-(5-(4-oxopiperidine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-6-oxo-5-(5-(4-oxopiperidine-1-carbonyl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(3-(5-(5-(4-(methoxymethyl)piperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-(4-(Methoxymethyl)piperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-(Methoxymethyl)piperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(3-(5-(5-(4-cyanopiperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-(4-Cyanopiperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(3-(5-(4-chloro-5-(morpholine-4-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

4-tert-Butyl-N-(2-methyl-3-(1-methyl-5-(5-(4-morpholinopiperidin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-morpholinopiperidin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-morpholinopiperidin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

4-tert-Butyl-N-(2-methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

4-tert-Butyl-N-(3-(5-(5-(4-methoxypiperidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-(4-Methoxypiperidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(3-(5-(5-(4-(dimethylamino)piperidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(5-Fluoro-2-methyl-3-(1-methyl-5-(5-(4-methylpiperazine-1-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-Cyanopiperidine-1-carbonyl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-Ethyl-6-(5-(5-fluoro-2-methyl-3-(4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamido)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-ylamino)-N-methylnicotinamide;

N-(3-(5-(5-(4-(Dimethylamino)piperidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(2-methyl-3-(1-methyl-5-(5-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

4-tert-Butyl-N-(2-methyl-5-(1-methyl-5-(5-(morpholine-4-carbonyl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(5-fluoro-2-methyl-3-(1-methyl-5-(5-morpholinopyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

4-tert-Butyl-N-(5-fluoro-2-methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

4-tert-Butyl-N-(5-fluoro-2-methyl-3-(1-methyl-5-(5-(4-morpholinopiperidin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzamide;

4-tert-Butyl-N-(5-fluoro-3-(5-(5-(4-hydroxy-4-methylpiperidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl) benzamide;

4-tert-Butyl-N-(3-(5-(5-(4-ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

4-tert-Butyl-N-(3-(5-(5-(4-isopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(3-(5-(5-(4-Isopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)benzo[b]thiophene-2-carboxamide;

5-tert-Butyl-N-(2-methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)pyrazine-2-carboxamide;

4-tert-Butyl-N-(3-(5-(5-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)benzamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4-(piperidin-1-yl)benzamide;

N-(3-(5-(5-(4-(2-Hydroxyethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-2-carboxamide;

4-tert-Butyl-N-(2-methyl-3-(1-methyl-6-oxo-5-(5-(piperazin-1-yl)pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)benzamide;

N-(3-(5-(5-(4-Hydroxy-4-methylpiperidin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-Ethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-Isopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

4-(Ethyl-methyl-amino)-N-(2-methyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-benzamide;

4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2,5-difluoro-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;

5,6,7,8-Tetrahydro-4H-cyclohepta[b]thio-phene-2-carboxylic acid (2,5-difluoro-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;

4-(1-Methyl-cyclopropyl)-N-(2-methyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-benzamide;

4,5,6,7-Tetrahydro-benzo[b]thiophene-2-carboxylic acid (2-methyl-3-{5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-amide;

5,6,7,8-Tetrahydro-4H-cyclohepta[b]thio-phene-2-carboxylic acid [2-fluoro-3-(5-{5-[4-(2-methoxy-ethyl)-piperazin-1-yl]-pyridin-2-ylamino}-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-amide;

4-(1-Ethyl-cyclopropyl)-N-(2-methyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-benzamide;

N-(3-(5-(5-(4-Cyclopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-fluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-(2-Cyanoethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-fluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(2-Fluoro-3-(5-(5-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

N-(2-Fluoro-3-(5-(5-(4-(2-fluoroethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(2-Fluoro-3-(1-methyl-5-(5-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

N-(2-Fluoro-3-(1-methyl-5-(5-(4-methyl-1,4-diazepan-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

N-(3-(5-(5-(1,4-Oxazepan-4-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro pyridin-3-yl)-2-fluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(2-Fluoro-3-(1-methyl-6-oxo-5-(5-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta [b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-Cyclopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

N-(3-(5-(5-(4-(2-Cyanoethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

N-(3-(5-(5-(4-(2-Methoxyethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta [b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-(2-Fluoroethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b] thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-methyl-1,4-diazepan-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(3-(5-(5-(1,4-Oxazepan-4-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro pyridin-3-yl)-2-methylphenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-6-oxo-5-(5-(5-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-5,6,7,8-tetrahydro-4H-cyclohepta [b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-Cyclopropylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-(2-Cyanoethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(3-(5-(5-(4-(2-Methoxyethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-2-carboxamide;

N-(3-(5-(5-(4-(2-Fluoroethyl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-2-carboxamide;

N-(2-Methyl-3-(1-methyl-5-(5-(4-methyl-1,4-diazepan-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide;

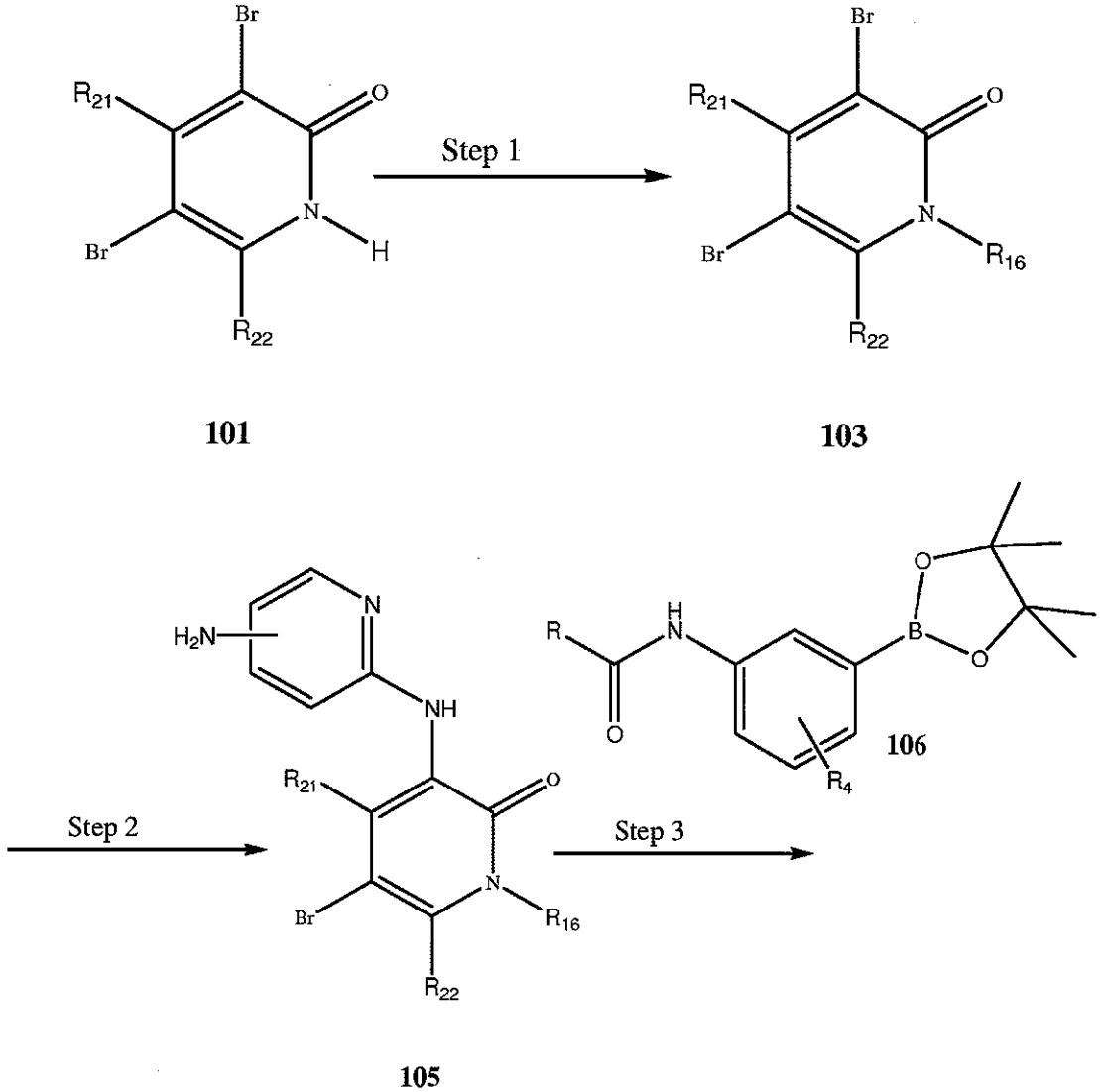
N-(3-(5-(5-(1,4-Oxazepan-4-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro pyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide; and

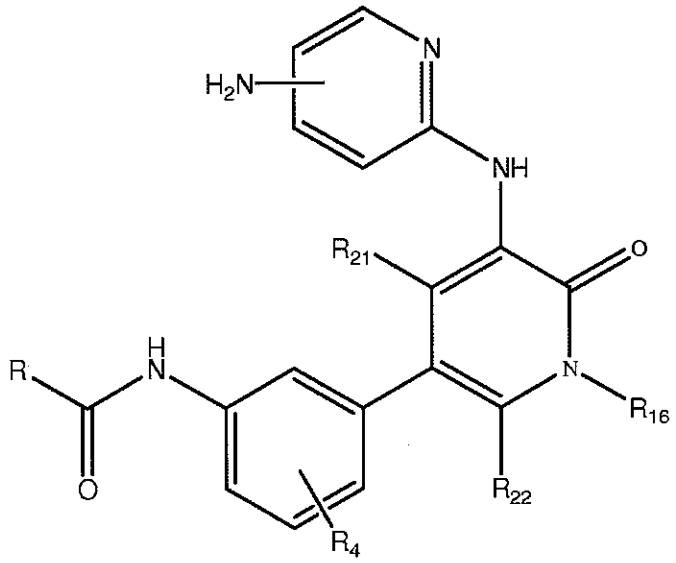
N-(2-Methyl-3-(1-methyl-6-oxo-5-(5 -(5-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-2-carboxamide.

[00108] The chemical entities described herein are potent inhibitors of Btk. While not being bound by any theory, that increased potency may result from the combination of a 2-aminopyridine head group with a pyridone core. In other words, the chemical entities described herein are more potent Btk inhibitors than similar compounds having a pyrazinone core or a different head group. For example, a compound having a 6-pyridone core with a phenylamino head group showed IC_{50} of 273 nM in a Btk biochemical assay (in the presence of 10 micromolar ATP) (see, Example 6), while a compound that is otherwise structurally identical except for the replacement of the phenylamino head group by 2-aminopyridyl showed IC_{50} of 12nM in the same assay. A compound having a 5-pyrazinone core with a 2-aminopyridyl head group showed IC_{50} of 193 nM in a Bkt biochemical assay (in the present of 10 micromolar ATP) as decribed in Example 6, while a compound that is otherwise structurally identical except for the replacement of the 5-pyrazinone core by 6-pyridone showed IC_{50} of 12nM in the same assay.

[00109] 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 scheme and examples below, and in the references cited herein.

Reaction Scheme 1





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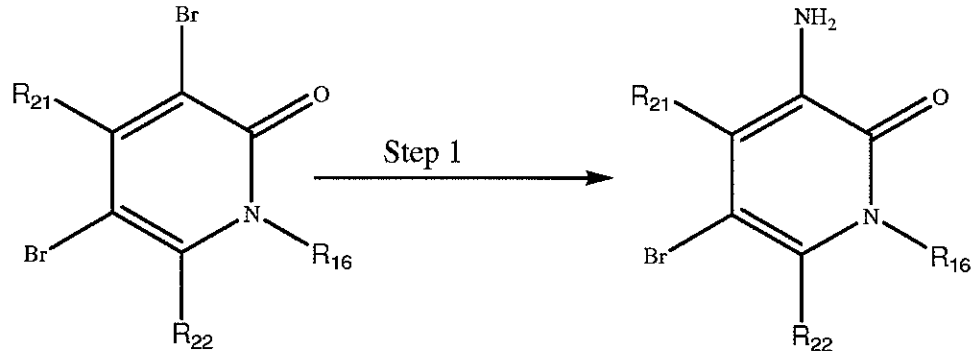
[00110] Referring to Reaction Scheme 1, Step 1, a compound of Formula 101 in a suitable solvent, such as anhydrous DMF, and an excess (such as at least 2 equivalents) of powdered potassium carbonate is stirred for about 15 minutes. An excess (such as about 1.1 equivalents) of a compound of Formula $R_{16}X$ where X is a leaving group, such as iodide, is added. The mixture is stirred at room temperature. The product, a compound of Formula 103 is isolated and optionally purified.

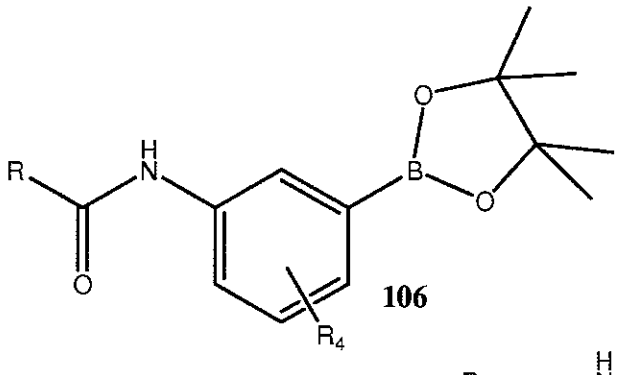
[00111] Referring to Reaction Scheme 1, Step 2, to a solution of an excess (such as about 1.2 equivalents) of diaminopyridine, a compound of Formula 103, 0.05 equivalent of $Pd_2(dba)_3$, about 0.15 equivalent of 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, and an excess (such as about 1.5 equivalents) of Cs_2CO_3 in dioxane is heated at about 95 °C for about 16 h. The product, a compound of Formula 105 was isolated and optionally purified.

[00112] Referring to Reaction Scheme 1, Step 3, a mixture of a compound of Formula 105, an excess (such as about 1.2 equivalents) of a compound of Formula 106, and about 0.05 equivalent of $Pd(PPh_3)_4$ in a suitable solvent such as DMF is heated at about 95 °C for about 16 h. The product, a compound of Formula 107, is isolated and optionally purified.

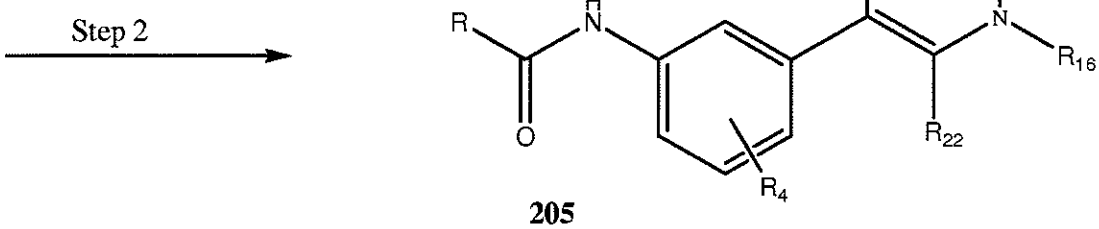
Reaction Scheme 2



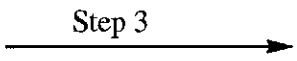
103 **203**

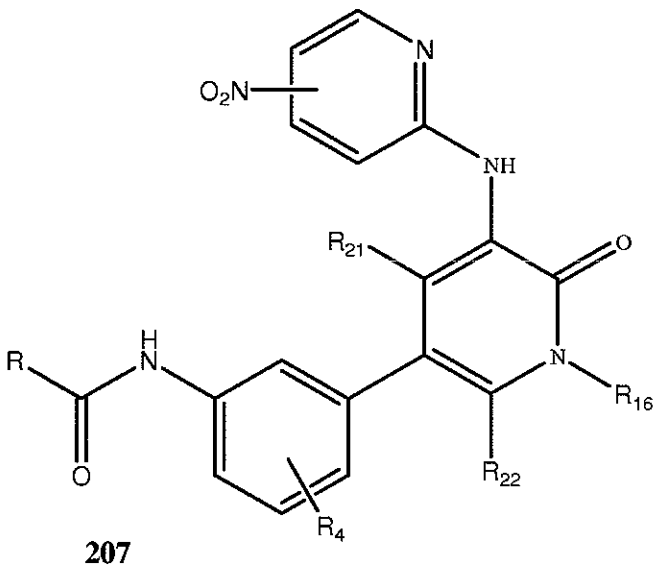


106

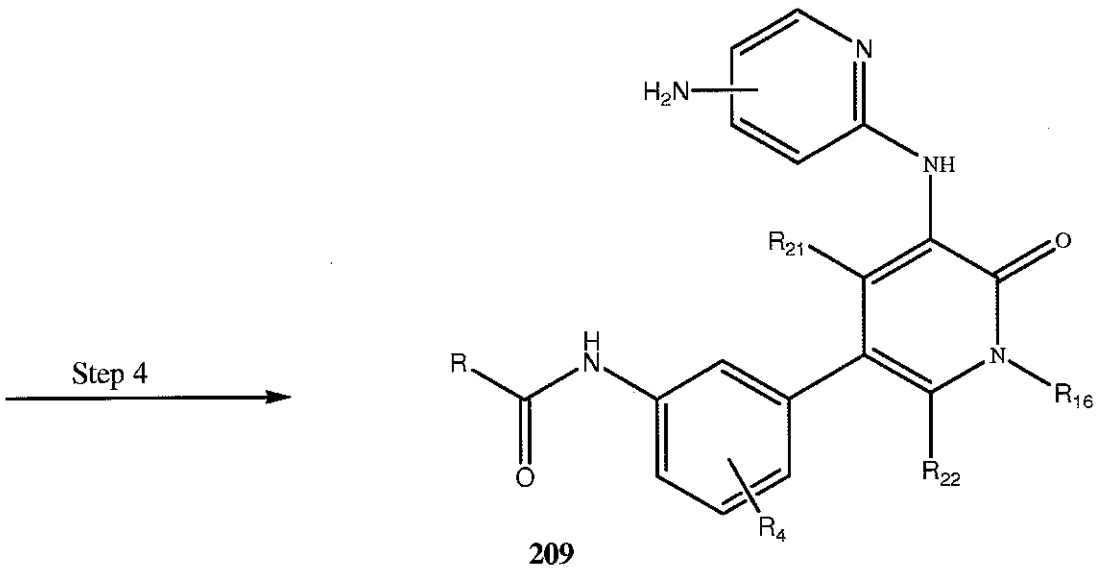


205





207



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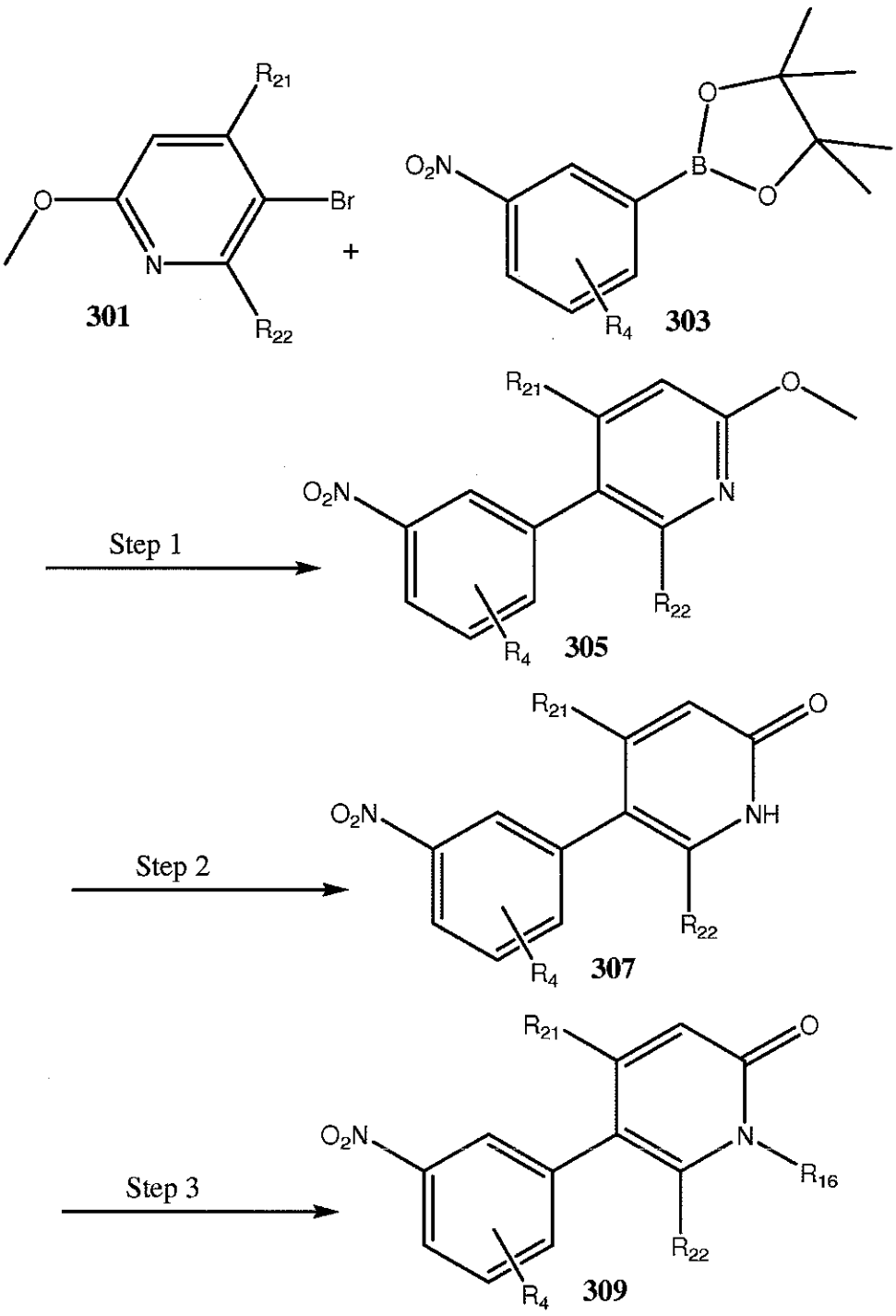
[00113] Referring to Reaction Scheme 2, Step 1, a mixture of an excess (such as about 1.2 equivalents) of benzophenone imine, a compound of Formula 103, about 0.6 equivalent of $Pd(OAc)_2$, 0.07 equivalent of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (rac-BINAP), and an excess (such as about 1.4 equivalents) of Cs_2CO_3 in a suitable solvent such as dioxane is heated at about 95 °C for about 16 h. The product, a compound of Formula 203, is isolated and optionally purified.

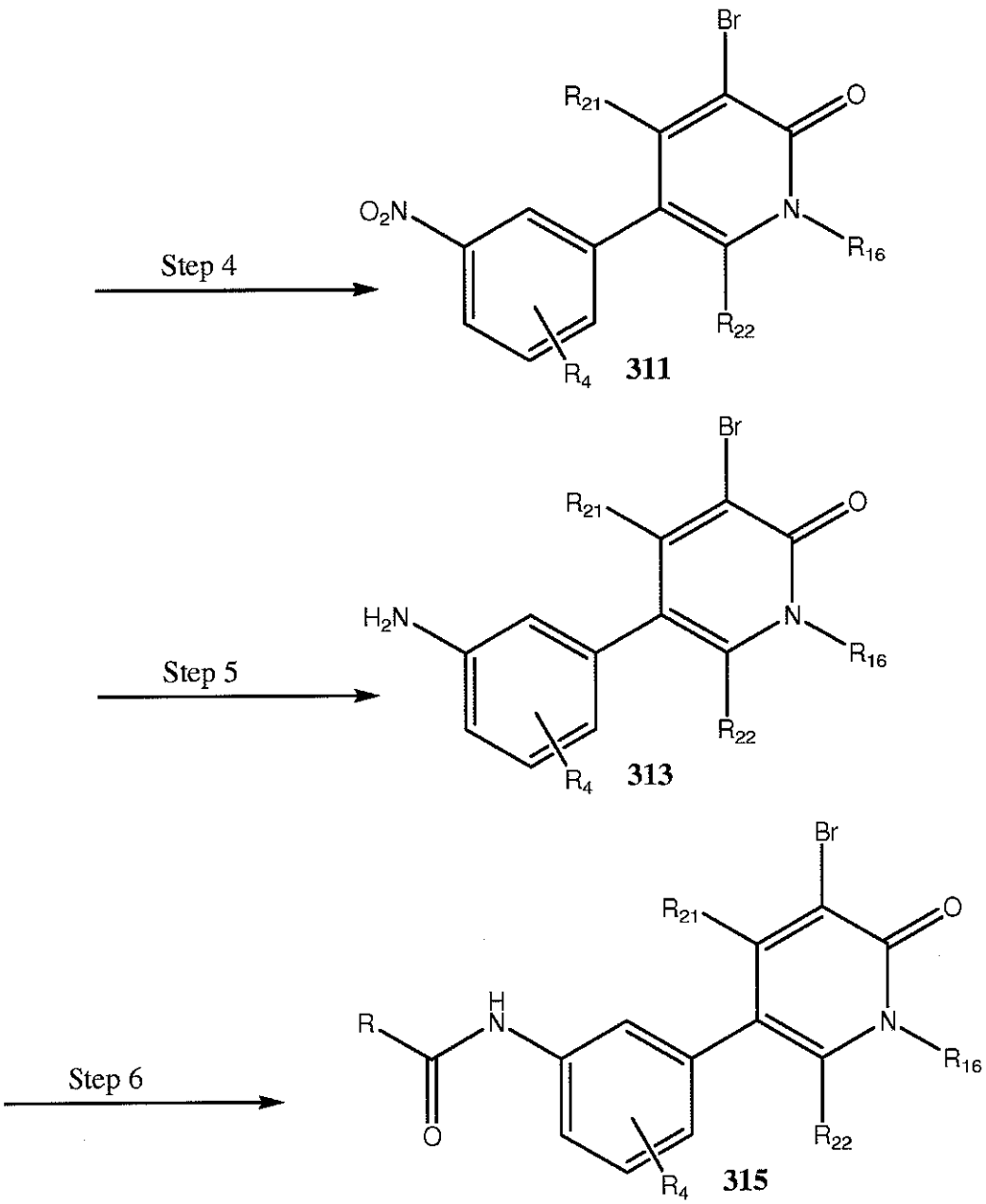
[00114] Referring to Reaction Scheme 2, Step 2, a mixture of a compound of Formula 203, an excess (such as about 1.4 equivalents) of a compound of Formula 106, and 0.05 equivalent of $Pd(PPh_3)_4$ in a suitable solvent such as DME with aqueous base, such as 1N Na_2CO_3 is heated at about 95 °C for about 16 h. The product, a compound of Formula 205, is isolated and optionally purified.

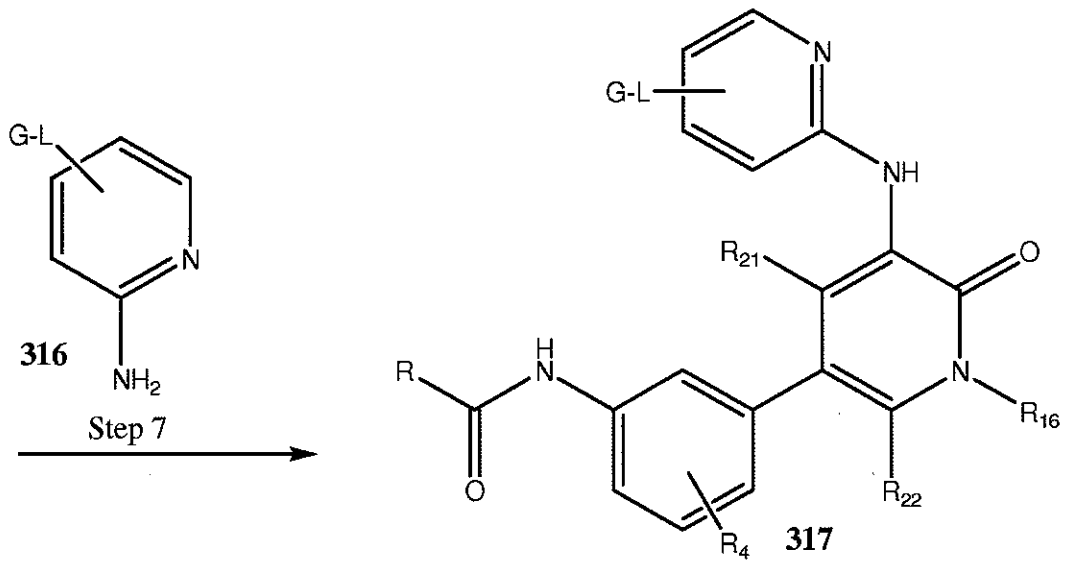
[00115] Referring to Reaction Scheme 2, Step 3, a mixture of a compound of Formula 205, an excess (such as about 1.09 equivalents) of 2-chloronitropyridine, about 0.09 equivalent of $Pd_2(dba)_3$, about 0.1 equivalent of 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene and an excess (such as about 2 equivalents) of Cs_2CO_3 in a suitable solvent such as dioxane is heated at about 95 °C for about 16 h. The product, a compound of Formula 207, is isolated and optionally purified.

[00116] Referring to Reaction Scheme 2, Step 4, a compound of Formula 207, 10% Pd/C, and cyclohexene in a suitable solvent such as EtOAc:MeOH is microwaved using 300 W of power at about 135 °C for about 10 min. The product, a compound of Formula 209, is isolated and optionally purified.

Reaction Scheme 3




Br
R21
O
O2N
N
R16
R22
R4
311
Step 4
Br
R21
O
H2N
N
R16
R22
R4
313
Step 5
Br
R21
O
R
H
N
N
R16
R22
O
R4
315
Step 6



[00117] Referring to Reaction Scheme 3, Step 1, to a compound of Formula 301, an excess (such as about 1.2 equivalents) of a compound of Formula 303 and aqueous base such as 2 M sodium carbonate in a suitable solvent such as 1,4-dioxane is added about 0.1 equivalent of tetrakis(triphenylphosphine)palladium and the reaction mixture is stirred at reflux for about 18 h. The product, a compound of Formula 305, is isolated and optionally purified.

[00118] Referring to Reaction Scheme 3, Step 2, a compound of Formula 305 and an eaxcess (such as about 4 equivalents) of pyridine hydrochloride is placed for about five min into an oil bath preheated to about 165 °C . The product, a compound of Formula 307, is isolated and optionally purified.

[00119] Referring to Reaction Scheme 3, Step 2, a compound of Formula 307, an excess (such as about 1.1 equivalents) of a compound of Formula $R_{16}X$ where X is a leaving group, such as iodide, and a base such as potassium carbonate in a suitable solvent such as DMF is stirred at room temperature for about 2 h. The product, a compound of Formula 309, is isolated and optionally purified.

[00120] Referring to Reaction Scheme 3, Step 4, to a solution of a compound of Formula 309 and glacial acetic acid is added an excess (such as about 1.5 equivalents) of bromine. The reaction is stirred for about 18 h at room temperature. The product, a compound of Formula 311, is isolated and optionally purified.

[00121] Referring to Reaction Scheme 3, Step 5, a mixture of a compound of Formula 311, iron powder and aqueous hydrochloric acid such as 2N hydrochloric

acid is stirred at reflux for about 4 h. The product, a compound of Formula 313, is isolated and optionally purified.

[00122] Referring to Reaction Scheme 3, Step 6, a compound of Formula 313, a base such as triethylamine, and an excess (such as about 1.1 equivalents) of a compound of formula RCOCl is stirred at room temperature for about 18 h. The product, a compound of Formula 315, is isolated and optionally purified.

[00123] Referring to Reaction Scheme 3, Step 7, a compound of Formula 315, a compound of Formula 316, about 0.09 equivalent of $Pd_2(dba)_3$,0.14 equivalent of 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, and an eaxcess (such as about 1.9 equivalents) of Cs_2CO_3 in a suitable solvent such as dioxane is heated at about 95 °C for about 16 h. Then, the reaction mixture was cooled to room temperature and poured into H_2O (10 mL). The product, a compound of Formula 317, is isolated and optionally purified.

[00124] 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, chelates, non-covalent complexes, prodrugs, and mixtures thereof, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients.

[00125] 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.

[00126] 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 as sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[00127] 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.

[00128] Effective concentrations of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, 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.

[00129] 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.

[00130] 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.

[00131] 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.

[00132] 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.

[00133] 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.

[00134] 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).

[00135] 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.

[00136] Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents; naturally-occurring phosphatides, 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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.

[00141] 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.

[00142] 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.

[00143] 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.

[00144] 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.

[00145] 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.

[00146] 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.

[00147] 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.

[00148] 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.

[00149] 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:

[00150] 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.

[00151] 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 and phosphatidylcholines.

[00152] 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.

[00153] 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).

[00154] 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.

[00155] 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.

[00156] 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, 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 and/or myeloid-cell activity. 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.

[00157] In all of the foregoing the chemical entities can be administered alone, as mixtures, or in combination with other active agents.

[00158] Accordingly, the invention includes a method of treating a patient, for example, a mammal, such as a human, having a disease responsive to inhibition of Btk activity, comprising administrating to the patient having such a disease, an effective amount of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[00159] To the extent that Btk is implicated in disease, alleviation of the disease, disease symptoms, preventative, and prophylactic treatment is within the scope of this invention. In some embodiments, 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.

[00160] Methods of treatment also include inhibiting Btk activity and/ or inhibiting B-cell and/or myeloid-cell activity, 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, chelates, non-covalent complexes, prodrugs, and mixtures thereof. An example of an effective concentration would be that concentration sufficient 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.

[00161] In some embodiments, the condition responsive to inhibition of Btk activity and/ or B-cell and/or myeloid-cell activity is cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction.

[00162] The invention includes a method of treating a patient having cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/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, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[00163] In some embodiments, the conditions and diseases that can be affected using chemical entities described herein, include, but are not limited to:

allergic disorders, including but not limited to eczema, allergic rhinitis or coryza, hay fever, bronchial asthma, urticaria (hives) and food allergies, and other atopic conditions;

autoimmune and/or inflammatory diseases, including but not limited to psoriasis, 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, osteoarthritis, chronic Idiopathic thrombocytopenic purpura (ITP), Addison's disease, Parkinson's disease, Alzheimer's disease, Diabetes mellitus (type 1), septic shock, myasthenia gravis, Ulcerative Colitis, Aplastic anemia, Coeliac disease, Wegener's granulomatosis and other diseases in which the cells and antibodies arise from and are directed against the individual's own tissues;

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 hematological malignancies, such as B-cell lymphoma, andacute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic and acute lymphocytic leukemia, hairy cell leukemia,

Hodgkin's disease, Non-Hodgkin lymphoma, multiple myeloma, and other diseases that are characterized by cancer of the blood or lymphatic system,
bone disorders, including but not limited to osteoporosis.

[00164] 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, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[00165] The invention provides methods of treatment in which at least one chemical entity chosen from compounds of Formula 1 pharmaceutically acceptable salts, solvates, 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, chelates, non-covalent complexes, prodrugs, and mixtures thereof, is given to a patient in combination with one or more additional active agents.

[00166] Thus in one embodiment the invention provides a method of treating cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction, which comprises administering to a patient in need thereof an effective amount of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, chelates, non-covalent complexes, prodrugs, and mixtures thereof, together with a second active agent, which can be useful for treating a cancer, a bone disorder, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/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, 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, 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.

[00167] 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.

[00168] 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, 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.

[00169] 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 (e.g., Rituxan®), IDEC 8, immunotoxins, and cytokines), tyrosine kinase inhibitors (e.g., Gleevec®), and the like.

[00170] Included herein are methods of treatment in which at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, 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.

[00171] 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.

[00172] In a further embodiment, the anti-inflammatory agent is a salicylate. Salicylates include but are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

[00173] 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.

[00174] In additional embodiments the anti-inflammatory therapeutic agent is a gold compound such as gold sodium thiomalate or auranofin.

[00175] 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.

[00176] 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, infliximab and adalimumab (Humira®) which are anti-TNF alpha monoclonal antibodies.

[00177] 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.

[00178] 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.

[00179] 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 an allergic disorder and/or autoimmune and/or inflammatory disease, 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.

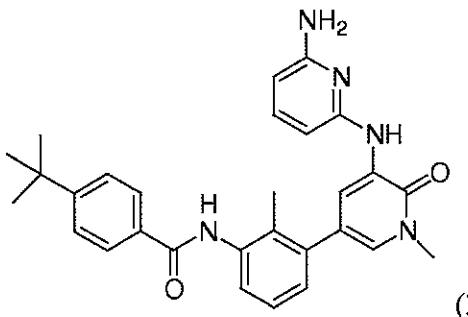
[00180] A labeled form of a compound of the invention can be used as a diagnostic for identifying and/or obtaining compounds that have the function of modulating an activity of a kinase as described herein. The compounds of the invention may additionally be used for validating, optimizing, and standardizing bioassays.

[00181] 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.

[00182] The invention is further illustrated by the following non-limiting examples.

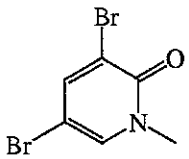
Example 1

_N_-{3-[5-(6-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-_tert_-butyl-benzamide (3)



(3)

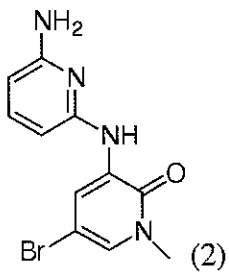
3,5-Dibromo-1-methyl-1H-pyridin-2-one (1)



(1)

[00183] A 1-L round-bottomed flask equipped with a magnetic stirrer was charged with 3,5-dibromo-1H-pyridin-2-one (7.0 g, 27.7 mmol), anhydrous DMF (280 mL) and powdered potassium carbonate (-350 mesh, 8.4 g, 61.1 mmol), and the suspension stirred for 15 min at ambient temperature. After this time, methyl iodide (4.3 g, 30.5 mmol) was added, and the mixture was stirred at room temperature under nitrogen for an additional 18 h. The reaction mixture was then diluted with water (200 mL), extracted with ethyl acetate (3 × 250 mL), dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica to give an 84% yield (6.2 g) of 3,5-dibromo-1-methyl-1H-pyridin-2-one **(1)** as an off-white solid; mp 87-88 °C; MS (ESI+) *m/z* 266 (M+H).

3-(6-Amino-pyridin-2-ylamino)-5-bromo-1-methyl-1*H*-pyridin-2-one (2)

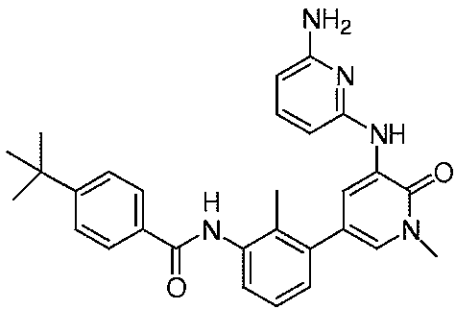


(2)

[00184] A 48-mL sealed tube equipped with a magnetic stirring bar was charged with 2,6-diaminopyridine (0.27 g, 1.2 mmol), 3,5-dibromo-1-methyl-1*H*-pyridin-2-one (**1**) (0.27 g, 1 mmol), $Pd_2(dba)_3$ (0.046 g, 0.05 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.089 g, 0.15 mmol), and Cs_2CO_3 (0.49 g, 1.5 mmol) in dioxane (10 mL). After the mixture was degassed for 15 min., it was heated

at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H_2O (10 mL). To this was added dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 %, MeOH in dichlormethane/Ether (1/1), to give 0.054 g (18 %) of 3-(6-amino-pyridin-2-ylamino)-5-bromo-1-methyl-1*H*-pyridin-2-one (**2**) as a solid.

***N*-{3-[5-(6-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-*tert*-butyl-benzamide (3)**

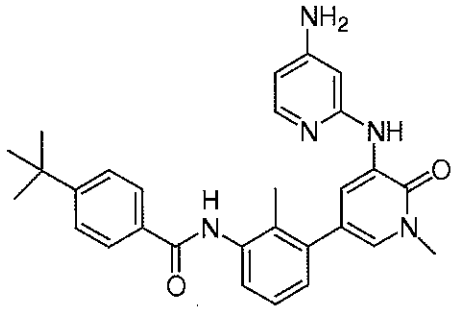


(3)

[00185] A 48-mL sealed tube equipped with a magnetic stirring bar was charged with 3-(6-amino-pyridin-2-ylamino)-5-bromo-1-methyl-1*H*-pyridin-2-one (**2**) (0.054 g, 0.18 mmol), 4-tert-butyl-*N*-[2-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-benzamide (0.086 g, 0.22 mmol), and $Pd(PPh_3)_4$ (0.010 g, 0.010 mmol) in DME (10 mL) and 1N Na_2CO_3 (5 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H_2O (10 mL). To this was added dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 %, MeOH in dichloromethane/ether (1/1), to afford 0.035 g (40 %) of *N*-{3-[5-(6-amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-*tert*-butyl-benzamide (**3**) as a solid; LCMS m/z 482.2018 (M^+).

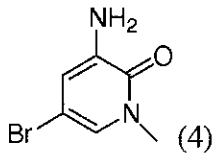
Example 2

N-{3-[5-(4-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-*tert*-butyl-benzamide (7)



(7)

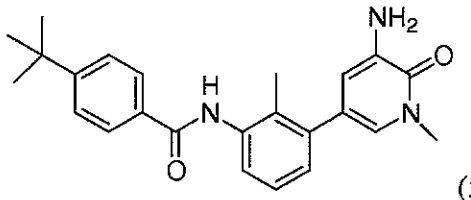
3-Amino-5-bromo-1-methyl-1*H*-pyridin-2-one (4)



(4)

[00186] A 48-mL sealed tube equipped with a magnetic stirring bar was charged with benzophenone imine (0.43 g, 2.4 mmol), 3,5-dibromo-1-methyl-1*H*-pyridin-2-one (1) (0.51 g, 2.0 mmol), $Pd(OAc)_2$ (0.025 g, 0.040 mmol), rac-BINAP (0.082 g, 0.13 mmol), and Cs_2CO_3 (0.92 g, 2.8 mmol) in dioxane (15 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H_2O (10 mL). To this was added dichloromethane and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was dissolved in 1 N HCl/MeOH (3 mL) and stirred for 1 h at room temperature. Then, to the reaction mixture was added sat. $NaHCO_3$ (10 mL) and dichloromethane (10 mL), and the phases were separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 % MeOH in dichloromethane/ether (1/1), to afford 0.22 g (54 %) of 3-amino-5-bromo-1-methyl-1*H*-pyridin-2-one (4) as a solid.

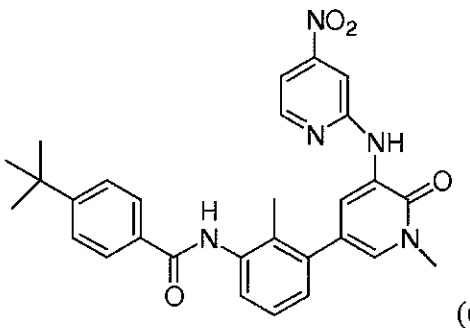
N-[3-(5-Amino-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-2-methyl-phenyl]-4-*tert*-butyl-benzamide (5)



(5)

[00187] A 48-mL sealed tube equipped with a magnetic stirring bar was charged with 3-amino-5-bromo-1-methyl-1*H*-pyridin-2-one (4) (0.10 g, 0.50 mmol), 4-tert-butyl-*N*-[2-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-benzamide (0.24 g, 0.70 mmol), and $Pd(PPh_3)_4$ (0.030 g, 0.025 mmol) in DME (10 mL) and 1N Na_2CO_3 (5 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H_2O (10 mL). To this was added dichloromethane and the phases were separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 % MeOH in dichloromethane/ether (1/1), to afford 0.14 g (68 %) of *N*-[3-(5-amino-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-2-methyl-phenyl]-4-*tert*-butyl-benzamide (5) as a solid.

4-*tert*-Butyl-*N*-{2-methyl-3-[1-methyl-5-(4-nitro-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-2-yl]-phenyl}-benzamide (6)

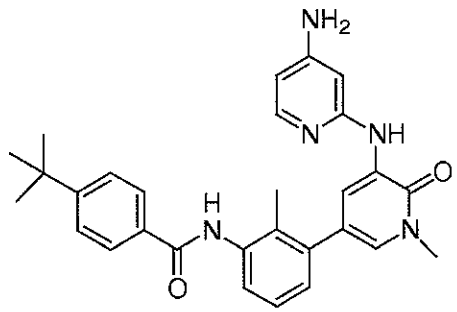


(6)

[00188] A 48-mL sealed tube equipped with a magnetic stirring bar was charged with *N*-[3-(5-amino-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-2-methyl-phenyl]-4-*tert*-butyl-benzamide (5) (0.14 g, 0.34 mmol), 2-chloro-4-nitropyridine (0.058 g, 0.37 mmol), $Pd_2(dba)_3$ (0.027 g, 0.030 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.020 g, 0.034 mmol), and Cs_2CO_3 (0.25 g, 0.70 mmol) in dioxane (10 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and

poured into H_2O (10 mL). To this was added dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 %, MeOH in dichloromethane/ether (1/1), to afford 0.15 g (85 %) of 4-*tert*-butyl-*N*-{2-methyl-3-[1-methyl-5-(4-nitro-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-2-yl]-phenyl}-benzamide (6) as a solid.

N-{3-[5-(4-Amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-*tert*-butyl-benzamide (7)

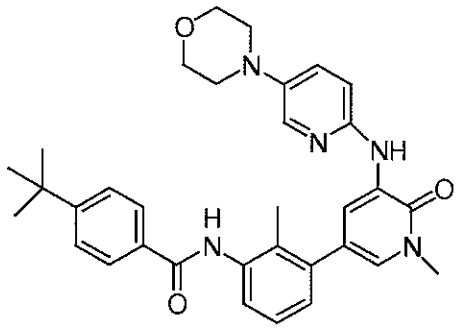


(7)

[00189] A 10-mL vial equipped with a magnetic stirring bar was charged with 4-*tert*-butyl-*N*-{2-methyl-3-[1-methyl-5-(4-nitro-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-2-yl]-phenyl}-benzamide **(6)** (0.10 g, 0.20 mmol), 10% Pd/C (0.10 g), and cyclohexene (2 mL) in EtOAc:MeOH (1:1, 4 mL). After the mixture was degassed for 5 min., it was microwaved using 300 W of power at 135 °C for 10 min. Then, the reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated and purified by column chromatography, gradient 0-10 % MeOH in dichloromethane/ether (1/1), to afford 0.015 g (15 %) of *N*-{3-[5-(4-amino-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl]-2-methyl-phenyl}-4-*tert*-butyl-benzamide **(7)** as a solid; LCMS m/z 482.2635 (M^+).

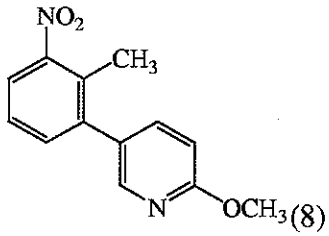
Example 3

4-*tert*-Butyl-*N*-{2-methyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl}-benzamide (14)



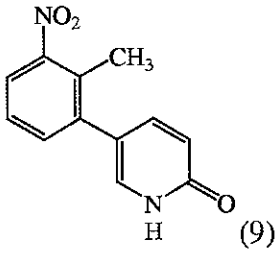
(14)

2-Methoxy-5-(2-methyl-3-nitrophenyl)pyridine (8)



[00190] A 100-mL single-neck round-bottomed flask equipped with a magnetic stirrer, reflux condenser and nitrogen inlet was charged with 1,4-dioxane (40 mL), aqueous 2 M sodium carbonate (8.0 mL, 16.0 mmol), 5-bromo-2-methoxy-pyridine (1.00 g, 5.32 mmol), and 4,4,5,5-tetramethyl-2-(2-methyl-3-nitro-phenyl)-[1,3,2]dixoaborolane (1.68 g, 6.40 mmol). After bubbling nitrogen through the resulting mixture for 30 min, tetrakis(triphenylphosphine)palladium (0.61 g, 0.53 mmol) was added and the reaction mixture then stirred at reflux for 18 h. After this time the reaction was cooled to room temperature and partitioned between ethyl acetate (150 mL) and water (75 mL). The organic layer was separated and washed with water (2 × 50 mL) followed by brine (100 mL) and dried over magnesium sulfate. The drying agent was then removed by filtration through a pad of Celite 521, and the filtrate concentrated under reduced pressure. The resulting residue was subjected to flash chromatography to afford 1.20 g (92 %) of 2-methoxy-5-(2-methyl-3-nitrophenyl)pyridine **(8)** as a white solid: mp 81–83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.11 (d, 1H, J = 2.4 Hz), 7.82 (dd, 1H, J = 7.8, 1.5 Hz), 7.53 (dd, 1H, J = 8.4, 2.4 Hz), 7.44 (dd, 1H, J = 7.8, 1.5 Hz), 7.39 (d, 1H, J = 7.8 Hz), 6.84 (d, 1H, J = 8.4 Hz), 4.00 (s, 3H), 2.37 (s, 3H); MS (ESI+) *m/z* 245 (M+H).

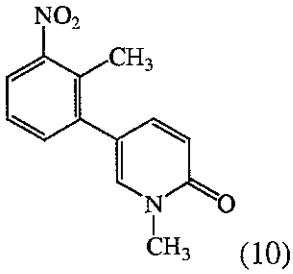
5-(2-Methyl-3-nitrophenyl)pyridin-2-one (9)



(9)

[00191] A 10-mL single-neck round-bottomed flask equipped with a magnetic stirrer, and nitrogen inlet was charged with 2-methoxy-5-(2-methyl-3-nitrophenyl) pyridine **(8)** (1.00 g, 4.10 mmol) and pyridine hydrochloride (1.90 g, 16.4 mmol) and purged with nitrogen. The flask was place for five min into an oil bath preheated to 165 °C. After this time the reaction was cooled to room temperature, and water (70 mL) was added. The resulting suspension was filtered, and the filter cake was washed with water (2 × 25 mL) and then dried in a 43 °C vacuum oven for 3 h to afford 0.97 g (99 %) of 5-(2-methyl-3-nitrophenyl)pyridin-2-one **(9)** as a white solid: mp 214–216 °C; ^{1}H NMR (300 MHz, DMSO–d_6) δ11.87 (br s, 1H),7.85 (dd, 1H, J = 8.1, 1.2 Hz), 7.56 (dd, 1H, J = 7.8, 1.5 Hz), 7.54 (dd, 1H, J = 8.4, 2.4 Hz), 7.53 (d, 1H, J = 9.3 Hz), 7.46 (dd, 1H, J = 7.8, 1.5 Hz), 6.41 (d, 1H, J = 9.3 Hz), 2.30 (s, 3H); MS (ESI+) *m/z* 231 (M+H).

1-Methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one (10)

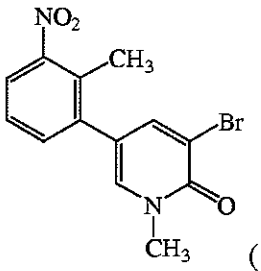


(10)

[00192] A 250-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was charged with 5-(2-methyl-3-nitrophenyl)pyridin-2-one **(9)** (0.92 g, 4.0 mmol), DMF (40 mL), potassium carbonate (1.21 g, 8.80 mmol) and iodomethane (625 mg, 4.40 mmol) and purged with nitrogen. The reaction mixture was stirred at room temperature for 2 h. After this time the reaction was cooled to room temperature and partitioned between ethyl acetate (150 mL) and water (75 mL). The organic layer was separated and washed with water (2 × 50 mL) followed by brine (100 mL) and dried over magnesium sulfate. The drying agent was then removed by filtration and the filtrate concentrated under reduced pressure to afford

0.92 g (94 %) of 1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one **(10)** as a white solid: mp 157–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.81 (dd, 1H, J = 7.8, 1.8 Hz), 7.41 (dd, 1H, J = 7.8, 1.8 Hz), 7.38(d, 1H, J = 7.5 Hz), 7.53 (d, 1H, J = 9.3 Hz), 7.32 (dd, 1H, J = 9.3, 2.7 Hz), 7.27 (d, 1H, J = 1.5 Hz), 6.68 (d, 1H, J = 9.3 Hz), 3.62 (s, 3H), 2.37 (s, 3H); MS (ESI+) *m/z* 245 (M+H).

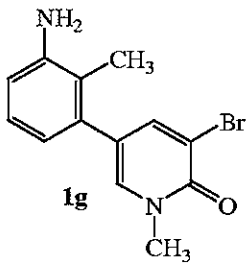
3-Bromo-1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one (11).



(11)

[00193] A 10-mL single-neck round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was purged with nitrogen and charged with 1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one **(10)** (0.60 mg, 2.46 mmol) and glacial acetic acid (5 mL). To the resulting solution bromine (0.59 g, 3.70 mmol) was added. The reaction was stirred for 18 h at room temperature. After this time the reaction was partitioned between water (25 mL) and ethyl acetate (75 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (2 × 25 mL), brine (50 mL) and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate concentrated to a constant weight under reduced pressure to afford 0.075 g (93 %) of 3-bromo-1-methyl-5-(2-methyl-3-nitrophenyl)pyridin-2-one **(11)** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.83 (dd, 1H, J = 7.2, 2.1 Hz), 7.75 (d, 1H, J = 2.4 Hz), 7.42 (dd, 1H, J = 7.8, 2.4 Hz), 7.38 (t, 1H, J = 7.5 Hz), 7.29 (d, 1H, J = 2.4 Hz), 3.70 (s, 3H), 2.40 (s, 3H); MS (ESI+) *m/z* 323 (M+H).

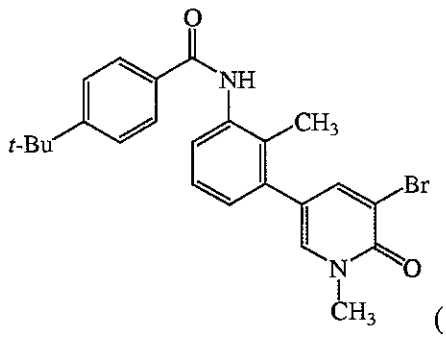
5-(3-Amino-2-methylphenyl)-3-bromo-1-methylpyridin-2-one (12).



[00194] A 50-mL single-neck round-bottomed flask equipped with a

mechanical stirrer was charged with 3-bromo-1-methyl-5-(2-methyl-3-nitrophenyl) pyridin-2-one **(11)** (0.70 g, 2.17 mmol), ethanol (15 mL), iron powder (-325 mesh, 1.20 g, 21.7 mmol), 2N hydrochloric acid (1.09 mL, 2.17 mmol) and stirred at reflux for 4 h. After this time the reaction was cooled to room temperature and solid potassium carbonate (0.738 g, 5.35 mmol) was added. The suspension was stirred for 0.5 h and then filtered through a pad of Celite 521. The filter cake was washed with ethanol (3 × 15 mL) and the combined filtrates were concentrated to a constant weight under reduced pressure to afford 0.71 g (88 %) of 5-(3-amino-2-methylphenyl)-3-bromo-1-methylpyridin-2-one **(12)** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.75 (dd, 1H, J = 2.1 Hz), 7.23 (d, 1H, J = 2.1 Hz), 7.05 (t, 1H, J = 7.8 Hz), 6.72 (d, 1H, J = 7.8 Hz), 6.60 (d, 1H, J = 7.2 Hz), 3.75 (br s, 2H), 3.66 (s, 3H), 2.07 (s, 3H); MS (ESI+) *m/z* 293 (M+H).

***N*-(3-(5-Bromo-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4-*tert*-butylbenzamide (13)**

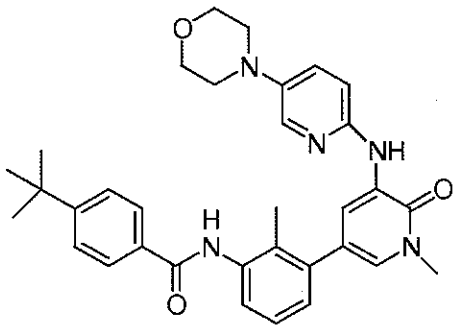


(13)

[00195] A 25-mL round bottomed flask was cooled to 0 °C with an ice/water bath and charged with 5-(3-amino-2-methylphenyl)-3-bromo-1-methylpyridin-2-one **(12)** (0.71 g, 2.20 mmol), triethylamine (489 mg, 4.84 mmol), methylene chloride (10 mL) and 4-*tert*-butyl-benzoyl chloride (0.48 g, 2.42 mmol) and the reaction mixture stirred at room temperature for 18 h. After this time the reaction was partitioned between water (25 mL) and ethyl acetate (50 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (2 × 25 mL), brine (50 mL) and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. The resulting residue was subjected to flash chromatography to afford 0.75 g (75 %) of *N*-(3-(5-bromo-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methylphenyl)-4-*tert*-butylbenzamide **(13)** as a white

solid: mp 149–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.87 (dd, 1H, J = 2.4 Hz), 7.86 (d, 2H, J = 8.4 Hz), 7.71 (br s, 1H), 7.54 (d, 2H, J = 8.7 Hz), 7.30 (t, 1H, J = 7.8 Hz), 7.27 (d, 1H, J = 1.8 Hz), 3.75 (br s, 2H), 7.05 (dd, 1H, J = 7.8, 1.5 Hz), 3.67 (s, 3H), 2.24 (s, 3H), 1.37 (s, 9H); MS (ESI+) *m/z* 453 (M+H).

4-*tert*-Butyl-*N*-{2-methyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl}-benzamide (14)

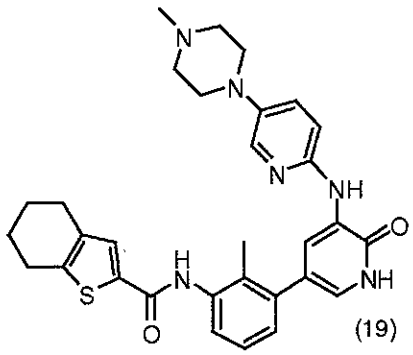


(14)

[00196] A 48-mL sealed tube equipped with a magnetic stirring bar was charged with 5-morpholin-4-yl-pyridin-2-ylamine (0.065 g, 0.36 mmol), *N*-[3-(5-bromo-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-2-methyl-phenyl]-4-*tert*-butyl-benzamide (13) (0.16 g, 0.35 mmol), $Pd_2(dba)_3$ (0.030 g, 0.030 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.030 g, 0.050 mmol), and Cs_2CO_3 (0.22 g, 0.66 mmol) in dioxane (10 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H_2O (10 mL). To this was added dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-10 % MeOH in dichloromethane/ether (1/1), to afford 0.080 g (41 %) of 4-*tert*-butyl-*N*-{2-methyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl}-benzamide (8) as a solid; LCMS m/z 552.2342 (M^+).

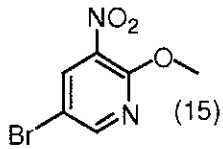
Example 4

N-(2-Methyl-3-(5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxamide (19)



(19)

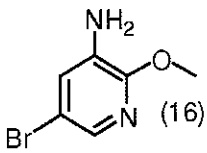
5-Bromo-2-methoxy-3-nitropyridine (15)



(15)

[00197] In a 1 L, round-bottomed, single-necked flask equipped with a magnetic stirring bar was placed 5-bromo-3-nitropyridin-2-ol (50.0 g, 0.23 mol) in $CHCl_3$ (500 mL) under nitrogen in the dark (wrapped in aluminum foil.) To this solution was added Ag_2CO_3 (75.5 g, 0.28 mol) and MeI (142.0 mL, 2.3 mol). After the mixture was stirred for 48 h at room temperature, it was filtered through a pad of Celite, washed with CH_2Cl_2, and concentrated. The crude mixture was purified by column chromatography (EtOAc:Hexane, 1:4) to give 24.0 g (45%) of 5-bromo-2-methoxy-3-nitropyridine (**15**) as a solid.

5- Bromo-2-methoxypyridin-3-amine (16)

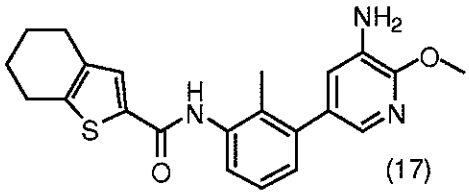


(16)

[00198] In a 500 mL, round-bottomed, single-necked flask equipped with a magnetic stirring bar was placed 5-bromo-2-methoxy-3-nitropyridine (**15**) (20.0 g, 0.086 mol), Fe (20.0 g, 0.36 mol), and NH_4Cl (20.0 g, 0.36 mol) in $EtOH/H_2O$ (150 mL, 1:1). After heating at 95 °C for 1 h, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated to give 16.5 g (95 %) of 5- bromo-2-

methoxypyridin-3-amine (**16**) as a solid.

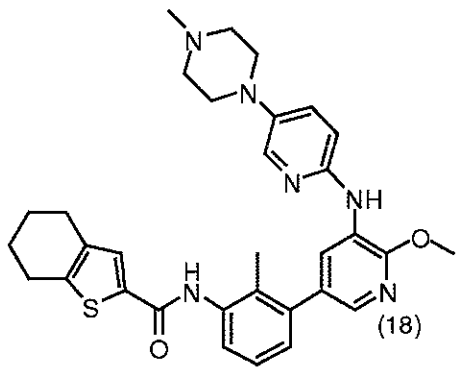
***N*-(3-(5-Amino-6-methoxypyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxamide (17)**



(17)

[00199] In a 48 mL sealed tube equipped with a magnetic stirring bar was placed 5- bromo-2-methoxypyridin-3-amine (**16**) (1.0 g, 4.0 mmol), *N*-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)phenyl)-4,5,6,7-tetrahydrobenzo[*b*] thiophene-2-carboxamide (1(2.4 g, 6.7 mmol), and $Pd(PPh_3)_4$ (0.30 g, 0.20 mmol) in DME/1N Na_2CO_3 (10 mL, 1/1). After the reaction mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the mixture was cooled to room temperature and diluted with dichloromethane (10 mL) and H_2O (10 mL), and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-25% MeOH in dichloromethane, to afford 1.0 g (65 %) of *N*-(3-(5-amino-6-methoxypyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[*b*] thiophene-2-carboxamide (**17**) as a solid.

***N*-(3-(6-Methoxy-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridine-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-carboxamide (18)**

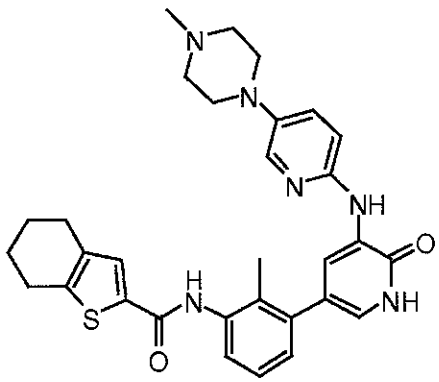


(18)

[00200] In a 48-mL seal tube equipped with a magnetic stirring bar was placed *N*-(3-(5-Amino-6-methoxypyridin-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[*b*] thiophene-2-carboxamide (**17**) (0.20 g, 0.5 mmol), 1-(6-chloro-pyridin-3-yl)-4-

methyl-piperazine (0.11 g, 0.5 mmol), $Pd_2(dba)_3$ (0.046 g, 0.050 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.040 g, 0.070 mmol), and Cs_2CO_3 (0.33 g, 1.0 mmol) in dioxane (10 mL). After the mixture was degassed for 15 min., it was heated at 95 °C for 16 h. Then, the reaction mixture was cooled to room temperature and poured into H_2O (10 mL). To this was added dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-33 % MeOH in dichloromethane, to afford 0.140 g (50 %) of *N*-(3-(6-Methoxy-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridine-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-carboxamide (**18**) as a solid.

_N_-(2-Methyl-3-(5-(5-(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxamide (19)

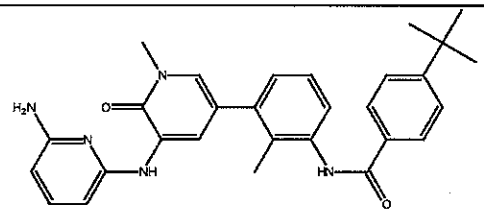
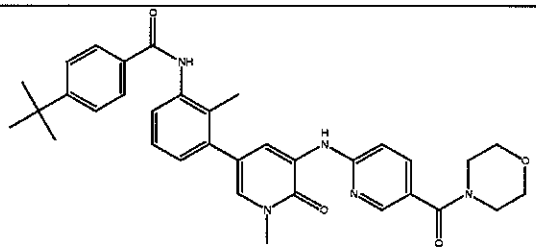
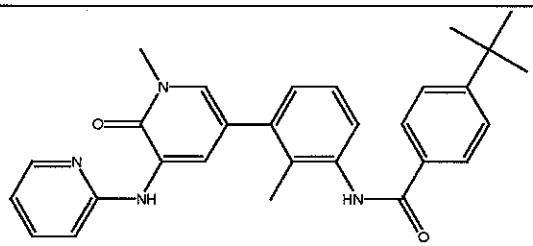
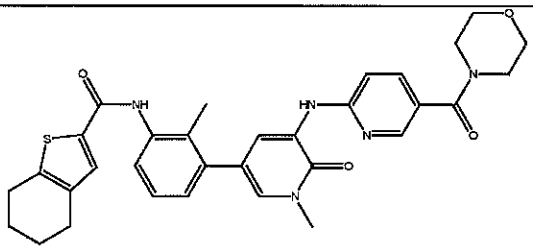


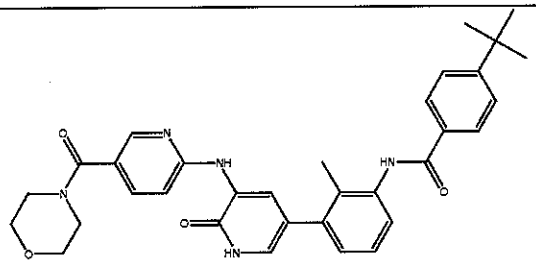
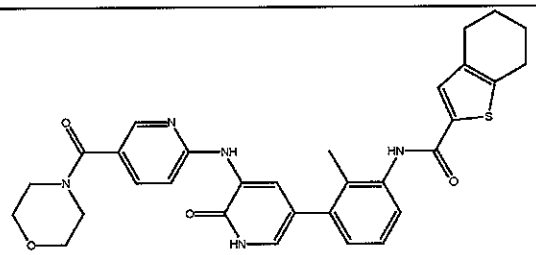
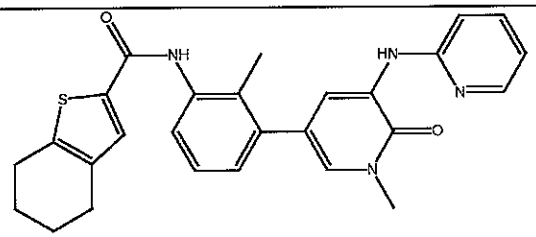
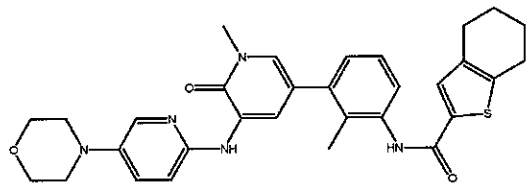
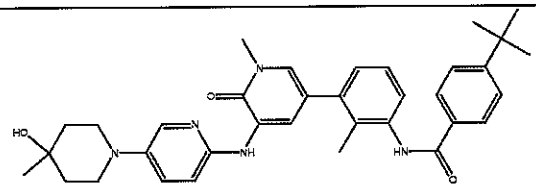
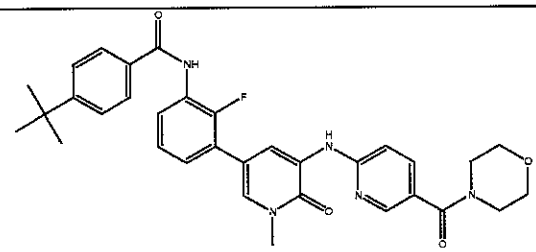
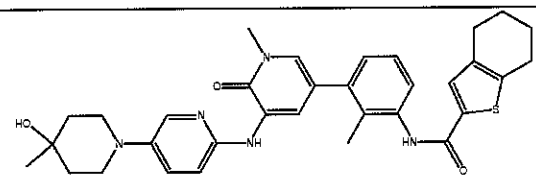
[00201] In a 25 mL, round-bottomed, single-necked flask equipped with a magnetic stirring bar and a condenser was placed *N*-(3-(6-methoxy-5-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)pyridine-3-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-carboxamide (**18**) (0.070 g, 0.13 mmol) and 3 N HCl (1 mL) in dioxane (3 mL). The reaction mixture was heated at 100 °C for 2 h. To this was added dichloromethane (10 mL) and H_2O (10 mL), and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography, gradient 0-33 % MeOH in dichloromethane, to afford 0.053 g (80%) of *N*-(2-methyl-3-(5-(5-

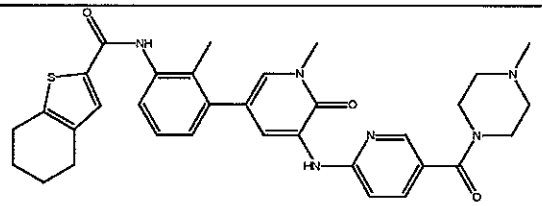
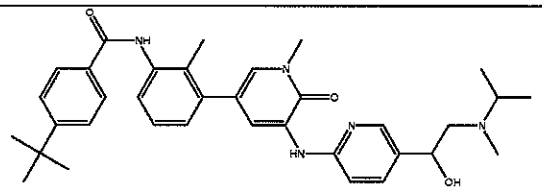
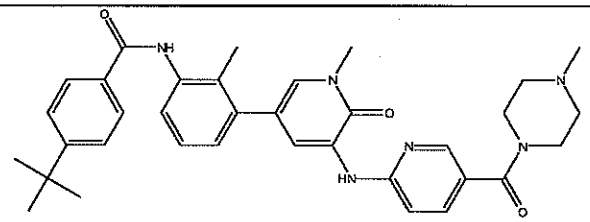
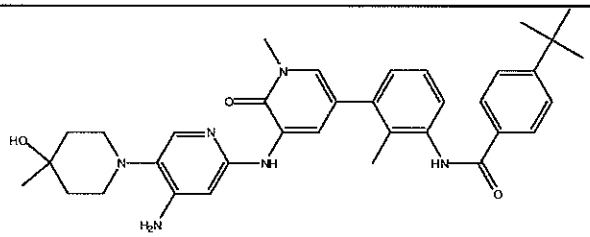
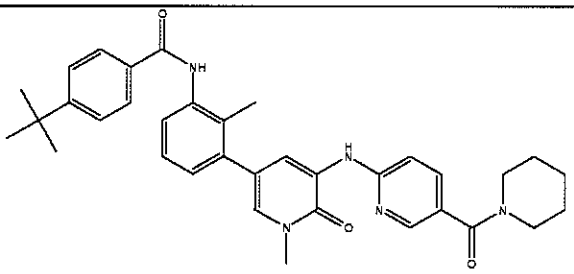
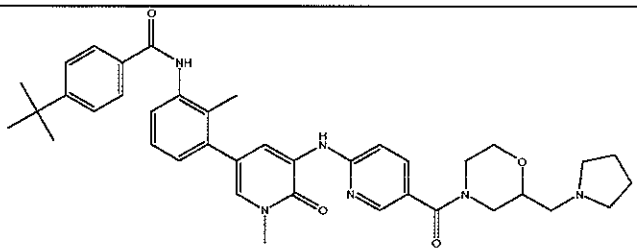
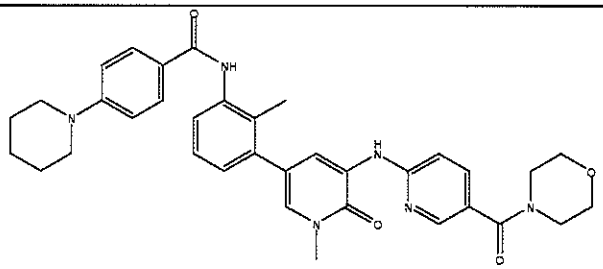
(4-methylpiperazin-1-yl)pyridine-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxamide (**19**); Exact mass *m/z* 554.25; M=H *m/z* 555.20.

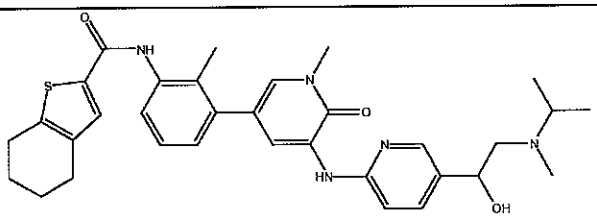
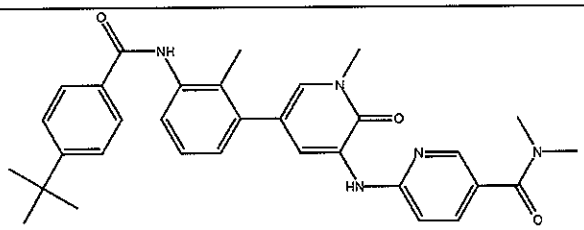
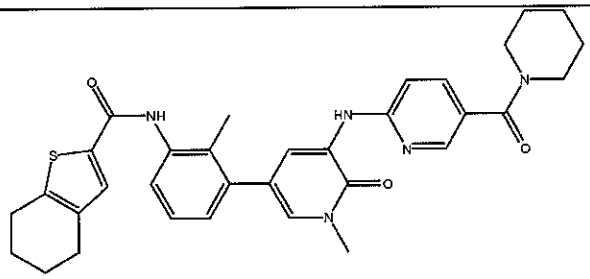
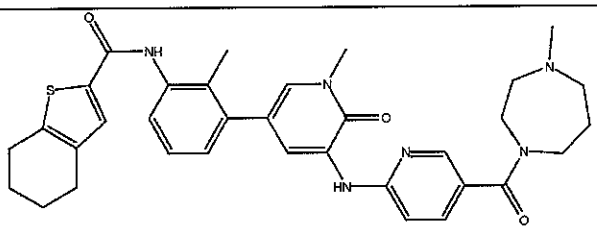
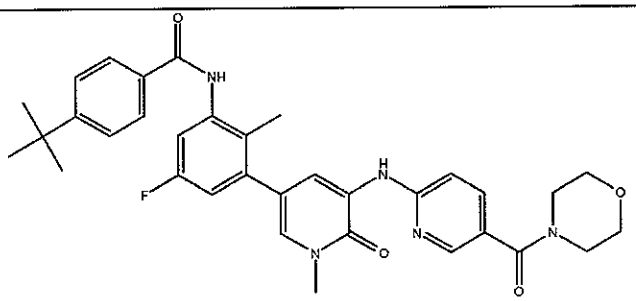
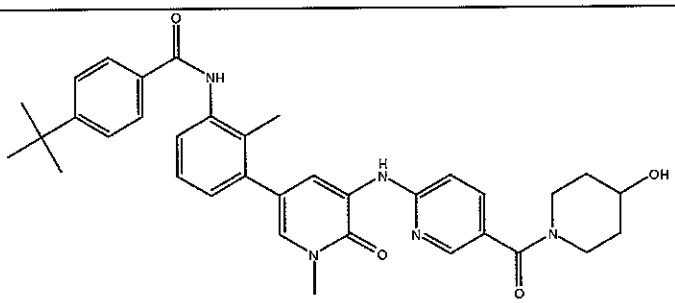
Example 5

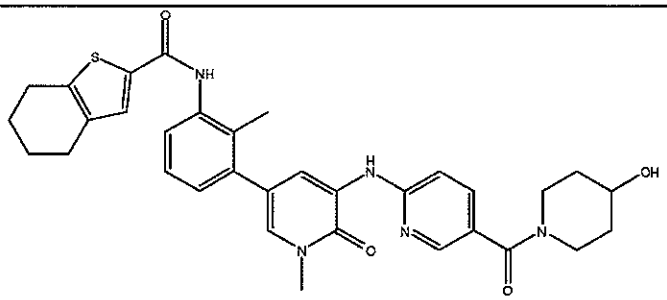
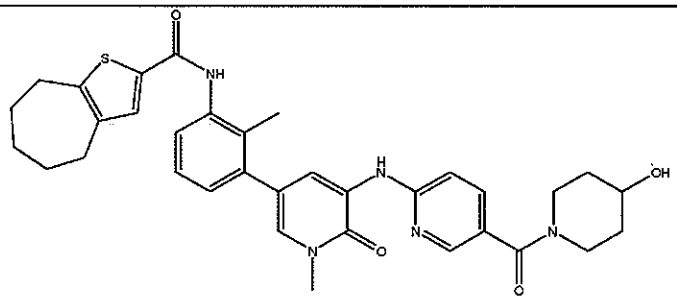
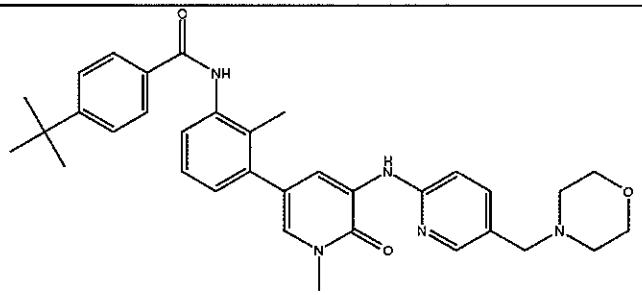
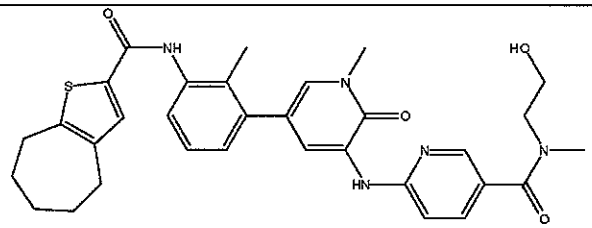
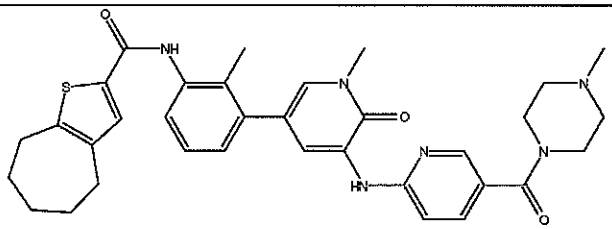
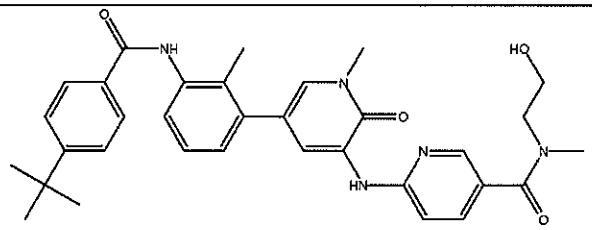
[00202] The following compounds were prepared using procedures similar to those described in Examples 1, 2, 3 and 4.

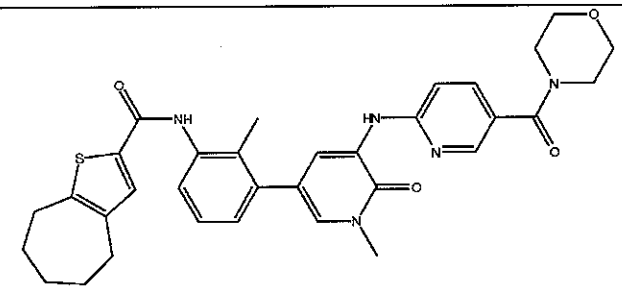
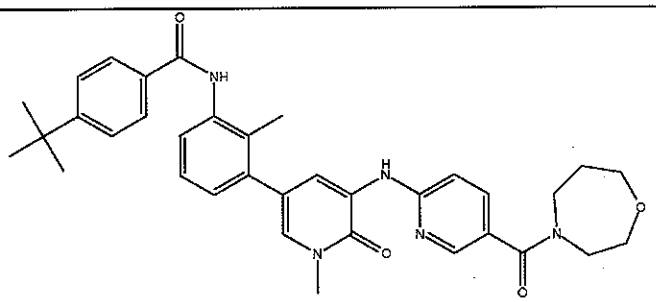
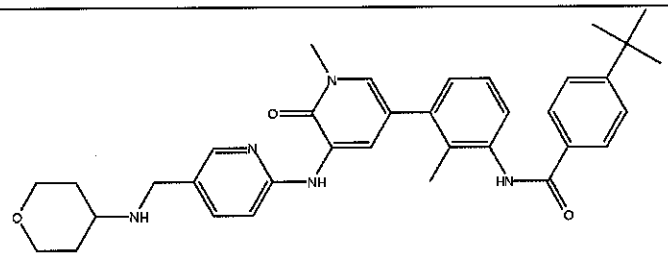
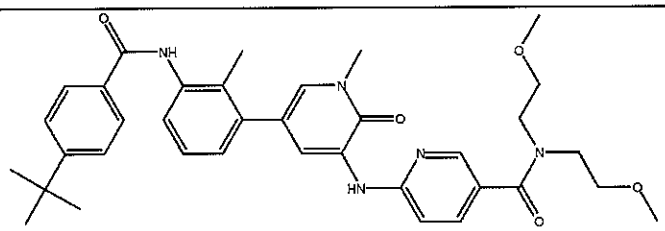
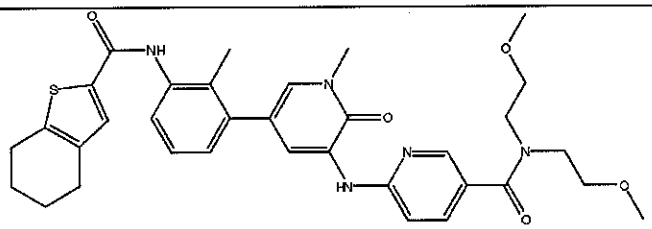
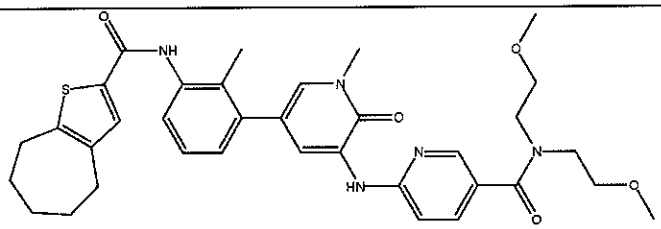
Structure	MW	MH+ m/z
	481.25	482.20
	579.28	580.33
	466.24	467.22
	583.23	584.17

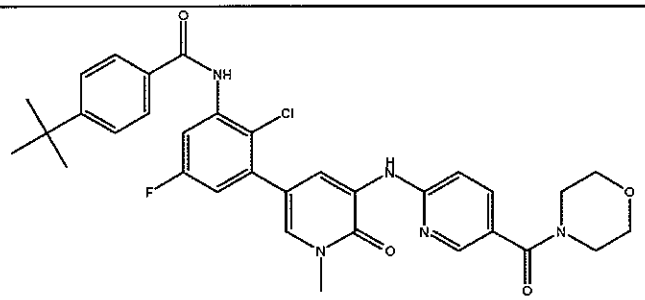
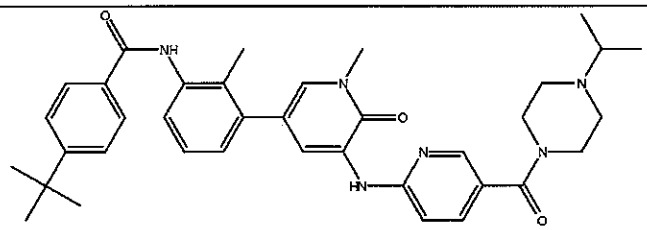
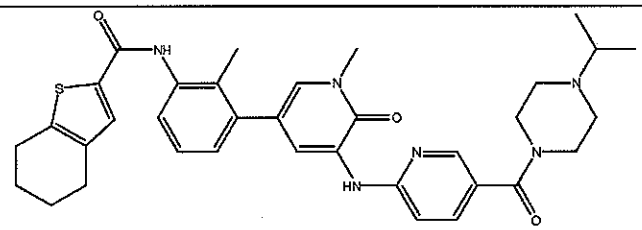
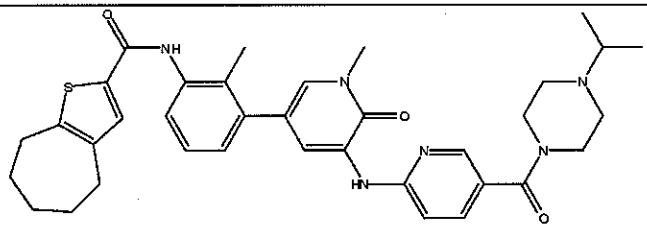
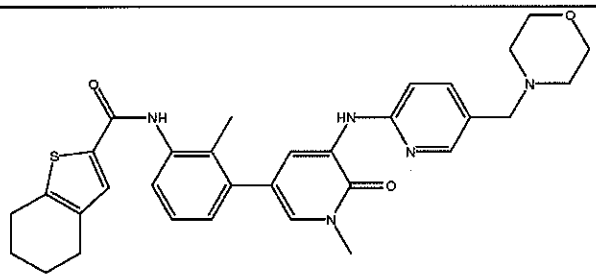
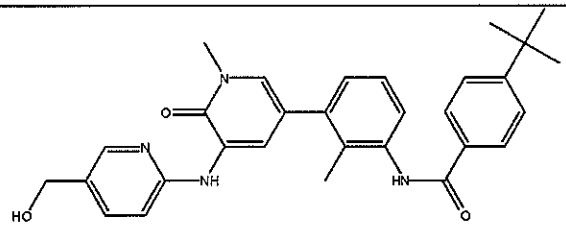
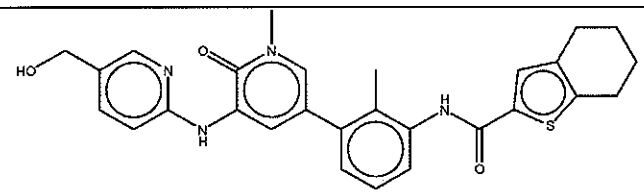
	565.27	566.26
	569.21	570.16
	470.18	471.15
	555.23	556.20
	579.32	580.36
	583.26	584.22
	583.26	584.23

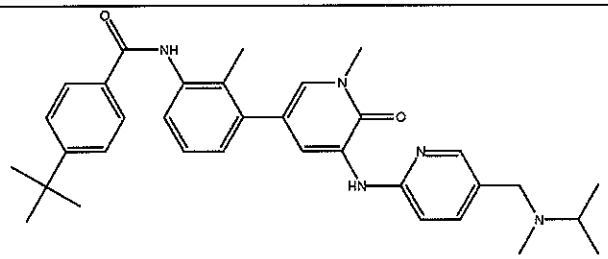
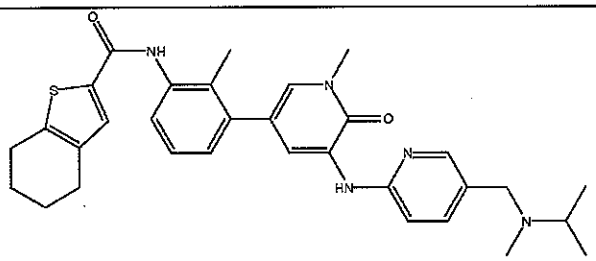
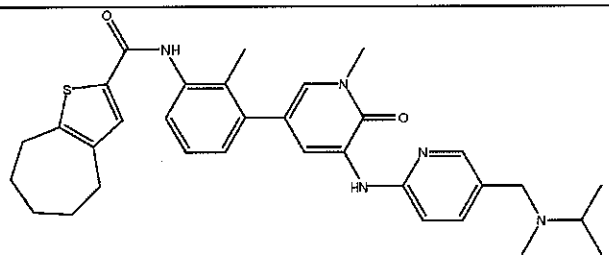
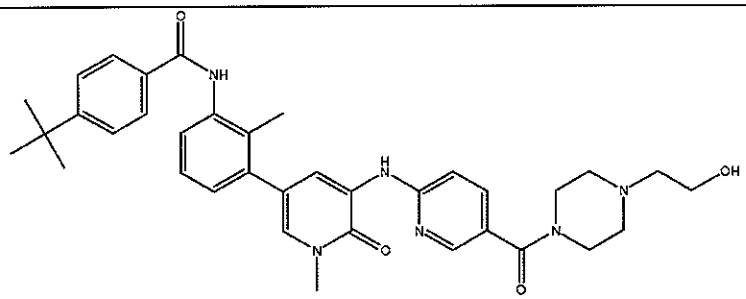
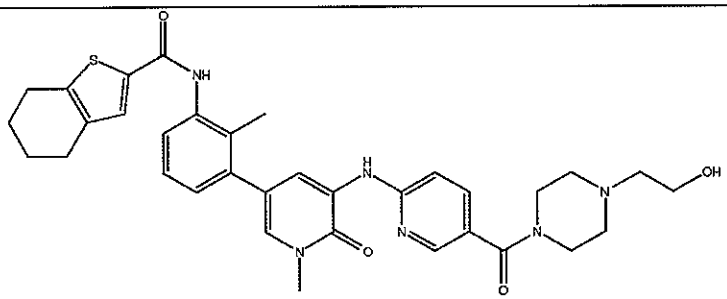
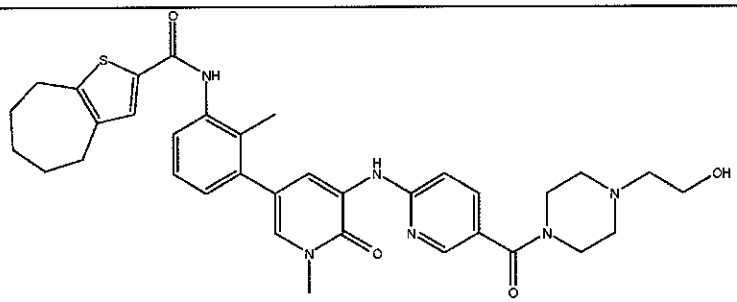
	596.26	596.99
	581.34	582.09
	592.3	593.13
	594.3	595.54
	577.3	578.16
	662.4	663.16
	606.3	607.1481

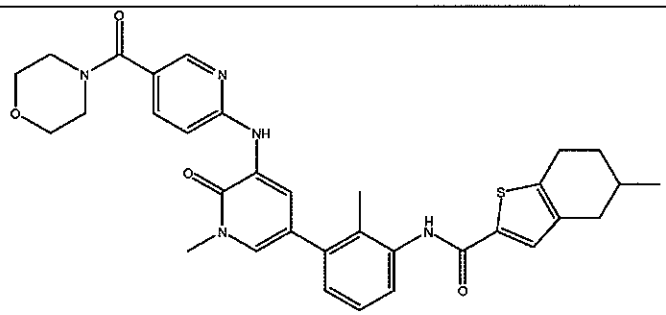
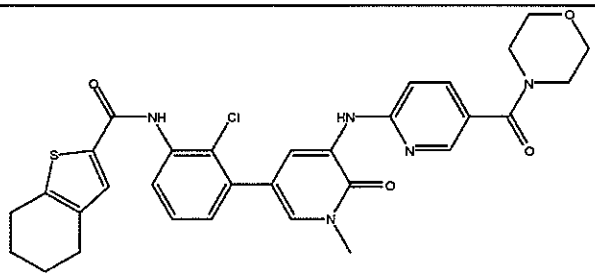
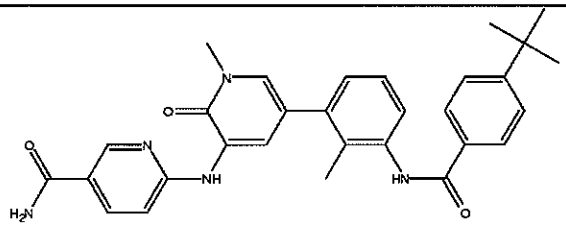
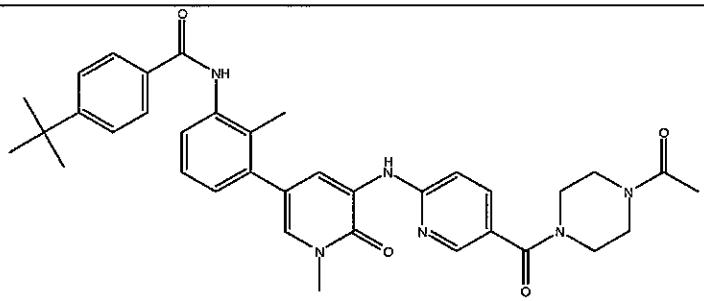
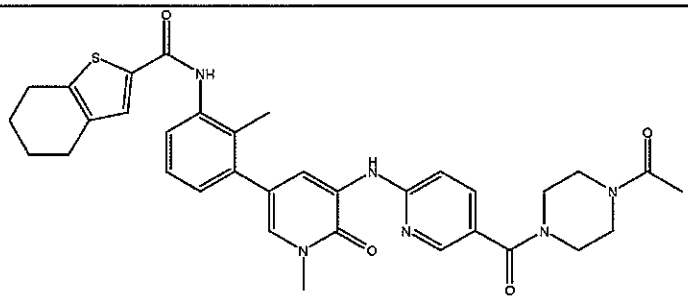
	585.3	586.15
	537.3	538.1
	581.2	582.08
	610.3	611.09
	597.3	598.49
	593.3	594.13

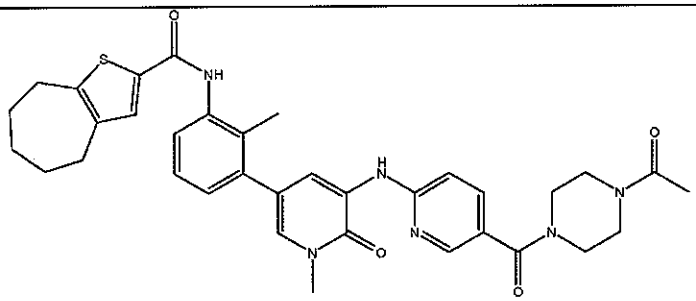
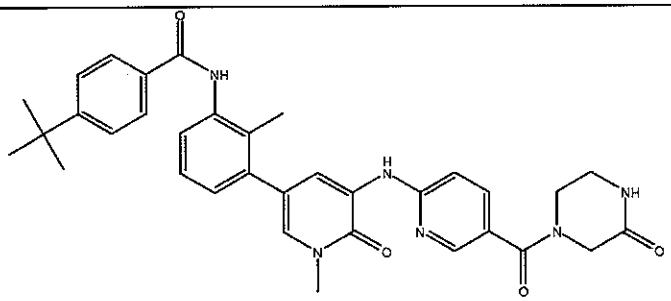
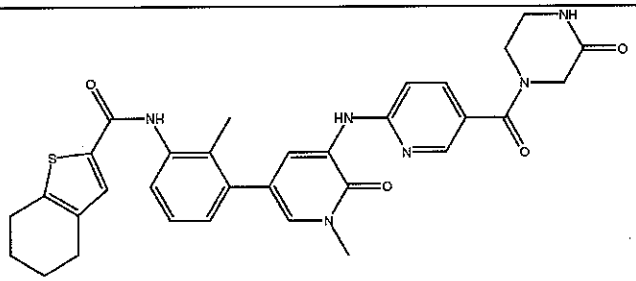
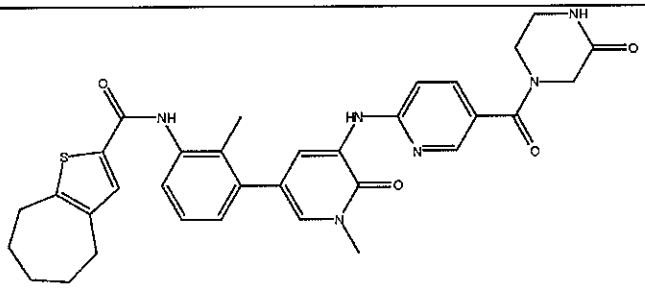
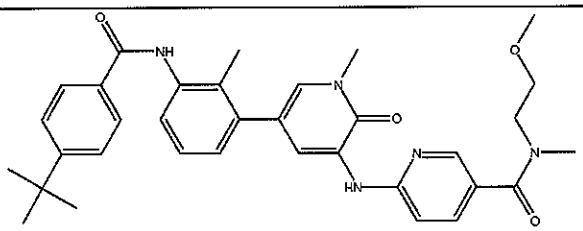
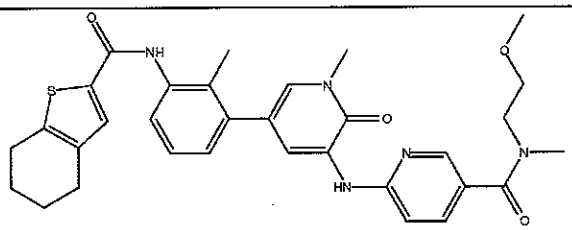
	597.2	598.08
	611.3	612.19
	565.3	566.14
	585.2	586.08
	610.3	611.12
	567.3	568.12

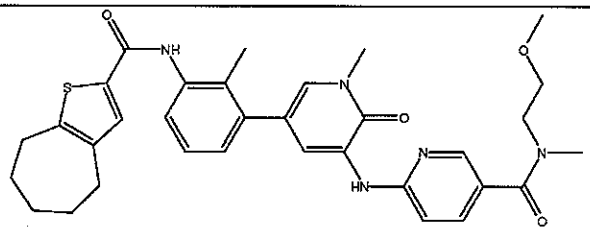
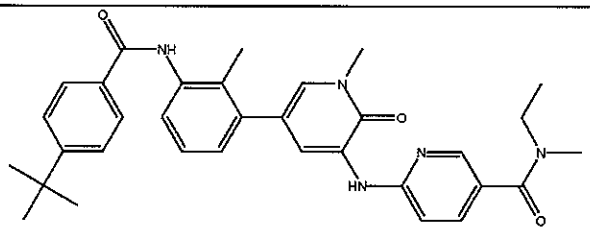
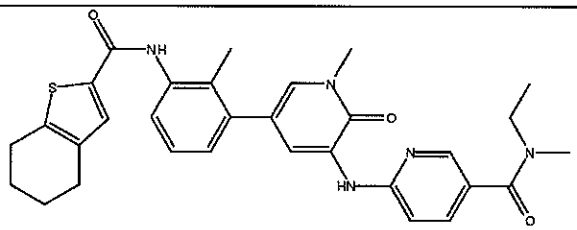
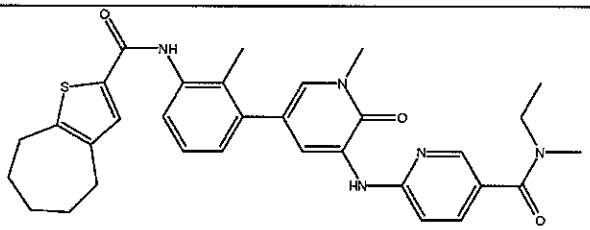
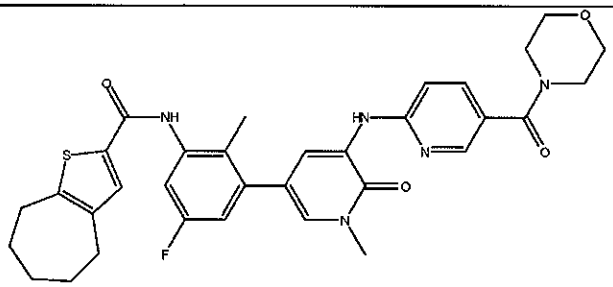
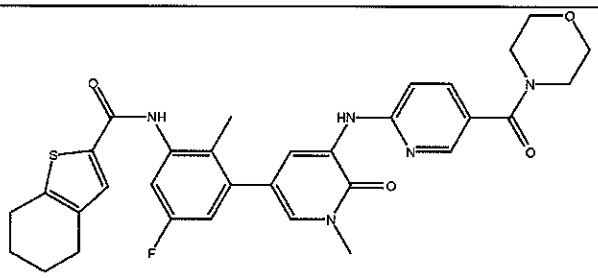
	597.2	598.14
	593.3	594.18
	579.3	580.15
	625.3	626.28
	629.3	630.06
	643.3	644.09

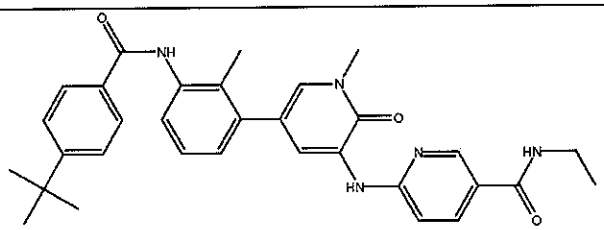
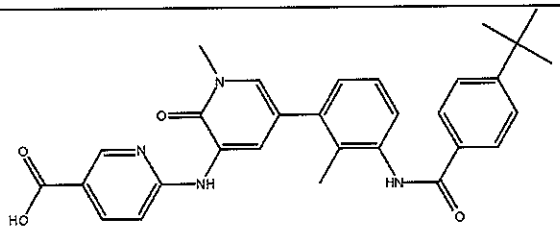
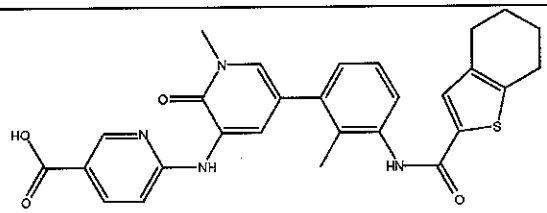
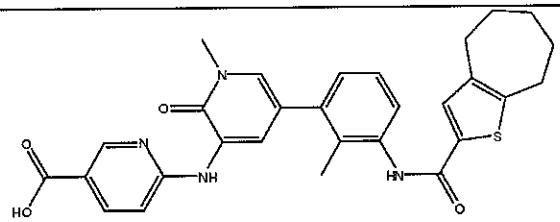
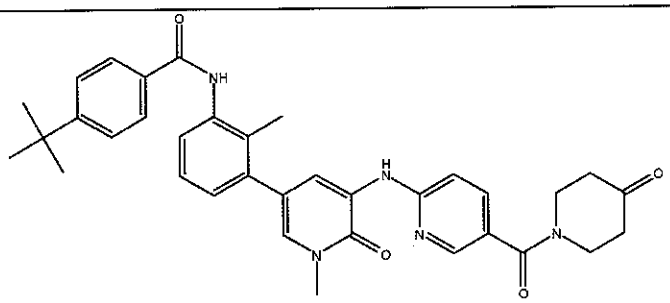
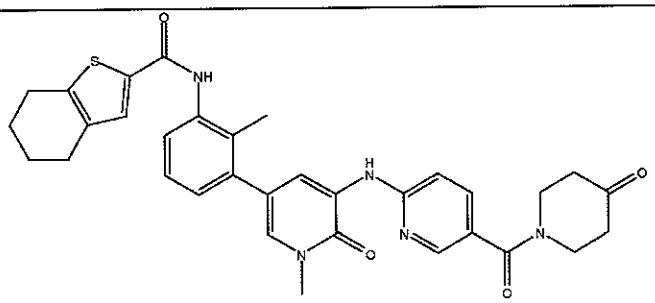
	617.2	618.41
	620.3	620.96
	624.3	624.91
	638.3	638.92
	569.2	570.07
	496.2	497.71
	500.2	501.17

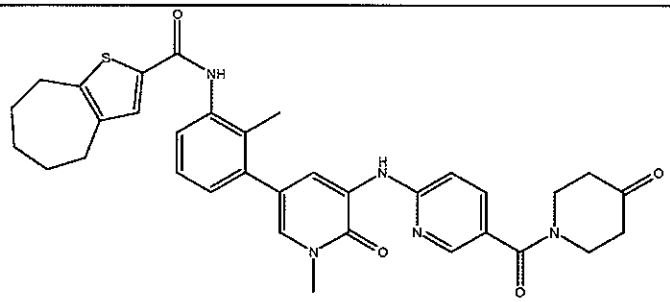
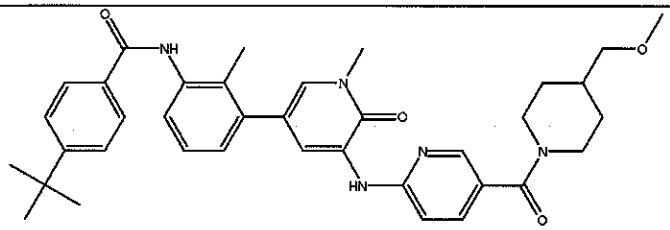
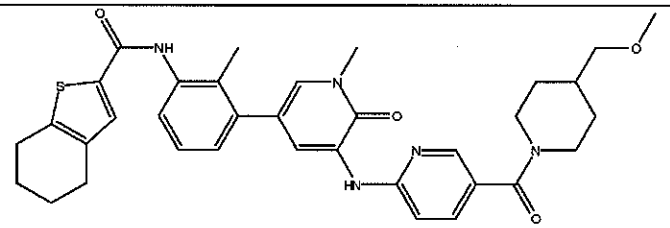
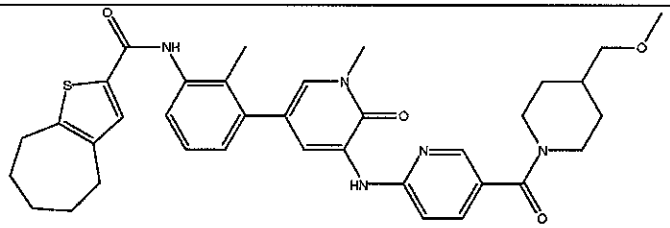
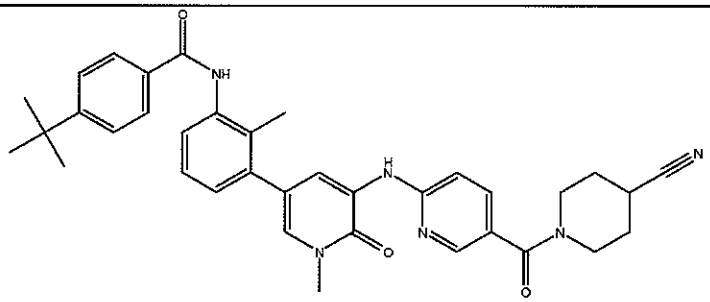
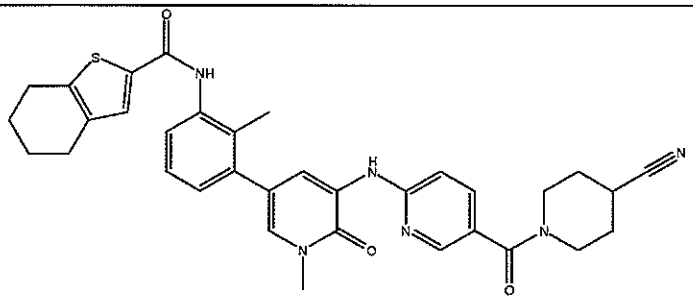
	551.3	551.99
	555.3	555.96
	569.3	569.95
	622.3	623.31
	626.3	627.25
	640.3	641.29

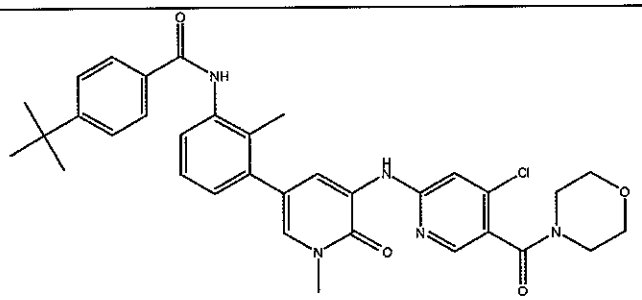
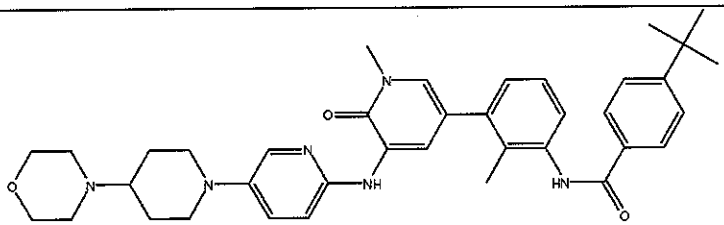
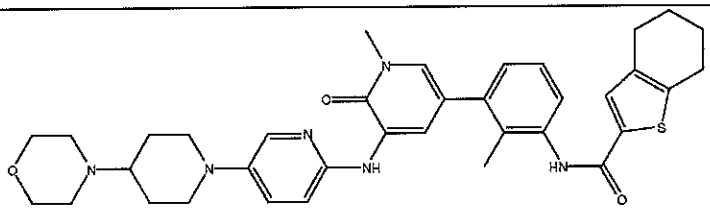
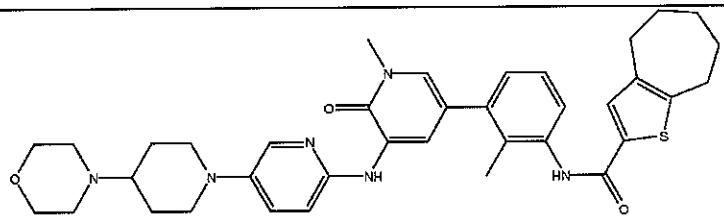
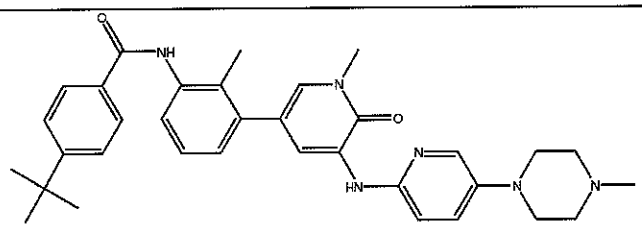
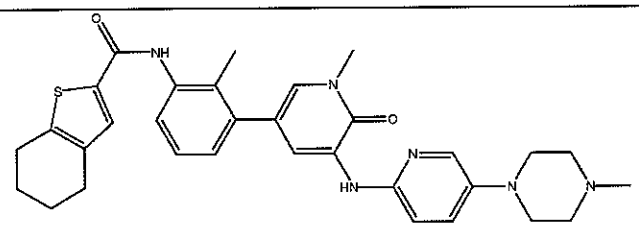
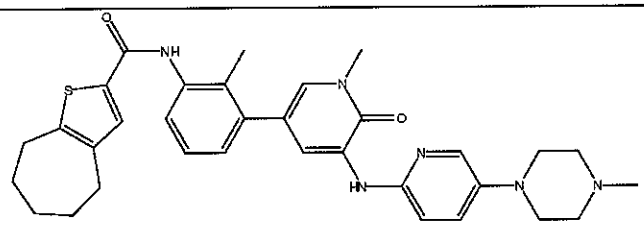
	597.2	598.27
	603.2	604.33
	509.2	510.26
	620.3	621.31
	624.3	625.24

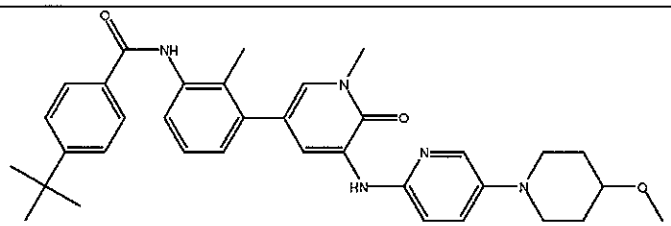
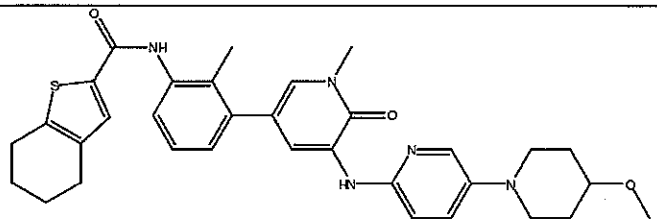
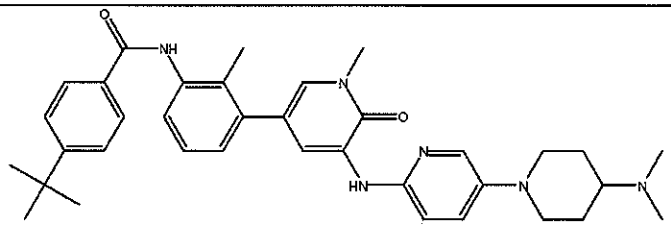
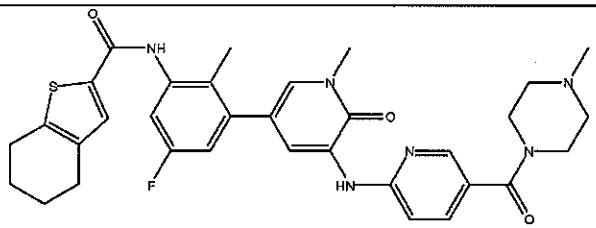
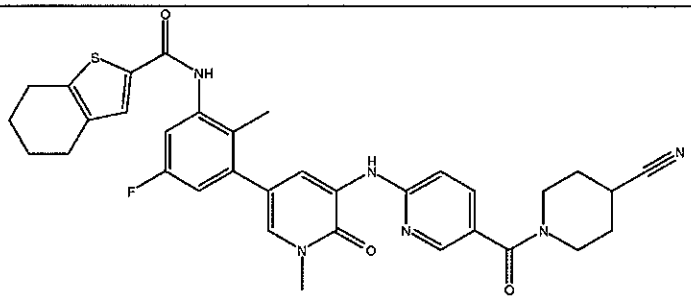
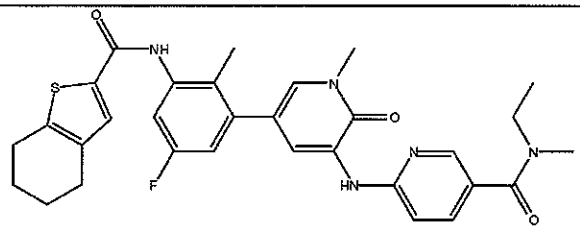
	638.3	639.29
	592.3	593.31
	596.2	597.25
	610.2	611.27
	581.3	582.29
	585.2	586.42

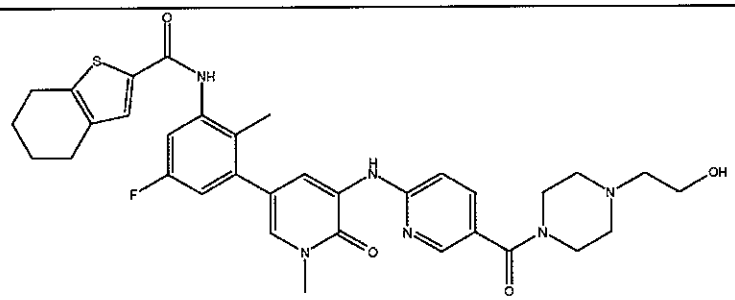
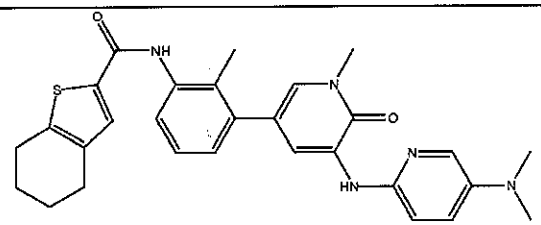
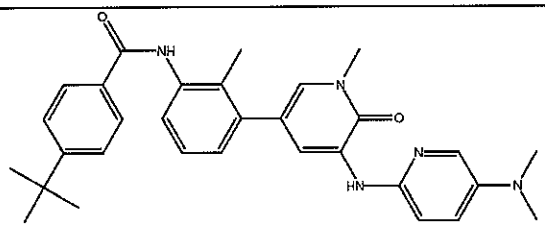
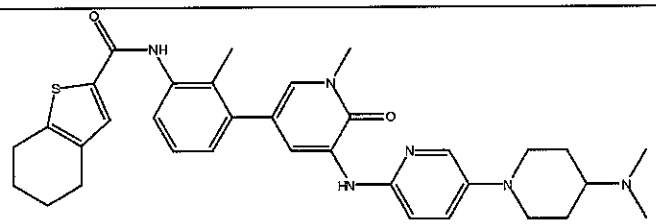
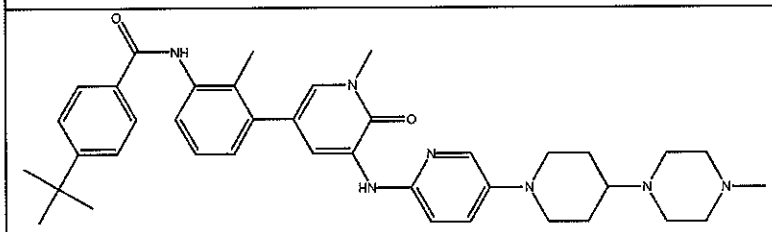
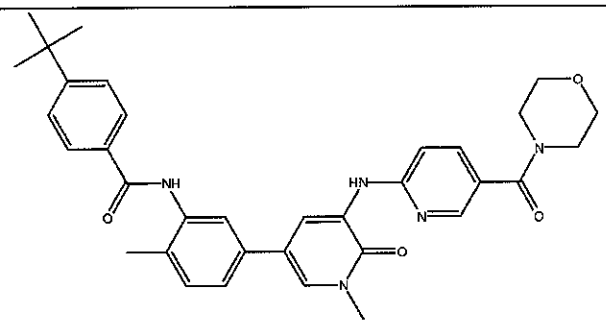
	599.3	600.26
	551.3	552.29
	555.2	556.25
	569.2	570.25
	615.2	616.32
	601.2	602.22

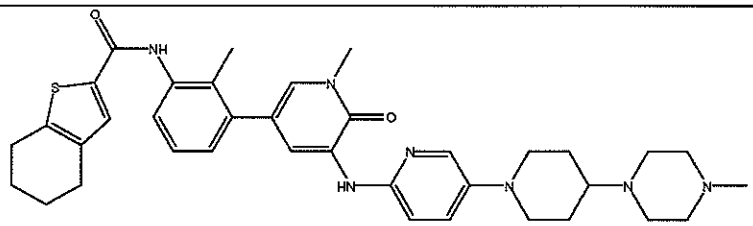
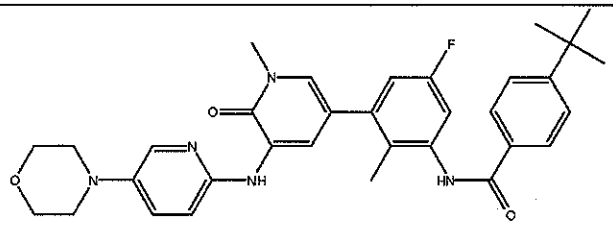
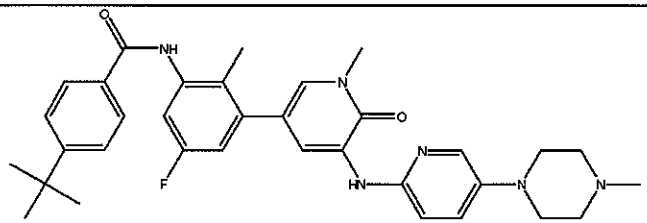
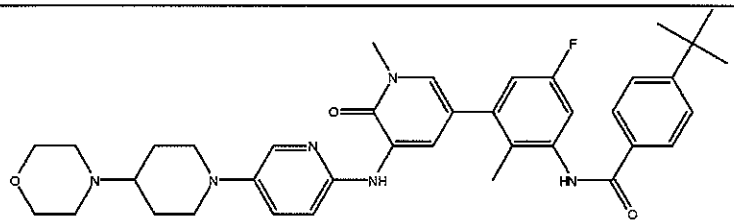
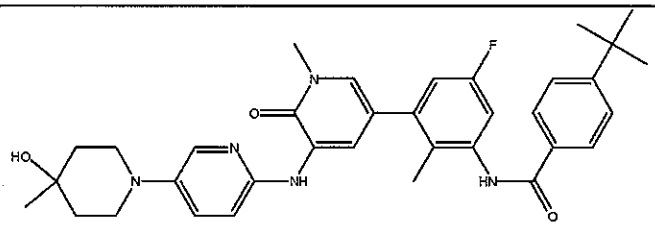
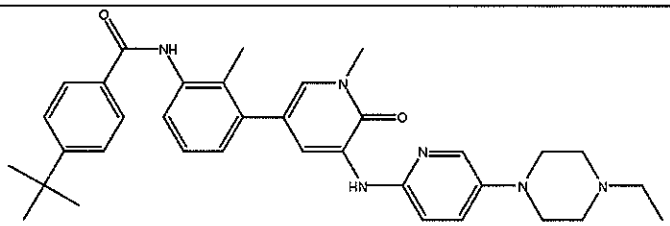
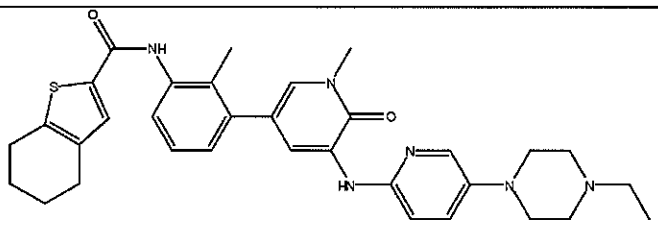
	537.3	538.28
	510.2	511.13
	514.2	515.21
	528.2	529.38
	591.3	592.33
	595.2	596.25

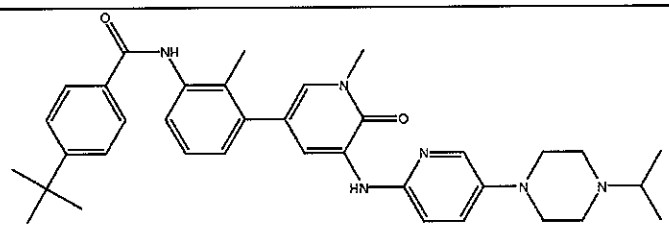
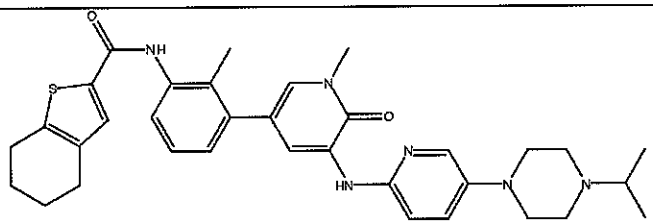
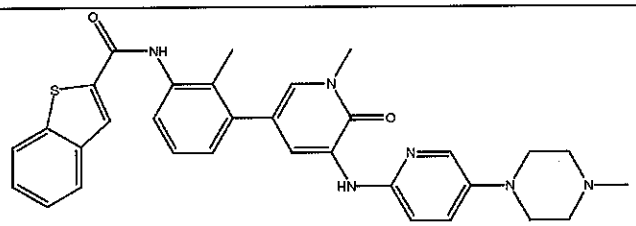
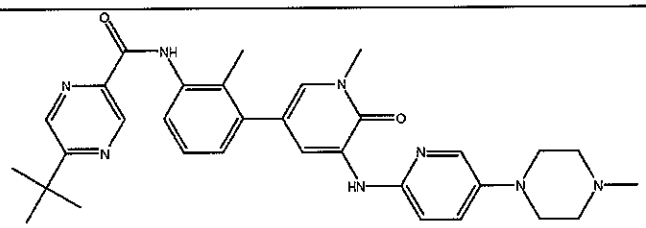
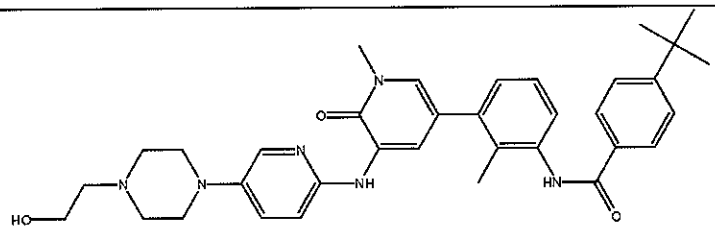
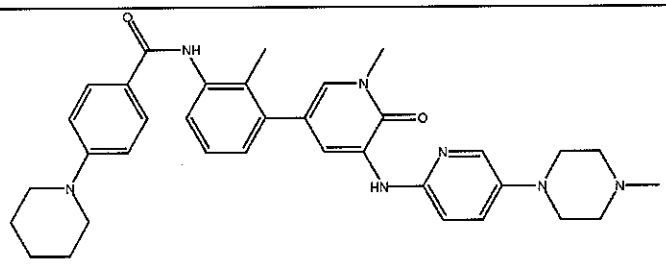
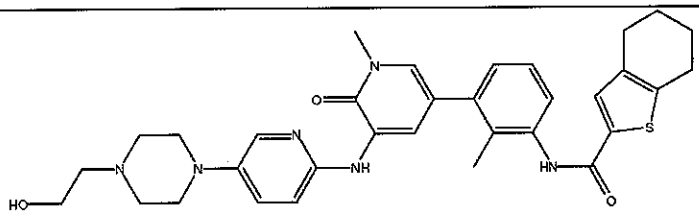
	609.2	610.26
	621.3	622.40
	625.3	626.22
	639.3	640.24
	602.3	603.27
	606.2	607.20

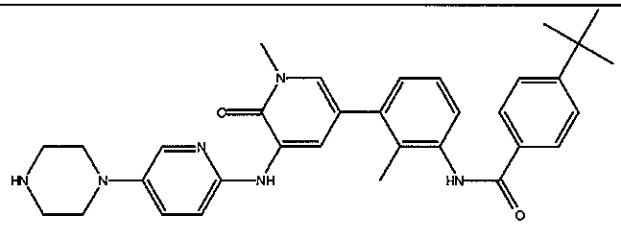
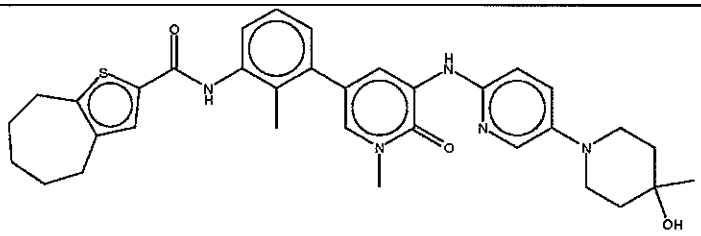
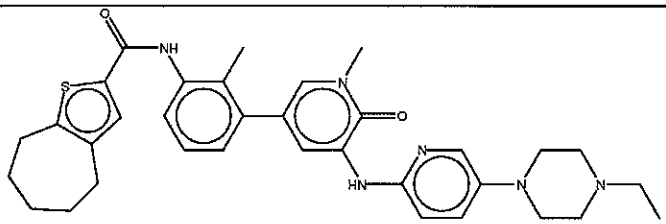
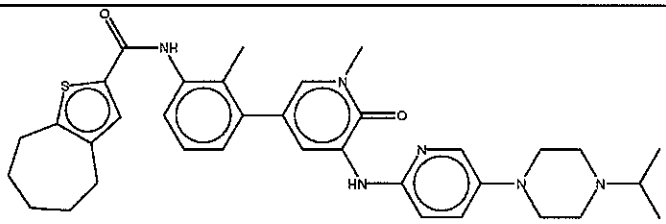
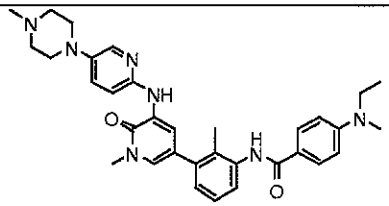
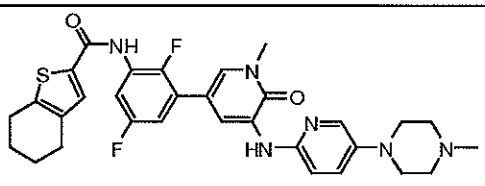
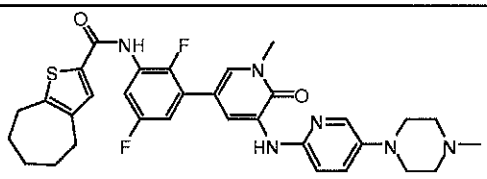
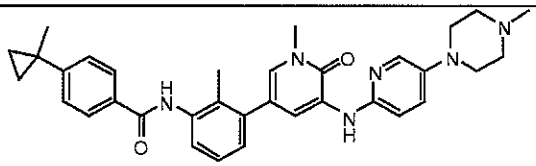
	613.2	613.90
	634.4	635.56
	638.3	639.53
	652.3	653.28
	564.3	565.28
	568.3	569.29
	582.3	583.29

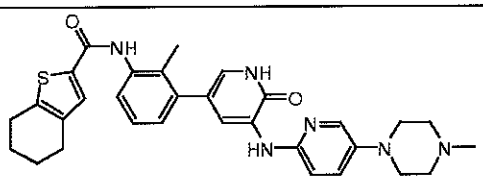
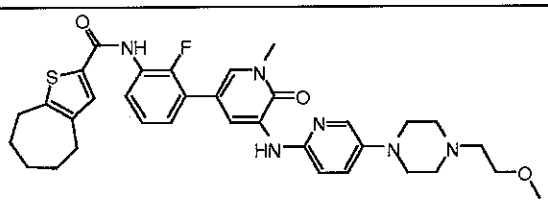
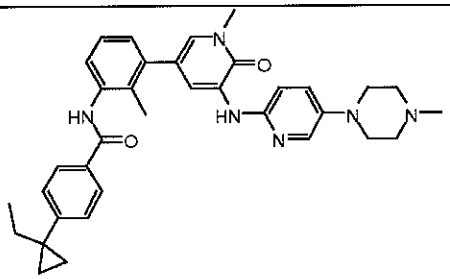
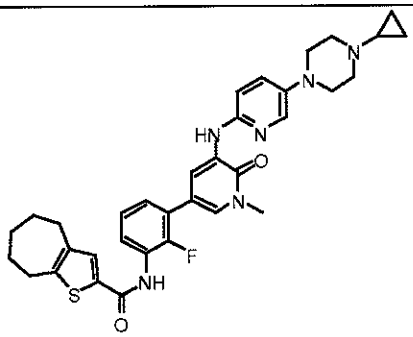
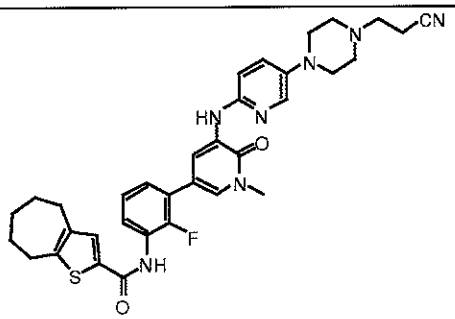
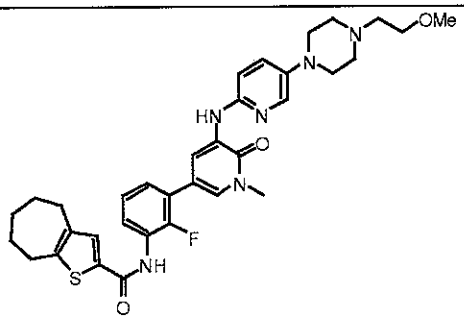
	579.3	580.36
	583.3	584.27
	592.4	593.50
	614.2	615.40
	624.2	625.47
	573.2	574.35

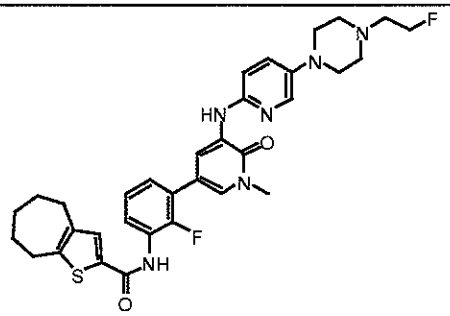
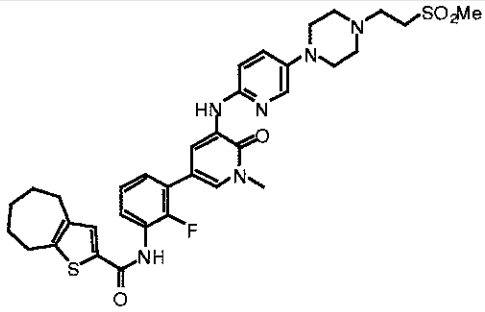
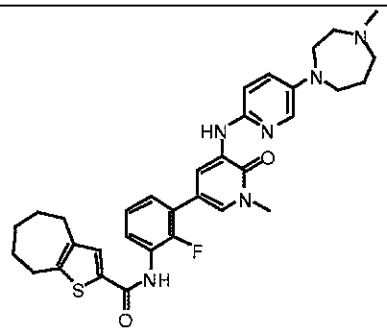
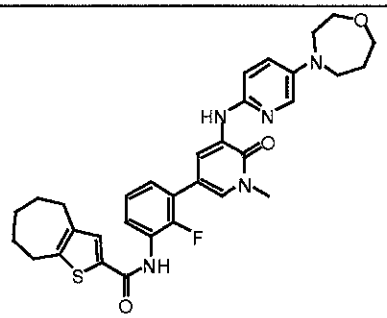
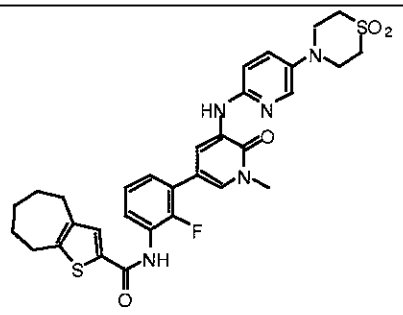
	644.3	645.364
	513.2	514.294
	509.3	510.304
	596.3	597.440
	647.4	648.610
	579.3	580.210

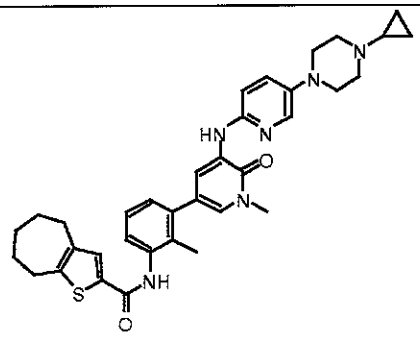
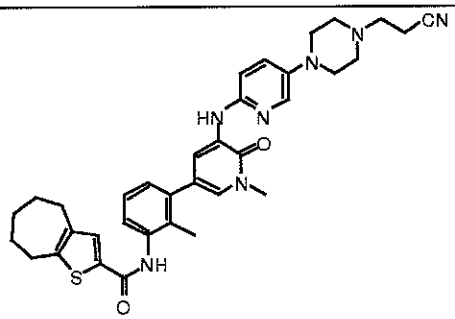
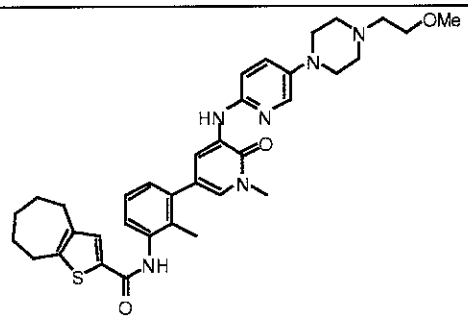
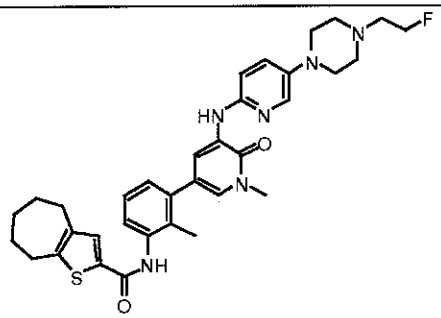
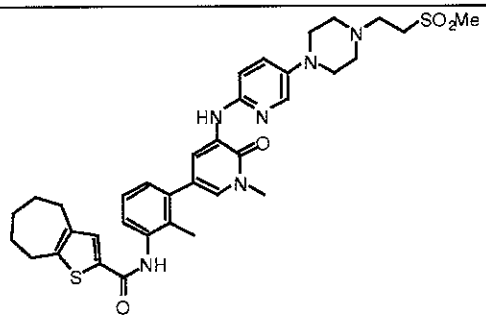
	651.3	652.536
	569.3	570.363
	582.3	583.358
	652.4	653.468
	597.3	598.363
	578.3	579.34
	582.3	583.31

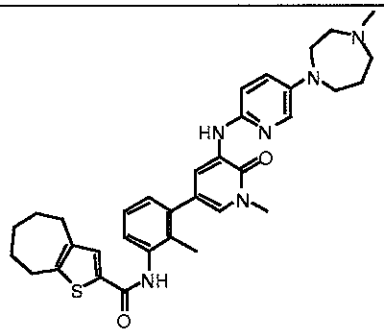
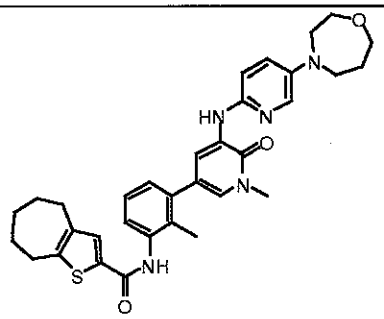
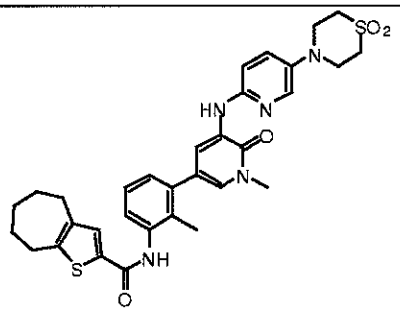
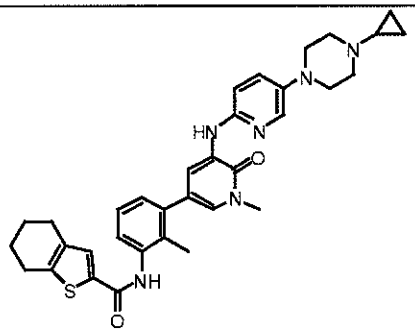
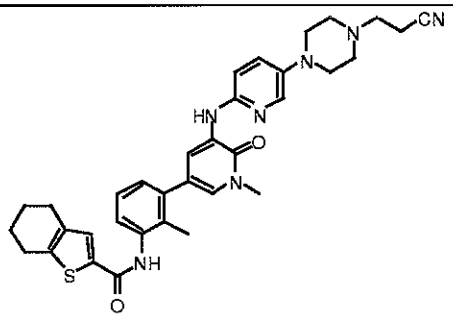
	592.4	593.38
	596.3	597.42
	564.2	565.71
	566.3	567.29
	594.3	595.36
	591.3	592.33
	598.3	599.31

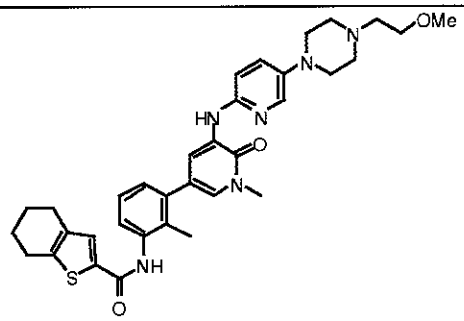
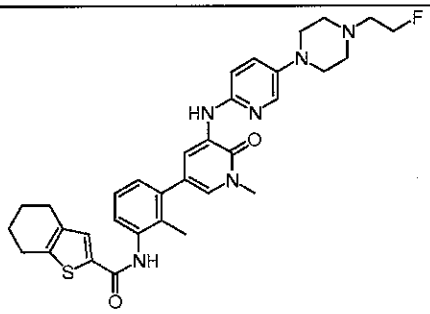
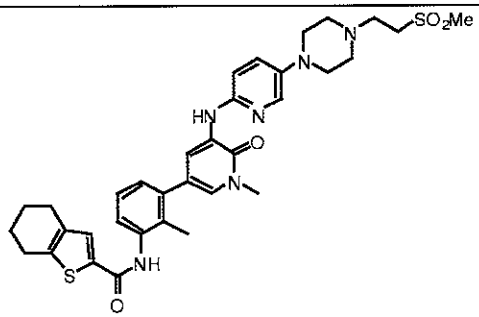
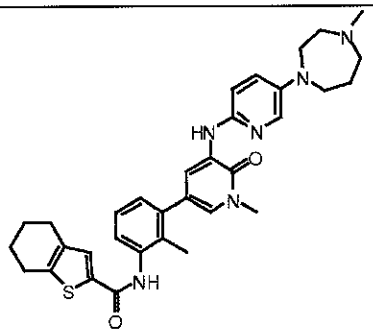
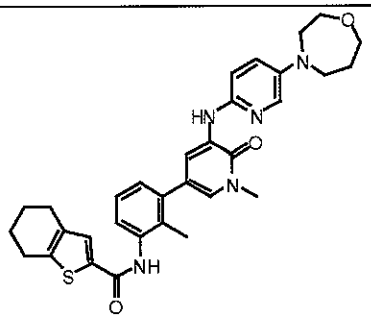
	550.3	551.25
	597.3	598.17
	596.3	597.26
	610.3	611.32
	565.32	566.40
	590.23	591.3
	604.24	605.2
	562.31	563.3

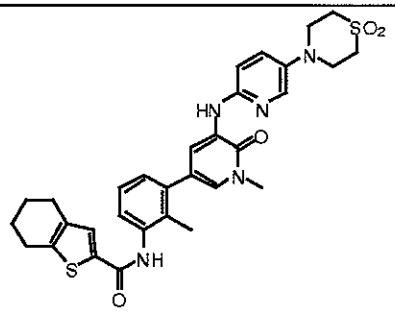
	554.25	555.2
	630.28	631.18
	576.32	577.4
	612.27	613.4
	625.26	626.3
	630.28	631.3

	618.26	619.4
	678.25	679.2
	600.27	601.2
	587.24	588.3
	621.19	622.2

	608.29	609.5
	621.29	622.3
	626.3	627.4
	614.28	615.3
	674.27	675.3

	596.29	597.3
	583.26	584.3
	617.21	618.3
	594.28	595.3
	607.27	608.3

	612.29	613.2
	600.27	601.3
	660.26	661.3
	582.28	583.3
	569.25	570.2

	603.2	604.2

Example 6

Biochemical Btk Assay

[00203] A generalized procedure for one standard biochemical Btk Kinase Assay that can be used to test compounds disclosed in this application is as follows.

[00204] 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 100 ng/well (0.06 mU/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 is 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 is used to infect Sf9 cells to overexpress the recombinant Btk protein. The Btk protein is then purified to homogeneity using Ni-NTA column. The purity of the final protein preparation is greater than 95% based on the sensitive Sypro-Ruby staining. A solution of 200 μM ATP is prepared in water and 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 200 μM ATP is added to that mixture in the 96-

well ½ area Costar polystyrene plate for final ATP concentration of 40 μM. 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 7

Biochemical Btk Assay

[00205] A generalized procedure for another standard biochemical Btk Kinase Assay that can be used to test compounds disclosed in this application is as follows.

[00206] A master mix minus Btk enzyme is prepared containing 1X Lanthascreen buffer (50 mM Hepes, pH 7.5, 2 mM dithiothreitol, 0.2 mM Na_3VO_4, 2 mM $MnCl_2$, 10 mM $MgCl_2$), 0.4 μM Fluorescein poly-Glu-Ala-Tyr peptide substrate, and 0.01% BSA. A master mix plus Btk enzyme is prepared containing 1X Lanthascreen buffer , 0.4 μM Fluorescein poly-Glu-Ala-Tyr peptide substrate, 0.01% BSA, and 100 pg/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 is 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 is used to infect Sf9 cells to overexpress the recombinant Btk protein. The Btk protein is then purified to homogeneity using Ni-NTA column. The purity of the final protein preparation is greater than 95% based on the sensitive Sypro-Ruby staining. A solution of 50 μM ATP is prepared in water and 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 50 μM ATP is added to that mixture in the 96-well ½ area Costar polystyrene plate for a final ATP

concentration of 10 μM. The reaction is allowed to incubate for 1 hour at room temperature. The reaction is stopped with 1X Lanthascreen TR-FRET dilution buffer containing 60 mM EDTA and 2 nM Tb-PY20 Ab. The plate is read using time-resolved fluorescence with a Perkin Elmer Envision using excitation filter 495 nm, emission filter 520 nm. IC_{50} values are subsequently calculated.

Example 8

Ramos Cell Btk Assay

[00207] Another generalized procedure for a standard cellular Btk Kinase Assay that can be used to test compounds disclosed in this application is as follows.

[00208] 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 9

B-Cell Proliferation Assay

[00209] 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.

[00210] 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 x 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 10

T Cell Proliferation Assay

[00211] A generalized procedure for a standard T cell proliferation assay that can be used to test compounds disclosed in this application is as follows.

[00212] 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 11

CD86 Inhibition Assay

[00213] 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.

[00214] 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 µ[g/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 12

B-ALL Cell Survival Assay

[00215] 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.

[00216] 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 5×10^5 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 13

[00217] The compounds disclosed in the examples above were tested in the Btk biochemical assay described herein (Example 6 or 7) and certain of those compounds exhibited an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 100 nM. Certain of those compounds exhibited an IC_{50} value less than or equal to 10 nM.

[00218] Some of the compounds disclosed in synthetic Examples 1-5 were tested in the B-cell proliferation assay (as described in Example 9) and exhibited an IC_{50} value less than or equal to 10 micromolar. Certain of those compounds exhibited

an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 500 nM in this assay.

[00219] Certain of those compounds did not inhibit T-cell proliferation and had IC_{50} values greater than or equal to 5 micromolar when assayed under conditions described herein (as described in Example 10).

[00220] Certain compounds disclosed herein exhibited 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.

[00221] Some of the compounds disclosed herein were tested in an assay for inhibition of B cell activity (under the conditions described in Example 11), and exhibited an IC_{50} value less than or equal to 10 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 1 micromolar. Certain of those compounds exhibited an IC_{50} value less than or equal to 500 nM in this assay.

[00222] Some of the compounds disclosed herein were tested in a B-cell leukemia cell survival assay (under the conditions described in Example 12), and exhibit an IC_{50} value less than or equal to 10 micromolar.

[00223] Some of the compounds disclosed in disclosed herein exhibited both biochemical and cell-based activity. For example, some of the compounds disclosed herein exhibited an IC_{50} value less than or equal to 10 micromolar in the Btk biochemical assay described herein (Example 6 or 7) 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 (Examples 8, 9, 11 or 12). Certain of those compounds exhibited an IC_{50} value less than or equal to 1 micromolar in the Btk biochemical assay described herein (Example 6 or 7) 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 (Examples 8, 9, 11 or 12). Certain of those compounds exhibited 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 (Examples 7, 8, 10 or 11).

[00224] 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.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the examples, all temperatures are set forth uncorrected in degrees Celsius and, all parts and percentages are by weight, unless otherwise indicated.

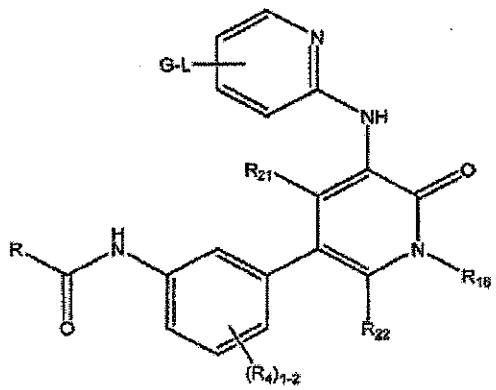
The entire disclosures of all applications, patents and publications, cited herein and of corresponding U.S. Provisional Application Serial No. 60/843,959, filed September 11, 2006, are incorporated by reference herein.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A compound of Formula 1:



(Formula 1)

or pharmaceutically acceptable salts or mixtures thereof, wherein

R is 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl; mono-, di-, or tri-substituted 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl wherein the substituents are independently chosen from hydroxyl, lower alkyl, sulfonyl, halo or lower alkoxy; 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl; mono-, di-, or tri-substituted 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl wherein the substituents are independently chosen from lower alkyl;

R_4 is hydrogen, optionally fluoro- substituted lower alkyl, optionally fluoro- substituted lower alkoxy, cyano, halo, or hydroxy;

R_{21} and R_{22} are independently hydrogen or lower alkyl;

R_{16} is chosen from hydrogen, cyano, cycloalkyl, lower alkyl or lower alkyl substituted by lower alkoxy or amino;

L is C_0-C_4alkylene, -O- C_0-C_4alkylene, -(C_0-C_4alkylene)(SO)-, -(C_0-C_4alkylene)(SO_2)-; or -(C_0-C_4alkylene)(C=O)-; and

G is hydrogen, halo, hydroxy, alkoxy, nitro, alkyl, amino, carbamimidoyl, cycloalkyl, 5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl, lower alkoxy, 1H-tetrazol-5-yl, N-methylethanolamino, morpholin-4-yl, piperazin-1-yl,

piperidin-1-yl, homopiperazin-1-yl, 4-acyl-piperazin-1-yl, 4-lower alkyl-piperazin-1-yl,

4-lower alkyl-piperidin-1-yl, 4-hydroxy-4-lower alkyl-piperidin-1-yl, 3-oxo-piperazin-1-yl, omopiperazin-1-yl, 4-lower alkyl-homopiperazin-1-yl, 4-lower alkyl-piperazin-1-yl wherein said alkyl is substituted with one or more substituents chosen from CN, lower alkoxy, halo, or SO_2-lower alkyl, 4-lower alkoxy-piperidin-1-yl, 4-CN-piperidin-1-yl, 4-cyclopropyl-piperazin-1-yl, 4-(4-methylpiperazin-1-yl)-piperidin-1-yl, 4-morpholinopiperidin-1-yl, oxazepan-4-yl, 1,1-dioxo-thiomorpholin-4-yl, or $-NR_7R_8$ wherein R_7 and R_8 are independently hydrogen or $(C_1$-$C_6)$alkyl, or wherein R_7 and R_8, together with the nitrogen to which they are bound, form a 5- to 7-membered nitrogen containing ring which optionally further includes one or two additional N, O, or S atoms.

2. The compound of claim 1 wherein R is 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl or mono-, di-, or tri-substituted 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl wherein the substituents are independently chosen from hydroxy, lower alkyl, sulfonyl, halo, or lower alkoxy.

3. The compound of claim 2 wherein R is 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl or mono-, di-, and tri-substituted 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl wherein the substituents are independently chosen from lower alkyl.

4. The compound of claim 3 wherein R is 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl.

5. The compound of claim 1 wherein R is 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl or mono-, di-, and tri-substituted 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl wherein the substituents are independently chosen from lower alkyl.

6. The compound of claim 5 wherein R is 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-2-yl.

7. The compound of claim 1 wherein L is C_0-C_4alkylene, -O- C_0-C_4alkylene, -(C_0-C_4alkylene)(SO_2)-; or -(C_0-C_4alkylene)(C=O)-.

8. The compound of claim 7 wherein L is C_0-C_4alkylene and -(C_0-C_4alkylene)(C=O)-.

9. The compound of claim 8 wherein L is a covalent bond.

10. The compound of claim 8 wherein L is -(C=O)-.

11. The compound of claim 1 wherein G is
hydrogen,
hydroxy,
$-NR_7R_8$ wherein R_7 and R_8 are independently chosen from hydrogen, acyl, or (C_1-C_6)alkyl; or wherein R_7 and R_8, together with the nitrogen to which they are bound, form a 5- to 7-membered nitrogen containing ring which optionally further includes one or two additional N, O, or S atoms;
5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl,
lower alkoxy, or
1H-tetrazol-5-yl.

12. The compound of claim 11 wherein G is
hydrogen,
amino;
hydroxy,
N-methylethanolamino,
morpholin-4-yl,
piperazin-1-yl,
piperidin-1-yl, and
homopiperazin-1-yl.

13. The compound of claim 12 wherein G is
hydrogen,
amino,
morpholin-4-yl,
4-acyl-piperazin-1-yl,
4-lower alkyl-piperazin-1-yl,
4-lower alkyl-piperidin-1-yl,
4-hydroxy-4-lower alkyl-piperidin-1-yl,
3-oxo-piperazin-1-yl,

homopiperazin-1-yl, or
4-lower alkyl-homopiperazin-1-yl.

14. The compound of claim 12 wherein G is
4-lower alkyl-piperazin-1-yl wherein said alkyl is substituted with one or more substituents chosen from CN, lower alkoxy, halo, and SO_2-lower alkyl, or
4-lower alkoxy-piperidin-1-yl.

15. The compound of claim 13 wherein G is
hydrogen,
amino,
morpholin-4-yl,
4-methyl-piperazin-1-yl,
4-methyl-piperidin-1-yl, or
4-hydroxy-4-methyl-piperidin-1-yl.

16. The compound of claim 11 wherein G is
4-CN-piperidin-1-yl,
4-cyclopropyl-piperazin-1-yl,
4-(4-methylpiperazin-1-yl)-piperidin-1-yl,
4-morpholinopiperidin-1-yl,
oxazepan-4-yl, or
1,1-dioxo-thiomorpholin-4-yl.

17. The compound of claim 1 wherein R_4 is chosen from hydrogen, lower alkyl, lower alkoxy, cyano, halo, or hydroxy.

18. The compound of claim 17 wherein R_4 is hydrogen, lower alkyl, lower alkoxy, halo, or hydroxy.

19. The compound of claim 18 wherein R_4 is methyl, trifluoromethyl, difluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, or fluoro.

20. The compound of claim 19 wherein R_4 is methyl.

21. The compound of claim 1 wherein R_{22} is hydrogen or lower alkyl.

22. The compound of claim 21 wherein R_{22} is hydrogen or methyl.

23. The compound of claim 22 wherein R_{22} is hydrogen.

24. The compound of claim 1 wherein R_{16} is hydrogen, lower alkyl, or lower alkyl substituted with a group chosen from alkoxy, amino, or acyl.

25. The compound of claim 24 wherein R_{16} is hydrogen or lower alkyl.

26. The compound of claim 25 wherein R_{16} is lower alkyl.

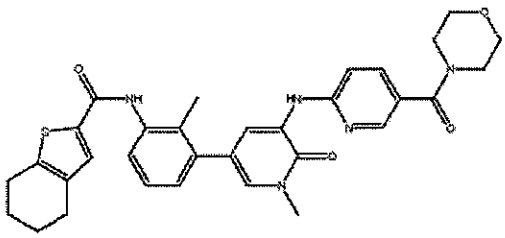
27. The compound of claim 26 wherein R_{16} is methyl or ethyl.

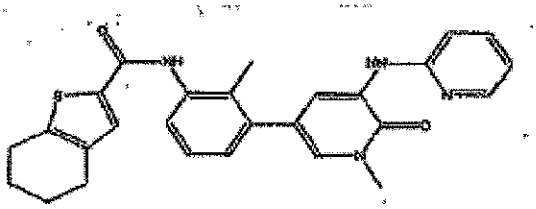
28. The compound of claim 1 wherein R_{21} is hydrogen or lower alkyl.

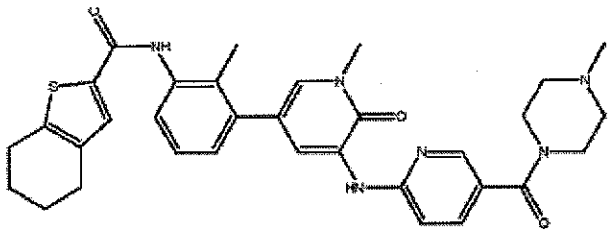
29. The compound of claim 28 wherein R_{21} is hydrogen or methyl.

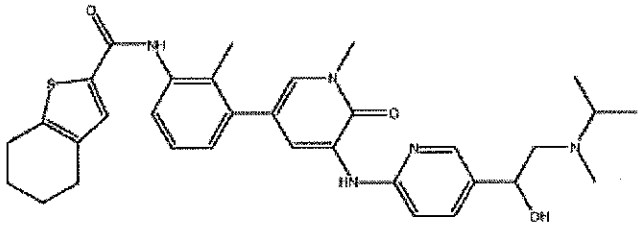
30. The compound of claim 29 wherein R_{21} is hydrogen.

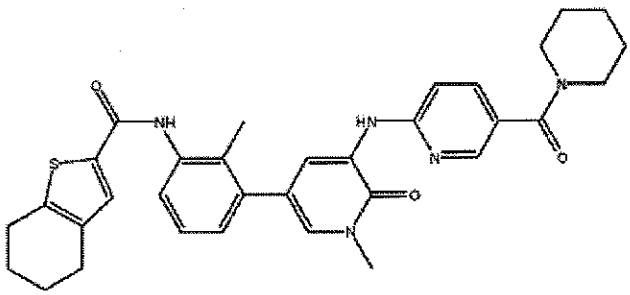
31. The compound of claim 1 wherein the compound of Formula 1 is

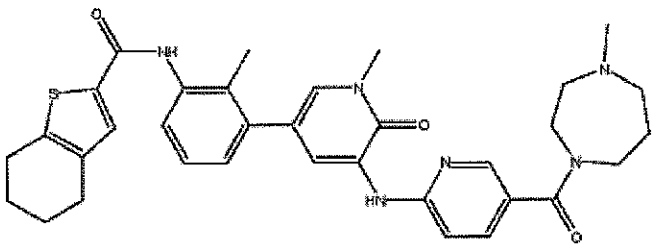


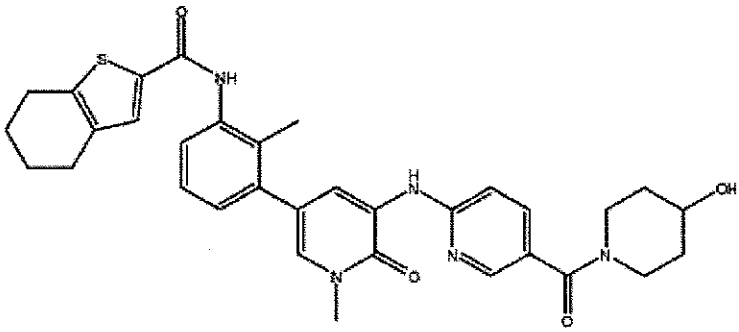


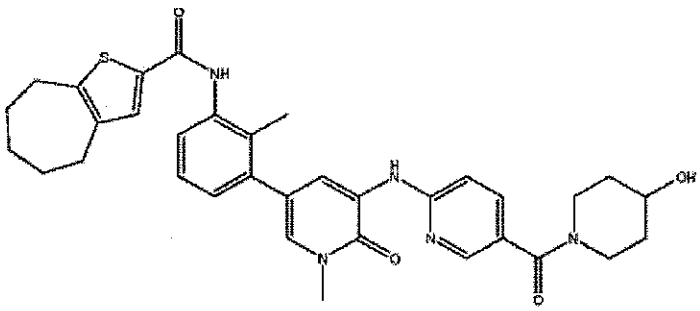


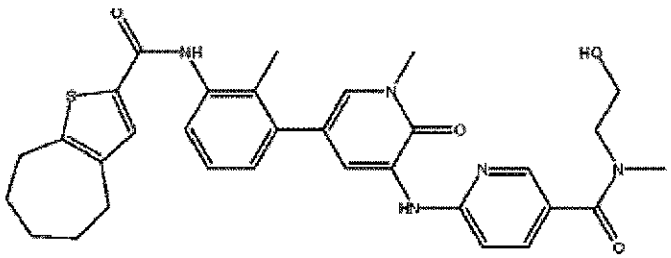


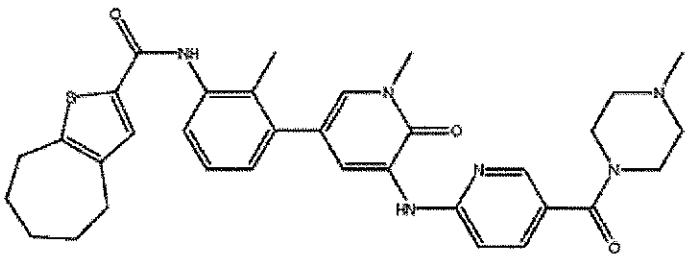


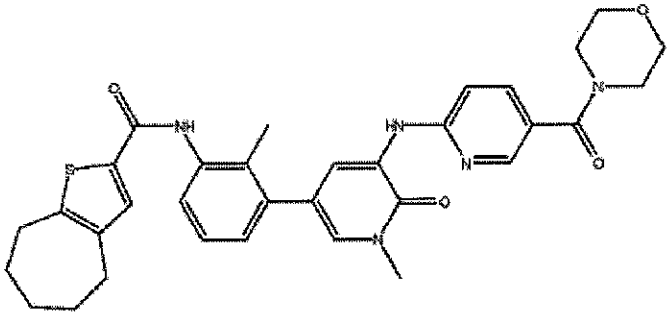


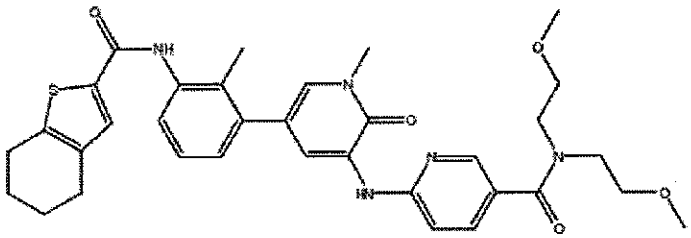


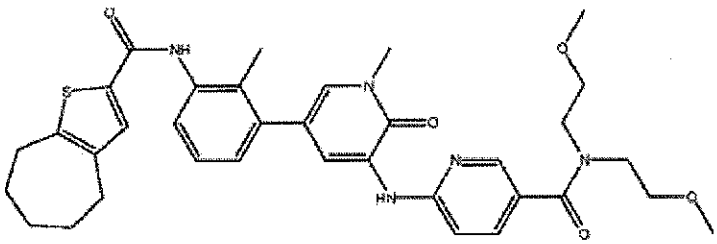


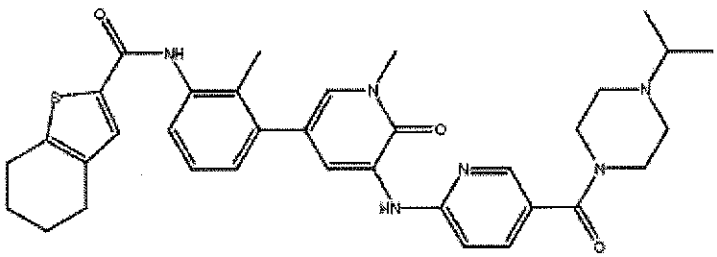


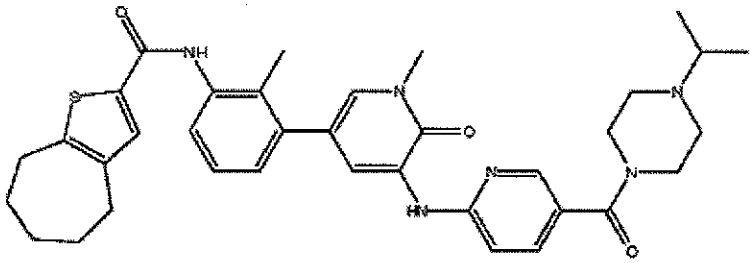


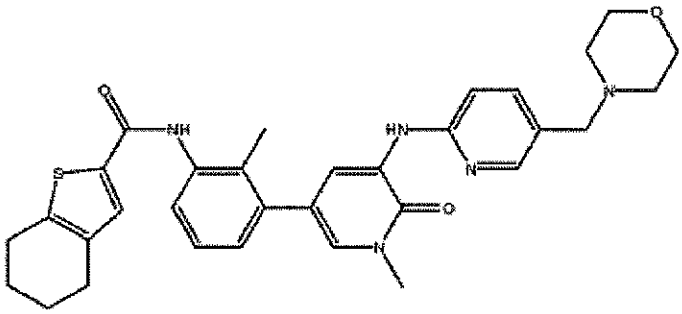


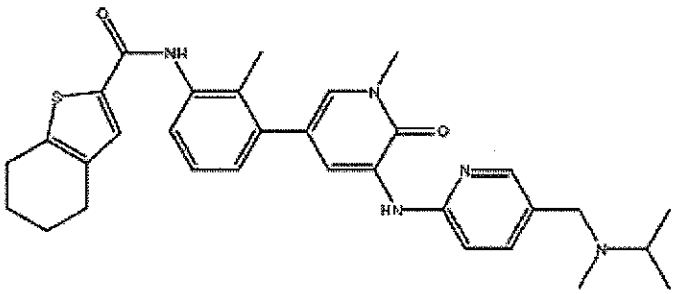


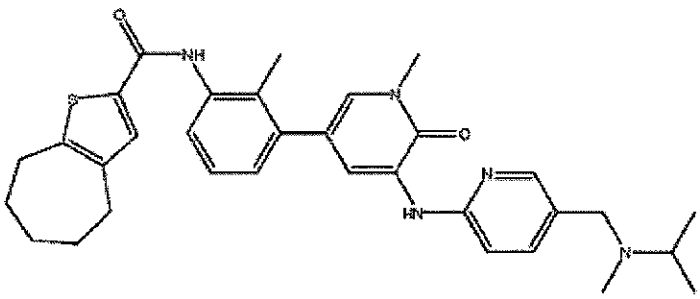


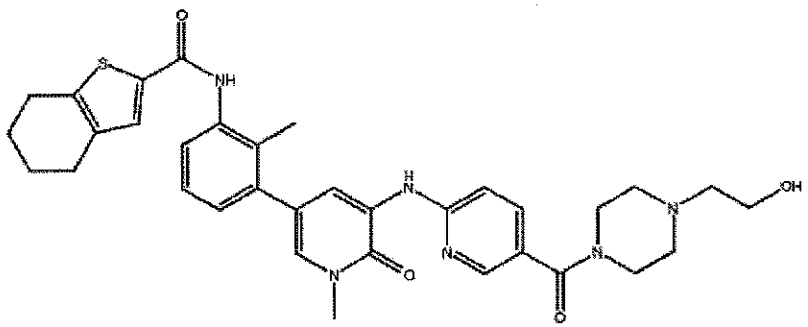


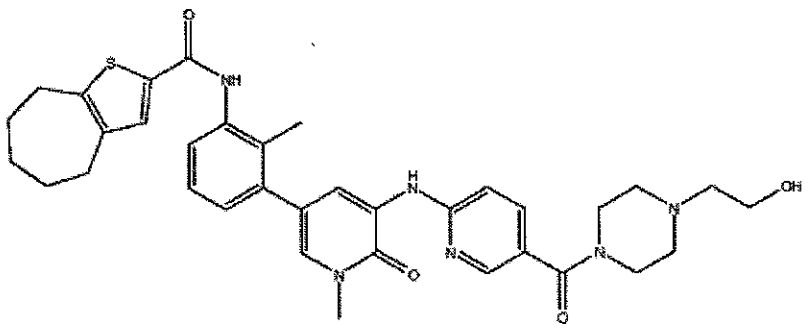


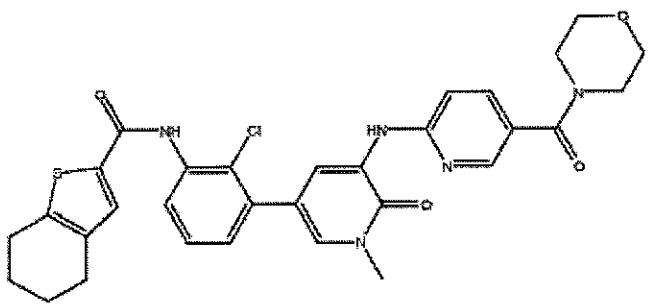


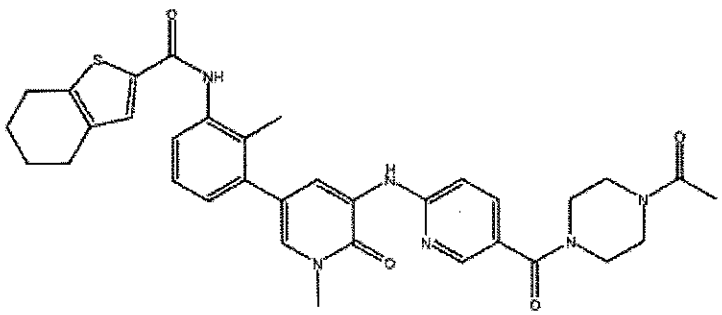


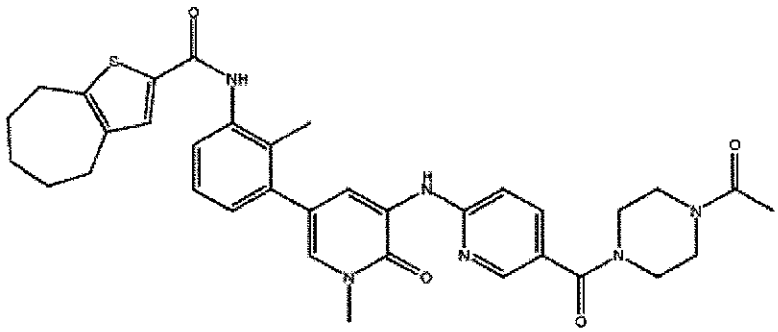


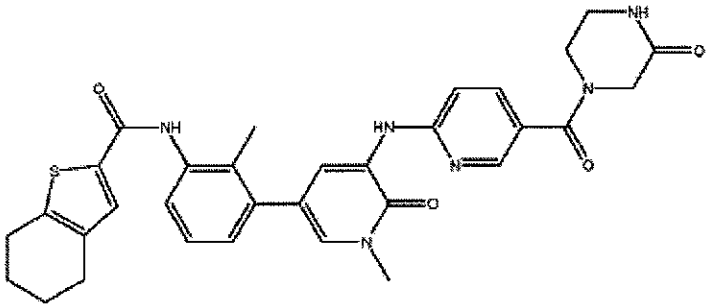


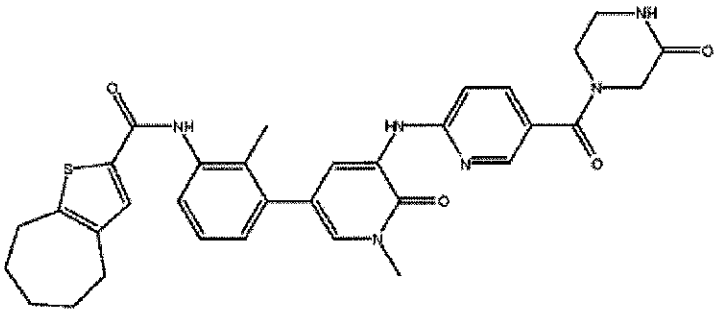


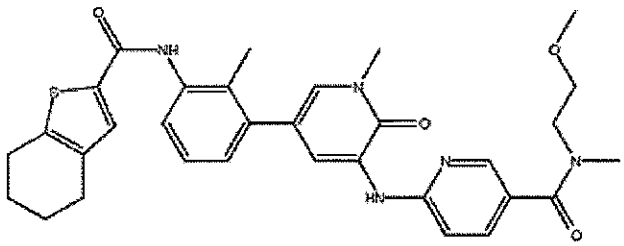


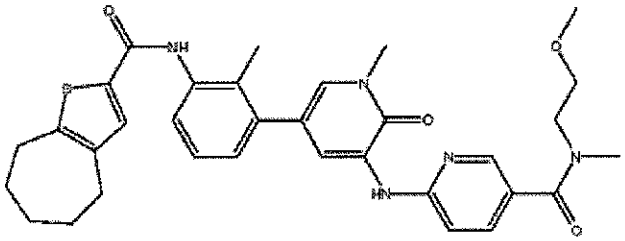


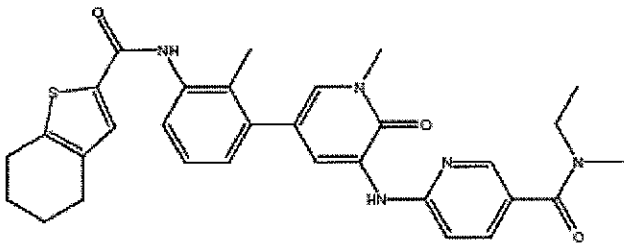


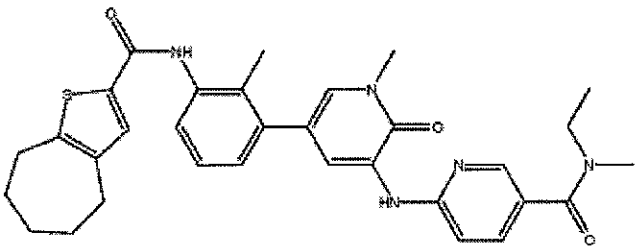


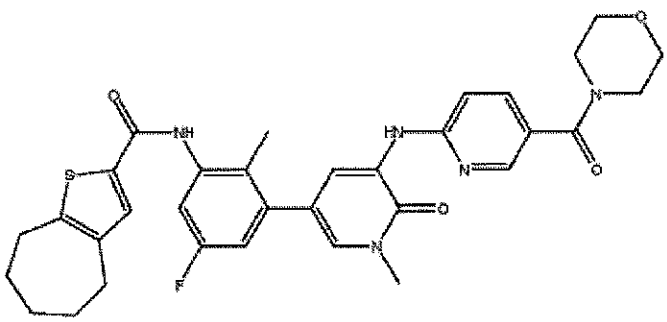


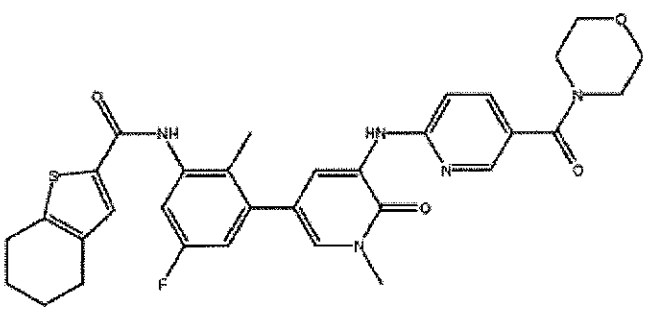


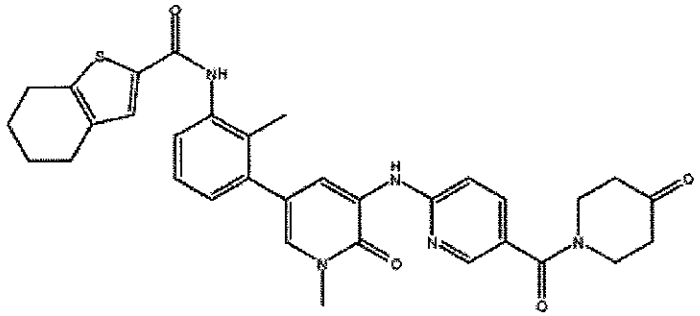


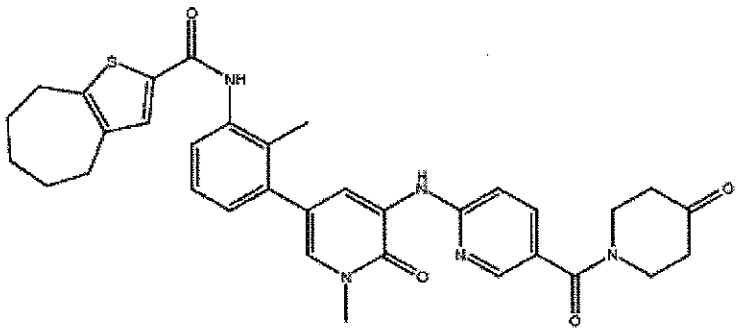


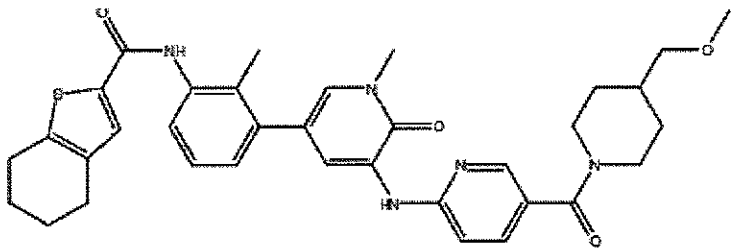


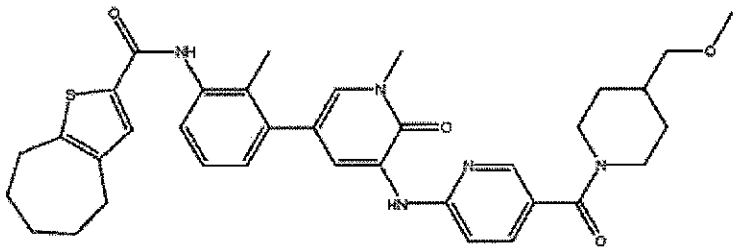


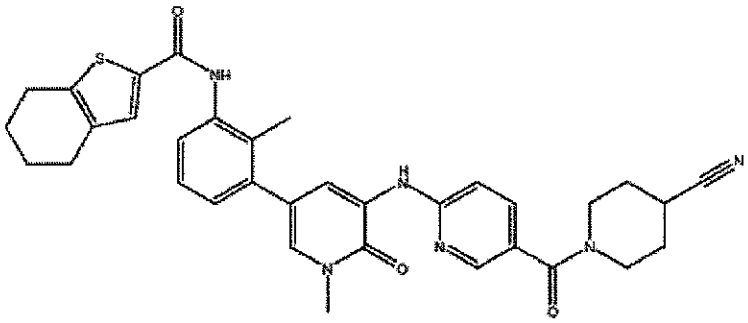


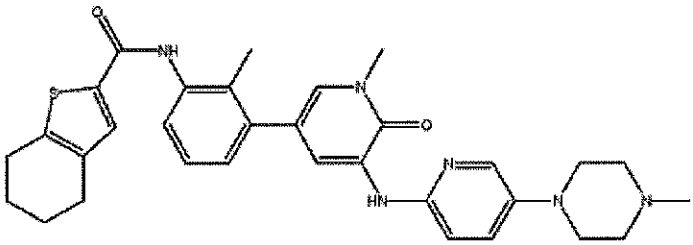


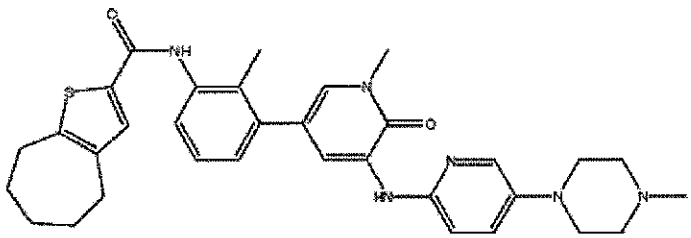


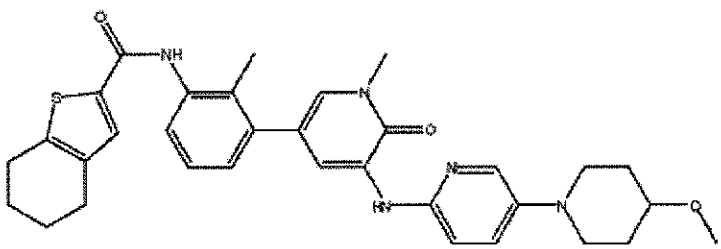


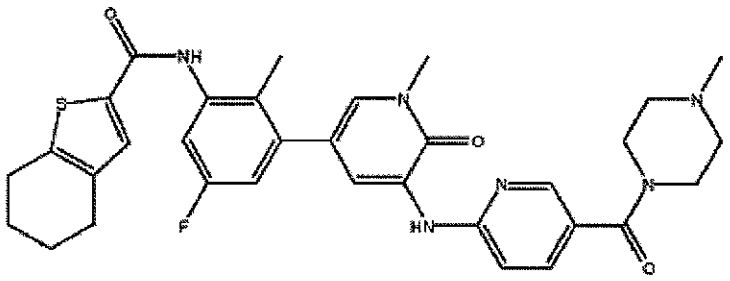


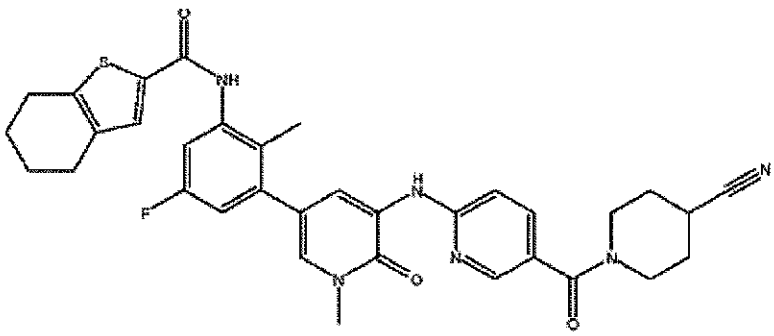


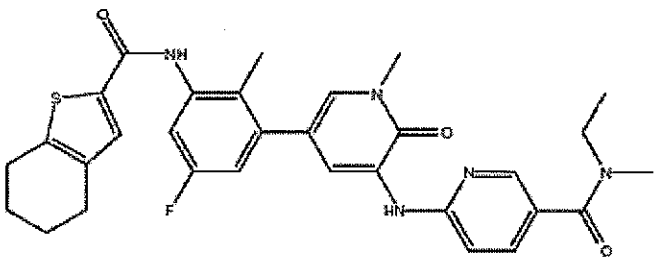


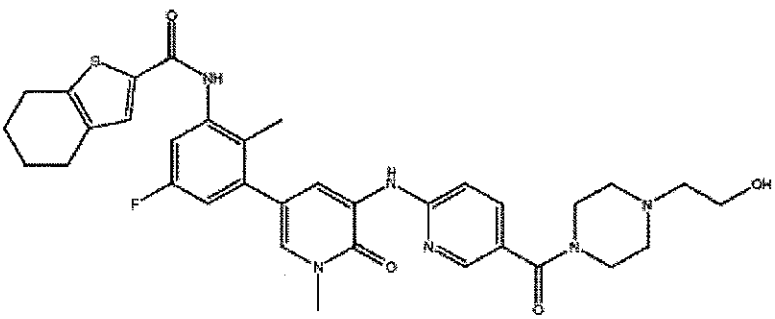


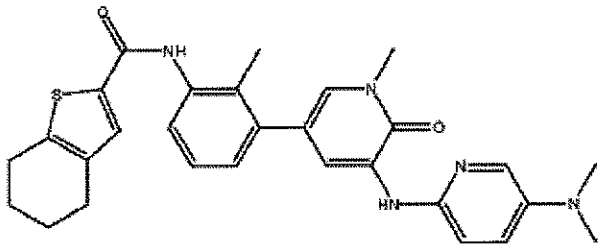


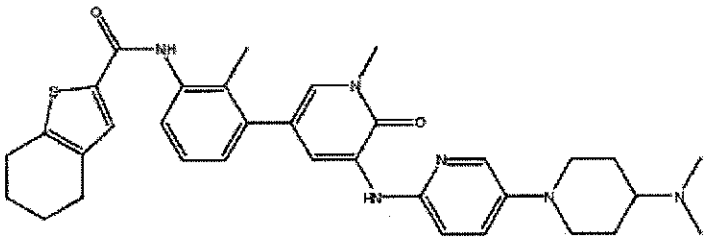


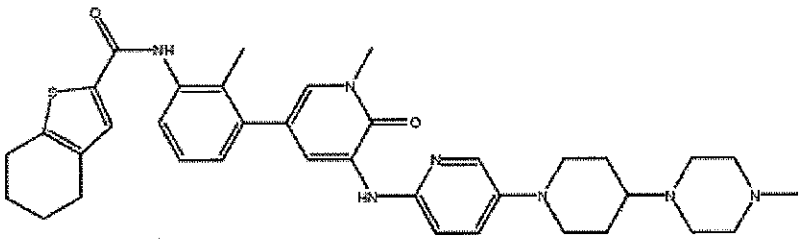


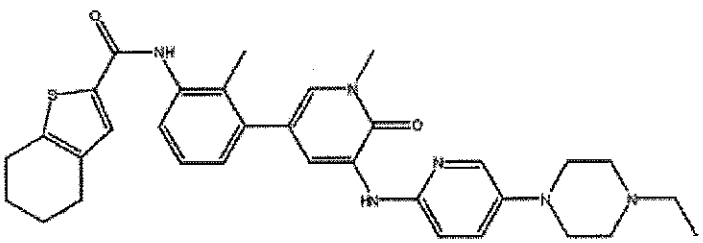


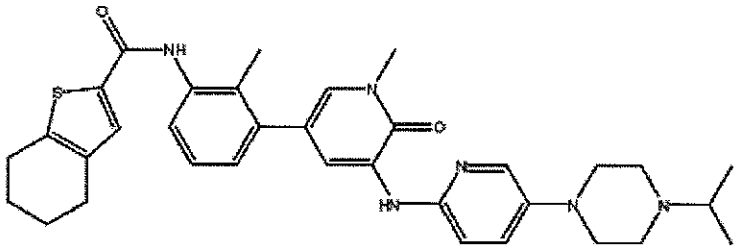


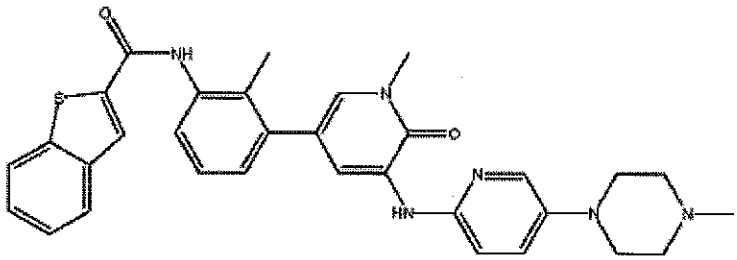


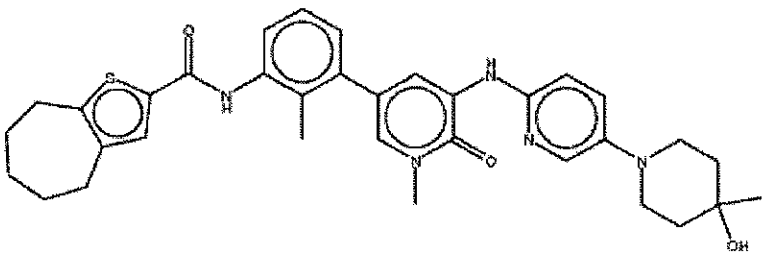


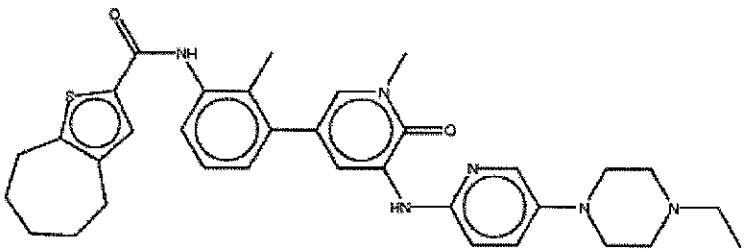


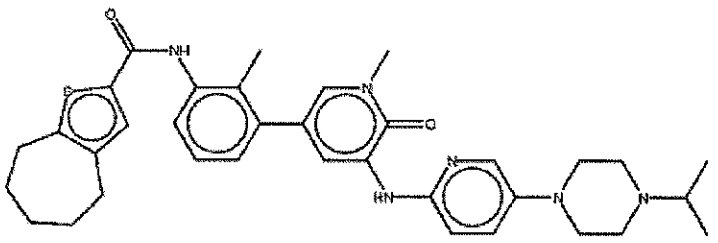


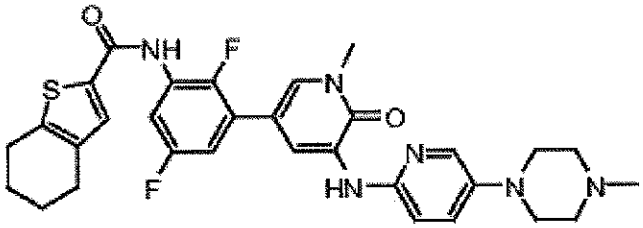


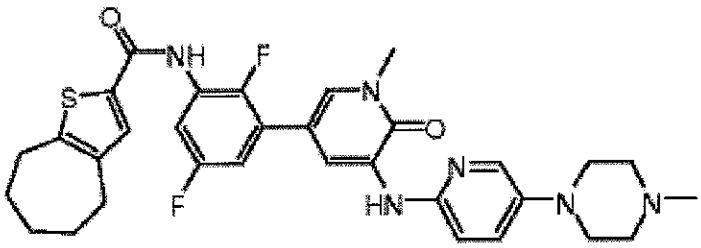


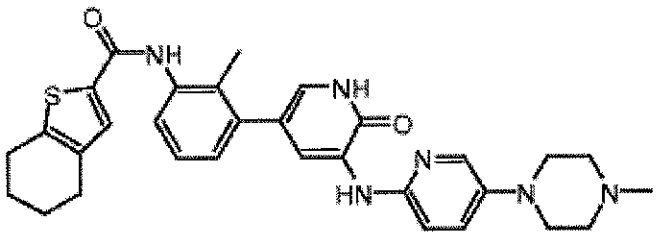


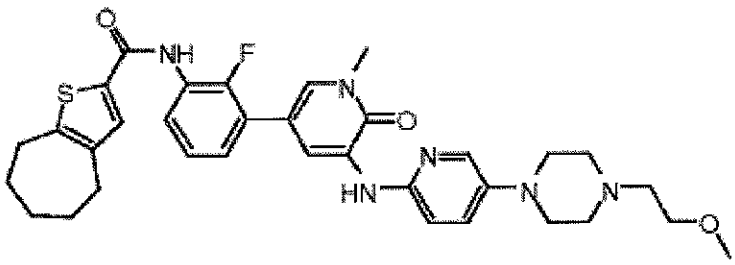


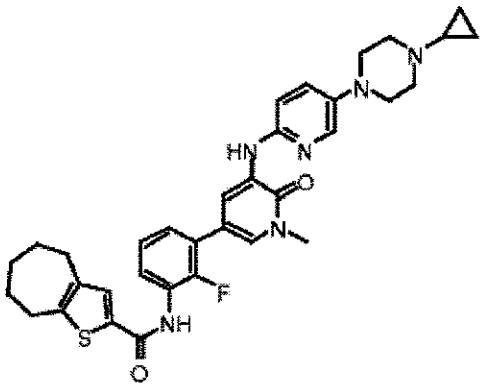


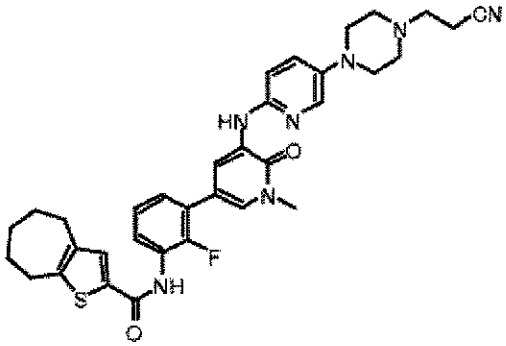


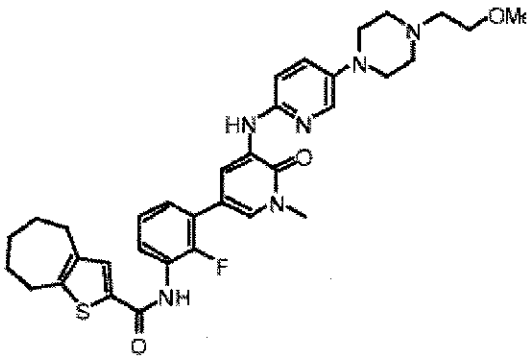


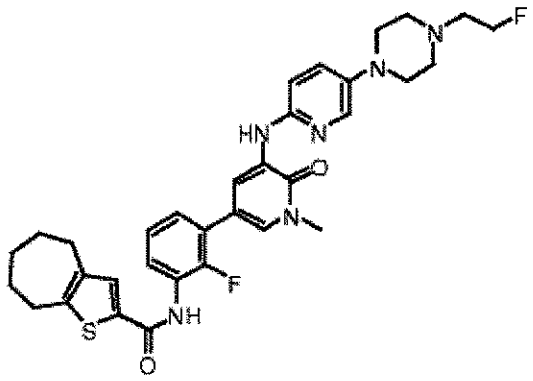


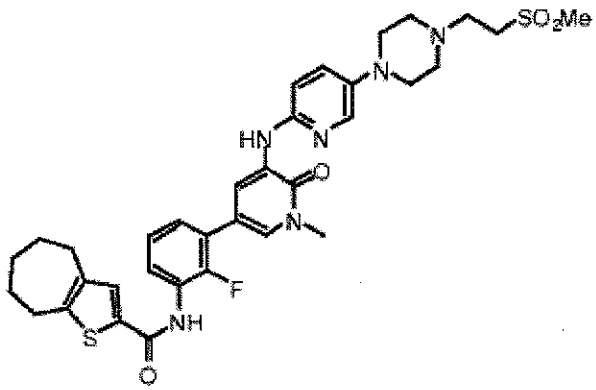


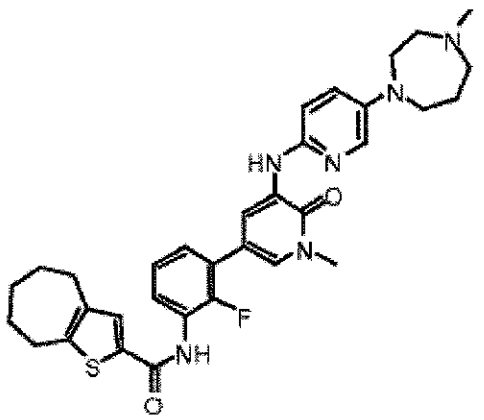


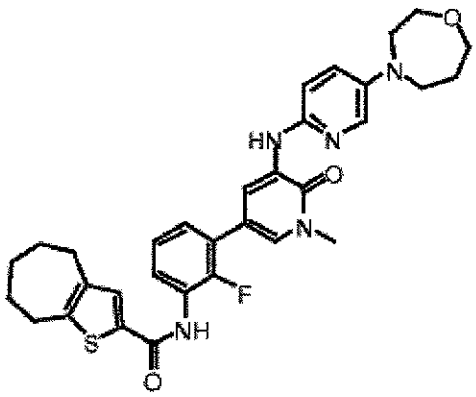


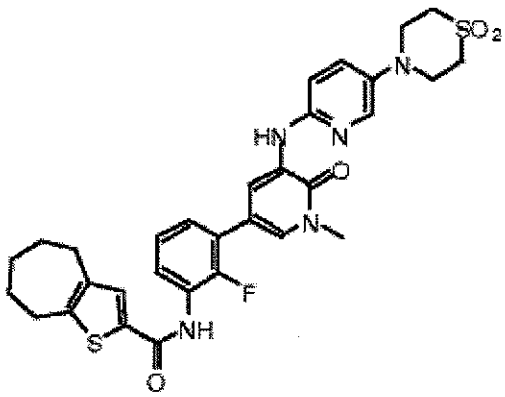


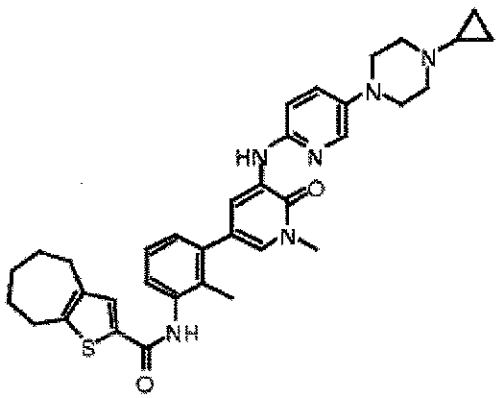


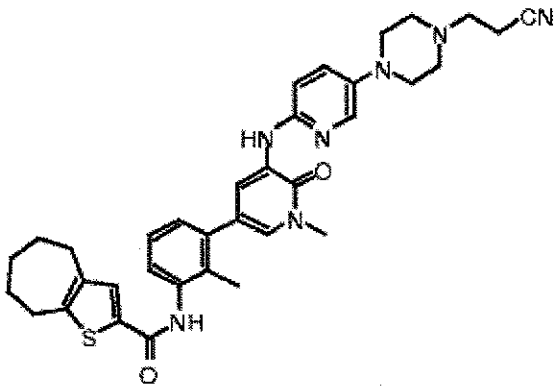








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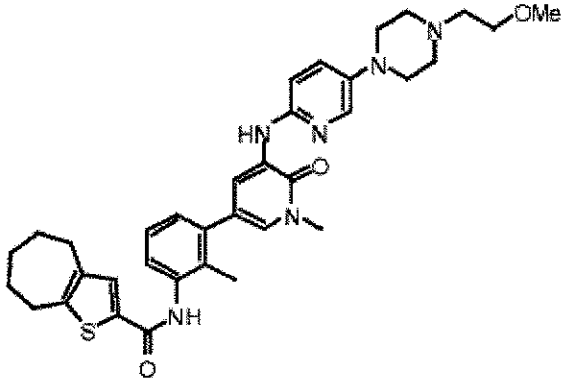
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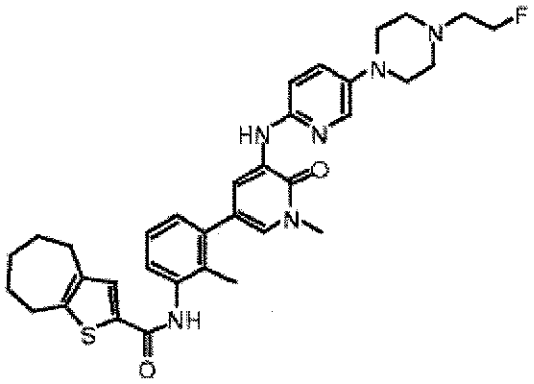
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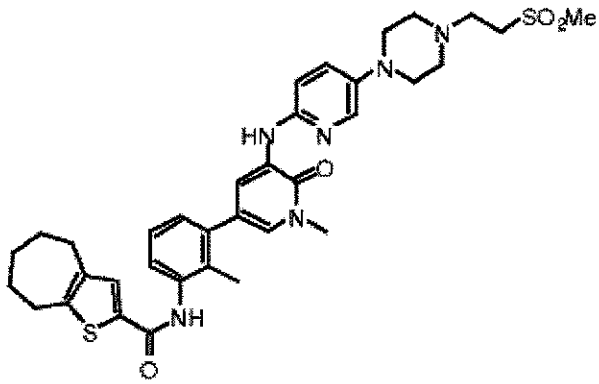
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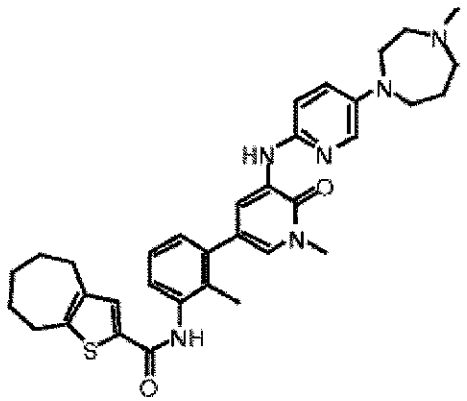
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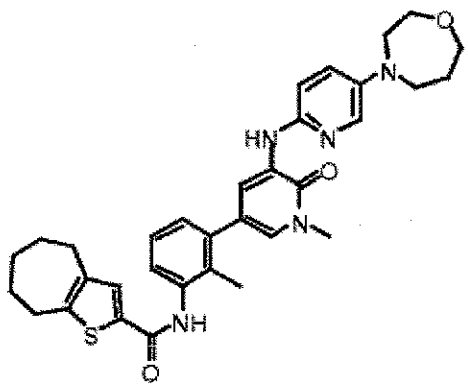
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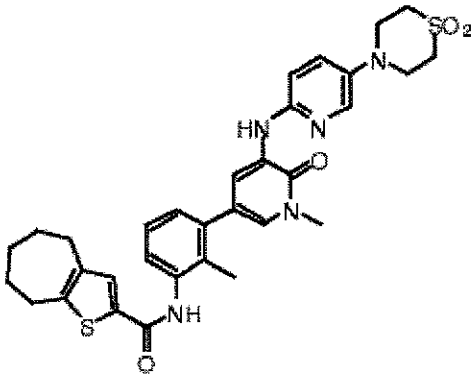

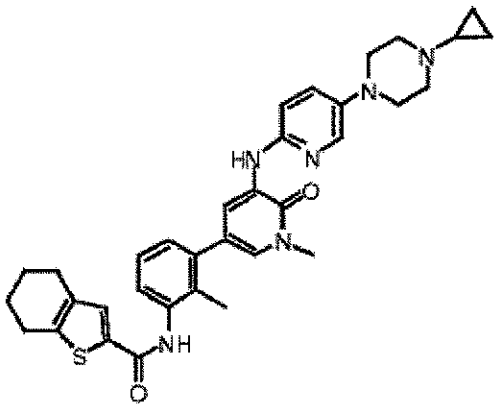

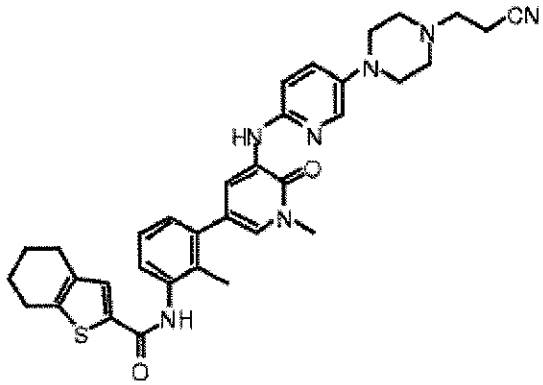

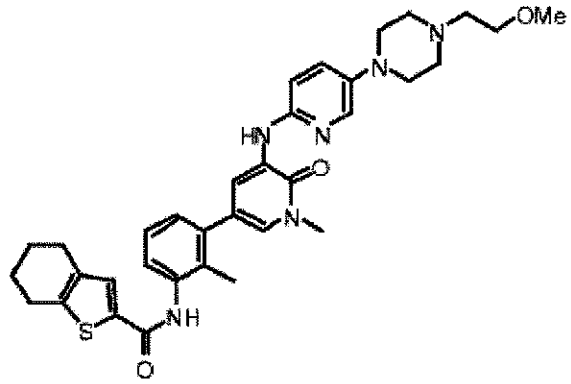
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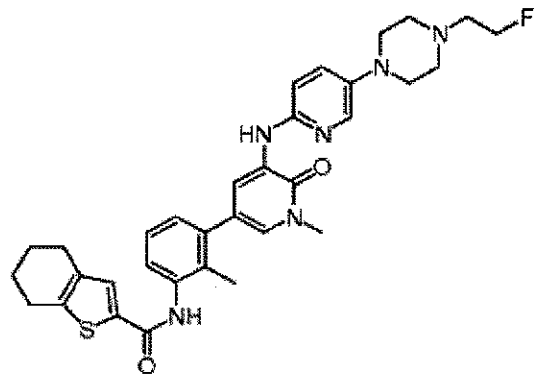
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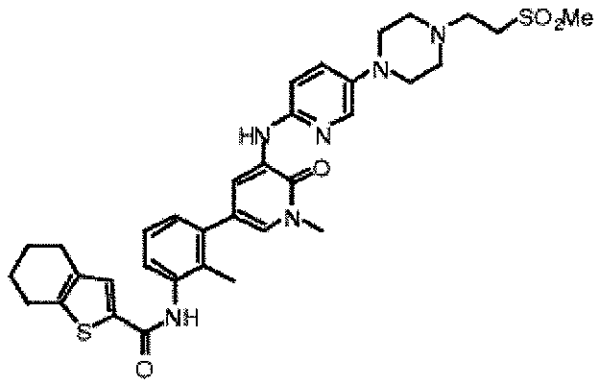
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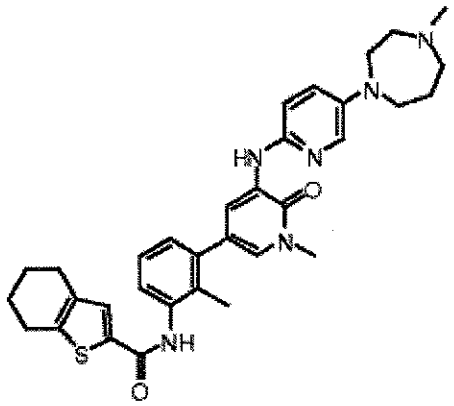

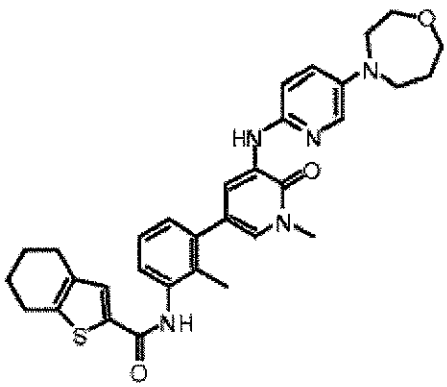

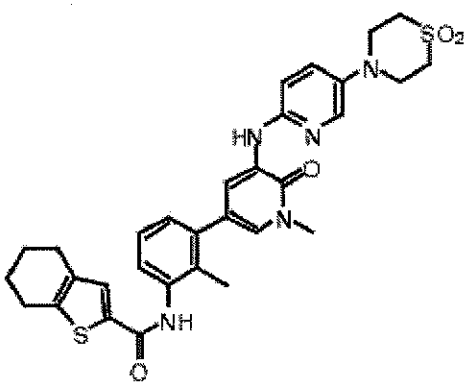

32. A pharmaceutical composition, comprising a compound of claim 1, together with at least one pharmaceutically acceptable vehicle that is a carrier, adjuvant or excipient.