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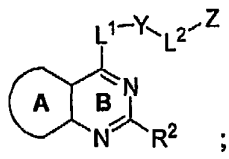
(54) **Title:** PYRAZOLO PYRIMIDINES USEFUL AS AURORA KINASE INHIBITORS



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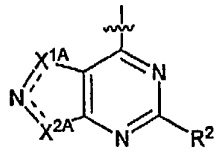
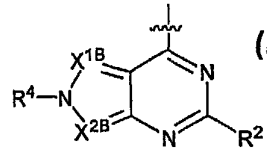
(II) 

or 

(III)

for the treatment of Aurora mediated diseases.

(57) **Abstract:** The present invention provides compounds having the formula: (I) wherein A-B together represent one of the following structures: (II) or (III) wherein one of ---- is a double bond, as valency permits; and R^2, R^4, X^{1A}, X^{2A}, X^{1B}, X^{2B}, L^1, L^2, Y an Z are as defined in classes and subclasess herein, and pharmaceutical compositions thereof, as described generally and in subclasses herein, which compounds are useful as inhibitors of protein kinase (e.g., Aurora), and thus are useful, for example,

WO 2007/013964 A1

PYRAZOLO PYRIMIDINES USEFUL AS AURORA KINASE INHIBITORS

PRIORITY

[0001] The present application claims priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No.: 60/701,695 filed July 22, 2005, the entire contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] The search for new therapeutic agents has been greatly aided in recent years by a better understanding of the structure of enzymes and other biomolecules associated with diseases. One important class of enzymes that has been the subject of extensive study is protein kinases.

[0003] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell. (See, Hardie, G. and Hanks, S. *The Protein Kinase Facts Book, I and II,* Academic Press, San Diego, CA: 1995). Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases may be categorized into families by the substrates they phosphorylate (*e.g.*, protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (See, for example, Hanks, S.K., Hunter, T., *FASEB J.* **1995**, *9*, 576-596; Knighton *et al., Science* **1991**, *253*, 407-414; Hiles *et al., Cell* **1992**, *70*, 419-429; Kunz *et al., Cell* **1993**, *73*, 585-596; Garcia-Bustos *et al., EMBO J.* **1994**, *13*, 2352-2361).

[0004] In general, protein kinases mediate intracellular signaling by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. These phosphorylation events are ultimately triggered in response to a variety of extracellular and other stimuli. Examples of such stimuli include environmental and chemical stress signals (*e.g.*, osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, and H_2O_2), cytokines (*e.g.*, interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α)), and growth factors (*e.g.*, granulocyte macrophage-

colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF)). An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

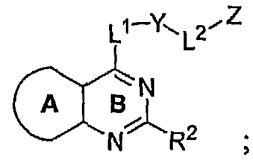
[0005] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents.

[0006] The Aurora family of serine/threonine kinases plays an important role in cell proliferation. The three known mammalian family members, Aurora-A ("2"), B ("1") and C ("3"), are highly homologous proteins responsible for chromosome segregation, mitotic spindle function and cytokinesis. Aurora expression is low or undetectable in resting cells, with expression and activity peaking during the G2 and mitotic phases in cycling cells. Elevated levels of all Aurora family members are observed in a wide variety of tumor cell lines. For example, the Aurora-2 protein has been found to be overexpressed in human colon cancer tissue [Bischoff *et al.*, *EMBO J.* **1998**, *17*, 3052-3065; Schumacher *et al.*, *J. Cell Biol.* **1998**, *143*, 1635-1646; Kimura *et al.*, *J. Biol. Chem.* **1997**, *272*, 13766-13771]. Aurora-2 has been implicated in human cancer, such as colon, breast and other solid tumors. This kinase is involved in protein phosphorylation events that regulate the cell cycle. Specifically, Aurora-2 plays a role in controlling the accurate segregation of chromosomes during mitosis. Thus, Aurora inhibitors have an important role in the treatment of Aurora-mediated diseases.

[0007] Accordingly, there is a great need to develop compounds useful as inhibitors of protein kinases. In particular, it would be desirable to develop compounds that are useful as inhibitors of Aurora, particularly given the inadequate treatments currently available for the majority of the disorders implicated in their activation.

SUMMARY OF THE INVENTION

[0008] As discussed above, there remains a need for the development of novel therapeutic agents and agents useful for treating disorders mediated by Aurora. In certain embodiments, the present invention provides novel compounds having the structure:



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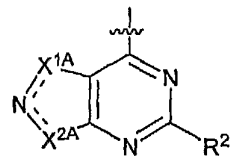
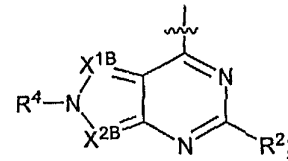
(I)

wherein A-B together represent one of the following structures:



or



;

wherein one of ----- is a double bond, as valency permits; and R^2, R^4, X^{1A}, X^{2A}, X^{1B}, X^{2B}, L^1, L^2, Y and Z are as defined in classes and subclasess herein, and pharmaceutical compositions thereof, as described generally and in subclasses herein, which compounds are useful as inhibitors of protein kinase (*e.g.*, Aurora), and thus are useful, for example, for the treatment of Aurora mediated diseases.

[0009] In certain other embodiments, the invention provides pharmaceutical compositions comprising an inventive compound, wherein the compound is present in an amount effective to inhibit Aurora activity. In certain other embodiments, the invention provides pharmaceutical compositions comprising an inventive compound and optionally further comprising an additional therapeutic agent. In yet other embodiments, the additional therapeutic agent is an agent for the treatment of cancer.

[0010] In yet another aspect, the present invention provides methods for inhibiting kinase activity (*e.g.*, Aurora) activity in a patient or a biological sample, comprising administering to said patient, or contacting said biological sample with an effective inhibitory amount of a compound of the invention. In still another aspect, the present invention provides methods for treating any disorder involving Aurora activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the invention.

BRIEF DESCRIPTION OF THE DRAWING

[0011] **Figure 1** depicts exemplary biochemical assay data (IC_{50} values) for selected compounds of the invention. The compounds were evaluated in: (i) Aurora A kinase inhibition assay, (ii) Aurora B kinase inhibition assay, (iii) HCS cell cycle assay and (iv) Phospho-Histone H3 HCS assay.

[0012] **Figure 2** depicts an exemplary western blot experiment of compound B using anti-Histone H3 and anti-phosphorylated Histone H3 antibodies as probes.

DEFINITIONS

[0013] It is understood that the compounds, as described herein, may be substituted with any number of substituents or functional moieties. In general, the term "substituted" whether preceded by the term "optionally" or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic, carbon and heteroatom substituents of organic compounds. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those that result in the formation of stable compounds useful in the treatment and prevention, for example of disorders, as described generally above. Examples of substituents include, but are not limited to aliphatic; heteroaliphatic; alicyclic; heteroalicyclic; aromatic, heteroaromatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; - or $-GR^{G1}$ wherein G is –O-, -S-, $-NR^{G2}$-, -C(=O)-, -S(=O)-, $-SO_2$-, -C(=O)O-, $-C(=O)NR^{G2}$-, -OC(=O)-, $-NR^{G2}C(=O)$-,

-OC(=O)O-, -OC(=O)NR^{G2}-, -NR^{G2}C(=O)O-, -NR^{G2}C(=O)NR^{G2}-, -C(=S)-, -C(=S)S-, -SC(=S)-, -SC(=S)S-, -C(=NR^{G2})-, -C(=NR^{G2})O-, -C(=NR^{G2})NR^{G3}-, -OC(=NR^{G2})-, -NR^{G2}C(=NR^{G3})-, -$NR^{G2}SO_2$-, -$NR^{G2}SO_2NR^{G3}$-, or -SO_2NR^{G2}-, wherein each occurrence of R^{G1}, R^{G2} and R^{G3} independently includes, but is not limited to, hydrogen, halogen, or an optionally substituted aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0014] The term "stable", as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

[0015] The term "aliphatic", as used herein, includes both saturated and unsaturated, straight chain (*i.e.*, unbranched) or branched aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl moieties. Thus, as used herein, the term "alkyl" includes straight and branched alkyl groups. An analogous convention applies to other generic terms such as "alkenyl", "alkynyl" and the like. Furthermore, as used herein, the terms "alkyl", "alkenyl", "alkynyl" and the like encompass both substituted and unsubstituted groups. In certain embodiments, as used herein, "lower alkyl" is used to indicate those alkyl groups (substituted, unsubstituted, branched or unbranched) having about 1-6 carbon atoms.

[0016] In certain embodiments, the alkyl, alkenyl and alkynyl groups employed in the invention contain about 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain about 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain about 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain about 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain about 1-4 carbon atoms. Illustrative aliphatic groups thus include, but are

not limited to, for example, methyl, ethyl, n-propyl, isopropyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, n-hexyl, sec-hexyl, moieties and the like, which again, may bear one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-l-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl and the like.

[0017] The term "alicyclic", as used herein, refers to compounds which combine the properties of aliphatic and cyclic compounds and include but are not limited to cyclic, or polycyclic aliphatic hydrocarbons and bridged cycloalkyl compounds, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "alicyclic" is intended herein to include, but is not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, which are optionally substituted with one or more functional groups. Illustrative alicyclic groups thus include, but are not limited to, for example, cyclopropyl, $-CH_2$-cyclopropyl, cyclobutyl, $-CH_2$-cyclobutyl, cyclopentyl, $-CH_2$-cyclopentyl-n, cyclohexyl, $-CH_2$-cyclohexyl, cyclohexenylethyl, cyclohexanylethyl, norborbyl moieties and the like, which again, may bear one or more substituents.

[0018] The term "cycloalkyl", as used herein, refers specifically to cyclic alkyl groups having three to seven, preferably three to ten carbon atoms. Suitable cycloalkyls include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, which, as in the case of aliphatic, heteroaliphatic or heterocyclic moieties, may optionally be substituted. An analogous convention applies to other generic terms such as "cycloalkenyl", "cycloalkynyl" and the like.

[0019] The term "heteroaliphatic", as used herein, refers to aliphatic moieties in which one or more carbon atoms in the main chain have been substituted with a heteroatom. Thus, a heteroaliphatic group refers to an aliphatic chain which contains one or more oxygen, sulfur, nitrogen, phosphorus or silicon atoms, *i.e.*, in place of carbon atoms. Thus, a 1-6 atom heteroaliphatic linker having at least one N atom in the heteroaliphatic main chain, as used herein, refers to a C_{1-6}aliphatic chain wherein at least one carbon atom is replaced with a nitrogen atom, and wherein any one or more of the remaining 5 carbon atoms may be replaced by an oxygen, sulfur, nitrogen, phosphorus or silicon atom. As used herein, a 1-atom heteroaliphatic linker

having at least one N atom in the heteroaliphatic main chain refers to –NH- or –NR- where R is aliphatic, heteroaliphatic, acyl, aromatic, heteroaromatic or a nitrogen protecting group. Heteroaliphatic moieties may be branched or linear unbranched. In certain embodiments, heteroaliphatic moieties are substituted by independent replacement of one or more of the hydrogen atoms thereon with one or more moieties including, any of the substituents described above.

[0020] The term "heteroalicyclic", "heterocycloalkyl" or "heterocyclic", as used herein, refers to compounds which combine the properties of heteroaliphatic and cyclic compounds and include but are not limited to saturated and unsaturated mono- or polycyclic heterocycles such as morpholino, pyrrolidinyl, furanyl, thiofuranyl, pyrrolyl etc., which are optionally substituted with one or more functional groups, as defined herein. In certain embodiments, the term "heterocyclic" refers to a non-aromatic 5-, 6- or 7- membered ring or a polycyclic group, including, but not limited to a bi- or tri-cyclic group comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 2 double bonds and each 6-membered ring has 0 to 2 double bonds, (ii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative heterocycles include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

[0021] Additionally, it will be appreciated that any of the alicyclic or heteroalicyclic moieties described above and herein may comprise an aryl or heteroaryl moiety fused thereto. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0022] In general, the term "aromatic moiety", as used herein, refers to stable substituted or unsubstituted unsaturated mono- or polycyclic hydrocarbon moieties having preferably 3-14 carbon atoms, comprising at least one ring satisfying the Huckel rule for aromaticity. Examples of aromatic moieties include, but are not limited to, phenyl, indanyl, indenyl, naphthyl, phenanthryl and anthracyl.

[0023] In general, the term "heteroaromatic moiety", as used herein, refers to stable substituted or unsubstituted unsaturated mono-heterocyclic or polyheterocyclic moieties having preferably 3-14 carbon atoms, comprising at least one ring satisfying the Huckel rule for aromaticity. Examples of heteroaromatic moieties include, but are not limited to, pyridyl, quinolinyl, dihydroquinolinyl, isoquinolinyl, quinazolinyl, dihydroquinazolyl, and tetrahydroquinazolyl.

[0024] It will also be appreciated that aromatic and heteroaromatic moieties, as defined herein, may be attached via an aliphatic (*e.g.*, alkyl) or heteroaliphatic (*e.g.*, heteroalkyl) moiety and thus also include moieties such as –(aliphatic)aromatic, -(heteroaliphatic)aromatic, -(aliphatic)heteroaromatic, –(heteroaliphatic)heteroaromatic, –(alkyl)aromatic, -(heteroalkyl)aromatic, -(alkyl)heteroaromatic, and –(heteroalkyl)heteroaromatic moieties. Thus, as used herein, the phrases "aromatic or heteroaromatic moieties" and "aromatic, heteroaromatic, –(alkyl)aromatic, -(heteroalkyl)aromatic, -(heteroalkyl)heteroaromatic, and –(heteroalkyl)heteroaromatic" are interchangeable. Substituents include, but are not limited to, any of the previously mentioned substituents resulting in the formation of a stable compound.

[0025] In general, the term "aryl" refers to aromatic moieties, as described above, excluding those attached via an aliphatic (*e.g.*, alkyl) or heteroaliphatic (*e.g.*, heteroalkyl) moiety. In certain embodiments of the present invention, "aryl" refers to a mono- or bicyclic carbocyclic ring system having one or two rings satisfying the Huckel rule for aromaticity, including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

[0026] Similarly, the term "heteroaryl" refers to heteroaromatic moieties, as described above, excluding those attached via an aliphatic (*e.g.*, alkyl) or heteroaliphatic (*e.g.*, heteroalkyl) moiety. In certain embodiments of the present invention, the term "heteroaryl", as used herein, refers to a cyclic unsaturated radical having from about five to about ten ring atoms of which one ring atom is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl,

thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

[0027] Substituents for aryl and heteroaryl moieties include, but are not limited to, any of the previously mentioned substitutents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound.

[0028] The terms "alkoxy" (or "alkyloxy"), and "thioalkyl" as used herein refers to an alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom ("alkoxy") or through a sulfur atom ("thioalkyl"). In certain embodiments, the alkyl group contains about 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl group contains about 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains about 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains about 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains about 1-4 aliphatic carbon atoms. Examples of alkoxy groups, include but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, neopentoxy and n-hexoxy. Examples of thioalkyl groups include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, and the like.

[0029] The term "amine" refers to a group having the structure $-N(R)_2$ wherein each occurrence of R is independently hydrogen, or an aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety, or the R groups, taken together, may form a heterocyclic moiety.

[0030] The term "alkylamino" refers to a group having the structure -NHR'wherein R' is alkyl, as defined herein. The term "aminoalkyl" refers to a group having the structure NH_2R'-, wherein R' is alkyl, as defined herein. In certain embodiments, the alkyl group contains about 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl group contains about 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain about 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains about 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains about 1-4 aliphatic carbon atoms. Examples of alkylamino include, but are not limited to, methylamino, ethylamino, iso-propylamino and the like.

[0031] The terms "halo" and "halogen" as used herein refer to an atom selected from fluorine, chlorine, bromine and iodine.

[0032] The term "halogenated" denotes a moiety having one, two, or three halogen atoms attached thereto.

[0033] The term "haloalkyl" denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

[0034] The term "acyloxy", as used herein, does not substantially differ from the common meaning of this term in the art, and refers to a moiety of structure –$OC(O)R_X$, wherein R_X is a substituted or unsubstituted aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety.

[0035] The term "acyl", as used herein, does not substantially differ from the common meaning of this term in the art, and refers to a moiety of structure –$C(O)R_X$, wherein R_X is a substituted or unsubstituted, aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety.

[0036] The term "imino", as used herein, does not substantially differ from the common meaning of this term in the art, and refers to a moiety of structure –$C(=NR_X)R_Y$, wherein R_X is hydrogen or an optionally substituted aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety; and R_Y is an optionally substituted aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety.

[0037] The term "$C_{1\text{-}6}$alkylene", as used herein, refers to a substituted or unsubstituted, linear or branched saturated divalent radical consisting solely of carbon and hydrogen atoms, having from one to six carbon atoms, having a free valence "-" at both ends of the radical.

[0038] The term "$C_{2\text{-}6}$alkenylene", as used herein, refers to a substituted or unsubstituted, linear or branched unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to six carbon atoms, having a free valence "-" at both ends of the radical, and wherein the unsaturation is present only as double bonds and wherein a double bond can exist between the first carbon of the chain and the rest of the molecule.

[0039] As used herein, the terms "aliphatic", "heteroaliphatic", "alkyl", "alkenyl", "alkynyl", "heteroalkyl", "heteroalkenyl", "heteroalkynyl", and the like

encompass substituted and unsubstituted, saturated and unsaturated, and linear and branched groups. Similarly, the terms "alicyclic", "heterocyclic", "heterocycloalkyl", "heterocycle" and the like encompass substituted and unsubstituted, and saturated and unsaturated groups. Additionally, the terms "cycloalkyl", "cycloalkenyl", "cycloalkynyl", "heterocycloalkyl", "heterocycloalkenyl", "heterocycloalkynyl", "aromatic", "heteroaromatic", "aryl", "heteroaryl" and the like, used alone or as part of a larger moiety, encompass both substituted and unsubstituted groups.

[0040] As used herein, the term "isolated", when applied to the compounds of the present invention, refers to such compounds that are (i) separated from at least some components with which they are associated in nature or when they are made and/or (ii) produced, prepared or manufactured by the hand of man.

[0041] The phrase, "pharmaceutically acceptable derivative", as used herein, denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of such compound, or any other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a compound as otherwise described herein, or a metabolite or residue thereof. Pharmaceutically acceptable derivatives thus include among others pro-drugs. A pro-drug is a derivative of a compound, usually with significantly reduced pharmacological activity, which contains an additional moiety that is susceptible to removal *in vivo* yielding the parent molecule as the pharmacologically active species. An example of a pro-drug is an ester which is cleaved *in vivo* to yield a compound of interest. Pro-drugs of a variety of compounds, and materials and methods for derivatizing the parent compounds to create the pro-drugs, are known and may be adapted to the present invention. Certain exemplary pharmaceutical compositions and pharmaceutically acceptable derivatives will be discussed in more detail herein below.

[0042] The term "Aurora-mediated disease" or "Aurora-mediated condition", as used herein, means any disease or other deleterious condition in which Aurora is known to play a role. The terms "Aurora-mediated disease" or "Aurora-mediated condition" also mean those diseases or conditions that are alleviated by treatment with an Aurora inhibitor. Such conditions include, without limitation, colon, breast, stomach, and ovarian cancer. The term "Aurora-mediated disease", as used herein, means any disease or other deleterious condition or disease in which Aurora is

known to play a role. Such diseases or conditions include, without limitation, cancers such as colon and breast cancer.

[0043] The term "treating", as used herein generally means that the compounds of the invention can be used in humans or animals with at least a tentative diagnosis of disease. In certain embodiments, compounds of the invention will delay or slow the progression of the disease thereby giving the individual a longer life span.

[0044] The term "preventing" as used herein means that the compounds of the present invention are useful when administered to a patient who has not been diagnosed as possibly having the disease at the time of administration, but who would normally be expected to develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development of disease symptoms, delay the onset of disease, or prevent the individual from developing the disease at all. Preventing also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due to familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers for the disease.

[0045] As used herein the term "*biological sample*" includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from an animal (*e.g.*, mammal) or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. For example, the term "biological sample" refers to any solid or fluid sample obtained from, excreted by or secreted by any living organism, including single-celled micro-organisms (such as bacteria and yeasts) and multicellular organisms (such as plants and animals, for instance a vertebrate or a mammal, and in particular a healthy or apparently healthy human subject or a human patient affected by a condition or disease to be diagnosed or investigated). The biological sample can be in any form, including a solid material such as a tissue, cells, a cell pellet, a cell extract, cell homogenates, or cell fractions; or a biopsy, or a biological fluid. The biological fluid may be obtained from any site (*e.g.* blood, saliva (or a mouth wash containing buccal cells), tears, plasma, serum, urine, bile, cerebrospinal fluid, amniotic fluid, peritoneal fluid, and pleural fluid, or cells therefrom, aqueous or vitreous humor, or any bodily secretion), a transudate, an exudate (*e.g.* fluid obtained from an abscess or any other site of infection or inflammation), or fluid obtained from a joint (*e.g.* a normal joint or a joint affected

by disease such as rheumatoid arthritis, osteoarthritis, gout or septic arthritis). The biological sample can be obtained from any organ or tissue (including a biopsy or autopsy specimen) or may comprise cells (whether primary cells or cultured cells) or medium conditioned by any cell, tissue or organ. Biological samples may also include sections of tissues such as frozen sections taken for histological purposes. Biological samples also include mixtures of biological molecules including proteins, lipids, carbohydrates and nucleic acids generated by partial or complete fractionation of cell or tissue homogenates. Although the sample is preferably taken from a human subject, biological samples may be from any animal, plant, bacteria, virus, yeast, etc. The term *animal,* as used herein, refers to humans as well as non-human animals, at any stage of development, including, for example, mammals, birds, reptiles, amphibians, fish, worms and single cells. Cell cultures and live tissue samples are considered to be pluralities of animals. In certain exemplary embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). An animal may be a transgenic animal or a human clone. If desired, the biological sample may be subjected to preliminary processing, including preliminary separation techniques.

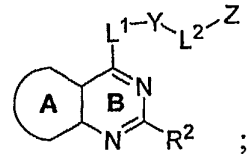
DETAILED DESCRIPTION OF CERTAIN PREFERRED EMBODIMENTS OF THE INVENTION

[0046] As noted above, there has been increasing interest in recent years in the development of protein kinase inhibitors, particularly Aurora inhibitors, as therapeutic agents for the treatment of diseases/conditions involving protein kinase-mediated events. In one aspect, the present invention provides Aurora inhibitors.

[0047] Compounds of this invention include those generally set forth above and described specifically herein, and are illustrated in part by the various classes, subgenera and species disclosed herein. Additionally, the present invention provides pharmaceutically acceptable derivatives of the inventive compounds, and methods of treating a subject using these compounds, pharmaceutical compositions thereof, or either of these in combination with one or more additional therapeutic agents.

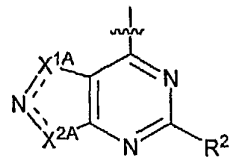
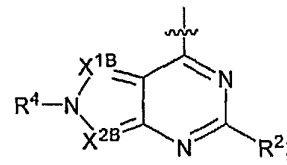
[0048] ***1) General Description of Compounds of the Invention***

[0049] In certain embodiments, the compounds of the invention include compounds of the general formula **(I)** as further defined below:



(I)

wherein A-B together represent one of the following structures:


or


and pharmaceutically acceptable derivatives thereof;

wherein one of ----- is a double bond, as valency permits;

$\mathbf{R^2}$ is hydrogen, halogen, cyano, nitro, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

$\mathbf{R^4}$ is hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

$\mathbf{X^{1A}}$ is NR^1 or $-C(R^{X1})-$; wherein R^1 taken together with a moiety present on L^1 may form an optionally substituted heterocyclic ring;

$\mathbf{X^{2A}}$ is NR^3 or $-C(R^{X1})-$; wherein one of X^{1A} and X^{2A} is $-C(R^{X1})-$, but not both;

$\mathbf{X^{1B}}$ and $\mathbf{X^{2B}}$ are -N- or $-C(R^{X1})-$; whereby one of X^{1B} and X^{2B} is $-C(R^{X1})-$, but not both;

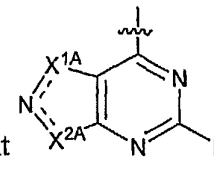
wherein R^1 and R^3 are independently hydrogen, a nitrogen protecting group, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety; and R^{X1} is hydrogen, halogen, cyano, nitro, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

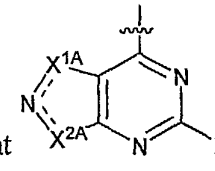
$\mathbf{L^1}$ is a 2-8 atom heteroaliphatic linker having at least one N, O or S atom in the heteroaliphatic main chain;

$\mathbf{L^2}$ is a 1-6 atom heteroaliphatic linker having at least one N atom in the heteroaliphatic main chain;

Y is an alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety; and

Z is an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety.

[0050] In certain embodiments, the following groups do not occur simultaneously as defined: A-B together represent  ; X^{1A} is NR^1 and X^{2A} is CR^{X1} or X^{1A} is CR^{X1} and X^{2A} is NR^3; L^1 is $-X(CHR^x)_{0-2}-$, wherein X is O, S, NH or NC_{1-4}alkyl, and R^x is H or C_{1-4}alkyl; Y is phenyl, thienyl, furanyl, pyrrolyl, pyridyl, pyrimidyl, imidazolyl, pyrazinyl, oxazolyl, thiazolyl, naphthyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, isoquinolinyl or quinazolinyl; and L^2-Z is lower alkyl (1-4 carbon atoms), cycloalkyl (3-8 carbon atoms), lower alkoxy (1-4 carbon atoms), cycloalkoxy (3-8 carbon atoms), lower perfluoroalkyl (1-4 carbon atoms), lower acyloxy (1-4 carbon atoms; -OC(O)R), amino, lower mono or dialkylamino (1-4 carbon atoms), lower mono or dicycloalkylamino (3-8 carbon atoms), hydroxymethyl, lower acyl (1-4 carbon atoms; -C(O)R), lower thioalkyl (1-4 carbon atoms), lower sulfinylalkyl (1-4 carbon atoms), lower sulfonylalkyl (1-4 carbon atoms), thiocycloalkyl (3-8 carbon atoms), sulfinylcycloalkyl (3-8 carbon atoms), sulfonylcycloalkyl (3-8 carbon atoms), sulfonamido, lower mono or dialkylsulfonamido (1-4 carbon atoms), mono or dicycloalkylsulfonamido (3-8 carbon atoms), mercapto, carboxy, carboxamido (-C(O)NH_2), lower mono or dialkylcarboxamido (1-4 carbon atoms), mono or dicycloalkylcarboxamido (3-8 carbon atoms), lower alkoxycarbonyl (1-4 carbon atoms), cycloalkoxycarbonyl (3-8 carbon atoms), lower alkenyl (2-4 carbon atoms), cycloalkenyl (4-8 carbon atoms), lower alkynyl (2-4 carbon atoms).

[0051] In certain embodiments, the following groups do not occur simultaneously as defined: A-B together represent  ; X^{1A} is NR^1 and X^{2A} is CR^{X1} or X^{1A} is CR^{X1} and X^{2A} is NR^3; R^{X1} is hydrogen, halo, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, -$CONR^aR^b$, -$O(CH_2)_nNR^aR^b$, -$(CH_2)_nNR^aR^b$ or $-NR^aR^b$; L^1 is -$NHCH_2$-; Y-L^2-Z is pyridinyl, pyrimidinyl, indazolyl, dihydroisoindolyl, benzisoxazolyl, oxazolyl, imidazolyl, oxadiazolyl or thiazolyl each optionally substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy, -$O(CH_2)_nNR^xR^y$, -$O(CH_2)_nOR^x$, -NR^xR^y, -$(CH_2)_nNR^xR^y$, -CH_2OR^x, -$COOR^x$, -$CONR^xR^y$, -$CH_2SO_2NR^xR^y$, -$SO_2NR^xR^y$, or

optionally substituted phenyl; and R^2 is pyridin-2-yl, C_{1-6}alkylpyridin-2-yl, C_{1-6}alkylpyrrol-2-yl or C_{1-6}alkylthiazol-2-yl; wherein R^a is H or C_{1-4}alkyl, R^b is C_{1-4}alkyl, or R^a and R^b together for a 3-7-membered heterocyclic ring; and R^x and R^y are independently H or C_{1-6}alkyl.

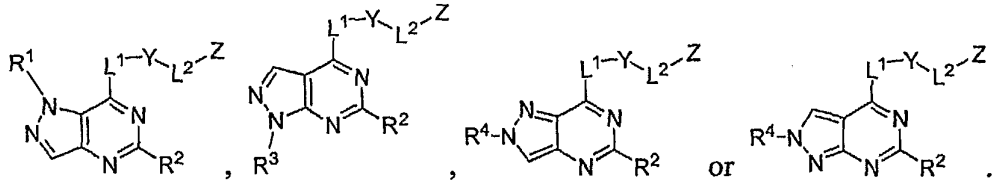
[0052] In certain embodiments, for compounds of formula (I), no occurrence of R^1, R^3, R^4 or R^{X1} is Q^1, Q^2 or Q^3, wherein

Q^1 is $-(CR^{1A}R^{1B})_mC{\equiv}C-(CR^{1A}R^{1B})_tR^{1C}$, $-(CR^{1A}R^{1B})_mC{=}C-(CR^{1A}R^{1B})_tR^{1C}$, $-C{=}NOR^{1D}$, or $-X^3R^{1D}$ wherein m is an integer from 0 to 3, t is an integer from 0 to 5, and X^3 is a divalent group derived from azetidine, oxetane or a C_{3-4}carbocyclic group;

Q^2 is $-(CR^{1A}R^{1B})_mC{\equiv}C-(CR^{1A}R^{1B})_kR^{1E}$, $-(CR^{1A}R^{1B})_mC{=}C-(CR^{1A}R^{1B})_kR^{1E}$ wherein k is an integer from 1 to 3 and m is an integer from 0 to 3; and

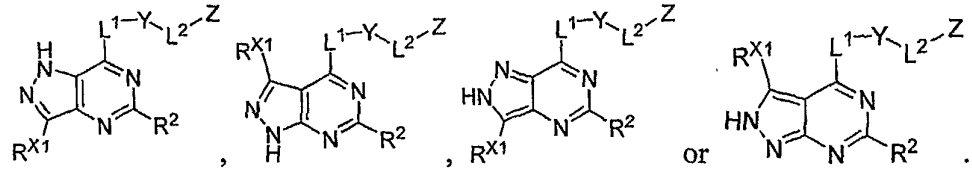
Q^3 is $-(CR^{1A}R^{1B})_tR^{1C}$, wherein t is an integer from 0 to 5 and the attachment point to R^{1C} is through a carbon atom of the R^{1C} group; wherein R^{1A} and R^{1B} are independently H or C_{1-6}alkyl; R^{1C} is an optionally substituted non-aromatic monocyclic ring, a fused or bridged bycyclic ring or a spirocyclic ring; R^{1E} is $-NR^{1A}R^{1D}$ or $-OR^{1D}$; R^{1D} is R^{1F}, $-C(=O)R^{1F}$, $-SO_2R^{1F}$, $-C(=O)N(R^{1F})_2$, $-SO_2N(R^{1F})_2$, or $-CO_2R^{1F}$, wherein R^{1F} is H, C_{1-6}alkyl, $-(CR^{1A}R^{1B})_t(C_{6-10}$aryl) or $-(CR^{1A}R^{1B})_t$(4-10 membered heterocyclic).

[0053] In certain embodiments, the present invention defines particular classes of compounds which are of special interest. For example, one class of compounds of special interest includes compounds of formulae (I^{A1}) though (I^{A4}):



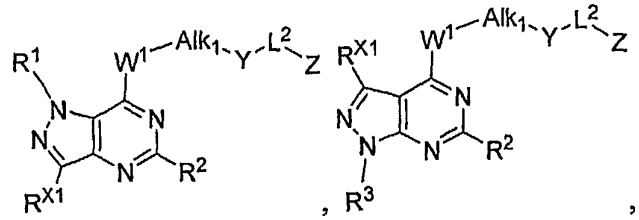
(I^{A1}) (I^{A2}) (I^{A3}) (I^{A4})

[0054] Another class of compounds of special interest includes compounds of formula3 (I^{B1}) though (I^{B4}):

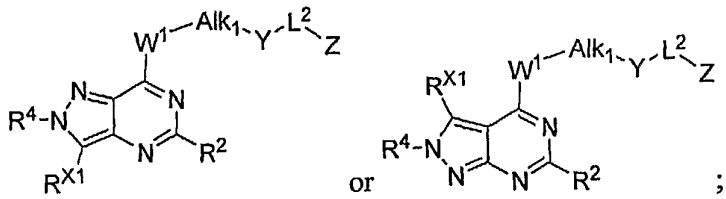


(I^{B1}) (I^{B2}) (I^{B3}) (I^{B4})

[0055] Another class of compounds of special interest includes compounds of formulae (I^{C1}) through (I^{C4}):



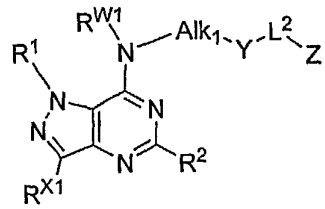
(I^{C1}) (I^{C2})



(I^{C3}) (I^{C4})

wherein W^1 is O or NR^{W1}, where R^{W1} is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, or acyl; and Alk_1 is a C_{1-6}alkylene or C_{2-6}alkenylene moiety.

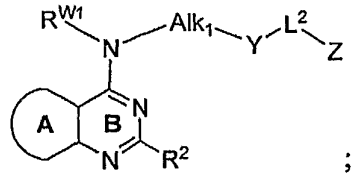
[0056] Another class of compounds of special interest includes compounds of formula (I^D):



(I^D)

wherein Alk_1 is a C_{1-6}alkylene or C_{2-6}alkenylene moiety; and R^{W1} is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, or acyl; or R^{W1} taken together with R^1 may form a heterocyclic moiety.

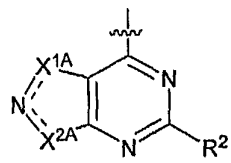
[0057] Another class of compounds of special interest includes compounds of formula (I^E):



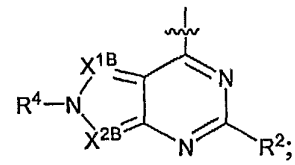
;

(I^E)

wherein A-B together represent one of the following structures:



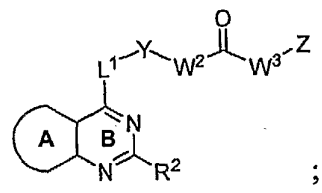
or



;

wherein R^{W1} is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, or acyl; Alk_1 is a C_{1-6}alkylene or C_{2-6}alkenylene moiety; or R^{W1} taken together with a carbon atom present on Alk_1 may form a heterocyclic moiety.

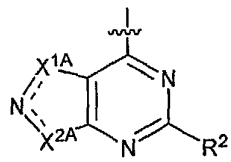
[0058] Another class of compounds of special interest includes compounds of formula (I^F):



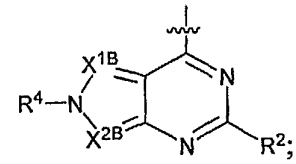
;

(I^F)

wherein A-B together represent one of the following structures:



or



;

wherein W^2 and W^3 are independently absent, O, NR^W, $CR^{W1}R^{W2}$ or $NR^WCR^{W1}R^{W2}$, where R^W is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, or acyl; and R^{W1} and R^{W2} are independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic; with the proviso that W^2 and W^3 are not each absent and at least one of W^2 and W^3 is NR^W or $NR^WCR^{W1}R^{W2}$.

[0059] A number of important subclasses of each of the foregoing classes deserve separate mention; these subclasses include subclasses of the foregoing classes in which:

[0060] i) R^2 is hydrogen, halogen, cyano, nitro, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl moiety;

[0061] ii) R^2 is $C_{1\text{-}3}$alkyl or $C_{1\text{-}3}$alkoxy;

[0062] iii) R^2 is methyl or $-CF_3$;

[0063] iv) R^2 is halogen;

[0064] v) R^2 is hydrogen;

[0065] vi) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, cyano, nitro, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl moiety;

[0066] vii) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl or heteroaryl moiety;

[0067] viii) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, or a lower alkyl, cycloalkyl, cycloalkenyl, lower heteroalkyl, heterocyclyl, aryl or heteroaryl moiety;

[0068] ix) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, or a lower alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety;

[0069] x) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, $C_{1\text{-}5}$alkyl, $C_{1\text{-}5}$alkoxy, $-CO_2H$, $-CO_2C_{1\text{-}5}$alkyl, -CN or $-NO_2$;

[0070] xi) X^{1A} is NR^1 and X^{2A} is CH;

[0071] xii) X^{2A} is NR^3 and X^{1A} is CH;

[0072] xiii) X^{1B} is N and X^{2B} is CH;

[0073] xiv) X^{2B} is N and X^{1B} is CH;

[0074] xv) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, -CN, $-NO_2$, $-C(=O)R^{1A}$, $-C(=O)OR^{1A}$, $-C(=O)NR^{1A}R^{1B}$, $-S(=O)_2R^{1C}$, $-P(=O)(R^{1C})_2$, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; wherein R^{1A} and R^{1B} are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; or taken together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring; and each occurrence of R^{1C} is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl;

[0075] xvi) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, $-NO_2$, -CN, $-C(=O)OR^{1A}$, $-S(=O)_2R^{1C}$, $-P(=O)(R^{1C})_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl or heteroaryl; wherein R^{1A} is hydrogen or C_{1-6}alkyl; and each occurrence of R^{1C} is independently C_{1-6}alkyl;

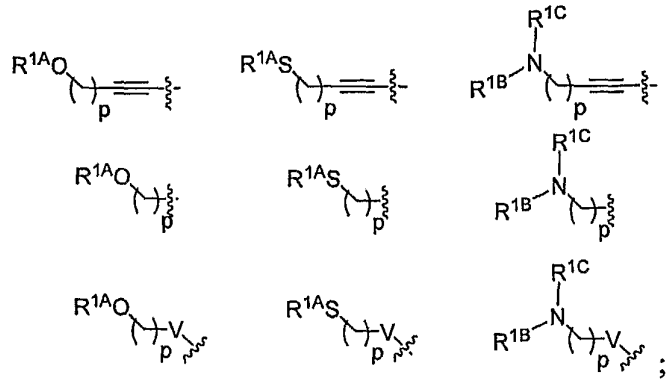
[0076] xvii) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, $-NO_2$, -CN, C_{1-5}alkyl or C_{1-5}alkoxy;

[0077] xviii) X^{1A} is NH and X^{2A} is –CH-, or X^{2A} is NH and X^{1A} is –CH-;

[0078] xix) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is F, Cl, Br or I;

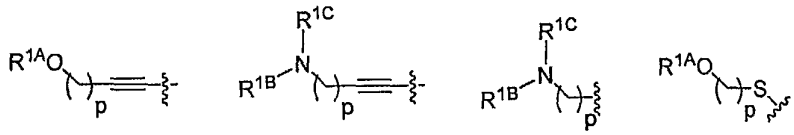
[0079] xx) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl or heteroalkynyl;

[0080] xxi) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is one of:



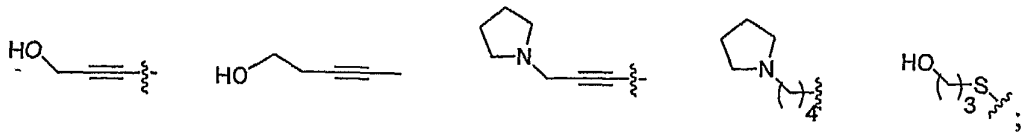
wherein V is O, S or R^{1B}; p is an integer from 0 to 6; and R^{1A} is hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, $-C(=O)N(R^{1B})_2$, $-C(=O)OR^{1B}$; wherein each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; or R^{1B} and R^{1C}, taken together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocyclic moiety;

[0081] xxii) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is –CN, lower alkyl, lower alkynyl, $-CO_2R^{1D}$, or one of:



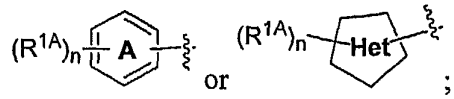
wherein p is an integer from 1 to 4; and R^{1A} is hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, $-C(=O)N(R^{1B})_2$, $-C(=O)OR^{1B}$; wherein each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; or R^{1B} and R^{1C}, taken together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocyclic moiety; and R^{1D} is hydrogen or lower alkyl;

[0082] xxiii) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is –CN, -C≡CH, methyl, $-CO_2H$, $-CO_2Me$, or one of:



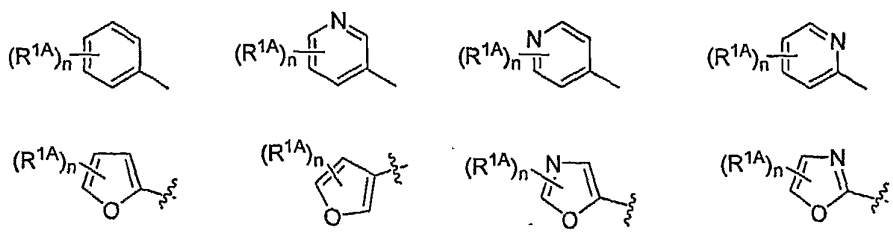
[0083] xxiv) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is aryl, heteroaryl or heterocyclyl;

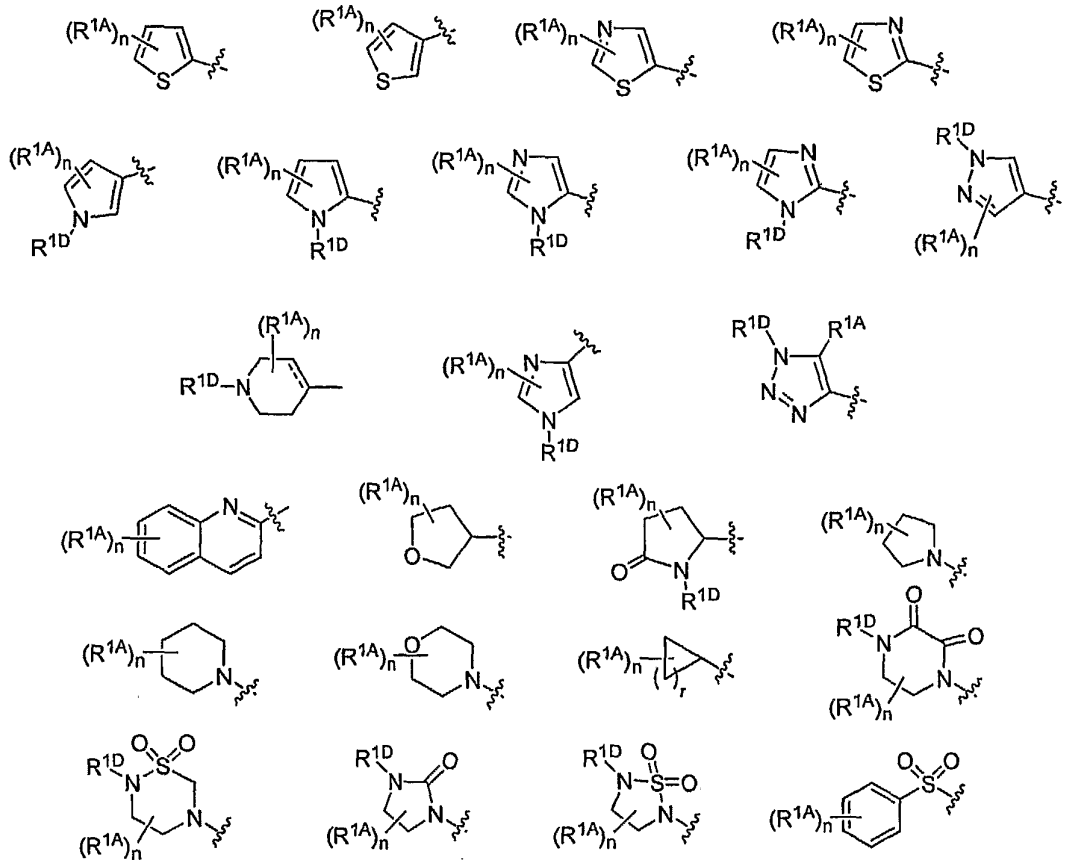
[0084] xxv) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is an aryl, heteroaryl or heterocyclyl moiety having one of the structures:



wherein the "A" cyclic moiety is a 6-membered aromatic ring comprising from 0-4 nitrogen atoms; the "Het" moiety represents a fully or partially saturated or unsaturated 5- to 6-membered ring comprising 1-4 heteroatoms selected from N, O and S; n is an integer from 0-6; and each occurrence of R^{1A} is independently hydrogen, alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)heterocyclyl, -(alkyl)aryl, -(alkyl)heteroaryl, $-OR^{1B}$, $-SR^{1B}$, $-N(R^{1B})_2$, $-SO_2N(R^{1B})_2$, $-SO_2R^{1E}$,$-C(=O)N(R^{1B})_2$, halogen, -CN, $-NO_2$, $-C(=O)OR^{1B}$, $-N(R^{1B})C(=O)R^{1C}$ or $-N(R^{1B})SO_2R^{1E}$; wherein each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, acyl; or any two occurrences of R^{1B}, taken together with the nitrogen atom to which they are attached (*e.g.*, $N(R^{1B})_2$), form a substituted or unsubstituted heterocyclic moiety; R^{1E} is alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, or -(alkyl)heteroaryl; and wherein any two adjacent occurrence of R^{1A} may form a fused 5- to 6-membered aryl, heteroaryl or heterocyclic ring;

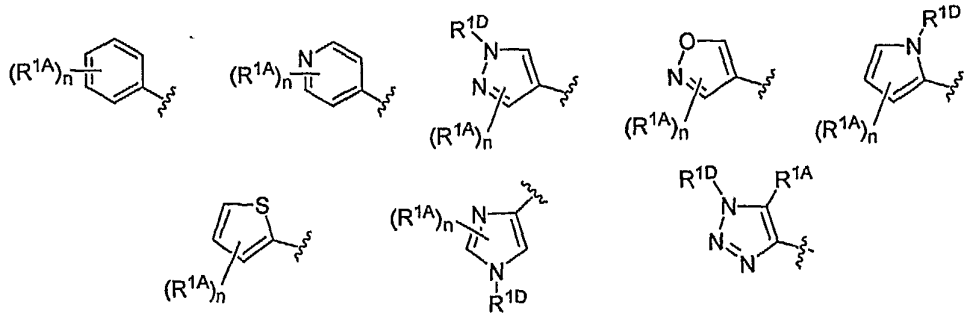
[0085] xxvi) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is one of:





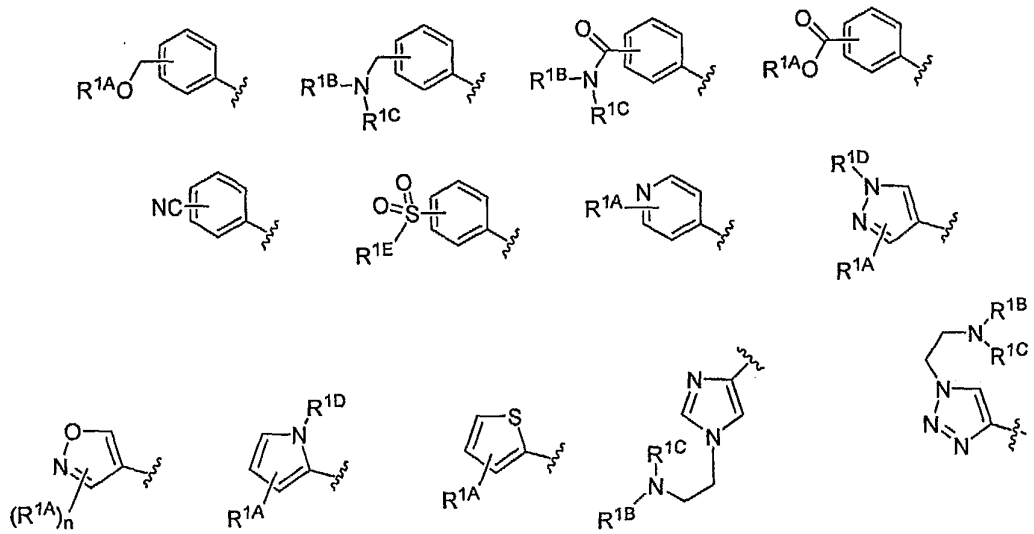
wherein each occurrence of R^{1A} is independently hydrogen, alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)heterocyclyl, -(alkyl)aryl, -(alkyl)heteroaryl, $-OR^{1B}$, $-SR^{1B}$, $-N(R^{1B})_2$, $-SO_2N(R^{1B})_2$, $-SO_2R^{1E}$,$-C(=O)N(R^{1B})_2$, halogen, -CN, $-NO_2$, $-C(=O)OR^{1B}$, $-N(R^{1B})C(=O)R^{1C}$ or $-N(R^{1B})SO_2R^{1E}$; wherein each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, acyl; or R^{1B} and R^{1C}, taken together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic moiety; R^{1D} is hydrogen, alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)heterocyclyl, -(alkyl)aryl, -(alkyl)heteroaryl, acyl or a nitrogen protecting group; and R^{1E} is lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, or -(alkyl)heteroaryl; wherein n is an integer from 0 to 3 and r is an integer from 1 to 6;

[0086] xxvii) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is one of:



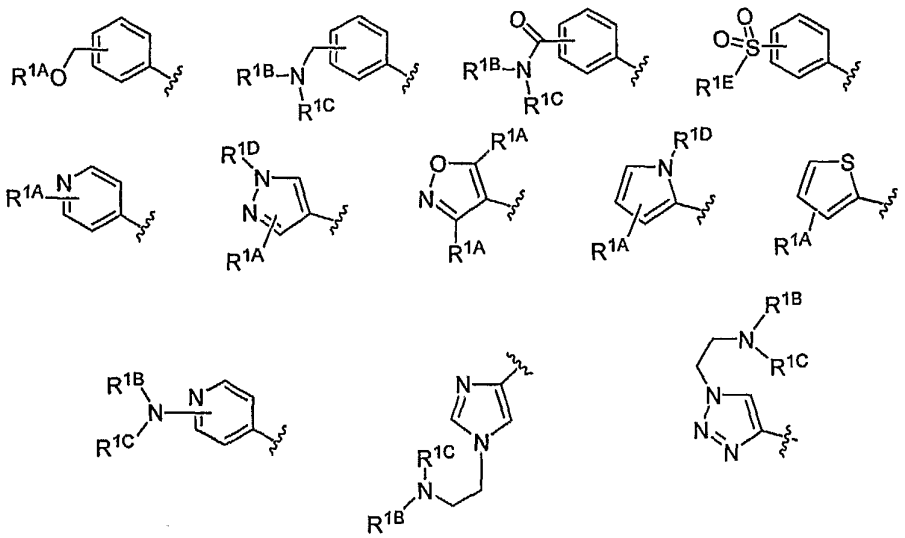
wherein n, R^{1A} and R^{1D} are as defined in xlii) above;

[0087] xxviii) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is one of:



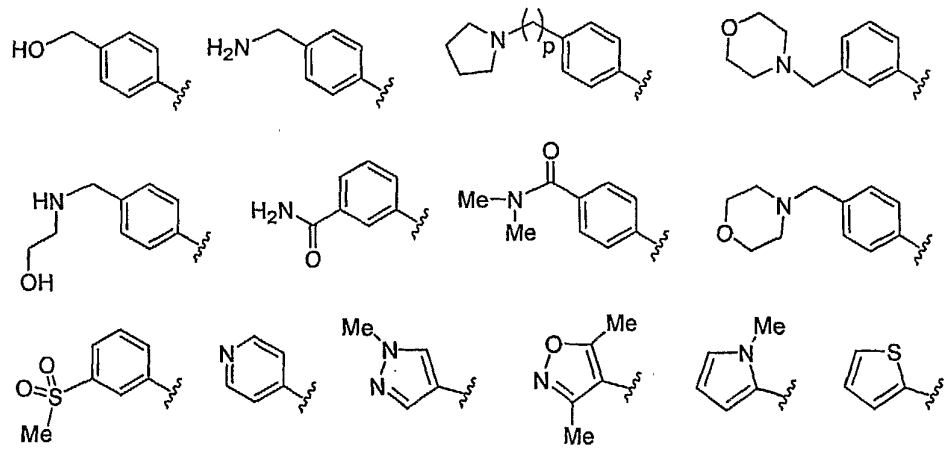
wherein n is 0-2; R^{1A} is hydrogen or lower alkyl; each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, or R^{1B} and R^{1C}, taken together with the nitrogen atom to which they are attached, form a substituted or unsubstituted 5-6 membered heterocyclic moiety; R^{1D} is hydrogen, or lower alkyl; R^{1E} is hydrogen, or lower alkyl;

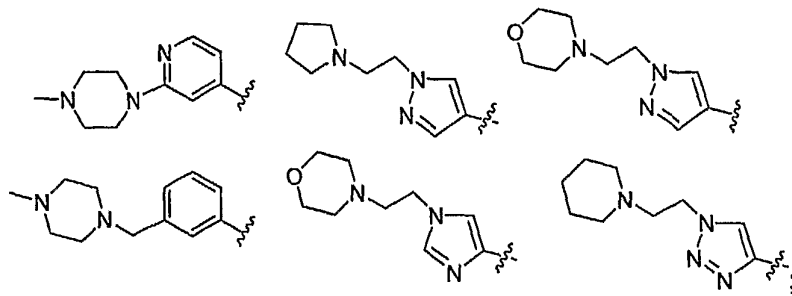
[0088] xxix) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is one of:



wherein each occurrence of R^{1A} is independently hydrogen or lower alkyl; each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, or R^{1B} and R^{1C}, taken together with the nitrogen atom to which they are attached, form a substituted or unsubstituted 5-6 membered heterocyclic moiety; R^{1D} is hydrogen, or lower alkyl; R^{1E} is hydrogen, or lower alkyl;

[0089] xxx) X^{1A} is NR^1 and X^{2A} is $-C(R^{X1})-$, or X^{2A} is NR^3 and X^{1A} is $-C(R^{X1})-$, or X^{1B} is N and X^{2B} is $-C(R^{X1})-$, or X^{2B} is N and X^{1B} is $-C(R^{X1})-$; wherein R^{X1} is one of:





[0090] xxxi) R^1 is hydrogen, $-C(=O)R^{1A}$, $-C(=O)OR^{1A}$, $-C(=O)NR^{1A}R^{1B}$, $-S(=O)_2R^{1C}$, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; wherein R^{1A} and R^{1B} are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; or taken together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring; and each occurrence of R^{1C} is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl;

[0091] xxxii) R^1 is hydrogen, $-C(=O)R^{1A}$, lower alkyl, lower alkenyl, heterocyclyl, aryl or heteroaryl; wherein R^{1A} is hydrogen, or lower alkyl, aryl, or heteroaryl;

[0092] xxxiii) R^1 is hydrogen or lower alkyl;

[0093] xxxiv) R^1 is hydrogen;

[0094] xxxv) R^1 is lower alkyl;

[0095] xxxvi) R^1 is methyl, ethyl or isopropyl;

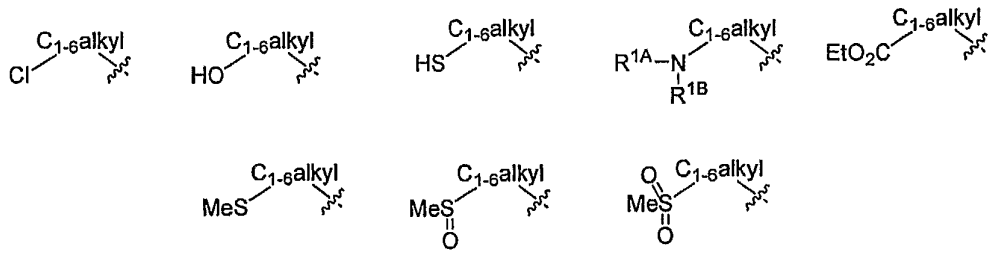
[0096] xxxvii) R^1 is $-C_{1-6}$alkyl$-GR^{G1}$ wherein G is –O-, -S-, $-NR^{G2}$-, -C(=O)-, $-S(=O)-$, $-SO_2-$, $-C(=O)O-$, $-C(=O)NR^{G2}-$, $-OC(=O)-$, $-NR^{G2}C(=O)-$, $-OC(=O)O-$, $-OC(=O)NR^{G2}-$, $-NR^{G2}C(=O)O-$, $-NR^{G2}C(=O)NR^{G3}-$, $-C(=S)-$, $-C(=S)S-$, $-SC(=S)-$, $-SC(=S)S-$, $-C(=NR^{G2})-$, $-C(=NR^{G2})O-$, $-C(=NR^{G2})NR^{G3}-$, $-OC(=NR^{G2})-$, $-NR^{G2}C(=NR^{G3})-$, $-NR^{G2}SO_2-$, $-NR^{G2}SO_2NR^{G3}-$, or $-SO_2NR^{G2}-$, or $-GR^{G1}$ is halogen, CN or N_3; wherein each occurrence of R^{G1}, R^{G2} and R^{G3} is independently hydrogen, halogen, or an optionally substituted aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, or

alkylheteroaryl moiety; and where G is -NR^{G2}-, R^{G1} and R^{G2} taken to gether with the nitrogen atom to which they are attached may form a 4- to 8-membered heterocyclic ring;

[0097] xxxviii) R^1 is –C_{1-6}alkyl–GR^{G1} wherein G is –O-, -S-, -NR^{G2}-, -C(=O)-, -S(=O)-, -SO_2-, -C(=O)O-, -C(=O)NR^{G2}-, -OC(=O)-, -NR^{G2}C(=O)-, -OC(=O)O-, -OC(=O)NR^{G2}-, -NR^{G2}C(=O)O-, -NR^{G2}C(=O)NR^{G3}-, -C(=S)-, -C(=S)S-, -SC(=S)-, -SC(=S)S-, -C(=NR^{G2})-, -C(=NR^{G2})O-, -C(=NR^{G2})NR^{G3}-, -OC(=NR^{G2})-, -NR^{G2}C(=NR^{G3})-, -$NR^{G2}SO_2$-, -$NR^{G2}SO_2NR^{G3}$-, or -SO_2NR^{G2}-, or –GR^{G1} is halogen, CN or N_3; wherein each occurrence of R^{G1}, R^{G2} and R^{G3} is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; and where G is -NR^{G2}-, R^{G1} and R^{G2} taken to gether with the nitrogen atom to which they are attached may form a 4- to 8-membered heterocyclic ring;

[0098] xxxix) R^1 is –C_{1-6}alkyl–GR^{G1} wherein G is –O-, -S-, -NR^{G2}-, -C(=O)O-, -C(=O)NR^{G2}-, -S(=O)-, -SO_2- or -C(=O)NR^{G2}-SO_2-, or –GR^{G1} is halogen; wherein each occurrence of R^{G1} and R^{G2} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; and where G is -NR^{G2}-, R^{G1} and R^{G2} taken to gether with the nitrogen atom to which they are attached may form a 5- to 6-membered heterocyclic ring;

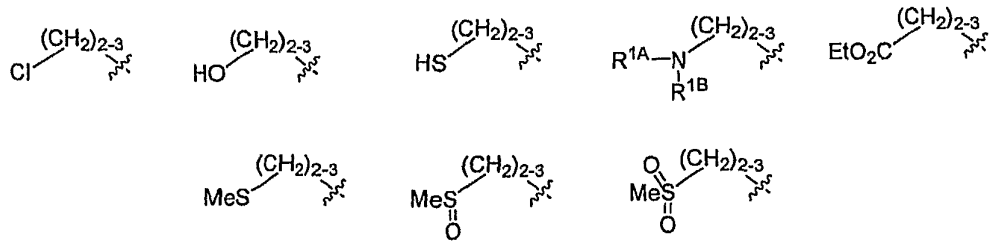
[0099] xl) R^1 is one of:



;

wherein the C_{1-6}alkyl moiety is optionally substituted; and R^{1A} and R^{1B} are independently hydrogen or lower alkyl;

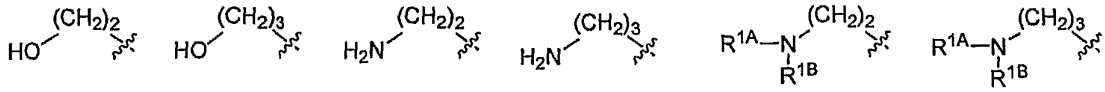
[0100] xli) R^1 is one of:



;

wherein R^{1A} and R^{1B} are independently hydrogen or lower alkyl;

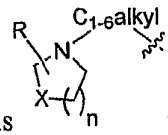
[0101] xlii) R^1 is one of:



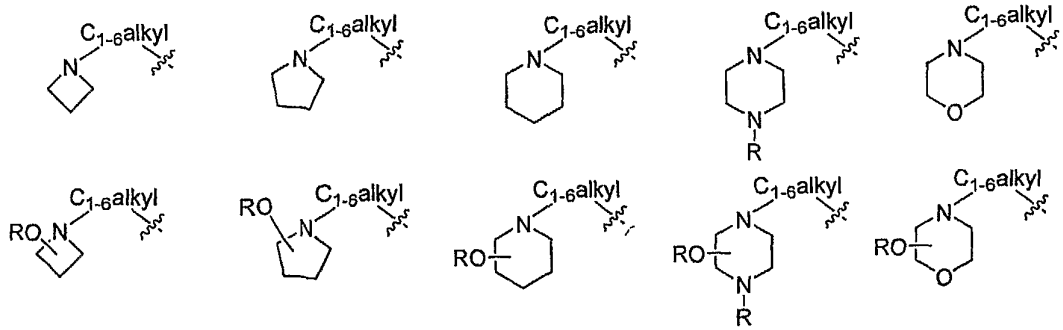
;

wherein R^{1A} and R^{1B} are independently hydrogen, methyl or ethyl;

[0102] xliii) R^1 is $-C_{1-6}alkyl-NR^{G1}R^{G2}$ wherein R^{G1} and R^{G2} taken together with the nitrogen atom to which they are attached may form an optionally substituted 5- to 6-membered heterocyclic ring;

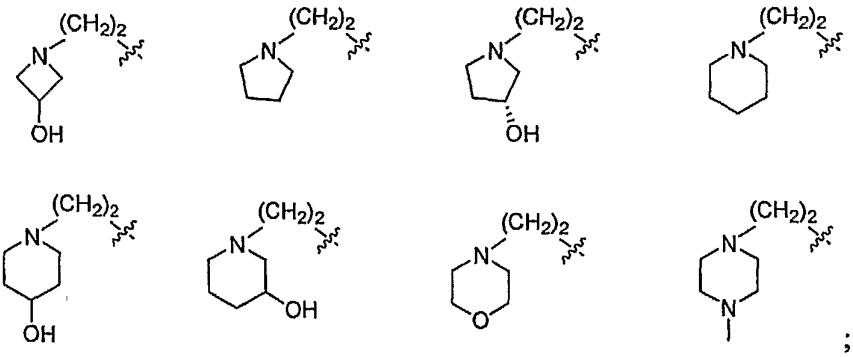
[0103] xliv) R^1 is  wherein n is 0, 1 or 2; R is hydrogen, halogen, lower alkyl or lower alkoxy; and X is O or NR′ where R′ is hydrogen or lower alkyl;

[0104] xlv) R^1 is:



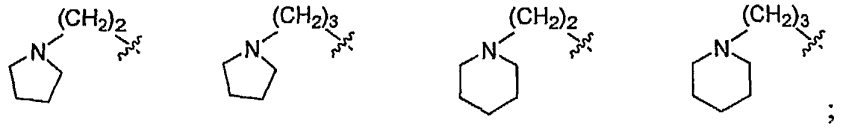
wherein the C_{1-6}alkyl moiety is optionally substituted; and R is hydrogen or lower alkyl;

[0105] xlvi) R^1 is:



;

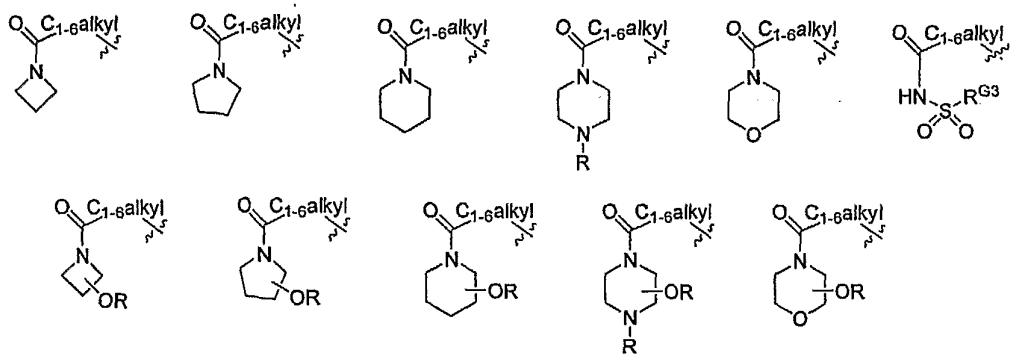
[0106] xlvii) R^1 is:



;

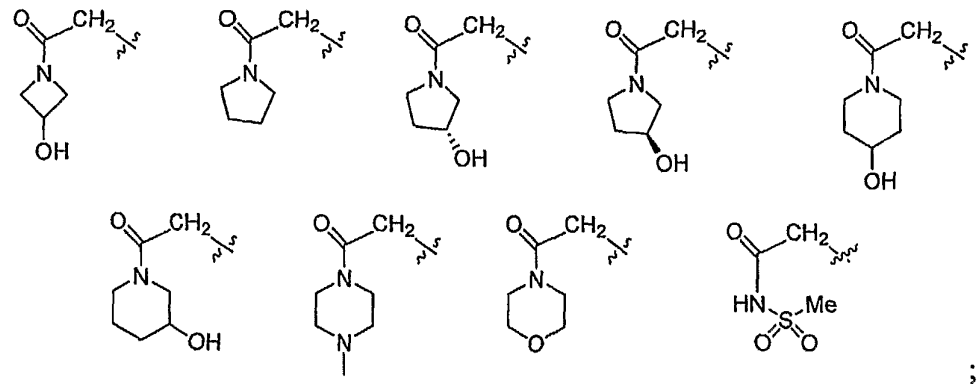
[0107] xlviii) R^1 is $-C_{1-6}alkyl-C(=O)-NR^{G1}R^{G2}$ or $-C_{1-6}alkyl-C(=O)-NHSO_2R^{G3}$ wherein R^{G1} and R^{G2} taken together with the nitrogen atom to which they are attached may form an optionally substituted 5- to 6-membered heterocyclic ring; and R^{G3} is lower alkyl;

[0108] xlix) R^1 is:



wherein the C_{1-6}alkyl moiety is optionally substituted; R is hydrogen or lower alkyl; and R^{G3} is lower alkyl;

[0109] l) R^1 is:



;

[0110] li) Compounds of subsets vi) through xxx) wherein R^1 has the definition given in subsets xxxi)- l);

[0111] lii) R^3 is hydrogen, $-C(=O)R^{3A}$, $-C(=O)OR^{3A}$, $-C(=O)NR^{3A}R^{3B}$, $-S(=O)_2R^{3C}$, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; wherein R^{3A} and R^{3B} are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; or taken together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring; and each occurrence of R^{3C} is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl;

[0112] liii) R^3 is hydrogen, $-C(=O)R^{3A}$, lower alkyl, lower alkenyl, heterocyclyl, aryl or heteroaryl; wherein R^{3A} is hydrogen, or lower alkyl, aryl, or heteroaryl;

[0113] liv) R^3 is hydrogen or lower alkyl;

[0114] lv) R^3 is hydrogen;

[0115] lvi) R^3 is lower alkyl;

[0116] lvii) R^3 is methyl, ethyl or isopropyl;

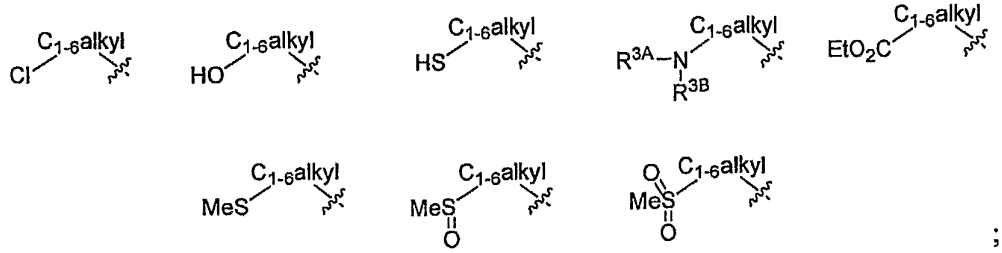
[0117] lviii) R^3 is $-C_{1\text{-}6}$alkyl$-GR^{G3}$ wherein G is –O-, -S-, $-NR^{G4}$-, -C(=O)-, -S(=O)-, $-SO_2$-, -C(=O)O-, $-C(=O)NR^{G4}$-, -OC(=O)-, $-NR^{G2}C(=O)$-, -OC(=O)O-, $-OC(=O)NR^{G4}$-, $-NR^{G4}C(=O)O$-, $-NR^{G4}C(=O)NR^{G4}$-, -C(=S)-, -C(=S)S-, -SC(=S)-, -SC(=S)S-, $-C(=NR^{G4})$-, $-C(=NR^{G4})O$-, $-C(=NR^{G2})NR^{G5}$-, $-OC(=NR^{G4})$-, $-NR^{G4}C(=NR^{G5})$-, $-NR^{G4}SO_2$-, $-NR^{G4}SO_2NR^{G5}$-, or $-SO_2NR^{G4}$-, or $-GR^{G3}$ is halogen,

CN or N_3; wherein each occurrence of R^{G3}, R^{G4} and R^{G5} is independently hydrogen, halogen, or an optionally substituted aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety; and where G is $-NR^{G4}-$, R^{G3} and R^{G4} taken to gether with the nitrogen atom to which they are attached may form a 4- to 8-membered heterocyclic ring;

[0118] lix) R^3 is $-C_{1-6}alkyl-GR^{G3}$ wherein G is –O-, -S-, $-NR^{G4}-$, -C(=O)-, -S(=O)-, $-SO_2-$, -C(=O)O-, $-C(=O)NR^{G4}-$, $-OC(=O)-$, $-NR^{G4}C(=O)-$, -OC(=O)O-, $-OC(=O)NR^{G4}-$, $-NR^{G4}C(=O)O-$, $-NR^{G4}C(=O)NR^{G5}-$, -C(=S)-, -C(=S)S-, -SC(=S)-, -SC(=S)S-, $-C(=NR^{G4})-$, $-C(=NR^{G4})O-$, $-C(=NR^{G4})NR^{G5}-$, $-OC(=NR^{G4})-$, $-NR^{G4}C(=NR^{G5})-$, $-NR^{G4}SO_2-$, $-NR^{G4}SO_2NR^{G5}-$, or $-SO_2NR^{G4}-$, or $-GR^{G3}$ is halogen, CN or N_3; wherein each occurrence of R^{G3}, R^{G4} and R^{G5} is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; and where G is $-NR^{G4}-$, R^{G3} and R^{G4} taken to gether with the nitrogen atom to which they are attached may form a 4- to 8-membered heterocyclic ring;

[0119] lx) R^3 is $-C_{1-6}alkyl-GR^{G3}$ wherein G is –O-, -S-, $-NR^{G4}-$, -C(=O)O-, $-C(=O)NR^{G4}-$, -S(=O)-, $-SO_2-$ or $-C(=O)NR^{G4}-SO_2-$, or $-GR^{G3}$ is halogen; wherein each occurrence of R^{G3} and R^{G4} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; and where G is $-NR^{G4}-$, R^{G3} and R^{G4} taken to gether with the nitrogen atom to which they are attached may form a 5- to 6-membered heterocyclic ring;

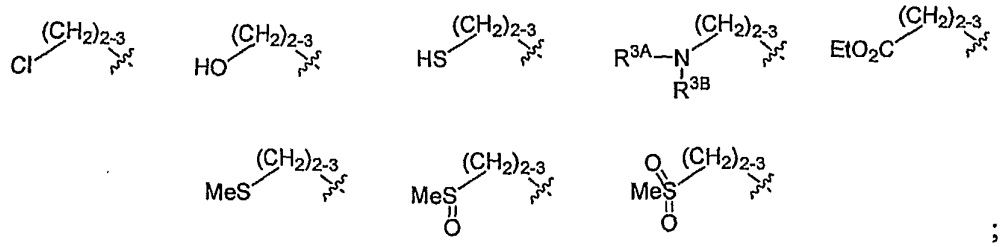
[0120] lxi) R^3 is one of:



;

wherein the $C_{1-6}alkyl$ moiety is optionally substituted; and R^{3A} and R^{3B} are independently hydrogen or lower alkyl;

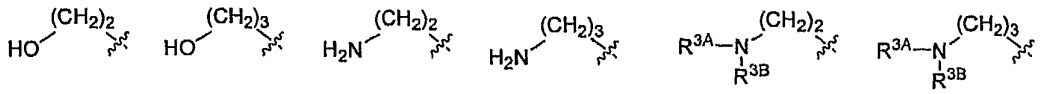
[0121] lxii) R^3 is one of:



;

wherein R^{3A} and R^{3B} are independently hydrogen or lower alkyl;

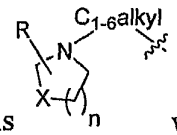
[0122] lxiii) R^3 is one of:



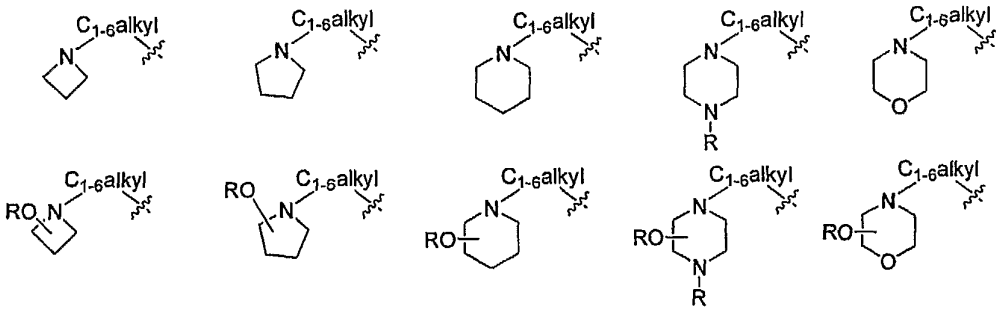
;

wherein R^{3A} and R^{3B} are independently hydrogen, methyl or ethyl;

[0123] lxiv) R^3 is $-C_{1\text{-}6}alkyl-NR^{G1}R^{G2}$ wherein R^{G1} and R^{G2} taken together with the nitrogen atom to which they are attached may form an optionally substituted 5- to 6-membered heterocyclic ring;

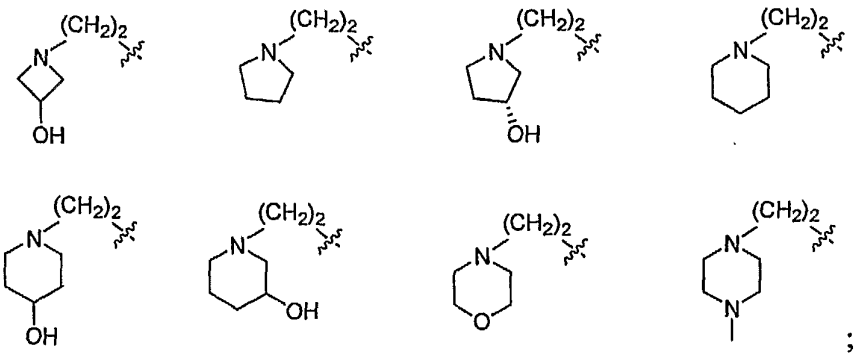
[0124] lxv) R^3 is  wherein n is 0, 1 or 2; R is hydrogen, halogen, lower alkyl or lower alkoxy; and X is O or NR´ where R´ is hydrogen or lower alkyl;

[0125] lxvi) R^3 is:



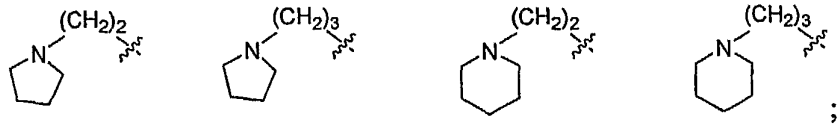
wherein the $C_{1\text{-}6}$alkyl moiety is optionally substituted; and R is hydrogen or lower alkyl;

[0126] lxvii) R^3 is:



;

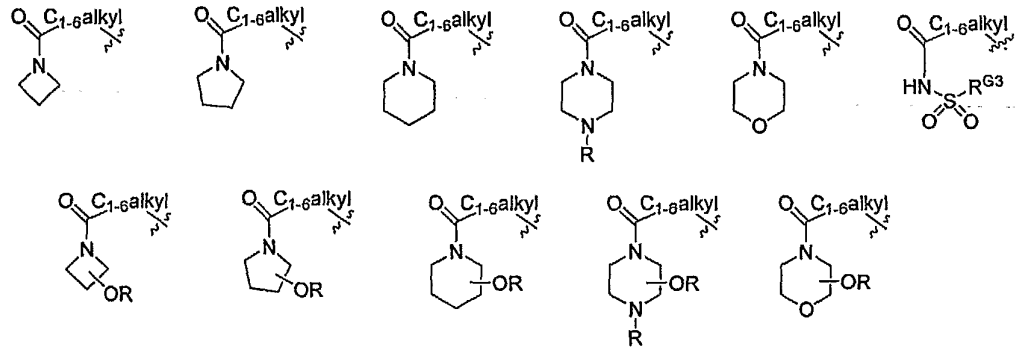
[0127] lxviii) R^3 is:

[0128] 

;

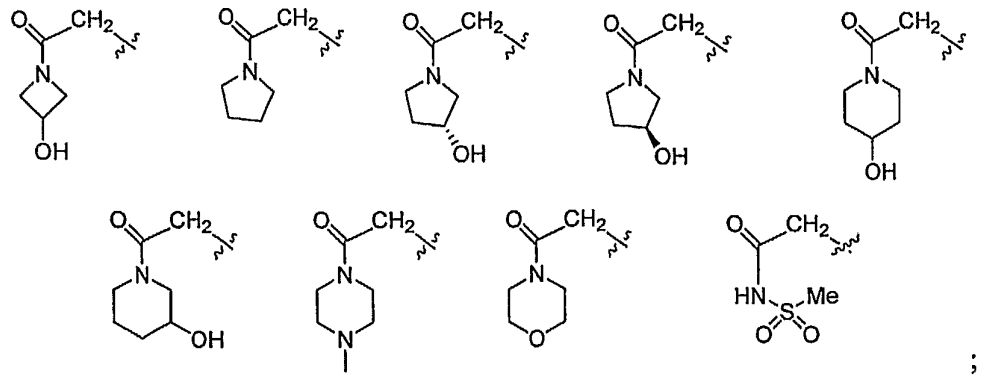
[0129] lxix) R^3 is $-C_{1-6}alkyl-C(=O)-NR^{G1}R^{G2}$ or $-C_{1-6}alkyl-C(=O)-NHSO_2R^{G3}$ wherein R^{G1} and R^{G2} taken together with the nitrogen atom to which they are attached may form an optionally substituted 5- to 6-membered heterocyclic ring; and R^{G3} is lower alkyl;

[0130] lxx) R^3 is:



wherein the C_{1-6}alkyl moiety is optionally substituted; R is hydrogen or lower alkyl; and R^{G3} is lower alkyl;

[0131] lxxi) R^3 is:



;

[0132] lxxii) Compounds of subsets vi) through xxx) wherein R^3 has the definition given in subsets lii)- lxxi);

[0133] lxxiii) R^4 is hydrogen, $-C(=O)R^{4A}$, $-C(=O)OR^{4A}$, $-C(=O)NR^{4A}R^{4B}$, $-S(=O)_2R^{4C}$, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; wherein R^{4A} and R^{4B} are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; or taken together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring; and each occurrence of R^{4C} is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl;

[0134] lxxiv) R^4 is hydrogen, $-C(=O)R^{4A}$, lower alkyl, lower alkenyl, heterocyclyl, aryl or heteroaryl; wherein R^{4A} is hydrogen, or lower alkyl, aryl, or heteroaryl;

[0135] lxxv) R^4 is hydrogen or lower alkyl;

[0136] lxxvi) R^4 is hydrogen;

[0137] lxxvii) R^4 is lower alkyl;

[0138] lxxviii) R^4 is methyl, ethyl or isopropyl;

[0139] lxxix) R^4 is $-C_{1-6}$alkyl$-GR^{G3}$ wherein G is –O-, -S-, $-NR^{G4}$-, -C(=O)-, -S(=O)-, $-SO_2$-, -C(=O)O-, $-C(=O)NR^{G4}$-, $-OC(=O)$-, $-NR^{G2}C(=O)$-, $-OC(=O)O$-, $-OC(=O)NR^{G4}$-, $-NR^{G4}C(=O)O$-, $-NR^{G4}C(=O)NR^{G4}$-, -C(=S)-, -C(=S)S-, -SC(=S)-, -SC(=S)S-, $-C(=NR^{G4})$-, $-C(=NR^{G4})O$-, $-C(=NR^{G2})NR^{G5}$-, $-OC(=NR^{G4})$-, -

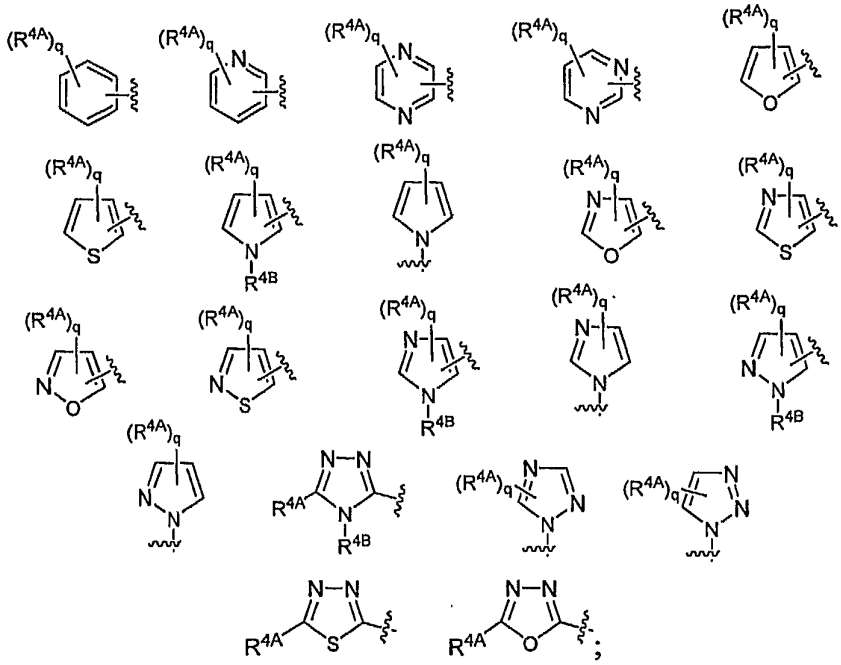
$NR^{G4}C(=NR^{G5})$-, $-NR^{G4}SO_2$-, $-NR^{G4}SO_2NR^{G5}$-, or $-SO_2NR^{G4}$-, or $-GR^{G3}$ is halogen, CN or N_3; wherein each occurrence of R^{G3}, R^{G4} and R^{G5} is independently hydrogen, halogen, or an optionally substituted aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety; and where G is $-NR^{G4}$-, R^{G3} and R^{G4} taken to gether with the nitrogen atom to which they are attached may form a 4- to 8-membered heterocyclic ring;

[0140] lxxx) R^4 is $-C_{1-6}$alkyl$-GR^{G3}$ wherein G is –O-, -S-, $-NR^{G4}$-, -C(=O)-, -S(=O)-, $-SO_2$-, -C(=O)O-, $-C(=O)NR^{G4}$-, -OC(=O)-, $-NR^{G4}C(=O)$-, -OC(=O)O-, $-OC(=O)NR^{G4}$-, $-NR^{G4}C(=O)O$-, $-NR^{G4}C(=O)NR^{G5}$-, -C(=S)-, -C(=S)S-, -SC(=S)-, -SC(=S)S-, $-C(=NR^{G4})$-, $-C(=NR^{G4})O$-, $-C(=NR^{G4})NR^{G5}$-, $-OC(=NR^{G4})$-, $-NR^{G4}C(=NR^{G5})$-, $-NR^{G4}SO_2$-, $-NR^{G4}SO_2NR^{G5}$-, or $-SO_2NR^{G4}$-, or $-GR^{G3}$ is halogen, CN or N_3; wherein each occurrence of R^{G3}, R^{G4} and R^{G5} is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; and where G is $-NR^{G4}$-, R^{G3} and R^{G4} taken to gether with the nitrogen atom to which they are attached may form a 4- to 8-membered heterocyclic ring;

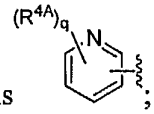
[0141] lxxxi) R^4 is $-C_{1-6}$alkyl$-GR^{G3}$ wherein G is –O-, -S-, $-NR^{G4}$-, -C(=O)O-, $-C(=O)NR^{G4}$-, -S(=O)-, $-SO_2$- or $-C(=O)NR^{G4}-SO_2$-, or $-GR^{G3}$ is halogen; wherein each occurrence of R^{G3} and R^{G4} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl; and where G is $-NR^{G4}$-, R^{G3} and R^{G4} taken to gether with the nitrogen atom to which they are attached may form a 5- to 6-membered heterocyclic ring;

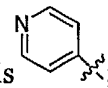
[0142] lxxxii) R^4 is aryl or heteroaryl;

[0143] lxxxiii) R^4 is one of:

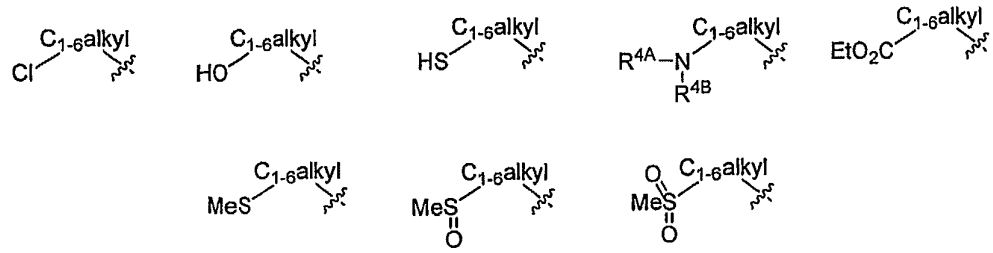


wherein q is an integer from 0 to 3; each occurrence of R^{4A} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{4C}, -SR^{4C}, -$NR^{4B}R^{4C}$, -$SO_2NR^{4B}R^{4C}$, -$C(=O)NR^{4B}R^{4C}$, halogen, -CN, -NO_2, -$C(=O)OR^{4C}$, -$N(R^{4B})C(=O)R^{4C}$, wherein each occcurrence of R^{4B} and R^{4C} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{4B} and R^{4C} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring;

[0144] lxxxiv) R^4 is  ;

[0145] lxxxv) R^4 is  ;

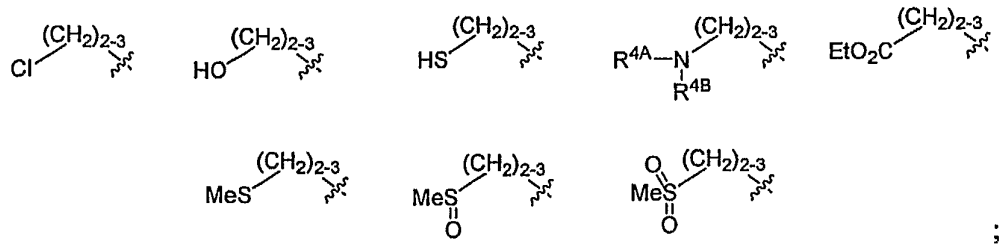
[0146] lxxxvi) R^4 is one of:



;

wherein the C_{1-6}alkyl moiety is optionally substituted; and R^{4A} and R^{4B} are independently hydrogen or lower alkyl;

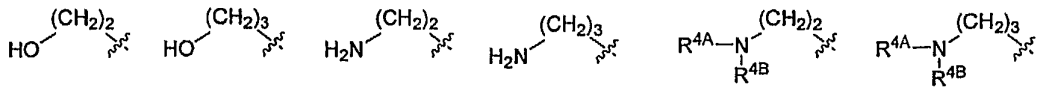
[0147] lxxxvii) R^4 is one of:



;

wherein R^{4A} and R^{4B} are independently hydrogen or lower alkyl;

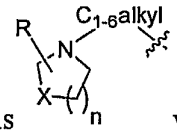
[0148] lxxxviii) R^4 is one of:



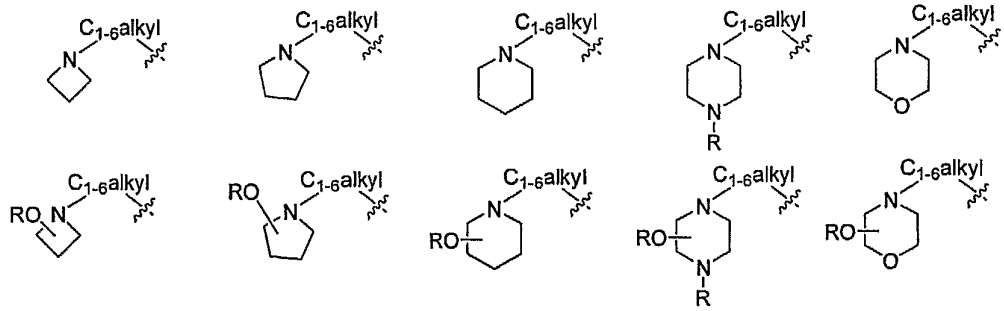
;

wherein R^{4A} and R^{4B} are independently hydrogen, methyl or ethyl;

[0149] lxxxix) R^4 is $-C_{1\text{-}6}alkyl-NR^{G1}R^{G2}$ wherein R^{G1} and R^{G2} taken together with the nitrogen atom to which they are attached may form an optionally substituted 5- to 6-membered heterocyclic ring;

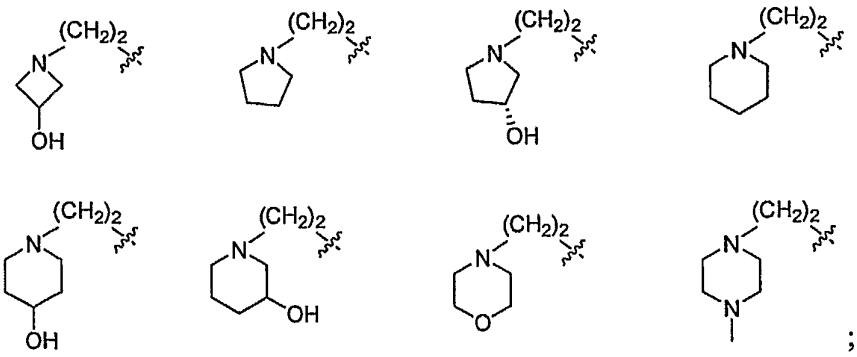
[0150] xc) R^4 is  wherein n is 0, 1 or 2; R is hydrogen, halogen, lower alkyl or lower alkoxy; and X is O or NR′ where R′ is hydrogen or lower alkyl;

[0151] xci) R^4 is:



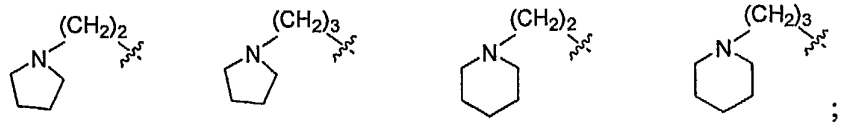
wherein the $C_{1\text{-}6}$alkyl moiety is optionally substituted; and R is hydrogen or lower alkyl;

[0152] xcii) R^4 is:



;

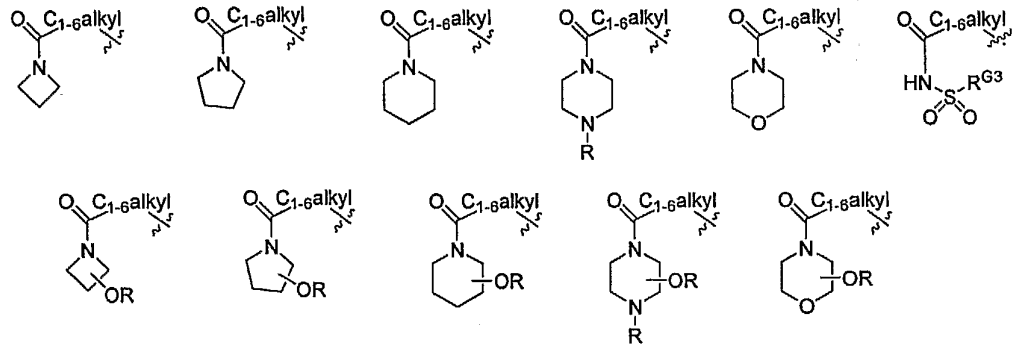
[0153] xciii) R^4 is:



;

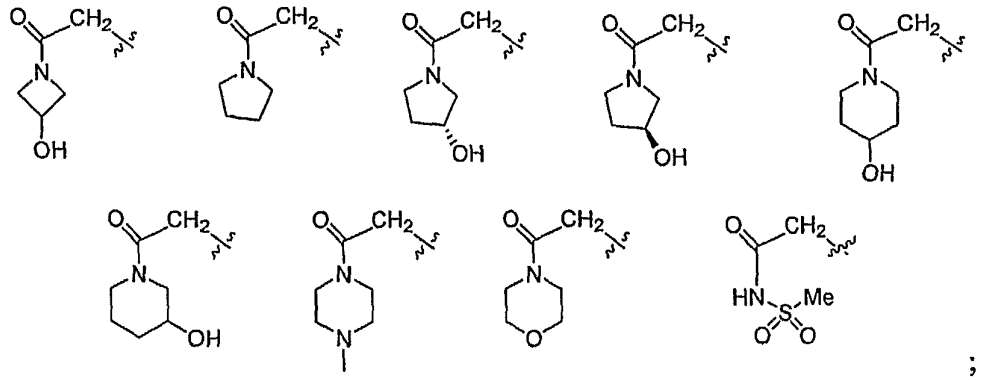
[0154] xciv) R^4 is $-C_{1-6}alkyl-C(=O)-NR^{G1}R^{G2}$ or $-C_{1-6}alkyl-C(=O)-NHSO_2R^{G3}$ wherein R^{G1} and R^{G2} taken together with the nitrogen atom to which they are attached may form an optionally substituted 5- to 6-membered heterocyclic ring; and R^{G3} is lower alkyl;

[0155] xcv) R^4 is:



wherein the C_{1-6}alkyl moiety is optionally substituted; R is hydrogen or lower alkyl; and R^{G3} is lower alkyl;

[0156] xcvi) R^4 is:



;

[0157] xcvii) Compounds of subsets vi) through xxx) wherein R^4 has the definition given in subsets lxxiii)- xcvi);

[0158] xcviii) L^1 is $-W^1\text{-}Alk_1\text{-}$; wherein W^1 is O, S, NR^{W1} or $-C(=O)NR^{W1}$ where R^{W1} is hydrogen, alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; and Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by $-C(=O)-$, $-CO_2-$, $-C(=O)C(=O)-$, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, $-S(=O)-$, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, $-O-$, $-S-$, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, alkyl, heteroalkyl, heterocyclyl, aromatic, heteroaromatic or acyl;

[0159] xcix) L^1 is $-W^1\text{-}Alk_1\text{-}$; wherein W^1 is O, S, NR^{W1} or $-C(=O)NR^{W1}$ where R^{W1} is hydrogen, lower alkyl, C_{3-6}cycloalkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; and Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by $-C(=O)-$, $-CO_2-$, $-C(=O)C(=O)-$, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, $-S(=O)-$, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, $-O-$, $-S-$, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl;

[0160] c) Compounds of subset xcix) above wherein W^1 is S;

[0161] ci) Compounds of subset xcix) above wherein W^1 is O or NR^{W1};

[0162] cii) L^1 is $-O\text{-}Alk_1$-; wherein Alk_1 is a substituted or unsubstituted C_2alkylene chain;

[0163] ciii) L^1 is –O-cyclopropyl-;

[0164] civ) L^1 is $-O\text{-}CH_2CH_2$-;

[0165] cv) L^1 is $-NR^{W1}\text{-}Alk_1$-; wherein R^{W1} is hydrogen, lower alkyl, C_{3-6}cycloalkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; and Alk_1 is a substituted or unsubstituted C_{2-6}alkylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -S(=O)-, $-SO_2$-, -O-, -S-, or $-NR^{L1A}$-; wherein R^{L1A} is hydrogen or lower alkyl;

[0166] cvi) L^1 is $-NR^{W1}\text{-}Alk_1$-; wherein R^{W1} is hydrogen, lower alkyl or lower heteroalkyl; and Alk_1 is a substituted or unsubstituted C_2alkylene chain;

[0167] cvii) L^1 is –NH-cyclopropyl-;

[0168] cviii) L^1 is $-NH\text{-}CH_2CH_2$-;

[0169] cix) L^1 is $-NH\text{-}CH_2CF_2$-;

[0170] cx) L^1 is $-NH\text{-}CH_2CH[(CH_2)_pOR^{W2}]$-; wherein p is 1 or 2 and R^{W2} is hydrogen or lower alkyl;

[0171] cxi) L^1 is $-NH\text{-}CH_2CH(CH_2OH)$-;

[0172] cxii) L^1 is $-NH\text{-}CH_2CH(CH_2CH_2OH)$-;

[0173] cxiii) L^1 is $-NR^{W1}\text{-}Alk_1$-; wherein R^{W1} is lower heteroalkyl; and Alk_1 is a substituted or unsubstituted C_2alkylene chain;

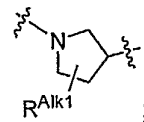
[0174] cxiv) L^1 is $-NR^{W1}\text{-}Alk_1$-; wherein R^{W1} is $-(CH_2)_2NR^{W2}R^{W3}$; Alk_1 is a substituted or unsubstituted C_2alkylene chain; and R^{W2} and R^{W3} are independently hydrogen or lower alkyl;

[0175] cxv) L^1 is $-NR^{W1}\text{-}(CH_2)_2$-; wherein R^{W1} is $-(CH_2)_2NR^{W2}R^{W3}$; and R^{W2} and R^{W3} are independently hydrogen or lower alkyl;

[0176] cxvi) L^1 is $-NR^{W1}\text{-}(CH_2)_2$-; wherein R^{W1} is $-(CH_2)_2NMe_2$;

[0177] cxvii) L^1 is $-NR^{W1}\text{-}Alk_1$-; wherein R^{W1} together with a carbon atom present on Alk_1 forms an optionally substituted 5- to 6-membered heterocyclic moiety;

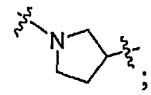
[0178] cxviii) L^1 has the structure:



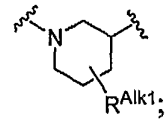
;

wherein R^{Alk1} is hydrogen, halohen, hydroxy, CN, nitro, lower alkyl, lower alkoxy, aryl, or heteroaryl;

[0179] cxix) L^1 has the structure:

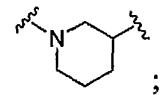


[0180] cxx) L^1 has the structure:



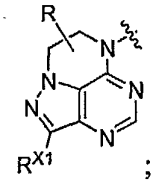
wherein R^{Alk1} is hydrogen, halohen, hydroxy, CN, nitro, lower alkyl, lower alkoxy, aryl, or heteroaryl;

[0181] cxxi) L^1 has the structure:



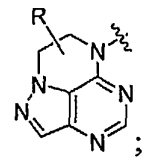
[0182] cxxii) X^{1A} is NR^1 and L^1 is $-NR^{W1}$-Alk_1-; wherein R^{W1} together with R^1 forms an optionally substituted 5- to 6-membered heterocyclic moiety;

[0183] cxxiii) Compounds of subset cxxii) above wherein R^{W1}, R^1 and the pyrazolo pyrimidine to which they are attached form the structure:

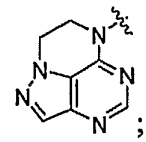


wherein R is hydrogen, halohen, hydroxy, CN, nitro, lower alkyl, lower alkoxy, aryl, or heteroaryl;

[0184] cxxiv) Compounds of subset cxxii) above wherein R^{W1}, R^1 and the pyrazolo pyrimidine to which they are attached form the structure:



[0185] cxxv) Compounds of subset cxxii) above wherein R^{W1}, R^1 and the pyrazolo pyrimidine to which they are attached form the structure:



[0186] cxxvi) L^1 is $-C(=O)NR^{W1}$-Alk_1-; wherein R^{W1} is hydrogen or lower alkyl; and Alk_1 is a substituted or unsubstituted C_1alkylene moiety;

[0187] cxxvii) L^1 is $-C(=O)NH-CH_2-$;

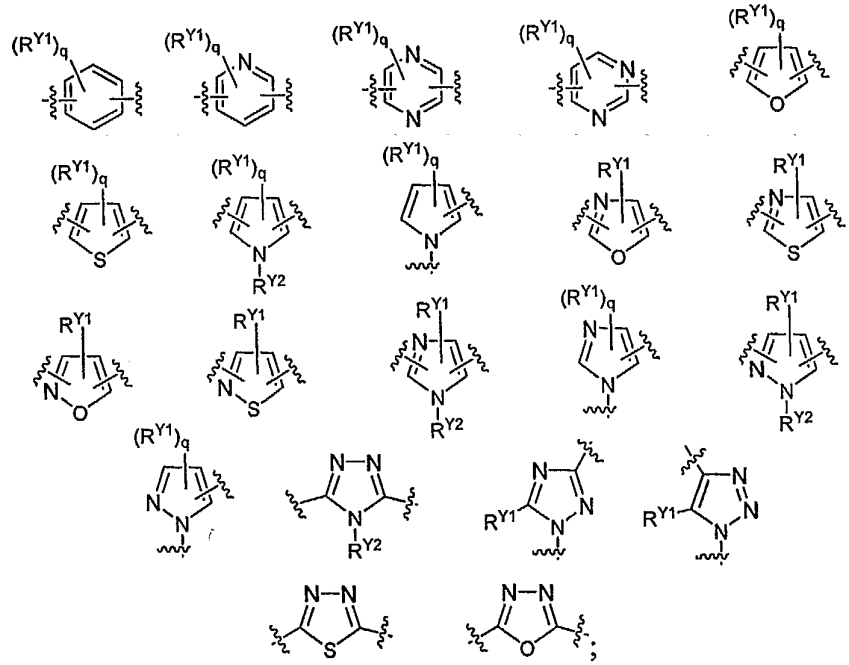
[0188] cxxviii) Y is a saturated or unsaturated cyclic ring system optionally comprising one or more heteroatoms selected from S, N and O;

[0189] cxxix) Y is a saturated or unsaturated monocyclic cyclic ring system optionally comprising one or more heteroatoms selected from S, N and O;

[0190] cxxx) Y is a cycloalkyl, cycloalkenyl, heterocylic, aryl or heteroaryl moiety;

[0191] cxxxi) Y is a 5-6 membered cycloalkyl, 5-6 membered cycloalkenyl, 5-6 membered heterocylic, 6-membered aryl or 6-membered heteroaryl moiety;

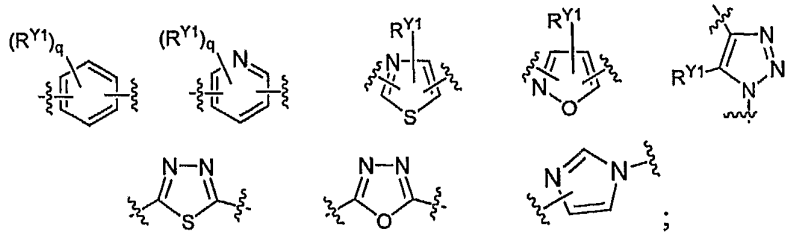
[0192] cxxxii) Y is one of:



wherein q is an integer from 0 to 3; each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -

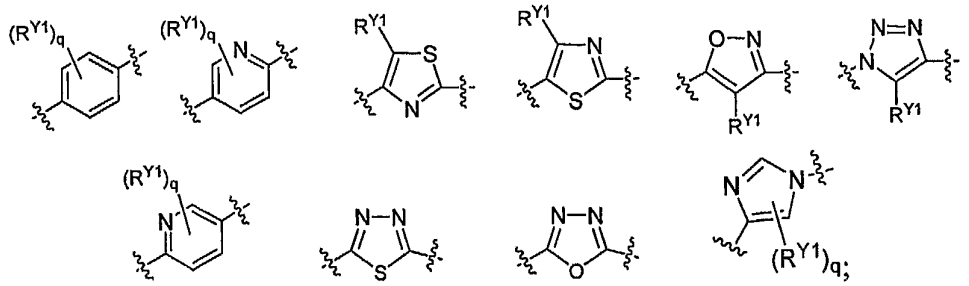
(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring;

[0193] cxxxiii) Y is one of:



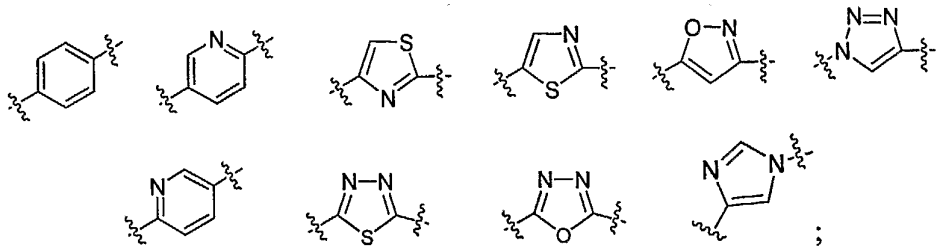
wherein q and R^{Y1} are as defined directly above;

[0194] cxxxiv) Y is one of:

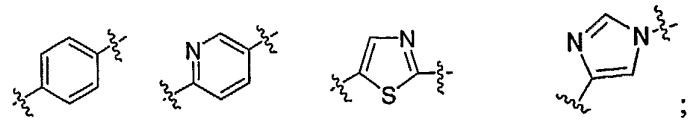


wherein q is 0-3; and R^{Y1} is hydrogen, halogen or lower alkyl;

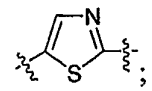
[0195] cxxxv) Y is one of:



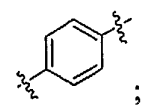
[0196] cxxxvi) Y is one of:



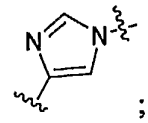
[0197] cxxxvii) Y is:



[0198] cxxxviii) Y is:

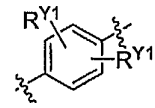


[0199] cxxxix) Y is:



;

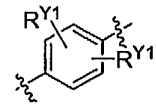
[0200] cxl) Y is:



;

wherein at least one R^{Y1} is halogen, the other is hydrogen or halogen;

[0201] cxli) Y is:



;

wherein at least one R^{Y1} is fluoro, the other is hydrogen or fluoro;

[0202] cxlii) L^2 is $-NR^{L2A}-$ or a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain interrupted with at least one nitrogen atom wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, -C(=O)NR^{L2A}-, -OC(=O)-, -OC(=O)NR^{L2A}-, $-NR^{L2A}NR^{L2B}-$, $-NR^{L2A}NR^{L2B}C(=O)-$, $-NR^{L2A}C(=O)-$, $-NR^{L2A}CO_2-$, $-NR^{L2A}C(=O)NR^{L2B}-$, -S(=O)-, $-SO_2-$, $-NR^{L2A}SO_2-$, $-SO_2NR^{L2A}-$, $-NR^{L2A}SO_2NR^{L2B}-$, -O-, -S-, or $-NR^{L2A}-$; wherein each occurrence of R^{L2A}, R^{L2B}, R^{L2C} and R^{L2D} is independently hydrogen, alkyl, heteroalkyl, heterocyclyl, aromatic, heteroaromatic or acyl;

[0203] cxliii) L^2 is $-NR^{L2A}-$ or a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain interrupted with at least one nitrogen atom wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, -C(=O)NR^{L2A}-, -OC(=O)-, -OC(=O)NR^{L2A}-, $-NR^{L2A}NR^{L2B}-$, $-NR^{L2A}NR^{L2B}C(=O)-$, $-NR^{L2A}C(=O)-$, $-NR^{L2A}CO_2-$, $-NR^{L2A}C(=O)NR^{L2B}-$, -S(=O)-, $-SO_2-$, $-NR^{L2A}SO_2-$, $-SO_2NR^{L2A}-$, $-NR^{L2A}SO_2NR^{L2B}-$, -O-, -S-, or $-NR^{L2A}-$; wherein each occurrence of R^{L2A}, R^{L2B}, R^{L2C} and R^{L2D} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl;

[0204] cxliv) L^2 is $-(CH_2)_mNR^{L2A}(CH_2)_m-$, $-(CH_2)_mC(=O)NR^{L2A}(CH_2)_m-$, $-(CH_2)_mOC(=O)NR^{L2A}(CH_2)_m-$, $-(CH_2)_mNR^{L2A}NR^{L2B}(CH_2)_m-$, $-(CH_2)_mNR^{L2A}NR^{L2B}C(=O)(CH_2)_m-$, $-(CH_2)_mNR^{L2A}C(=O)(CH_2)_m-$, $-(CH_2)_mNR^{L2A}C(=O)O(CH_2)_m-$, $-(CH_2)_mNR^{L2A}C(=O)NR^{L2B}(CH_2)_m-$, -

$(CH_2)_mNR^{L2A}C(=O)NR^{L2B}CR^{L2C}R^{L2D}(CH_2)_m$-, -$(CH_2)_mCR^{L2C}R^{L2D}C(=O)NR^{L2B}(CH_2)_m$-, -$(CH_2)_mNR^{L2A}SO_2(CH_2)_m$-, -$(CH_2)_mSO_2NR^{L2A}(CH_2)_m$-, -$(CH_2)_mNR^{L2A}SO_2NR^{L2B}(CH_2)_m$-; wherein each occurrence of m is independently 0-4; and each occurrence of R^{L2A}, R^{L2B}, R^{L2C} and R^{L2D} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl;

[0205] cxlv) L^2 is –NR^{L2A}-, -C(=O)NR^{L2A}-, -OC(=O)NR^{L2A}-, -$NR^{L2A}NR^{L2B}$-, -$NR^{L2A}NR^{L2B}C(=O)$-, -$NR^{L2A}C(=O)$-, -$NR^{L2A}CO_2$-, -$NR^{L2A}C(=O)NR^{L2B}$-, -$NR^{L2A}C(=O)NR^{L2B}CR^{L2C}R^{L2D}$, -$CR^{L2C}R^{L2D}C(=O)NR^{L2B}$, -$NR^{L2A}SO_2$-, -$SO_2NR^{L2A}$-, -$NR^{L2A}SO_2NR^{L2B}$-, wherein each occurrence of R^{L2A}, R^{L2B}, R^{L2C} and R^{L2D} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl;

[0206] cxlvi) L^2 is –NR^{L2A}-, -C(=O)NR^{L2A}-, -$NR^{L2A}C(=O)$-, -OC(=O)NR^{L2A}-, -$NR^{L2A}CO_2$-, -$NR^{L2A}C(=O)NR^{L2B}$-, -$NR^{L2A}C(=O)NR^{L2B}CR^{L2C}R^{L2D}$ or -$CR^{L2C}R^{L2D}C(=O)NR^{L2B}$, wherein each occurrence of R^{L2A}, R^{L2B}, R^{L2C} and R^{L2D} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl;

[0207] cxlvii) L^2 is –NR^{L2A}-, -$NR^{L2A}C(=O)$-, -$NR^{L2A}C(=O)NR^{L2B}$-, -$NR^{L2A}C(=O)NR^{L2B}CR^{L2C}R^{L2D}$ or -$CR^{L2C}R^{L2D}C(=O)NR^{L2B}$, wherein each occurrence of R^{L2A}, R^{L2B}, R^{L2C} and R^{L2D} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl;

[0208] cxlviii) L^2 is –NH-, -NHC(=O)-, -NHC(=O)O-, -NHC(=O)NH-, -CH_2-C(=O)NH- or –NHC(=O)NHCH_2-;

[0209] cl) L^2 is -NH-;

[0210] cli) L^2 is -NHC(=O)NH-;

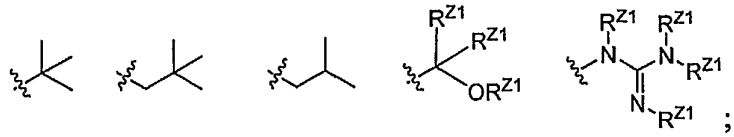
[0211] clii) L^2 is -CH_2-C(=O)NH-;

[0212] cliii) L^2 is –NHC(=O)NHCH_2-;

[0213] cliv) Z is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl or heteroaryl moiety;

[0214] clv) Z is a branched alkyl, alkenyl, alkynyl, heteroalkyl or heteroalkenyl moiety;

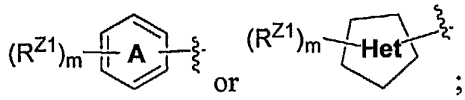
[0215] clvi) Z is one of:



wherein each occurrence of R^{Z1} is independently hydrogen, lower alkyl, lower alkenyl, aryl, heteroaryl or acyl;

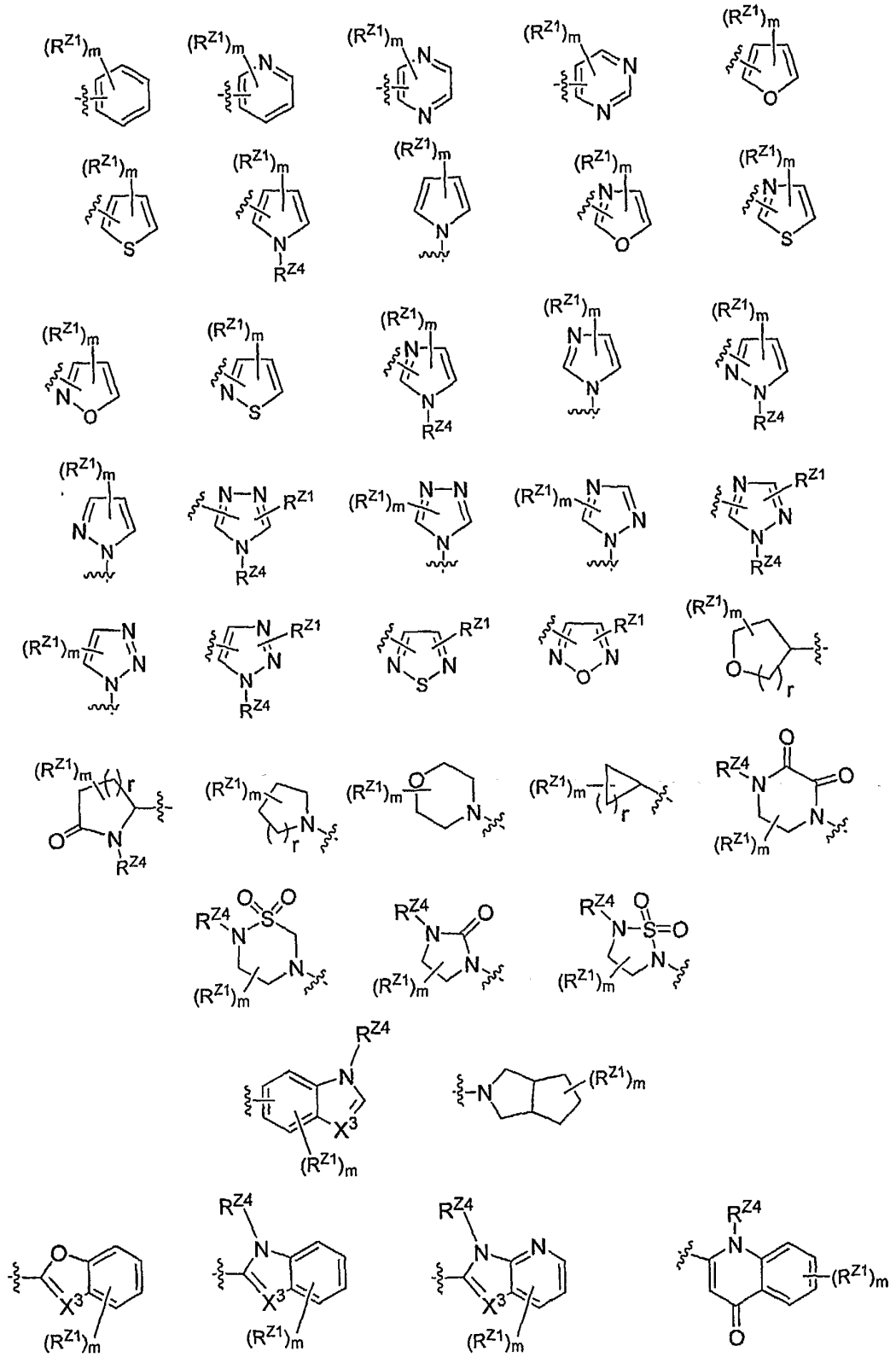
[0216] clvii) Z is a cycloalkyl, cycloalkenyl, heterocyclyl, aryl or heteroaryl moiety;

[0217] clviii) Z is cycloalkyl, cycloalkenyl, or a heterocyclyl, aryl or heteroaryl moiety having one of the structures:



wherein the "A" cyclic moiety is a 6- to 10-membered mono- or fused bicyclic aromatic ring comprising from 0-4 nitrogen atoms; the "Het" moiety represents a fully or partially saturated or unsaturated 5- to 8-membered mono- or fused bicyclic ring comprising 1-4 heteroatoms selected from N, O and S; m is an integer from 0-6; and each occurrence of R^{Z1} is independently hydrogen, alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)heterocyclyl, -(alkyl)aryl, -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-N(R^{Z2})_2$, $-SO_2N(R^{Z2})_2$, $-SO_2R^{Z4}$,-$C(=O)N(R^{Z2})_2$, halogen, $-CN$, $-NO_2$, $-C(=O)OR^{Z2}$, $-N(R^{Z2})C(=O)R^{Z3}$ or $-N(R^{Z2})SO_2R^{Z4}$; wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, acyl; or any two occurrences of R^{Z2}, taken together with the nitrogen atom to which they are attached (*e.g.*, $N(R^{Z2})_2$), form a substituted or unsubstituted heterocyclic moiety; and R^{Z4} is alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, or -(alkyl)heteroaryl; and wherein any two adjacent occurrence of R^{Z1} may form a fused 5- to 6-membered aryl, heteroaryl or heterocyclic ring;

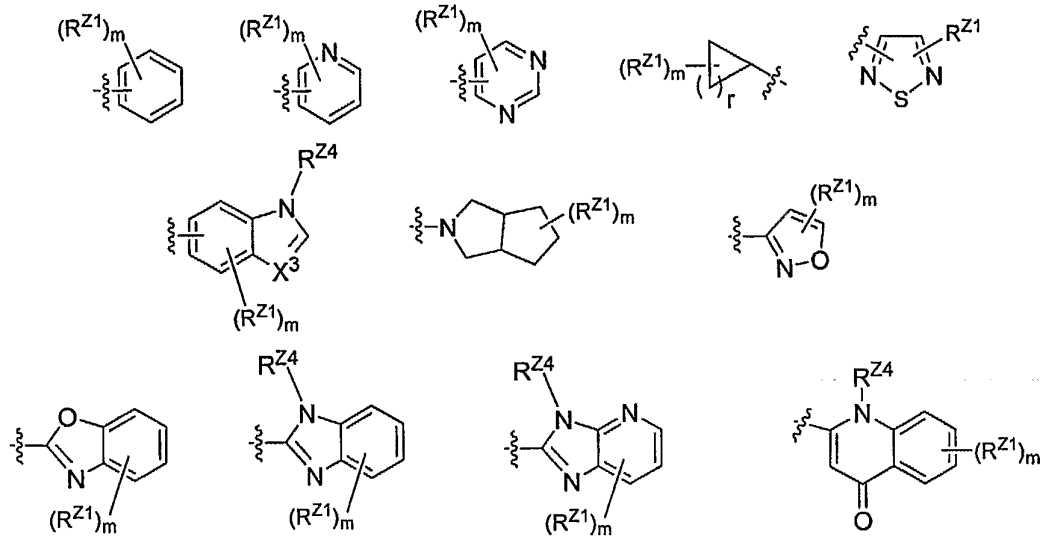
[0218] clix) Z is one of:



;

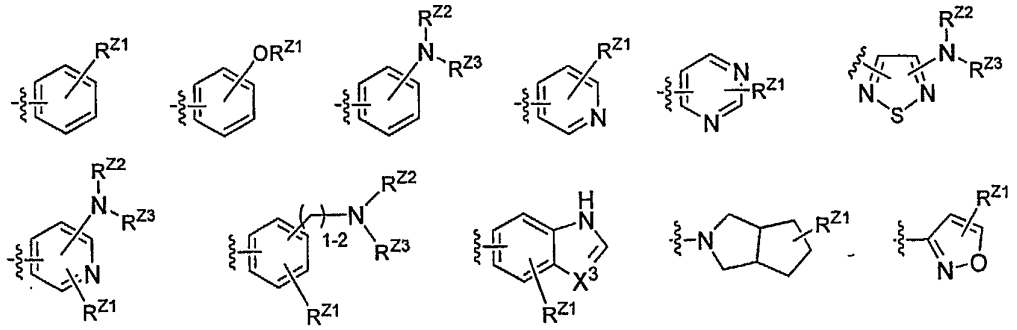
wherein m is an integer from 0 to 3; r is an integer from 1 to 4; X^3 is N or CR^{Z1}; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring; and R^{Z4} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl;

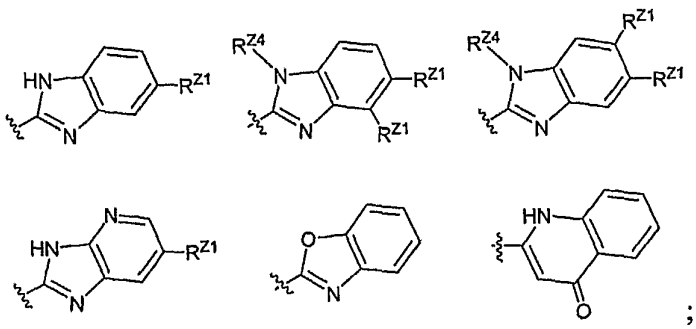
[0219] clx) Z is one of:



;

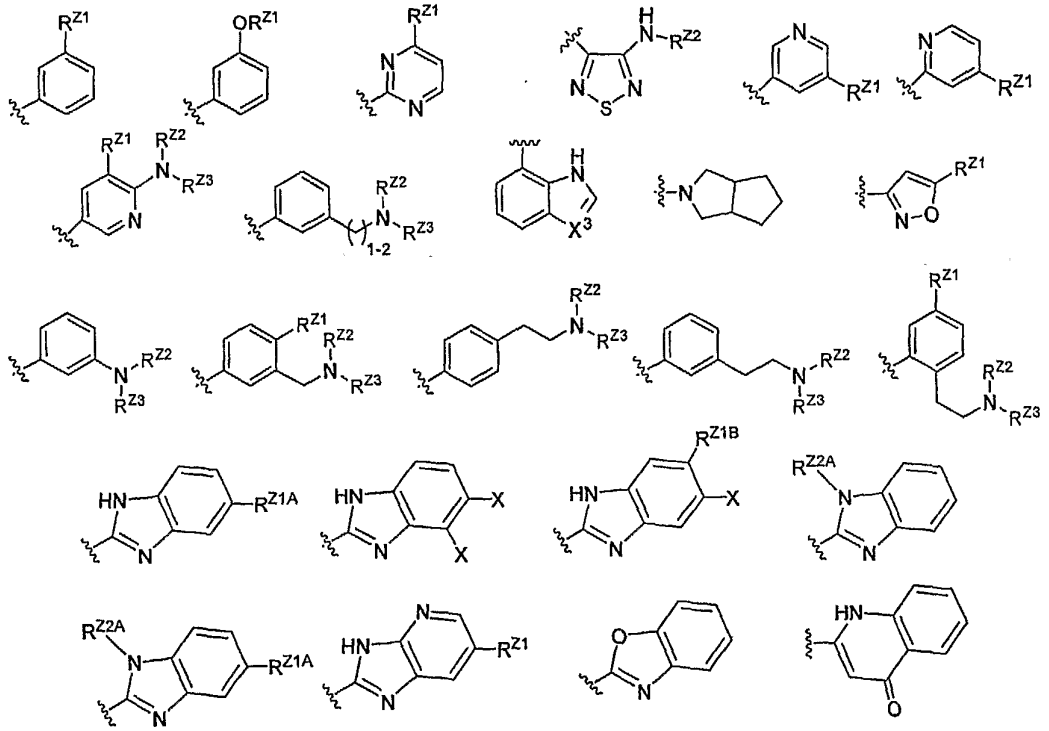
[0220] clxi) Z is one of:





wherein X^3 is N or CR^{Z1}; R^{Z1} is hydrogen, halogen, lower alkyl, lower hydroxyalkyl or lower haloalkyl; R^{Z2} and R^{Z3} are independently hydrogen, lower alkyl, lower heteroalkyl, acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; and R^{Z4} is hydrogen or lower alkyl;

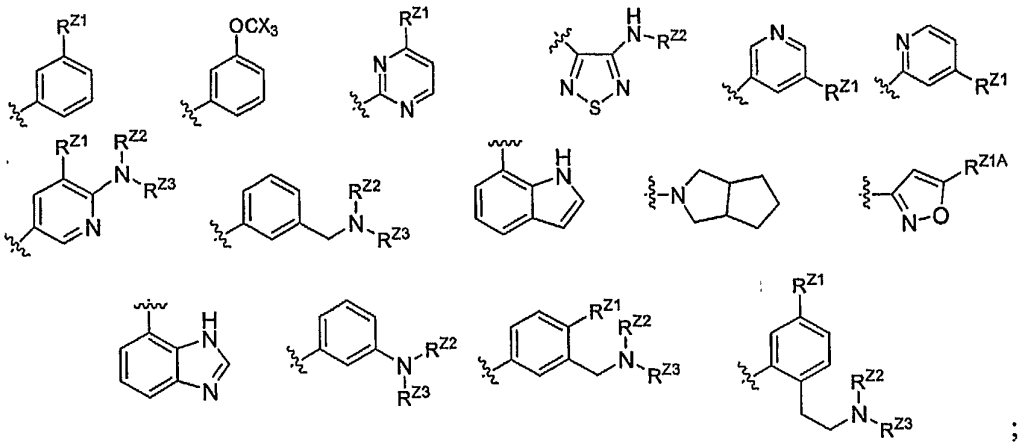
[0221] clxii) Z is one of:



wherein X^3 is N or CR^{Z1}; R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl; and R^{Z2} and R^{Z3} are independently hydrogen, lower alkyl, lower heteroalkyl, acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; X is halogen, R^{Z1A} is hydrogen, halogen, -CN, lower alkyl, lower alkoxy, lower haloalkyl or $-SO_2R^{Z4}$;

wherein R^{Z4} is lower alkyl; R^{Z1B} is hydrogen or halogen; and R^{Z2A} is hydrogen or lower alkyl;

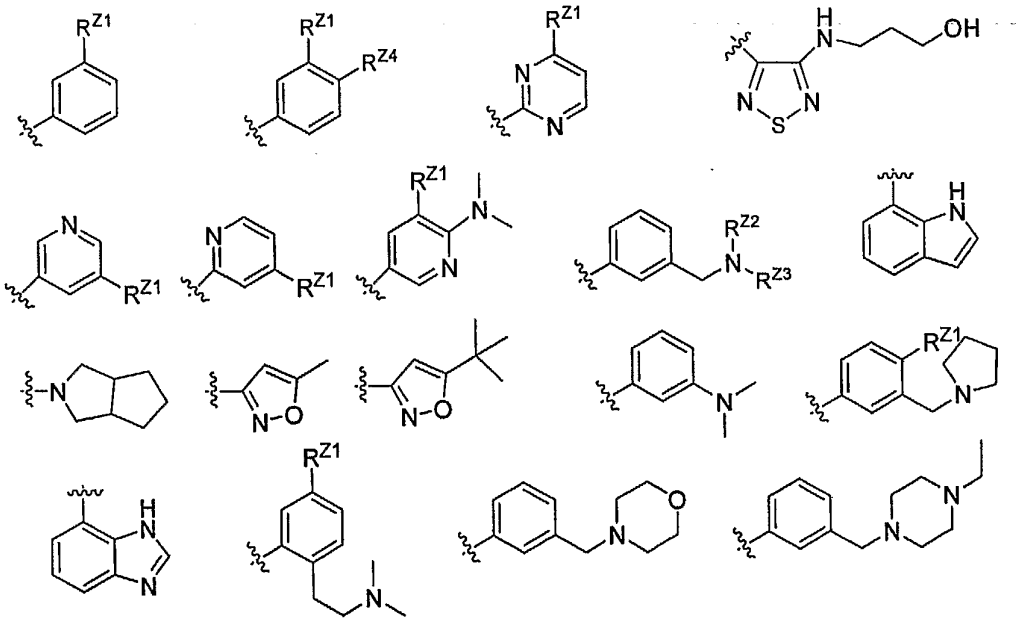
[0222] clxiii) Z is one of:

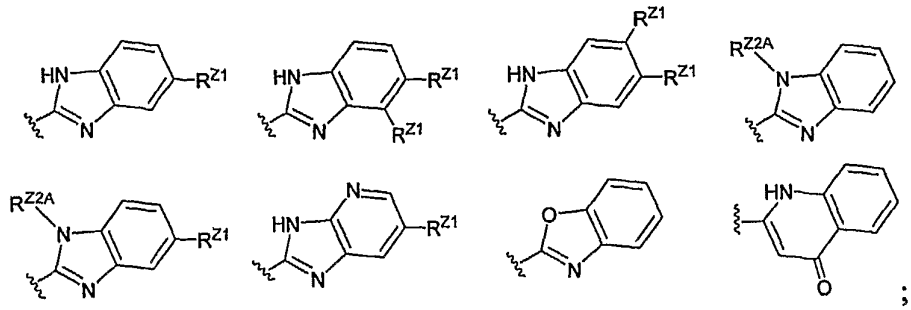


;

wherein X is halogen; R^{Z1A} is lower alkyl; R^{Z1} is halogen, lower alkyl or lower haloalkyl; and R^{Z2} and R^{Z3} are independently lower alkyl, or R^{Z2} and R^{Z3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring;

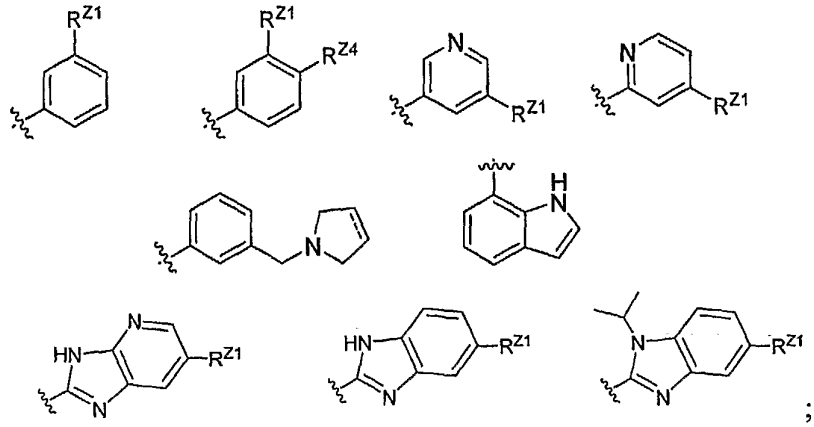
[0223] clxiv) Z is one of:





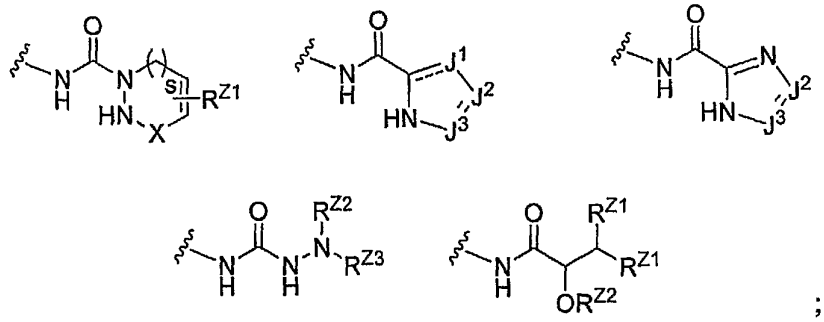
wherein R^{Z1} is Cl, F, methyl or CF_3; R^{Z2} and R^{Z3} are each methyl or ethyl, or taken together with the nitrogen atom to which they are attached form a saturated or unsaturated pyrrolidinyl ring; R^{Z2A} is hydrogen, methyl or isopropyl; and R^{Z4} is hydrogen or cyano;

[0224] clxv) Z is one of:



wherein R^{Z1} is Cl, F, methyl or CF_3; and R^{Z4} is hydrogen or cyano;

[0225] clxvi) $-L^2-Z$ together represent a moiety having one of the following structures:

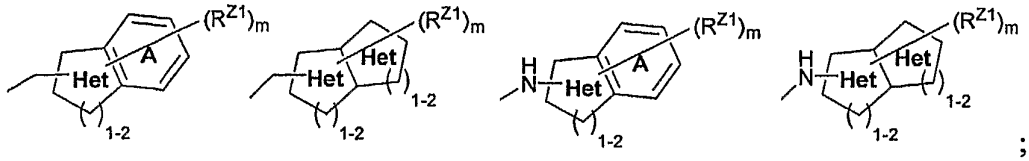


wherein s is 0 or 1; X is $-C(R^{Z1})_2$, -C(=O)- or $-SO_2-$; J^1, J^2 and J^3 are independently N, S, O, NR^{Z1} or CR^{Z1}; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, -

NO_2, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring;

[0226] clxvii) $-L^2-Z$ together represent $-CH_2$-Cy or –NH-Cy where Cy is an optionally substituted bicyclic heterocycle;

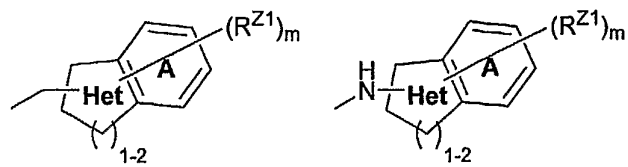
[0227] clxviii) $-L^2-Z$ together represent a moiety having one of the following structures:



;

wherein the "A" cyclic moiety is a 6-membered aromatic ring comprising from 0-4 nitrogen atoms; each "Het" moiety independently represents a fully or partially saturated or unsaturated 5- to 6-membered ring comprising 1-4 heteroatoms selected from N, O and S; m is an integer from 0-6; and each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-N(R^{Z2})_2$, $-SO_2N(R^{Z2})_2$, $-SO_2R^{Z4}$,$-C(=O)N(R^{Z2})_2$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z2}$, $-N(R^{Z2})C(=O)R^{Z3}$ or $-N(R^{Z2})SO_2R^{Z4}$; wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, acyl; or any two occurrences of R^{Z2}, taken together with the nitrogen atom to which they are attached (*e.g.*, $N(R^{Z2})_2$), form a substituted or unsubstituted heterocyclic moiety; and R^{Z4} is alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, or -(alkyl)heteroaryl; and wherein any two adjacent occurrence of R^{Z1} may form a fused 5- to 6-membered aryl, heteroaryl or heterocyclic ring;

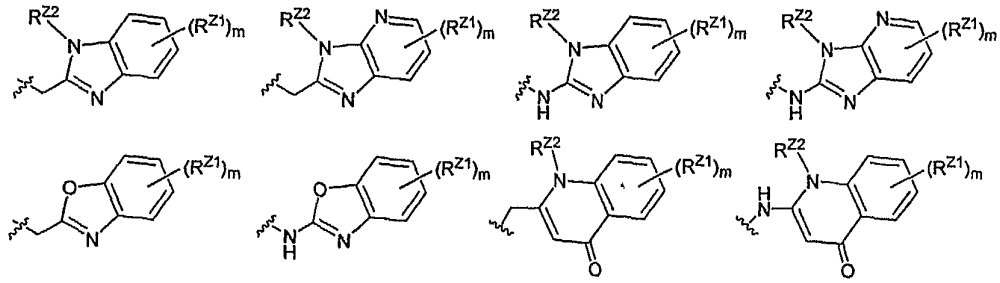
[0228] clxix) $-L^2-Z$ together represent a moiety having one of the following structures:



;

wherein the "A" cyclic moiety is a 6-membered aromatic ring comprising from 0-4 nitrogen atoms; each "Het" moiety independently represents a fully or partially saturated or unsaturated 5- to 6-membered ring comprising 1-4 heteroatoms selected from N, O and S; m is an integer from 0-6; and each occurrence of R^{Z1} is independently hydrogen, lower alkyl, lower alkoxy, $-SO_2R^{Z4}$, halogen or -CN; wherein R^{Z4} is lower alkyl;

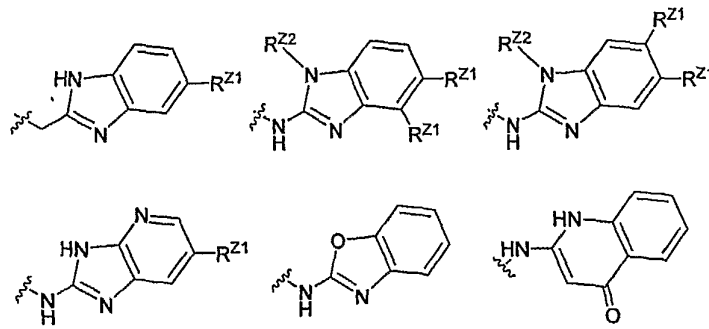
[0229] clxx) $-L^2-Z$ together represent a moiety having one of the following structures:



;

wherein m is an integer from 0-4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-N(R^{Z2})_2$, $-SO_2N(R^{Z2})_2$, $-SO_2R^{Z4}$,$-C(=O)N(R^{Z2})_2$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z2}$, $-N(R^{Z2})C(=O)R^{Z3}$ or $-N(R^{Z2})SO_2R^{Z4}$; wherein each occcurrence of R^{Z2} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; and wherein any two adjacent occurrence of R^{Z1} may form a fused 5- to 6-membered aryl, heteroaryl or heterocyclic ring;

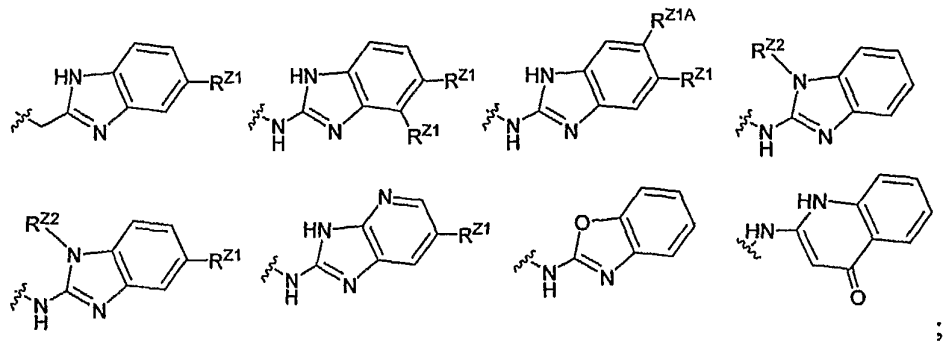
[0230] clxxi) $-L^2-Z$ together represent a moiety having one of the following structures:



;

wherein R^{Z2} is hydrogen or lower alkyl; each occurrence of R^{Z1} is independently hydrogen, halogen, -CN, lower alkyl, lower alkoxy, lower haloalkyl or $-SO_2R^{Z4}$; wherein R^{Z4} is lower alkyl;

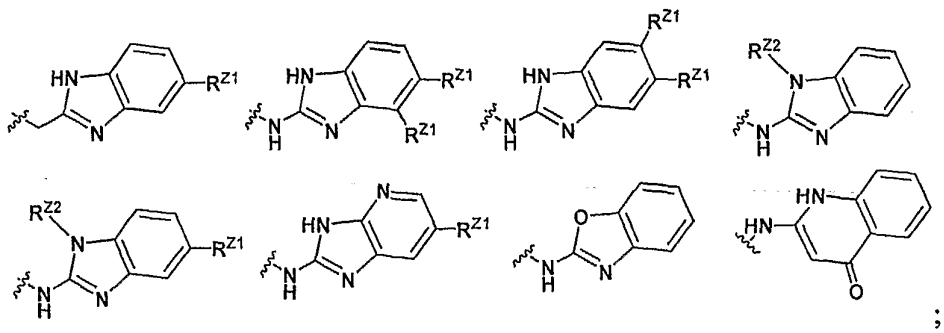
[0231] clxxii) $-L^2-Z$ together represent a moiety having one of the following structures:



;

wherein X is halogen, R^{Z1A} is hydrogen, halogen, -CN, lower alkyl, lower alkoxy, lower haloalkyl or $-SO_2R^{Z4}$; wherein R^{Z4} is lower alkyl; and R^{Z2} is hydrogen or lower alkyl;

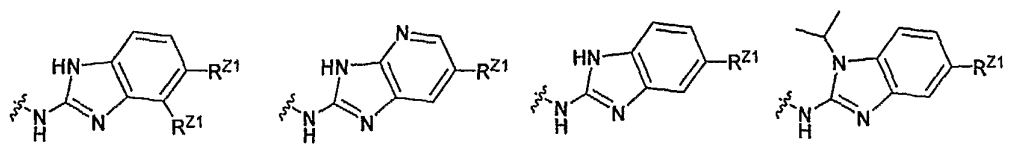
[0232] clxxiii) $-L^2-Z$ together represent a moiety having one of the following structures:



;

wherein R^{Z1} is Cl, F, methyl or CF_3; and R^{Z2} is hydrogen, methyl or isopropyl; and/or

[0233] clxxiv) $-L^2-Z$ together represent a moiety having one of the following structures:



wherein R^{Z1} is Cl, F, methyl or CF_3.

[0234] It will be appreciated that for each of the classes and subclasses described above and herein, any one or more occurrences of aliphatic or heteroaliphatic may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched,

saturated or unsaturated and any one or more occurrences of aryl, heteroaryl, cycloaliphatic, cycloheteroaliphatic may be substituted or unsubstituted.

[0235] The reader will also appreciate that any and all possible combinations of the variables described in i)- through clxxiv) above (*e.g.*, R^2, L^1, L^2, X^1, X^2, Y and Z, among others) are considered part of the invention. Thus, the invention encompasses any and all compounds of formula **I** generated by taking any possible permutation of variables R^2, L^1, L^2, X^1, X^2, Y and Z, and other variables/substituents (*e.g.*, R^1, R^3, R^{X1A}, R^{X2A}, R^{X1B}, R^{X2B}, R^{Y1}, R^{Z1} etc.) as further defined for R^2, L^1, L^2, X^1, X^2, Y and Z, described in i)- through lii) above.

[0236] For example, an exemplary combination of variables described in i)- through clxxiv) above includes those compounds of Formula **I** wherein:

$\mathbf{R^2}$ is hydrogen, halogen, cyano, nitro, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl moiety;

$\mathbf{R^4}$ is hydrogen, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl moiety;

$\mathbf{X^{1A}}$ is NR^1 or $-C(R^{X1})-$; wherein R^1 taken together with a moiety present on L^1 may form an optionally substituted heterocyclic ring;

$\mathbf{X^{2A}}$ is NR^3 or $-C(R^{X1})-$; wherein one of X^{1A} and X^{2A} is $-C(R^{X1})-$, but not both;

$\mathbf{X^{1B}}$ and $\mathbf{X^{2B}}$ are -N- or $-C(R^{X1})-$; whereby one of X^{1B} and X^{2B} is $-C(R^{X1})-$, but not both;

wherein R^1 and R^3 are independently hydrogen, a nitrogen protecting group, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl moiety; and R^{X1} is hydrogen, halogen, cyano, nitro, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl moiety;

$\mathbf{L^1}$ is $-W^1\text{-}Alk_1-$; wherein W^1 is O or NR^{W1}, where R^{W1} is hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; and Alk_1 is a

substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, alkyl, heteroalkyl, heterocyclyl, aromatic, heteroaromatic or acyl;

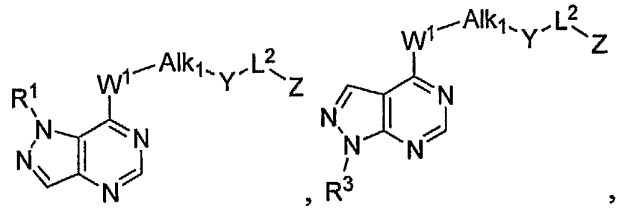
L^2 is -C(=O)NR^{L2A}-, -OC(=O)NR^{L2A}-, -$NR^{L2A}NR^{L2B}$-, -$NR^{L2A}NR^{L2B}$C(=O)-, -NR^{L2A}C(=O)-, -$NR^{L2A}CO_2$-, -NR^{L2A}C(=O)NR^{L2B}-, -$NR^{L2A}SO_2$-, -SO_2NR^{L2A}-, -$NR^{L2A}SO_2NR^{L2B}$-, or a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain interrupted with at least one nitrogen atom wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L2A}-, -OC(=O)-, -OC(=O)NR^{L2A}-, -$NR^{L2A}NR^{L2B}$-, -$NR^{L2A}NR^{L2B}$C(=O)-, -NR^{L2A}C(=O)-, -$NR^{L2A}CO_2$-, -NR^{L2A}C(=O)NR^{L2B}-, -S(=O)-, -SO_2-, -$NR^{L2A}SO_2$-, -SO_2NR^{L2A}-, -$NR^{L2A}SO_2NR^{L2B}$-, -O-, -S-, or -NR^{L2A}-; wherein each occurrence of R^{L2A} and R^{L2B} is independently hydrogen, alkyl, heteroalkyl, heterocyclyl, aromatic, heteroaromatic or acyl;

Y is a saturated or unsaturated cyclic ring system optionally comprising one or more heteroatoms selected from S, N and O;

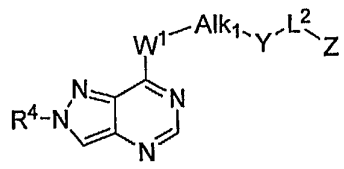
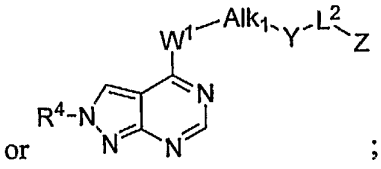
Z is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl or heteroaryl moiety.

[0237] Other exemplary combinations are illustrated by compounds of the following subgroups **I** through **XVI**:

[0238] I. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



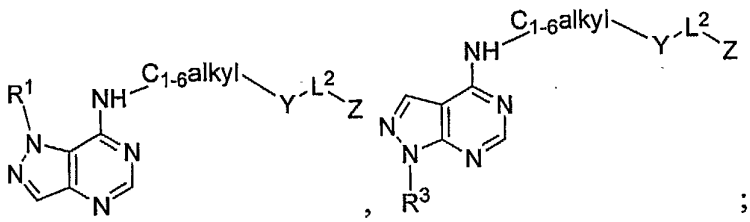
(SP 1) **(SP 2)**

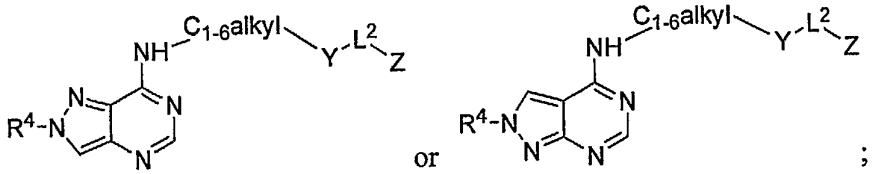
(SP 3) (SP 4)

wherein R^1, R^3, R^4, L^2, Y and Z are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; and Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl..

[0239] In certain embodiments, compounds of the invention have one of the structures **(SP 1^A)** through **(SP 4^A)** below:



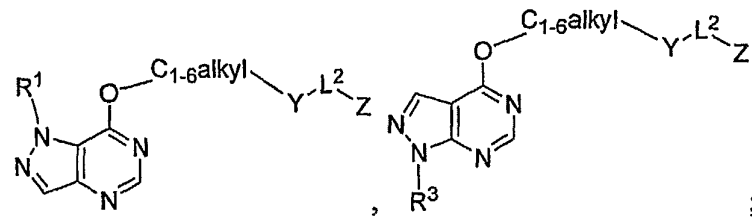
(SP 1^A) (SP 2^A)



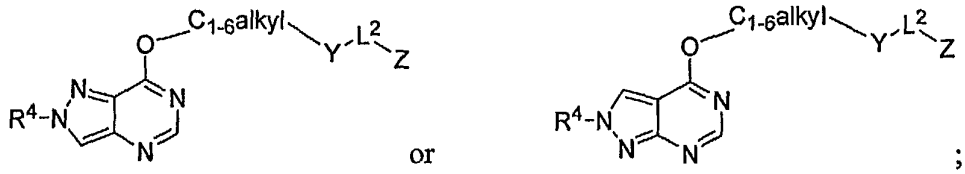
(SP 3^A) (SP 4^A)

wherein the C_{1-6}alkyl moiety may be substituted or unsubstituted.

[0240] In certain embodiments, compounds of the invention have one of the structures **(1^B)** through **(4^B)** below:



(SP 1^B) (SP 2^B)

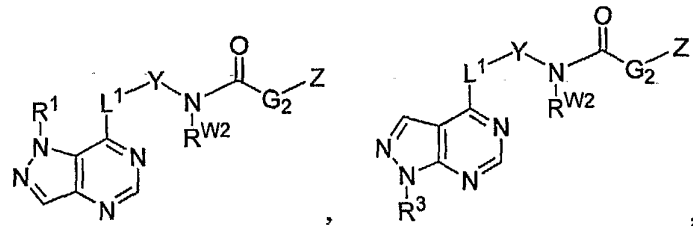


(SP 3^B) (SP 4^B)

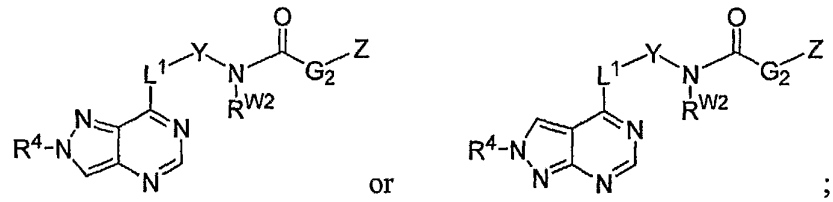
wherein the $C_{1\text{-}6}$alkyl moiety may be substituted or unsubstituted.

[0241] In certain embodiments, for compounds of formulae (1^A)-(4^A) and (1^B)-(4^B), the $C_{1\text{-}6}$alkyl moiety is a substituted or unsubstituted C_2alkyl moiety. In certain exemplary embodiments, the $C_{1\text{-}6}$alkyl moiety is $-CH_2CH_2-$.

[0242] II. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



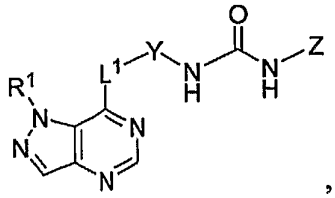
(SP 5) (SP 6)



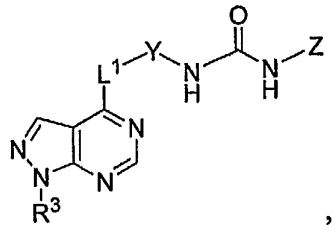
(SP 7) (SP 8)

wherein R^1, R^3, R^4, L^1, Y and Z are as defined generally and in classes and subclasses herein; G_2 is absent, O or NR^{G2}; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

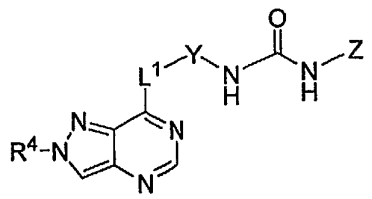
[0243] In certain embodiments, $-N(R^{W2})C(=O)G_2-$ is $-NHC(=O)-$, $-NHC(=O)O-$, or $-NHC(=O)NH-$. In certain embodiments, compounds of the invention have one of the structures **(SP 5^A)** - **(SP 8^A)** below:



(SP 5^A)

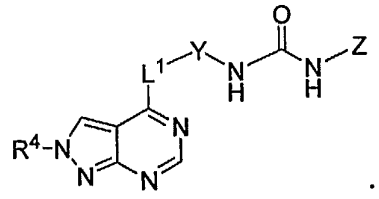


(SP 6^A)



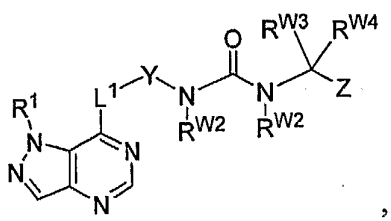
(SP 7^A)

or

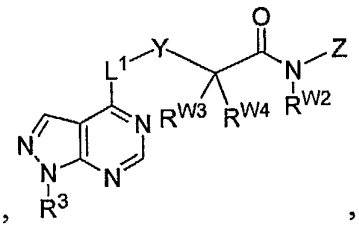


(SP 8^A)

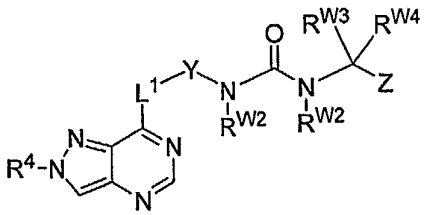
[0244] **III. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**



(SP 9)

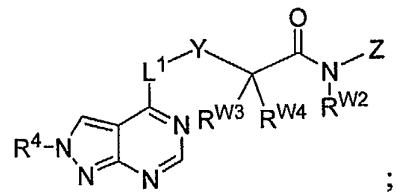


(SP 10)



(SP 11)

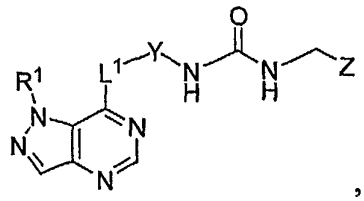
or



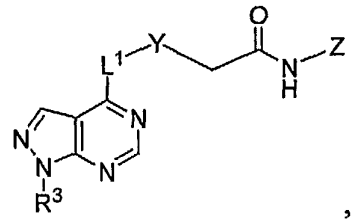
(SP 12)

wherein R^1, R^3, R^4, L^1, Y and Z are as defined generally and in classes and subclasses herein; and R^{W2}, R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

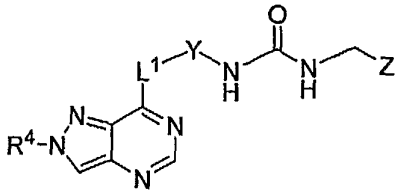
[0245] In certain embodiments, compounds of the invention have one of the structures **(SP 9^A)** - **(SP 12^A)** below:



(SP 9[A]),

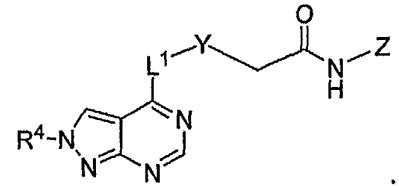


(SP 10[A]),



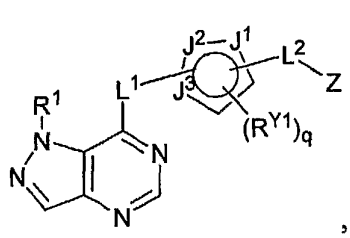
(SP 11[A])

or

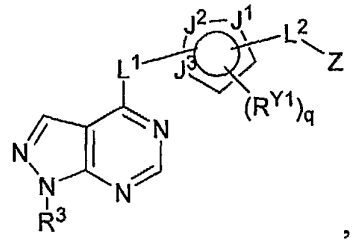


(SP 12[A]).

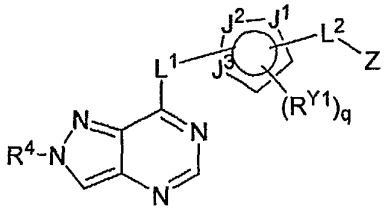
[0246] IV. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



(SP 13),

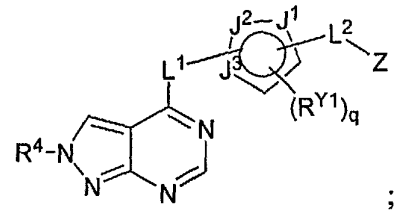


(SP 14),



(SP 15)

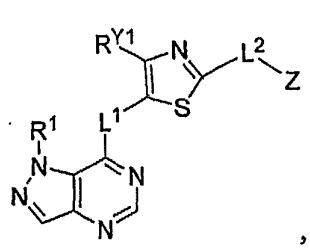
or



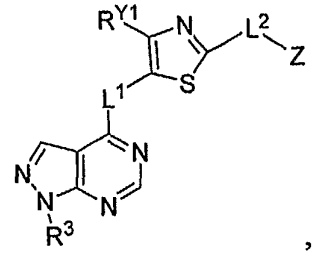
(SP 16);

wherein q is an integer from 0-2; R^1, R^3, R^4, L^1, L^2 and Z are as defined generally and in classes and subclasses herein; and J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Yl}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring.

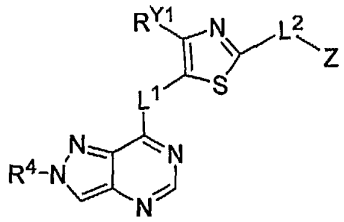
[0247] In certain embodiments, compounds of the invention have one of the structures (SP 13^{A1}) - (SP 16^{A1}) below:



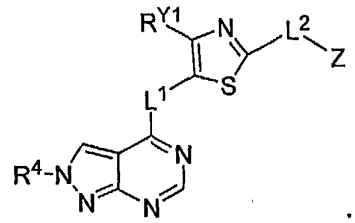
(SP 13^{A1})



(SP 14^{A1})

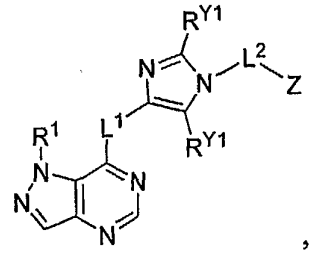


or

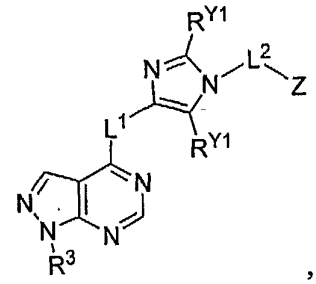


(SP 15^{A1}) (SP 16^{A1})

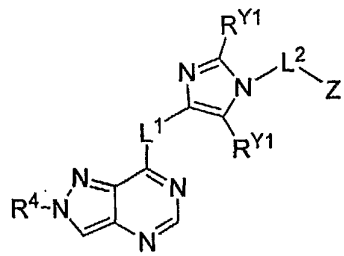
[0248] In certain embodiments, compounds of the invention have one of the structures (SP 13^{A2}) - (SP 16^{A2}) below:



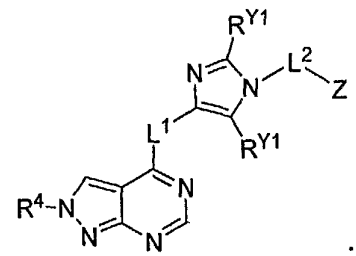
(SP 13^{A2})



(SP 14^{A2})

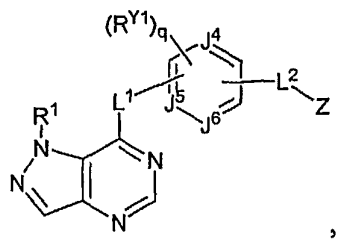


or

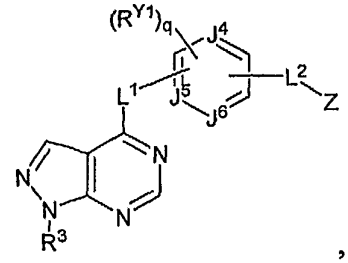


(SP 15^{A2}) (SP 16^{A2})

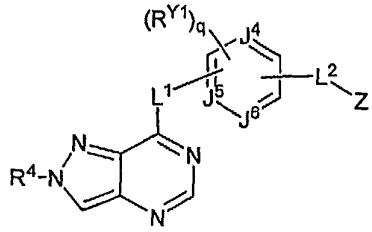
[0249] **V. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**



(SP 17)

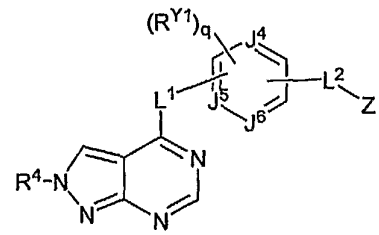


(SP 18)



(SP 19)

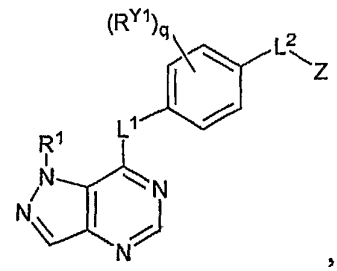
or



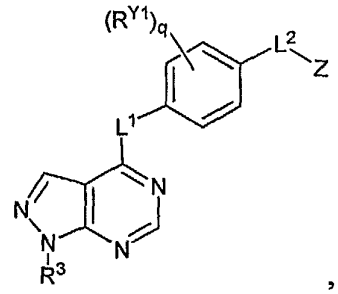
(SP 20)

wherein q is an integer from 0-3; R^1, R^3, R^4, L^1, L^2 and Z are as defined generally and in classes and subclasses herein; and J^4, J^5 and J^6 are independently N or CR^{Yl}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring.

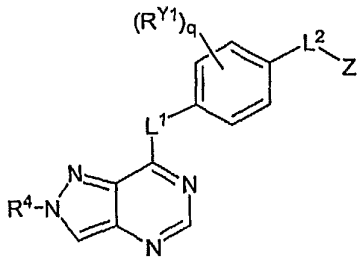
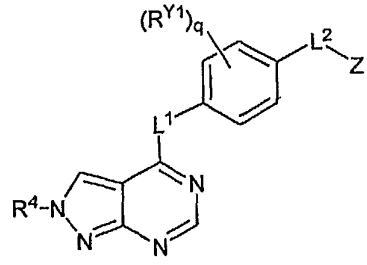
[0250] In certain embodiments, compounds of the invention have one of the structures **(SP 17^A)** - **(SP 20^A)** below:



(SP 17^A)

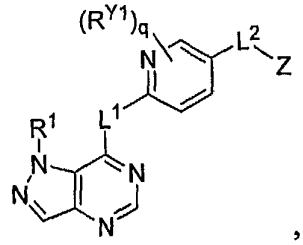
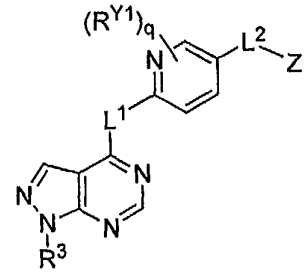


(SP 18^A)

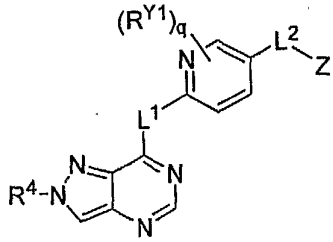
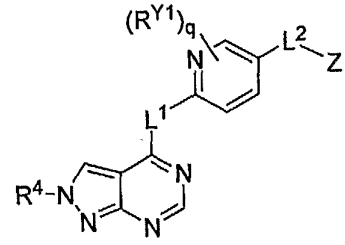



(SP 19^A) or (SP 20^A)

[0251] In certain embodiments, compounds of the invention have one of the structures (SP 17^B) - (SP 20^B) below:

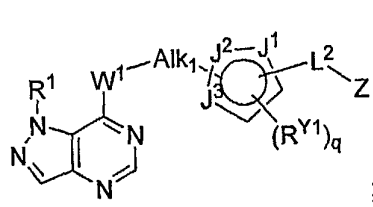
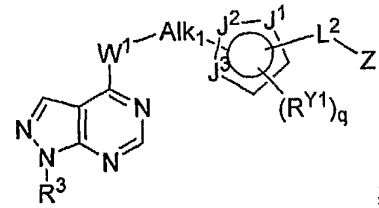



(SP 17^B) (SP 18^B)

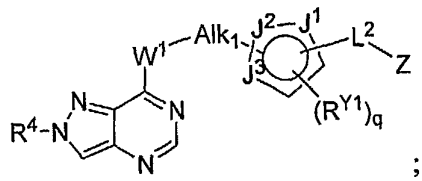
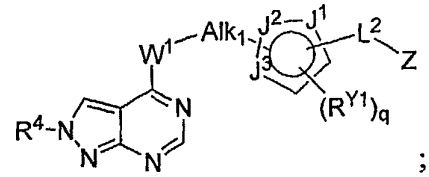



(SP 19^B) or (SP 20^B)

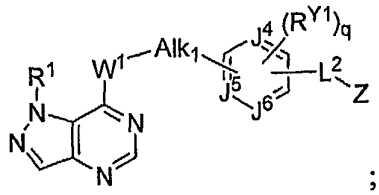
[0252] **VI. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**

(SP 21) (SP 22)

(SP 23) (SP 24)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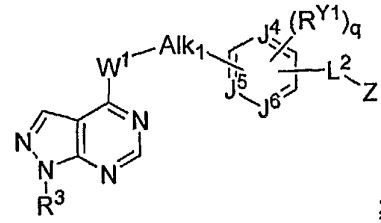
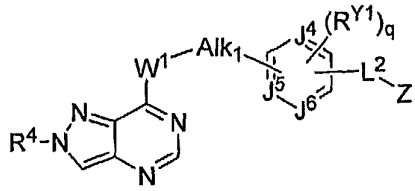
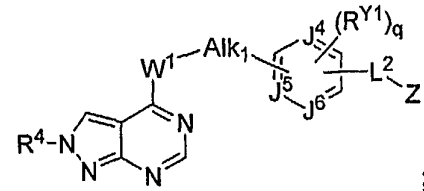
(SP 25)


;

(SP 26)


or

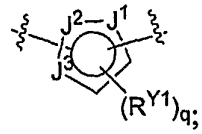
(SP 27)


;

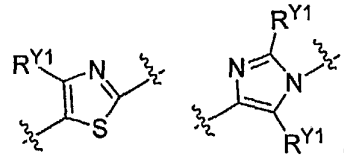
(SP 28)

wherein R^1, R^3, R^4, L^2 and Z are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Y3}, -SR^{Y3}, -$NR^{Y2}R^{Y3}$, -$SO_2NR^{Y2}R^{Y3}$, -C(=O)$NR^{Y2}R^{Y3}$, halogen, -CN, -NO_2, -C(=O)OR^{Y3}, -$N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring.

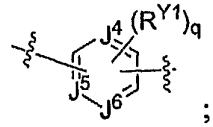
[0253] In certain embodiments, in compounds of the formulae **(SP 21)** - **(SP 24)** the 5-membered ring having the structure:



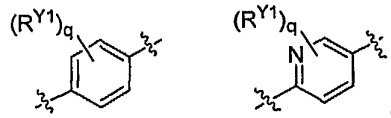
has one of the following structures:



[0254] In certain embodiments, in compounds of the formulae **(SP 25) - (SP 28)** the 6-membered ring having the structure:

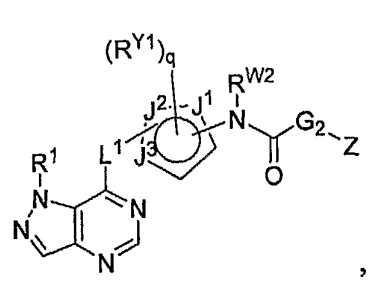


has one of the following structures:

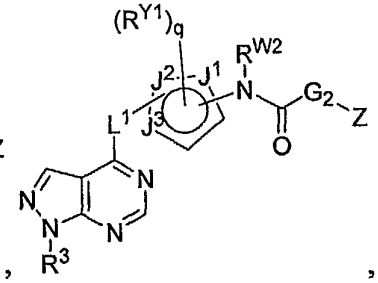


[0255] In certain embodiments, $-W^1-Alk_1-$ is $-NHC_{1-6}alkyl-$ or $-OC_{1-6}alkyl-$. In certain embodiments, $-W^1-Alk_1-$ is $-NHC_2alkyl-$ or $-OC_2alkyl-$. In certain embodiments, $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

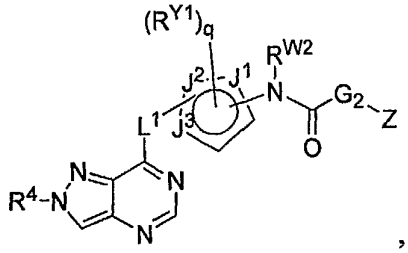
[0256] VII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):

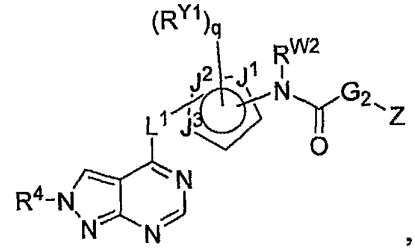


(SP 29)

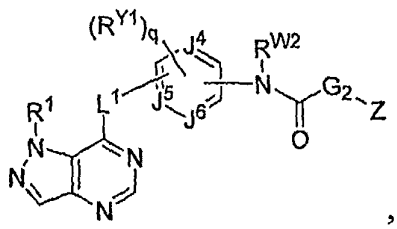


(SP 30)



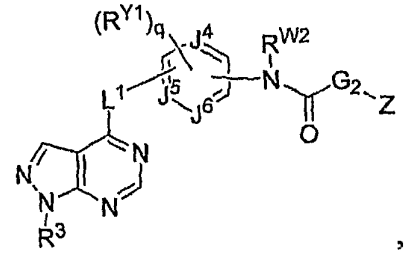


(SP 31)



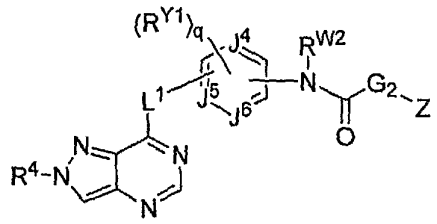
,

(SP 32)



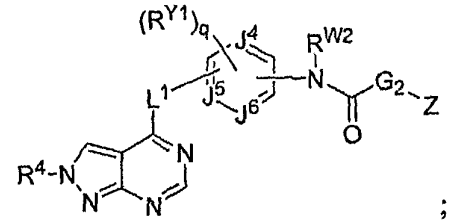
,

(SP 33)



or

(SP 34)

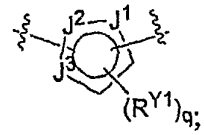


;

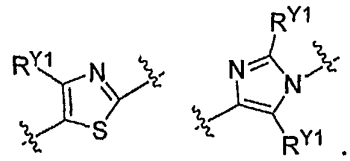
(SP 35) **(SP 36)**

wherein R^1, R^3, R^4, L^1 and Z are as defined generally and in classes and subclasses herein; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; G_2 is absent, O or NR^{G2}; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

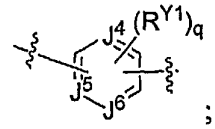
[0257] In certain embodiments, in compounds of formulae **(SP 29) - (SP 32)** the 5-membered ring having the structure:



has one of the following structures:

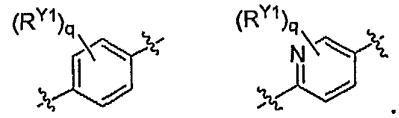


[0258] In certain embodiments, in compounds of formulae **(SP 33) - (SP 36)** the 6-membered ring having the structure:



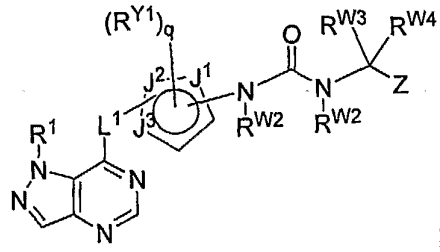
;

has one of the following structures:



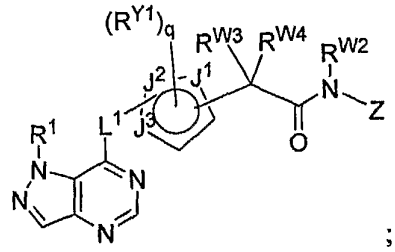
[0259] In certain embodiments, $-N(R^{W2})C(=O)G_2-$ is –NHC(=O)-, –NHC(=O)O-, or –NHC(=O)NH-.

[0260] VIII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



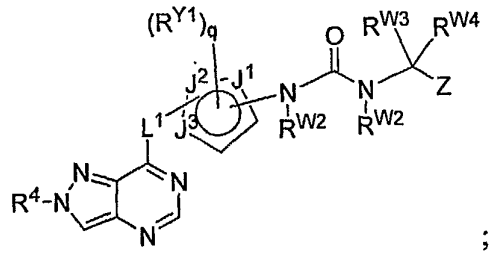
;

(SP 37^A)



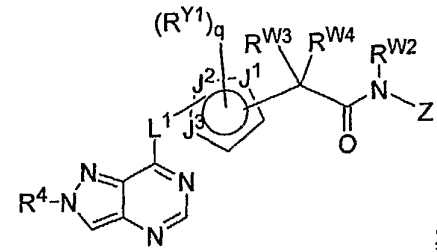
;

(SP 38^A)



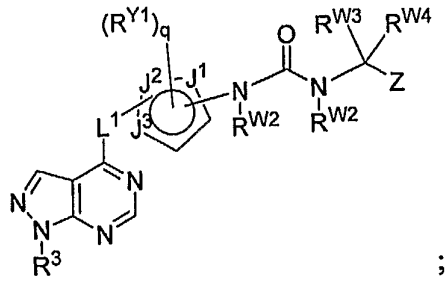
;

(SP 39^A)



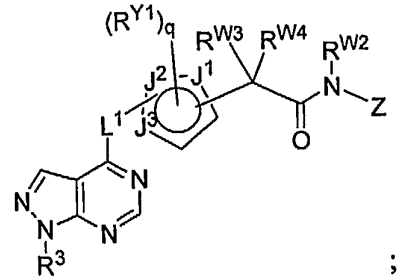
;

(SP 40^A)



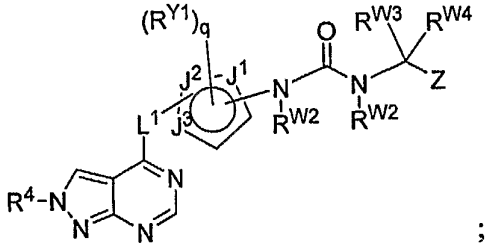
;

(SP 37^{B})



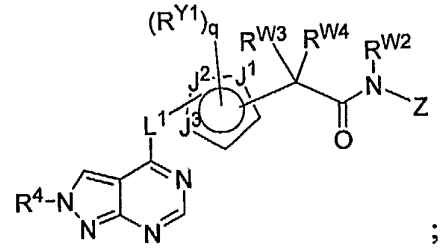
;

(SP 38^{B})



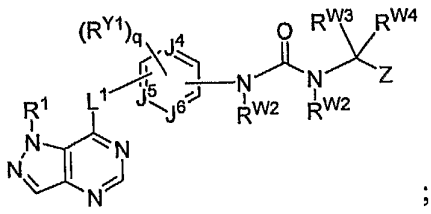
;

(SP 39^{B})



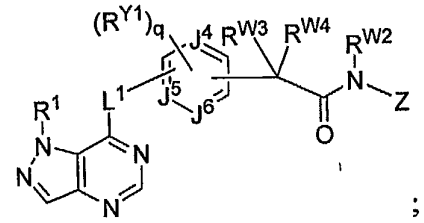
;

(SP 40^{B})



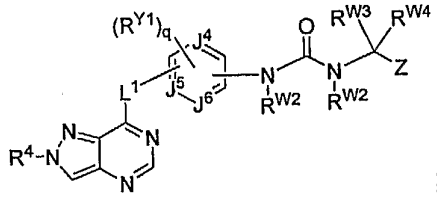
;

(SP 41^{A})



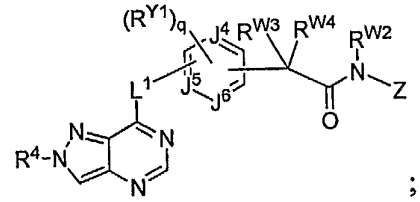
;

(SP 42^{A})



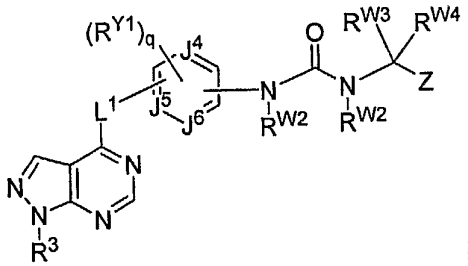
;

(SP 43^{A})



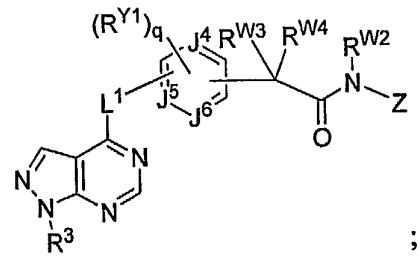
;

(SP 44^{A})



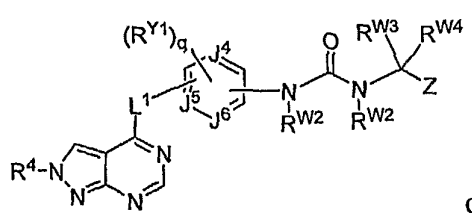
;

(SP 41^{B})

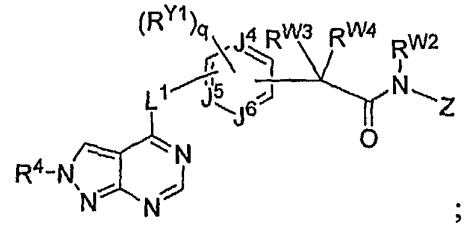


;

(SP 42^{B})



or

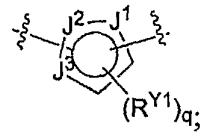


;

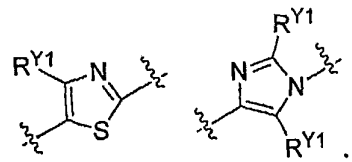
(SP 43^{B}) **(SP 44^{B})**

wherein R^1, R^3, R^4, L^1 and Z are as defined generally and in classes and subclasses herein; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; and R^{W2} is hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

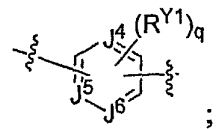
[0261] In certain embodiments, in compounds of formulae **(SP 37^{A-B})** through **(SP 40^{A-B})** the 5-membered ring having the structure:



has one of the following structures:

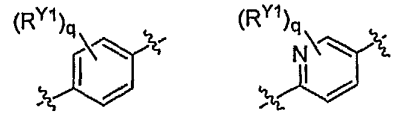


[0262] In certain embodiments, in compounds of formulae **(SP 41^{A-B})** through **(SP 44^{A-B})** the 6-membered ring having the structure:



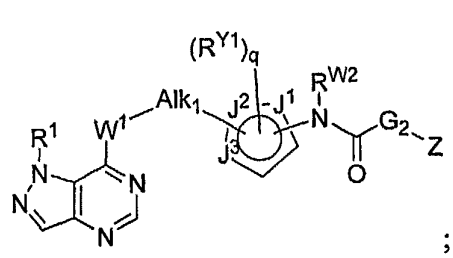
;

has one of the following structures:

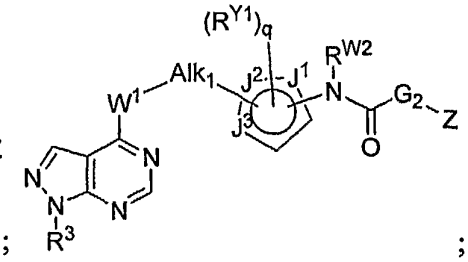


[0263] In certain embodiments, $-N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}-$ is $-NHC(=O)NHCH_2-$, and $-CR^{W3}R^{W4}C(=O)N(R^{W2})-$ is $-CH_2C(=O)NH-$.

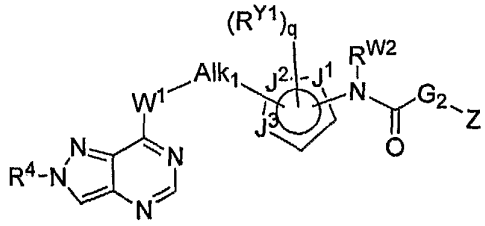
[0264] IX. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



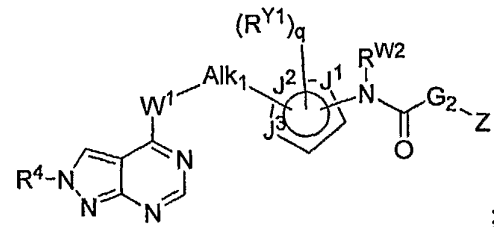
; **(SP 45)**



; **(SP 46)**



or **(SP 47)**

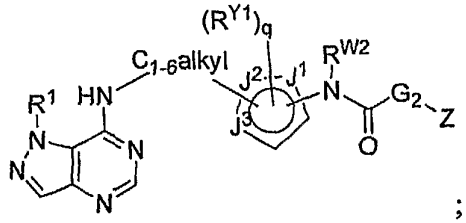


; **(SP 48)**

wherein R^1, R^3, R^4 and Z are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by $-C(=O)-$, $-CO_2-$, $-C(=O)C(=O)-$, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, $-S(=O)-$, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, $-O-$, $-S-$, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, $-CN$, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of

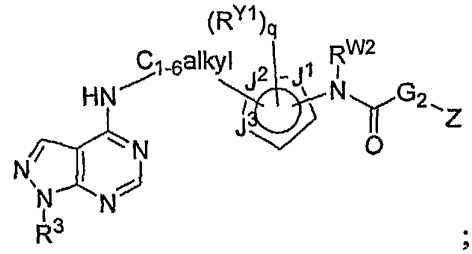
R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; G_2 is absent, O or NR^{G2}; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

[0265] In certain embodiments, compounds of this class have the structure **(SP 45^{A-B})**, **(SP 46^{A-B})**, **(SP 47^{A-B})** or **(SP 48^{A-B})** below:



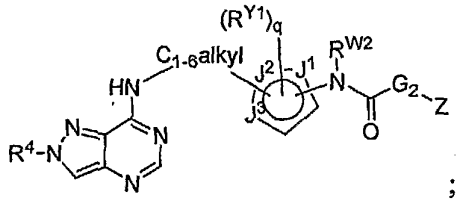
;

(SP 45^{A})



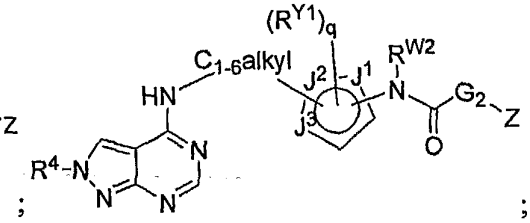
;

(SP 46^{A})



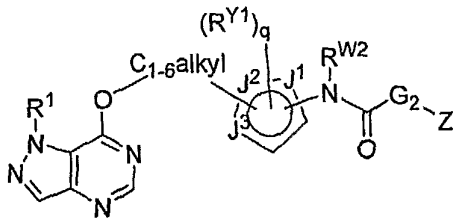
;

(SP 47^{A})



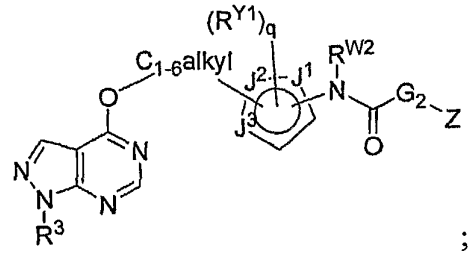
;

(SP 48^{A})



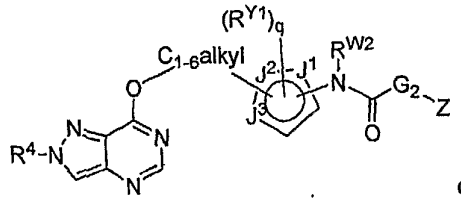
or

(SP 45^{B})



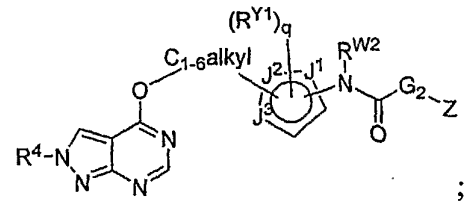
;

(SP 46^{B})



or

(SP 47^{B})



;

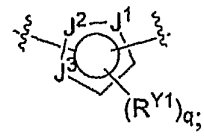
(SP 48^{B})

wherein the C_{1-6}alkyl moiety may be substituted or unsubstituted.

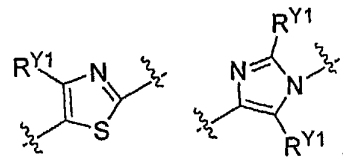
[0266] In certain embodiments, for compounds of formulae **(SP 45)-(SP 48)**, -W^1-Alk1- is–NHC_2alkyl- or –OC_2alkyl-. In certain embodiments, -W^1-Alk_1- is –$NHCH_2CH_2$-, –OCH_2CH_2- or –NH-$CH_2CH(CH_2OH)$-.

[0267] In certain embodiments, for compounds of formulae **(SP 45^{A-B})-(SP 48^{A-B})** the C_{1-6}alkyl moiety is a substituted or unsubstituted C_2alkyl moiety. In certain exemplary embodiments, the C_{1-6}alkyl moiety is -CH_2CH_2-.

[0268] In certain embodiments, in compounds of formulae **(SP 45)-(SP 48)**, and **(SP 45^{A-B})-(SP 48^{A-B})** the 5-membered ring having the structure:

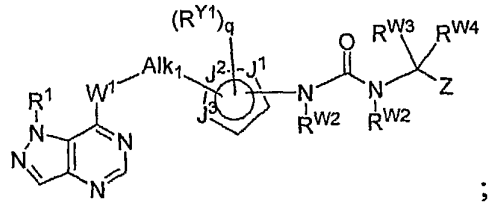


has one of the following structures:



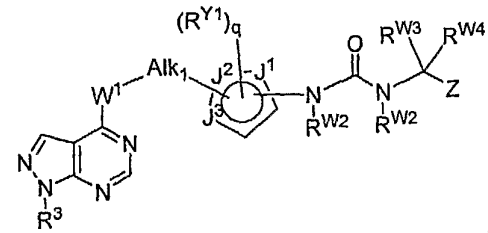
In certain embodiments, -$N(R^{W2})C(=O)G_2$- is –NHC(=O)-, –NHC(=O)O-, or –NHC(=O)NH-.

[0269] X. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



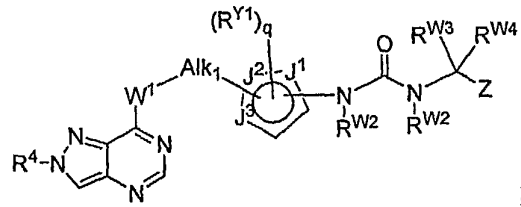
;

(SP 49^A)



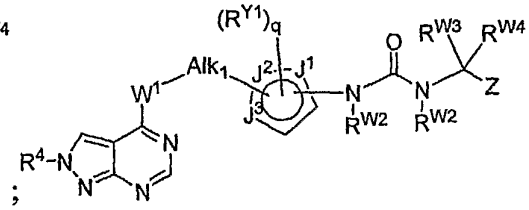
;

(SP 50^A)



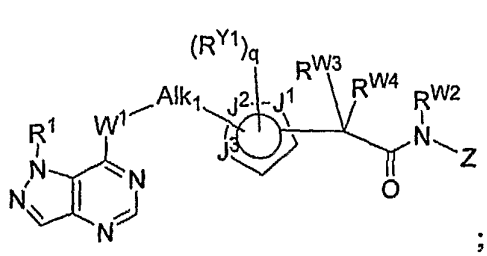
;

(SP 51^A)



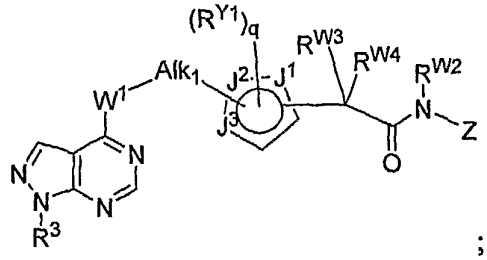
;

(SP 52^A)



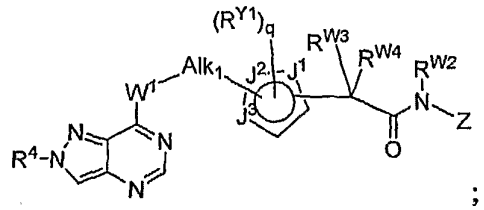
;

(SP 49^B)



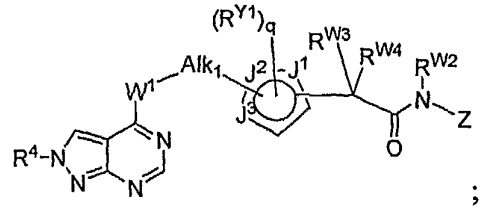
;

(SP 50^B)



;

(SP 51^B)



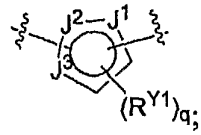
;

(SP 52^B)

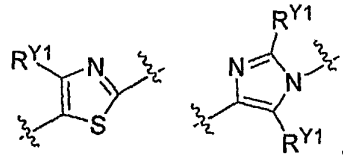
wherein R^1, R^3, R^4 and Z are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Y3}, -SR^{Y3}, -$NR^{Y2}R^{Y3}$, -$SO_2NR^{Y2}R^{Y3}$, -C(=O)$NR^{Y2}R^{Y3}$, halogen, -CN, -NO_2, -C(=O)OR^{Y3}, -N(R^{Y2})C(=O)R^{Y3}, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; and R^{W2} is hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

[0270] In certain embodiments, -W^1-Alk_1- is –NHC_{1-6}alkyl- or –OC_{1-6}alkyl-. In certain embodiments, -W^1-Alk_1- is –NHC_2alkyl- or –OC_2alkyl-. In certain embodiments, -W^1-Alk_1- is –$NHCH_2CH_2$-, –OCH_2CH_2- or –NH-$CH_2CH(CH_2OH)$-.

[0271] In certain embodiments, in compounds of the formulae **(SP 49^{A-B})** through **(SP 52^{A-B})**, the 5-membered ring having the structure:

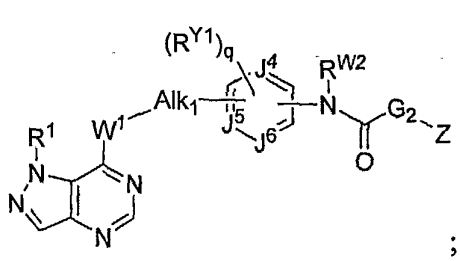


has one of the following structures:

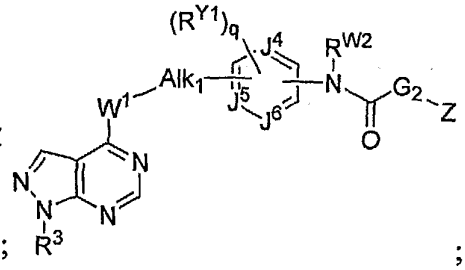


[0272] In certain embodiments, -$N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}$- is –$NHC(=O)NHCH_2$-, and -$CR^{W3}R^{W4}C(=O)N(R^{W2})$- is –$CH_2C(=O)NH$-.

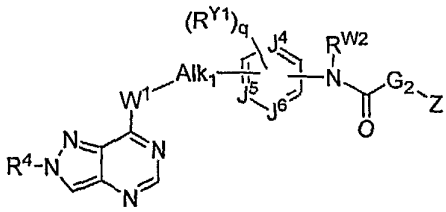
[0273] **XI. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**



(SP 53)

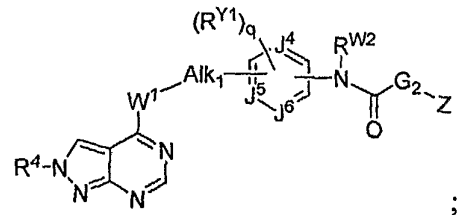


(SP 54)



(SP 55)

or

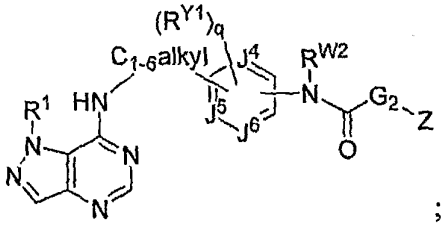


(SP 56)

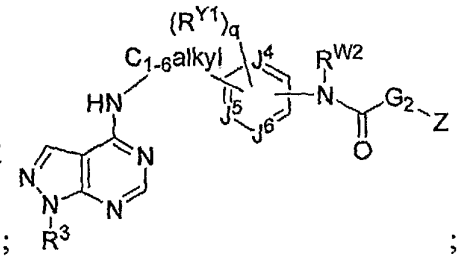
wherein R^1, R^3, R^4 and Z are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -

CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Y3}, -SR^{Y3}, -$NR^{Y2}R^{Y3}$, -$SO_2NR^{Y2}R^{Y3}$, -C(=O)$NR^{Y2}R^{Y3}$, halogen, -CN, -NO_2, -C(=O)OR^{Y3}, -N(R^{Y2})C(=O)R^{Y3}, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; G_2 is absent, O or NR^{G2}; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

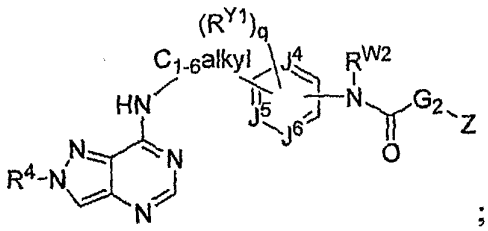
[0274] In certain embodiments, the compounds have the following structures:



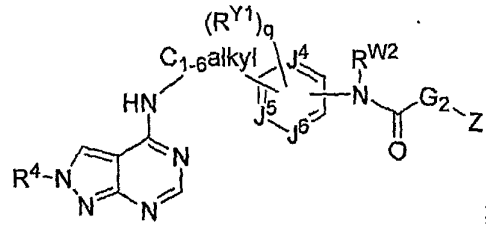
; **(SP 53^A)**



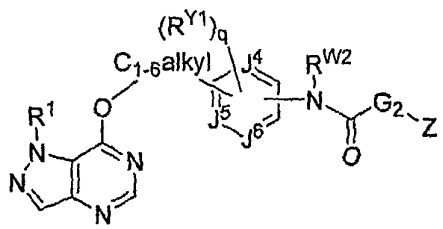
; **(SP 54^A)**



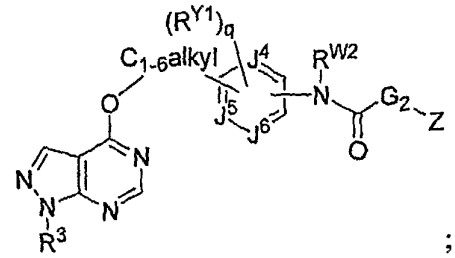
; **(SP 55^A)**



; **(SP 56^A)**

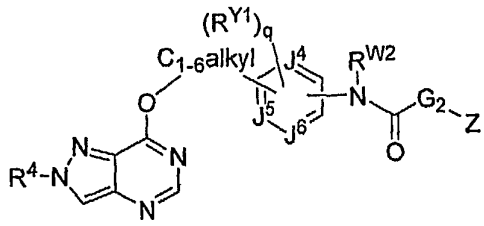


or



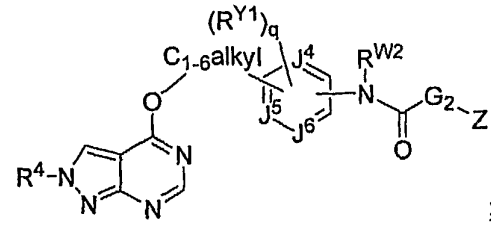
;

(SP 53^{B})



or

(SP 54^{B})



;

(SP 55^{B})

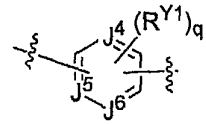
(SP 56^{B})

wherein the C_{1-6}alkyl moiety may be substituted or unsubstituted.

[0275] In certain embodiments, for compounds of formulae **(SP 53)-(SP 56)**, -W^1-Alk1- is–NHC_2alkyl- or –OC_2alkyl-. In certain embodiments, -W^1-Alk_1- is –$NHCH_2CH_2$-, –OCH_2CH_2- or –NH-$CH_2CH(CH_2OH)$-.

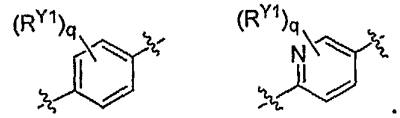
[0276] In certain embodiments, for compounds of formulae **(SP 53^{A-B})** through **(SP 56^{A-B})**, the C_{1-6}alkyl moiety is a substituted or unsubstituted C_2alkyl moiety. In certain exemplary embodiments, the C_{1-6}alkyl moiety is -CH_2CH_2-.

[0277] In certain embodiments, in compounds of the formulae **(SP 53)-(SP 56)** and **(SP 53^{A-B})** through **(SP 56^{A-B})**, the 6-membered ring having the structure:



;

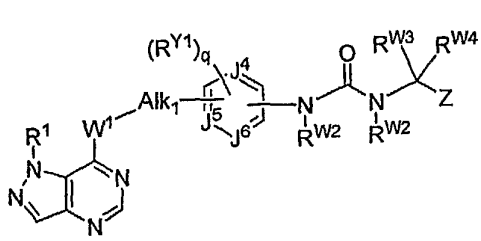
has one of the following structures:



.

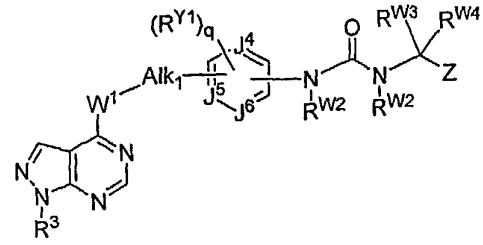
In certain embodiments, -$N(R^{W2})C(=O)G_2$- is –NHC(=O)-, –NHC(=O)O-, or –NHC(=O)NH-.

[0278] XII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



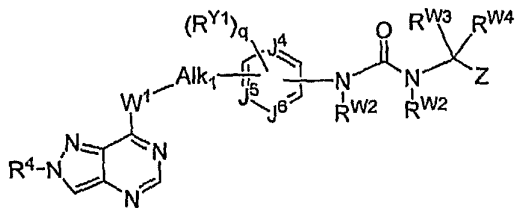
;

(SP 57^{A})

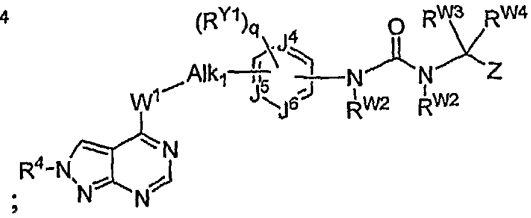


;

(SP 58^{A})

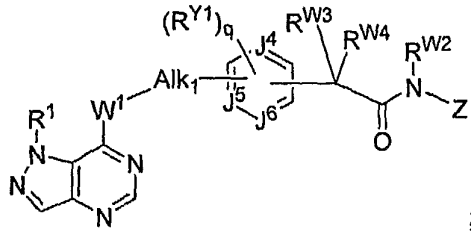


;



;

(SP 59^A) **(SP 60^A)**



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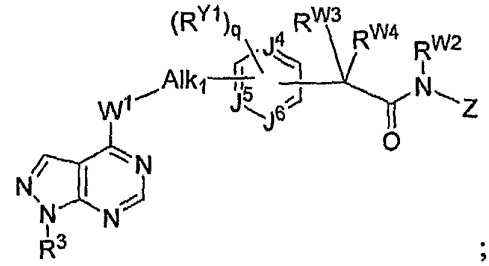
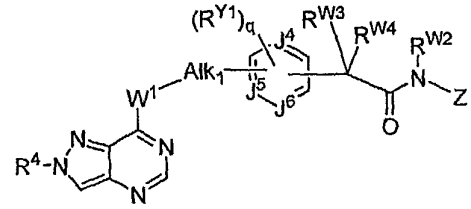
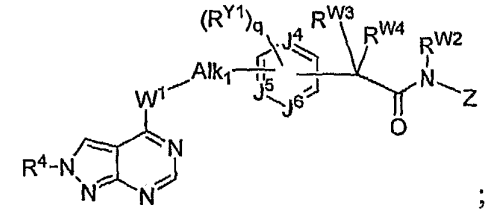


;

(SP 57^B) **(SP 58^B)**



or



;

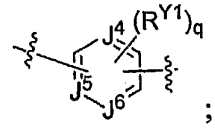
(SP 59^B) **(SP 60^B)**

wherein R^1, R^3, R^4 and Z are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Y3}, -SR^{Y3}, -$NR^{Y2}R^{Y3}$, -$SO_2NR^{Y2}R^{Y3}$, -C(=O)$NR^{Y2}R^{Y3}$, halogen, -CN, -NO_2, -C(=O)OR^{Y3}, -N(R^{Y2})C(=O)R^{Y3}, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -

(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; and R^{W2} is hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

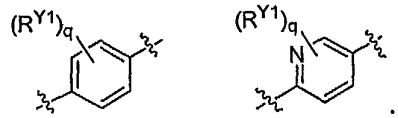
[0279] In certain embodiments, $-W^1-Alk_1-$ is $-NHC_{1-6}alkyl-$ or $-OC_{1-6}alkyl-$. In certain embodiments, $-W^1-Alk_1-$ is $-NHC_2alkyl-$ or $-OC_2alkyl-$. In certain embodiments, $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

[0280] In certain embodiments, in compounds of the formulae **(SP 57^{A-B}) - (SP 60^{A-B})** the 6-membered ring having the structure:



;

has one of the following structures:

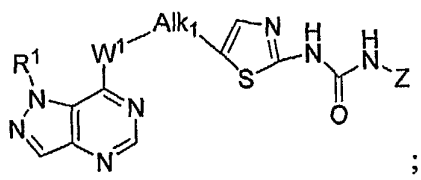


.

[0281] In certain embodiments, $-N(R^{W2})C(=O)G_2-$ is $-NHC(=O)-$, $-NHC(=O)O-$, or $-NHC(=O)NH-$.

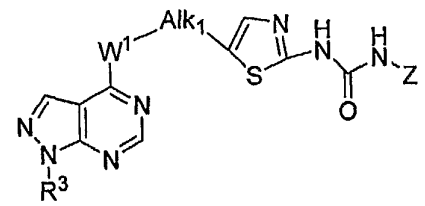
[0282] In certain embodiments, $-N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}-$ is $-NHC(=O)NHCH_2-$, and $-CR^{W3}R^{W4}C(=O)N(R^{W2})-$ is $-CH_2C(=O)NH-$.

[0283] XIII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):

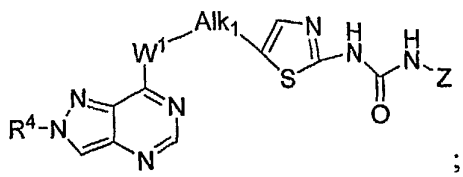


;

(SP 61^A)

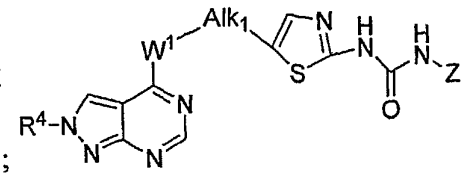


(SP 62^A)

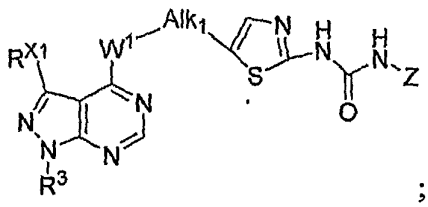


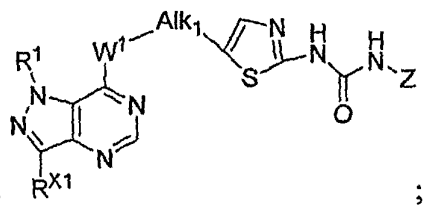
;

(SP 63^A)



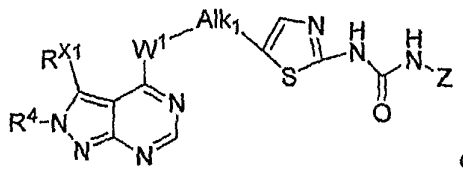
(SP 64^A)

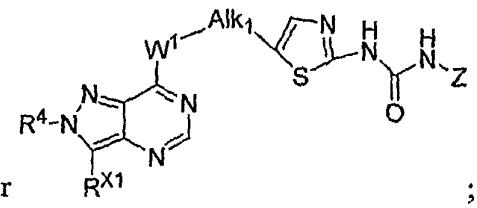


; 

;

(SP 61[B]) (SP 62[B])



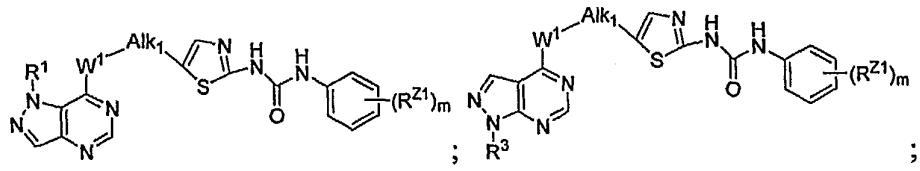
or 

;

(SP 63[B]) (SP 64[B])

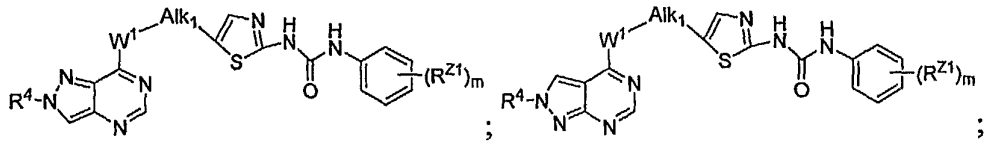
wherein R^1, R^3, R^4 and R^{X1} are as defined generally and in classes and subclasses herein; Z is an aryl, heteroaryl or heterocyclic moiety; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, -OC(=O)-, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, -S(=O)-, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; and each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

[0284] XIV. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



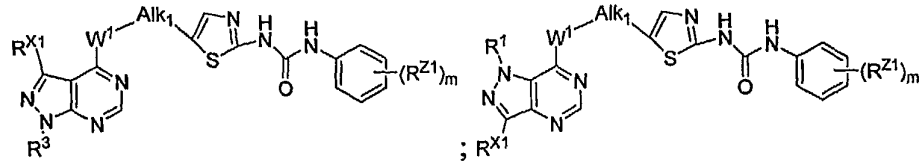
; ;

(SP 65^A) (SP 66^A)

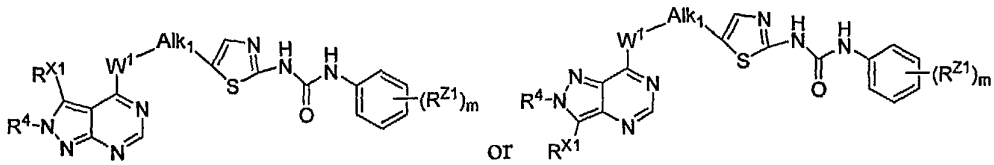


; ;

(SP 67^A) (SP 68^A)



(SP 65^B) (SP 66^B)



(SP 67^B) (SP 68^B)

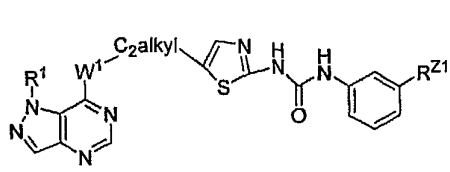
wherein R^1, R^3, R^4 and R^{X1} are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Z2}, -SR^{Z2}, -$NR^{Z2}R^{Z3}$, -$SO_2NR^{Z2}R^{Z3}$, -SO_2R^{Z1}, -C(=O)$NR^{Z2}R^{Z3}$, halogen, -CN, -NO_2, -C(=O)OR^{Z3}, -N(R^{Z2})C(=O)R^{Z3}, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -

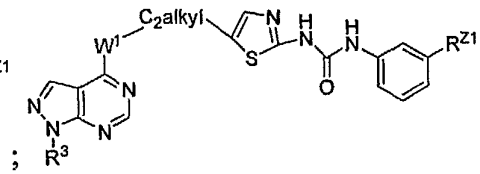
(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

[0285] In certain embodiments, for compounds of groups **XIII** and **XIV**, -W^1-Alk_1- is –NHC_{1-6}alkyl- or –OC_{1-6}alkyl-; wherein the C_{1-6}alkyl moiety may be substituted or unsubstituted. In certain embodiments, -W^1-Alk1- is–NHC_2alkyl- or –OC_2alkyl-. In certain embodiments, -W^1-Alk_1- is –$NHCH_2CH_2$-, –OCH_2CH_2- or –NH-$CH_2CH(CH_2OH)$-.

[0286] In certain embodiments, for compounds of group **XIV**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is Cl, F, methyl or $–CF_3$. In certain embodiments, m is 1 and R^{Z1} is lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is $–CF_3$. In certain embodiments, m is 2 and each occurrence of R^{Z1} is independently CN, Cl, F, methyl or $–CF_3$. In certain embodiments, m is 2 and each occurrence of R^{Z1} is CN, Cl, F, methyl or $–CF_3$. In certain embodiments, m is 2 and one occurrence of R^{Z1} is Cl, F, methyl or $–CF_3$ and the other is CN.

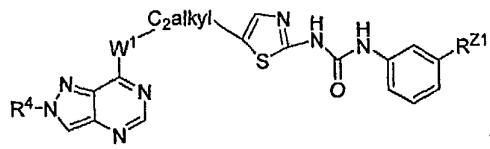
[0287] In certain embodiments, compounds of group **XIV** have the structure:

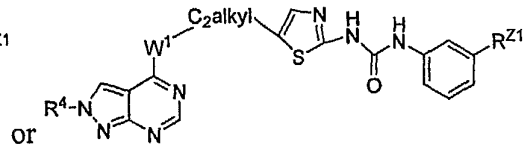


; 

;

(SP 65^{A1}) **(SP 66^{A1})**



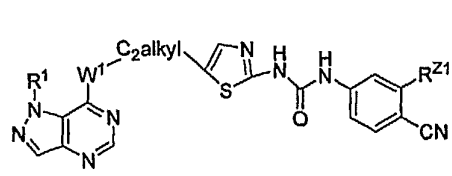
or 

;

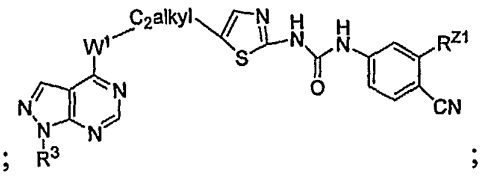
(SP 67^{A1}) **(SP 68^{A1})**

wherein W^1 is NH or O; the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $–CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{Z1} is halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{Z1} is Cl, F, methyl or $–CF_3$. In certain exemplary embodiments, R^{Z1} is Cl or $–CF_3$. In certain exemplary embodiments, the C_2alkyl moiety is $–CH_2CH_2$-.

[0288] In certain embodiments, compounds of group **XIV** have the structure:

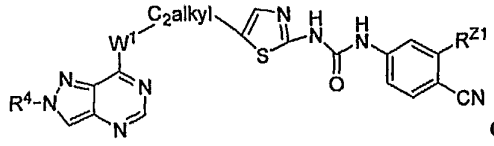


;

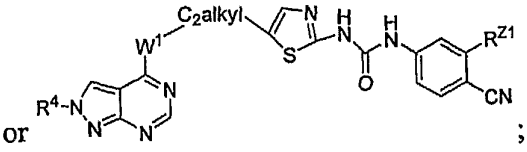


;

(SP 65^{A2}) (SP 66^{A2})



or

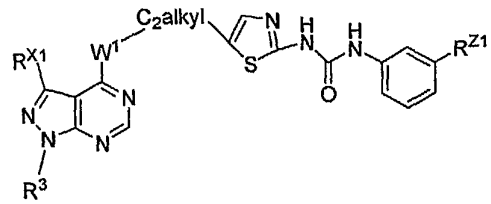


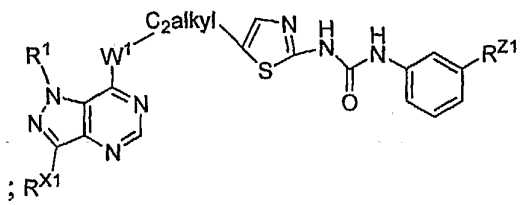
;

(SP 67^{A2}) (SP 68^{A2})

wherein W^1 is NH or O; the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{Z1} is halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{Z1} is Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, R^{Z1} is Cl or $-CF_3$. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

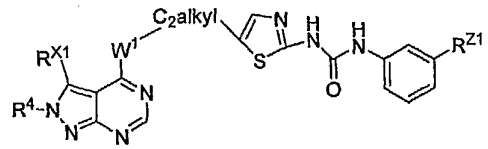
[0289] In certain embodiments, compounds of group **XIV** have the structure:



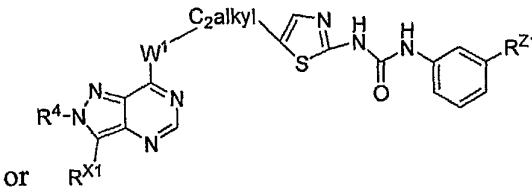


;

(SP 65^{B1}) (SP 66^{B1})



or

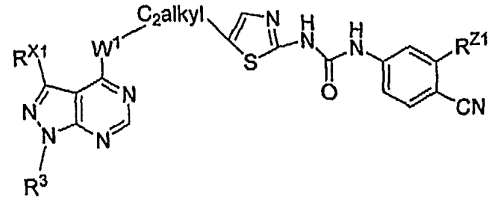


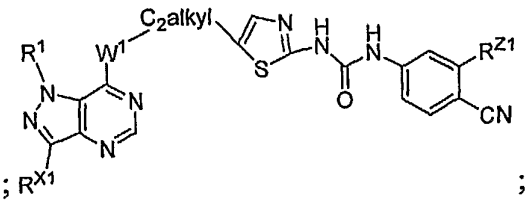
;

(SP 67^{B1}) (SP 68^{B1})

wherein W^1 is NH or O; the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl; R^{Z1} is Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

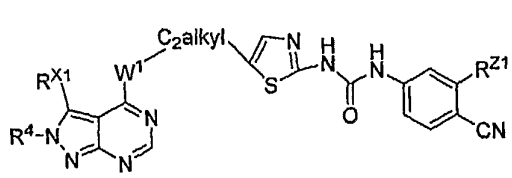
[0290] In certain embodiments, compounds of group **XIV** have the structure:

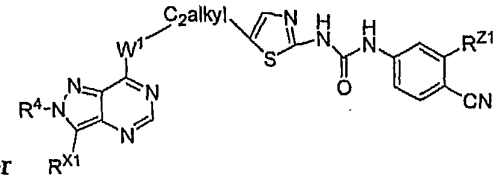


; 

;

(SP 65^{B2}) (SP 66^{B2})



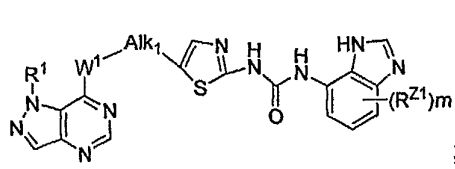
or 

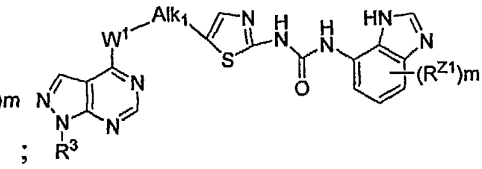
;

(SP 67^{B2}) (SP 68^{B2})

wherein W^1 is NH or O; the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl; and R^{Z1} is Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

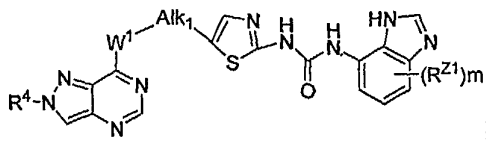
[0291] XV. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):

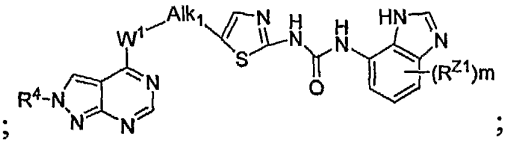


; 

;

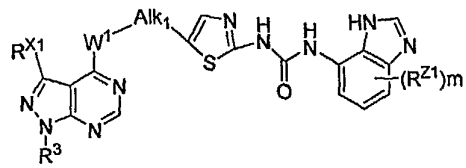
(SP 69^{A}) (SP 70^{A})

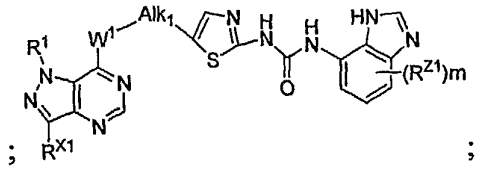


; 

;

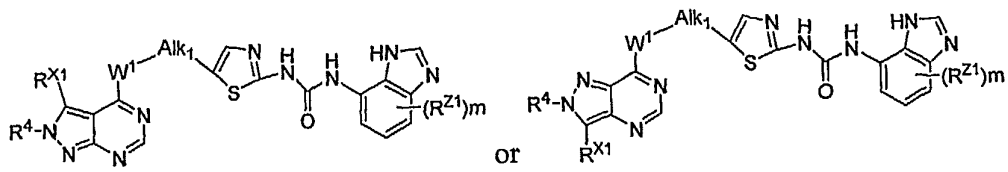
(SP 71^{A}) (SP 72^{A})



; 

;

(SP 69^{B}) (SP 70^{B})



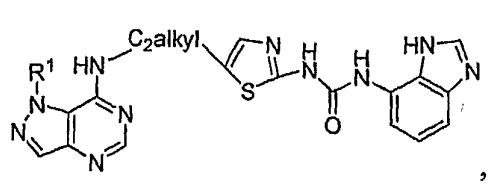
(SP 71^B) or (SP 72^B)

wherein R^1, R^3, R^4 and R^{X1} are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Z2}, -SR^{Z2}, -$NR^{Z2}R^{Z3}$, -$SO_2NR^{Z2}R^{Z3}$, -SO_2R^{Z1}, -C(=O)$NR^{Z2}R^{Z3}$, halogen, -CN, -NO_2, -C(=O)OR^{Z3}, -N(R^{Z2})C(=O)R^{Z3}, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

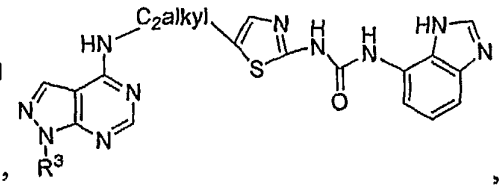
[0292] In certain embodiments, for compounds of group **XV**, -W^1-Alk_1- is –NHC_{1-6}alkyl- or –OC_{1-6}alkyl-. In certain embodiments, -W^1-Alk1- is–NHC_2alkyl- or –OC_2alkyl-. In certain embodiments, -W^1-Alk_1- is –$NHCH_2CH_2$-, –OCH_2CH_2- or –NH-$CH_2CH(CH_2OH)$-.

[0293] In certain embodiments, for compounds of group **XV**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 0.

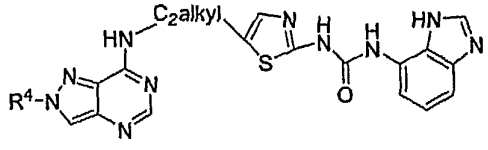
[0294] In certain embodiments, compounds of group **XV** have the structure:



(SP 69^{A1})

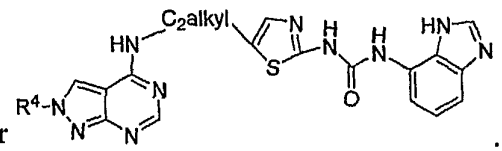


(SP 70^{A1})



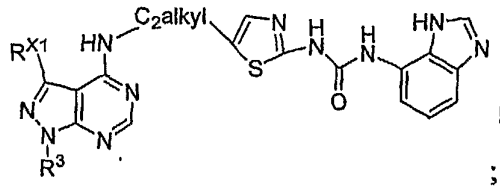
(SP 71^{A1})

or

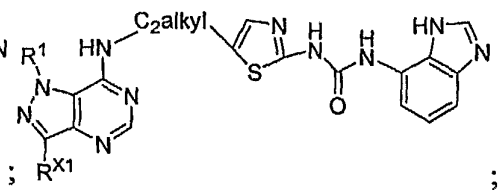


(SP 72^{A1})

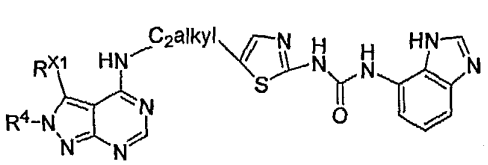
[0295] In certain embodiments, compounds of group **XV** have the structure:



(SP 69^{B1})

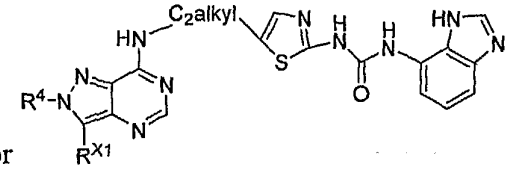


(SP 70^{B1})



(SP 71^{B1})

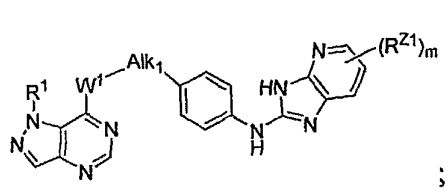
or



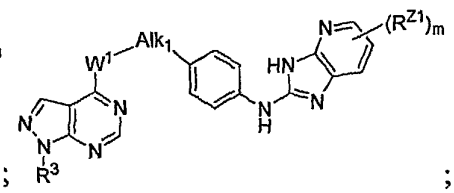
(SP 72^{B1})

In certain embodiments, in the compounds having one of the structures **(SP 69^{A1})** through **(SP 72^{A1})** and **(SP 69^{B1})** through **(SP 72^{B1})** above, the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; and R^{X1} is hydrogen, lower alkyl or heterocyclyl. In certain exemplary embodiments, R^1, R^3 and R^4 are independently hydrogen or methyl; and R^{X1} is hydrogen, methyl or thienyl. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

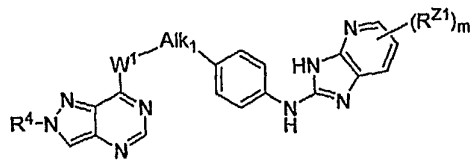
[0296] XVI. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



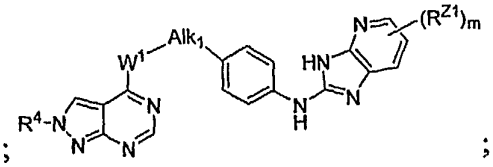
(SP 72^{A})



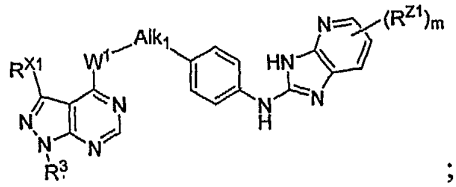
(SP 73^{A})


;

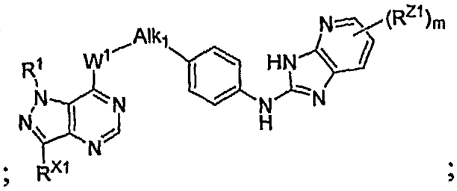
(SP 74^{A})


;

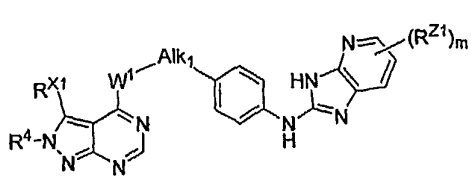
(SP 75^{A})

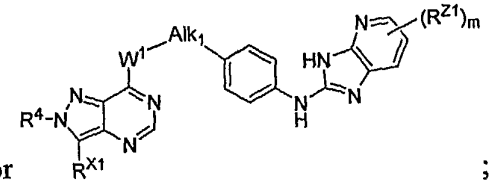

;

(SP 72^{B})


;

(SP 73^{B})


or


;

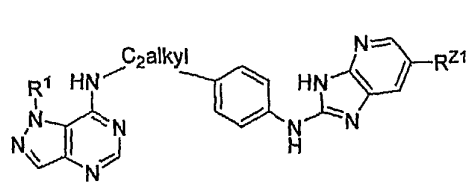
(SP 74^{B}) (SP 75^{B})

wherein R^1, R^3, R^4 and R^{X1} are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Z2}, -SR^{Z2}, -$NR^{Z2}R^{Z3}$, -$SO_2NR^{Z2}R^{Z3}$, -SO_2R^{Z1}, -C(=O)$NR^{Z2}R^{Z3}$, halogen, -CN, -NO_2, -C(=O)OR^{Z3}, -N(R^{Z2})C(=O)R^{Z3}, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

[0297] In certain embodiments, for compounds of group **XVI**, -W^1-Alk_1- is –$NHC_{1\text{-}6}$alkyl- or –$OC_{1\text{-}6}$alkyl-. In certain embodiments, -W^1-Alk1- is–NHC_2alkyl- or –OC_2alkyl-. In certain embodiments, -W^1-Alk_1- is –$NHCH_2CH_2$-, –OCH_2CH_2- or –NH-$CH_2CH(CH_2OH)$-.

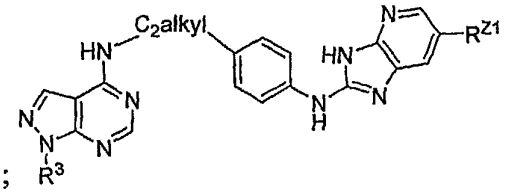
[0298] In certain embodiments, for compounds of group **XVI**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is Cl, F, methyl or $-CF_3$. In certain embodiments, m is 1 and R^{Z1} is lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is $-CF_3$.

[0299] In certain embodiments, compounds of group **XVI** have the structure:

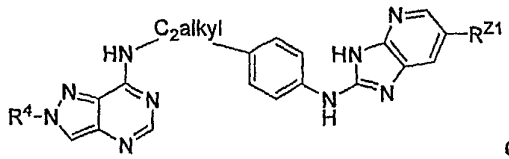


(SP 72^{A1})

;

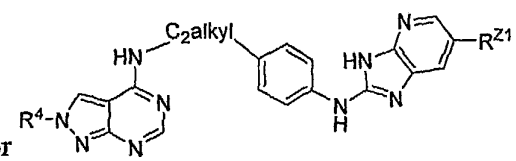


(SP 73^{A1})



(SP 74^{A1})

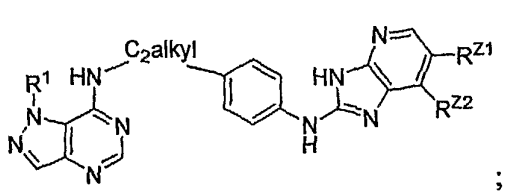
or



(SP 75^{A1})

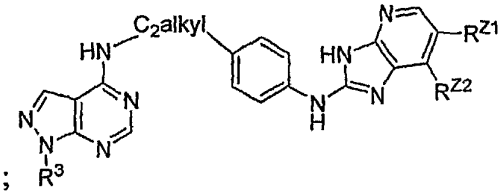
wherein the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{Z1} is halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{Z1} is Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2$-.

[0300] In certain embodiments, compounds of group **XVI** have the structure:

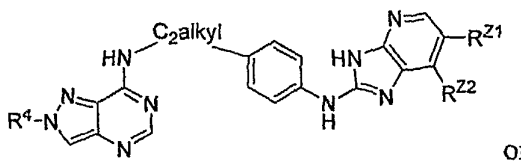


(SP 72^{A2})

;

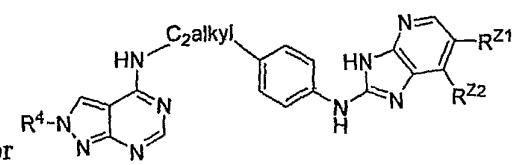


(SP 73^{A2})



(SP 74^{A1})

or

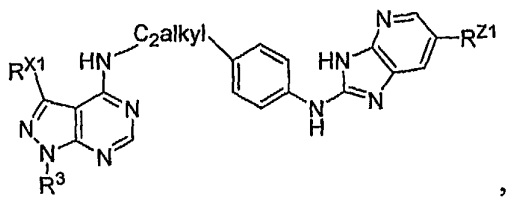


(SP 75^{A1})

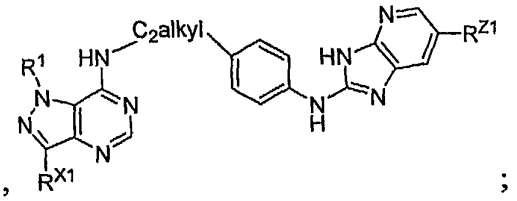
(SP 74^{A2}) (SP 75^{A2})

wherein the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{Z1} and R^{Z2} are independently halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{Z1} and R^{Z2} are independently Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$. In certain embodiments, R^{Z1} and R^{Z2} are each Cl, F, methyl or $-CF_3$.

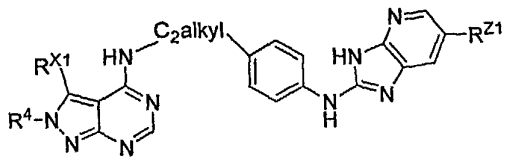
[0301] In certain embodiments, compounds of group **XVI** have the structure:



(SP 72^{B1})

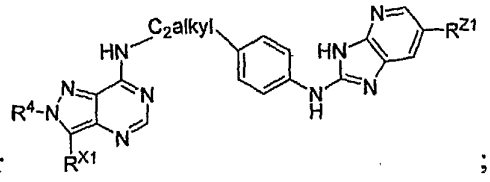


(SP 73^{B1})



(SP 74^{B1})

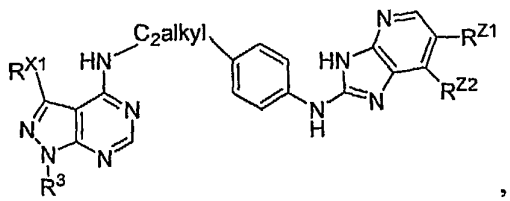
or



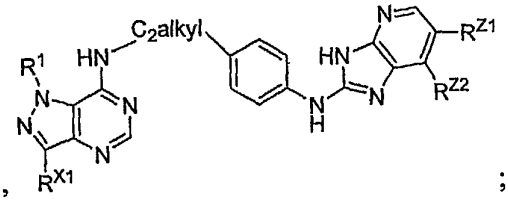
(SP 75^{B1})

wherein the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl; and R^{Z1} is Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

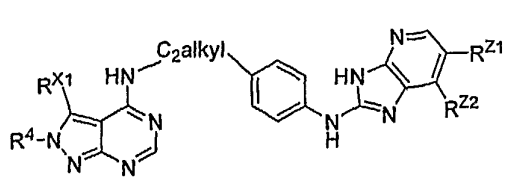
[0302] In certain embodiments, compounds of group **XVI** have the structure:



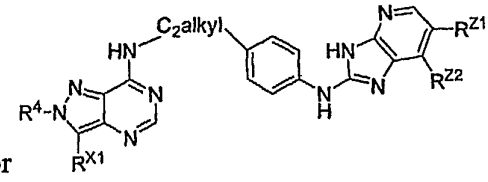
(SP 72^{B2})



(SP 73^{B2})



or

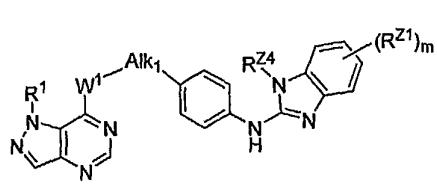


;

(SP 74^{B2}) (SP 75^{B2})

wherein the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} and R^{Z2} are independently halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl; and R^{Z1} and R^{Z2} are independently Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$. In certain embodiments, R^{Z1} and R^{Z2} are each Cl, F, methyl or $-CF_3$.

[0303] XVII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



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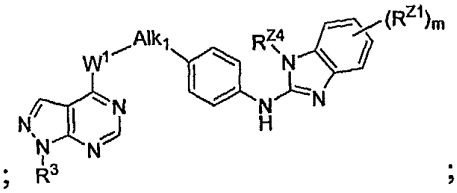
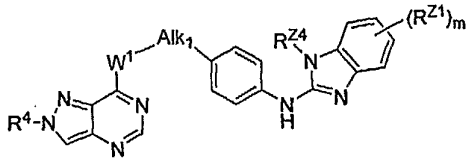


;

(SP 76^A) (SP 77^A)



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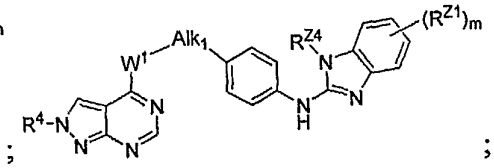
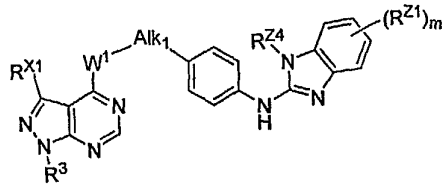
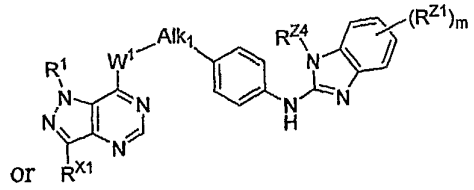


;

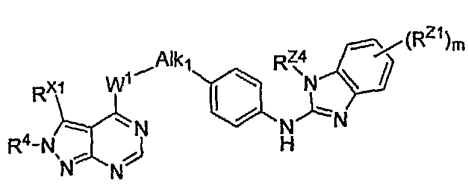
(SP 78^A) (SP 79^A)



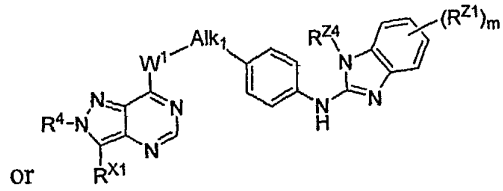
or



(SP 76^B) (SP 77^B)



or



(SP 78^B) (SP 79^B)

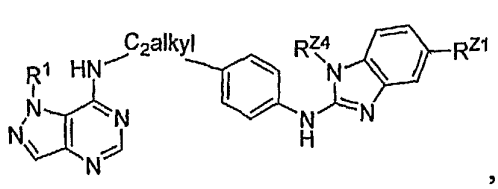
wherein R^1, R^3, R^4 and R^{X1} are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Z2}, -SR^{Z2}, -$NR^{Z2}R^{Z3}$, -$SO_2NR^{Z2}R^{Z3}$, -SO_2R^{Z1}, -C(=O)$NR^{Z2}R^{Z3}$, halogen, -CN, -NO_2, -C(=O)OR^{Z3}, -N(R^{Z2})C(=O)R^{Z3}, and wherein each occcurrence of R^{Z2}, R^{Z3} and R^{Z4} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

[0304] In certain embodiments, for compounds of group **XVII**, -W^1-Alk_1- is –NHC_{1-6}alkyl- or –OC_{1-6}alkyl-. In certain embodiments, -W^1-Alk1- is–NHC_2alkyl- or –OC_2alkyl-. In certain embodiments, -W^1-Alk_1- is –$NHCH_2CH_2$-, –OCH_2CH_2- or –NH-$CH_2CH(CH_2OH)$-.

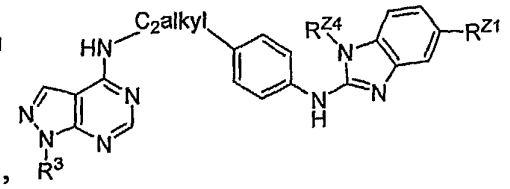
[0305] In certain embodiments, for compounds of group **XVII**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is Cl, F, methyl or –CF_3. In certain embodiments, m is 1 and R^{Z1} is lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is –CF_3. In certain embodiments, m is 2 and each occurrence of R^{Z1} is independently Cl, F, methyl or –CF_3. In certain embodiments, m is 2 and each occurrence of R^{Z1} is Cl, F, methyl or –CF_3. In certain embodiments, m is 2 and each occurrence of R^{Z1} is F.

[0306] In certain embodiments, for compounds of group **XVII**, R^{Z4} is hydrogen, or lower alkyl. In certain embodiments, R^{Z4} is lower alkyl. In certain embodiments, R^{Z4} is isopropyl.

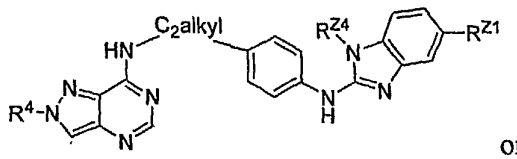
[0307] In certain embodiments, compounds of group **XVII** have the structure:



(SP 76^{A1})

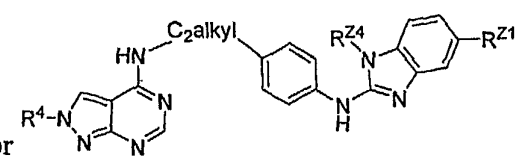


(SP 77^{A1})



(SP 78^{A1})

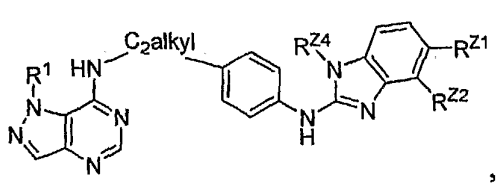
or



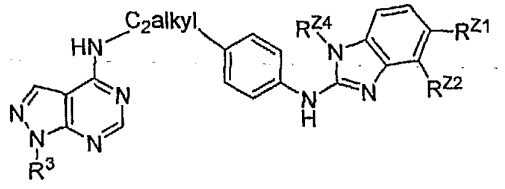
(SP 79^{A1})

wherein the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{Z1} is halogen, lower alkyl or lower haloalkyl and R^{Z4} is hydrogen or lower alkyl. In certain exemplary embodiments, R^{Z1} is Cl, F, methyl or $-CF_3$ and R^{Z4} is hydrogen or isopropyl. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

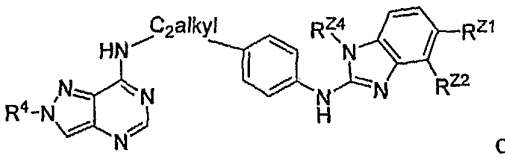
[0308] In certain embodiments, compounds of group **XVII** have the structure:



(SP 76^{A2})

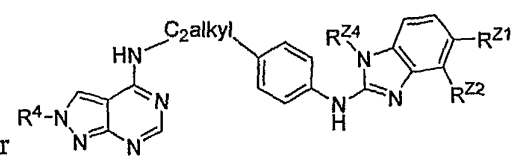


(SP 77^{A2})



(SP 78^{A2})

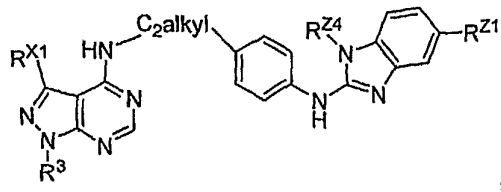
or



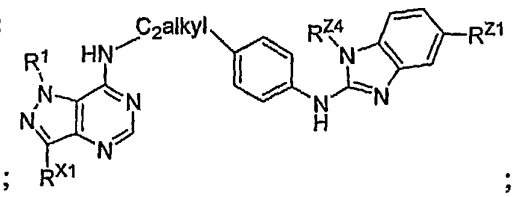
(SP 79^{A2})

wherein the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{Z1} and R^{Z2} are independently halogen, lower alkyl or lower haloalkyl and R^{Z4} is hydrogen or lower alkyl. In certain exemplary embodiments, R^{Z1} and R^{Z2} are independently Cl, F, methyl or $-CF_3$; and R^{Z4} is hydrogen or isopropyl. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$. In certain embodiments, R^{Z1} and R^{Z2} are each Cl, F, methyl or $-CF_3$.

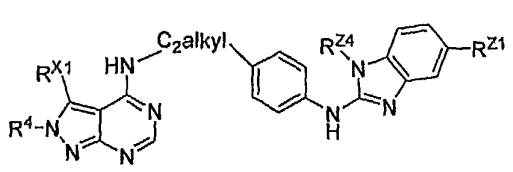
[0309] In certain embodiments, compounds of group **XVII** have the structure:



; **(SP 76^{B1})**

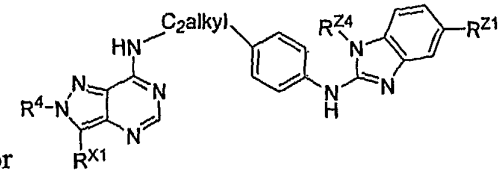


; **(SP 77^{B1})**



(SP 78^{B1})

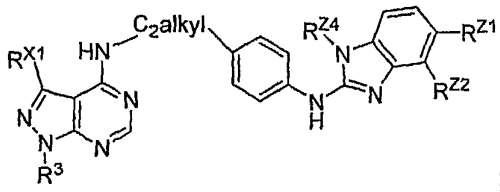
or



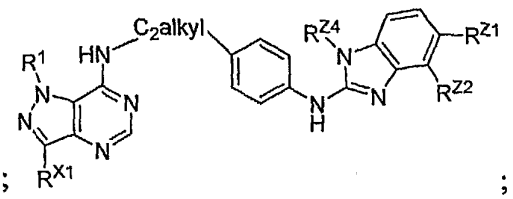
; **(SP 79^{B1})**

wherein the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; R^{Z1} is halogen, lower alkyl or lower haloalkyl and R^{Z4} is hydrogen or lower alkyl. In certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl; R^{Z1} is Cl, F, methyl or $-CF_3$; and R^{Z4} is hydrogen or isopropyl. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

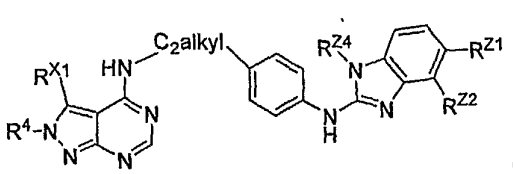
[0310] In certain embodiments, compounds of group **XVII** have the structure:



; **(SP 76^{B2})**

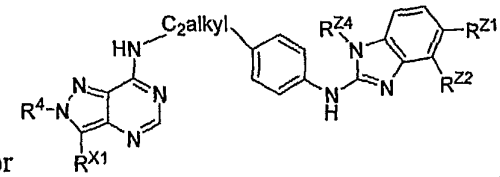


; **(SP 77^{B2})**



(SP 78^{B2})

or

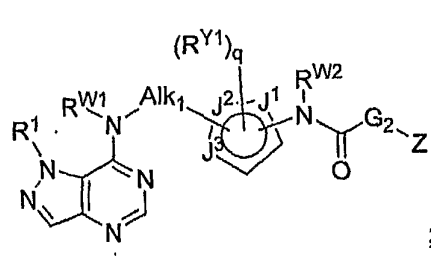


; **(SP 79^{B2})**

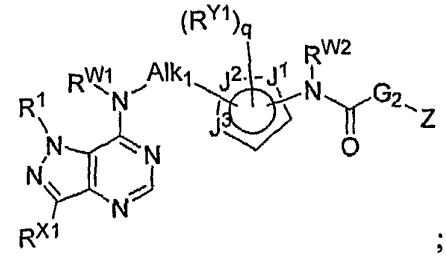
wherein the C_2alkyl moiety is optionally substituted; R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; R^{Z1} and R^{Z2} are independently halogen, lower alkyl or lower haloalkyl and R^{Z4} is hydrogen or lower alkyl. In

certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl; R^{Z1} and R^{Z2} are independently Cl, F, methyl or $-CF_3$ and R^{Z4} is hydrogen or isopropyl. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$. In certain embodiments, R^{Z1} and R^{Z2} are each Cl, F, methyl or $-CF_3$.

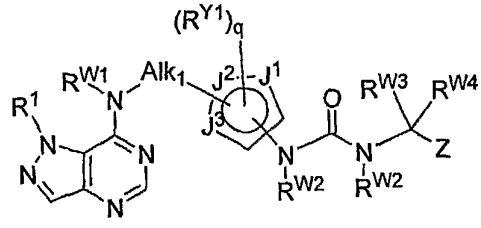
[0311] XVIII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



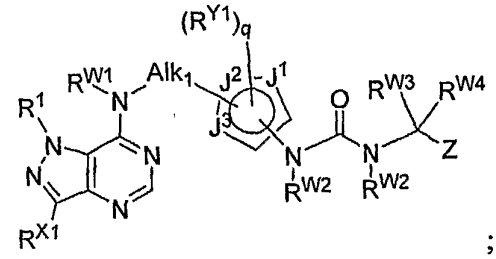
; **(SP 80^{A1})**



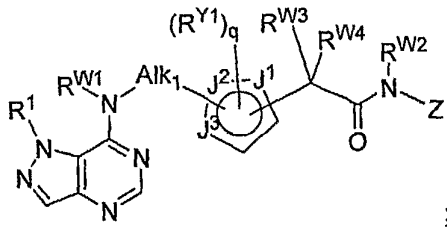
; **(SP 80^{B1})**



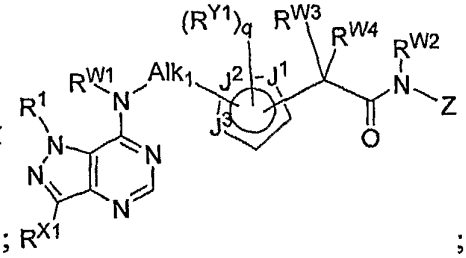
; **(SP 80^{A2})**



; **(SP 80^{B2})**



; **(SP 80^{A3})**



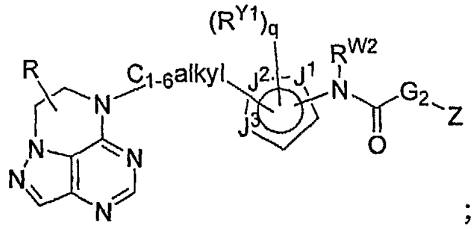
; **(SP 80^{B3})**

wherein R^{X1} and Z are as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, -OC(=O)-, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, -S(=O)-, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently

hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; G_2 is absent, O or NR^{G2}; R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

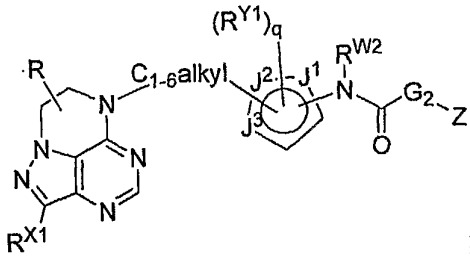
[0312] In certain embodiments, for compounds of group **XVIII**, $-W^1-Alk_1-$ is $-NHC_{1-6}alkyl-$ or $-OC_{1-6}alkyl-$. In certain embodiments, $-W^1-Alk1-$ is $-NHC_2alkyl-$ or $-OC_2alkyl-$. In certain embodiments, $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

[0313] In certain embodiments, compounds of this class have the structure **(SP 80^{A4-6})**, or **(SP 80^{B4-6})** below:



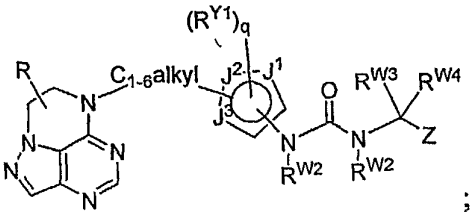
;

(SP 80^{A4})



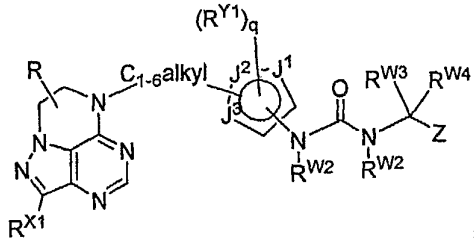
;

(SP 80^{B4})



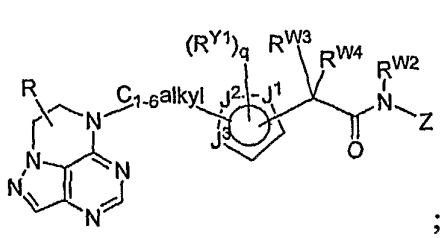
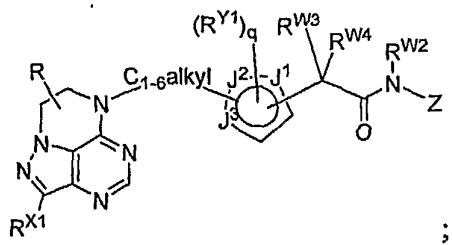
;

(SP 80^{A5})



;

(SP 80^{B5})

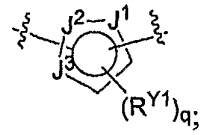



(SP 80^{A6}) (SP 80^{B6})

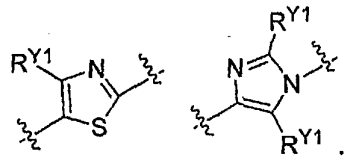
wherein the C_{1-6}alkyl moiety may be substituted or unsubstituted.

[0314] In certain embodiments, for compounds of formulae (SP 80^{A4-6}) and (SP 80^{B4-6}) the C_{1-6}alkyl moiety is a substituted or unsubstituted C_2alkyl moiety. In certain exemplary embodiments, the C_{1-6}alkyl moiety is $-CH_2CH_2-$.

[0315] In certain embodiments, in compounds of formulae (SP 80^{A1-6}) and (SP 80^{B1-6}) the 5-membered ring having the structure:

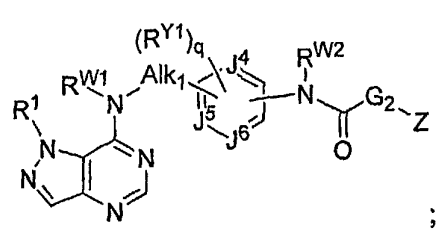
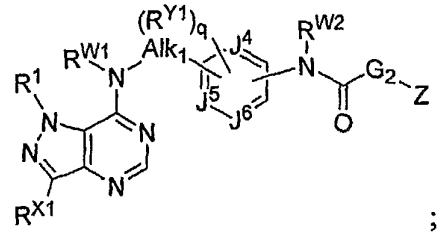


has one of the following structures:

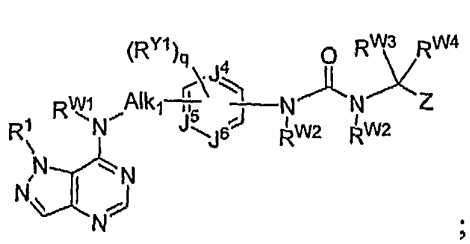


[0316] In certain embodiments, $-N(R^{W2})C(=O)G_2-$ is $-NHC(=O)-$, $-NHC(=O)O-$, or $-NHC(=O)NH-$. In certain embodiments, $-N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}-$ is $-NHC(=O)NHCH_2-$, and $-CR^{W3}R^{W4}C(=O)N(R^{W2})-$ is $-CH_2C(=O)NH-$.

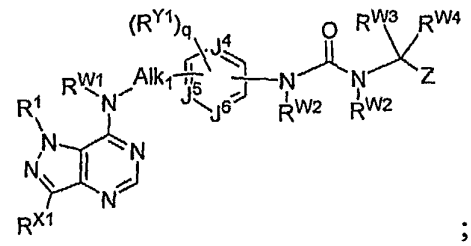
[0317] XIX. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):

(SP 81^{A1}) (SP 81^{B1})

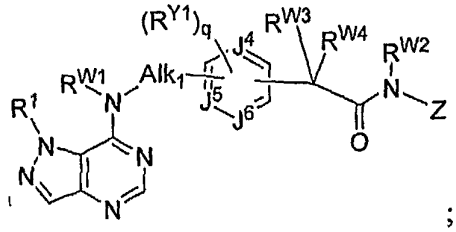


;

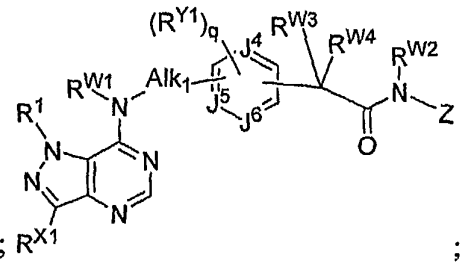


;

(SP 81^{A2}) (SP 81^{B2})



; R^{X1}



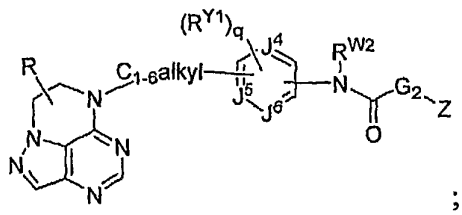
;

(SP 81^{A3}) (SP 81^{B3})

wherein R^{X1} and Z are as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Y3}, -SR^{Y3}, -$NR^{Y2}R^{Y3}$, -$SO_2NR^{Y2}R^{Y3}$, -C(=O)$NR^{Y2}R^{Y3}$, halogen, -CN, -NO_2, -C(=O)OR^{Y3}, -N(R^{Y2})C(=O)R^{Y3}, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; G_2 is absent, O or NR^{G2}; R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

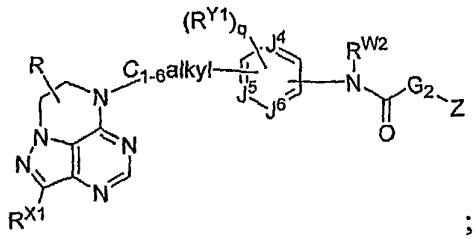
[0318] In certain embodiments, for compounds of group **XVIII**, -W^1-Alk_1- is –$NHC_{1\text{-}6}$alkyl- or –$OC_{1\text{-}6}$alkyl-. In certain embodiments, -W^1-Alk1- is–NHC_2alkyl- or –OC_2alkyl-. In certain embodiments, -W^1-Alk_1- is –$NHCH_2CH_2$-, –OCH_2CH_2- or –NH-$CH_2CH(CH_2OH)$-.

[0319] In certain embodiments, compounds of this class have the structure (**SP 80$^{A4\text{-}6}$**), or (**SP 80$^{B4\text{-}6}$**) below:



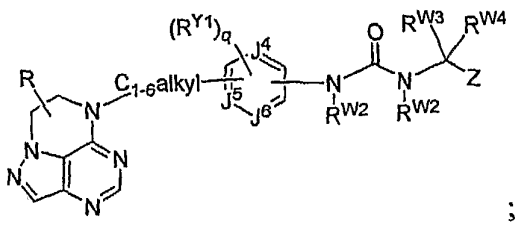
;

(SP 81^{A4})



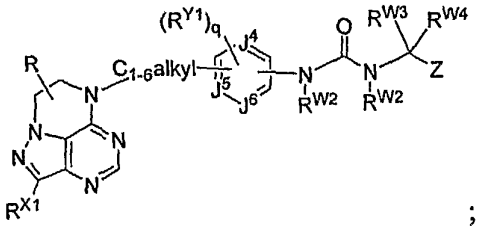
;

(SP 81^{B4})



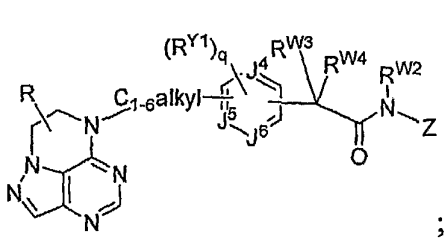
;

(SP 81^{A5})



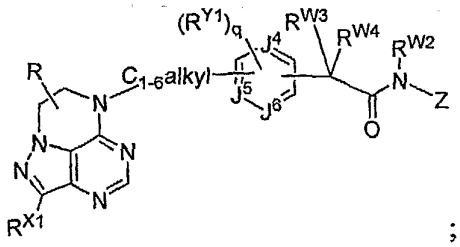
;

(SP 81^{B5})



;

(SP 81^{A6})



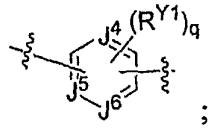
;

(SP 81^{B6})

wherein the $C_{1\text{-}6}$alkyl moiety may be substituted or unsubstituted.

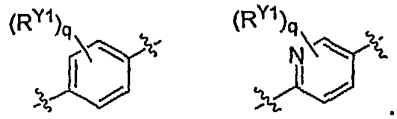
[0320] In certain embodiments, for compounds of formulae (**SP 81$^{A4\text{-}6}$**) and (**SP 81$^{B4\text{-}6}$**) the $C_{1\text{-}6}$alkyl moiety is a substituted or unsubstituted C_2alkyl moiety. In certain exemplary embodiments, the $C_{1\text{-}6}$alkyl moiety is -CH_2CH_2-.

[0321] In certain embodiments, in compounds of formulae (**SP 81$^{A1\text{-}6}$**) and (**SP 81$^{B1\text{-}6}$**) the 6-membered ring having the structure:



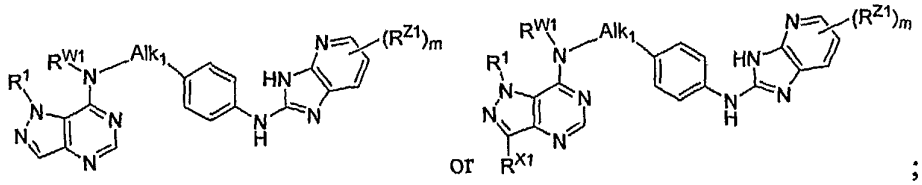
;

has one of the following structures:



[0322] In certain embodiments, $-N(R^{W2})C(=O)G_2-$ is $-NHC(=O)-$, $-NHC(=O)O-$, or $-NHC(=O)NH-$. In certain embodiments, $-N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}-$ is $-NHC(=O)NHCH_2-$, and $-CR^{W3}R^{W4}C(=O)N(R^{W2})-$ is $-CH_2C(=O)NH-$.

[0323] **XX. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**



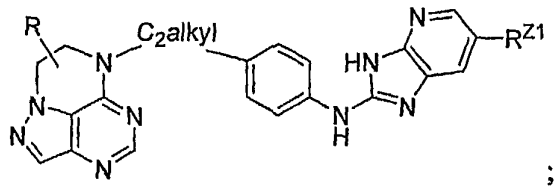
(SP 82) **(SP 83)**

wherein R^{X1} is as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by $-C(=O)-$, $-CO_2-$, $-C(=O)C(=O)-$, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, $-S(=O)-$, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, $-O-$, $-S-$, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, $-CN$, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

[0324] In certain embodiments, for compounds of group **XX**, $-W^1-Alk_1-$ is $-NHC_{1-6}alkyl-$ or $-OC_{1-6}alkyl-$. In certain embodiments, $-W^1-Alk1-$ is $-NHC_2alkyl-$ or $-OC_2alkyl-$. In certain embodiments, $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

[0325] In certain embodiments, for compounds of group **XX**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is H, Cl, F, methyl or $-CF_3$. In certain embodiments, m is 1 and R^{Z1} is hydrogen.

[0326] In certain embodiments, compounds of group **XX** have the structure:

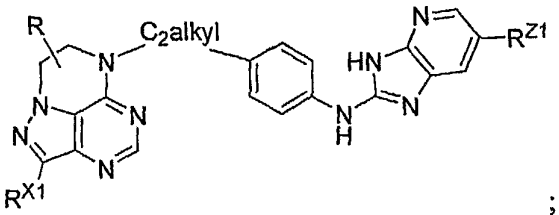


;

(SP 82^A)

wherein R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; and R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{Z1} is hydrogen, Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, R^{Z1} is hydrogen. In certain embodiments, R is hydrogen.

[0327] In certain embodiments, compounds of group **XX** have the structure:

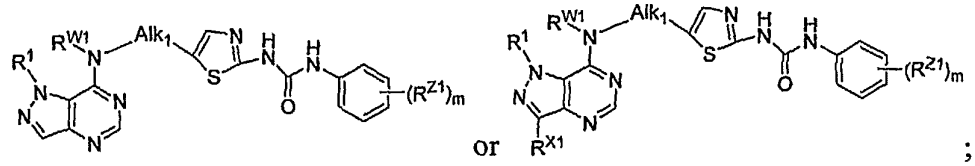


;

(SP 83^A)

wherein R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R is hydrogen or lower alkyl; R^{X1} is hydrogen, methyl or thienyl; and R^{Z1} is hydrogen, Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, R and R^{Z1} are each hydrogen; and R^{X1} is hydrogen, methyl or thienyl.

[0328] XXI. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



(SP 84) (SP 85)

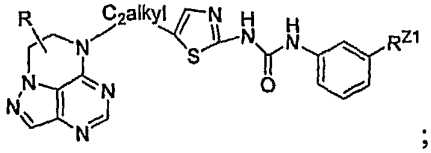
wherein R^{X1} is as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, -S(=O)-, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

[0329] In certain embodiments, for compounds of group **XXI**, $-W^1-Alk_1-$ is $-NHC_{1-6}$alkyl- or $-OC_{1-6}$alkyl-. In certain embodiments, $-W^1$-Alk1- is$-NHC_2$alkyl- or $-OC_2$alkyl-. In certain embodiments, $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

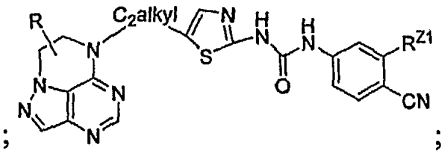
[0330] In certain embodiments, for compounds of group **XXI**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is Cl, F, methyl or $-CF_3$. In certain embodiments, m is 1 and R^{Z1} is lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is $-CF_3$. In certain embodiments, m is 2 and each occurrence of R^{Z1} is independently CN, Cl, F, methyl or $-CF_3$. In certain embodiments, m is 2 and each occurrence of R^{Z1} is CN, Cl, F, methyl or $-CF_3$. In

certain embodiments, m is 2 and one occurrence of R^{Z1} is Cl, F, methyl or $-CF_3$ and the other is CN.

[0331] In certain embodiments, compounds of group **XXI** have the structure:

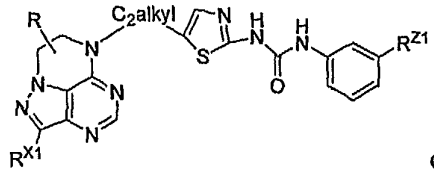


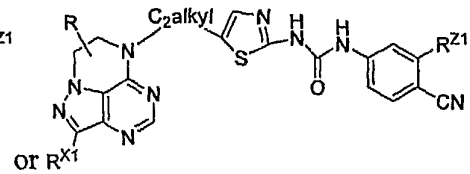
;



;

(SP 84^{A1}) **(SP 84^{A2})**



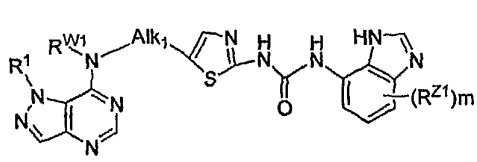


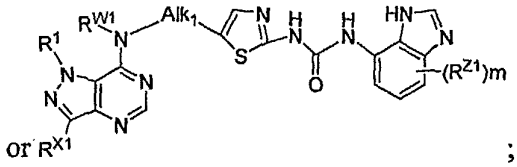
or R^{X1} ;;

(SP 85^{A1}) **(SP 85^{A2})**

wherein the C_2alkyl moiety is optionally substituted; R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl; and R^{Z1} is hydrogen, Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, in compounds of formulae **(SP 84^{A1})** and **(SP 85^{A1})**, R^{Z1} is hydrogen. In certain exemplary embodiments, in compounds of formulae **(SP 84^{A2})** and **(SP 85^{A2})**, R^{Z1} is Cl or $-CF_3$. In certain embodiments, R is hydrogen. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

[0332] XXII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):





or R^{X1} ;

(SP 86) **(SP 87)**

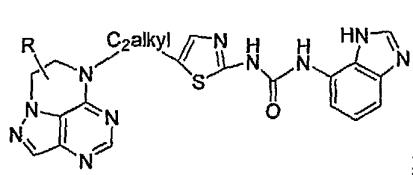
wherein R^{X1} is as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, -OC(=O)-, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, -

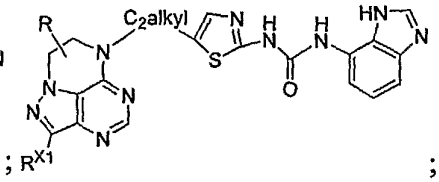
$NR^{L1A}NR^{L1B}C(=O)$-, $-NR^{L1A}C(=O)$-, $-NR^{L1A}CO_2$-, $-NR^{L1A}C(=O)NR^{L1B}$-, $-S(=O)$-, $-SO_2$-, $-NR^{L1A}SO_2$-, $-SO_2NR^{L1A}$-, $-NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or $-NR^{L1A}$-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

[0333] In certain embodiments, for compounds of group **XXII**, $-W^1$-Alk_1- is $-NHC_{1-6}$alkyl- or $-OC_{1-6}$alkyl-. In certain embodiments, $-W^1$-Alk1- is–NHC_2alkyl- or $-OC_2$alkyl-. In certain embodiments, $-W^1$-Alk_1- is $-NHCH_2CH_2$-, $-OCH_2CH_2$- or –NH-$CH_2CH(CH_2OH)$-.

[0334] In certain embodiments, for compounds of group **XXII**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 0.

[0335] In certain embodiments, compounds of group **XXII** have the structure:



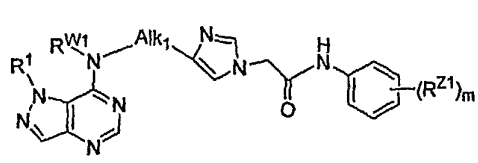
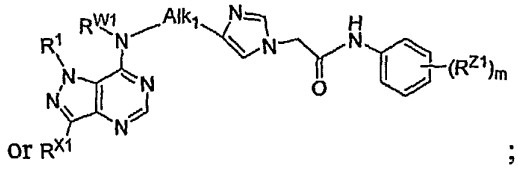
; 

;

(SP 86^{A1}) **(SP 87^{A1})**

wherein the C_2alkyl moiety is optionally substituted; R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; and R^{X1} is hydrogen, lower alkyl or heterocyclyl. In certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl. In certain embodiments, R is hydrogen. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2$-.

[0336] XXIII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):

(SP 88) (SP 89)

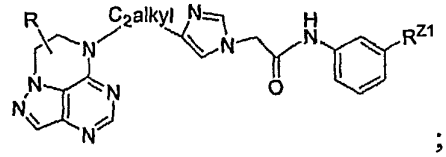
wherein R^{X1} is as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, -OC(=O)-, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, -S(=O)-, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

[0337] In certain embodiments, for compounds of group **XXIII**, $-W^1-Alk_1-$ is $-NHC_{1-6}$alkyl- or $-OC_{1-6}$alkyl-. In certain embodiments, $-W^1-$Alk1- is $-NHC_2$alkyl- or $-OC_2$alkyl-. In certain embodiments, $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

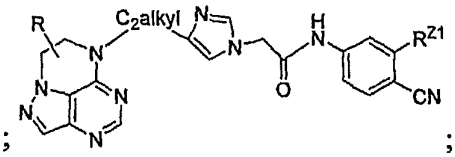
[0338] In certain embodiments, for compounds of group **XXIII**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is Cl, F, methyl or $-CF_3$. In certain embodiments, m is 1 and R^{Z1} is lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is $-CF_3$. In certain embodiments, m is 2 and each occurrence of R^{Z1} is independently CN, Cl, F, methyl or $-CF_3$. In certain embodiments, m is 2 and each occurrence of R^{Z1} is CN, Cl, F, methyl or –

CF_3. In certain embodiments, m is 2 and one occurrence of R^{Z1} is Cl, F, methyl or $-CF_3$ and the other is CN.

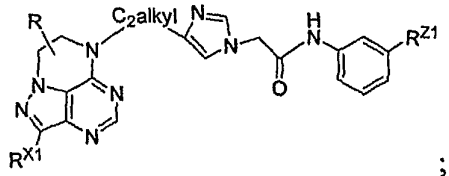
[0339] In certain embodiments, compounds of group **XXIII** have the structure:



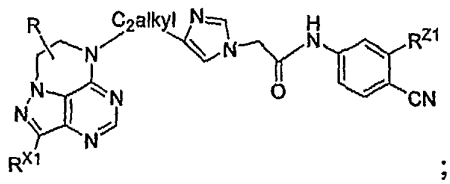
; **(SP 88^{A1})**



; **(SP 88^{A2})**



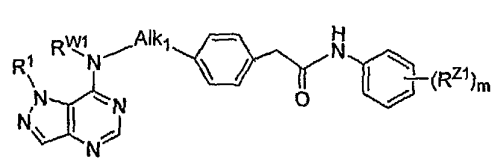
; **(SP 89^{A1})**



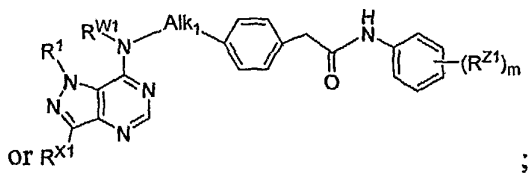
;; **(SP 89^{A2})**

wherein the C_2alkyl moiety is optionally substituted; R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl; and R^{Z1} is hydrogen, Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, in compounds of formulae **(SP 88^{A1})** and **(SP 89^{A1})**, R^{Z1} is hydrogen. In certain exemplary embodiments, in compounds of formulae **(SP 88^{A2})** and **(SP 89^{A2})**, R^{Z1} is Cl or $-CF_3$. In certain embodiments, R is hydrogen. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

[0340] XXIV. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



(SP 90)



; **(SP 91)**

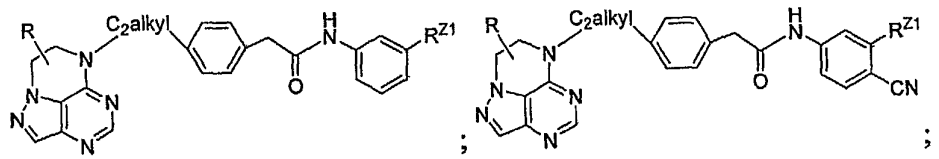
wherein R^{X1} is as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, -OC(=O)-, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, -

$NR^{L1A}NR^{L1B}C(=O)$-, $-NR^{L1A}C(=O)$-, $-NR^{L1A}CO_2$-, $-NR^{L1A}C(=O)NR^{L1B}$-, $-S(=O)$-, $-SO_2$-, $-NR^{L1A}SO_2$-, $-SO_2NR^{L1A}$-, $-NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or $-NR^{L1A}$-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

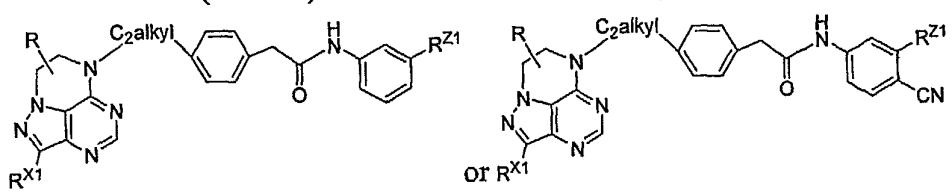
[0341] In certain embodiments, for compounds of group **XXIV**, $-W^1$-Alk_1- is $-NHC_{1-6}$alkyl- or $-OC_{1-6}$alkyl-. In certain embodiments, $-W^1$-Alk1- is$-NHC_2$alkyl- or $-OC_2$alkyl-. In certain embodiments, $-W^1$-Alk_1- is $-NHCH_2CH_2$-, $-OCH_2CH_2$- or $-NH$-$CH_2CH(CH_2OH)$-.

[0342] In certain embodiments, for compounds of group **XXIV**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is Cl, F, methyl or $-CF_3$. In certain embodiments, m is 1 and R^{Z1} is lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is $-CF_3$. In certain embodiments, m is 2 and each occurrence of R^{Z1} is independently CN, Cl, F, methyl or $-CF_3$. In certain embodiments, m is 2 and each occurrence of R^{Z1} is CN, Cl, F, methyl or $-CF_3$. In certain embodiments, m is 2 and one occurrence of R^{Z1} is Cl, F, methyl or $-CF_3$ and the other is CN.

[0343] In certain embodiments, compounds of group **XXIV** have the structure:



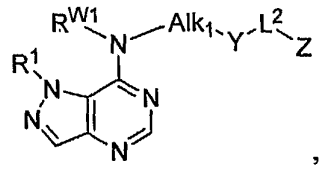
(SP 90^{A1}) **(SP 90^{A2})**



(SP 91^{A1}) **(SP 91^{A2})**

wherein the C_2alkyl moiety is optionally substituted; R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^{X1} is hydrogen, methyl or thienyl; and R^{Z1} is hydrogen, Cl, F, methyl or $-CF_3$. In certain exemplary embodiments, in compounds of formulae **(SP 90^{A1})** and **(SP 91^{A1})**, R^{Z1} is hydrogen. In certain exemplary embodiments, in compounds of formulae **(SP 90^{A2})** and **(SP 91^{A2})**, R^{Z1} is Cl or $-CF_3$. In certain embodiments, R is hydrogen. In certain exemplary embodiments, the C_2alkyl moiety is $-CH_2CH_2-$.

[0344] XXV. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



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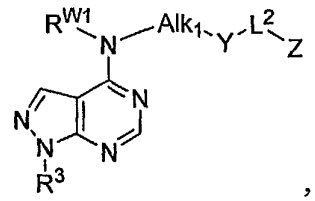
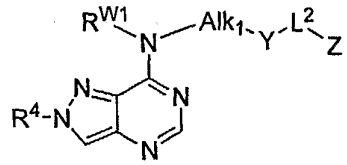
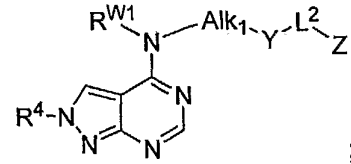


,

(SP 92) **(SP 93)**



or

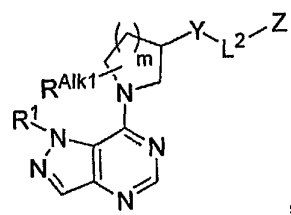


;

(SP 94) **(SP 95)**

wherein R^1, R^3, R^4, L^2, Y and Z are as defined generally and in classes and subclasses herein; and R^{W1} together with a carbon atom present on Alk_1 forms an optionally substituted 5- to 6-membered heterocyclic ring.

[0345] In certain embodiments, compounds of the invention have one of the structures **(SP 92^{A})** - **(SP 95^{A})** below:



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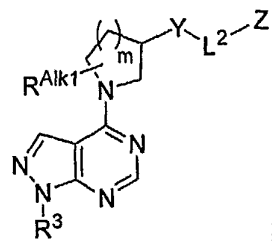
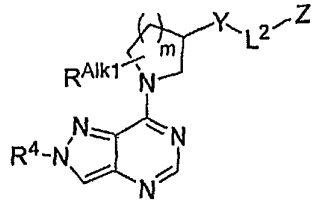
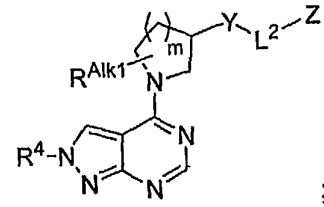


;

(SP 92^{A}) **(SP 93^{A})**

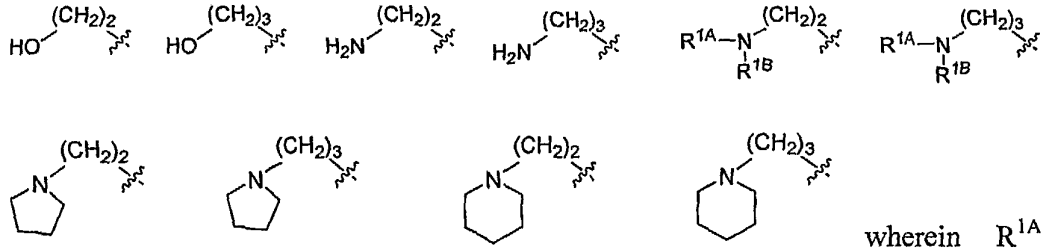



or ;

(SP 94^A) **(SP 95^A)**

wherein m is 1 or 2 and R^{Alk1} is hydrogen, halohen, hydroxy, CN, nitro, lower alkyl, lower alkoxy, aryl, or heteroaryl. In certain embodiments, R^{Alk1} is hydrogen.

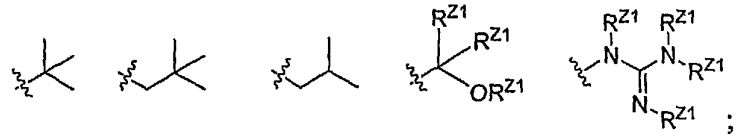
[0346] In certain embodiments for compounds as described in subgroups **I-XVII** and **XXV** above, R^1, R^3 and R^4 are independently hydrogen or lower alkyl. In certain embodiments, R^1, R^3 and R^4 are independently hydrogen. In certain embodiments, R^1, R^3 and R^4 are independently hydrogen, methyl, ethyl, isopropyl or one of:



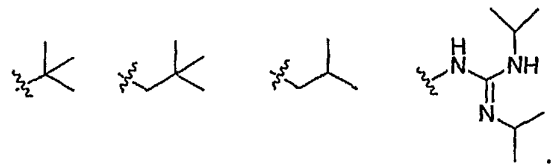
wherein R^{1A} and R^{1B} are independently hydrogen, methyl or ethyl.

[0347] In certain embodiments, for compounds as described in subgroups **I-XXV** above, R^{WI} together with a carbon atom present on Alk_1 forms an optionally substituted 5- to 6-membered heterocyclic ring.

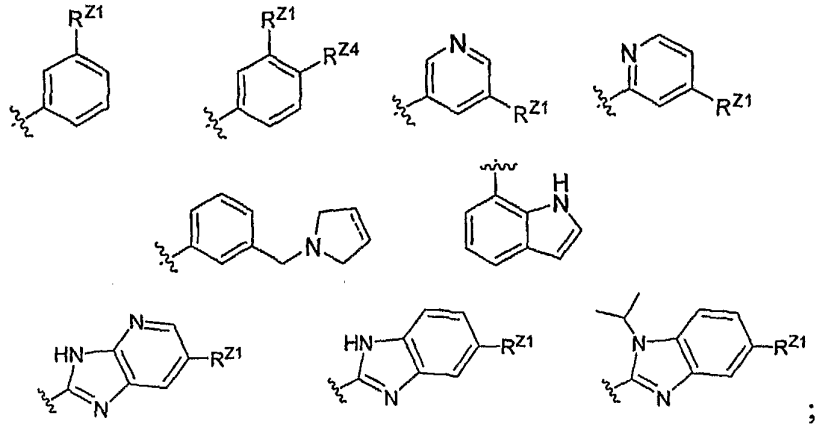
[0348] In certain embodiments, for compounds as described in subgroups **I-XIII**, **XVIII-XIX** and **XXV** above, Z is a branched alkyl, alkenyl, alkynyl, heteroalkyl or heteroalkenyl moiety. In certain exemplary embodiments, Z has one of the following structures:



wherein each occurrence of R^{Z1} is independently hydrogen, lower alkyl, lower alkenyl, aryl, heteroaryl or acyl. In certain embodiments, Z has one of the following structures:

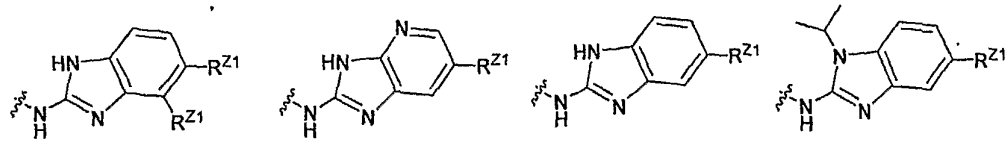


[0349] In certain embodiments, for compounds as described in subgroups **I-XIII, XVIII-XIX** and **XXV** above, Z is a cycloalkyl, cycloalkenyl, heterocyclyl, aryl or heteroaryl moiety. In certain exemplary embodiments, Z has one of the following structures:



wherein R^{Z1} is Cl, F, methyl or CF_3; and R^{Z4} is hydrogen or cyano.

[0350] In certain embodiments, for compounds as described in subgroups **I, IV-VI** and **XXV** above, $-L^2-Z$ together represent a moiety having one of the following structures:



wherein R^{Z1} is Cl, F, methyl or CF_3.

[0351] It will also be appreciated that for each of the subgroups **I-XXV** described above, a variety of other subclasses are of special interest, including, but not limited to those classes described above i)- clxxiv) and classes, subclasses and species of compounds described above and in the examples herein.

[0352] Some of the foregoing compounds can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, stereoisomers and/or diastereomers. Thus, inventive compounds and pharmaceutical compositions thereof may be in the form of an individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of stereoisomers. In certain

embodiments, the compounds of the invention are enantiopure compounds. In certain other embodiments, mixtures of stereoisomers or diastereomers are provided.

[0353] Furthermore, certain compounds, as described herein may have one or more double bonds that can exist as either the Z or E isomer, unless otherwise indicated. The invention additionally encompasses the compounds as individual isomers substantially free of other isomers and alternatively, as mixtures of various isomers, *e.g.*, racemic mixtures of stereoisomers. In addition to the above-mentioned compounds *per se*, this invention also encompasses pharmaceutically acceptable derivatives of these compounds and compositions comprising one or more compounds of the invention and one or more pharmaceutically acceptable excipients or additives.

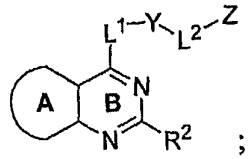
[0354] Compounds of the invention may be prepared by crystallization of compound of formula **(I)** under different conditions and may exist as one or a combination of polymorphs of compound of general formula **(I)** forming part of this invention. For example, different polymorphs may be identified and/or prepared using different solvents, or different mixtures of solvents for recrystallization; by performing crystallizations at different temperatures; or by using various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffractogram and/or other techniques. Thus, the present invention encompasses inventive compounds, their derivatives, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them.

[0355] ***2) Synthetic Overview:***

[0356] The practitioner has a a well-established literature of pyrazolo pyrimidine chemistry to draw upon, in combination with the information contained herein, for guidance on synthetic strategies, protecting groups, and other materials and methods useful for the synthesis of the compounds of this invention, including compounds containing the various R^2 and R^3 substituents and L^1, L^2, Y and Z moieties.

[0357] Moreover, the practitioner is directed to the specific guidance and examples provided in this document relating to various exemplary compounds and intermediates thereof.

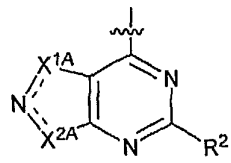
[0358] As described above, the present invention provides novel compounds, specifically compounds having the following general structure:



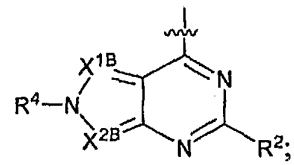
;

(I)

wherein A-B together represent one of the following structures:



or

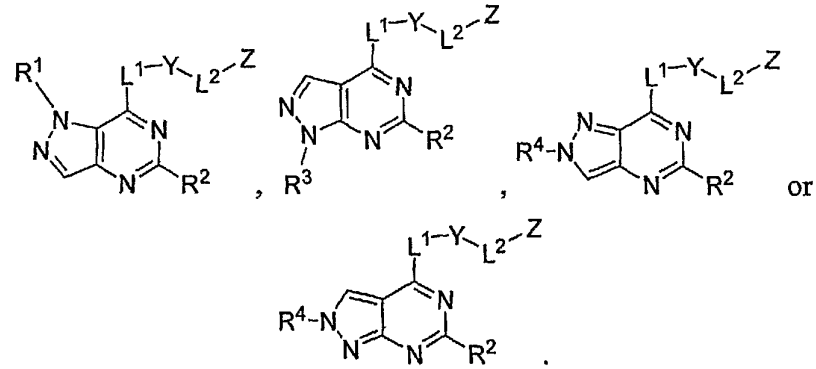


;

and pharmaceutically acceptable derivatives thereof;

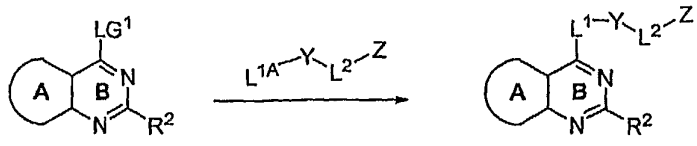
wherein R^2, R^4, X^{1A}, X^{2A}, X^{1B}, X^{2B}, L^1, L^2, Y and Z are as defined in classes and subclasess herein.

[0359] It will be appreciated that for compounds as generally described above, certain classes of compounds are of special interest. For example, one class of compounds of special interest includes pyrazolo pyrimidines having formulae (I^{A1}) though (I^{A4}):



(I^{A1}) (I^{A2}) (I^{A3}) (I^{A4})

[0360] In yet another aspect of the invention, methods for producing intermediates useful for the preparation of compounds of formulae (I) and (I^{A1}) though (I^{A4}) are provided, embodiments of said methods being depicted generally in Scheme A:

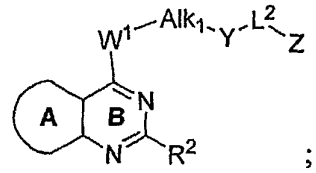


(1) (I)

Scheme A

where LG^1 is a suitable leaving group and L^{1A} is adapted to displace LG^1 upon reaction with pyrazolo pyrimidine (1).

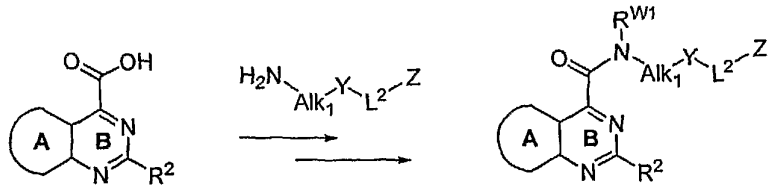
[0361] In certain embodiments, the methodology may be used to generate inventive compounds of the general formula (I^B):



(I^B)

wherein W^1 is O or NR^{W1}, where R^{W1} is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, or acyl; and Alk_1 is a C_{1-6}alkylene or C_{2-6}alkenylene moiety.

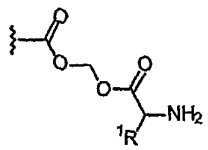
[0362] In yet another aspect of the invention, methods for producing intermediates useful for the preparation of compounds of Formula (I^{C1}) and (I^{C2}) wherein W^1 is $-C(=O)N(R^{W1})-$, where R^{W1} is as defined above, are provided, embodiments of said methods being depicted generally in Scheme B:



(2)

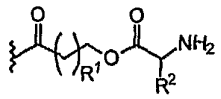
Scheme B

[0363] Numerous suitable prodrug moieties, and information concerning their selection, synthesis and use are well known in the art. Examples of prodrug moieties of interest include, among others, prodrug moieties that can be attached to primary or secondary amine-containing functionalities. For instance, prodrug moieties of interest include those that can be attached to group $-NH_2$. Examples of such prodrug moieties include the following:



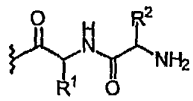
R^1 = all natural, unnatural amino acids

For the synthesis of the prodrug groups, see Borchardt, R.T. et al , J. Org. Chem. **1997**, *62*, 1356-1362 and 1363-1367.



R^1 = C1-C4 alkyl, cycloalkyl, oxyalkyl, aminoalkyl, etc.
R^2 = all natural, unnatural amino acids

For the synthesis of the prodrug groups, see Zhou, X-X. et. al., PCT WO 99/51613.



R^1, R^2 = all natural, unnatural amino acids

For the synthesis of the prodrug groups, see Ezra, A. et. al., *J. Med. Chem.* **2000**, *43*, 3641-3652.

[0364] The present invention encompasses any prodrug form of the compounds described herein. Although certain other exemplary prodrug moieties generated from the inventive compounds amino group are detailed herein, it will be appreciated that the present invention is not intended to be limited to these prodrug moieties; rather, a variety of additional prodrug moieties can be readily identified by a person skilled in the relevant art.

[0365] **3) Pharmaceutical Compositions**

[0366] As discussed above, the present invention provides compounds that are inhibitors of protein kinases (*e.g.*, Aurora kinase), and thus the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to melanoma, leukemia, or cancers such as colon, breast, gastric, ovarian, cervical, renal, prostate, lymphoma, neuroblastoma, pancreatic and blader cancer. Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[0367] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a

pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0368] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a Aurora kinase.

[0369] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.,* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, *66*, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate,

palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0370] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-

polyoxypropylene-block polymers, wool fat, 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 cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; cyclodextrin-type compounds such as Captisol®; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0371] *Uses of Compounds and Pharmaceutically acceptable compositions*

[0372] *Research Uses*

[0373] According to the present invention, the inventive compounds may be assayed in any of the available assays known in the art for identifying compounds having protease inhibitory activity. For example, the assay may be cellular or non-cellular, *in vivo* or *in vitro*, high- or low-throughput format, etc.

[0374] In certain exemplary embodiments, compounds of this invention were assayed for their ability to inhibit protein kinases, more specifically Aurora.

[0375] Thus, in one aspect, compounds of this invention which are of particular interest include those which:

- are inhibitors of protein kinases;
- exhibit the ability to inhibit Aurora kinase;
- are useful for treating mammals (*e.g.*, humans) or animals suffering from an Aurora-mediated disease or condition, and for helping to prevent or delay the onset of such a disease/condition;
- exhibit a favorable therapeutic profile (*e.g.*, safety, efficacy, and stability).

[0376] In certain embodiments, compounds of the invention are Aurora kinase inhibitors. In certain exemplary embodiments, inventive compounds are Aurora-A inhibitors. In certain exemplary embodiments, inventive compounds have $^{Cell}IC_{50}$

values ≤100 μM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 75 μM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 50 μM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 25 μM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 10 μM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 7.5 μM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 5 μM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 2.5 μM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 1 μM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 800 nM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 600 nM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 500 nM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 300 nM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 200 nM. In certain other embodiments, inventive compounds have $^{Cell}IC_{50}$ values ≤ 100 nM.

[0377] In yet another aspect, a method for the treatment or lessening the severity of an Aurora-mediated disease or condition is provided comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of an Aurora-mediated disease or condition. The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of an Aurora-mediated disease or condition. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical

judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0378] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0379] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0380] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable

preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. 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 can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0381] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0382] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0383] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0384] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0385] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[0386] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch.

Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0387] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0388] As described generally above, the compounds of the invention are useful as inhibitors of protein kinases. In one embodiment, the compounds and compositions of the invention are Aurora kinase inhibitors, and thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation of Aurora kinase is implicated in the disease, condition, or disorder. When activation of Aurora kinase is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as "Aurora-mediated disease" or disease symptom. Accordingly, in another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation of Aurora kinase is implicated in the disease state.

[0389] The activity of a compound utilized in this invention as an Aurora kinase inhibitor, may be assayed *in vitro, in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of activated Aurora A, B and/or C. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to Aurora A, B and/or C. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/Aurora A, B and/or C, complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with Aurora A, B and/or C bound to known radioligands.

[0390] The term "measurably inhibit", as used herein means a measurable change in Aurora A, B and/or C activity between a sample comprising said composition and a Aurora A, B and/or C kinase and an equivalent sample comprising Aurora A, B and/or C kinase in the absence of said composition.

[0391] The term "Aurora-mediated disease" or "Aurora-mediated condition", as used herein, means any disease or other deleterious condition in which Aurora is known to play a role. The terms "Aurora-mediated disease" or "Aurora-mediated condition" also mean those diseases or conditions that are alleviated by treatment with an Aurora inhibitor. Such conditions include, without limitation, colon, breast, stomach, and ovarian cancer. The term "Aurora-mediated disease", as used herein, means any disease or other deleterious condition or disease in which Aurora is known to play a role. Such diseases or conditions include, without limitation, cancers such as colon and breast cancer.

[0392] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to

treat the same disorder), or they may achieve different effects (*e.g.*, control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0393] For example, other therapies, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of therapies or anticancer agents that may be used in combination with the inventive anticancer agents of the present invention include surgery, radiotherapy (in but a few examples, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF) to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (*e.g.*, antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabile, Gemcitabine), spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), Gleevec™, adriamycin, dexamethasone, and cyclophosphamide. For a more comprehensive discussion of updated cancer therapies see, The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference. See also the National Cancer Institute (CNI) website (www.nci.nih.gov) and the Food and Drug Administration (FDA) website for a list of the FDA approved oncology drugs (www.fda.gov/cder/cancer/druglistframe – See Appendix).

[0394] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as

beta interferon (*e.g.*, Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[0395] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0396] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating implantable medical devices, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device.

[0397] Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[0398] Another aspect of the invention relates to inhibiting Aurora A, B and/or C activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula **I** or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0399] Inhibition of Aurora A, B and/or C kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

TREATMENT KIT

[0400] In other embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. In general, the pharmaceutical pack or kit comprises one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages, and may also include a card having the dosages oriented in the order of their intended use. If desired, a memory aid can be provided, for example in the

form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium dietary supplements, either in a form similar to or distinct from the dosages of the pharmaceutical compositions, can be included to provide a kit in which a dosage is taken every day. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

EQUIVALENTS

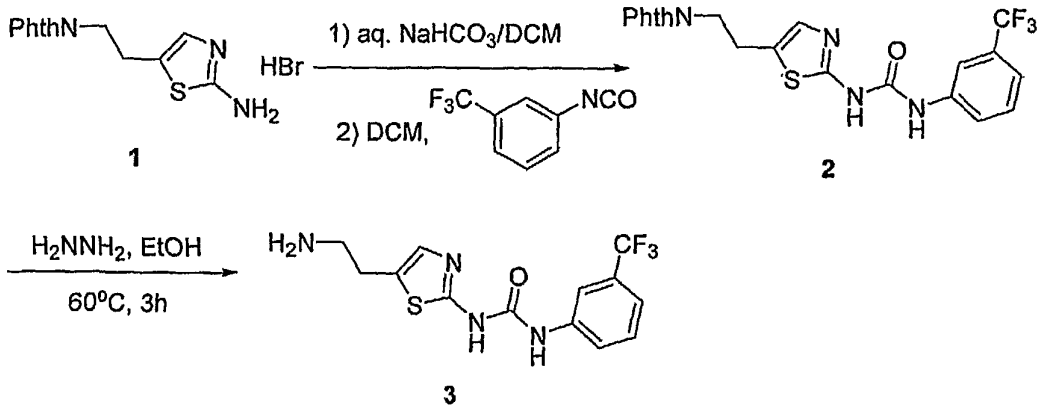
[0401] The representative examples that follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. It should further be appreciated that the contents of those cited references are incorporated herein by reference to help illustrate the state of the art.

[0402] The following examples contain important additional information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and the equivalents thereof.

EXEMPLIFICATION

[0403] The compounds of this invention and their preparation can be understood further by the examples that illustrate some of the processes by which these compounds are prepared or used. It will be appreciated, however, that these examples do not limit the invention. Variations of the invention, now known or further developed, are considered to fall within the scope of the present invention as described herein and as hereinafter claimed.

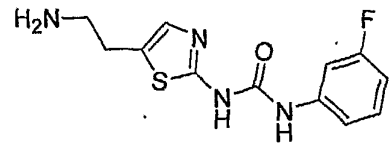
[0404] **EXAMPLE 1**



[0405] **Compound 2:** A mixture of **1** (15.5 g, 44.0 mmol, Eriks, J.C. *et al. J.Med.Chem.*, **1992**, 3239.) in 250 mL aqueous sat. $NaHCO_3$ and 150 mL water was extracted three times with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in dichloromethane (500 mL) and carefully treated with 3-trifluoromethylphenyl isocyanate (6.1 mL, 44.3 mmol). After 3h at room temperature, another 0.50 mL of the isocyanate was added. After 5 h, the resulting white precipitate was filtered off and washed with dichloromethane to afford **2**, ES (+) MS m/e = 461 (M+1).

[0406] **Compound 3:** The solid (**2**) obtained in the previous step was taken up in ethanol and treated with hydrazine (8.5 mL). The mixture was heated at 60 °C for 5 h. After cooling to ambient temperature, the mixture was filtered and concentrated to yield 12.4 g (61% for 2 steps) of a white solid **3**, ES (+) MS m/e = 331 (M+1).

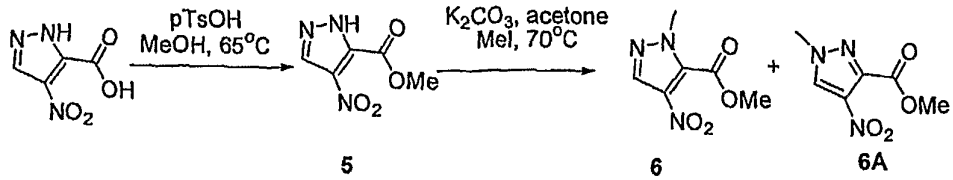
[0407] **EXAMPLE 2**



4

[0408] **Compound 4:** This compound was made according to procedures towards the synthesis of **2** and **3** except that 3-fluorophenyl isocyanate was used in place of 3-trifluoromethylphenyl isocyanate in the first step in preparation of **2**.

[0409] **EXAMPLE 3**

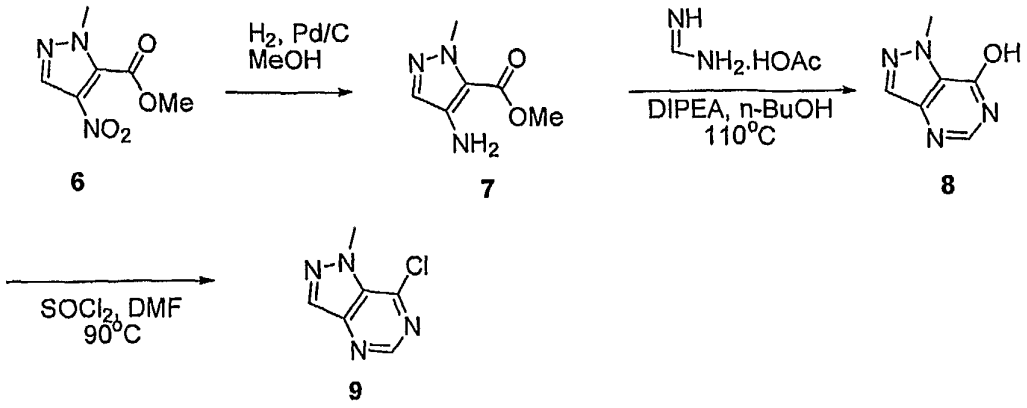


5 6 6A

[0410] **Compound 5:** p-Toluene sulfonic acid monohydrate (0.3 g , 1.6 mmol) was added to a solution of 4-nitro-3-pyrazole carboxylic acid (5.0 g ,31.8 mmol) in 60 mL of methanol. The reaction mixture was heated and stirred overnight at 65°C. After the reaction mixture was cooled to room temperature, saturated sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate (x3). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford **5** (4.79 g, 88%) as white solid. ^1H NMR (d6-DMSO) δ 3.85 (s, 3H) 8.81 (s, 1H); ES (+) MS m/e = 172 (M+1).

[0411] **Compound 6 and 6A:** To a mixture containing **5** (3.1 g, 18.1 mmol) and potassium carbonate (5.0 g, 36.2 mmol) in 60 mL of acetone was added methyl iodide (2.2 mL, 36.2 mmol). The resulting solution was heated and stirred at 70°C for 2 hours. After the reaction mixture was cooled to room temperature, water was added and the mixture was extractred with ethyl acetate (x3). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using 20% ethyl acetate in hexanes as the eluent to afford **6** (1.1 g, 33%) as white solid. ^1H NMR (d6-DMSO) δ 3.96 (s, 3H) 3.98 (s, 3H) 8.36 (s, 1H); ES (+) MS m/e = 186 (M+1) and using 30% ethyl acetate in hexanes to afford **6A** (2.2 g, 66%) as white solid. ^1H NMR (d-$CDCl_3$) δ 3.98 (s, 3H) 4.00 (s, 3H) 8.13 (s, 1H); ES (+) MS m/e = 186 (M+1).

[0412] **EXAMPLE 4**

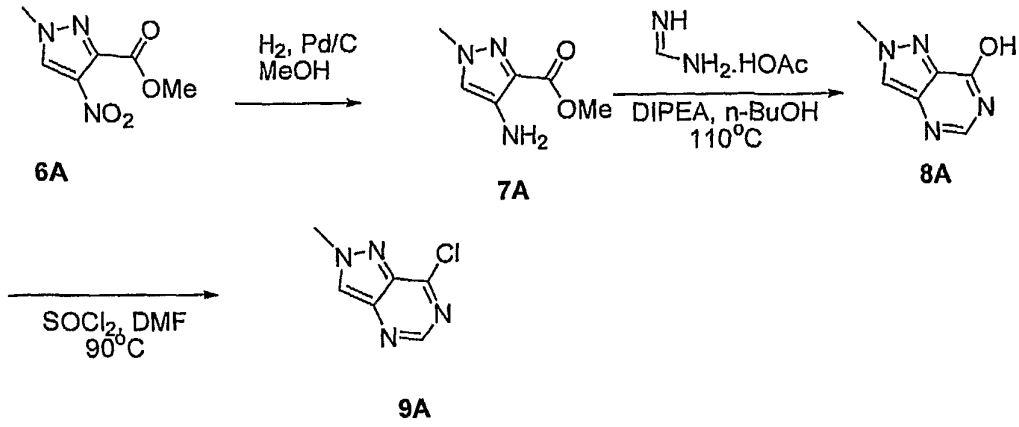


[0413] **Compound 7:** 10% wt. Pd/C (0.15 g, 0.14 mmol) was added to a solution containing **6** (0.26 g, 1.4 mmol) in 10 mL of methanol. The mixture was stirred under a hydrogen atmosphere at ambient temperature. After 3 hours, the reaction mixture was filtered thru a plug of Celite. The resulting filtrate was concentrated under reduced pressure to afford **7** (0.20 g, 91%), ES (+) MS m/e = 156 (M+1).

[0414] **Compound 8:** To a solution of **7** (0.92 g, 5.9 mmol) in 5 mL of Hunig's base and 5 mL of n-butanol was added formamidine acetate (0.68 g, 6.5 mmol). The reaction mixture was heated and stirred at 110°C for 1 hour. After cooling to room temperature, the white precipitate was collected by filtration and washed with diethyl ether. The resulting white precipitate was dried under reduced pressure to afford **8** (0.83g, 94%). ^{1}H NMR (d6-DMSO) δ 4.33 (s, 3H) 8.50 (s, 1H) 8.80 (s, 1H); ES (+) MS m/e = 151 (M+1).

[0415] **Compound 9:** To a solution of **8** (0.835 g, 5.5 mmol) in 10 mL thionyl chloride was added 0.5 mL DMF. The resulting mixture was heated to 90°C under nitrogen for 1 hour. After cooling to room temperature, the solvents were removed under reduced pressure. Water was added to the resulting residue and the mixture was extracted with dichloromethane (x3). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford **9** (0.94 g, 100%), ES (+) MS m/e = 169 (M+1).

[0416] **EXAMPLE 5**



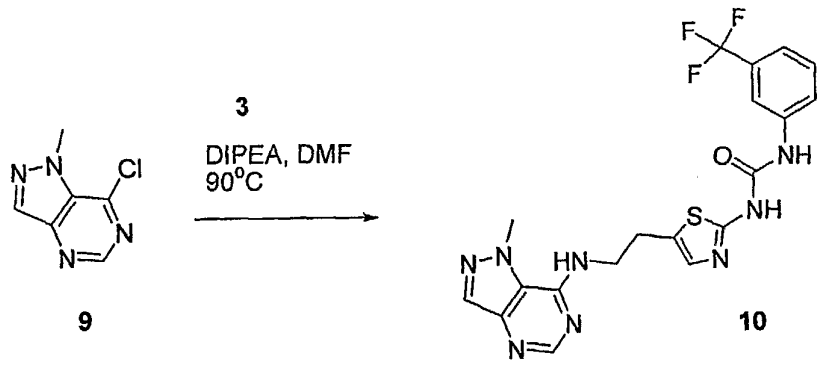
6A 7A 8A 9A

[0417] **Compound 7A:** This compound was made according to procedures towards the synthesis of **7**, except that **6A** was used in place of **6**, ES (+) MS m/e = 156 (M+1).

[0418] **Compound 8A:** This compound was made according to procedures towards the synthesis of **8**, except that **7A** was used in place of **7**, ES (+) MS m/e = 151 (M+1).

[0419] **Compound 9A:** This compound was made according to procedures towards the synthesis of **9**, except that **8A** was used in place of **8**, ES (+) MS m/e = 169 (M+1).

[0420] **EXAMPLE 6**

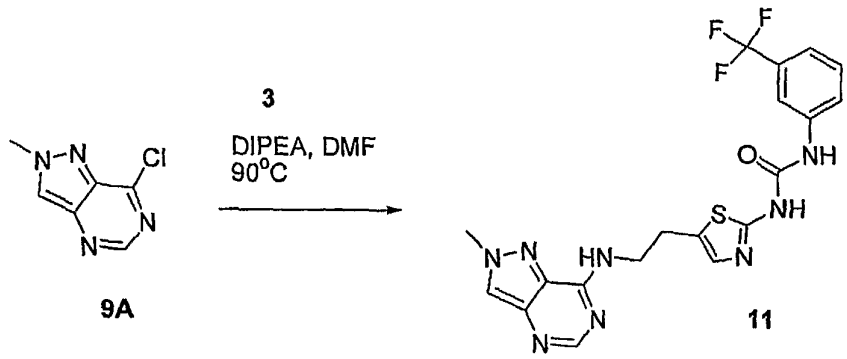


9 10

[0421] **Compound 10:** To a solution of **3** (0.33g, 1.0 mmol) and Hunig's base (0.52 mL, 3.0 mmol) in 3 mL of DMF was added **9** (0.169 g, 1.0 mmol). The resulting mixture was heated and stirred at 90°C for 1 hour. After the reaction was cooled to room temperature, water was added and washed with ethyl acetate (x3). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated

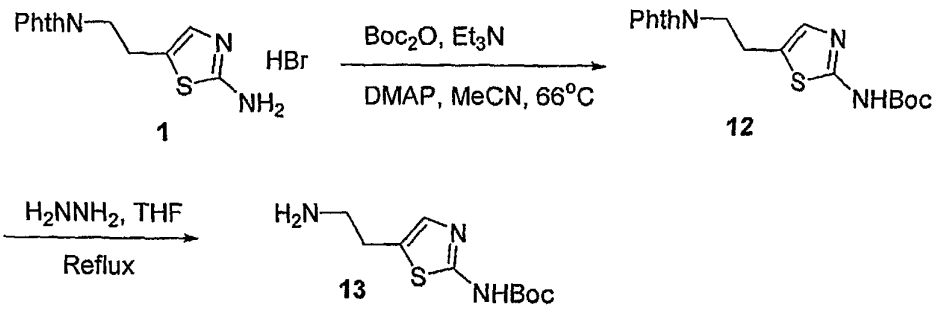
under reduced pressure. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **10** (59 mg, 9%) as the bis TFA salt. ^{1}H NMR (d6-DMSO) δ 3.10 – 3.13 (m, 2H) 3.90 – 3.92 (m, 2H) 4.33 (s, 3H) 7.19 (s, 1H) 7.36 (m, 1H) 7.51 – 7.55 (m, 1H) 7.62 – 7.64 (m, 1H) 8.01 (s, 1H) 8.16 (s, 1H) 8.72 (s, 1H) 9.02 (bs, 1H) 9.57 (s, 1H); ES (+) MS m/e = 463 (M+1).

[0422] EXAMPLE 7



[0423] Compound 11: This compound was made according to procedures towards the synthesis of **10**, except that **9A** was used in place of **9**, ES (+) MS m/e = 463 (M+1).

[0424] EXAMPLE 8

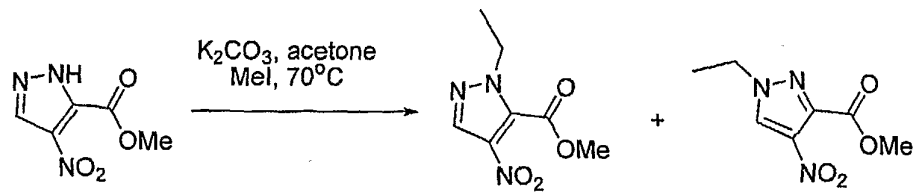


[0425] Compound 12: **1** (60g, 170 mmol) was slurried in 190 ml acetonitrile. DMAP (.05 eq, 1g) and Et_3N (1.1 eq, 26 ml) were added, turning the reaction yellow, forming more precipitate and raising the reaction temperature to 31°C. Boc_2O (1.2 eq, 44g) was added and the reaction heated to reflux at 66°C. As the

temperature rose, the thick reaction mixture became easier to stir. After 45 min, the yellow color had disappeared and the reaction was done by TLC (50/50 EtOAc/hexane.) The reaction was cooled to 0°C, the solid collected *via* filtration and washed with cold ACN. The solid was then slurried with water, collected *via* filtration. Drying *in vacuo* gave 55g white solid (86% yield.).

[0426] Compound 13: **12** (40g, 107 mmol) were slurried in 500 ml THF and heated to reflux, dissolving almost all of the phthalimide. Anhydrous hydrazine (2 eq., 6.7 ml) was added and the reaction stirred 2hr at which time TLC (50/50 EtOAc/hexane) showed the reaction to be ~75% complete. 1 eq. hydrazine was added and after 1 more hr at reflux the reaction was complete by TLC. The reaction was cooled to 40°C and the white precipitate was filtered off and washed with 200 ml THF. The filtrate was concentrated *in vacuo* to ~200 ml at which time a little white solid forms. The mixture was diluted with 200 ml hexane, giving a milky solution, and let stand overnight. The solid was removed *via* filtration (4g of 1:1 product: phthalic hydrazide) and the filtrate concentrated *in vacuo* to give 23g white solid (88% yield.).

[0427] EXAMPLE 9

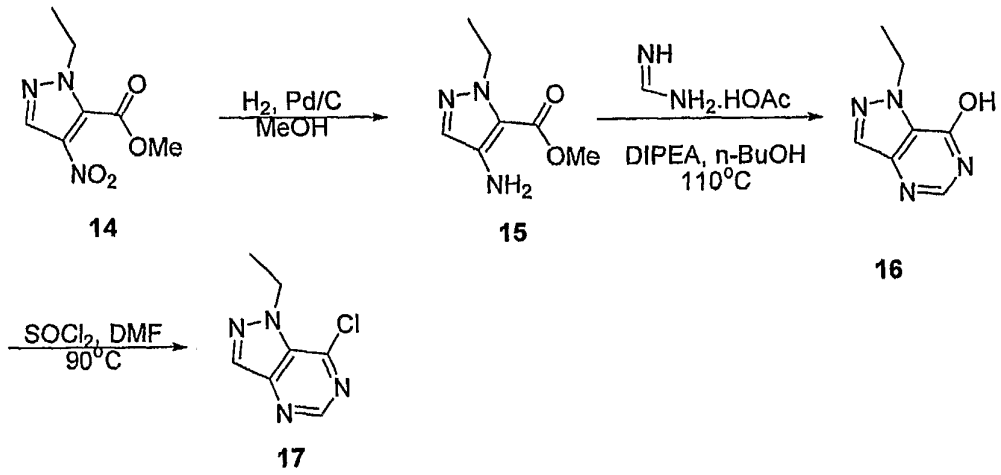


5 **14** **14A**

[0428] Compound 14 and 14A: To a mixture of **5** (1.9 g, 11.1 mmol) and potassium carbonate (3.07 g, 22.2 mmol) in 100 mL of acetone was added iodoethane (3.46 g, 22.2 mmol). The reaction was heated and stirred for 2 hours at 70°C. After cooling to room temperature, the mixture was diluted with water extracted with ethyl acetate (x2). The combined organics were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography using 20% ethyl acetate in hexanes to afford **14** (0.65 g, 29%). ^1H NMR (d6-DMSO) δ 1.37 (t, 3H, J = 7.3 Hz) 3.97 (s, 3H) 4.28 (q, 2H, J = 7.3 Hz) 8.39 (s, 1H); ES (+) MS m/e = 200 (M+1) and using 30% ethyl

acetate in hexanes to afford **14A** (1.3 g, 58%). ^{1}H NMR (d6-DMSO) δ 1.40 (t, 3H, J = 7.3 Hz) 3.87 (s, 3H) 4.22 (q, 2H, J = 7.3 Hz) 9.00 (s, 1H); ES (+) MS m/e = 200 (M+1)

[0429] EXAMPLE 10



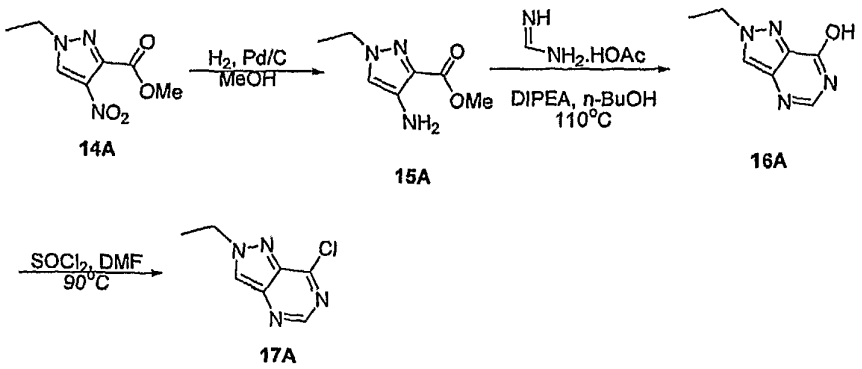
[0430] Compound 15: 10% wt. Pd/C (0.35 g, 0.33 mmol) was added to a solution containing **14** (0.65 g, 3.3 mmol) in 30 mL of methanol. Atmospheric hydrogen pressure was introduced via balloon. After stirring for 3 hours, the reaction mixture was filtered thru a plug of Celite. The resulting filtrate was concentrated under reduced pressure to afford **15** (0.55 g, 100%), ES (+) MS m/e = 170 (M+1).

[0431] Compound 16: Formamidine acetate (0.37 g, 3.6 mmol) was added to a solution of **15** (0.55 g, 3.3 mmol) in 5 mL of Hunig's base and 5 mL of n-butanol. The reaction mixture was heated and stirred at 110°C for 1 hour. After the reaction mixture was cooled, brine water was added and washed with ethyl acetate (x3). The combined organics were dried with $MgSO_4$, filtered, and concentrated to afford **16** (0.51 g, 97%). ES (+) MS m/e = 165 (M+1).

[0432] Compound 17: 0.2 mL of DMF was added to a solution containing **16** (0.51 g, 3.1 mmol) in 6 mL of thionyl chloride. The reaction mixture was heated to 90°C for 1 hour. After the reaction mixture was cooled to room temperature, the solvents were removed under reduced pressure. Water was added to the resulting residue and extracted with dichloromethane (x3). The combined organics were

dried with $MgSO_4$, filtered and concentrated to afford **17** (0.57 g, 100%), ES (+) MS m/e = 183 (M+1).

[0433] EXAMPLE 11

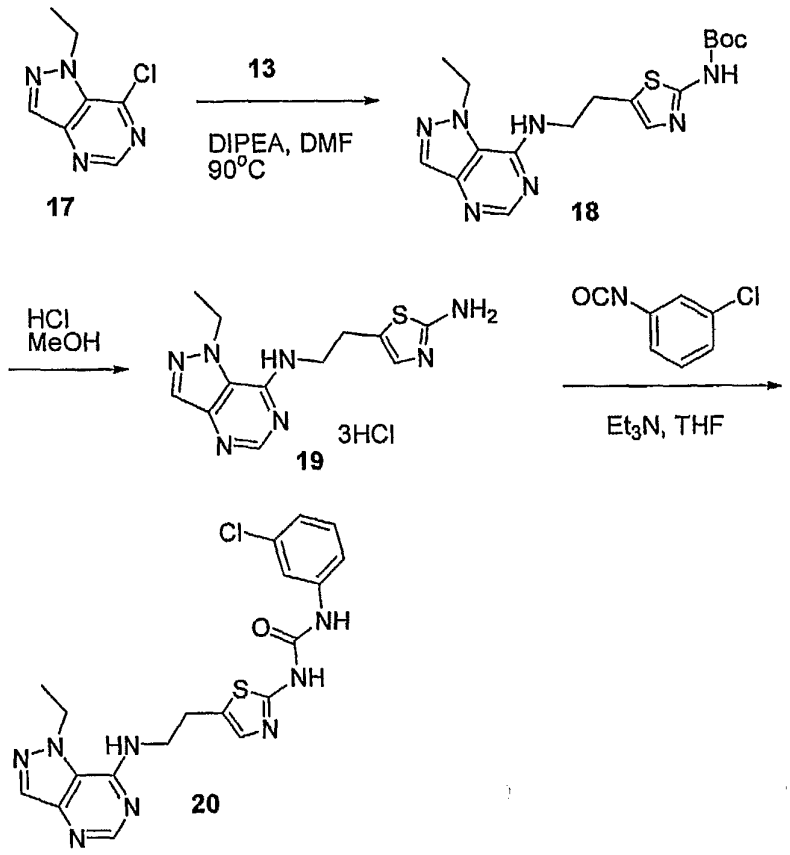


[0434] Compound 15A: This compound was made according to procedures towards the synthesis of **15**, except that **14A** was used in place of **14**, ES (+) MS m/e = 170 (M+1).

[0435] Compound 16A: This compound was made according to procedures towards the synthesis of **16**, except that **15A** was used in place of **15**, ES (+) MS m/e = 165 (M+1).

[0436] Compound 17A: This compound was made according to procedures towards the synthesis of **17**, except that **16A** was used in place of **16**, ES (+) MS m/e = 183 (M+1).

[0437] EXAMPLE 12



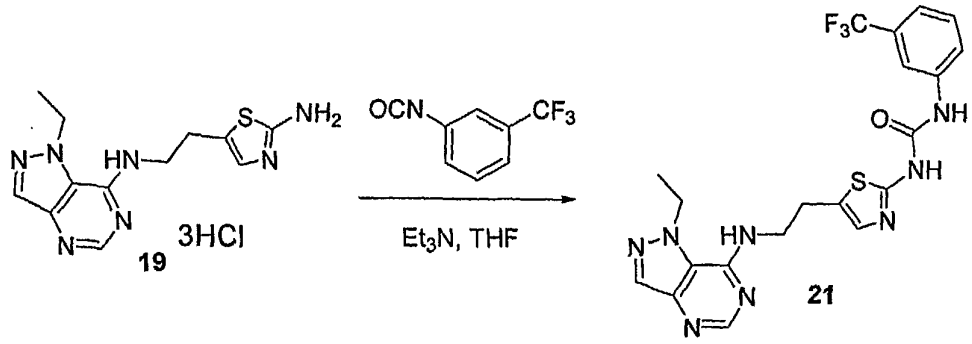
[0438] **Compound 18:** To a solution containing **13** (0.75g, 3.1 mmol) and Hunig's base (1.6 mL, 9.3 mmol) in 3 mL of DMF was added **17** (0.57 g, 3.1 mmol). The resulting mixture was heated and stirred at 90°C for 1 hour. After cooling to room temperature, the mixture was diluted with water and extracted with ethyl acetate (x3). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using 10% MeOH in DCM to afford **18** (0.726 g, 60%). ES (+) MS m/e = 390 (M+1).

[0439] **Compound 19:** To a solution of **18** (0.73 g, 1.9 mmol) in 1 mL MeOH was added 5 mL of 4.0M HCl in dioxanes. The reaction mixture was stirred for 1 hour then concentrated under reduced pressure to afford **19** (0.74 g, 100%). ES (+) MS m/e = 290 (M+1).

[0440] **Compound 20:** 3-chlorophenyl isocyanate (64 mgs, 0.42 mmol) was added to a solution containing **19** (80 mgs, 0.21 mmol) and triethylamine (0.14 mL, 1.0 mmol) in 3 mL of THF. The reaction mixture was stirred for 30 minutes,

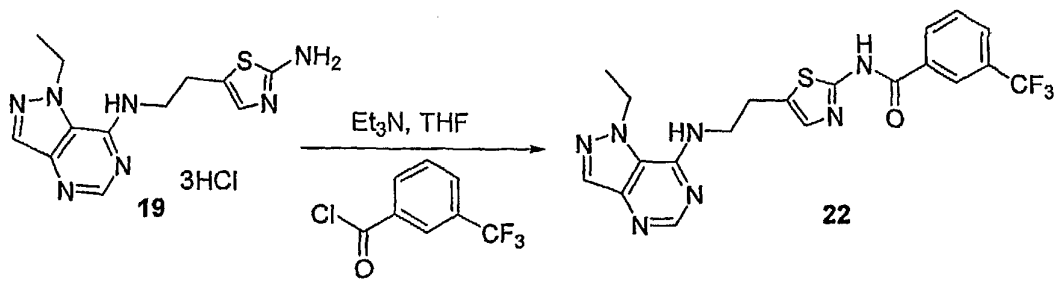
concentrated, and purified by prep RP-HPLC to afford **20**. ^{1}H NMR (d6-DMSO) δ 1.32 – 1.36 (t, 3H, J = 6.8 Hz) 3.12 – 3.15 (m, 2H) 3.92 – 3.93 (m, 2H) 4.67 – 4.72 (q, 2H, J = 7.4 Hz) 7.06 (bs, 1H) 7.15 (s, 1H) 7.30 – 7.32 (m, 1H) 7.70 (s, 1H) 8.21 (s, 1H) 8.74 (s, 1H) 8.91 (bs, 1H) 9.37 (s, 1H); ES (+) MS m/e = 443 (M+1).

[0441] EXAMPLE 13



[0442] Compound 21: 3-trifluorophenyl isocyanate (77 mgs, 0.42 mmol) was added to a solution containing **19** (0.21 mmol, 80 mgs) and triethylamine (0.14 mL, 1.0 mmol) in 3 mL of THF. The reaction mixture was stirred for 30 minutes, concentrated, and purified by prep RP-HPLC to afford **21**. ^{1}H NMR (d6-DMSO) δ 1.32 – 1.35 (t, 3H, J = 7.4 Hz) 3.12 – 3.15 (m, 2H) 3.92 – 3.93 (m, 2H) 4.67 – 4.72 (q, 2H, J = 7.4 Hz) 7.16 (bs, 1H) 7.34 – 7.36 (m, 1H) 7.50 – 7.52 (m, 1H) 7.61 – 7.63 (m, 1H) 8.02 (s, 1H) 8.21 (s, 1H) 8.74 (s, 1H) 8.91 (bs, 1H) 9.55 (s, 1H); ES (+) MS m/e = 477 (M+1).

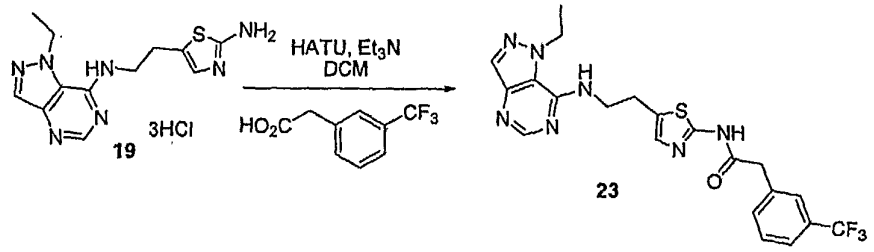
[0443] EXAMPLE 14



[0444] Compound 22: To a mixture of **19** (0.072 g, 0.18 mmol) and triethylamine (0.13 mL, 0.9 mmol) in 3 mL of THF was added 3-(trifluoromethyl)-

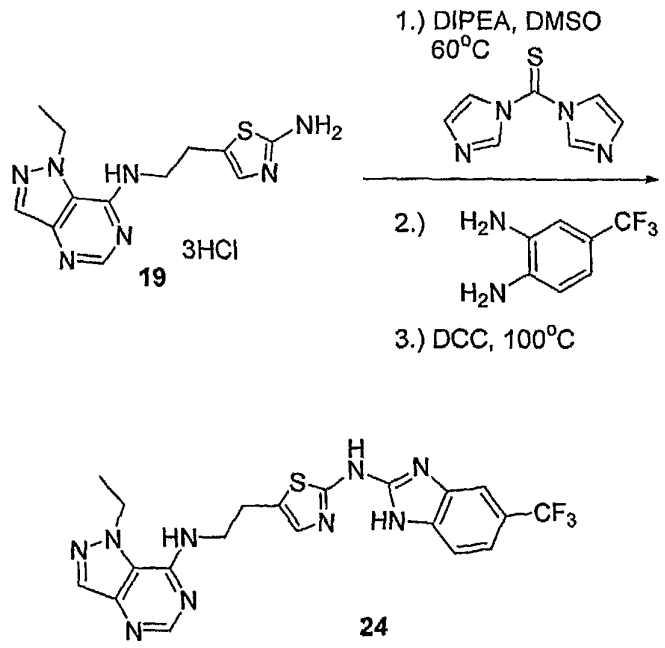
benzoyl chloride (0.038 g, 0.18 mmol). After stirring for 0.5h, the reaction was quenched with methanol and concentrated under reduced pressure to yield an oily residue. The crude was purified by prep RP-HPLC to afford **22**. ES (+) MS m/e = 462 (M+1).

[0445] EXAMPLE 15



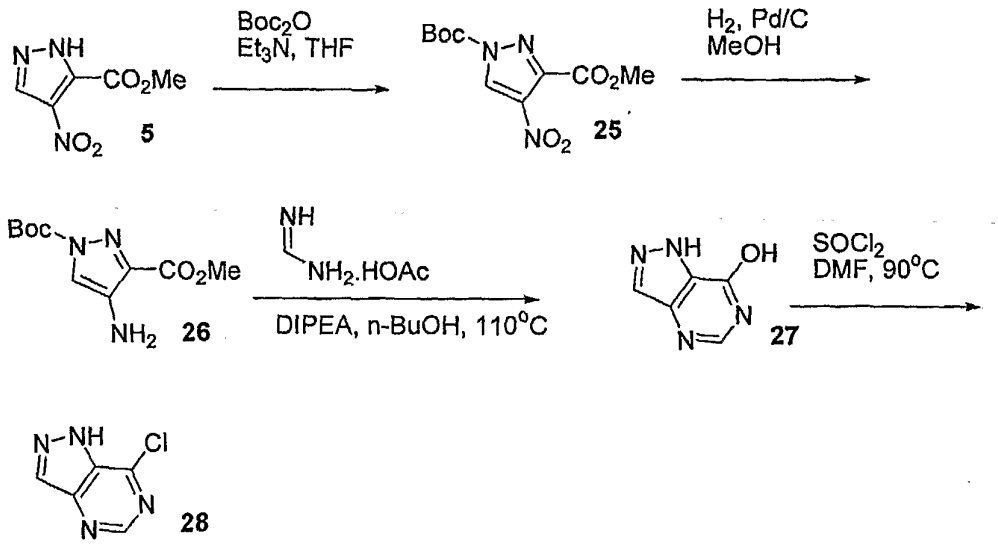
[0446] Compound 23: HATU (0.085 g, 0.22 mmol) was added to a solution containing trifluoro-m-tolyl acetic acid (0.046 g, 0.22 mmol), **19** (0.089 g, 0.22 mmol) and triethylamine (0.16 mL, 1.1 mmol) in 3 mL of DCM. The reaction mixture was stirred for 30 minutes and quenched with methanol. The reaction mixture was then concentrated under reduced pressure resulting in an oily residue. The crude was purified by prep HPLC to afford **23**. ES (+) MS m/e = 476 (M+1).

[0447] EXAMPLE 16



[0448] **Compound 24:** 1,1'-thiocarbonyldiimidazole (0.054 g, 0.3 mmol) was added to a solution containing **19** (0.12g, 0.3 mmol) and Hunig's base (0.2 mL, 1.2 mmol) in 3 mL of DMSO. The reaction mixture was heated at 60°C. After 30 minutes, 4-(trifluoromethyl)-o-phenylenediamine (0.053 g, 0.3 mmol) was added. The reaction mixture continued to be stirred and heated at 60°C overnight. DCC (0.062 g, 0.33 mmol) was added and the reaction was heated to 100°C. After 1 hour, the reaction mixture was cooled to room temperature. Water was added and the heterogeneous solution was stirred for 15 minutes. The dark brown precipitate was collected and purified by prep RP-HPLC to afford **24**. ES (+) MS m/e = 474 (M+1).

[0449] **EXAMPLE 17**



[0450] **Compound 25:** Boc_2O (12.75 g, 58.4 mmol) was added to a solution containing **5** (10.0 g, 58.4 mmol) and Et_3N (8.1 mL, 58.4 mmol) in THF (200 mL). The reaction mixture was stirred at room temperature for 1 hour and was then diluted with water. The aqueous layer was extracted with ethyl acetate. The combined organic phases were dried with $MgSO_4$, filtered and concentrated to afford **25** (14.7 g, 93%), ES(+) MS m/e = 272 (M+1)..

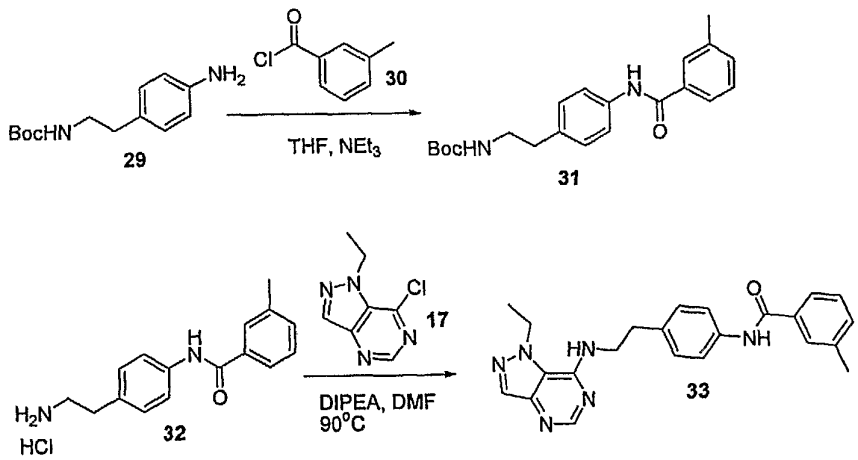
[0451] **Compound 26:** 10%wt Pd/C (2.88 g, 2.7 mmol) was added to a solution containing **25** (14.7 g, 54.2 mmol) in MeOH (200mL). The reaction

mixture was stirred under 1 atm H_2 pressure for 4 hours. The mixture was then filtered thru a plug of Celite and concentrated to afford **26** (11.1 g, 85%), ES (+) MS m/e = 242 (M+1).

[0452] **Compound 27:** Formamidine acetate (40.3 mmol, 4.2 g) was added to a solution containing **26** (8.85 g, 36.7 mmol) in Hunig's base (40 mL) and n-BuOH (40mL). The stirred solution was heated at 110°C for 1 hour. After cooling to ambient temperature the resulting solid was collected, washed with dichloromethane, and dried under reduced pressure to afford **27** (4.46 g, 89%), ES (+) MS m/e = 137.

[0453] **Compund 28:** DMF (1.05 mL) was added to a solution containing **27** (1.0 g, 7.3 mmol) in thionyl chloride (21 mL). Heated the stirring solution to 90°C for 1 hour. Cooled the homogeneous reaction mixture to room temperature. Concentrated to remove volatiles and diluted the reaction mixture with EtOAc followed by ice. Extracted the aqueous layer with EtOAc. Combined the organics, washed with saturated $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated to afford **28** (0.73 g, 64%), ES (+) MS m/e = 155.

[0454] **EXAMPLE 18**

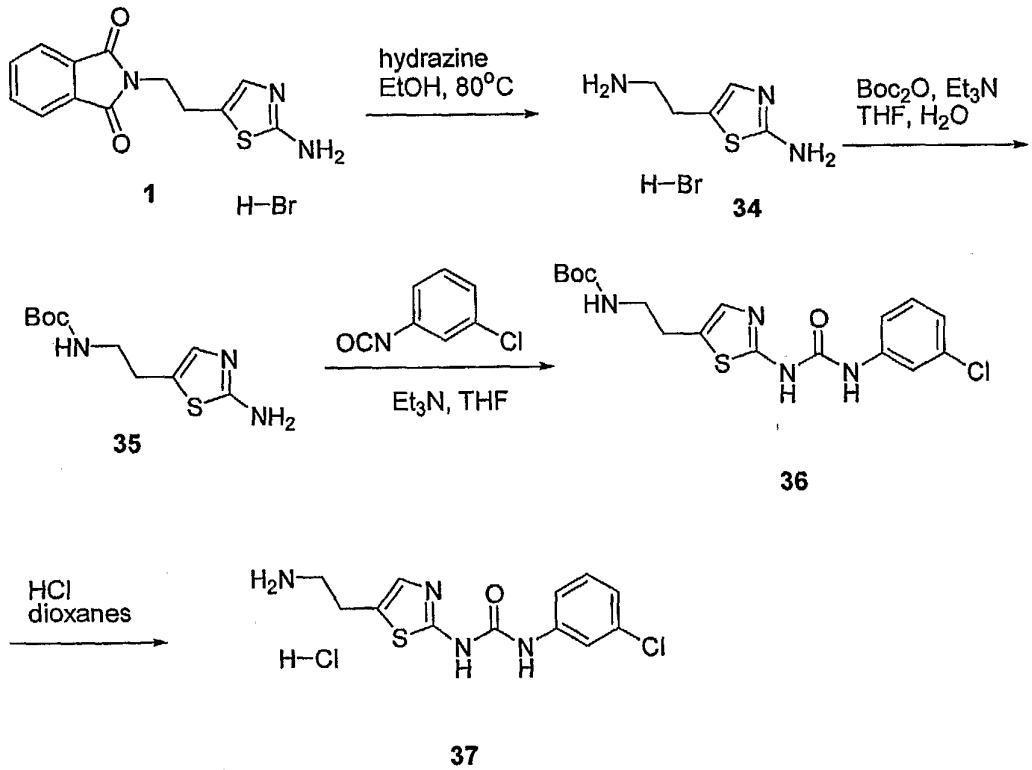


[0455] **Compound 31**: Add **30** (1.0 mmol) drop-wise to a solution of **29** (1.0 mmol) and NEt_3 (2.0 mmol) in THF 10.0 mL under nitrogen at 0°C. When the reaction is completed, dilute with ethyl acetate. Wash with 1.0 M HCl, aqueous sat. $NaHCO_3$, and brine. Dry with Na_2SO_4, concentrate, and purify by flash column chromatography to obtain **31**.

[0456] **Compound 32:** Stir a mixture of **31** (0.5 mmol) in 4.0M HCl in dioxane. After completion, concentrate the mixture and dry the residue under high-vacuum to afford **32.**

[0457] **Compound 33:** Add **17** (1.0 mmol) to a solution containing **32** (1.0 mmol), Hunig's base (2.0 mmol) in 10 mL of DMF. Heat the stirring solution to 90°C for 1 hour. Cool the reaction mixture to room temperature and dilute with water. Extract the aqueous layer with ethyl acetate (x3). Combine organics, dry with $MgSO_4$, filter, and concentrate to obtain crude residue. Purify using prep. RP-HPLC to afford **33.**

[0458] **EXAMPLE 19**



[0459] **Compound 34:** Hydrazine monohydrate (8.4 mL, 173.6 mmol) was added to a heterogeneous solution of **1** (15.37 g, 43.4 mmol, Eriks, J.C. *et al. J.Med.Chem.*, **1992**, 3239.) in THF (150mL) and EtOH (150mL). The reaction mixture was stirred and heated to 80°C for 5 hours. The reaction mixture was cooled to room temperature and filtered. The resulting white solid was washed with

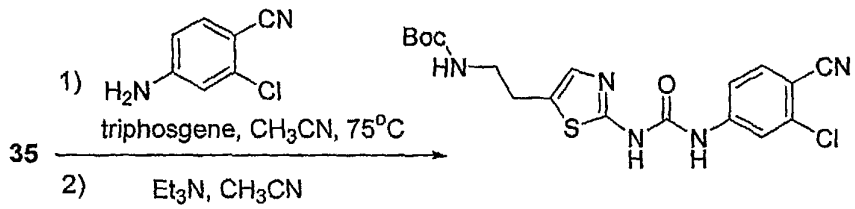
methanol. The filtrate was then concentrated to obtain **34** (9.72 g, 100%) as a white solid, ES (+) MS m/e = 144 (M+1).

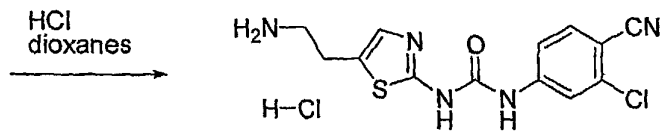
[0460] **Compound 35:** Boc_2O (10.4 g, 47.7 mmol) was added to a solution of **34** (9.72 g, 43.4 mmol) in Et_3N (12.1 mL, 86.7 mmol), THF (220 mL) and H_2O (20 mL). The reaction mixture was stirred for 1 hour and was then diluted with water/EtOAc (1:1, 600 mL). The layers were separated and the aqueous layer was extracted with EtOAc (150mL x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to afford **35** (10.55 g, 100%) as a white solid, ES (+) MS m/e = 244 (M+1).

[0461] **Compound 36:** 3-Chlorophenyl isocyanate (5.2 mL, 43.3 mmol) was added to a solution of **35** (10.55 g, 43.3 mmol), Et_3N (12.7 mL, 91.0 mmol), and THF (220mL). The reaction mixture was stirred for 3 hours and concentrated under reduced pressure. The resulting solid was triturated with 1:1 DCM: hexanes to afford **36** (16g, 93%) as a white solid, ES (+) MS m/e = 397 (M+1).

[0462] **Compound 37:** HCl (50 mL, 4M in dioxanes) was added to a solution of **36** (16 g, 40.3 mmol) in MeOH (200 mL). The reaction mixture was stirred for 1 hour and concentrated to afford **37** (13.43 g, 100%) as a white solid, ES (+) MS m/e = 297 (M+1).

[0463] **EXAMPLE 20**





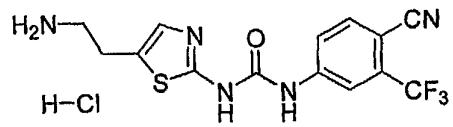
39

[0464] **Compound 38:** Triphosgene (0.48 g, 1.61 mmol) was added to a solution of 4-amino-2-chlorobenzonitrile (0.62g, 4.1 mmol) in CH_3CN (10mL). The

reaction mixture was heated to 75°C for 1.5 hours and then slowly cooled to room temperature. A solution containing **35** (0.99 g, 4.1 mmol), Et_3N (2.2 mL, 16.3 mmol) and CH_3CN (10mL) was added and stirred for 15 minutes. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel using 20% MeOH in DCM to afford **6** (0.43 g, 30%).

[0465] **Compound 39:** HCl (2 mL, 4M in dioxanes) was added to a solution of **38** (0.43 g, 1.0 mmol) in MeOH (5 mL). The reaction mixture was stirred for 1 hour and concentrated to afford **39** (0.37 g, 100%) as a white solid, ES (+) MS m/e = 322 (M+1).

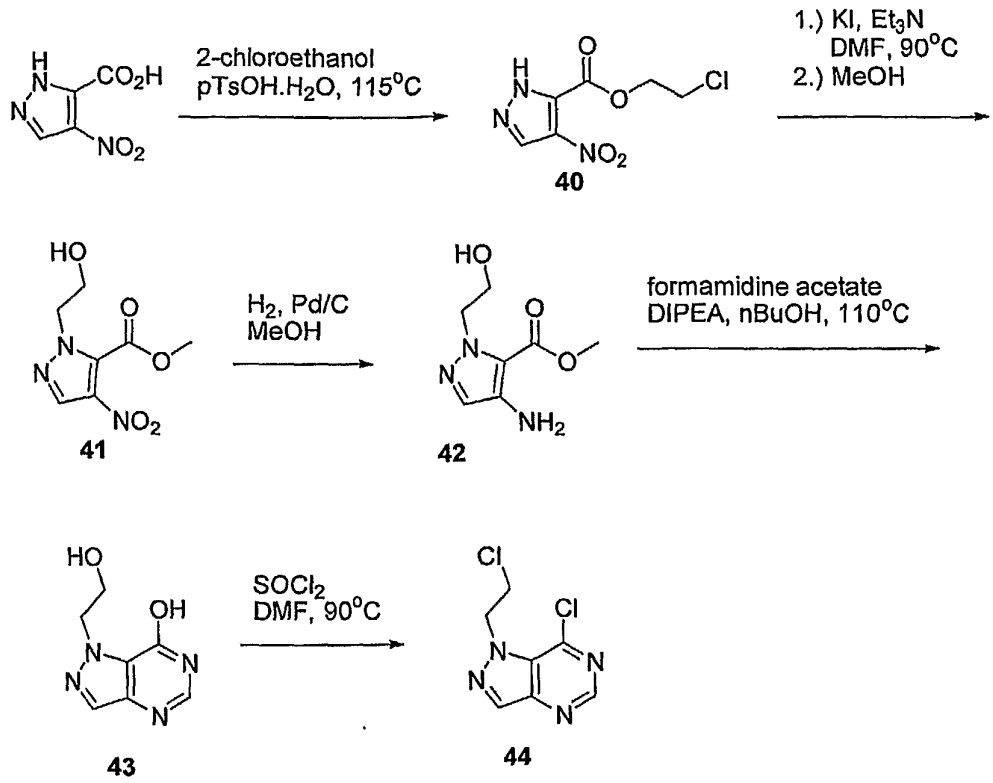
[0466] **EXAMPLE 21**



39A

[0467] **Compound 39A:** This compound was made according to procedures towards the synthesis of **38** and **39** except that 4-amino-2-trifluoromethylbenzonitrile was used in place of 4-amino-2-chlorobenzonitrile, ES (+) MS m/e = 356 (M+1).

[0468] **EXAMPLE 22**



[0469] **Compound 40:** pTsOH monohydrate (1.2 g, 6.4 mmol) was added to a solution containing 4-nitro-3-pyrazole carboxylic acid (10 g, 63.7 mmol) in 2-chloroethanol (64 mL). The reaction mixture was heated to 115°C for 2 hours and cooled to room temperature. The bulk solvent was removed under reduced pressure. The residue was diluted with EtOAc and aqueous saturated $NaHCO_3$. The layers were separated and the aqueous phase was extractred with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford **40** (14 g, 100%), ES (+) MS m/e = 220 (M+1).

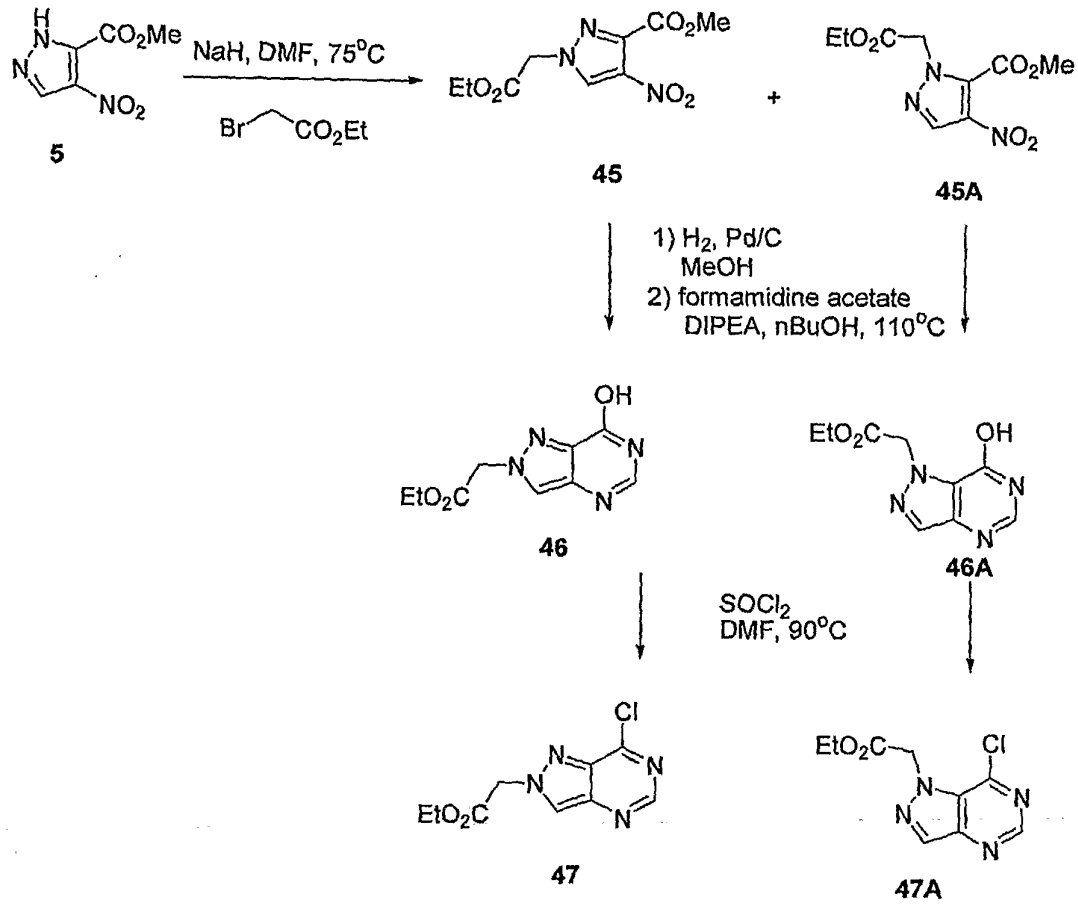
[0470] **Compound 41:** Et_3N (18 mL, 127.5 mmol) was added to a solution of **40** (14 g, 63.8 mmol) and KI (1.0 g, 6.4 mmol) in DMF (200 mL). The reaction mixture was heated to 90°C and stirred for 16 hours. Methanol (100 mL) was added and stirred at 90°C for 1 hour. The reaction mixture was cooled to room temperature. Excess methanol was removed under reduced pressure. The reaction mixture was diluted with H_2O. The aqueous layer was extracted with EtOAc, the combined organics were dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel using 50% EtOAc in hexanes to afford **41** (6.08 g, 44%), ES (+) MS m/e = 216 (M+1).

[0471] **Compound 42:** **41** (6.0 g, 27.9 mmol) was placed in a flask containing 10%wt Pd/C (1.48 g, 1.4 mmol) in MeOH (100mL) with 1 atm H_2, via balloon. After stirring overnight, the reaction mixture was filtered thru a plug of Celite and concentrated to afford **42** (5.16 g, 100%), ES (+) MS m/e = 186 (M+1).

[0472] **Compound 43:** Formamidine acetate (3.34 g, 30.7 mmol) was added to a solution containing **42** (5.16 g, 27.9 mmol), Hunig's base (30 mL) and n-butanol (30 mL). The reaction mixture was heated to 110°C for 1 hour. The reaction mixture was cooled to room temperature. Et_2O (30 mL) was added and the resulting solid was collected, washed with Et_2O, and dried under vacuum to afford **43** (4.3g, 85%), ES (+) MS m/e = 181 (M+1).

[0473] **Compound 44:** DMF (8mL) was added to a solution containing **43** (4.32 g, 24.0 mmol) in $SOCl_2$ (80 mL). The heterogeneous reaction mixture was heated to 90°C for 30 minutes and the homogeneous solution was cooled to room temperature. The solvents were removed under reduced pressure. The resulting residue was diluted with EtOAc, followed by ice. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were washed with saturated $NaHCO_3$, followed by brine. The resulting organics were dried with $MgSO_4$, filtered, and concentrated to afford **44** (3.02 g, 58%), ES (+) MS m/e = 218 (M+1).

[0474] **EXAMPLE 23**



[0475] **Compound 45 and 45A:** Ethyl bromoacetate (3.9 mL, 35.0 mmol) was added to a preheated solution of **5** (4.0 g, 23.4 mmol) and 60% wt of NaH (1.4 g, 35.0 mmol) in DMF (50 mL) at 75°C. The reaction mixture was stirred for 30 minutes and then cooled to room temperature. The reaction mixture was diluted with H_2O. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel using 20% EtOAc in hexanes to afford **45A** (0.79 g, 13%), ES (+) MS m/e = 258 (M+1) and using 30% EtOAc in hexanes to afford **45** (3.3 g, 55%), ES (+) MS m/e = 258 (M+1).

[0476] **Compound 46:** **45** (6.12 g, 23.8 mmol) was placed in a flask containing 10%wt Pd/C (1.27 g, 1.2 mmol) in MeOH (30mL) with 1 atm H_2, via balloon. The reaction was stirred overnight. Filtered thru a plug of Celite and concentrated to afford oily residue. The residue was diluted with n-butanol (50 mL) followed by Hunig's base (50 mL). Formamidine acetate (2.72 g, 26.2 mmol) was added and the reaction was heated to 110°C for 1 hour. The reaction was cooled to room temperature and concentrated to remove solvents. The resulting residue was diluted with H_2O. The aqueous layer was extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated to afford **46** (3.86 g, 73%), ES (+) MS m/e = 223 (M+1).

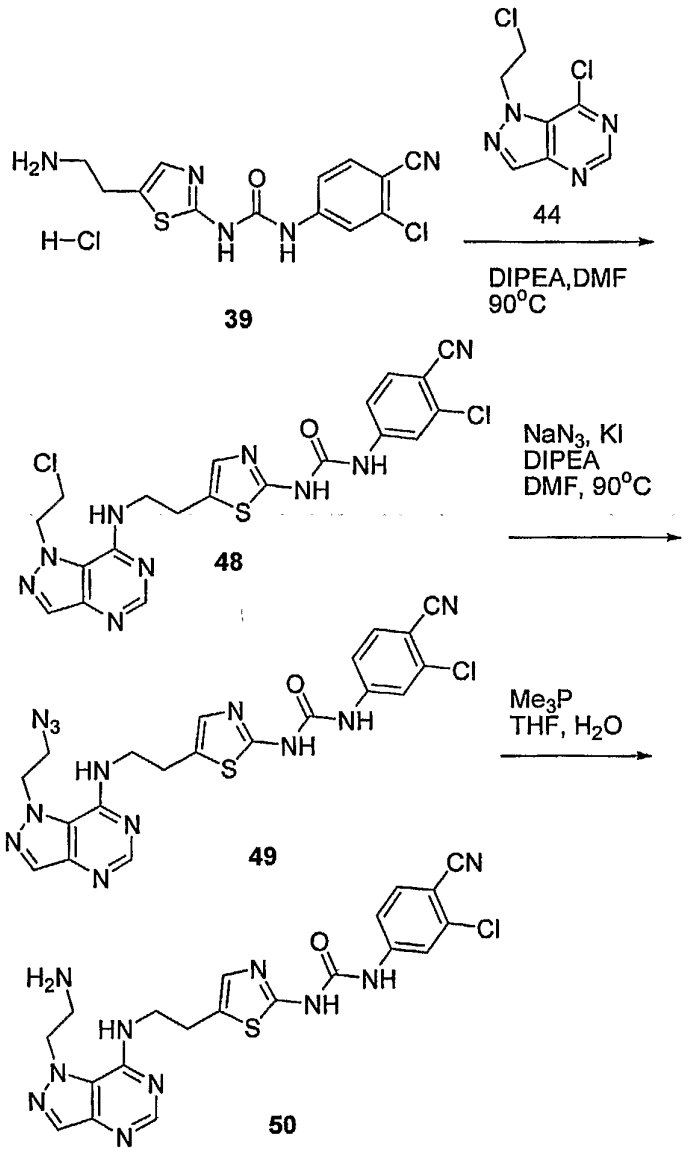
[0477] **Compound 46A:** **45A** (0.79 g, 3.1 mmol) was placed in a flask containing 10%wt Pd/C (0.32 g, 0.3 mmol) in MeOH (30mL) with 1 atm H_2, via balloon. The reaction was stirred overnight. Filtered thru a plug of Celite and concentrated to afford oily residue. The residue was diluted with n-butanol (6 mL) followed by Hunig's base (6 mL). Formamidine acetate (0.33 g, 3.1 mmol) was added and the reaction was heated to 110°C for 1 hour. The reaction was cooled to room temperature and concentrated to remove solvents. The resulting residue was diluted with H_2O. The aqueous layer was extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated to afford **46A** (0.63 g, 95%), ES (+) MS m/e = 223 (M+1).

[0478] **Compound 47:** DMF (2.5 mL) was added to a solution containing **46** (1.69 g, 7.6 mmol) in $SOCl_2$ (25 mL). The heterogeneous reaction mixture was heated to 90°C for 30 minutes and the homogeneous solution was cooled to room temperature. The solvents were removed under reduced pressure. The resulting residue was diluted with EtOAc, followed by ice. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were washed with saturated $NaHCO_3$, followed by brine. The resulting organics were dried with $MgSO_4$, filtered, and concentrated to afford **47** (1.56 g, 92%), ES (+) MS m/e = 241 (M+1).

[0479] **Compound 47A:** DMF (1.0 mL) was added to a solution containing **46A** (0.63 g, 2.8 mmol) in $SOCl_2$ (10 mL). The heterogeneous reaction mixture was heated to 90°C for 30 minutes and the homogeneous solution was cooled to room temperature. The solvents were removed under reduced pressure. The

resulting residue was diluted with EtOAc, followed by ice. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were washed with saturated $NaHCO_3$, followed by brine. The resulting organics were dried with $MgSO_4$, filtered, and concentrated to afford The resulting organics were dried with $MgSO_4$, filtered, and concentrated to afford **18** (0.52 g, 76%), ES (+) MS m/e = 241 (M+1).

[0480] EXAMPLE 24



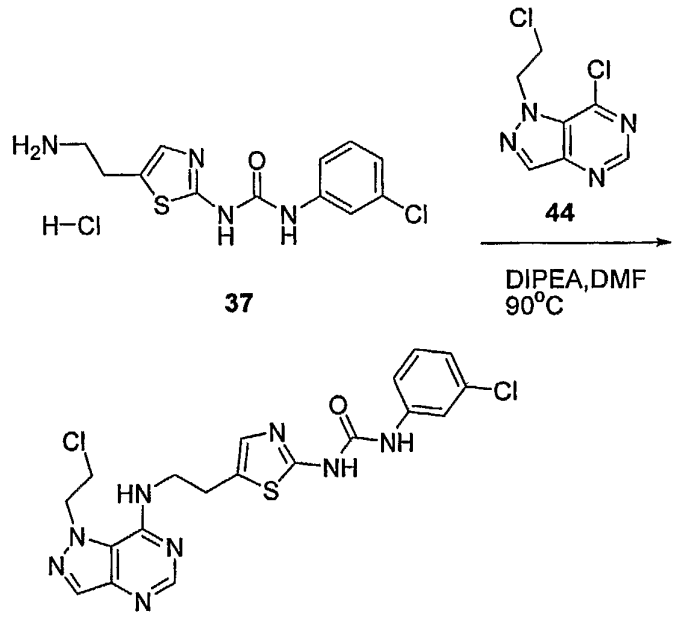
[0481] Compound 48: **39** (3.07 g, 8.6 mmol) was added to a solution containing **44** (1.86 g, 8.6 mmol) and Hunig's base (5.9 mL, 34.3 mmol) in DMF

(30 mL). The reaction mixture was heated to 90°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction was diluted with H_2O and extracted aqueous layer with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated. Purification on silica gel using 10% MeOH in DCM afforded **48** (1.78 g, 41%), ES (+) MS m/e = 503 (M+1).

[0482] **Compound 49:** Sodium azide (0.15 g, 2.4 mmol) was added to a solution containing **48** (0.6 g, 1.2 mmol), KI (0.02 g, 0.1 mmol), and Hunig's base (0.64 mL, 3.6 mmol) in DMF (5 mL). The reaction mixture was heated to 90°C and stirred for 1 hour. The reaction mixture was cooled to room temperature. The reaction was diluted with H_2O and extracted aqueous layer with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated. Purification on silica gel using 10% MeOH in DCM afforded **49** (0.33 g, 54%), ES (+) MS m/e = 510 (M+1).

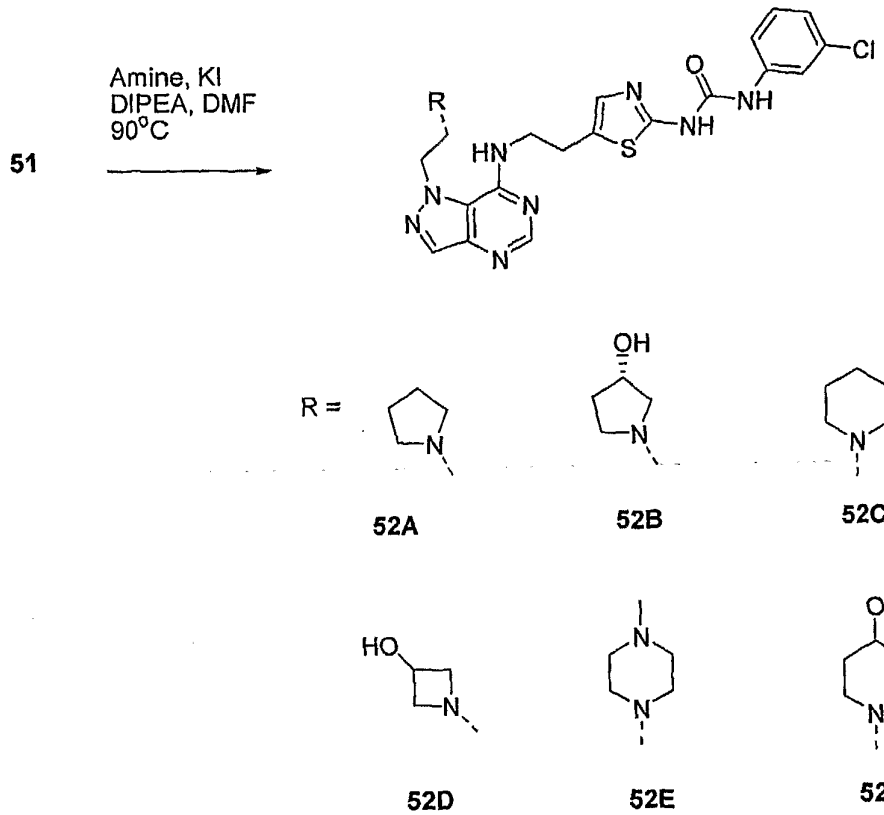
[0483] **Compound 50:** Trimethylphosphine (1.3 mL, 1.0M in THF) was added to a solution containing **49** (0.33g, 0.6 mmol) in THF (5mL) and H_2O (0.5mL). The reaction mixture was stirred overnight. The reaction mixture was concentrated and triturated with DCM and hexanes to afford **50** (0.31g, 100%), ES (+) MS m/e = 484 (M+1).

[0484] **EXAMPLE 25**



[0485] **Compound 51:** **37** (0.35 g, 1.6 mmol) was added to a solution containing **44** (0.54 g, 1.6 mmol) and Hunig's base (1.1 mL, 6.4 mmol) in DMF (16 mL). The reaction mixture was heated to 90°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction was diluted with H_2O and extracted aqueous layer with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated. Purification on silica gel using 10% MeOH in DCM afforded **51** (0.41 g, 54%), ES (+) MS m/e = 478 (M+1).

[0486] **EXAMPLE 26**



[0487] **Compound 52A:** Pyrrolidine (16 mgs, 0.02 mmol) was added to a solution containing **51** (55 mgs, 0.01 mmol), Hunig's base (0.05 mL, 0.3 mmol), and KI (2 mgs) in DMF (3 mL). The reaction mixture was heated to 90 °C overnight. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The

residue thus obtained was lyophilized under high-vacuum to yield **52A** as the tris TFA salt, ES (+) MS m/e = 513 (M+1).

[0488] **Compound 52B:** This compound was made according to procedures towards the synthesis of **52A** except that S(+)-3-pyrrolidinol was used in place of pyrrolidine, ES (+) MS m/e = 528 (M+1).

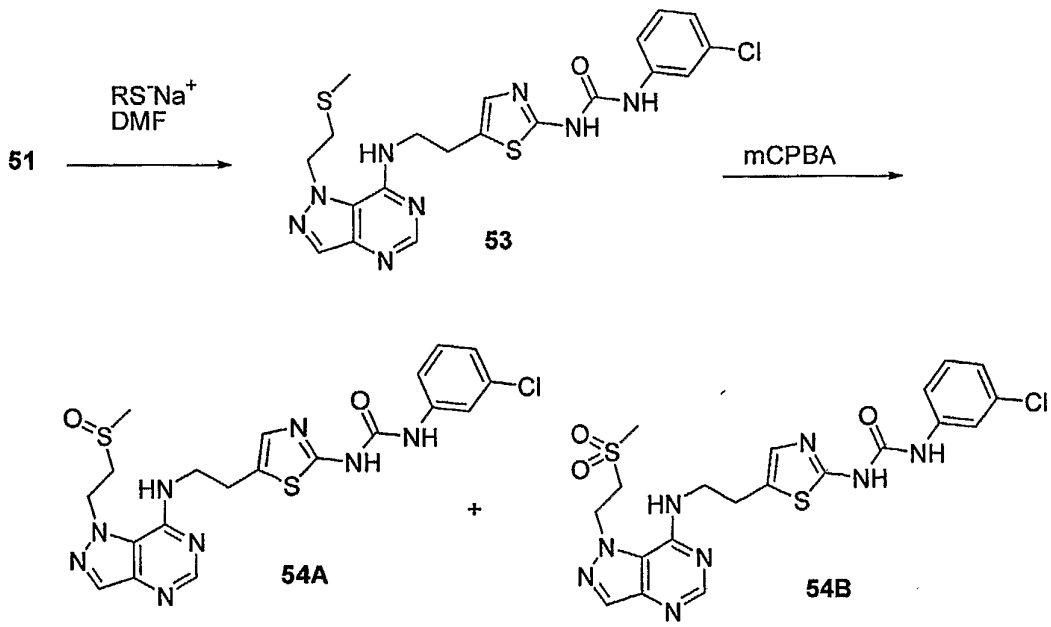
[0489] **Compound 52C:** This compound was made according to procedures towards the synthesis of **52A** except that 3-hydroxypiperidine was used in place of pyrrolidine, ES (+) MS m/e = 542 (M+1).

[0490] **Compound 52D:** This compound was made according to procedures towards the synthesis of **52A** except that 3-hydroxyazetidine was used in place of pyrrolidine, ES (+) MS m/e = 514 (M+1).

[0491] **Compound 52E:** This compound was made according to procedures towards the synthesis of **52A** except that 4-methylpiperazine was used in place of pyrrolidine, ES (+) MS m/e = 541 (M+1).

[0492] **Compound 52F:** This compound was made according to procedures towards the synthesis of **52A** except that 4-hydroxypiperidine was used in place of pyrrolidine, ES (+) MS m/e = 542 (M+1).

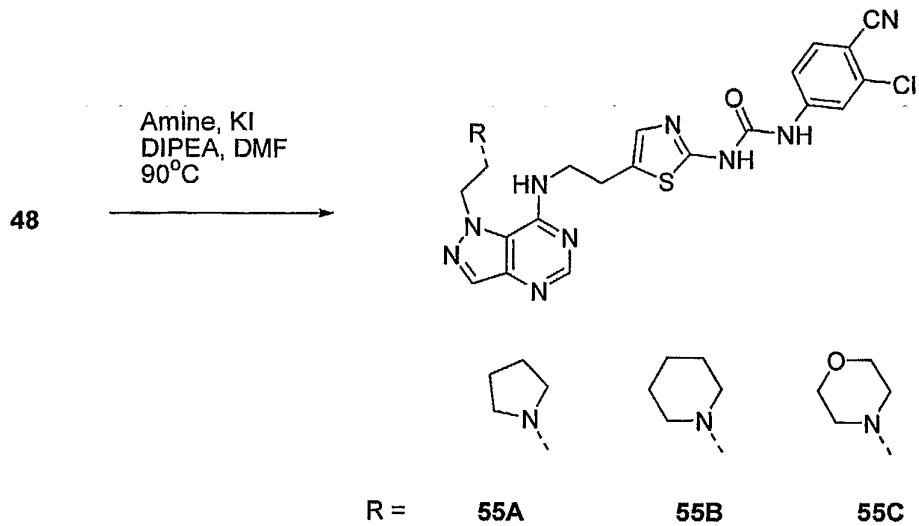
[0493] **EXAMPLE 27**



[0494] **Compound 53:** Sodium thiomethoxide (57 mgs, 0.81 mmol) was added to a solution containing **51** (0.31 g, 0.65 mmol) in DMF (3 mL). The reaction mixture was stirred for 30 minutes. The solvent was removed under reduced pressure and purified by column chromatography on silica gel using 10% MeOH in DCM to afford **53** (0.21 g, 66%), ES (+) MS m/e = 489 (M+1).

[0495] **Compound 54A and 54B:** 77%wt of mCPBA (0.13 g, 0.74 mmol) was added to a solution containing **51** (0.26 g, 0.53 mmol) in DCM. The reaction mixture was stirred overnight. Diluted reaction mixture with saturated $NaHCO_3$ and extracted aqueous layer with EtOAc. The combined organics were dried, filtered, and concentrated. . The crude residue was purified by prep RP-HPLC. The fractions containing pure compounds were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **54A** as the bis TFA salt, ES (+) MS m/e = 505 (M+1) and **54B** as the bis TFA salt, ES (+) MS m/e = 521 (M+1).

[0496] **EXAMPLE 28**



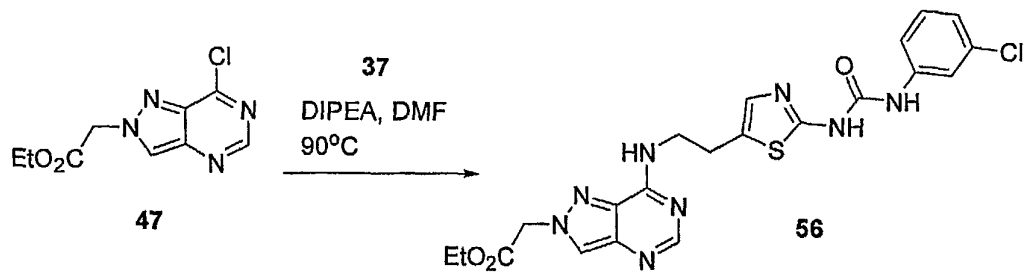
[0497] **Compound 55A:** Pyrrolidine (0.033 mL, 0.4 mmol) was added to a solution containing **48** (0.1 g, 0.2 mmol), Hunig's base (0.1 mL, 0.6 mmol) and KI (3 mgs) in DMF (3 mL). The reaction mixture was heated to 90 °C overnight. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus

obtained was lyophilized under high-vacuum to yield **55A** as the tris TFA salt, ES (+) MS m/e = 538 (M+1).

[0498] **Compound 55B:** Piperidine (0.04 mL, 0.4 mmol) was added to a solution containing **48** (0.1 g, 0.2 mmol), Hunig's base (0.1 mL, 0.6 mmol) and KI (3 mgs) in DMF (3 mL). The reaction mixture was heated to 90 °C overnight. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **55B** as the tris TFA salt, ES (+) MS m/e = 552 (M+1).

[0499] **Compound 55C:** Morpholine (0.035 mL, 0.4 mmol) was added to a solution containing **48** (0.1 g, 0.2 mmol), Hunig's base (0.1 mL, 0.6 mmol) and KI (3 mgs) in DMF (3 mL). The reaction mixture was heated to 90 °C overnight. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **55C** as the tris TFA salt, ES (+) MS m/e = 554 (M+1).

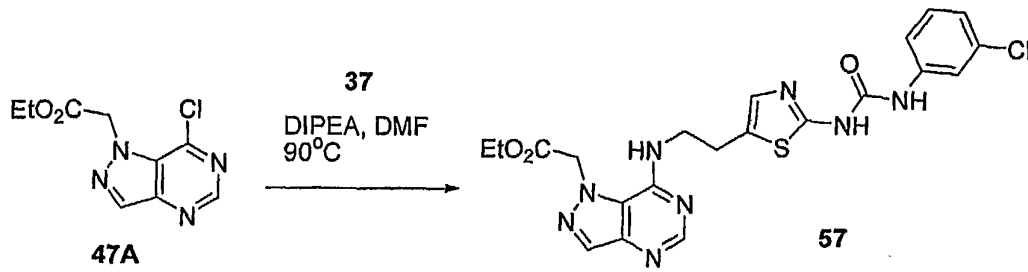
[0500] **EXAMPLE 29**



[0501] **Compound 56:** **37** (1.44 g, 4.2 mmol) was added to a solution containing **47** (1.04 g, 4.2 mmol) and Hunig's base (2.2 mL, 13.0 mmol) in DMF (10 mL). The reaction mixture was heated to 90°C for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with water and extracted three times with EtOAc. The combined organics were dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography on silica

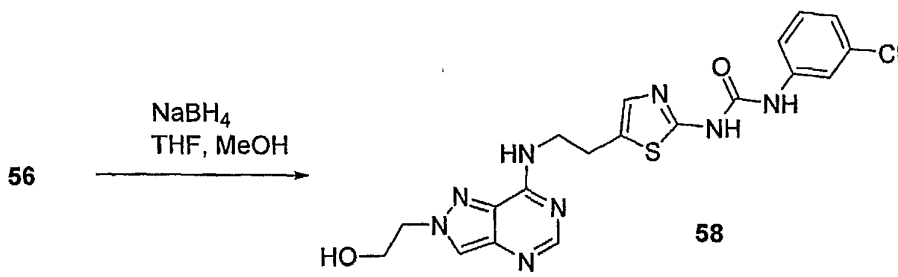
gel using 10% MeOH in DCM to afford **56** (1.0 g, 46%), ES (+) MS m/e = 502 (M+1).

[0502] EXAMPLE 30



[0503] Compound 57: **37** (0.72 g, 2.1 mmol) was added to a solution containing **47A** (0.52 g, 2.1 mmol) and Hunig's base (1.1 mL, 6.5 mmol) in DMF (3 mL). The reaction mixture was heated to 90°C for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with water and extracted three times with EtOAc. The combined organics were dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography on silica gel using 10% MeOH in DCM to afford **57** (0.3 g, 28%), ES (+) MS m/e = 502 (M+1).

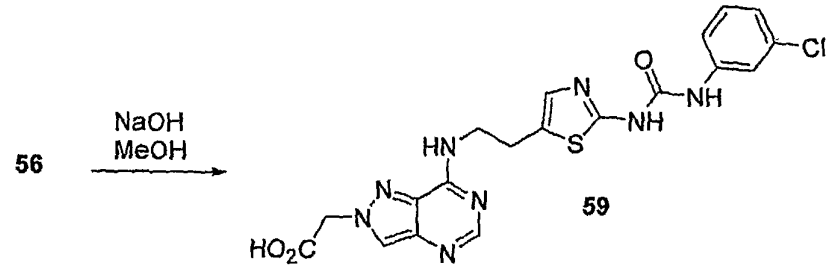
[0504] EXAMPLE 31



[0505] Compound 58: Sodium borohydride (8 mgs, 0.2 mmol) to a solution containing **56** (0.05 g, 0.1 mmol) in THF (3 mL) and MeOH (0.3 mL). The reaction mixture was stirred for 1 hour. The reaction mixture was diluted with and extracted three times with EtOAc. The combined organics were dried ($MgSO_4$) and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus

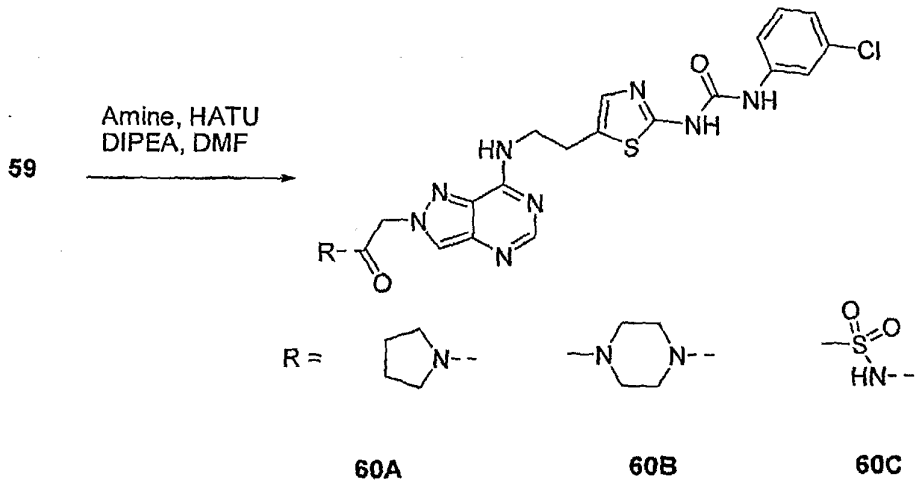
obtained was lyophilized under high-vacuum to yield **58** as the bis TFA salt, ES (+) MS m/e = 460 (M+1).

[0506] EXAMPLE 32



[0507] Compound 59: 2M NaOH (1 mL) was added to a solution containing **56** (0.6 g, 1.2 mmol) in MeOH (10 mL). The reaction mixture was stirred for 10 minutes. The mixture was then concentrated followed by the addition of water (3 mL). Aqueous 1M HCl was added until solid precipitated from the solution. The solid was collected and dried to yield **59** (0.4 g, 70%), ES (+) MS m/e = 474 (M+1).

[0508] EXAMPLE 33



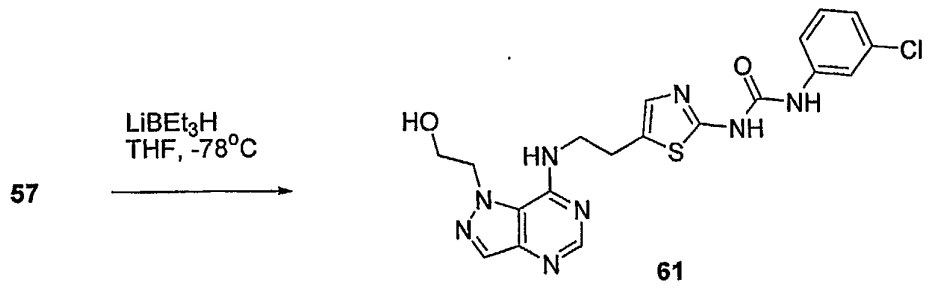
[0509] Compound 60A: HATU (0.136 g, 0.36 mmol) was added to a solution containing **59** (0.085 g, 0.18 mmol), Hunig's base (0.16 mL, 0.9 mmol), pyrrolidine (26 mgs, 0.36 mmol) in DMF (3 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. The aqueous layer was extracted twice with EtOAc. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated.

The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **60A** as the bis TFA salt, ES (+) MS m/e = 527 (M+1).

[0510] **Compound 60B:** HATU (0.136 g, 0.36 mmol) was added to a solution containing **59** (0.085 g, 0.18 mmol), Hunig's base (0.16 mL, 0.9 mmol), N-methyl piperazine (36 mgs, 0.36 mmol) in DMF (3 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature.. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **60B** as the tris TFA salt, ES (+) MS m/e = 556 (M+1).

[0511] **Compound 60C:** HATU (0.136 g, 0.36 mmol) was added to a solution containing **59** (0.085 g, 0.18 mmol), Hunig's base (0.16 mL, 0.9 mmol), methanesulfonamide (30 mgs, 0.36 mmol) in DMF (3 mL). The reaction mixture was heated to 70°C and stirred for overnight. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **60C** as the bis TFA salt, ES (+) MS m/e = 551 (M+1).

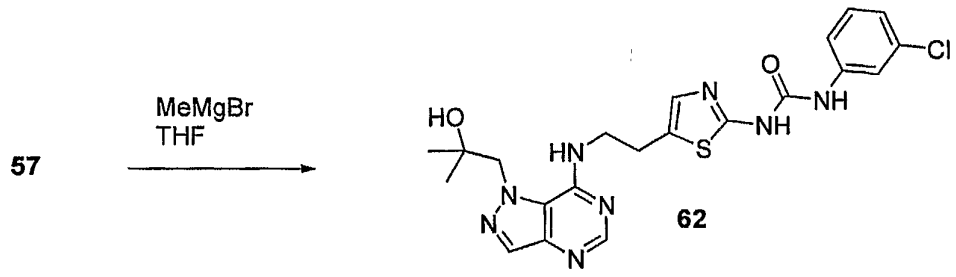
[0512] **EXAMPLE 34**



[0513] **Compound 61:** $LiBEt_3H$ (0.3 mL, 1.0M in THF) was added to a pre-cooled solution of **57** (73 mgs, 0.15 mmol) in THF (5 mL) at –78°C. The reaction

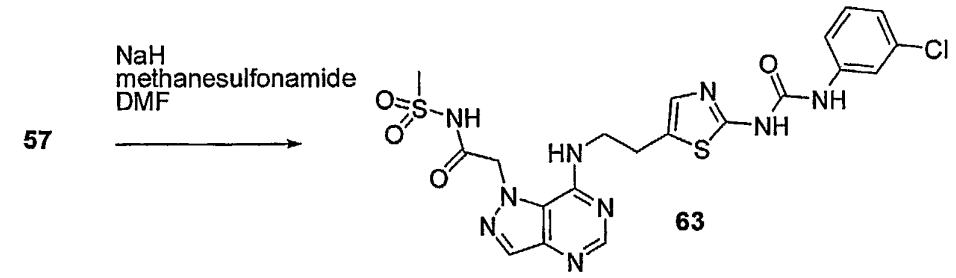
mixture was stirred at –78°C for 1 hour and warmed to room temperature. The reaction mixture was diluted with 1M $NaHCO_3$ and extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **61** as the bis TFA salt, ES (+) MS m/e = 460 (M+1).

[0514] EXAMPLE 35



[0515] Compound 62: Methyl magnesium bromide (0.2 mL, 3.0M in Et_2O) was added to a solution of **57** (75 mgs, 0.15 mmol) in THF. The reaction mixture was stirred for 30 minutes. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **62** as the bis TFA salt, ES (+) MS m/e = 488 (M+1).

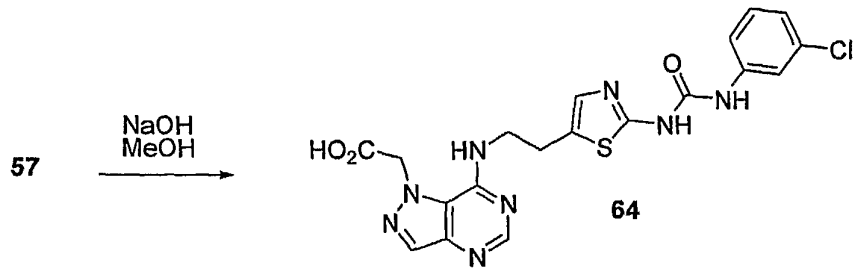
[0516] EXAMPLE 36



[0517] Compound 63: 60%wt of NaH (20 mgs, 0.5 mmol) was added to a solution containing **57** (50 mgs, 0.1 mmol) and methanesulfonamide (20mgs, 0.2 mmol) in DMF (3 mL). The reaction mixture was stirred for 30 minutes. The

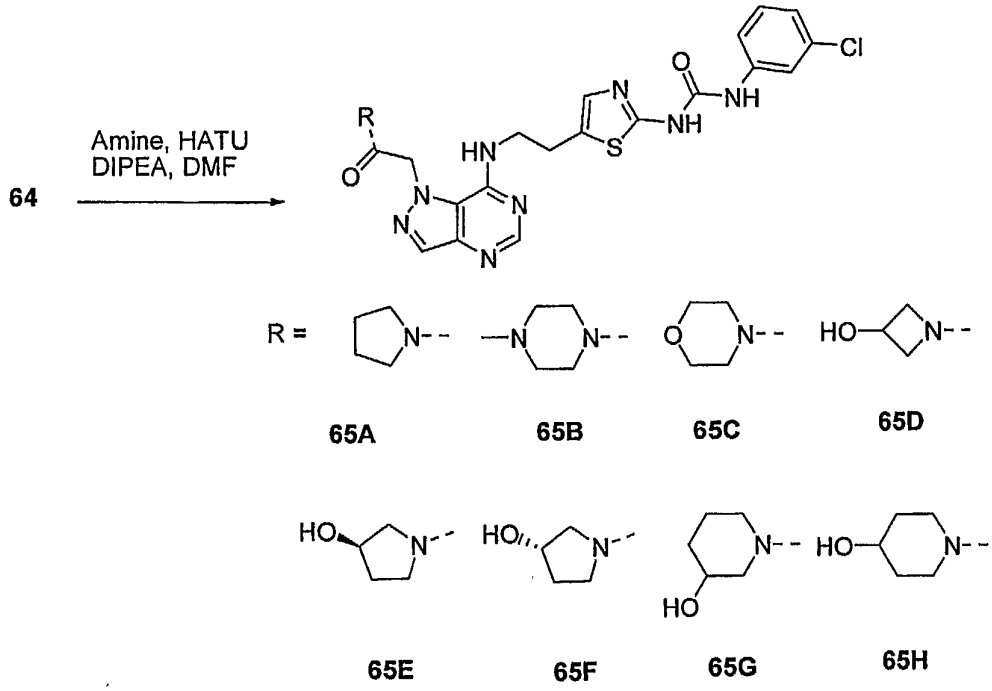
reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **63** as the bis TFA salt, ES (+) MS m/e = 552 (M+1).

[0518] EXAMPLE 37



[0519] Compound 64: 2M NaOH (2.6 mL) was added to a solution of **57** (1.28 g, 2.6 mmol) in MeOH (20 mL). The reaction mixture was stirred for 10 minutes. Concentrated to remove methanol and added H_2O (3 mL). Added 1M HCl until solid precipitated from the solution. Filtered, collected, and dried precipitate as **64** (1.2 g, 99%), ES (+) MS m/e = 474 (M+1).

[0520] EXAMPLE 38



[0521] **Compound 65A:** HATU (0.1 g, 0.27 mmol) was added to a solution containing **64** (0.07 g, 0.13 mmol), Hunig's base (0.12 mL, 0.69 mmol), pyrrolidine (19 mgs, 0.27 mmol) in DMF (2 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **65A** as the bis TFA salt, ES (+) MS m/e = 527 (M+1).

[0522] **Compound 65B:** HATU (0.1 g, 0.27 mmol) was added to a solution containing **64** (0.07 g, 0.13 mmol), Hunig's base (0.12 mL, 0.69 mmol), N-methyl piperazine (28 mgs, 0.27 mmol) in DMF (2 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **65B** as the tris TFA salt, ES (+) MS m/e = 556 (M+1).

[0523] **Compound 65C:** HATU (0.1 g, 0.27 mmol) was added to a solution containing **64** (0.07 g, 0.13 mmol), Hunig's base (0.12 mL, 0.69 mmol), morpholine (24 mgs, 0.27 mmol) in DMF (2 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **65C** as the bis TFA salt, ES (+) MS m/e = 543 (M+1).

[0524] **Compound 65D:** HATU (0.1 g, 0.27 mmol) was added to a solution containing **64** (0.07 g, 0.13 mmol), Hunig's base (0.12 mL, 0.69 mmol), 3-hydroxyazetidine hydrochloride (30 mgs, 0.27 mmol) in DMF (2 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **65D** as the bis TFA salt, ES (+) MS m/e = 529 (M+1).

[0525] **Compound 65E:** HATU (0.1 g, 0.27 mmol) was added to a solution containing **64** (0.07 g, 0.13 mmol), Hunig's base (0.12 mL, 0.69 mmol), R(+)-3-pyrrolidinol (24 mgs, 0.27 mmol) in DMF (2 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **65E** as the bis TFA salt, ES (+) MS m/e = 543 (M+1).

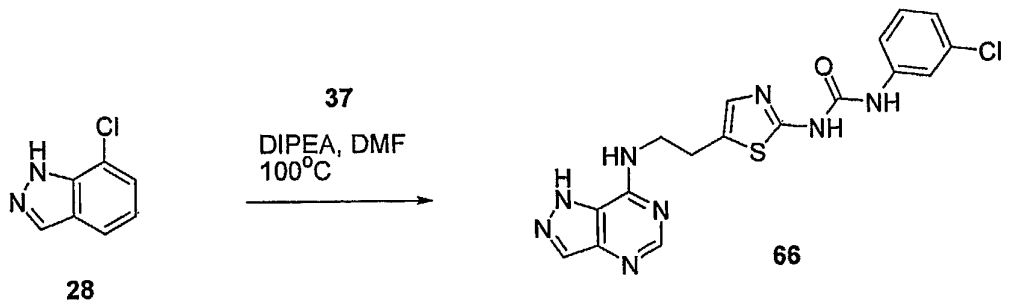
[0526] **Compound 65F:** HATU (0.1 g, 0.27 mmol) was added to a solution containing **64** (0.07 g, 0.13 mmol), Hunig's base (0.12 mL, 0.69 mmol), S(+)-3-pyrrolidinol (24 mgs, 0.27 mmol) in DMF (2 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc.

Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **65F** as the bis TFA salt, ES (+) MS m/e = 543 (M+1).

[0527] **Compound 65G:** HATU (0.1 g, 0.27 mmol) was added to a solution containing **64** (0.07 g, 0.13 mmol), Hunig's base (0.12 mL, 0.69 mmol), 3-hydroxypiperidine (29 mgs, 0.27 mmol) in DMF (2 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **65G** as the bis TFA salt, ES (+) MS m/e = 557 (M+1).

[0528] **Compound 65H:** HATU (0.1 g, 0.27 mmol) was added to a solution containing **64** (0.07 g, 0.13 mmol), Hunig's base (0.12 mL, 0.69 mmol), R(+)-3-pyrrolidinol (24 mgs, 0.27 mmol) in DMF (2 mL). The reaction mixture was heated to 70°C and stirred for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **65H** as the bis TFA salt, ES (+) MS m/e = 543 (M+1).

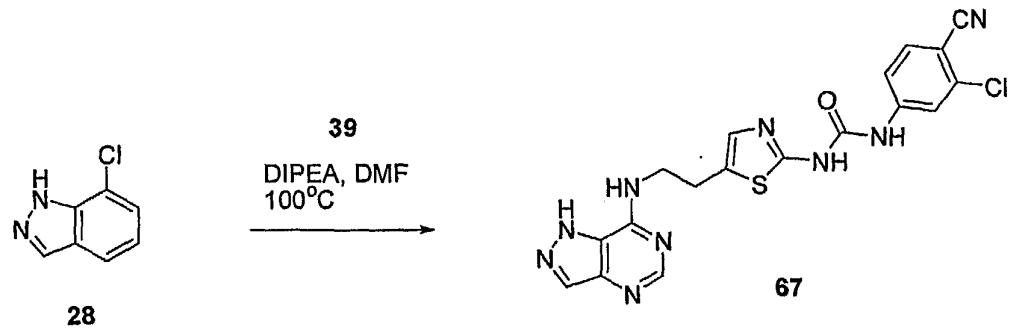
[0529] **EXAMPLE 39**



28 **66**

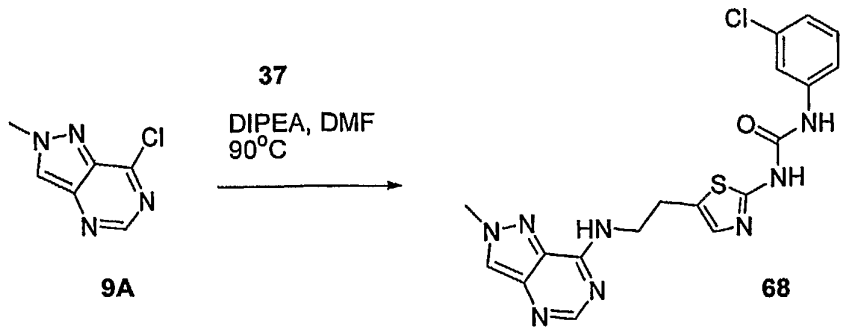
[0530] **Compound 66:** **37** (0.67 g, 2.0 mmol) was added to a solution containing **28** (0.67 g, 2.0 mmol) and Hunig's base (1.4 mL, 8.0 mmol) in DMF (15 mL). The reaction mixture was heated to 100°C for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel using 10% MeOH in DCM to afford **66** (0.45 g, 54%), ES (+) MS m/e = 416 (M+1).

[0531] **EXAMPLE 40**



[0532] **Compound 67:** **39** (0.69 g, 2.0 mmol) was added to a solution containing **28** (0.67 g, 2.0 mmol) and Hunig's base (1.4 mL, 8.0 mmol) in DMF (15 mL). The reaction mixture was heated to 100°C for 1 hour. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel using 10% MeOH in DCM to afford **67** (0.40 g, 49%), ES (+) MS m/e = 440 (M+1).

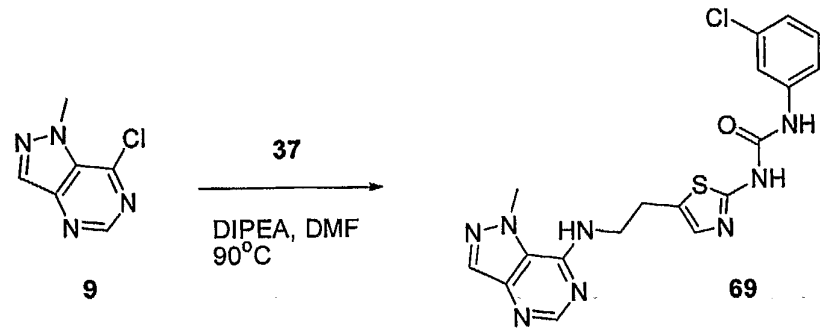
[0533] **EXAMPLE 41**



9A 68

[0534] **Compound 68:** This compound was made according to procedures towards the synthesis of **10**, except that **9A** and **37** was used in place of **9** and **3** respectively, ES (+) MS m/e = 429 (M+1).

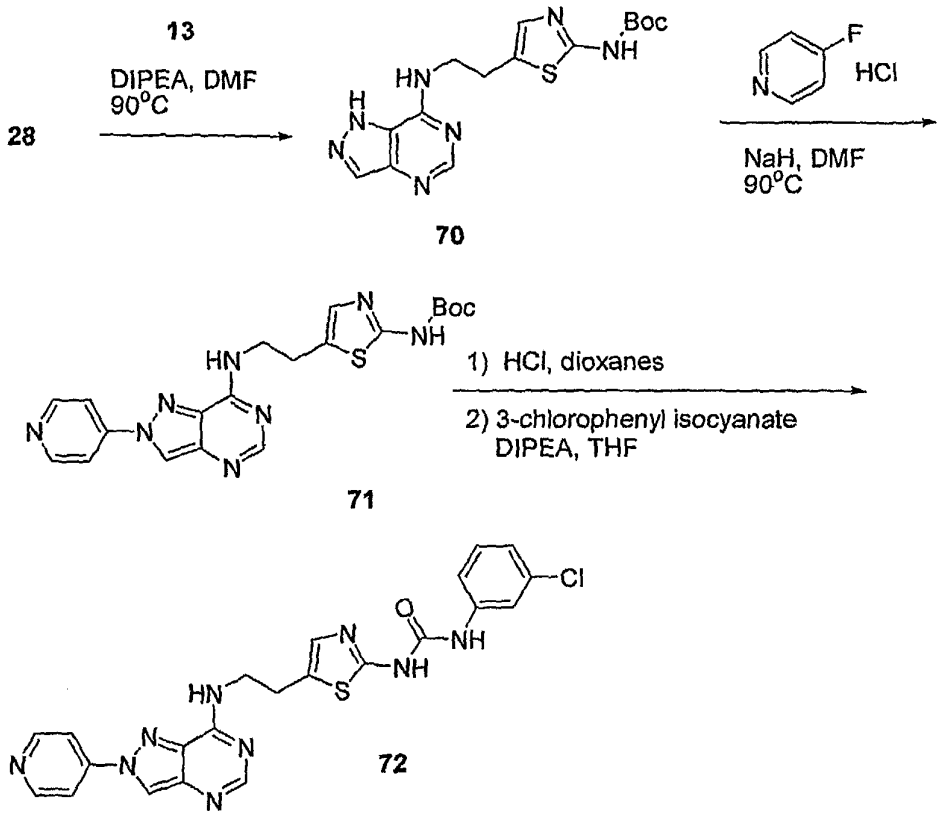
[0535] **EXAMPLE 42**



9 69

[0536] **Compound 69:** This compound was made according to procedures towards the synthesis of **10**, except that **37** was used in place of **3**, ES (+) MS m/e = 429 (M+1).

[0537] **EXAMPLE 43**

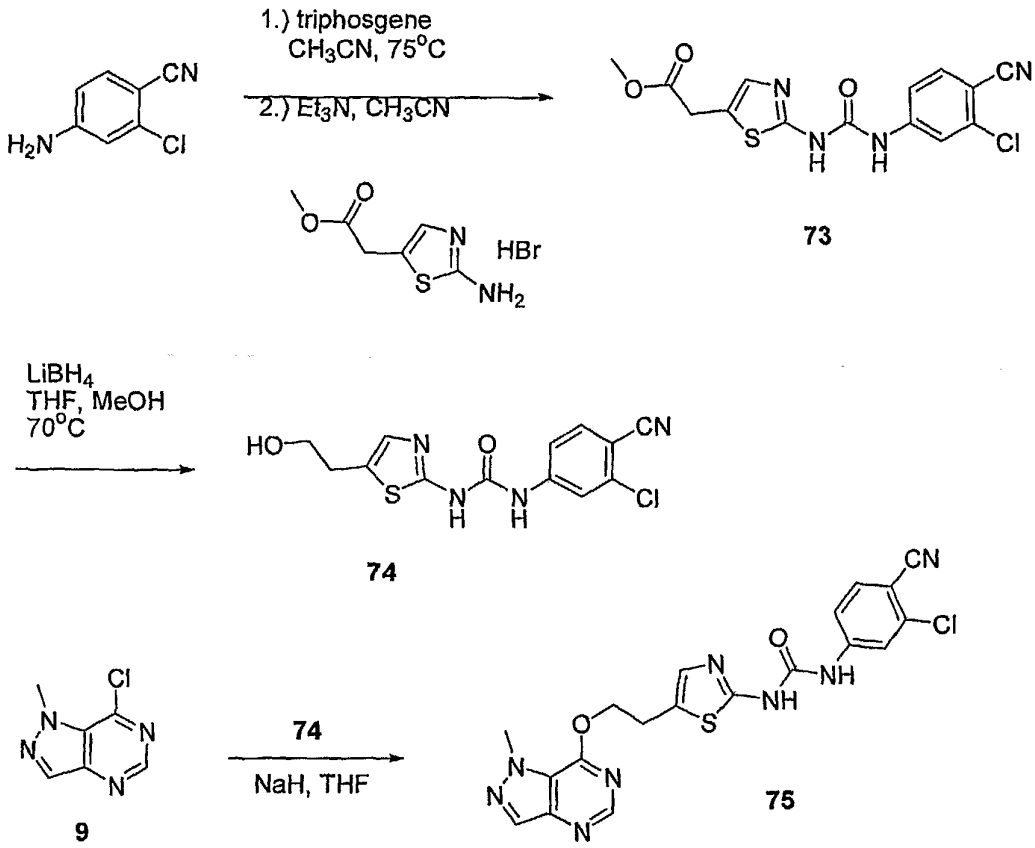


[0538] **Compound 70:** **13** (0.86 g, 3.5 mmol) was added to a solution containing **28** (0.55 g, 3.5 mmol) and Hunig's base (1.2 mL, 7.1 mmol) in DMF (12 mL). The reaction mixture was heated to 90°C and stirred for 1 hour. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel using 100% EtOAc to afford **70** (0.5 g, 39%), ES (+) MS m/e = 362 (M+1).

[0539] **Compound 71:** 60%wt of NaH (0.11 g, 0.66 mmol) was added to a solution containing **70** (0.2 g, 0.55 mmol) and 4-fluoropyridine hydrochloride (0.09 g, 0.66 mmol) in DMF (2 mL). The reaction mixture was heated to 90°C and stirred overnight. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel using 100% EtOAc to afford **71** (0.09 g, 36%), ES (+) MS m/e = 439 (M+1).

[0540] **Compound 72:** HCl (1 mL, 4.0M in dioxanes) was added to a solution of **71** (0.09 g, 0.2 mmol) in dioxanes (1 mL). The reaction mixture was stirred for 1 hour and concentrated. The resulting residue was dissolved in Hunig's base (0.21 mL) and THF (5 mL). 3-chlorophenyl isocyanate (56 mgs, 0.36 mmol) was added and the reaction stirred for 3 hours. The reaction mixture was concentrated. The crude residue was purified by prep *RP-HPLC*. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **72** as the bis TFA salt, ES (+) MS m/e = 492 (M+1).

[0541] **EXAMPLE 44**



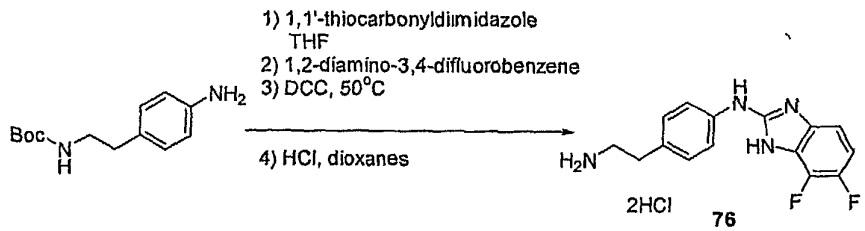
[0542] **Compound 73:** Triphosgene (0.74 g, 2.5 mmol) was added to a solution containing 4-amino-2-chlorobenzonitrile (1.05g, 6.9 mmol) in acetonitrile (28 mL). The reaction mixture was heated to 75°C and stirred for 1.5 hours. The reaction was cooled to room temperature. A solution containing (2-amino-thiazol-5-

yl)-acetic acid methyl ester hydrobromide (1.58 g, 6.2 mmol) [See Patent Application Publication US 2006/0035908], and Et_3N (4.4 mL, 31.2 mmol) in acetonitrile (12 mL) was added to the reaction mixture and stirred for 15 minutes. The reaction mixture was diluted with H_2O. The aqueous layer was extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated. The crude residue was triturated with DCM and hexanes to afford **73** (1.9 g, 87%), ES (+) MS m/e = 351 (M+1).

[0543] **Compound 74:** $LiBH_4$ (0.48 g, 21.6 mmol) was added to a solution containing **73** (1.9 g, 5.4 mmol) in THF (50 mL) and MeOH (5 mL). The reaction mixture was heated to 70°C for overnight. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with H_2O and the aqueous layer was extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated to afford **74** (1.7 g, 97%), ES (+) MS m/e = 323 (M+1).

[0544] **Compound 75:** 60%wt of NaH (52 mgs, 1.3 mmol) was added to a solution of 4-chlorothieno[3,2-d]pyrimidine (63 mgs, 0.4 mmol) and **74** (0.12 g, 0.4 mmol) in THF (4 mL). The reaction mixture was stirred for overnight. The reaction mixture was diluted with H_2O and extracted aqueous layer with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **75** as the bis TFA salt, ES (+) MS m/e = 457 (M+1).

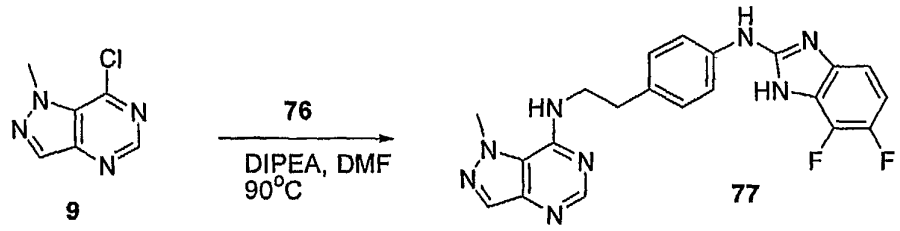
[0545] **EXAMPLE 45**



[0546] **Compound 76:** 1,1'-thiocarbonyldiimidazole (0.68 g, 4.6 mmol) was added to a solution containing [2-(4-amino-phenyl)-ethyl]-carbamic acid t-butyl ester (1.1 g, 4.6 mmol). The reaction mixture was stirred for 30 minutes. 1,2-diamino-3,4-difluorobenzene (0.66 g, 4.6 mmol) was added to the reaction mixture and stirred for 3 hours. DCC (0.94 g, 4.6 mmol) was added and the reaction mixture

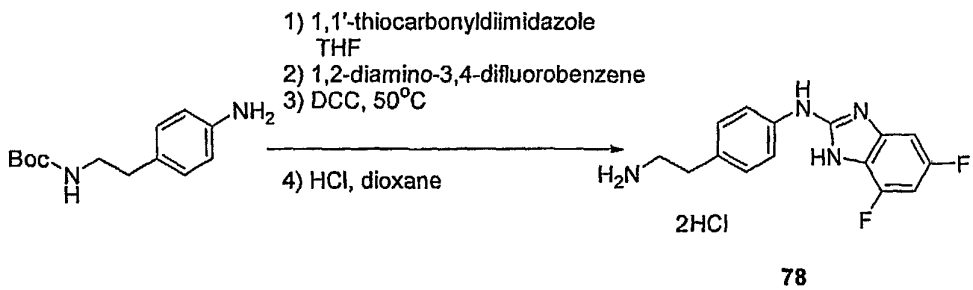
was heated to 50°C for 2 hours. The reaction mixture was cooled to room temperature and stirred overnight. The reaction mixture was diluted with H_2O and extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel using 40% EtOAc in hexanes to obtain solid. The resulting solid was dissolved in dioxanes (5mL) and HCl (3 mL, 4.0M in dioxanes) was added. The reaction mixture was stirred for overnight and concentrated to afford **76** (1.45 g, 87%), ES (+) MS m/e = 289 (M+1).

[0547] EXAMPLE 46



[0548] Compound 77: **76** (0.3 g, 0.84 mmol) was added to a solution containing **9** (0.14 g, 0.84 mmol) and Hunig's base (0.7 mL, 4.2 mmol) in DMF (5 mL). The reaction mixture was heated to 90°C and stirred for 1 hour. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with H_2O and extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel using 5% CH_3CN in EtOAc to afford **77** (0.11 g, 31%), ES (+) MS m/e = 421 (M+1).

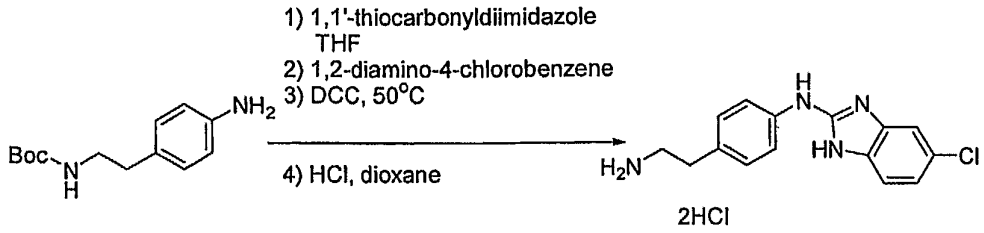
[0549] EXAMPLE 47



78

[0550] **Compound 78:** This compound was made according to procedures towards the synthesis of **76** except that 1,2-diamino-3,5-difluorobenzene was used in place of 1,2-diamino-3,4-difluorobenzene, ES (+) MS m/e = 289 (M+1).

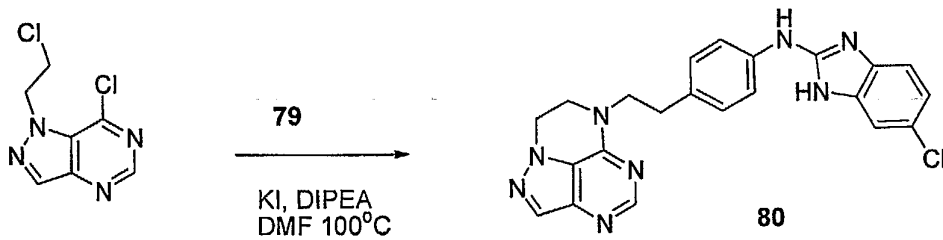
[0551] **EXAMPLE 48**



79

[0552] **Compound 79:** This compound was made according to procedures towards the synthesis of **76** except that 1,2-diamino-4-chlorobenzene was used in place of 1,2-diamino-3,4-difluorobenzene, ES (+) MS m/e = 287 (M+1).

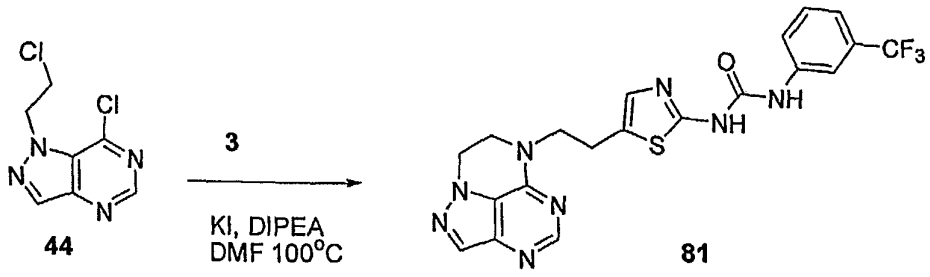
[0553] **EXAMPLE 49**



44 **80**

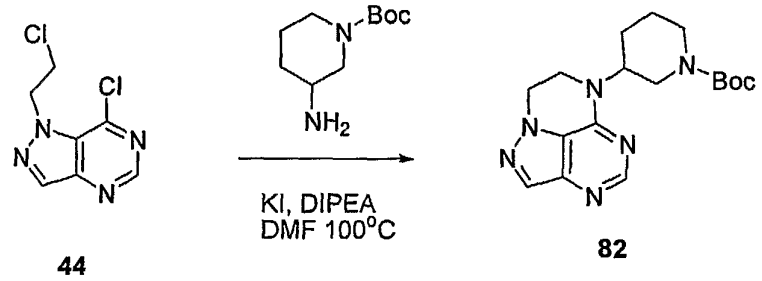
[0554] **Compound 80:** **79** (0.11 g, 0.3 mmol) was added to a solution containing **44** (0.066 g, 0.3 mmol), KI (51 mgs, 0.3 mmol) and Hunig's base (0.27 mL, 1.5 mmol) in DMF (5 mL). The reaction mixture was heated to 100°C for overnight. The reaction was cooled to room temperature. The reaction mixture was diluted with H_2O. Extracted the aqueous layer with EtOAc. Combined the organics, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **80** as the bis TFA salt, ES (+) MS m/e = 431 (M+1).

[0555] **EXAMPLE 50**



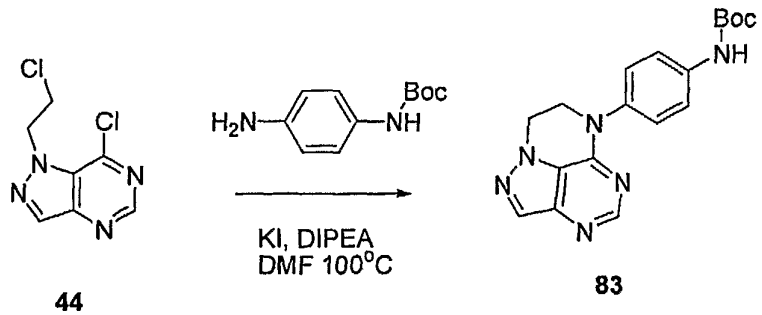
[0556] **Compound 81:** This compound was made according to procedures towards the synthesis of **80**, except that **3** was used in place of **79**, ES (+) MS m/e = 475 (M+1).

[0557] **EXAMPLE 51**



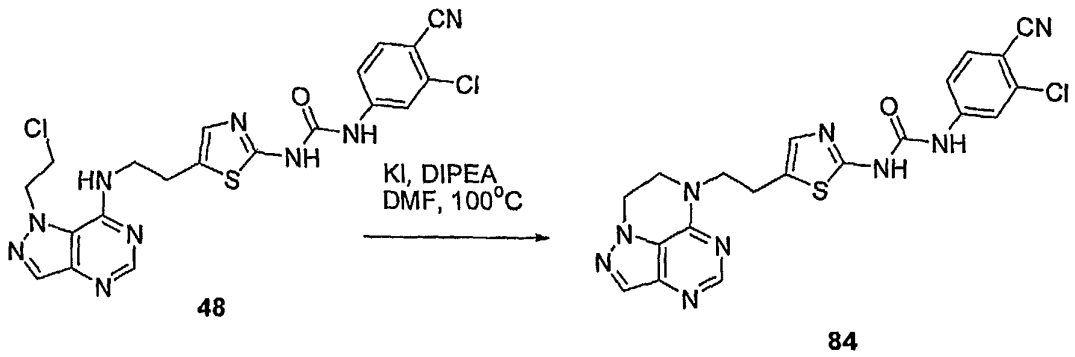
[0558] **Compound 82:** This compound was made according to procedures towards the synthesis of **80**, except that 3-amino-piperidine-1-carboxylic acid t-butyl ester was used in place of **79**, ES (+) MS m/e = 345 (M+1).

[0559] **EXAMPLE 52**



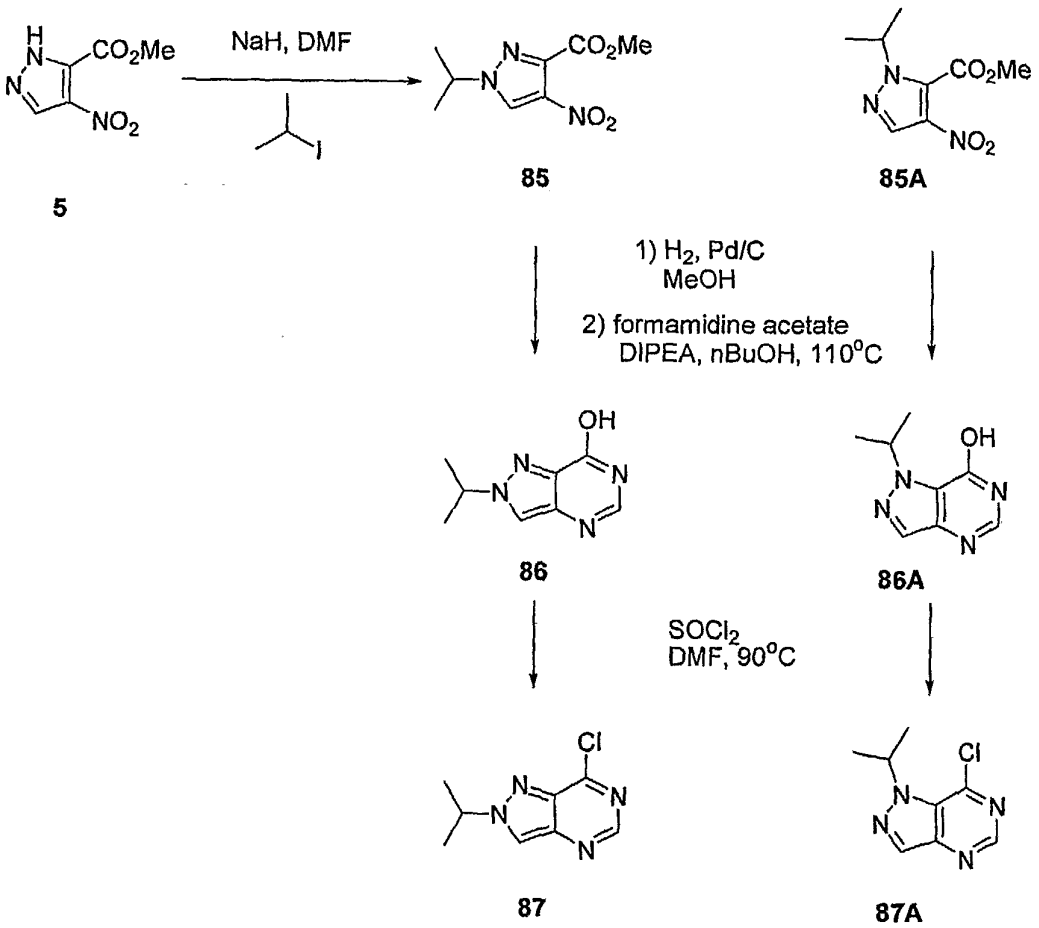
[0560] **Compound 83:** This compound was made according to procedures towards the synthesis of **80** except that (4-amino-phenyl)-carbamic acid t-butyl ester was used in place of **79**, ES (+) MS m/e = 353 (M+1).

[0561] EXAMPLE 53



[0562] Compound 84: This compound was made according to procedures towards the synthesis of **80**, ES (+) MS m/e = 466 (M+1).

[0563] EXAMPLE 54



[0564] **Compound 85 and 85A:** 2-iodopropane (4.0 mL, 40.0 mmol) was added to a solution of **5** (2.3 g, 13.5 mmol) and 60% wt of NaH (0.68 g, 16.9 mmol) in DMF (50 mL). The reaction mixture was stirred for 2 hours. The reaction mixture was diluted with H_2O. Separated the layers and the aqueous layer was extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated. Purified the residue by column chromatography on silica gel using 30% EtOAc in hexanes to afford **85A** (0.66 g, 23%), ES (+) MS m/e = 214 (M+1) and using 40% EtOAc in hexanes to afford **85** (1.09 g, 38%), ES (+) MS m/e = 214 (M+1).

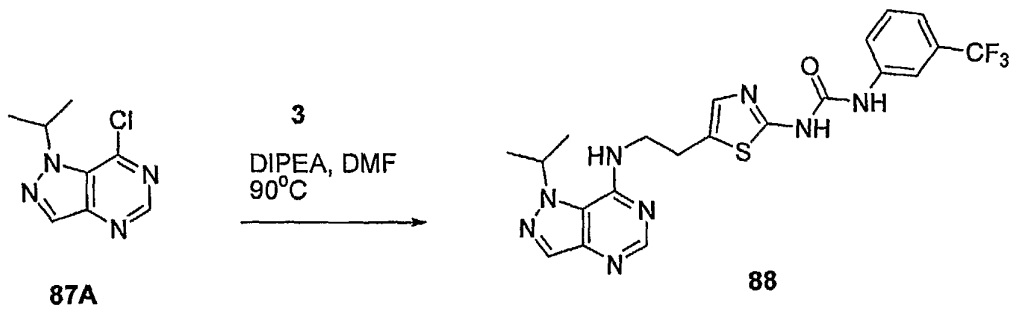
[0565] **Compound 86:** This compound was made according to procedures towards the synthesis of **46**, except that **85** was used in place of **45**, ES (+) MS m/e = 179 (M+1).

[0566] **Compound 86A:** This compound was made according to procedures towards the synthesis of **46**, except that **85A** was used in place of **45**, ES (+) MS m/e = 179 (M+1).

[0567] **Compound 87:** This compound was made according to procedures towards the synthesis of **47**, except that **86** was used in place of **46**, ES (+) MS m/e = 197 (M+1).

[0568] **Compound 87A:** This compound was made according to procedures towards the synthesis of **47**, except that **86A** was used in place of **46**, ES (+) MS m/e = 197 (M+1).

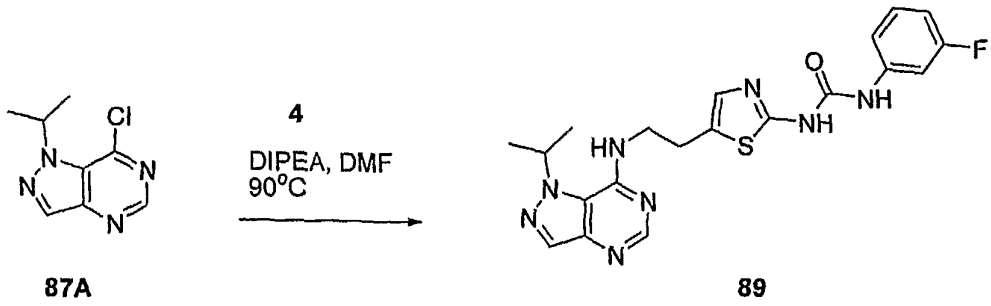
[0569] **EXAMPLE 55**



87A **88**

[0570] **Compound 88:** This compound was made according to procedures towards the synthesis of **10**, except that **87A** was used in place of **9**, ES (+) MS m/e = 491 (M+1).

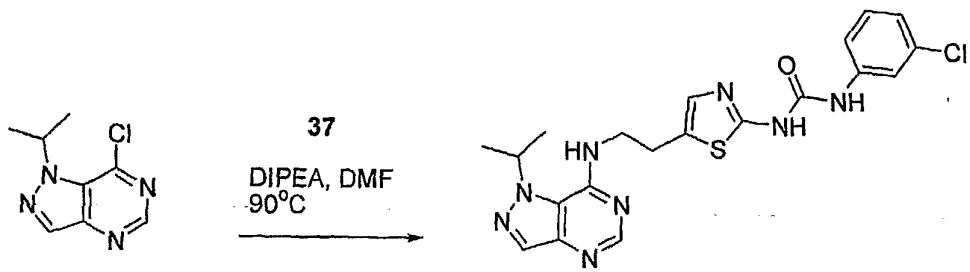
[0571] **EXAMPLE 56**



87A 89

[0572] **Compound 89:** This compound was made according to procedure towards the synthesis of **10**, except that **87A** and **4** were used in place of **9** and **3** respectively, ES (+) MS m/e = 441 (M+1).

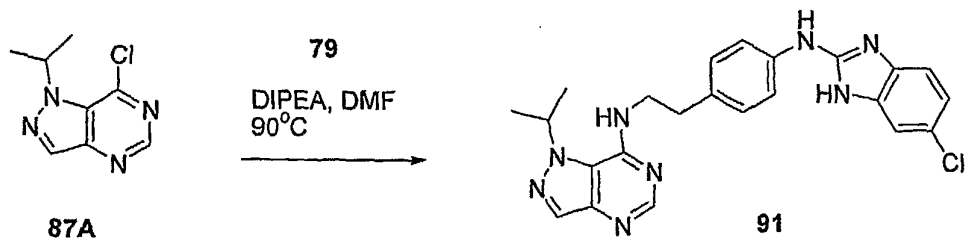
[0573] **EXAMPLE 57**



87A 90

[0574] **Compound 90:** This compound was made according to procedures towards the synthesis of **10**, except that **87A** and **37** were used in place of **9** and **3** respectively, ES (+) MS m/e = 457 (M+1).

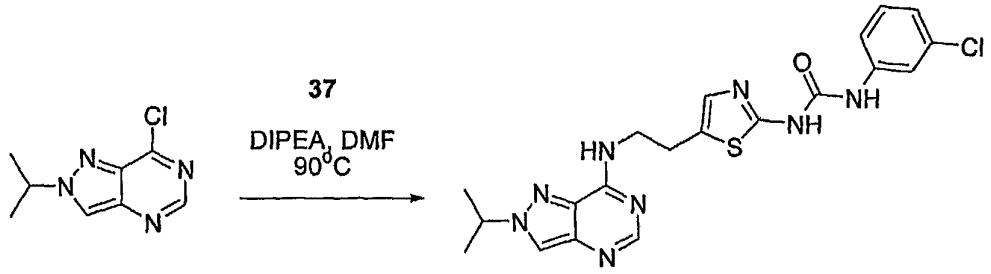
[0575] **EXAMPLE 58**



87A 91

[0576] **Compound 91:** This compound was made according to procedures towards the synthesis of **10**, except that **87A** and **79** were used in place of **9** and **3** respectively, ES (+) MS m/e = 447 (M+1).

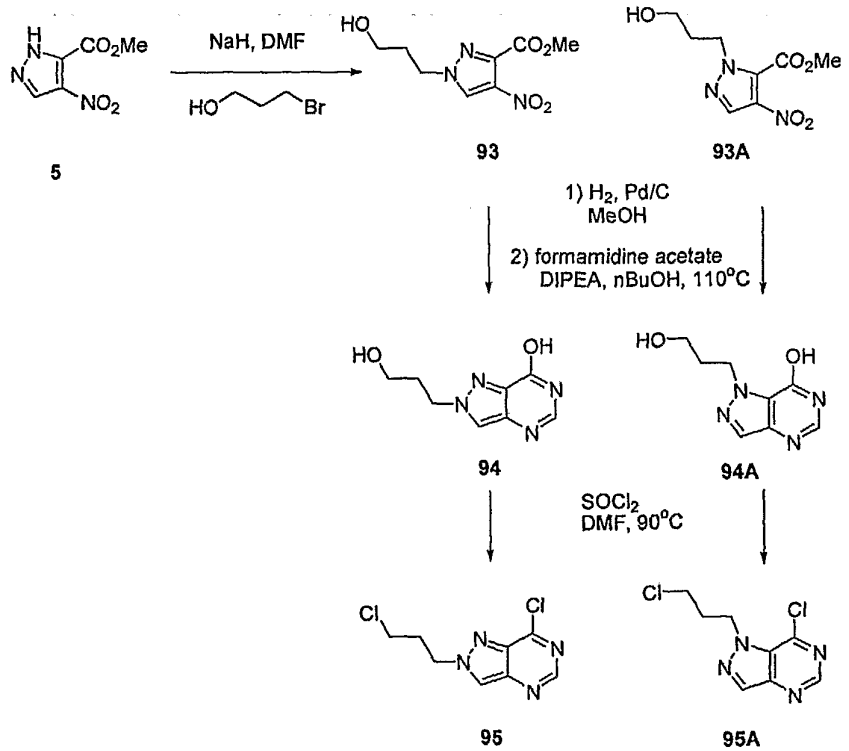
[0577] **EXAMPLE 59**



87 **92**

[0578] **Compound 92:** This compound was made according to procedures towards the synthesis of **10**, except that **87** and **37** were used in place of **9** and **3** respectively, except for using **46** in place of **1.8** and **5** in place of **1.3**. ES (+) MS m/e = 457 (M+1).

[0579] **EXAMPLE 60**



5 **93** **93A**

94 **94A**

95 **95A**

[0580] **Compound 93 and 93A:** These compounds were made according to procedures towards the synthesis of **44** and **44A** except that 3-bromo-1-propanol was used in place of 2-iodopropane, ES (+) MS m/e = 230.

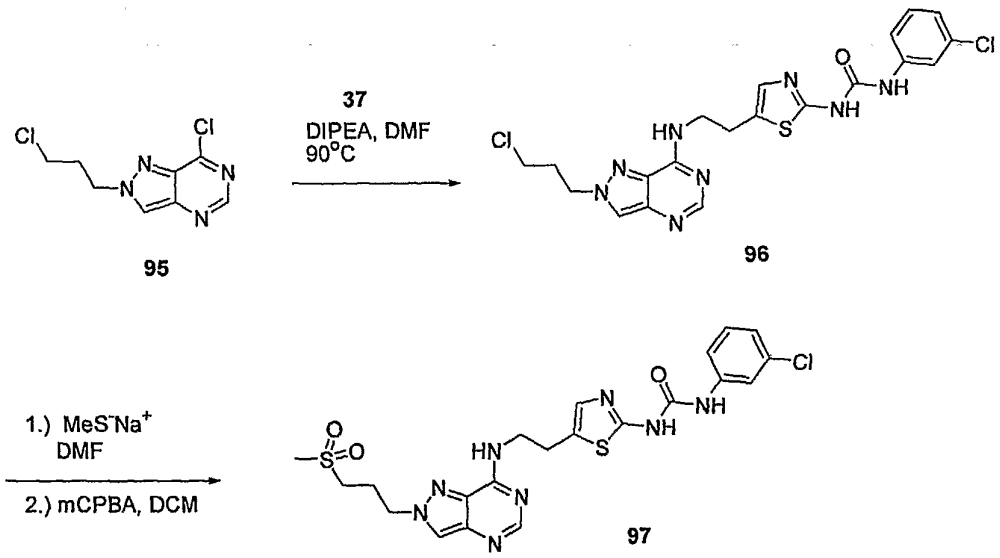
[0581] **Compound 94:** This compound was made according to procedures towards the synthesis of **46**, except that **93** was used in place of **45**, ES (+) MS m/e = 195 (M+1).

[0582] **Compound 94A:** This compound was made according to procedures towards the synthesis of **46**, except that **93A** was used in place of **45**, ES (+) MS m/e = 195 (M+1).

[0583] **Compound 95:** This compound was made according to procedures towards the synthesis of **47**, except that **94** was used in place of **46**, ES (+) MS m/e = 231 (M+1).

[0584] **Compound 95A:** This compound was made according to procedures towards the synthesis of **47**, except that **94A** was used in place of **46**, ES (+) MS m/e = 231 (M+1).

[0585] **EXAMPLE 61**

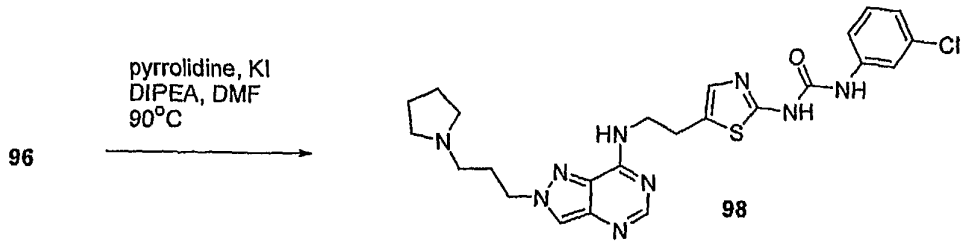


95 96 97

[0586] **Compound 96:** This compound was made according to procedures towards the synthesis of **51**, except that **95** was used in place of **44**, ES (+) MS m/e = 491 (M+1).

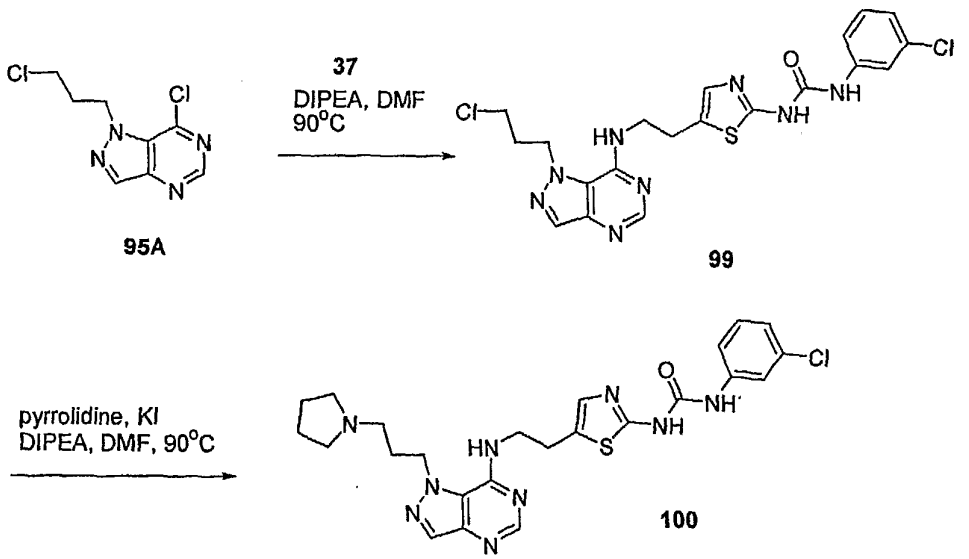
[0587] **Compound 97:** This compound was made according to procedures towards the synthesis of **53** and **54B**, except that **96** was used in place of **51**, ES (+) MS m/e = 535 (M+1).

[0588] **EXAMPLE 62**



[0589] **Compound 98:** Pyrrolidine (16 mgs, 0.02 mmol) was added to a solution containing **96** (60 mgs, 0.01 mmol), Hunig's base (0.05 mL, 0.3 mmol), and KI (2 mgs) in DMF (3 mL). The reaction mixture was heated at 90 °C overnight. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude residue was purified by prep RP-HPLC. The fractions containing pure compound were consolidated and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield **98** as the tris TFA salt, ES (+) MS m/e = 526 (M+1).

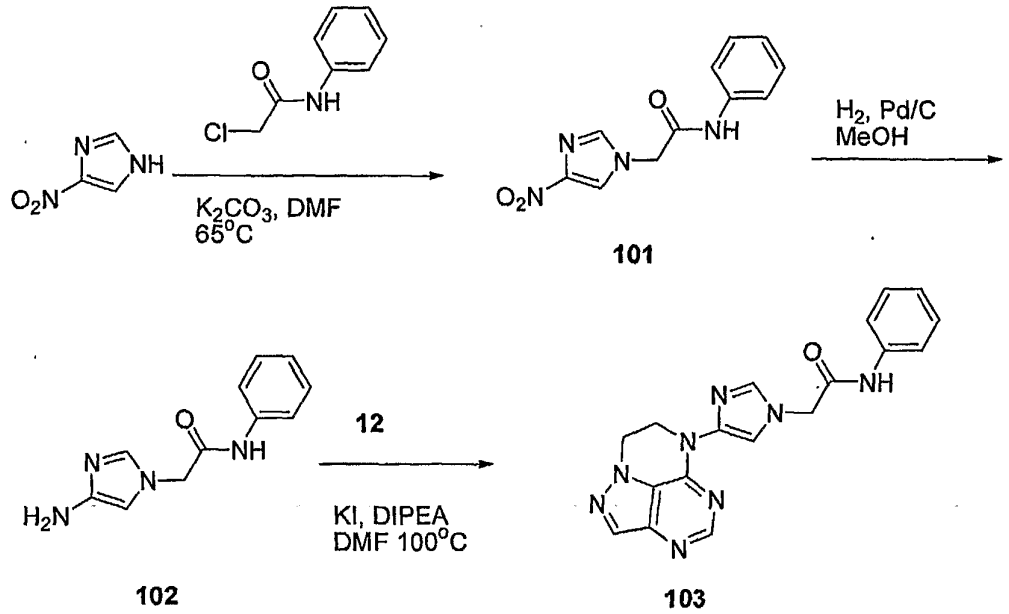
[0590] **EXAMPLE 63**



[0591] **Compound 99:** This compound was made according to procedures towards the synthesis of **51**, except that **95A** was used in place of **44**, ES (+) MS m/e = 491 (M+1).

[0592] **Compound 100:** This compound was made according to procedures towards the synthesis of **98**, except that **99** was used in place of **96**, ES (+) MS m/e = 526 (M+1).

[0593] **EXAMPLE 64**

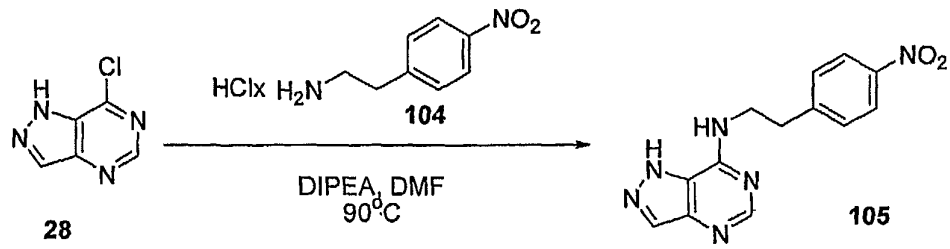


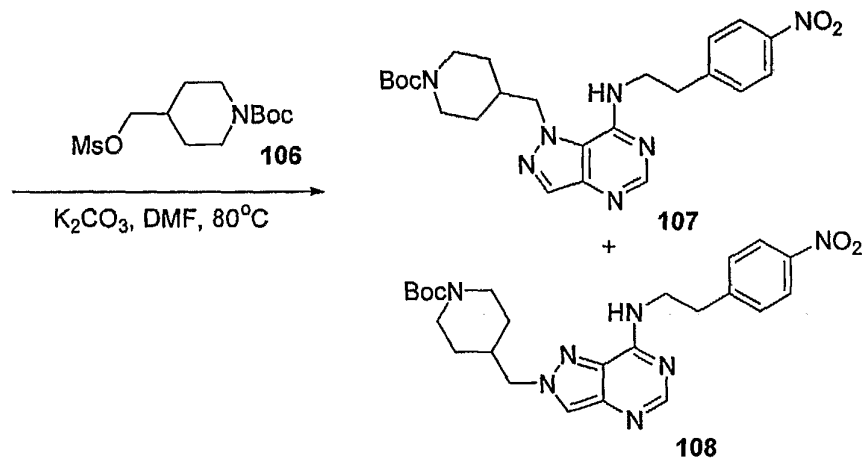
[0594] **Compound 101:** 2-chloro-N-phenylacetamide (0.15 g, 0.9 mmol) was added to a solution containing 4-nitroimidazole (0.1 g, 0.9 mmol) in DMF (5 mL). The reaction mixture was heated to 65°C for 1 hour. The reaction mixture was diluted with H_2O. Separated the layers and the aqueous layer was extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated to afford **101** (0.22 g, 100%), ES (+) MS m/e = 247 (M+1).

[0595] **Compound 102:** 10% wt. Pd/C (0.1 g, 0.09 mmol) was added to a solution containing **101** (0.22 g, 0.88 mmol) in 10 mL of methanol. The mixture was stirred under a hydrogen atmosphere at ambient temperature. After 3 hours, the reaction mixture was filtered thru a plug of Celite. The resulting filtrate was concentrated under reduced pressure to afford **102** (0.19 g, 100%).

[0596] **Compound 103:** This compound was made according to procedures towards the synthesis of **80** except that **102** was used in place of **79**, ES (+) MS m/e = 361 (M+1).

[0597] **EXAMPLE 65**

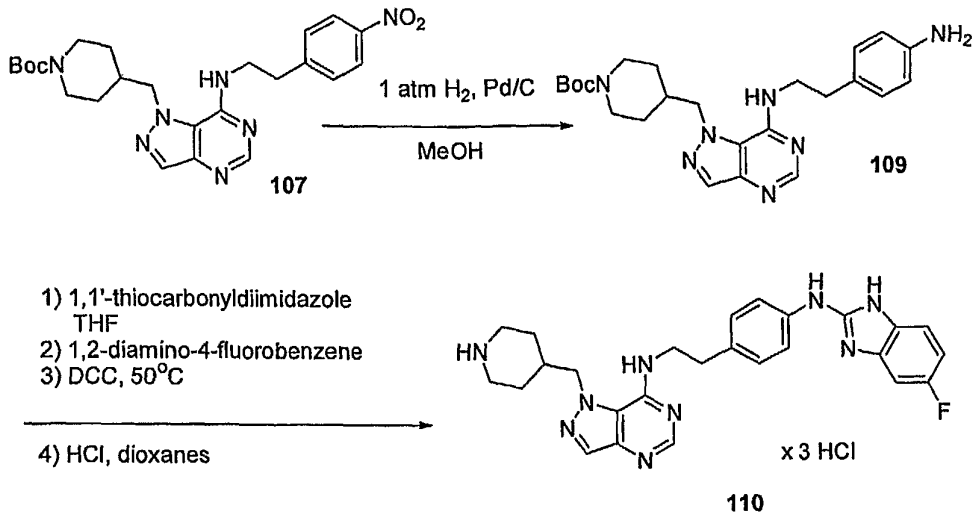




[0598] **Compound 105:** This compound was made according to example **10** except that **28** and **104** sere used in place of **9** and **3**, respectively. ES (+) MS m/e = 285 (M+1).

[0599] **Compounds 107 and 108:** A mixture of **105**, **106**, and K_2CO_3 in DMF was heated at 80 °C. After 4.5 h, the mixture was concentrated and the residue was partitioned between water and EtOAc. The aqueous layer was extracted twice with EtOAc and the combined organic phases were dried (Na_2SO_4) and concentrated. The crude residue thus obtained was purified by column chromatography (SiO_2; 0 to 5% MeOH in EtOAc) to yield 50 mg of **107** and 108 mg of **108**. **107**: R_f 0.59 (SiO; 5% MeOH in EtOAc), ES (+) MS m/e = 482 (M+1). **108**: R_f 0.47 (SiO; 5% MeOH in EtOAc), ES (+) MS m/e = 482 (M+1).

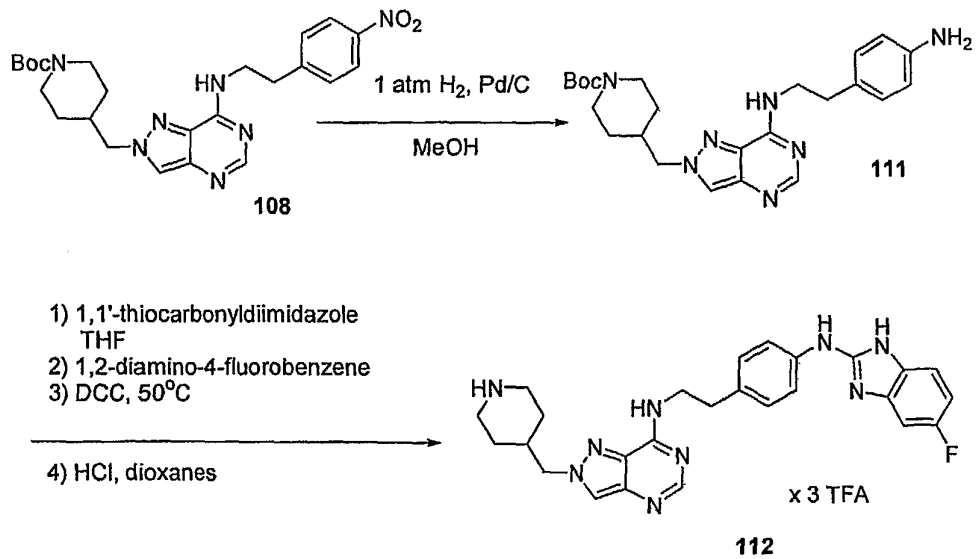
[0600] EXAMPLE 66



[0601] Compound 109: This compound was made according to procedures towards the synthesis of **15** except that **107** was used in place of **14**. ES (+) MS m/e = 452 (M+1).

[0602] Compound 110: This compound was made according to procedures towards the synthesis of **76** except that **109** was used in place of [2-(4-amino-phenyl)-ethyl]-carbamic acid t-butyl ester and 1,2-diamino-4-fluorobenzene was used in place of 1,2-diamino-3,4-difuorobenzene. ES (+) MS m/e = 586 (M+1).

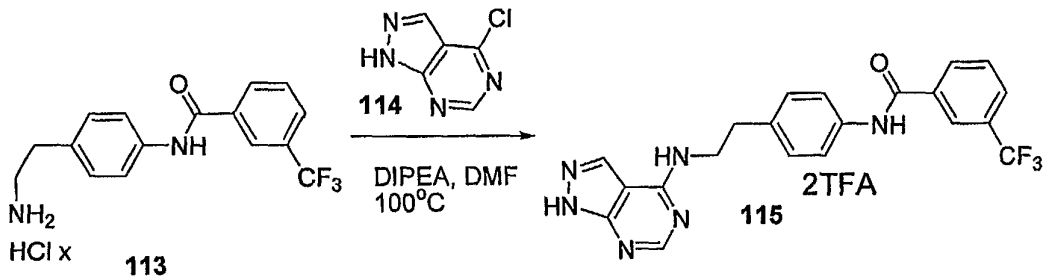
[0603] EXAMPLE 67



[0604] **Compound 111:** This compound was made according to procedures towards the synthesis of **15** except that **108** was used in place of **14**. ES (+) MS m/e = 452 (M+1).

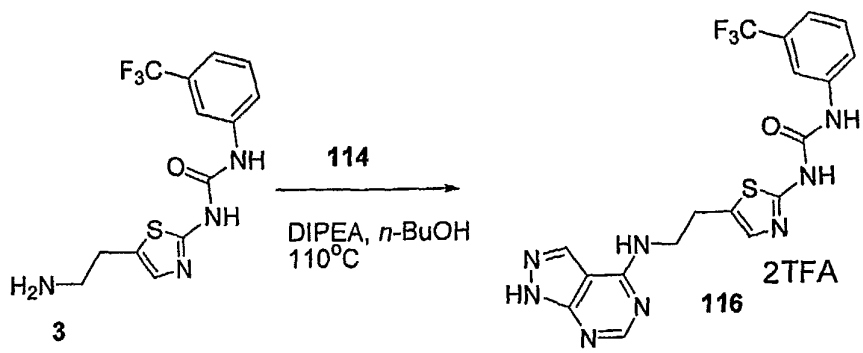
[0605] **Compound 112:** This compound was made according to procedures towards the synthesis of **76** except that **111** was used in place of [2-(4-amino-phenyl)-ethyl]-carbamic acid t-butyl ester and 1,2-diamino-4-fluorobenzene was used in place of 1,2-diamino-3,4-difuorobenzene. The crude product was purified using RP-preparative HPLC. ES (+) MS m/e = 586 (M+1).

[0606] **EXAMPLE 68**



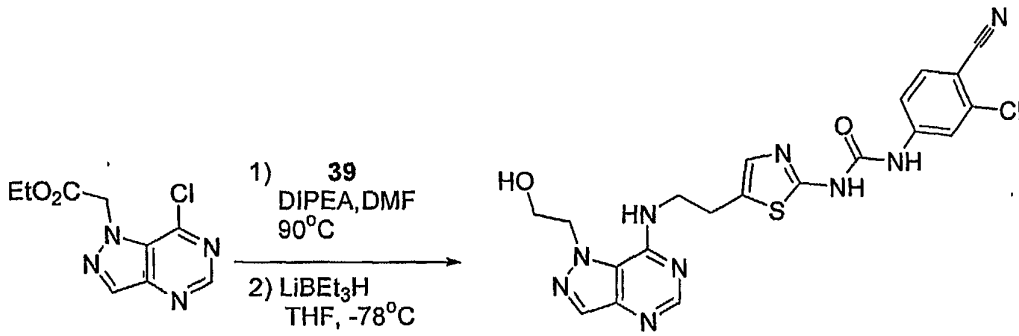
[0607] **Compound 115:** To a solution of **114** (0.22 g, 0.6 mmol) and DIPEA (0.34 mL, 1.9 mmol) in DMF (3.0 mL) was added **114** (0.10 g, 0.60 mmol, Chern, J.-H. et al. *Bioorg. Med. Chem. Lett.*, **2004**, 2519). The resulting solution was stirred at 100°C for 1 hour and was then cooled to room temperature. The solvents were removed under reduced pressure using high-vacuum and a heated water bath. The resulting residue was diluted with methanol and purified by prep HPLC to afford **115** (40 mg, 10%) as a white solid. ES (+) MS m/e = 427 (M+1).

[0608] **EXAMPLE 69**



[0609] **Compound 116:** A mixture of **3** (100 mg, 0.303 mmol), **114** (47 mg, 0.303 mmol), and DIPEA (1.0 mL) in *n*-butanol (1.0 mL) was stirred at 110°C for 2 hours. The solution was then concentrated and the residue was purified by prep. RP-HPLC. The fractions containing pure compound were combined and concentrated. The residue thus obtained was lyophilized under high-vacuum to yield 40 mg of a solid. ES (+) MS m/e = 449 (M+1).

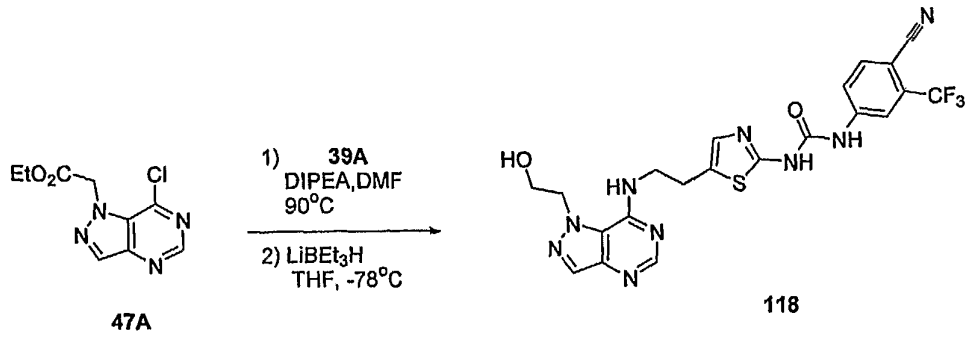
[0610] **EXAMPLE 70**



47A **117**

[0611] **Compound 117:** Add **39** (1.0 mmol) to a solution containing **47A** (1.0 mmol) and Hunig's base (3.0 mmol) in DMF.(10 mL). Heat the reaction mixture to 90°C for 1 hour and cool to room temperature. Dilute the reaction mixture with H_2O. Extract the aqueous layer with EtOAc. Combine organics, dry with $MgSO_4$, filter and concentrate. Purify by column chromatography on silica gel using 10% MeOH in hexanes. Dilute the resulting residue with THF (10mL) and cool to –78°C. Add $LiBEt_3H$ (2.0 mL, 1.0M in THF) to the reaction mixture. Stir the reaction mixture at –78°C for 1 hour and warm to room temperature. Dilute the reaction mixture with 1M $NaHCO_3$ and extract with EtOAc. Combine organics, dry with $MgSO_4$, filter, and concentrate. Purify resulting residue by prep RP-HPLC to afford **117**.

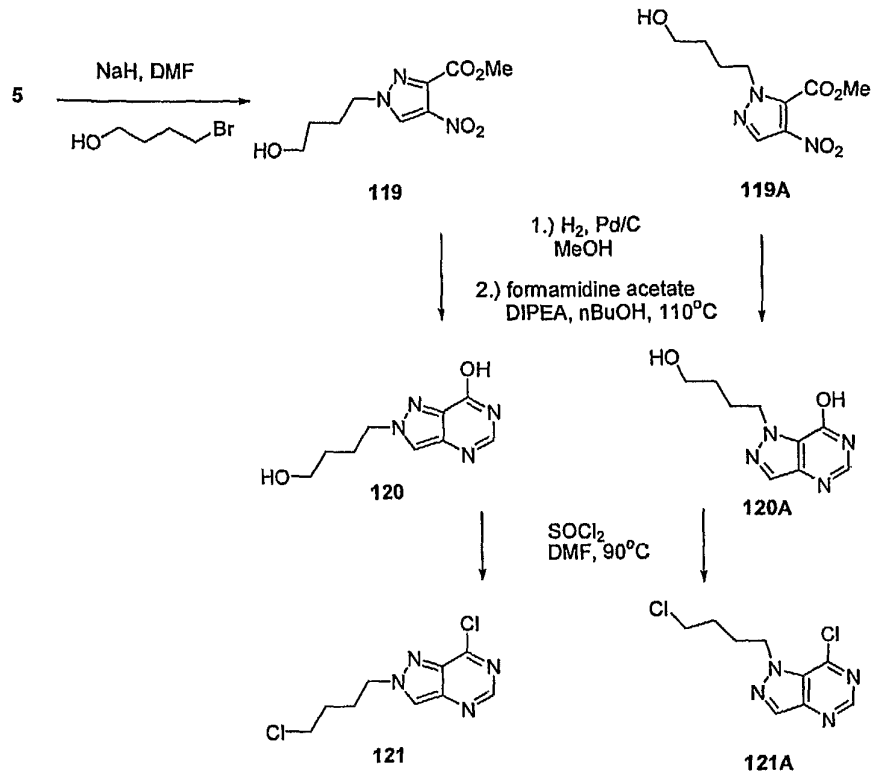
[0612] **EXAMPLE 71**



47A 118

[0613] **Compound 118:** Add **39A** (1.0 mmol) to a solution containing **47A** (1.0 mmol) and Hunig's base (3.0 mmol) in DMF.(10 mL). Heat the reaction mixture to 90°C for 1 hour and cool to room temperature. Dilute the reaction mixture with H_2O. Extract the aqueous layer with EtOAc. Combine organics, dry with $MgSO_4$, filter and concentrate. Purify by column chromatography on silica gel using 10% MeOH in hexanes. Dilute the resulting residue with THF (10mL) and cool to –78°C. Add $LiBEt_3H$ (2.0 mL, 1.0M in THF) to the reaction mixture. Stir the reaction mixture at –78°C for 1 hour and warm to room temperature. Dilute the reaction mixture with 1M $NaHCO_3$ and extract with EtOAc. Combine organics, dry with $MgSO_4$, filter, and concentrate. Purify resulting residue by prep RP-HPLC to afford **118**.

[0614] **EXAMPLE 72**



[0615] **Compound 119 and 119A:** Add 4-bromo-1-butanol (35.0 mmol) to a solution containing **1.4** (23.4 mmol) and 60%wt of NaH (35.0 mmol) in DMF (50 mL). Stir the reaction mixture for 2 hours. Dilute the reaction mixture with H_2O. Extract the aqueous layer with EtOAc. Combine organics, dry with $MgSO_4$, filter and concentrate. Purify the residue with column chromatography on silica gel to isolate both **63** and **64**.

[0616] **Compound 120:** Combine **119** (12 mmol) and 10%wt of Pd/C (0.6 mmol) in MeOH (30mL) with 1 atm H_2, via balloon. Stir the reaction mixture overnight. Filter the reaction mixture thru a plug of Celite and concentrate to afford residue. Dilute residue with n-butanol (25 mL) followed by Hunig's base (25 mL). Add formamidine acetate (13 mmol) and heat the reaction mixture to 110°C for 1 hour. Cool the reaction mixture to room temperature and concentrate. Dilute the reaction mixture with H_2O and extract the aqueous layer with EtOAc. Combine organics, dry with $MgSO_4$, filter, and concentrate to afford **120**.

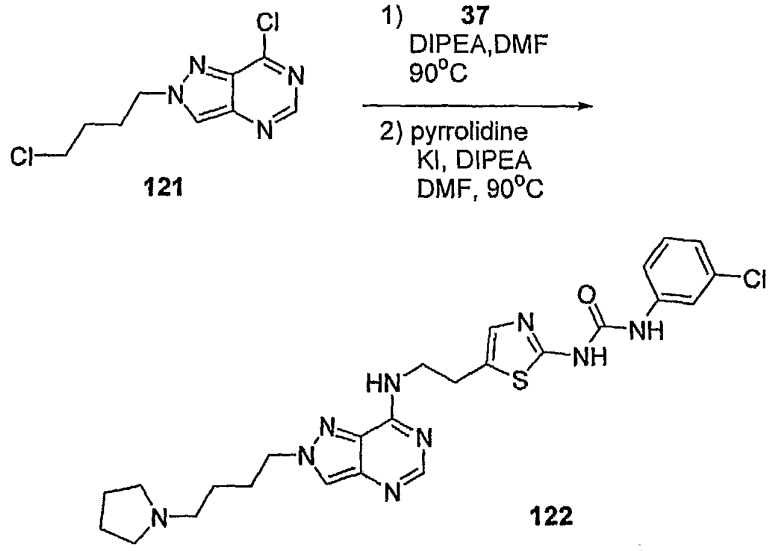
[0617] **Compound 120A:** Combine **119A** (6 mmol) and 10%wt of Pd/C (0.3 mmol) in MeOH (15mL) with 1 atm H_2, via balloon. Stir the reaction mixture overnight. Filter the reaction mixture thru a plug of Celite and concentrate to afford

residue. Dilute residue with n-butanol (13 mL) followed by Hunig's base (13 mL). Add formamidine acetate (8 mmol) and heat the reaction mixture to 110°C for 1 hour. Cool the reaction mixture to room temperature and concentrate. Dilute the reaction mixture with H_2O and extract the aqueous layer with EtOAc. Combine organics, dry with $MgSO_4$, filter, and concentrate to afford **120A**.

[0618] **Compound 121:** Add DMF (2.5 mL) to a solution containing **120** (7.6 mmol) in $SOCl_2$ (25 mL). Heat the heterogeneous reaction mixture to 90°C for 30 minutes. Cool the homogeneous solution for room temperature. Concentrate the reaction mixture. Dilute with EtOAc, followed by ice. Separate the layers and extract the aqueous layer with EtOAc. Combine organics and wash with saturated $NaHCO_3$, followed by brine. Dry with $MgSO_4$, filter, and concentrate to afford **121**.

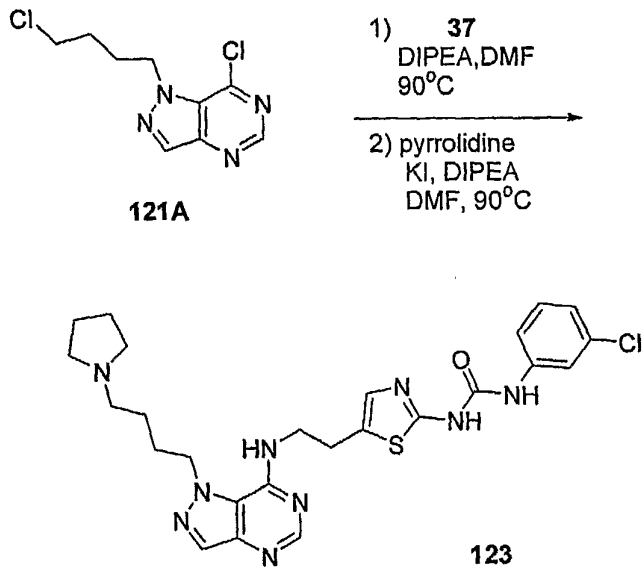
[0619] **Compound 121A:** Add DMF (1.3 mL) to a solution containing **120A** (3.8 mmol) in $SOCl_2$ (13 mL). Heat the heterogeneous reaction mixture to 90°C for 30 minutes. Cool the homogeneous solution for room temperature. Concentrate the reaction mixture. Dilute with EtOAc, followed by ice. Separate the layers and extract the aqueous layer with EtOAc. Combine organics and wash with saturated $NaHCO_3$, followed by brine. Dry with $MgSO_4$, filter, and concentrate to afford **121A**.

[0620] **EXAMPLE 73**



[0621] **Compound 122:** Add **37** (1.0 mmol) to a solution containing **121** (1.0 mmol) and Hunig's base (3.0 mmol) in DMF.(10 mL). Heat the reaction mixture to 90°C for 1 hour and cool to room temperature. Dilute the reaction mixture with H_2O. Extract the aqueous layer with EtOAc. Combine organics, dry with $MgSO_4$, filter and concentrate. Purify by column chromatography on silica gel using 10% MeOH in hexanes. Dilute the resulting residue in DMF (10 mL). Add KI (1.0 mmol), Hunig's base (1.0 mmol), and pyrrolidine (2.0 mmol). Heat the reaction mixture to 90°C. Cool the reaction mixture to room temperature. Dilute the reaction mixture with H_2O. Extract the aqueous layer with EtOAc. Combine organics, dry with $MgSO_4$, filter and concentrate. Purify resulting residue by prep RP-HPLC to afford **122**.

[0622] **EXAMPLE 74**



[0623] **Compound 123:** Add 37 (1.0 mmol) to a solution containing **121A** (1.0 mmol) and Hunig's base (3.0 mmol) in DMF.(10 mL). Heat the reaction mixture to 90°C for 1 hour and cool to room temperature. Dilute the reaction mixture with H_2O. Extract the aqueous layer with EtOAc. Combine organics, dry with $MgSO_4$, filter and concentrate. Purify by column chromatography on silica gel using 10% MeOH in hexanes. Dilute the resulting residue in DMF (10 mL). Add KI (1.0 mmol), Hunig's base (1.0 mmol), and pyrrolidine (2.0 mmol). Heat the reaction mixture to 90°C. Cool the reaction mixture to room temperature. Dilute the reaction

mixture with H_2O. Extract the aqueous layer with EtOAc. Combine organics, dry with $MgSO_4$, filter and concentrate. Purify resulting residue by prep RP-HPLC to afford **123**.

[0624] EXAMPLE 75

[0625] Formulation of Compounds

[0626] The solubility of poorly soluble compounds are improved by making them as acid salts. Illustrative examples of such acids include methane sulfonic acid and citric acid. Solubility of these compounds can be additionally improved by the addition of solubility enhancing agents such as Tween-80 and PEG-400. Illustrative formuations of poorly soluble compounds of the present invention include 10%/30%/60% , 5%/30%/65%, and 2.5%/30%/67.5% respectively of Tween-80, PEG-400 and water. The pH of these formulations can also also be varied to identify a range for optimal solubility.

[0627] EXAMPLE 76

[0628] Biochemical assays (See Figure 2).

[0629] *Aurora A kinase assay*

[0630] Aurora A protein kinase assays contained 10mM Tris HCl, pH7.2, 10mM $MgCl_2$, 0.1% BSA, 0.01%Triton X-100, 1mM DTT, 20μM ATP, 120nM H3 peptide substrate, compound inhibitor (5% final DMSO concentration) and 25nM Aurora A protein in a total volume of 40μl. Reactions were incubated at room temperature for 60 min, stopped with 28μl of 50mM EDTA pH9, and further incubated at room temperature for 60 min. An equal volume of stopped reaction was incubated with detection buffer containing 50mM HEPES pH 7.0, 0.5M KF, 0.1% BSA, 0.25 μg/mL α-Phospho H3 antibody, and 0.016μM StreptAvidin-XL665 for 60 min, and subsequently read on the Analyst (LjL BioSystems) at excitation 330-370nm, and detection 665nm, 620nm.

[0631] *Aurora B kinase assay*

[0632] Aurora B protein kinase assays contained 10mM Tris HCl, pH7.2, 10mM MgCl2, 0.1% BSA, 0.01%Triton X-100, 1mM DTT, 80μM ATP, 120nM H3 peptide substrate, compound inhibitor (5% final DMSO concentration) and 1.5nM Aurora B protein in a total volume of 40μl. Reactions were incubated at room temperature for 60 min, stopped with 28μl of 50mM EDTA pH9, and further incubated at room temperature for 60 min. An equal volume of stopped reaction was incubated with

detection buffer containing 50mM HEPES pH 7.0, 0.5M KF, 0.1% BSA, 0.25 µg/mL α-Phospho H3 antibody, and 0.016µM StreptAvidin-XL665 for 60 min, and subsequently read on the Analyst (LjL BioSystems) at excitation 330-370nm, and detection 665nm, 620nm.

[0633] *HCS Cell Cycle Assay*

[0634] The HCS Cell Cycle assay is used to measure the amount of cells with DNA content of 4N or greater. Inhibiting Aurora kinases in cells can cause failed mitosis and endoreduplication. This yields cells with 4N DNA content or greater.

[0635] Protocol: Plate 10,000 cells per well in a 96 well, clear bottom plate. (This assay is routinely done with HCT-116 cells, but has also been performed with a number of other adherent human cell lines.) Grow overnight. The next day, add compound to each well at the desired concentration. Incubate at 37° C for 16 hours. Remove compound and fix cells with 4% Formaldehyde for 12 minutes at room temperature. Remove Formaldehyde and wash once with PBS. Add DNA stain in blocking solution (10% FBS in PBS) to the cells, and incubate for one hour at 37° C. Remove stain solution and wash cells one time with PBS. Visualize the cells on a high content imager to quantitate the DNA content of the cells.

[0636] *Phospho-Histone H3 HCS Assay*

[0637] The Phospho-Histone H3 HCS assay is done to measure a compounds ability to inhibit Aurora B in tumor cell lines. As Aurora B is inhibited, it is unable to phosphorylate Histone H3 on Serine 10, and this lack of phosphorylation can be measured by a high content imager.

[0638] Protocol: Plate 10,000 cells per well in a 96 well, clear bottom plate. (This assay is routinely done with HCT-116 cells, but has also been performed with a number of other adherent human cell lines.) Grow overnight. The next day, add compound to each well at the desired concentration. Incubate at 37° C for one hour. Remove compound and fix cells with 4% Formaldehyde for 12 minutes at room temperature. Remove Formaldehyde and permeabilize cells with 0.1% Triton X-100 for 5 minutes at room temperature. Remove Triton X-100 and wash once with PBS. Block cells overnight with blocking solution (10% FBS in PBS) at 4° C. Remove blocking agent and add phospho-histone H3 Serine 10 antibody in blocking solution to the cells, and incubate for two hours at 37° C. Remove primary antibody solution and wash cells twice with PBS. Add a fluorescent antibody and DNA stain in

blocking solution to the cells, and incubate for one hour at room temperature. Remove secondary antibody solution and wash cells three times with PBS. Visualize the cells on a high content imager to quantitate the levels of phospho-histone H3 Serine 10 in the cells.

[0639] EXAMPLE 77

[0640] Target Modulation studies (See Figure 1).

[0641] Nu/nu mice are subcutaneously injected into their hind flank with human HCT-116 cells and 50% Matrigel (Becton-Dickinson). Human HCT-116 tumors are then allowed to grow to 400 mm^3. The tumor bearing mice are then either given an administration of SPD or vehicle (Sigma-Aldrich) (orally, intravenously or intraperitoneally). At prescribed time points post dose, mice are anesthetized and blood taken via terminal cardiac puncture, and sacrificed. The HCT-116 tumors are excised from the mice, pulverized using liquid nitrogen-cooled mortar and pestle, and flash-frozen in liquid nitrogen. Tumor lysates are made from the pulverized samples by addition of lysis buffer.

[0642] For detection of response markers by Western blotting, the protein concentration of the lysates is determined by colorimetric detection. Twenty-five micrograms of protein is loaded per lane on an SDS-PAGE gel. Proteins are separated by gel electrophoresis, blotted onto nitrocellulose membranes, and probed using anti-Histone H3 and anti-phosphorylated Histone H3 antibodies, (both from Cell Signaling Technology)

[0643] EXAMPLE 78

[0644] Maximum Tolerated Dose studies.

[0645] Maximum Tolerated Dose (MTD) is defined as the dose at which the mouse is no longer able to function normally and is determined by either significant toxicity (eg. body weight loss) or mortality. Mice (nu/nu) are sorted according to weight and randomized into groups prior to being dosed with a test compound, by oral, intravenous or intraperitoneal routes. Escalating doses of a test cmpound are used. Animal weights are measured daily for 5 days and about every 3 days after that until the animal is removed from the study due to body weight loss of > 20% or any alterations in physiological function that would affect normal function. Clinical observations are performed throughout the study to note any toxicity and mice are monitored until the end of the study.

[0646] EXAMPLE 79

[0647] Efficacy studies.

[0648] Nu/nu mice are subcuntaneously injected into their hind flank with human HCT-116 cells and 50% Matrigel (Becton-Dickinson). Human HCT-116 tumors are allowed to grow to 150-200 mm^3. The tumor bearing mice are then either given an administration of a test compound or a vehicle control. The tumor dimensions (length [l mm] and width [w mm]) are measured by electronic calipers and the tumor volume (mm^3) determined from the equation ([w^2 X l] ÷2). Weights of the mice and their respective tumor volumes are measured twice weekly until the animal is removed from the study, either because there is a body weight loss of greater than 20% or a tumor volume greater than 2000 mm^3. Clinical observations are performed throughout the study, which usually lasted for up to 70 days after the initial implantation of the tumor cells. Tumor volume increases are compared to negative (vehicle) and positive controls. Percentage tumor growth inhibition (TGI) is calculated from the equation [(tumor volume T – tumor volume)÷tumor volume C] x 100, where T = treatment group and C = control or vehicle group. The tumor volume for both groups is usually determined at defined times after the administration of the last dose of compound. Survival plots (Kaplan-Maier) are also performed to examine the pattern of survival.

[0649] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

- APPENDIX -

FDA Approved Oncology Drugs

Drug	Drug Trade Name	Approved Use	Manufacturer/Dist
abarelix	Plenaxis depot	For the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia	Praecis
aldesleukin	Prokine	Treatment of adults with metastatic melanoma	Chiron
Aldesleukin	Proleukin	Treatment of adults with metastatic renal cell carcinoma	Chiron Corp
Alemtuzumab	Campath	Accel. Approv. (clinical benefit not established) Campath is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.	Millennium and ILE Partners, LP
alitretinoin	Panretin	Topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.	Ligand Pharmaceuti
allopurinol	Zyloprim	Patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels and who cannot tolerate oral therapy.	GlaxoSmithKline
altretamine	Hexalen	Single agent palliative treatment of patients with persistent or recurrent ovarian cancer following first-line therapy with a cisplatin and/or alkylating agent based combination.	US Bioscience
amifostine	Ethyol	To reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer	US Bioscience
amifostine	Ethyol	Accel. Approv. (clinical benefit not established) Reduction of platinum toxicity in non-small cell lung cancer	US Bioscience
amifostine	Ethyol	To reduce post-radiation xerostomia for head and neck cancer where the radiation port includes a substantial portion of the parotid glands.	US Bioscience
anastrozole	Arimidex	Accel. Approv. (clinical benefit not established) for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer	AstraZeneca
		Conversion to regular approval for the adjuvant treatment of postmenopausal	

anastrozole	Arimidex	women with hormone receptor positive early breast cancer	AstraZeneca
anastrozole	Arimidex	Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.	AstraZeneca Pharmaceuticals
anastrozole	Arimidex	For first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.	AstraZeneca Pharmaceuticals
arsenic trioxide	Trisenox	Second line treatment of relapsed or refractory APL following ATRA plus an anthracycline.	Cell Therapeutic
asparaginase	Elspar	Therapy of patients with acute lymphocytic leukemia	Merck
Asparaginase	Elspar	ELSPAR is indicated in the therapy of patients with acute lymphocytic leukemia. This agent is useful primarily in combination with other chemotherapeutic agents in the induction of remissions of the disease in pediatric patients.	Merck & Co, Inc
azacitidine	Vidaza	For use for the treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia and requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia	Pharmion
BCG Live	TICE BCG		Organon Teknika C
bevacuzimab	Avastin	First-line treatment of patients with metastatic carcinoma of the colon and rectum (in combination with intravenous 5-fluorouracil-based chemotherapy)	Genentech
bexarotene capsules	Targretin	For the treatment by oral capsule of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.	Ligand Pharmaceut
bexarotene gel	Targretin	For the topical treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.	Ligand Pharmaceut
bleomycin	Blenoxane		Bristol-Myers Squil
bleomycin	Blenoxane	Sclerosing agent for the treatment of malignant pleural effusion (MPE) and prevention of recurrent pleural effusions.	Bristol-Myers Squil
		Accel. Approv. (clinical benefit not established) for the treatment of multiple	

bortezomib	Velcade	myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy	Millenium
bortezomib	Velcade	Conversion to regular approval for treatment of multiple myeloma patients who have received as least one prior therapy	Millenium
busulfan intravenous	Busulfex	Use in combination with cyclophoshamide as conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.	Orphan Medical, In
busulfan oral	Myleran	Chronic Myelogenous Leukemia- palliative therapy	GlaxoSmithKline
calusterone	Methosarb		Pharmacia & Upjol Company
capecitabine	Xeloda	Accel. Approv. (clinical benefit subsequently established) Treatment of metastatic breast cancer resistant to both paclitaxel and an anthracycline containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m2 of doxorubicin or doxorubicin equivalents	Roche
capecitabine	Xeloda	Initial therapy of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival benefit over 5_FU/LV has not been demonstrated with Xeloda monotherapy.	Roche
capecitabine	Xeloda	Conversion to regular approval for treatment in combination with docetaxel of patients with metastatic breast cancer after failure of prior anthracycline containing chemotherapy	Roche
capecitabine	Xeloda	Adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred	Roche
carboplatin	Paraplatin	Palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.	Bristol-Myers Squil
carboplatin	Paraplatin	Initial chemotherapy of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents.	Bristol-Myers Squil
carmustine	BCNU, BiCNU		Bristol-Myers Squil
carmustine	Gliadel	Treatment of patients with malignant glioma undergoing primary surgical resection	MGI Pharma

PCT/US06/28154			
carmustine with Polifeprosan 20 Implant	Gliadel Wafer	For use in addition to surgery to prolong survival in patients with recurrent glioblastoma multiforme who qualify for surgery.	Guilford Pharmacet Inc.
celecoxib	Celebrex	Accel. Approv. (clinical benefit not established) Reduction of polyp number in patients with the rare genetic disorder of familial adenomatous polyposis.	Searle
cetuximab	Erbitux	Accel. Approv. (clinical benefit not established) for treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy (in combination with irinotecan); as a single agent, treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy	Imclone
cetuximab	Erbitux	For use in combination with radiation therapy (RT) for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) or as a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.	Imclone
chlorambucil	Leukeran		GlaxoSmithKline
cisplatin	Platinol	Metastatic testicular-in established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors whoc have already received appropriate surgical and/or radiotherapeutic procedures. An established combination therapy consists of Platinol, Blenoxane and Velbam.	Bristol-Myers Squit
cisplatin	Platinol	Metastatic ovarian tumors - in established combination therapy with other approved chemotherapeutic agents: Ovarian-in established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of Platinol and Adriamycin. Platinol, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received Platinol therapy.	Bristol-Myers Squit
cisplatin	Platinol	as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments such as surgery and/or radiotherapy.	Bristol-Myers Squit

cladribine	Leustatin, 2-CdA	Treatment of active hairy cell leukemia.	R.W. Johnson Pharmaceutical Res Institute
clofarabine	Clolar	Accel. Approv. (clinical benefit not established) for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens	Genzyme
cyclophosphamide	Cytoxan, Neosar		Bristol-Myers Squil
cyclophosphamide	Cytoxan Injection		Bristol-Myers Squil
cyclophosphamide	Cytoxan Injection		Bristol-Myers Squil
cyclophosphamide	Cytoxan Tablet		Bristol-Myers Squil
cytarabine	Cytosar-U		Pharmacia & Upjol Company
cytarabine liposomal	DepoCyt	Accel. Approv. (clinical benefit not established) Intrathecal therapy of lymphomatous meningitis	Skye Pharmaceutic
dacarbazine	DTIC-Dome		Bayer
dactinomycin, actinomycin D	Cosmegen		Merck
dactinomycin, actinomycin D	Cosmegan		Merck
Darbepoetin alfa	Aranesp	Treatment of anemia associated with chronic renal failure.	Amgen, Inc
Darbepoetin alfa	Aranesp	Aranesp is indicated for the treatment of anemia in patients with non- myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.	Amgen, Inc
daunorubicin liposomal	DanuoXome	First line cytotoxic therapy for advanced, HIV related Kaposi's sarcoma.	Nexstar, Inc.
daunorubicin, daunomycin	Daunorubicin	Leukemia/myelogenous/monocytic/erythroid of adults/remission induction in acute lymphocytic leukemia of children and adults.	Bedford Labs
daunorubicin, daunomycin	Cerubidine	In combination with approved anticancer drugs for induction of remission in adult ALL.	Wyeth Ayerst
decitabine	Dacogen	for the treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts	MGI PHARMA IN

		in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.	
Denileukin diftitox	Ontak	Accel. Approv. (clinical benefit not established) treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor	Seragen, Inc
dexrazoxane	Zinecard	Accel. Approv. (clinical benefit subsequently established) Prevention of cardiomyopathy associated with doxorubicin administration	Pharmacia & Upjoh Company
dexrazoxane	Zinecard	Conversion to regular approval for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m2 and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy.	Pharmacia & Upjoh Company
docetaxel	Taxotere	Accel. Approv. (clinical benefit subsequently established) Treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.	Aventis Pharmaceut
docetaxel	Taxotere	Conversion to regular approval - treatment of locally advanced or metastatic breast cancer which has progressed during anthracycline-based treatment or relapsed during anthracycline-based adjuvant therapy.	Aventis Pharmaceut
docetaxel	Taxotere	For locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.	Aventis Pharmaceut
docetaxel	Taxotere	for use in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.	Aventis Pharmaceut
docetaxel	Taxotere	For use in combination with prednisone as a treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer	Aventis Pharmaceut

List of Approved Oncology Drugs with Approved Indications

docetaxel	Taxotere	For use in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable nodepositive breast cancer	Aventis Pharmaceu
doxorubicin	Adriamycin PFS	For use in combination with cyclophosphamide as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer	Pharmacia
doxorubicin	Adriamycin, Rubex		Pharmacia & Upjoh Company
doxorubicin	Adriamycin PFS Injectionintravenous injection	Antibiotic, antitumor agent.	Pharmacia & Upjoh Company
doxorubicin liposomal	Doxil	Conversion to regular approval for treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy	Alza
doxorubicin liposomal	Doxil	Accel. Approv. (clinical benefit not established) Treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.	Sequus Pharmaceut Inc.
doxorubicin liposomal	Doxil	Accel. Approv. (clinical benefit not established) Treatment of metastatic carcinoma of the ovary in patient with disease that is refractory to both paclitaxel and platinum based regimens	Sequus Pharmaceut Inc.
DROMOSTANOLONE PROPIONATE	DROMOSTANOLONE		Eli Lilly
DROMOSTANOLONE PROPIONATE	MASTERONE INJECTION		SYNTEX
Elliott's B Solution	Elliott's B Solution	Diluent for the intrathecal administration of methotrexate sodium and cytarabine for the prevention or treatment of meningeal leukemia or lymphocytic lymphoma.	Orphan Medical, In
epirubicin	Ellence	A component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.	Pharmacia & Upjoh Company
Epoetin alfa	epogen	EPOGENB is indicated for the reatment of anemia related to therapy with zidovudine in HIV- infected patients. EPOGENB is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. EPOGEND is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis or	Amgen, Inc

		gastrointestinal bleeding, which should be managed appropriately.	
Epoetin alfa	epogen	EPOGENB is indicated for the treatment of anemic patients (hemoglobin > 10 to _< 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.	Amgen, Inc
Epoetin alfa	epogen	EPOGENB is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. EPOGEND is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. EPOGENB is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding, which should be managed appropriately.	Amgen, Inc
Epoetin alfa	epogen	EPOGEN is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis.	Amgen, Inch
erlotinib	Tarceva	For treatment of locally advanced or metastatic Non Small-Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapy regimen	OSI
erlotinib	Tarceva	For use in combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer	OSI
estramustine	Emcyt	palliation of prostate cancer	Pharmacia & Upjoh Company
etoposide phosphate	Etopophos	Management of refractory testicular tumors, in combination with other approved chemotherapeutic agents.	Bristol-Myers Squil
etoposide phosphate	Etopophos	Management of small cell lung cancer, first-line, in combination with other approved chemotherapeutic agents.	Bristol-Myers Squil
etoposide phosphate	Etopophos	Management of refractory testicular tumors and small cell lung cancer.	Bristol-Myers Squil
etoposide, VP-16	Vepesid	Refractory testicular tumors-in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic and radiotherapeutic therapy.	Bristol-Myers Squil
etoposide, VP-16	VePesid	In combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung	Bristol-Myers Squil

PCT/US06/28154		cancer.	
etoposide, VP-16	Vepesid	In combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.	Bristol-Myers Squib
exemestane	Aromasin	For adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN® for completion of a total of five consecutive years of adjuvant hormonal therapy	Pharmacia
exemestane	Aromasin	Treatment of advance breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.	Pharmacia & Upjoh Company
Filgrastim	Neupogen	Decrease incidence of infection in patients with nonmyeloid malignancies	Amgen, Inc
Filgrastim	Neupogen	NEUPOGEN is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever.	Amgen, Inc
Filgrastim	Neupogen	NEUPOGEN is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation hemotherapy treatment of adults with AML.	Amgen, Inc
Filgrastim	Neupogen	NEUPOGEN is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation.	Amgen, Inc
floxuridine (intraarterial)	FUDR		Roche
fludarabine	Fludara	Palliative treatment of patients with B-cell lymphocytic leukemia (CLL) who have not responded or have progressed during treatment with at least one standard alkylating agent containing regimen.	Berlex Laboratories
fluorouracil, 5-FU	Adrucil	prolong survival in combination with leucovorin	ICN Puerto Rico
fulvestrant	Faslodex	the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy	IPR
		Accel. Approv. (clinical benefit not established) as monotherapy for the treatment of patients with locally advanced	

gefitinib	Iressa	or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies	AstraZenca
gemcitabine	Gemzar	Treatment of patients with locally advanced (nonresectable stage II or III) or metastatic (stage IV) adenocarcinoma of the pancreas. Indicated for first-line treatment and for patients previously treated with a 5-fluorouracil-containing regimen.	Eli Lilly
gemcitabine	Gemzar	For use in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.	Eli Lilly
gemicitabine	Gemzar	For use in combination with paclitaxel for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated	Lilly
gemtuzumab ozogamicin	Mylotarg	Accel. Approv. (clinical benefit not established) Treatment of CD33 positive acute myeloid leukemia in patients in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy.	Wyeth Ayerst
goserelin acetate	Zoladex		AstraZeneca Pharmaceuticals
goserelin acetate	Zoladex Implant	Palliative treatment of advanced breast cancer in pre- and perimenopausal women.	AstraZeneca Pharmaceuticals
histrelin acetate	Histrelin implant	For the palliative treatment of advanced prostate cancer	Valera
hydroxyurea	Hydrea		Bristol-Myers Squib
hydroxyurea	Hydrea	Decrease need for transfusions in sickle cell anemia	Bristol-Myers Squib
Ibritumomab Tiuxetan	Zevalin	Accel. Approv. (clinical benefit not established) treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab refractory follicular non-Hodgkin's lymphoma.	IDEC Pharmaceutic Corp
idarubicin	Idamycin	For use in combination with other approved antileukemic drugs for the treatment of acute myeloid leukemia (AML) in adults.	Adria Laboratories
idarubicin	Idamycin	In combination with other approved antileukemic drugs for the treatment of acute non-lymphocytic leukemia in adults.	Pharmacia & Upjoh Company
ifosfamide	IFEX	Third line chemotherapy of germ cell testicular cancer when used in combination	Bristol-Myers Squib

		with certain other approved antineoplastic agents.	
imatinib mesylate	Gleevec	Accel. Approv. (clinical benefit not established) Initial therapy of chronic myelogenous leukemia	Novartis
imatinib mesylate	Gleevec	Accel. Approv. (clinical benefit not established) metastatic or unresectable malignant gastrointestinal stromal tumors	Novartis
Imatinib mesylate	Gleevec	Accel. Approv. (clinical benefit not established) Treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).	Novartis
imatinib mesylate	Gleevec	Accel. Approv. (clinical benefit not established) Initial treatment of newly diagnosed Ph+ chronic myelogenous leukemia (CML).	Novartis
imatinib mesylate	Gleevec	Accel. Approv. (clinical benefit not established) for treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase. Follow-up is limited. Gleevec is also indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival in patients with CML blast crisis, accelerated phase or chronic phase after failure of alpha interferon. Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)	Novartis
imatinib mesylate	Gleevec	Accel. Approv. (clinical benefit not established) Treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy.	Novartis
imatinib mesylate	Gleevec	Conversion to regular approval for treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy	Novartis
interferon alfa 2a	Roferon A	Treatment of patients with hairy cell leukemia	Roche
		Chronic phase, Philadelphia chromosome	

PCT/US06/28154

interferon alfa 2a	Roferon A	positive chronic myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of diagnosis)	Roche
Interferon alfa-2a	Roferon-A		Hoffmann-La Roche
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for Injection is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia.	Schering Corp
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for Injection is indicated for intralesional treatment of selected patients 18 years of age or older with condylomata acuminata involving external surfaces of the genital and perianal areas.	Schering Corp
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated for the treatment of selected patients 18 years of age or older with AIDS-related Kaposi's Sarcoma. The likelihood of response to INTRON A therapy is greater in patients who are without systemic symptoms, who have limited lymphadenopathy and who have a relatively intact immune system as indicated by total CD4 count.	Schering Corp
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence within 56 days of surgery.	Schering Corp
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for Injection is indicated for the initial treatment of clinically aggressive follicular non-Hodgkin's Lymphoma in conjunction with anthracycline-containing combination chemotherapy in patients 18 years of age or older.	Schering Corp
Interferon alfa-2b	Intron A Intron A		Schering Corp
irinotecan	Camptosar	Accel. Approv. (clinical benefit subsequently established) Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	Pharmacia & Upjohn Company
irinotecan	Camptosar	Conversion to regular approval - treatment of metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	Pharmacia & Upjohn Company
irinotecan	Camptosar	For first line treatment n combination with 5-FU/leucovorin of metastatic carcinoma of the colon or rectum.	Pharmacia & Upjohn Company

lenalidomide	Revlimid	for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities	Celgene
letrozole	Femara	Treatment of advanced breast cancer in postmenopausal women.	Novartis
letrozole	Femara	First-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.	Novartis
letrozole	Femara		Novartis
letrozole	Femara	Accel. Approv. (clinical benefit not established) for the extended adjuvant treatment of early breast cancer in postmenopausal women who have received five years of adjuvant tamoxifen therapy.	Novartis
leucovorin	Wellcovorin, Leucovorin	Leucovorin calcium is indicated fro use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.	Immunex Corporati
leucovorin	Leucovorin		Immunex Corporati
leucovorin	Leucovorin		Immunex Corporati
leucovorin	Leucovorin		Immunex Corporati
leucovorin	Leucovorin	In combination with fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.	Lederle Laboratorie
Leuprolide Acetate	Eligard	palliative treatment of advanced prostate cancer.	QLT USA
levamisole	Ergamisol	Adjuvant treatment in combination with 5-fluorouracil after surgical resection in patients with Dukes' Stage C colon cancer.	Janssen Research Foundation
lomustine, CCNU	CeeBU		Bristol-Myers Squib
meclorethamine, nitrogen mustard	Mustargen		Merck
megestrol acetate	Megace		Bristol-Myers Squib
melphalan, L-PAM	Alkeran		GlaxoSmithKline
melphalan, L-PAM	Alkeran	Systemic administration for palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.	GlaxoSmithKline
mercaptopurine, 6-MP	Purinethol		GlaxoSmithKline

PCT/US06/28154

mesna	Mesnex	Prevention of ifosfamide-induced hemorrhagic cystitis	Asta Medica
mesna	Mesnex tabs	Reducing the incidence of ifosfamide-induced hemorrhagic cystitis	Baxter
methotrexate	Methotrexate		Lederle Laboratories
methotrexate	Methotrexate		Lederle Laboratories
methotrexate	Methotrexate		Lederle Laboratories
methotrexate	Methotrexate		Lederle Laboratories
methotrexate	Methotrexate	osteosarcoma .	Lederle Laboratories
methotrexate	Methotrexate		Lederle Laboratories
methoxsalen	Uvadex	For the use of UVADEX with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.	Therakos
mitomycin C	Mutamycin		Bristol-Myers Squib
mitomycin C	Mitozytrex	therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.	Supergen
mitotane	Lysodren		Bristol-Myers Squib
mitoxantrone	Novantrone	For use in combination with corticosteroids as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.	Immunex Corporatic
mitoxantrone	Novantrone	For use with other approved drugs in the initial therapy for acute nonlymphocytic leukemia (ANLL) in adults.	Lederle Laboratories
nandrolone phenpropionate	Durabolin-50		Organon
nelarabine	Arranon	Accel. Approv. (clinical benefit not established) for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens	GlaxoSmithKline
Nofetumomab	Verluma		Boehringer Ingelhei Pharma KG (former Karl Thomae GmbH
Oprelvekin	Neumega	Prevention of severe thrombocytopenia	Genetics Institute, Ir

		following myelosuppressive chemotherapy	
Oprelvekin	Neumega	Neumega is indicated for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia.	Genetics Institute, Ir
Oprelvekin	Neumega		Genetics Institute, Ir
oxaliplatin	Eloxatin	Accel. Approv. (clinical benefit not established) in combination with infusional 5-FU/LV, is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and irinotecan.	Sanofi Synthelabo
oxaliplatin	Eloxatin	Conversion to regular approval for use in combination with infusional 5-Fluorouracil (5-FU) and Leucovorin (LV) for the treatment of patients previously untreated for advanced colorectal cancer	Sanofi Synthelabo
oxaliplatin	Eloxatin	for use in combination with infusional 5-FU/LV, for the adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor	Sanofi Synthelabo
paclitaxel	Paxene	treatment of advanced AIDS-related Kaposi's sarcoma after failure of first line or subsequent systemic chemotherapy	Baker Norton Pharmaceuticals, Inc
paclitaxel	Taxol	Treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy.	Bristol-Myers Squib
paclitaxel	Taxol	Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.	Bristol-Myers Squib
paclitaxel	Taxol	New dosing regimen for patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary	Bristol-Myers Squib
paclitaxel	Taxol	second line therapy for AIDS related Kaposi's sarcoma.	Bristol-Myers Squib
paclitaxel	Taxol	For first-line therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin.	Bristol-Myers Squib
paclitaxel	Taxol	for use in combination with cisplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for	Bristol-Myers Squib

PCT/US2006/028154		potentially curative surgery and/or radiation therapy.	
paclitaxel	Taxol	For the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination therapy.	Bristol-Myers Squib
paclitaxel	Taxol	First line ovarian cancer with 3 hour infusion.	Bristol-Myers Squib
paclitaxel protein-bound particles	Abraxane	For the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracyline unless clinically contraindicated	AM Bioscience
palifermin	Kepivance	Decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoetic stem cell support	Amgen
pamidronate	Aredia	Treatment of osteolytic bone metastases of breast cancer in conjunction with standard antineoplastic therapy.	Novartis
pegademase	Adagen (Pegademase Bovine)	Enzyme replacement therapy for patients with severe combined immunodeficiency asa result of adenosine deaminase deficiency.	Enzon
pegaspargase	Oncaspar	Acute lymphocytic leukemia in L-asparaginase hypersensitive patients	Enzon, Inc
Pegfilgrastim	Neulasta	Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	Amgen, Inc
pemetrexed disodium	Alimta	For use in the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery	Lilly
pemetrexed disodium	Alimta	Accel. Approv. (clinical benefit not established) as a single agent for the treatment of patients with locally advanced or metastatic non-small lung cancer after prior chemotherapy	Lilly
pentostatin	Nipent	Single agent treatment for adult patients with alpha interferon refractory hairy cell leukemia.	Parke-Davis Pharmaceutical Co.
pentostatin	Nipent	Single-agent treatment for untreated hairy cell leukemia patients with active disease as defined by clinically significant anemia, neutropenia, thrombocytopenia, or disease-related symptoms. (Supplement for front -	Parke-Davis Pharmaceutical Co.

PCT/US06/28154		line therapy.)	
ipobroman	Vercyte		Abbott Labs
licamycin, nithramycin	Mithracin		Pfizer Labs
porfimer sodium	Photofrin	For the ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy	Axcan Scandipharm
porfimer sodium	Photofrin	For use in photodynamic therapy (PDT) for palliation of patients with completely obstructing esophageal cancer, or patients with partially obstructing esophageal cancer who cannot be satisfactorily treated with ND-YAG laser therapy.	QLT Phototherapeut
porfimer sodium	Photofrin	For use in photodynamic therapy for treatment of microinvasive endobronchial nonsmall cell lung cancer in patients for whom surgery and radiotherapy are not indicated.	QLT Phototherapeut
porfimer sodium	Photofrin	For use in photodynamic therapy (PDT) for reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobroncial nonsmall cell lung cancer (NSCLC).	QLT Phototherapeut
procarbazine	Matulane		Sigma Tau Pharms
quinacrine	Atabrine		Abbott Labs
Rasburicase	Elitek	ELITEK is indicated for the initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid.	Sanofi-Synthelabo, I
Rituximab	Rituxan	for use in the first-line treatment of patients with diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination with CHOP or other anthracycline-based chemotherapy regimens.	Genentech, Inc
Rituximab	Rituxan	Treatment of patients with relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma	Genentech, Inc
sargramostim	Leukine	Acceleration of myeloid recovery following autologous bone marrow transplant in patients with non-Hodgkin's lymphoma, acute lymphocytic leukemia, or Hodgkin's disease	Berlex
Sargramostim	Prokine		Immunex Corp
sorafenib	Nexavar	For the treatment of patients with advanced	Bayer

PCT/US2006/028154

		renal cell carcinoma	
streptozocin	Zanosar	Antineoplastic agent.	Pharmacia & Upjohn Company
sunitinib maleate	Sutent	treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate	Pfizer
sunitinib maleate	Sutent	Accel. Approv. (clinical benefit not established) for the treatment of advanced renal cell carcinoma. Approval for advanced renal cell carcinoma is based on partial response rates and duration of responses. There are no randomized trials of SUTENT demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in renal cell carcinoma.	Pfizer
talc	Sclerosol	For the prevention of the recurrence of malignant pleural effusion in symptomatic patients.	Bryan
tamoxifen	Nolvadex		AstraZeneca Pharmaceuticals
tamoxifen	Nolvadex	As a single agent to delay breast cancer recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T1-3, N1, M0)	AstraZeneca Pharmaceuticals
tamoxifen	Nolvadex	For use in premenopausal women with metastatic breast cancer as an alternative to oophorectomy or ovarian irradiation	AstraZeneca Pharmaceuticals
tamoxifen	Nolvadex	For use in women with axillary node-negative breast cancer adjuvant therapy.	AstraZeneca Pharmaceuticals
tamoxifen	Nolvadex	Metastatic breast cancer in men.	AstraZeneca Pharmaceuticals
tamoxifen	Nolvadex	Equal bioavailability of a 20 mg Nolvadex tablet taken once a day to a 10 mg Nolvadex tablet taken twice a day.	AstraZeneca Pharmaceuticals
tamoxifen	Nolvadex	to reduce the incidence of breast cancer in women at high risk for breast cancer	AstraZeneca Pharmaceuticals
tamoxifen	Nolvadex	In women with DCIS, following breast surgery and radiation, Nolvadex is indicated to reduce the risk of invasive breast cancer.	AstraZeneca Pharmaceuticals
temozolomide	Temodar	Accel. Approv. (clinical benefit not established) Treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse with disease progression on a nitrosourea and procarbazine containing regimen	Schering
temozolomide	Temodar	Conversion to regular approval for the treatment of patients with newly diagnosed high grade gliomas concomitantly with radiotherapy and then as adjuvant treatment	Schering
		In combination with other approved	

teniposide, VM-26	Vumon	anticancer agents for induction therapy in patients with refractory childhood acute lymphoblastic leukemia (all).	Bristol-Myers Squib
testolactone	Teslac		Bristol-Myers Squib
testolactone	Teslac		Bristol-Myers Squib
thioguanine, 6-TG	Thioguanine		GlaxoSmithKline
thiotepa	Thioplex		Immunex Corporatic
thiotepa	Thioplex		Immunex Corporatic
thiotepa	Thioplex		Lederle Laboratories
topotecan	Hycamtin	Treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.	GlaxoSmithKline
topotecan	Hycamtin	Treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy. In clinical studies submitted to support approval, sensitive disease was defined as disease responding to chemotherapy but subsequently progressing at least 60 days (in the phase 3 study) or at least 90 days (in the phase 2 studies) after chemotherapy	GlaxoSmithKline
toremifene	Fareston	Treatment of advanced breast cancer in postmenopausal women.	Orion Corp.
Tositumomab	Bexxar	Accel. Approv. (clinical benefit not established) Treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy	Corixa Corporation
Tositumomab/I-131 tositumomab	Bexxar	Expand the indication to include patients with relapsed or refractory low grade follicular transformed CD20-positive non-Hodgkin's lymphoma who have not received rituximab	GlaxoSmithKline
Trastuzumab	Herceptin	HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease.	Genentech, Inc
Trastuzumab	Herceptin	Herceptin in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER-2 protein and had not received chemotherapy for their metastatic	Genentech, Inc

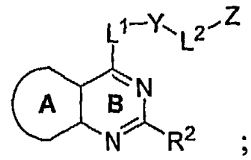
PCT/US2006/028154		disease	
Trastuzumab	Herceptin		Genentech, Inc
Trastuzumab	Herceptin		Genentech, Inc
retinoin, ATRA	Vesanoid	Induction of remission in patients with acute promyelocytic leukemia (APL) who are refractory to or unable to tolerate anthracycline based cytotoxic chemotherapeutic regimens.	Roche
Uracil Mustard	Uracil Mustard Capsules		Roberts Labs
valrubicin	Valstar	For intravesical therapy of BCG-refractory carcinoma in situ (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.	Anthra --> Medeva
vinblastine	Velban		Eli Lilly
vincristine	Oncovin		Eli Lilly
vincristine	Oncovin		Eli Lilly
vincristine	Oncovin		Eli Lilly
vincristine	Oncovin		Eli Lilly
vincristine	Oncovin		Eli Lilly
vincristine	Oncovin		Eli Lilly
vincristine	Oncovin		Eli Lilly
vinorelbine	Navelbine	Single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small cell lung cancer (NSCLC).	GlaxoSmithKline
vinorelbine	Navelbine	Navelbine is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unreseactable, advanced non-small cell lung cancer (NSCLC). In patients with Stage IV NSCLC, Navelbine is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, Navelbine is indicated in combination with cisplatin.	GlaxoSmithKline
zoledronate	Zometa	the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have	Novartis

		progressed after treatment with at least one hormonal therapy	
zoledronic acid	Zometa	Treatment of hypercalcemia of malignancy	Novartis

CLAIMS

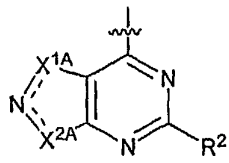
What is claimed is:

1. An isolated compound having the structure:

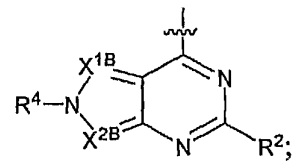


(I)

wherein A-B together represent one of the following structures:



or



or pharmaceutically acceptable derivative thereof;

wherein one of ----- is a double bond, as valency permits;

$\mathbf{R^2}$ is hydrogen, halogen, cyano, nitro, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

$\mathbf{R^4}$ is hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

$\mathbf{X^{1A}}$ is NR^1 or $-C(R^{X1})-$; wherein R^1 taken together with a moiety present on L^1 may form an optionally substituted heterocyclic ring;

$\mathbf{X^{2A}}$ is NR^3 or $-C(R^{X1})-$; wherein one of X^{1A} and X^{2A} is $-C(R^{X1})-$, but not both;

$\mathbf{X^{1B}}$ and $\mathbf{X^{2B}}$ are -N- or $-C(R^{X1})-$; whereby one of X^{1B} and X^{2B} is $-C(R^{X1})-$, but not both;

wherein R^1 and R^3 are independently hydrogen, a nitrogen protecting group, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety; and R^{X1} is hydrogen, halogen, cyano, nitro, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

$\mathbf{L^1}$ is a 2-8 atom heteroaliphatic linker having at least one N, O or S atom in the heteroaliphatic main chain;

$\mathbf{L^2}$ is a 1-6 atom heteroaliphatic linker having at least one N atom in the heteroaliphatic main chain;

Y is an alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety; and

Z is an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

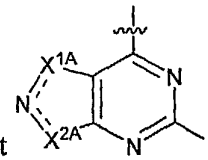
with the proviso that no occurrence of R^1, R^3, R^4 or R^{X1} is Q^1, Q^2 or Q^3, wherein

Q^1 is $-(CR^{1A}R^{1B})_mC\equiv C-(CR^{1A}R^{1B})_tR^{1C}$, $-(CR^{1A}R^{1B})_mC=C-(CR^{1A}R^{1B})_tR^{1C}$, $-C=NOR^{1D}$, or $-X^3R^{1D}$ wherein m is an integer from 0 to 3, t is an integer from 0 to 5, and X^3 is a divalent group derived from azetidine, oxetane or a C_{3-4}carbocyclic group;

Q^2 is $-(CR^{1A}R^{1B})_mC\equiv C-(CR^{1A}R^{1B})_kR^{1E}$, $-(CR^{1A}R^{1B})_mC=C-(CR^{1A}R^{1B})_kR^{1E}$ wherein k is an integer from 1 to 3 and m is an integer from 0 to 3; and

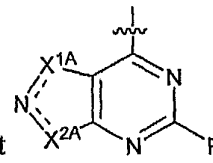
Q^3 is $-(CR^{1A}R^{1B})_tR^{1C}$, wherein t is an integer from 0 to 5 and the attachment point to R^{1C} is through a carbon atom of the R^{1C} group; wherein R^{1A} and R^{1B} are independently H or C_{1-6}alkyl; R^{1C} is an optionally substituted non-aromatic monocyclic ring, a fused or bridged bycyclic ring or a spirocyclic ring; R^{1E} is $-NR^{1A}R^{1D}$ or $-OR^{1D}$; R^{1D} is R^{1F}, $-C(=O)R^{1F}$, $-SO_2R^{1F}$, $-C(=O)N(R^{1F})_2$, $-SO_2N(R^{1F})_2$, or $-CO_2R^{1F}$, wherein R^{1F} is H, C_{1-6}alkyl, $-(CR^{1A}R^{1B})_t(C_{6-10}$aryl) or $-(CR^{1A}R^{1B})_t$(4-10 membered heterocyclic).

2. The compound of claim 1 wherein in any one or more of the following groups, the recited variables do not occur simultaneously as defined:

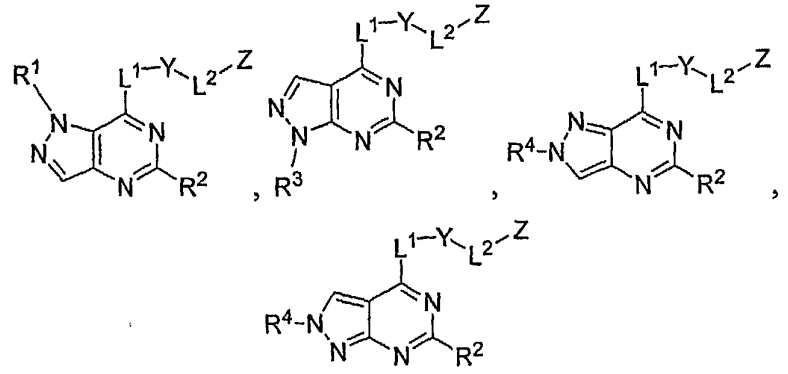
(i) A-B together represent 

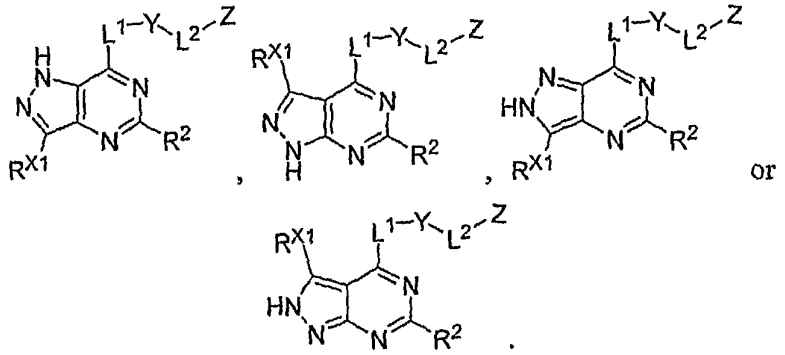
; X^{1A} is NR^1 and X^{2A} is CR^{X1} or X^{1A} is CR^{X1} and X^{2A} is NR^3; L^1 is $-X(CHR^x)_{0-2}-$, wherein X is O, S, NH or NC_{1-4}alkyl, and R^x is H or C_{1-4}alkyl; Y is phenyl, thienyl, furanyl, pyrrolyl, pyridyl, pyrimidyl, imidazolyl, pyrazinyl, oxazolyl, thiazolyl, naphthyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, isoquinolinyl or quinazolinyl; and L^2-Z is lower alkyl (1-4 carbon atoms), cycloalkyl (3-8 carbon atoms), lower alkoxy (1-4 carbon atoms), cycloalkoxy (3-8 carbon atoms), lower perfluoroalkyl (1-4 carbon atoms), lower acyloxy (1-4 carbon atoms; -OC(O)R), amino, lower mono or dialkylamino (1-4 carbon atoms), lower mono or dicycloalkylamino (3-8 carbon atoms), hydroxymethyl, lower acyl (1-4 carbon atoms; -C(O)R), lower thioalkyl (1-4 carbon

atoms), lower sulfinylalkyl (1-4 carbon atoms), lower sulfonylalkyl (1-4 carbon atoms), thiocycloalkyl (3-8 carbon atoms), sulfinylcycloalkyl (3-8 carbon atoms), sulfonylcycloalkyl (3-8 carbon atoms), sulfonamido, lower mono or dialkylsulfonamido (1-4 carbon atoms), mono or dicycloalkylsulfonamido (3-8 carbon atoms), mercapto, carboxy, carboxamido (-C(O)NH_2), lower mono or dialkylcarboxamido (1-4 carbon atoms), mono or dicycloalkylcarboxamido (3-8 carbon atoms), lower alkoxycarbonyl (1-4 carbon atoms), cycloalkoxycarbonyl (3-8 carbon atoms), lower alkenyl (2-4 carbon atoms), cycloalkenyl (4-8 carbon atoms), lower alkynyl (2-4 carbon atoms); and

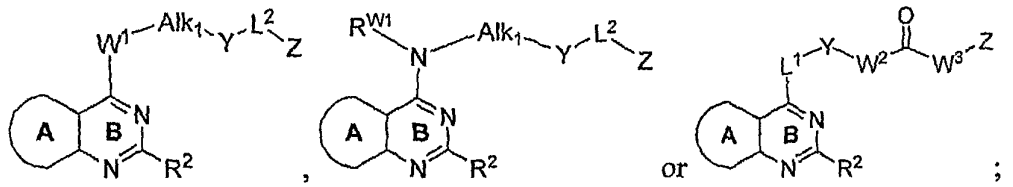
(ii) A-B together represent  ; X^{1A} is NR^1 and X^{2A} is CR^{X1} or X^{1A} is CR^{X1} and X^{2A} is NR^3; R^{X1} is hydrogen, halo, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, -$CONR^aR^b$, -$O(CH_2)_nNR^aR^b$, -$(CH_2)_nNR^aR^b$ or –NR^aR^b; L^1 is -$NHCH_2$-; Y-L^2-Z is pyridinyl, pyrimidinyl, indazolyl, dihydroisoindolyl, benzisoxazolyl, oxazolyl, imidazolyl, oxadiazolyl or thiazolyl each optionally substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy, -$O(CH_2)_nNR^xR^y$, -$O(CH_2)_nOR^x$, -NR^xR^y, -$(CH_2)_nNR^xR^y$, -CH_2OR^x, -$COOR^x$, -$CONR^xR^y$, -$CH_2SO_2NR^xR^y$, -$SO_2NR^xR^y$, or optionally substituted phenyl; and R^2 is pyridin-2-yl, C_{1-6}alkylpyridin-2-yl, C_{1-6}alkylpyrrol-2-yl or C_{1-6}alkylthiazol-2-yl; wherein R^a is H or C_{1-4}alkyl, R^b is C_{1-4}alkyl, or R^a and R^b together for a 3-7-membered heterocyclic ring; and R^x and R^y are independently H or C_{1-6}alkyl.

3. The compound of claim 1 having the structure:

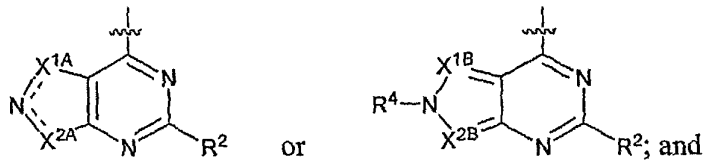




4. The compound of claim 1 having the structure:

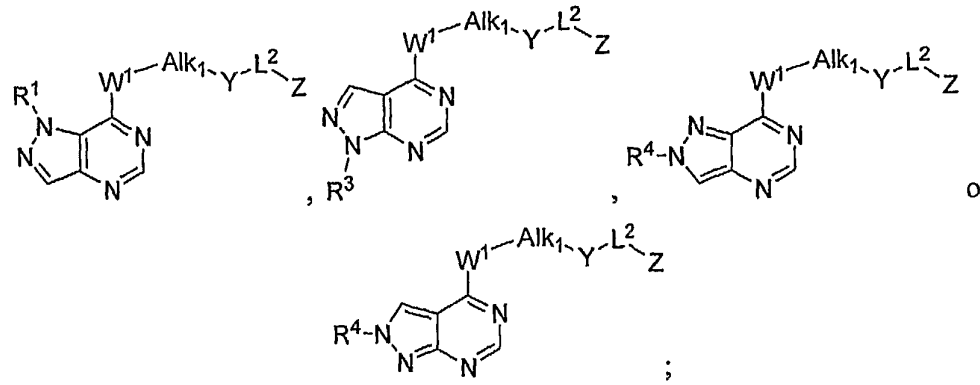


wherein A-B together represent one of the following structures:



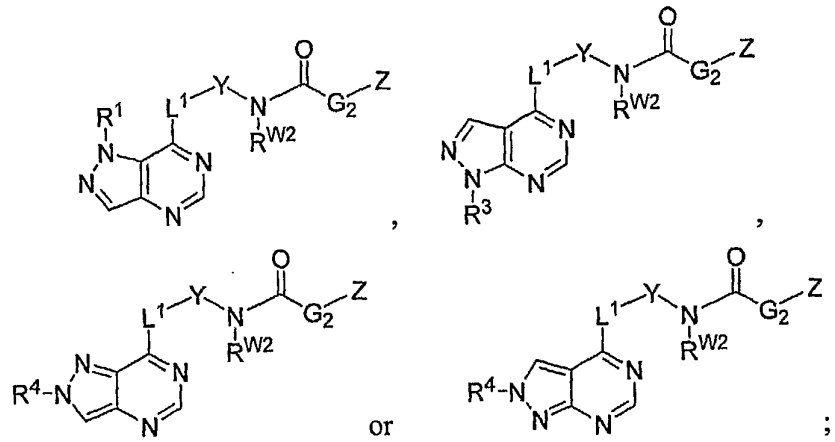
wherein W^1 is O or NR^{W1}, where R^{W1} is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, or acyl; and Alk_1 is a C_{1-6}alkylene or C_{2-6}alkenylene moiety; W^2 and W^3 are independently absent, O, NR^W, $CR^{W1}R^{W2}$ or $NR^WCR^{W1}R^{W2}$, where R^W is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, or acyl; and R^{W1} and R^{W2} are independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic; with the proviso that W^2 and W^3 are not each absent and at least one of W^2 and W^3 is NR^W or $NR^WCR^{W1}R^{W2}$; or R^{W1} taken together with a carbon atom present on Alk_1 may form a heterocyclic moiety.

5. The compound of claim 1 having the structure:



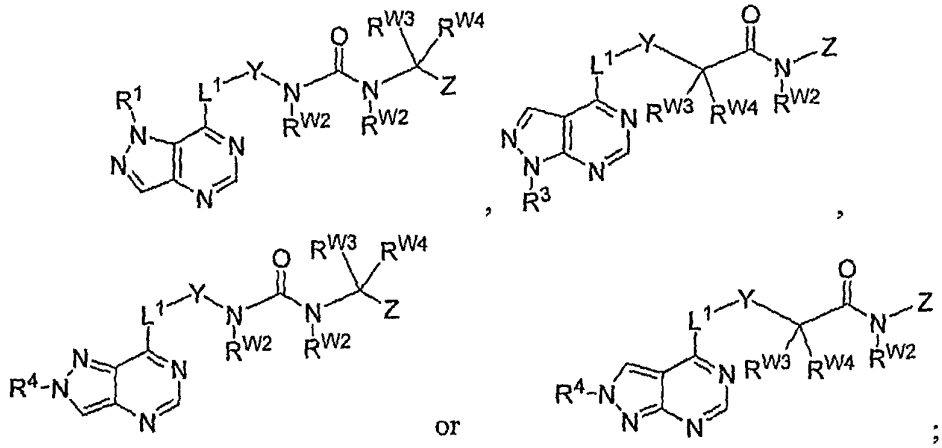
wherein R^1, R^3, R^4, L^2, Y and Z are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; and Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2-$, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, $-SO_2-$, -$NR^{L1A}SO_2-$, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl.

6. The compound of claim 1 having the structure:



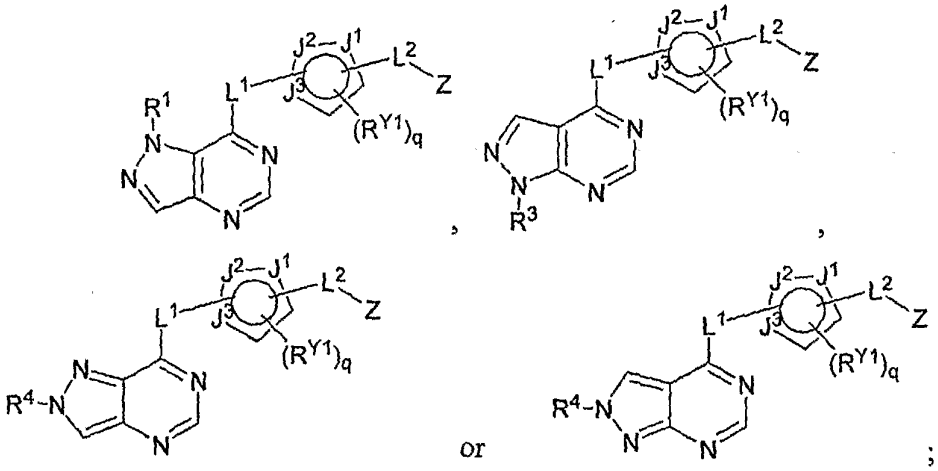
wherein R^1, R^3, R^4, L^1, Y and Z are as defined in claim 1; G_2 is absent, O or NR^{G2}; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

7. The compound of claim 1 having the structure:



wherein R^1, R^3, R^4, L^1, Y and Z are as defined in claim 1; and R^{W2}, R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl.

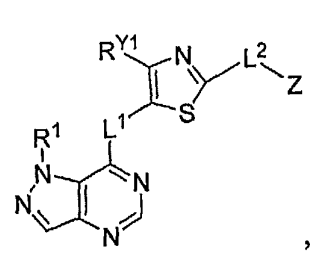
8. The compound of claim 1 having the structure:



wherein q is an integer from 0-2; R^1, R^3, R^4, L^1, L^2 and Z are as defined in claim 1; and J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, $-CN$, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3}

taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring.

9. The compound of claim 8 having the structure: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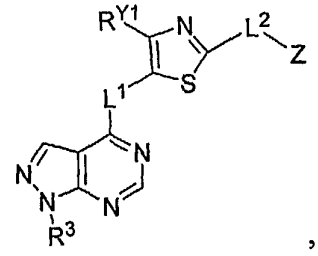
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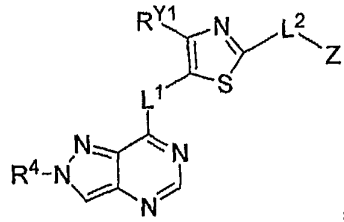
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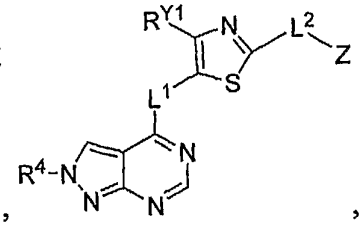
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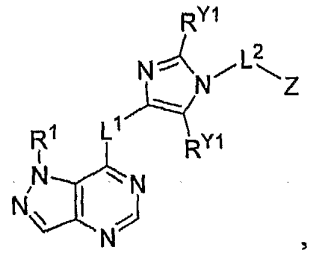
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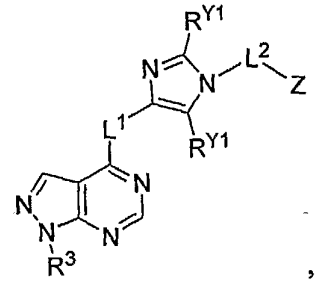
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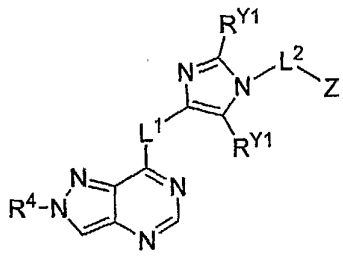
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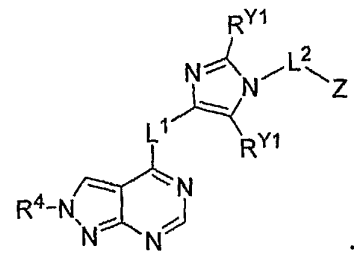
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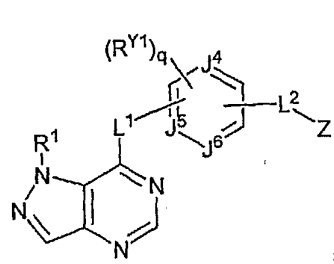
10. The compound of claim 1 having the structure: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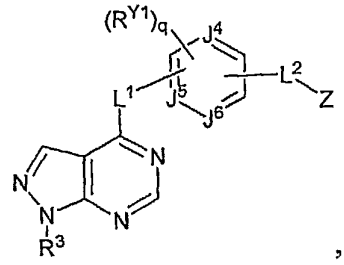
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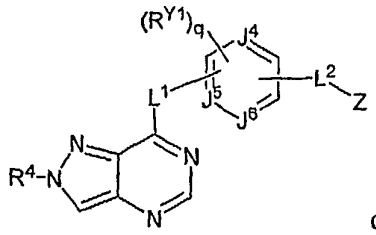
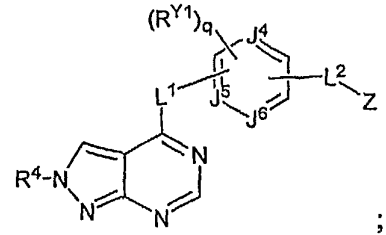
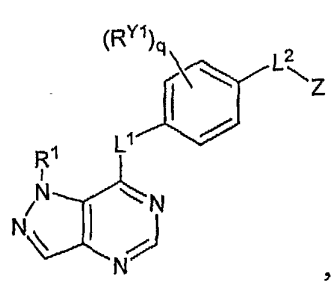
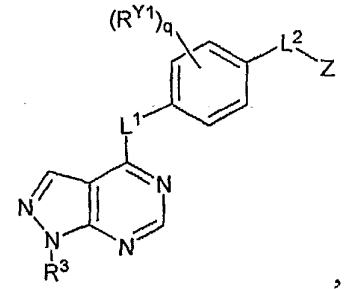
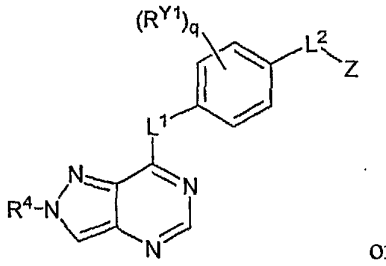
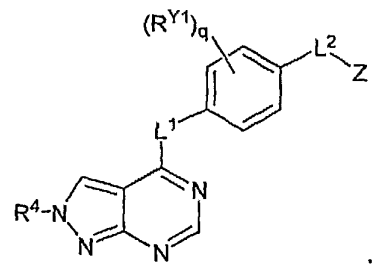
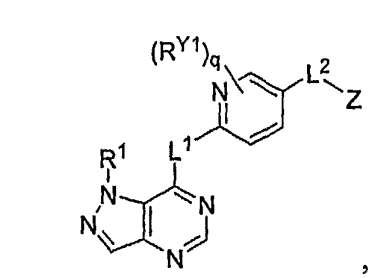



wherein q is an integer from 0-3; R^1, R^3, R^4, L^1, L^2 and Z are as defined in claim 1; and J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring.

11. The compound of claim 11 having the structure:

12. The compound of claim 11 having the structure: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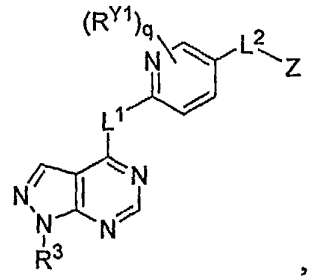
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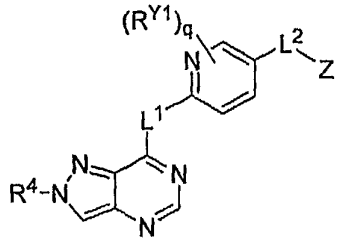
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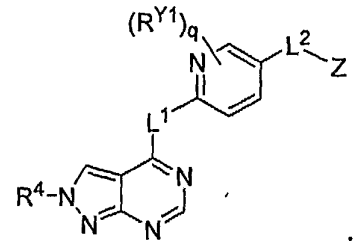
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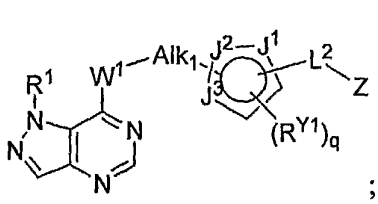
13. The compound of claim 1 having the structure: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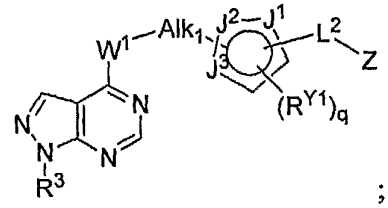
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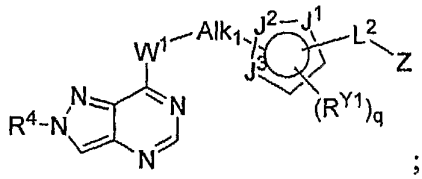
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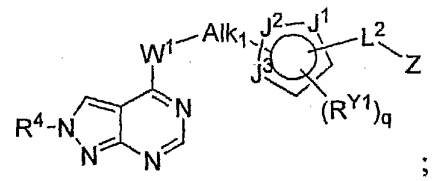
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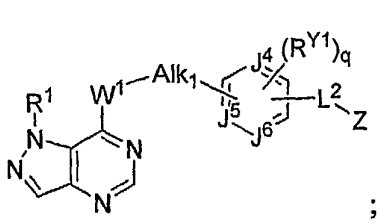
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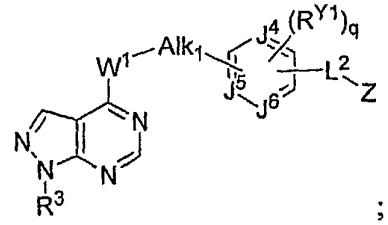
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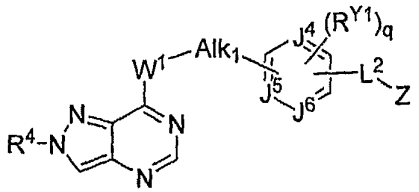
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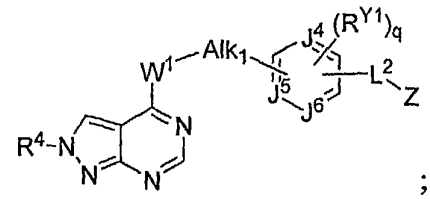
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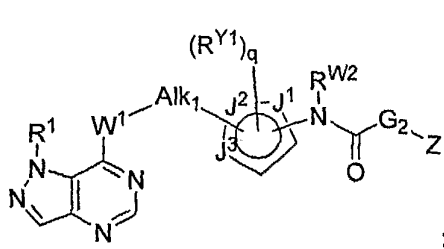
wherein R^1, R^3, R^4, L^2 and Z are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently

optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Y3}, -SR^{Y3}, -$NR^{Y2}R^{Y3}$, -$SO_2NR^{Y2}R^{Y3}$, -C(=O)$NR^{Y2}R^{Y3}$, halogen, -CN, -NO_2, -C(=O)OR^{Y3}, -N(R^{Y2})C(=O)R^{Y3}, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring.

14. The compound of claim 1 having the structure: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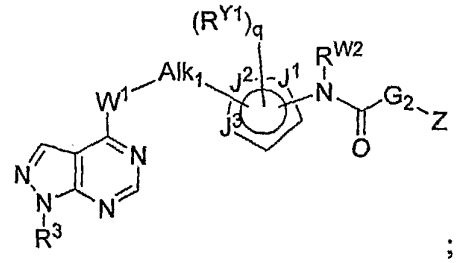
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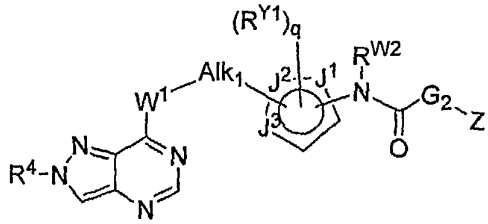
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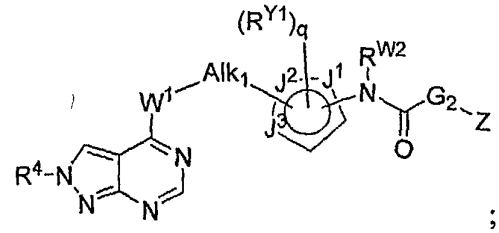
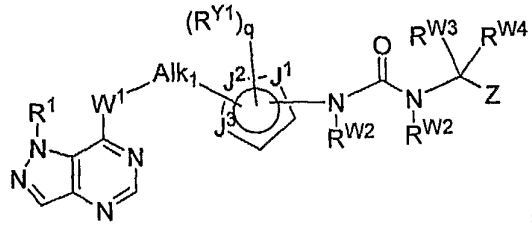

;

wherein R^1, R^3, R^4 and Z are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently

hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; G_2 is absent, O or NR^{G2}; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

15. The compound of claim 1 having the structure:



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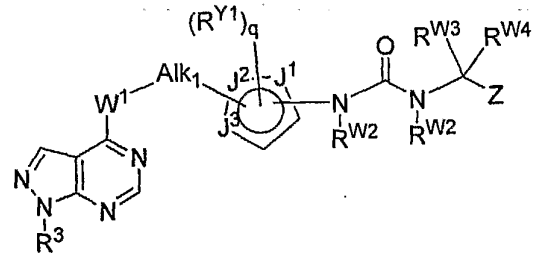

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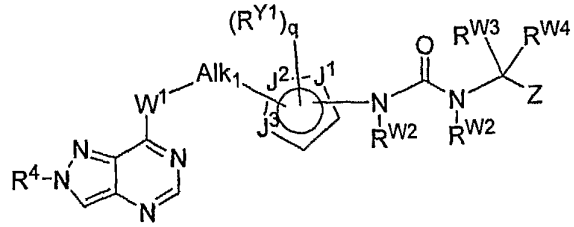

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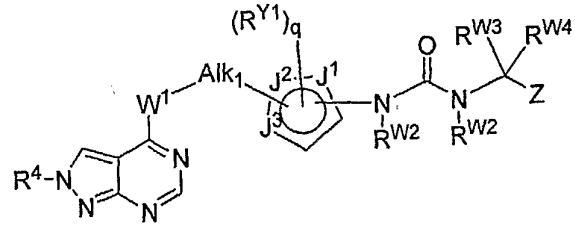

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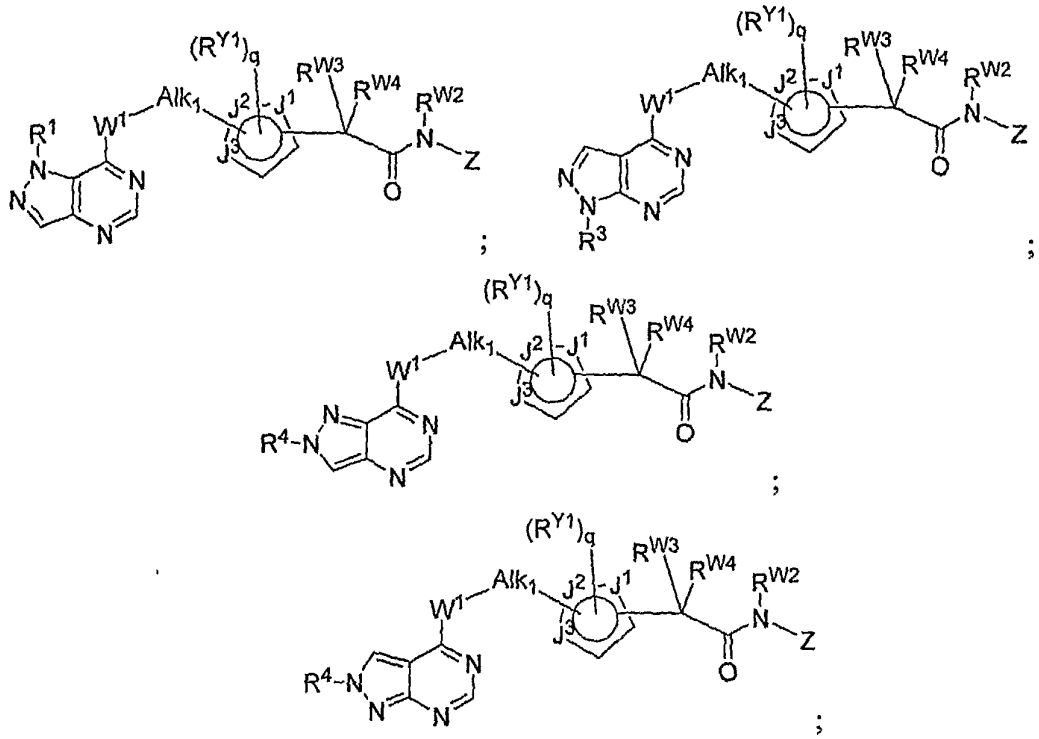
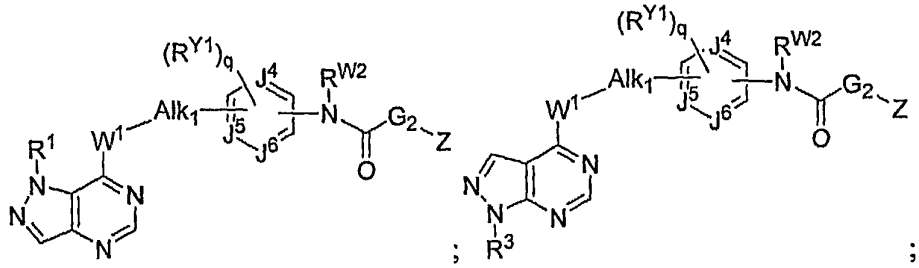


wherein R^1, R^3, R^4 and Z are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, -OC(=O)-, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, -S(=O)-, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; and R^{W2}, R^{W3} and

R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

16. The compound of claim 1 having the structure: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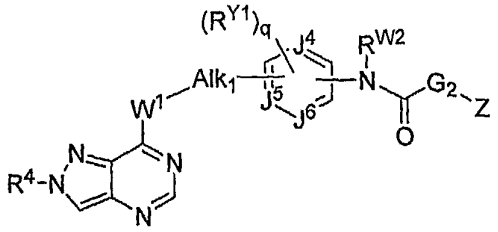
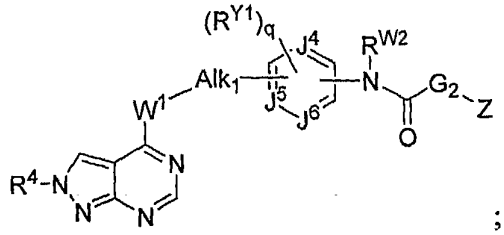
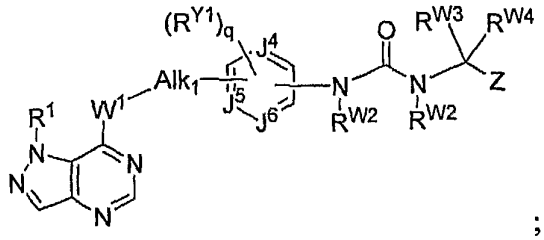

or


;

wherein R^1, R^3, R^4 and Z are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, -S(=O)-, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower

heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; G_2 is absent, O or NR^{G2}; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

17. The compound of claim 1 having the structure: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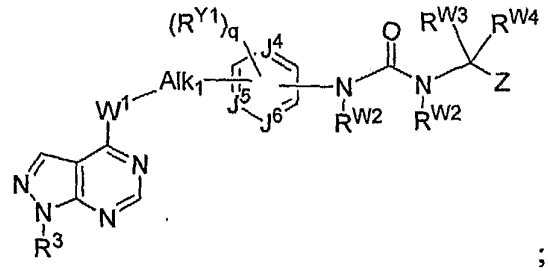
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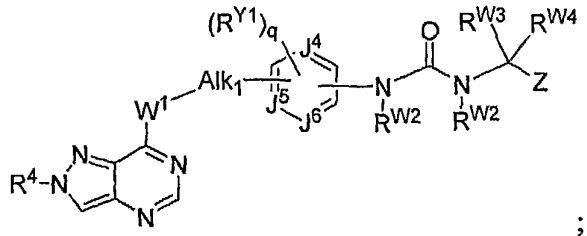
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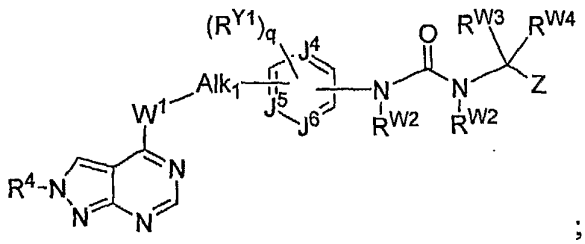
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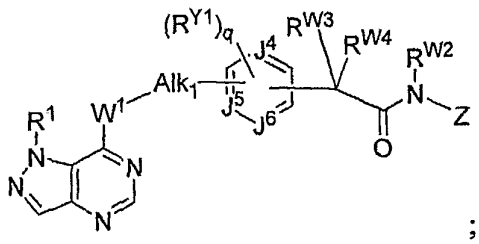
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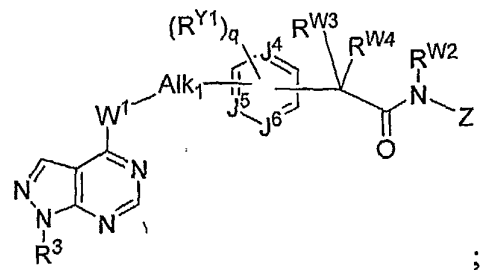
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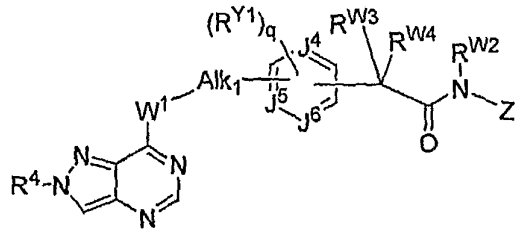
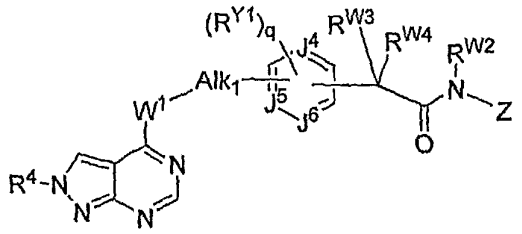
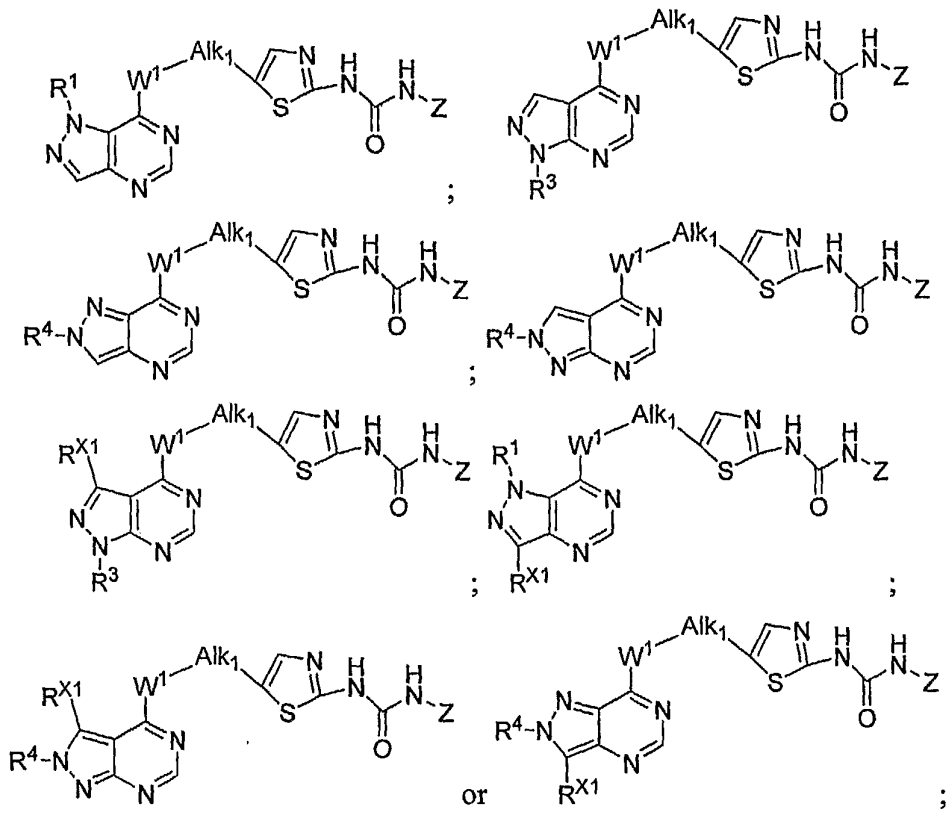


or



wherein R^1, R^3, R^4 and Z are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; q is an integer from 0-3; J^4, J^5 and J^6 are independently N or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Y3}, -SR^{Y3}, -$NR^{Y2}R^{Y3}$, -$SO_2NR^{Y2}R^{Y3}$, -C(=O)$NR^{Y2}R^{Y3}$, halogen, -CN, -NO_2, -C(=O)OR^{Y3}, -N(R^{Y2})C(=O)R^{Y3}, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Y2} and R^{Y3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring; and R^{W2}, R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

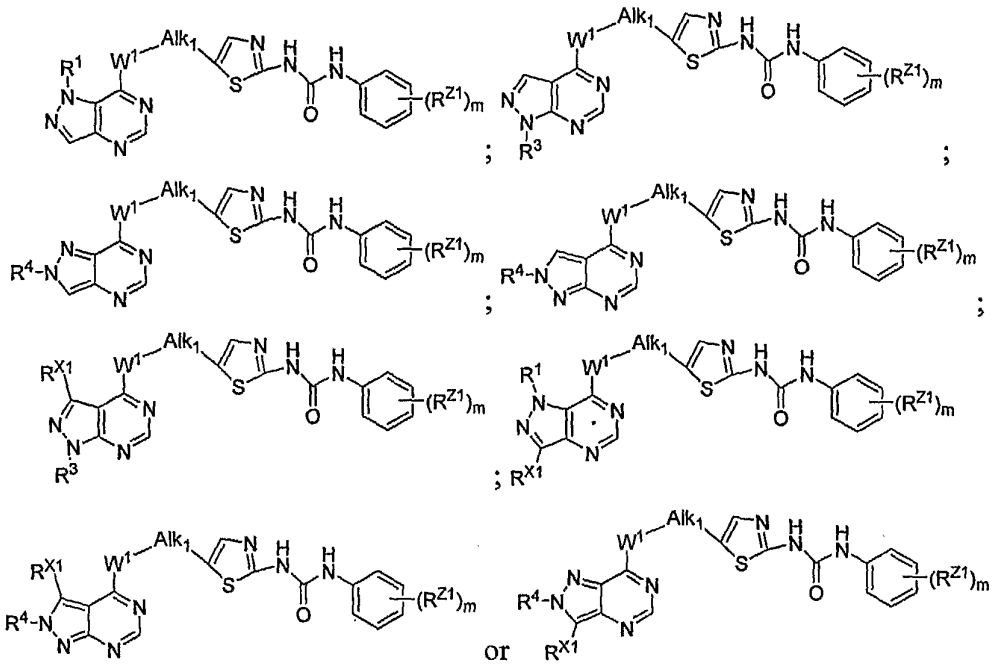
18. The compound of claim 1 having the structure:



wherein R^1, R^3, R^4 and R^{X1} are as defined in claim 1; Z is an aryl, heteroaryl or heterocyclic moiety; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Z2}, -SR^{Z2}, -$NR^{Z2}R^{Z3}$, -$SO_2NR^{Z2}R^{Z3}$, -SO_2R^{Z1}, -C(=O)$NR^{Z2}R^{Z3}$, halogen, -CN, -NO_2, -C(=O)OR^{Z3}, -N(R^{Z2})C(=O)R^{Z3}, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the

nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

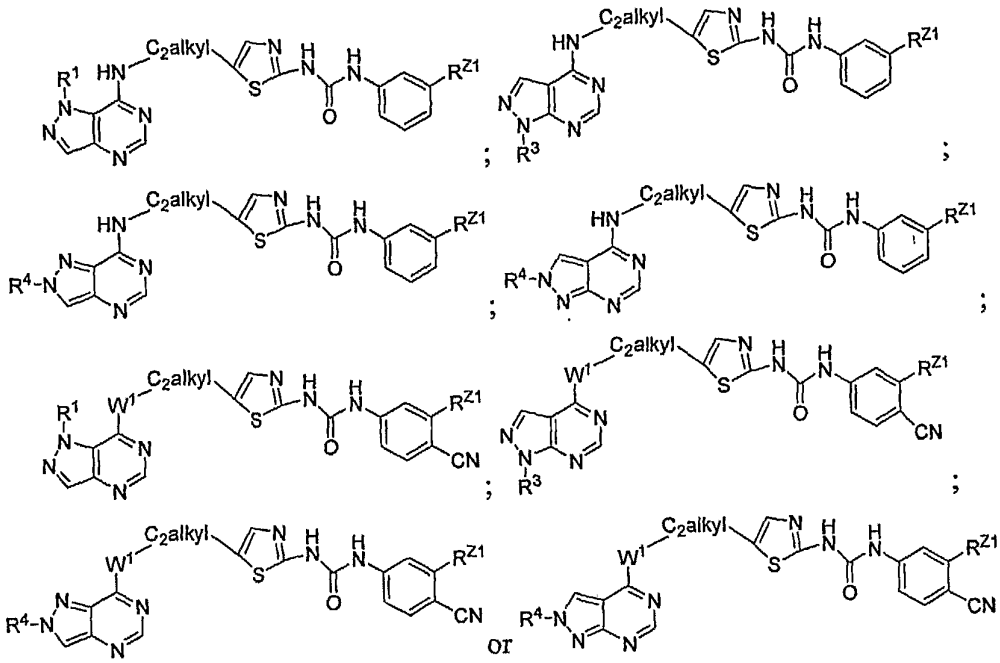
19. The compound of claim 1 having the structure:



wherein R^1, R^3, R^4 and R^{X1} are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, -CO_2-, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, -SO_2-, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Z2}, -SR^{Z2}, -$NR^{Z2}R^{Z3}$, -$SO_2NR^{Z2}R^{Z3}$, -SO_2R^{Z1}, -C(=O)$NR^{Z2}R^{Z3}$, halogen, -CN, -NO_2, -C(=O)OR^{Z3}, -N(R^{Z2})C(=O)R^{Z3}, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with

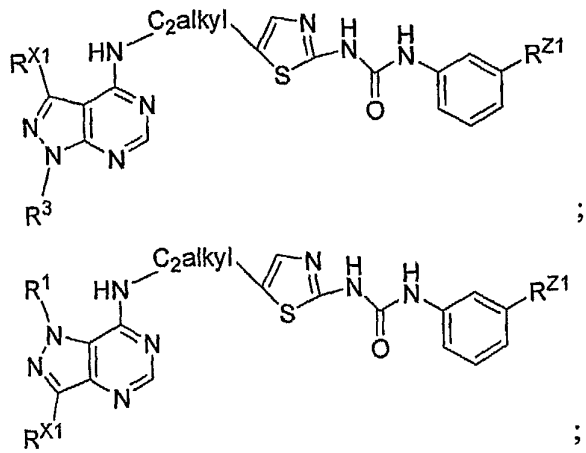
the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

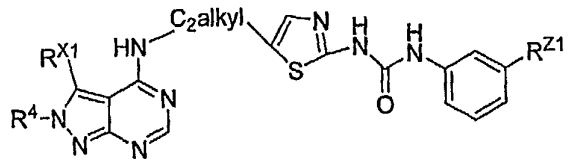
20. The compound of claim 19 having the structure:



wherein R^{Z1} is halogen, lower alkyl or lower haloalkyl.

21. The compound of claim 19 having the structure:

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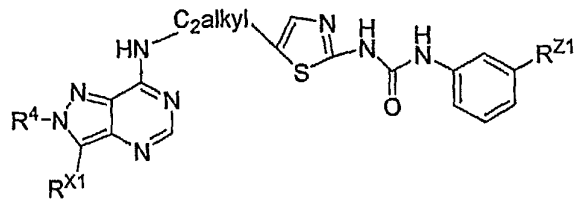
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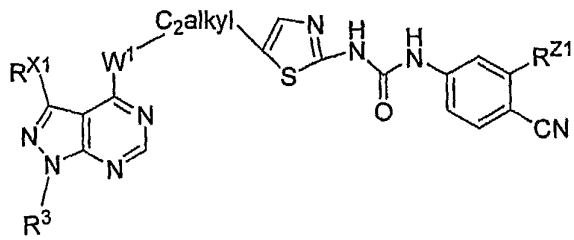
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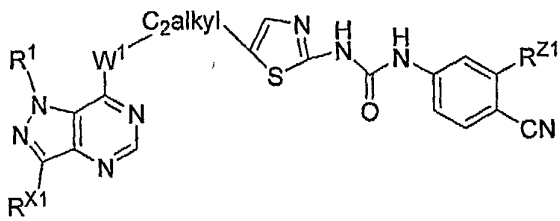
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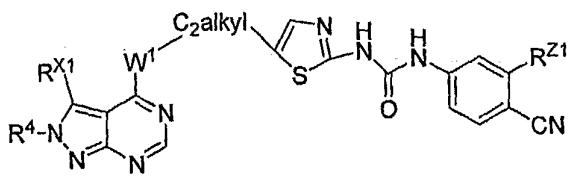
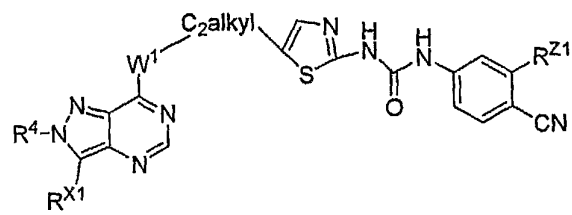
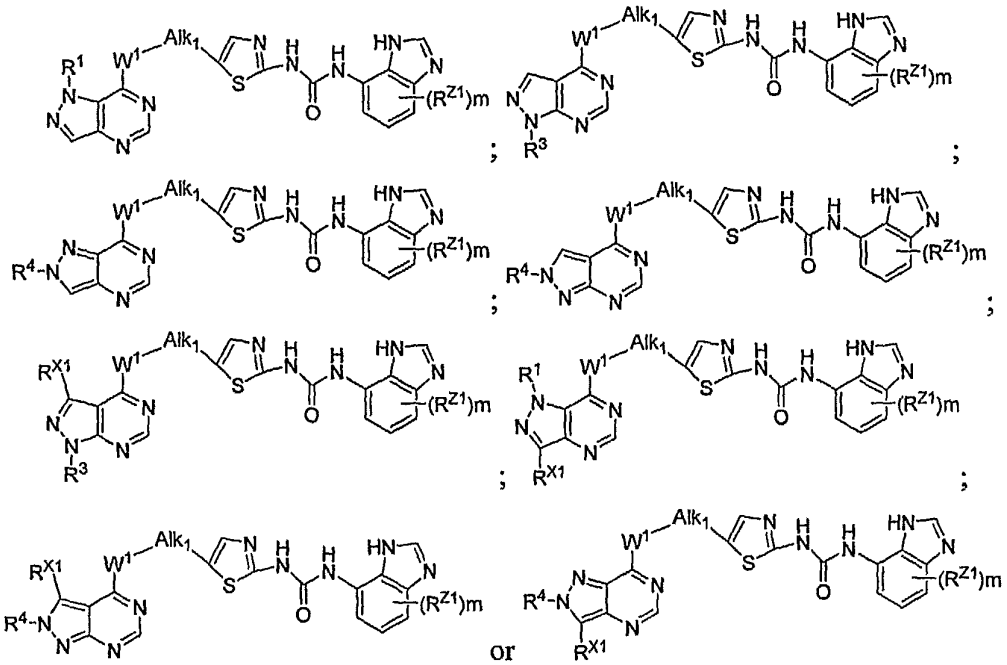

or



wherein R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is halogen, lower alkyl or lower haloalkyl.

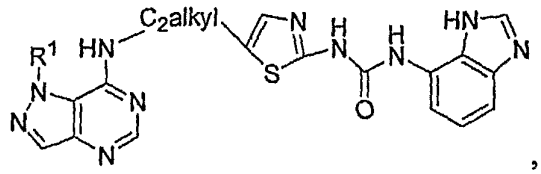
22. The compound of claim 20 or 21 wherein R^{Z1} is Cl, F, methyl or $-CF_3$.

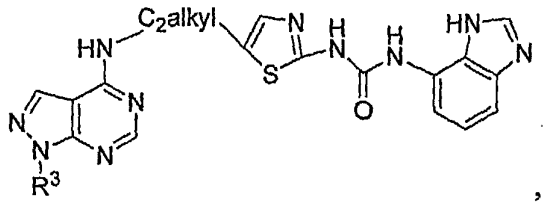
23. The compound of claim 1 having the structure:

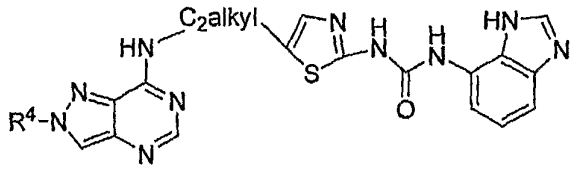


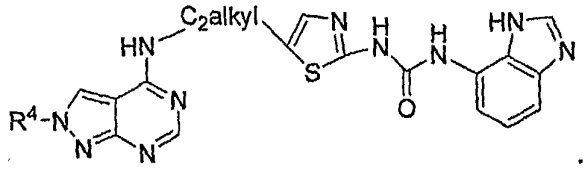
wherein R^1, R^3, R^4 and R^{X1} are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, $-SO_2-$, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, -OR^{Z2}, -SR^{Z2}, -$NR^{Z2}R^{Z3}$, -$SO_2NR^{Z2}R^{Z3}$, -SO_2R^{Z1}, -C(=O)$NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, -C(=O)OR^{Z3}, -$N(R^{Z2})$C(=O)R^{Z3}, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

24. The compound of claim 23 having the structure:

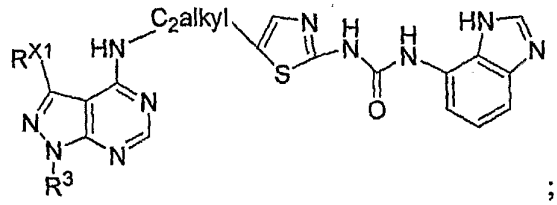

,


,


or


.

25. The compound of claim 23 having the structure: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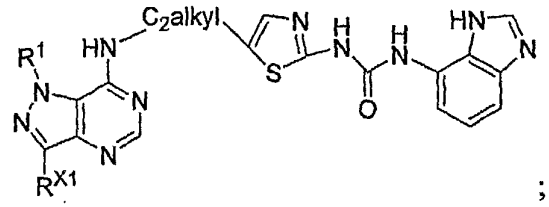
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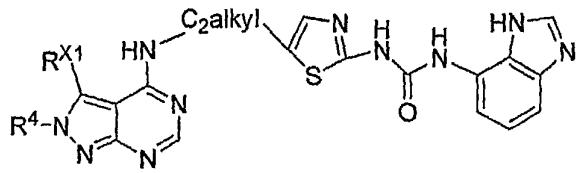
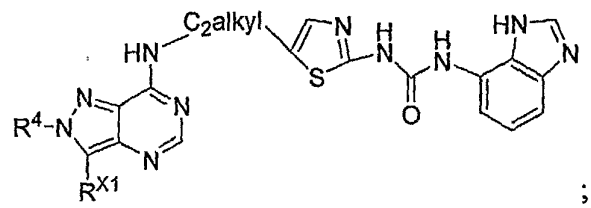
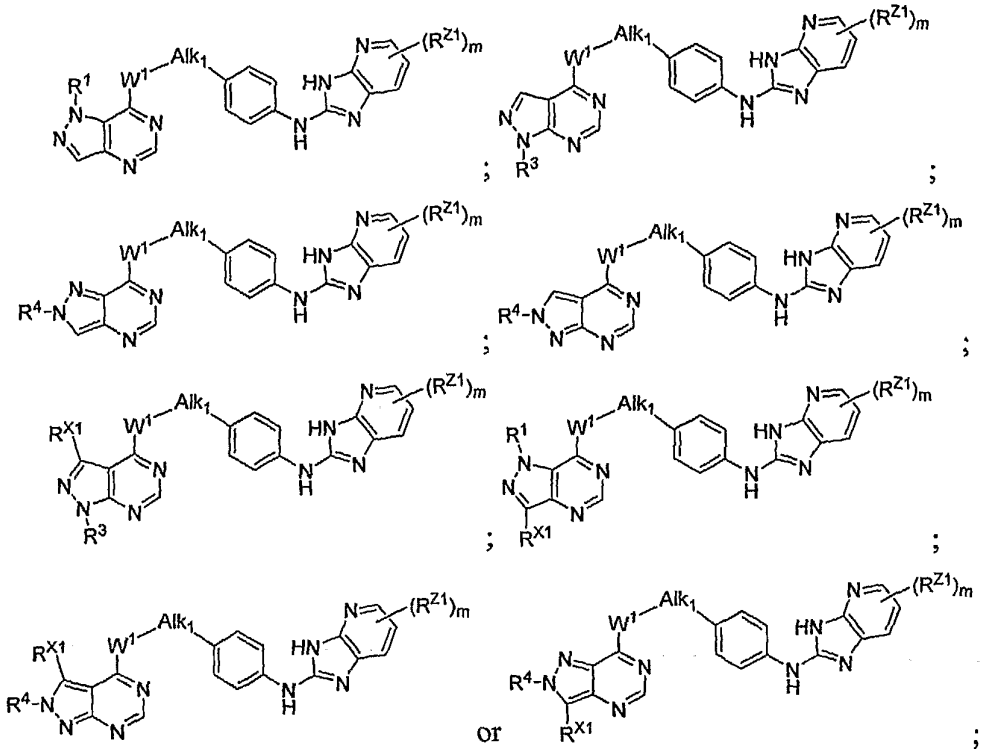

or


;

wherein R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; and R^{X1} is hydrogen, lower alkyl or heterocyclyl.

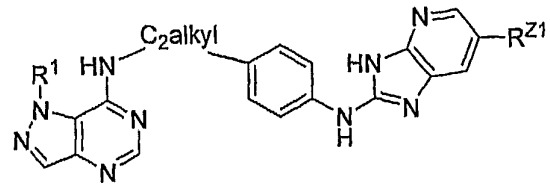
26. The compound of claim 1 having the structure:



wherein R^1, R^3, R^4 and R^{X1} are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, -OC(=O)-, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, -S(=O)-, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of

R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

27. The compound of claim 26 having the structure:



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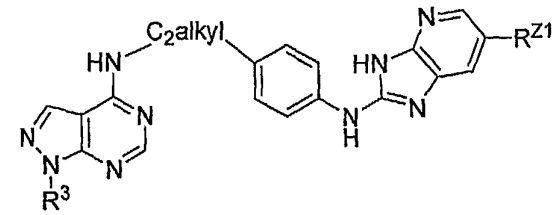

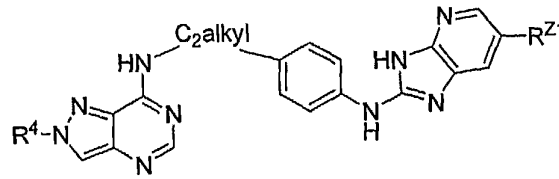

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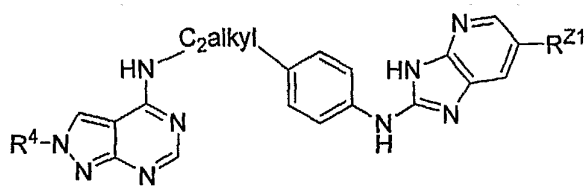
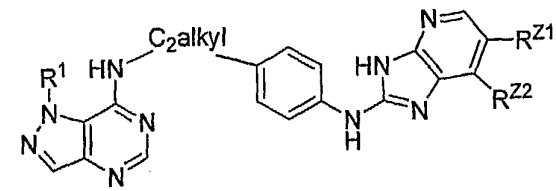


;



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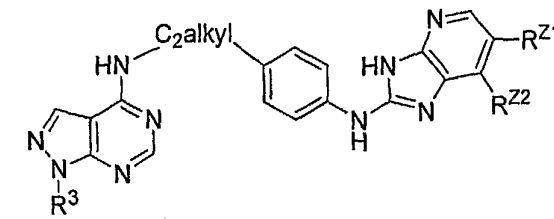
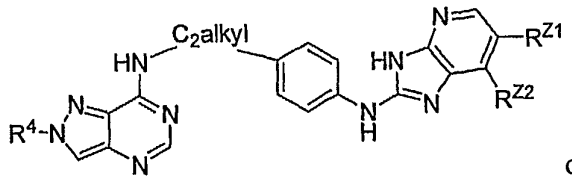
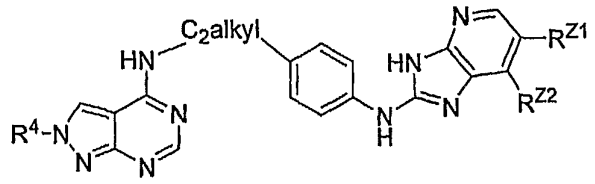


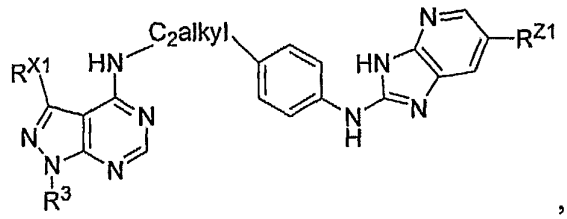


or



wherein R^{Z1} and R^{Z2} are independently halogen, lower alkyl or lower haloalkyl.

28. The compound of claim 26 having the structure:



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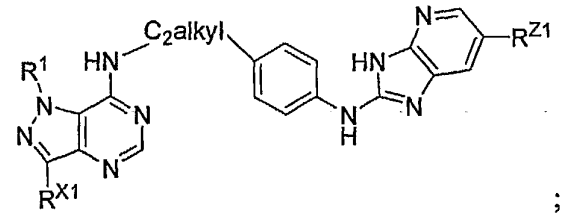

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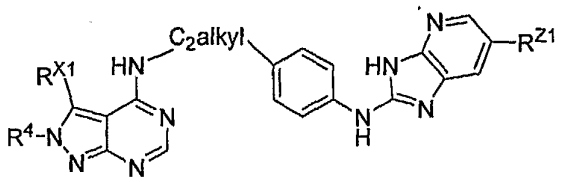

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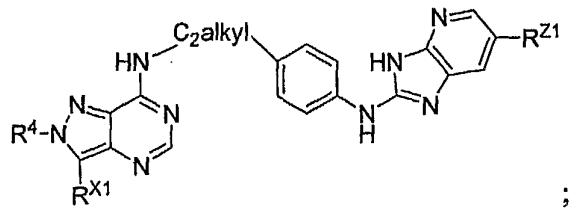

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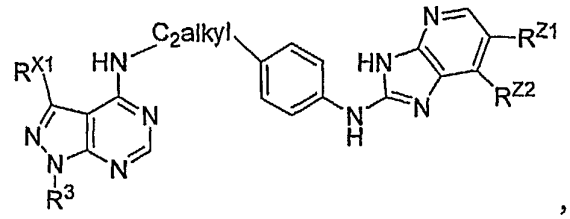
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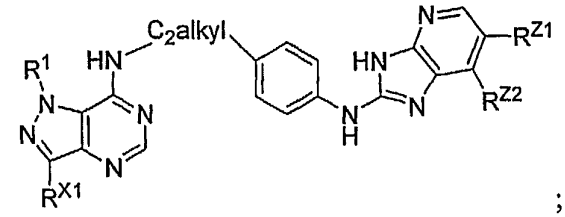
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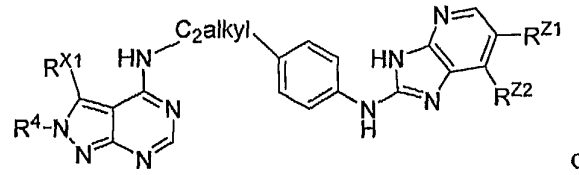
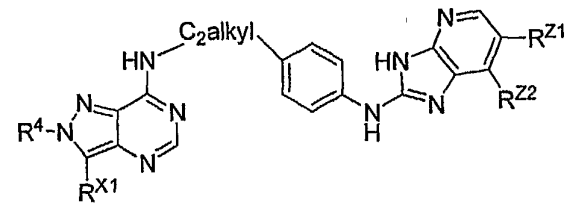
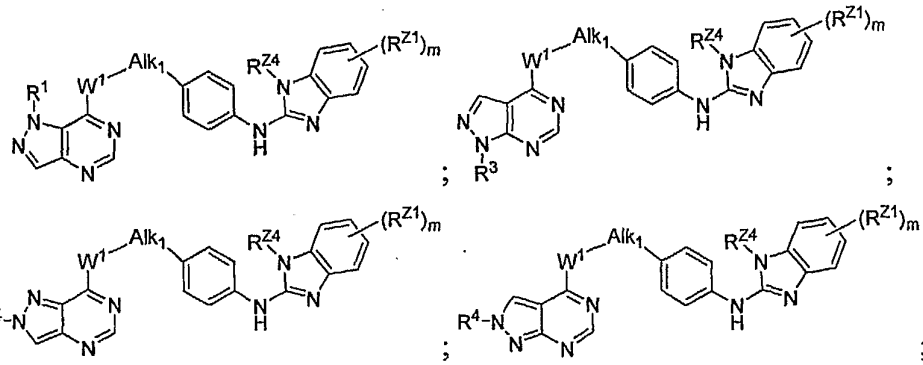

or

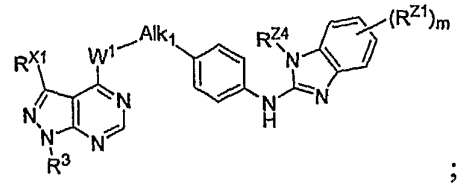
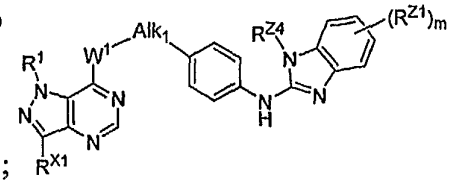


wherein R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} and R^{Z2} are independently halogen, lower alkyl or lower haloalkyl.

29. The compound of claim 27 or 28 wherein R^{Z1} and R^{Z2} are each Cl, F, methyl or $-CF_3$.

30. The compound of claim 1 having the structure:

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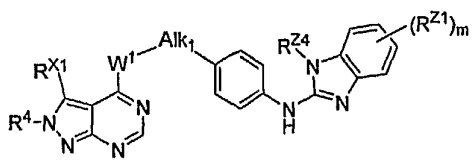
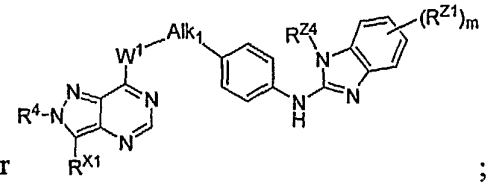
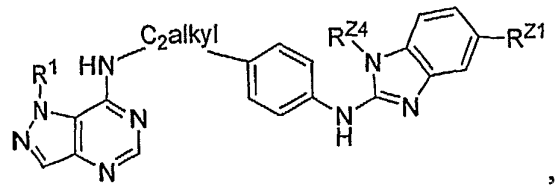

or

;

wherein R^1, R^3, R^4 and R^{X1} are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, -S(=O)-, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, and wherein each occcurrence of R^{Z2}, R^{Z3} and R^{Z4} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

31. The compound of claim 30 having the structure: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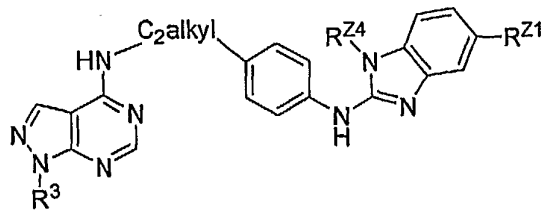
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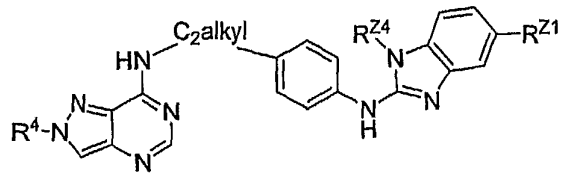
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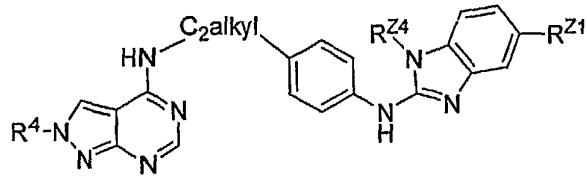
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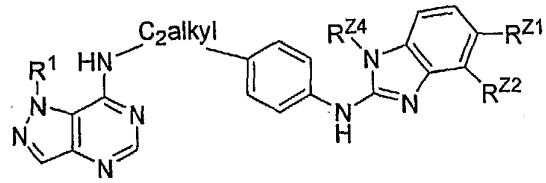
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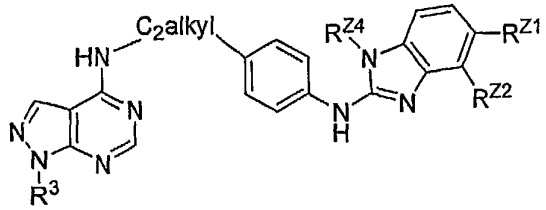
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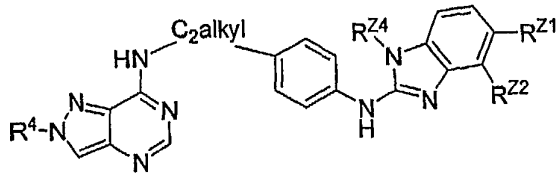
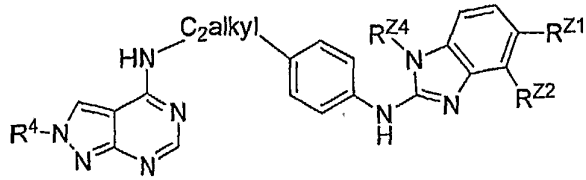
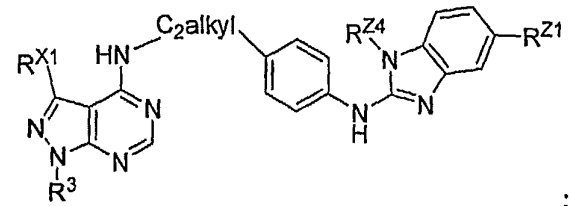

or



wherein R^{Z1} and R^{Z2} are independently halogen, lower alkyl or lower haloalkyl and R^{Z4} is lower alkyl.

32. The compound of claim 30 having the structure: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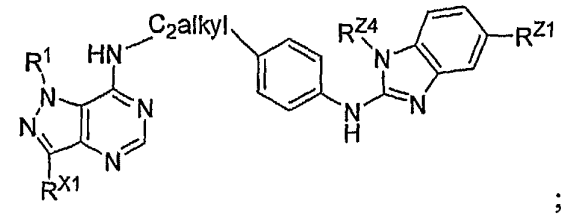
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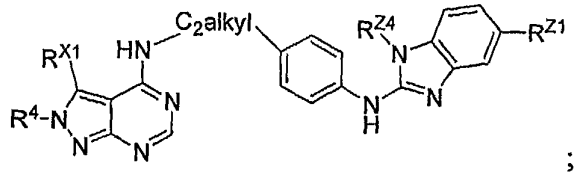
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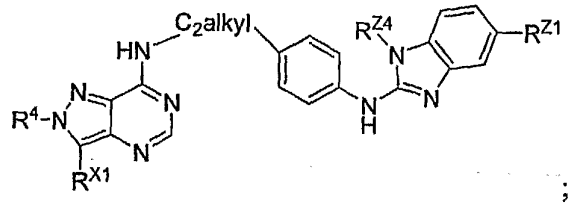
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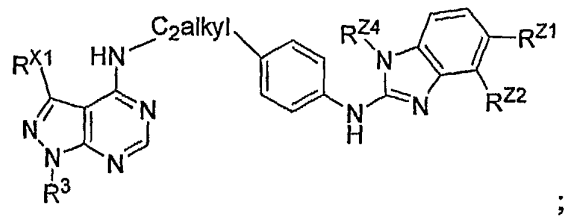
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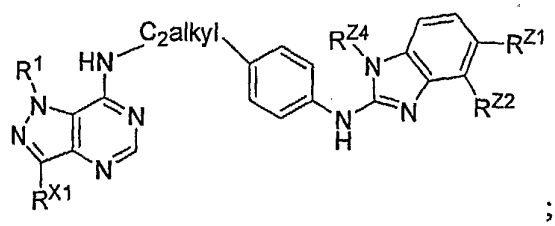
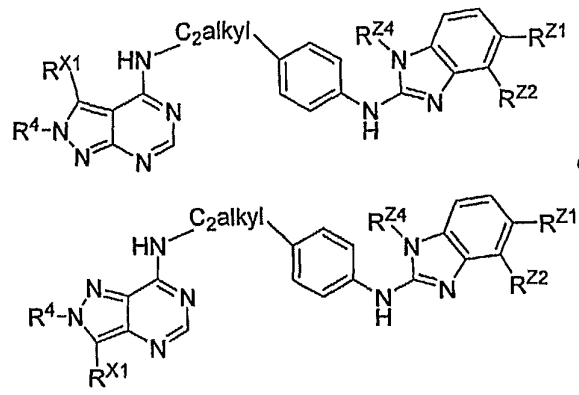

;



or

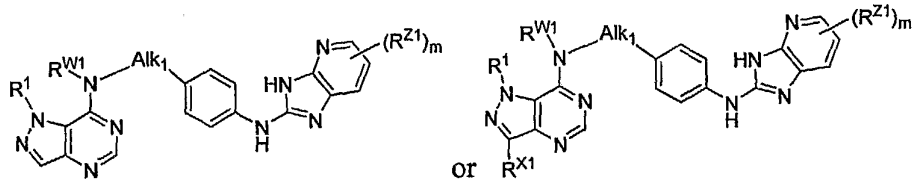
;

wherein R^1, R^3 and R^4 are independently hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; R^{Z1} and R^{Z2} are independently halogen, lower alkyl or lower haloalkyl and R^{Z4} is hydrogen or lower alkyl.

33. The compound of claim 31 or 32 wherein R^{Z1} and R^{Z2} are each Cl, F, methyl or $-CF_3$.

34. The compound of claim 31 or 32 wherein R^{Z4} is hydrogen or isopropyl.

35. The compound of claim 1 having the structure:

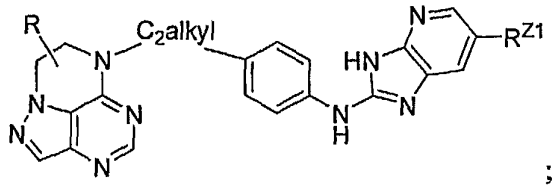


or

wherein R^{X1} are as defined in claim 1; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, -C(=O)NR^{L1A}-, -OC(=O)-, -OC(=O)NR^{L1A}-, -$NR^{L1A}NR^{L1B}$-, -$NR^{L1A}NR^{L1B}$C(=O)-, -NR^{L1A}C(=O)-, -$NR^{L1A}CO_2$-, -NR^{L1A}C(=O)NR^{L1B}-, -S(=O)-, $-SO_2-$, -$NR^{L1A}SO_2$-, -SO_2NR^{L1A}-, -$NR^{L1A}SO_2NR^{L1B}$-, -O-, -S-, or -NR^{L1A}-; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl,

heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

36. The compound of claim 35 having the structure:

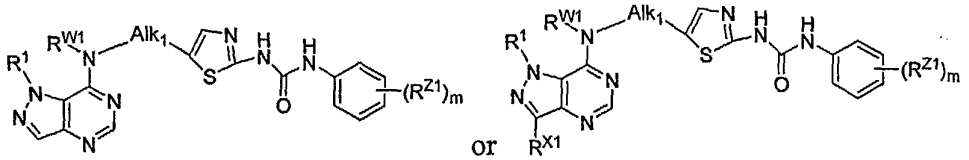


;

wherein R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; and R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl.

37. The compound of claim 36 wherein R and R^{Z1} are each hydrogen.

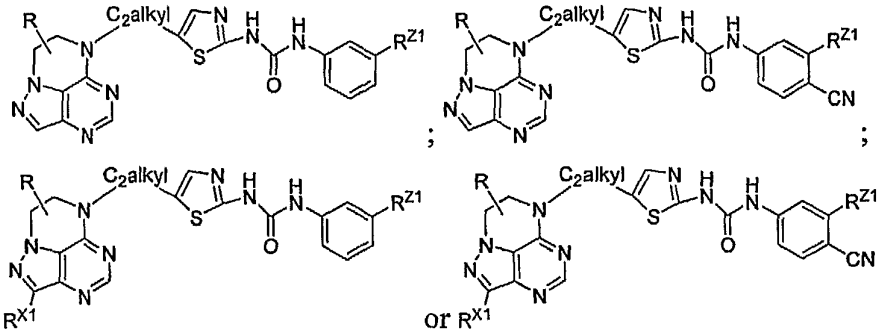
38. The compound of claim 1 having the structure:



wherein R^{X1} is as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, $-S(=O)-$, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, -

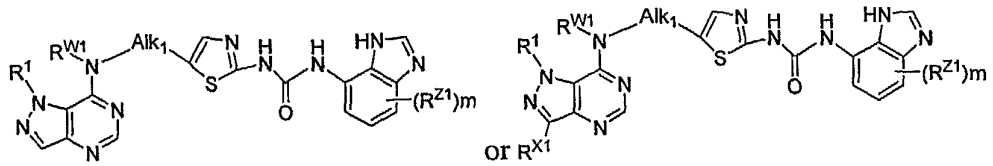
$NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

39. The compound of claim 38 having the structure:



wherein R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; R^{X1} is hydrogen, methyl or thienyl and R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl.

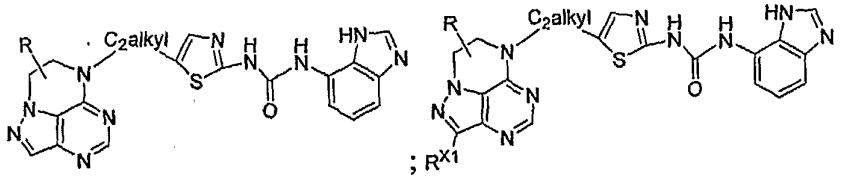
40. The compound of claim 1 having the structure:



wherein R^{X1} is as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, $-S(=O)-$, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an

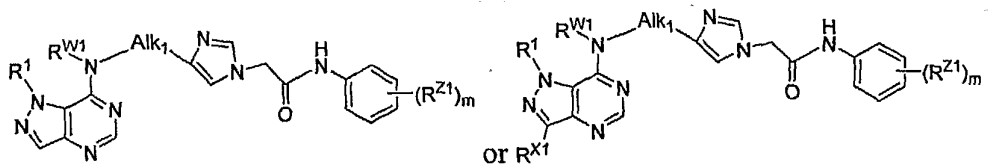
integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

41. The compound of claim 40 having the structure:



wherein R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; and R^{X1} is hydrogen, methyl or thienyl.

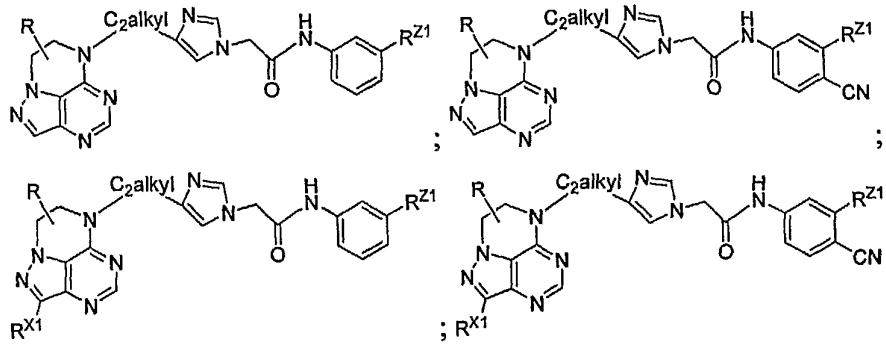
42. The compound of claim 1 having the structure:



wherein R^{X1} is as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, $-S(=O)-$, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, -

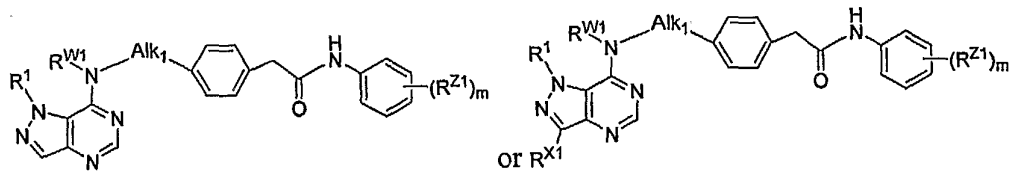
$NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

43. The compound of claim 42 having the structure:



wherein R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; R^{X1} is hydrogen, methyl or thienyl and R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl.

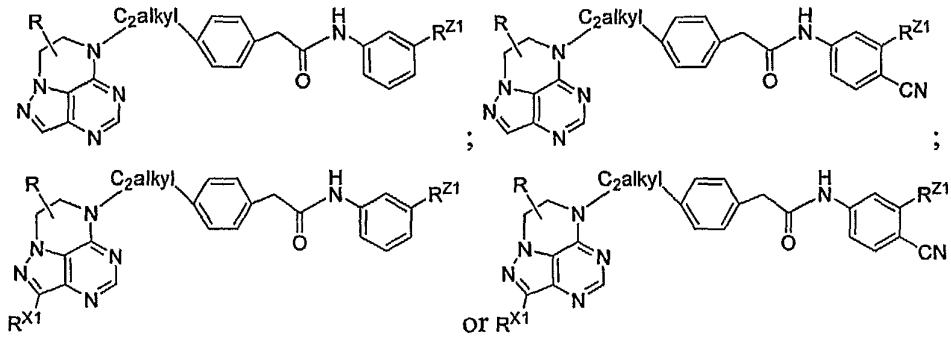
44. The compound of claim 1 having the structure:



wherein R^{X1} is as defined generally and in classes and subclasses herein; R^1 and R^{W1} taken together form an optionally substituted 5- to 6-membered ring; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units are independently optionally replaced by -C(=O)-, $-CO_2-$, -C(=O)C(=O)-, $-C(=O)NR^{L1A}-$, $-OC(=O)-$, $-OC(=O)NR^{L1A}-$, $-NR^{L1A}NR^{L1B}-$, $-NR^{L1A}NR^{L1B}C(=O)-$, $-NR^{L1A}C(=O)-$, $-NR^{L1A}CO_2-$, $-NR^{L1A}C(=O)NR^{L1B}-$, -S(=O)-, $-SO_2-$, $-NR^{L1A}SO_2-$, $-SO_2NR^{L1A}-$, $-NR^{L1A}SO_2NR^{L1B}-$, -O-, -S-, or $-NR^{L1A}-$; wherein each occurrence of R^{L1A} and R^{L1B} is independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl; m is an integer from 0 to 3; r is an

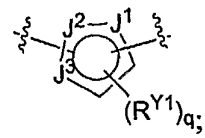
integer from 1 to 4; each occurrence of R^{Z1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Z3}$, $-N(R^{Z2})C(=O)R^{Z3}$, wherein each occcurrence of R^{Z2} and R^{Z3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen or carbon atom to which they are attached form a 5-6 membered heterocyclic, aryl or heteroaryl ring.

45. The compound of claim 44 having the structure:

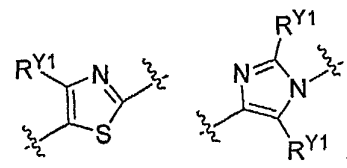


wherein R is hydrogen, halogen, hydroxyl, lower alkyl or lower alkoxy; R^{X1} is hydrogen, methyl or thienyl and R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl.

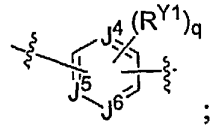
46. The compound of claim 13, 14 or 15 wherein the 5-membered ring having the structure:



has one of the following structures:

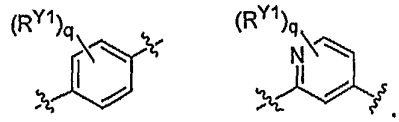


47. The compound of claim 13, 16 or 17 wherein the 6-membered ring having the structure:



;

has one of the following structures:



48. The compound of claim 6, 13, 14, 15, 16, 17 or 18 wherein $-W^1$-Alk_1- is –NH-C_{1-6}alkyl- or –O-C_{1-6}alkyl-; wherein the C_{1-6}alkyl moiety may be substituted or unsubstituted.

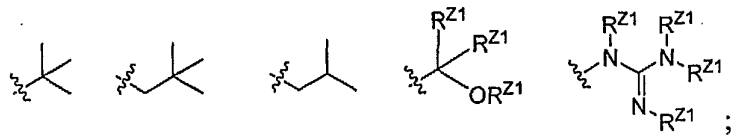
49. The compound of claim 48 wherein $-W^1$-Alk_1- is $–NHCH_2CH_2$-, $–OCH_2CH_2$- or –NH-$CH_2CH(CH_2OH)$-.

50. The compound of claim 7, 14 or 16 wherein $-N(R^{W2})C(=O)G_2$- is –NHC(=O)-, –NHC(=O)O-, or –NHC(=O)NH-.

51. The compound of claim 50 wherein $-N(R^{W2})C(=O)G_2$- is –NHC(=O)NH-.

52. The compound of claim 8, 15 or 17 wherein $-N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}$- is $–NHC(=O)NHCH_2$-, and $-CR^{W3}R^{W4}C(=O)N(R^{W2})$ - is $–CH_2C(=O)NH$-.

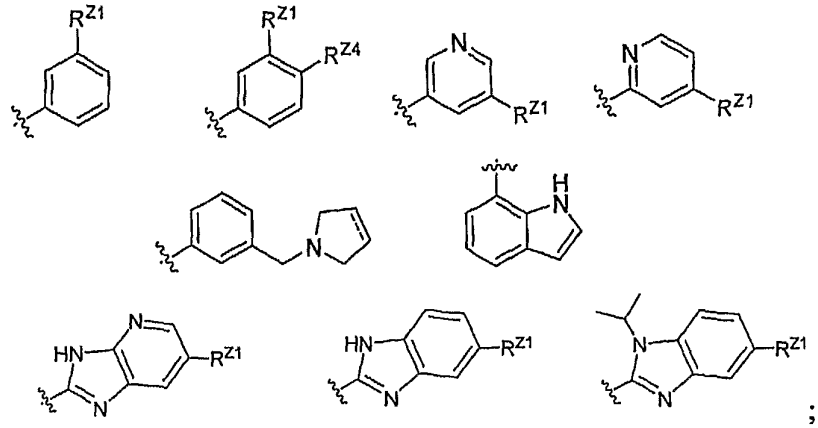
53. The compound of claim 1, wherein Z has one of the following structures:



;

wherein each occurrence of R^{Z1} is independently hydrogen, lower alkyl, lower alkenyl, aryl, heteroaryl or acyl.

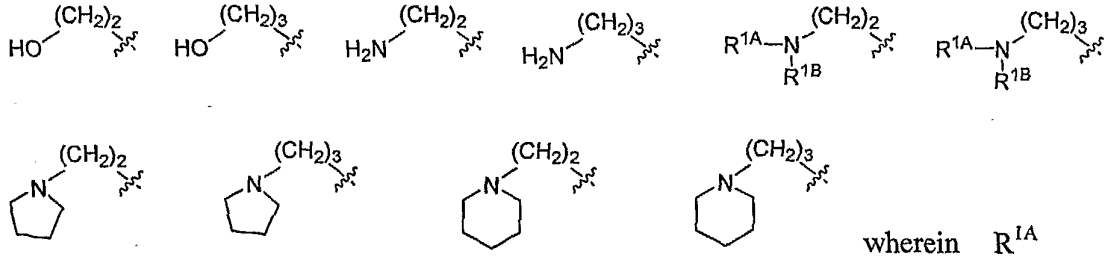
54. The compound of claim 1, wherein Z has one of the following structures:



wherein R^{Z1} is Cl, F, methyl or CF_3; and R^{Z4} is hydrogen or cyano.

55. The compound of any one of claims 1-54 wherein R^1, R^3 and R^4 are independently hydrogen or lower alkyl.

56. The compound of claim 55 wherein R^1, R^3 and R^4 are independently hydrogen, methyl, ethyl, isopropyl or one of:



wherein R^{1A} and R^{1B} are independently hydrogen, methyl or ethyl.

57. A composition comprising an effective amount of compound of any one of claims 1-56, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

58. The composition of claim 57, wherein the compound is in an amount to detectably inhibit Aurora protein kinase activity.

59. The composition of claim 57, additionally comprising a therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating destructive bone

disorders, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

60. A method of inhibiting Aurora kinase activity in:

(a) a subject; or

(b) a biological sample;

which method comprises administering to said patient, or contacting said biological sample with:

a) a composition of claim 57; or

b) a compound of any one of claims 1-56.

61. The method of claim 60, wherein the method comprises inhibiting Aurora kinase activity.

62. A method of treating or lessening the severity of a disease of condition selected from a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder, comprising the step of administering to said patient:

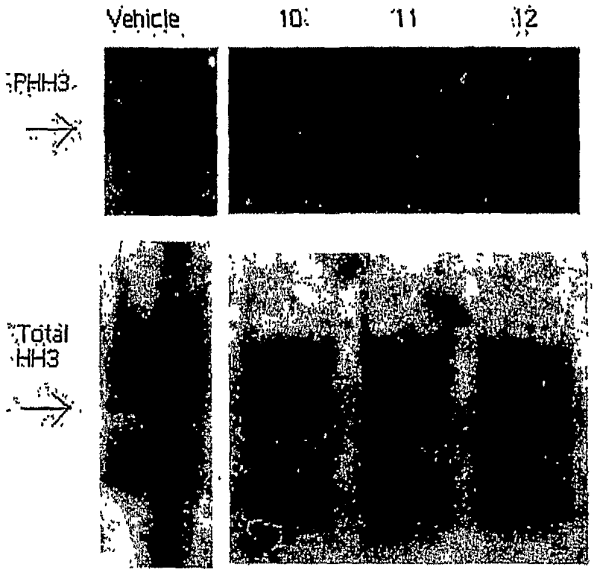
a) a composition of claim 57; or

b) a compound of any one of claims 1-56.

63. The method according to claim 62, comprising the additional step of administering to said patient an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating destructive bone disorders, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and

said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.



Western Blot of Compound **B**, 100mpk, 10 (10-12) hour post dose.

Time (hr)	Animal #	% pHH3 inhibition	Average	STDEV
10	10	81.28	85.58	7.16
	11	81.61		
	12	93.85		

Figure 1

Compound#	Aurora A (μM)	Aurora B (μM)	HCS CC (μM)	HCS pHH3 (μM)
A	0.010	0.021	0.016	0.035
B	0.006	0.018	0.016	0.011
C	0.005	0.010	0.011	0.017
D	0.069	0.032	0.190	0.210
E	0.004	0.085	0.041	0.048
F	0.047	0.250	0.073	0.110
G	0.024	0.003	0.054	0.008

Figure 2