THIENOPYRIMIDINES USEFUL AS AURORA KINASE INHIBITORS

PRIORITY

[0001] The present application claims priority to U.S. Provisional Patent Application Nos.: 60/632,568 filed December 1, 2004 and 60/588,718 filed July 16, 2004; The entire contents of each of these applications 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.

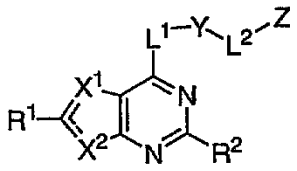
[0005] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, 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 ("1"), B ("2") 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:



(I)

wherein R^1, R^2, X^1, X^2, 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 histograms of G2/M phase cell growth arrest experiments using four compounds of the invention.

[0012] Figure 2 depicts results of Histone H3 phosphorylation inhibition experiments in HCT-116 cells. A compound of the invention, cultured with HCT-116 cells, exhibits a concentration-related inhibition of histone H3 serine phosphorylation.

[0013] Figure 3 depicts results of Histone H3 phosphorylation inhibition experiments in a HCT-116 tumor xenograft model. A compound of the invention was administered intra-peritoneally (single dose, 75 mg/kg) to mice implanted with HCt-116 tumors. The compound inhibits histone H3 serine phosphorylation in HCT-116 tumors for up to 10 hours after administration to implanted mice.

[0014] Figure 4 depicts results of tumor growth inhibition experiments in a HCT-116 tumor xenograft model. A compound of the invention was administered intra-peritoneally (IP) to mice implanted with HCt-116 tumors. The compound inhibits tumor growth following a dosing regimen of 75 mg/kg, once a week, for 3 weeks.

[0015] Figure 5 depicts results of phosphorylated Histone H3 modulation experiments in a HCT-116 tumor xenograft model. A compound of the invention was administered intravenously as a single dose at 6h (50 mg/kg) and 10h (75 mg/kg).

DEFINITIONS

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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.

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] 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.

[0030] 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.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] The terms "halo" and "halogen" as used herein refer to an atom selected from fluorine, chlorine, bromine and iodine.

[0035] The term "halogenated" denotes a moiety having one, two, or three halogen atoms attached thereto.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

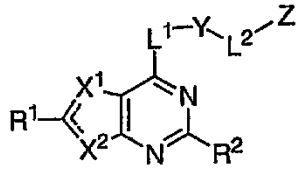
DETAILED DESCRIPTION OF CERTAIN PREFERRED EMBODIMENTS OF THE INVENTION

[0049] 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.

[0050] 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.

[0051] ***1) General Description of Compounds of the Invention***

[0052] In certain embodiments, the compounds of the invention include compounds of the general formula (I) as further defined below:



(I)

and pharmaceutically acceptable derivatives thereof;

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

R^1 and R^2 are independently hydrogen, halogen, cyano, nitro, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

one of X^1 and X^2 is S, the other is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, cyano, nitro, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

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

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.

[0053] In certain embodiments, the following groups do not occur simultaneously as defined: L^1 is $-OCH_2-$, $-CH_2O-$, $-N(R)CH_2-$ or $-CH_2N(R)-$, wherein R is H or C_{1-8}alkyl; Y is phenyl; and Z is a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl.

[0054] In certain embodiments, the following groups do not occur simultaneously as defined: L^1-Y is $-NHCH_2CH_2$-phenyl or $-OCH_2CH_2$-phenyl; L^2 is $-C(R)=N-O-$, wherein R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl; and R^1 and R^{X1} (or R^1 and R^{X2}, when X^1 is S) are independently hydrogen, halogen or C_{1-4}alkyl.

[0055] In certain embodiments, the following groups do not occur simultaneously as defined: L^1 is $-OCH(R)-$, $-OCH(R)-C_{1-6}$alkylO- or $-OCH(R)-C_{1-6}$alkylC(=NR_x)- where R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl and R_x is H, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic; Y and Z are each optionally substituted phenyl; and L^2 is $-OCH_2-$ or $-OSO_2-$; and R^1 and R^{X1} (or R^1 and R^{X2}, when X^1 is S) are independently hydrogen, halogen or alkyl.

[0056] In certain embodiments, the following groups do not occur simultaneously as defined: X^1 is CR^{X1} wherein R^{X1} is Q_4; X^2 is S; R^1 is Q_5; Y and Z are independently optionally substituted aryl, carbocycle or 5-membered monocyclic heterocycle; and L^1 is –W-N=CH- wherein W is O or NR, wherein R is H, C_{1-6}alk(en/yn)yl, C_{3-8}cycloalk(en)yl, aryl, hydroxyC_{1-6}alk(en/yn)yl, C_{3-8}cycloalk(en)yl-C_{1-6}alk(en/yn)yl or acyl; wherein Q_4 is hydrogen, halogen, cyano, nitro, C_{1-6}alk(en/yn)yl, C_{1-6}alk(en/yn)yloxy, C_{1-6}alk(en/yn)yloxy-C_{1-6}alk(en/yn)yl, C_{1-6}alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}alk(en/yn)yl, halo-C_{1-6}alk(en/yn)yl, halo-C_{1-6}alk(en/yn)yloxy, C_{3-8}cycloalk(en)yl, C_{3-8}cycloalk(en)yl-C_{1-6}alk(en/yn)yl, acyl, C_{1-6}alk(en/yn)yloxycarbonyl, C_{1-6}alk(en/yn)ylsulfonyl, $-NR^{X1A}R^{X1B}$ or $R^{X1A}R^{X1B}NC_{1-}$

$_{6}$alk(en/yn)yl; and Q5 is hydrogen, halogen, C_{1-6}alk(en/yn)yl, C_{1-6}alk(en/yn)yloxy, C_{1-6}alk(en/yn)yloxy-C_{1-6}alk(en/yn)yl, C_{1-6}alk(en/yn)ylsulfanyl, acyl, hydroxy, hydroxy-C_{1-6}alk(en/yn)yl, C_{3-8}cycloalk(en/yn)yl, C_{3-8}cycloalk(en/yn)yloxy, aryl, heterocyclyl, -$NR^{X1A}R^{X1B}$ or $R^{X1A}R^{X1B}NC_{1-6}$alk(en/yn)yl, where R^{X1A} and R^{X1B} are independently hydrogen or C_{1-6}alk(en/yn)yl.

[0057] In certain embodiments, neither R^1 nor R^{X1} (or neither R^1 nor R^{X2} , when X^1 is S) 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).

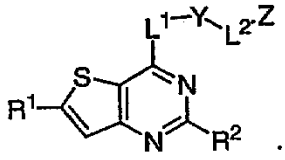
[0058] In certain embodiments, the following groups do not occur simultaneously as defined: one of R^1 and R^{X1} (or one of R^1 and R^{X2}, when X^1 is S) is hydrogen, the other is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; L^1 is $-NHC_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$heteroalkyl or $-OC_{1-6}$heteroalkyl; Y is cycloalkyl, aryl, heteroaryl or heterocyclyl; L^2-Z is -X-R^x where X is -NR-, -C(=O)NH-, -NHC(=O)-, $-SO_2NH-$ or $-NHSO_2-$ and R^x is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl.

[0059] In certain embodiments, the following groups do not occur simultaneously as defined: one of X^1 and X^2 is CH, the other is S; L^1 is $-NR(CR^x)_{1-2}-$ or $-O(CR^x)_{1-2}-$ wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, OH, NH_2 or $-C_{1-4}$alkylNH; 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; L^2-Z is $-SO_2NHC_{3-8}$cycloalkyl, $-SO_2N(C_{3-8}$cycloalkyl$)_2$, $-C(=O)NHC_{3-8}$cycloalkyl or $-C(=O)N(C_{3-8}$cycloalkyl$)_2$.

[0060] In certain embodiments, the following groups do not occur simultaneously as defined: R^1 is hydrogen, halogen, nitro or C_{1-4}alkyl; one of X^1 and X^2 is S, the other is CR^{XA} wherein R^{XA} is hydrogen, C_{1-4}alkyl or phenyl optionally substituted with halogen, (halo)C_{1-4}alkyl or (halo)C_{1-4}alkoxy; L^1 is $-NRC_{1-6}$alkyl-,$-OC_{1-6}$alkyl- or $-SC_{1-6}$alkyl- wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}acyl; Y is phenyl; L^2–Z is a C_{1-12}alkyl saturated or unsaturated hydrocarbon chain including -NR- and optionally substituted with haloC_{1-4}alkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{1-4}acyl, phenoxy, phenyl or phenylthio.

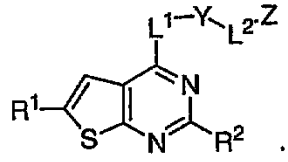
[0061] In certain embodiments, compounds specifically and/or generically disclosed in Japanese Application Nos.: JP 3-173872 and JP 3-063271 (which are incorporated herein by reference) are excluded.

[0062] 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 formula (I^A):



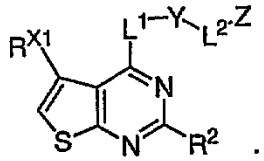
(I^A)

[0063] Another class of compounds of special interest includes compounds of formula (I^B):



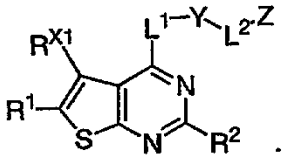
(I^B)

[0064] Another class of compounds of special interest includes compounds of formula (I^C):



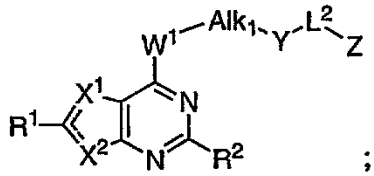
(I^C)

[0065] Another class of compounds of special interest includes compounds of formula (I^D):



(I^D)

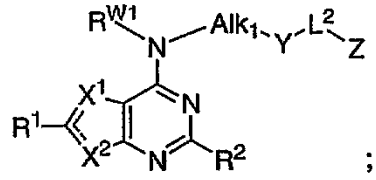
[0066] Another class of compounds of special interest includes compounds of formula (I^E):



(I^E)

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.

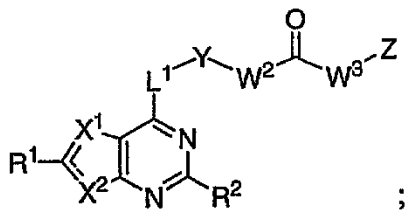
[0067] Another class of compounds of special interest includes compounds of formula (I^F):



(I^F)

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.

[0068] Another class of compounds of special interest includes compounds of formula (I^G):



(I^G)

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 $NR^WCR^{W1}R^{W2}$.

[0069] A number of important subclasses of each of the foregoing classes deserve separate mention; these subclasses include subclasses of the foregoing classes in which:

[0070] i) neither R^1 nor R^{X1} (or neither R^1 nor R^{X2} , when X^1 is S) 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=N$OR^{1D}$, 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; 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);

[0071] ii) neither R^1 nor R^{X1} (or neither R^1 nor R^{X2} , when X^1 is S) 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;

[0072] iii) neither R^1 nor R^{X1} (or neither R^1 nor R^{X2} , when X^1 is S) 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;

[0073] iv) R^1 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;

[0074] v) R^1 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 $C_{1\text{-}6}$alkyl; and each occurrence of R^{1C} is independently $C_{1\text{-}6}$alkyl;

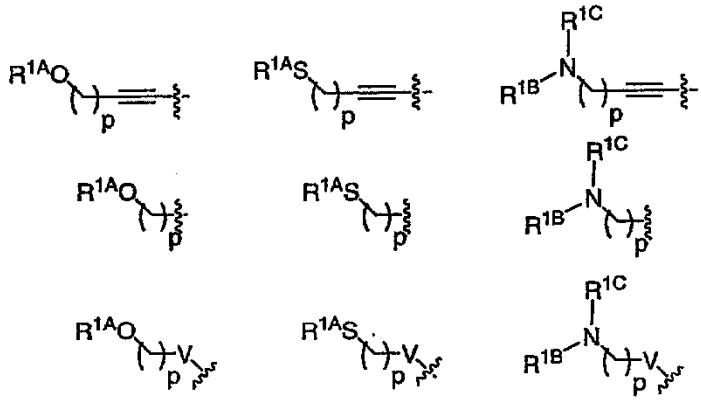
[0075] vi) R^1 is hydrogen, halogen, $-NO_2$, -CN, $C_{1\text{-}5}$alkyl or $C_{1\text{-}5}$alkoxy;

[0076] vii) R^1 is hydrogen;

[0077] viii) R^1 is F, Cl, Br or I;

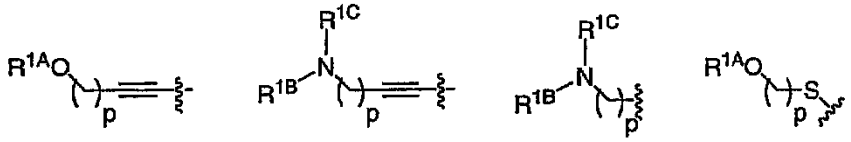
[0078] ix) R^1 is alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl or heteroalkynyl;

[0079] x) R^1 is one of:



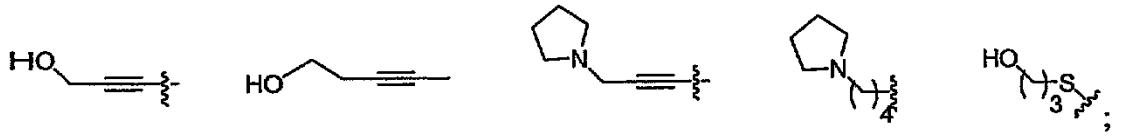
wherein V is O, S or R^{1B}; p is an integer from 0 to 6; and R^{1A} is hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, $-C(=O)N(R^{1B})_2$, $-C(=O)OR^{1B}$; wherein each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, 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;

[0080] xi) R^1 is –CN, lower alkyl, lower alkynyl, $-CO_2R^{1D}$, or one of:



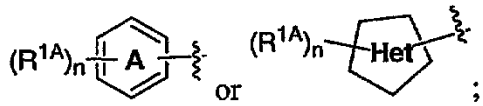
wherein p is an integer from 1 to 4; and R^{1A} is hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, $-C(=O)N(R^{1B})_2$, $-C(=O)OR^{1B}$; wherein each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(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;

[0081] xii) R^1 is –CN, -C≡CH, methyl, $-CO_2H$, $-CO_2Me$, or one of:



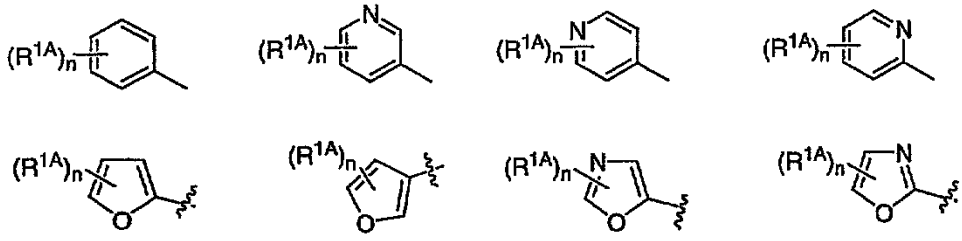
[0082] xiii) R^1 is aryl, heteroaryl or heterocyclyl;

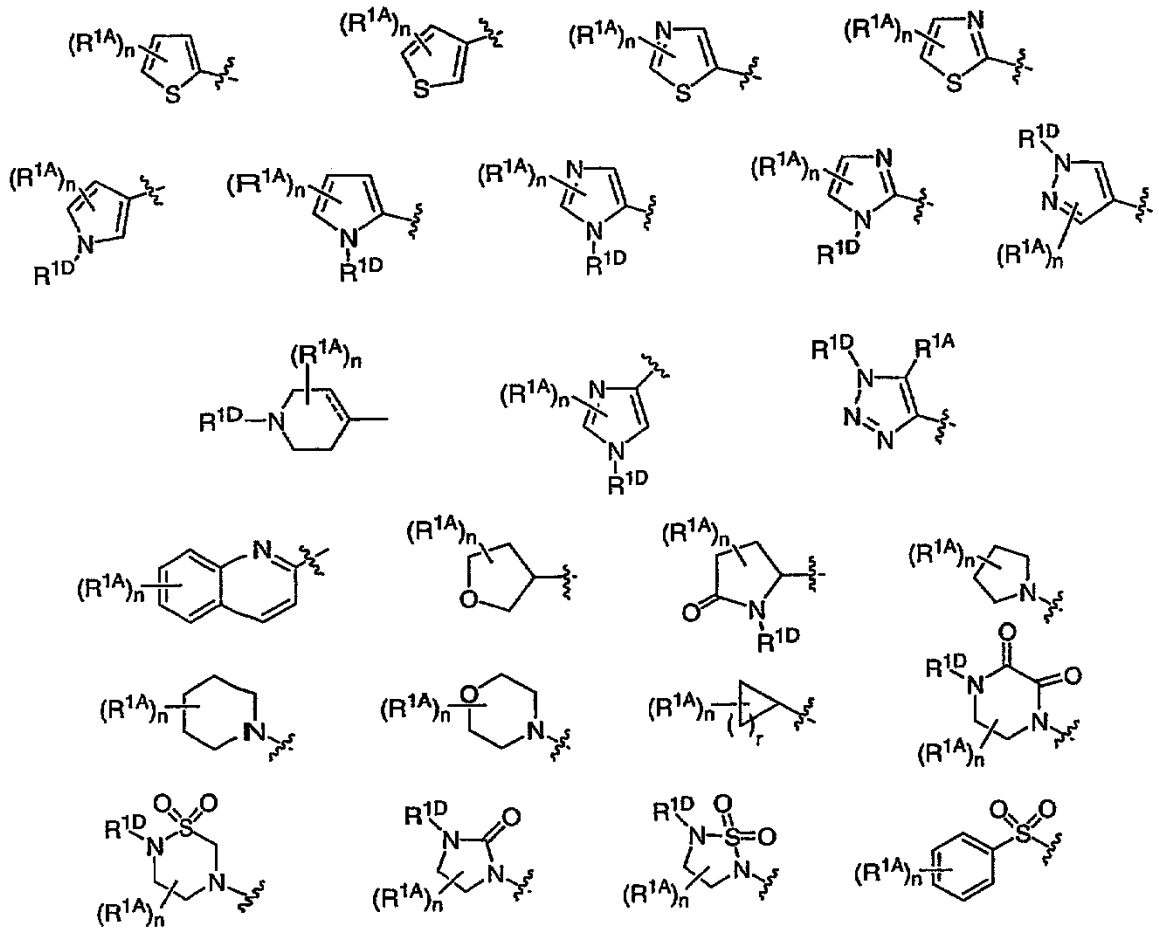
[0083] xiv) R^1 is an aryl, heteroaryl or heterocyclyl moiety having one of the structures:



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;

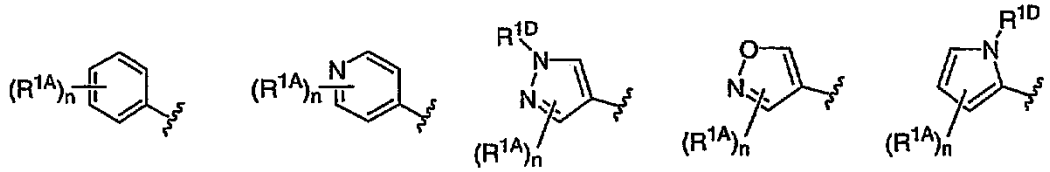
[0084] xv) R^1 is one of:





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;

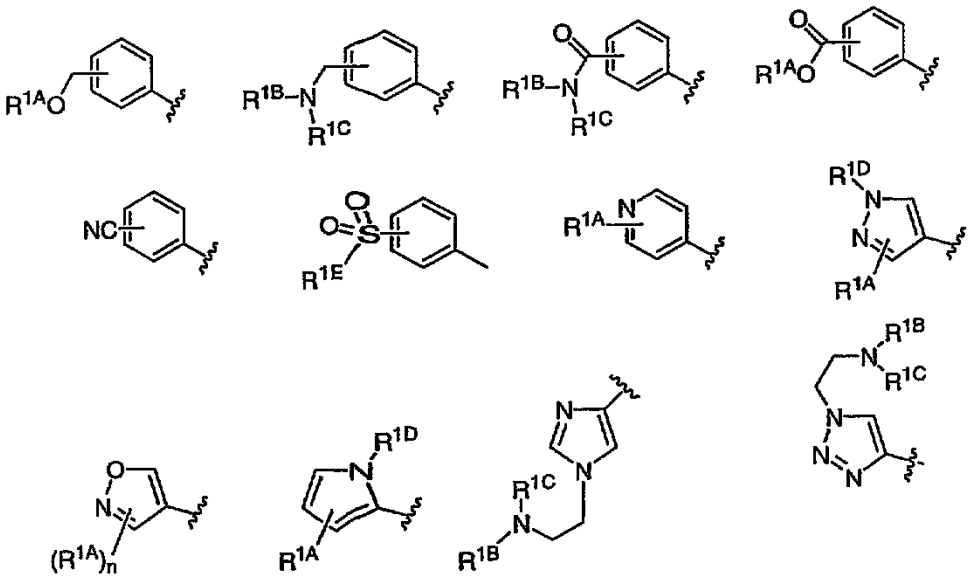
[0085] xvi) R^1 is one of:





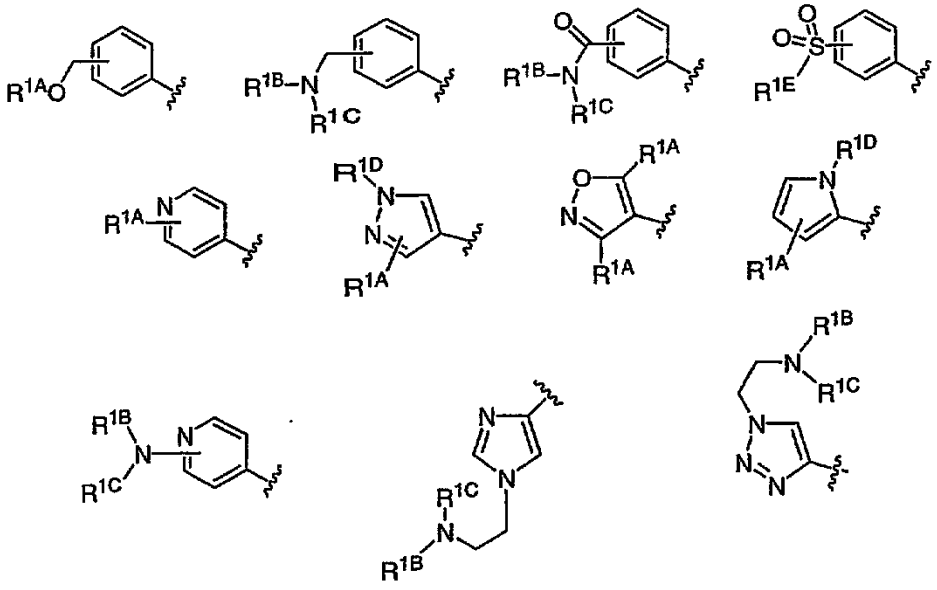
wherein n, R^{1A} and R^{1D} are as defined in xiv) above;

[0086] xvii) R^{I} is one of:



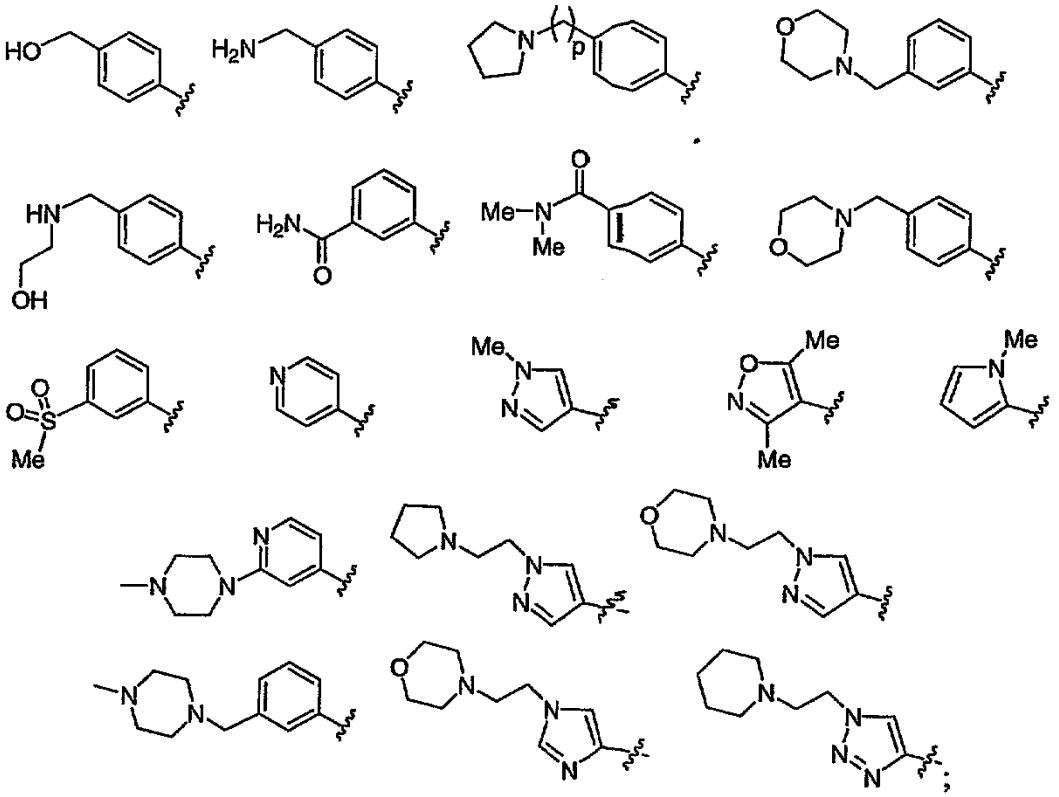
wherein n is 0-2; R^{1A} is hydrogen or lower alkyl; each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, or R^{1B} and R^{1C}, taken together with the nitrogen atom to which they are attached, form a substituted or unsubstituted 5-6 membered heterocyclic moiety; R^{1D} is hydrogen,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

[0087] xviii) R^{1} 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;

[0088] xix) R^1 is one of:



wherein p is 1 or 3;

[0089] xx) 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;

[0090] xxi) R^2 is C_{1-3}alkyl or C_{1-3}alkoxy;

[0091] xxii) R^2 is methyl or $-CF_3$;

[0092] xxiii) R^2 is halogen;

[0093] xxiv) R^2 is hydrogen;

[0094] xxv) one of X^1 and X^2 is S, the other is $-C(R^{XA})-$; wherein R^{XA} 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;

[0095] xxvi) one of X^1 and X^2 is S, the other is $-C(R^{XA})-$; wherein R^{XA} is hydrogen, halogen, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl or heteroaryl moiety;

[0096] xxvii) one of X^1 and X^2 is S, the other is $-C(R^{XA})-$; wherein R^{XA} is hydrogen, halogen, or a lower alkyl, cycloalkyl, cycloalkenyl, lower heteroalkyl, heterocyclyl, aryl or heteroaryl moiety;

[0097] xxviii) one of X^1 and X^2 is S, the other is $-C(R^{XA})-$; wherein R^{XA} is hydrogen, halogen, or a lower alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety;

[0098] xxix) one of X^1 and X^2 is S, the other is $-C(R^{XA})-$; wherein R^{XA} is hydrogen, halogen, C_{1-5}alkyl, C_{1-5}alkoxy, $-CO_2H$, $-CO_2C_{1-5}$alkyl, -CN or $-NO_2$;

[0099] xxx) X^1 is S and X^2 is CH;

[0100] xxxi) X^2 is S and X^1 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;

[0101] xxxii) X^2 is S and X^1 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;

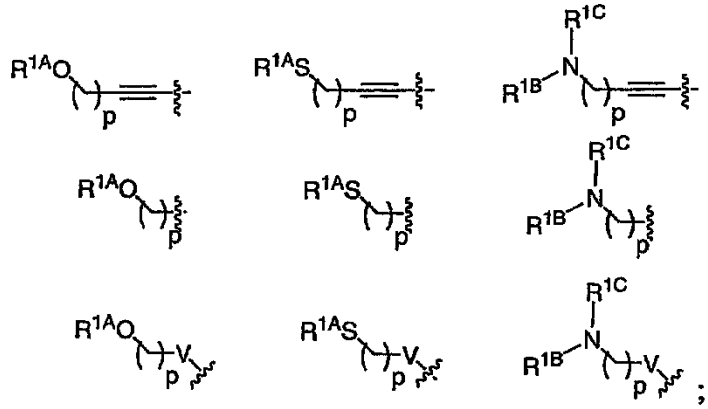
[0102] xxxiii) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, $-NO_2$, -CN, C_{1-5}alkyl or C_{1-5}alkoxy;

[0103] xxxiv) X^2 is S and X^1 is CH;

[0104] xxxv) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is F, Cl, Br or I;

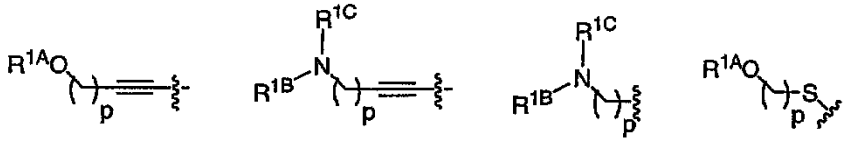
[0105] xxxvi) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl or heteroalkynyl;

[0106] xxxvii) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is one of:



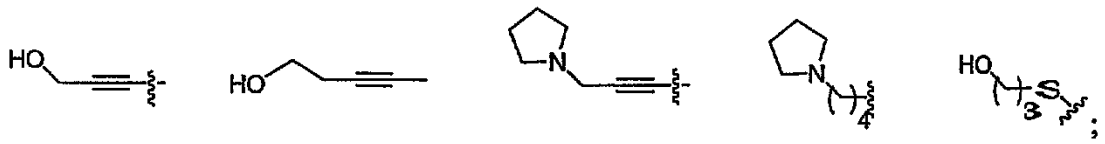
wherein V is O, S or R^{1B}; p is an integer from 0 to 6; and R^{1A} is hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, $-C(=O)N(R^{1B})_2$, $-C(=O)OR^{1B}$; wherein each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, 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;

[0107] xxxviii) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is –CN, lower alkyl, lower alkynyl, $-CO_2R^{1D}$, or one of:



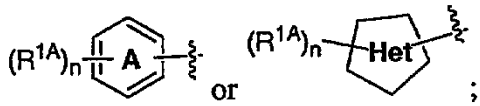
wherein p is an integer from 1 to 4; and R^{1A} is hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, $-C(=O)N(R^{1B})_2$, $-C(=O)OR^{1B}$; wherein each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(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;

[0108] xxxix) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is –CN, -C≡CH, methyl, $-CO_2H$, $-CO_2Me$, or one of:



[0109] xl) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is aryl, heteroaryl or heterocyclyl;

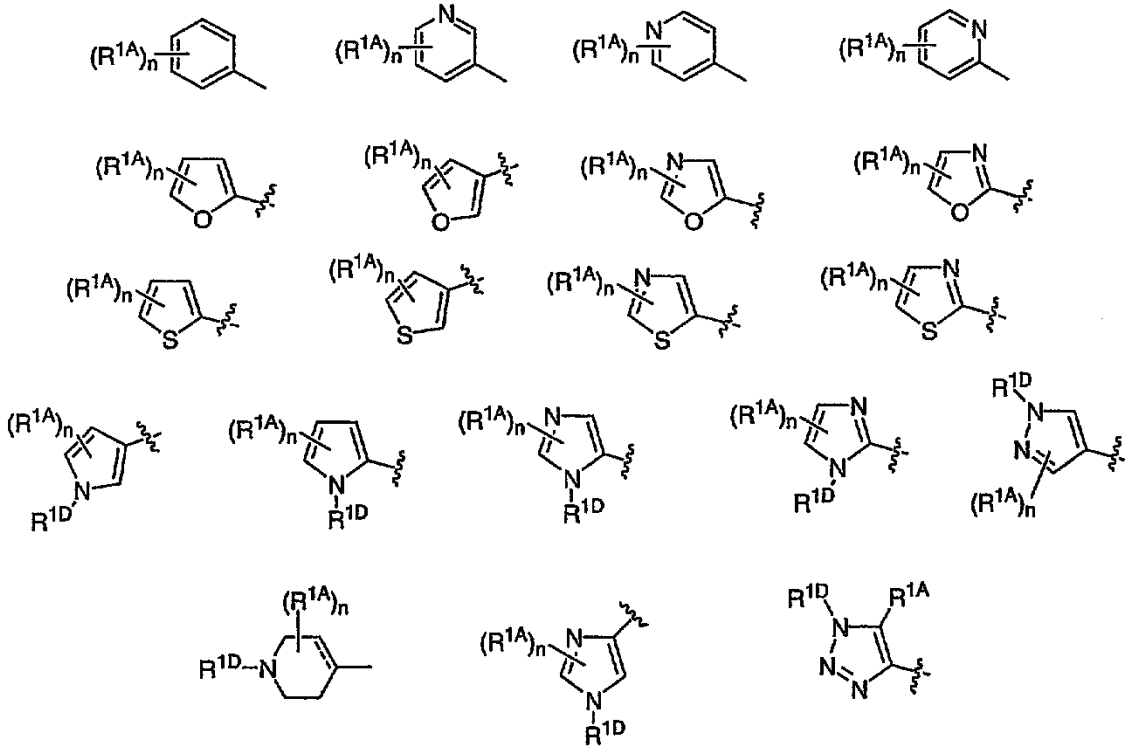
[0110] xli) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is an aryl, heteroaryl or heterocyclyl moiety having one of the structures:

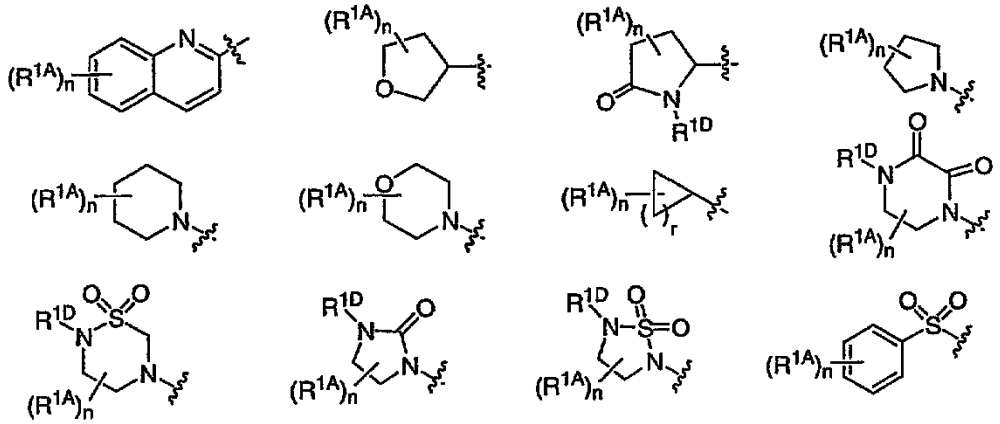


;

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;

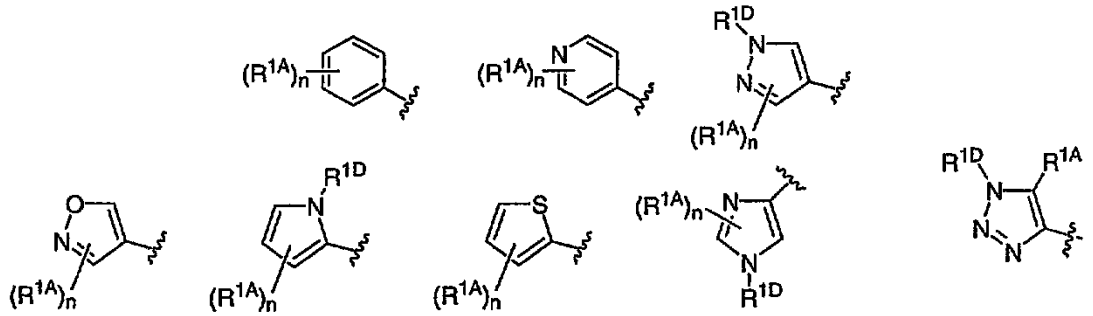
[0111] xlii) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is one of:





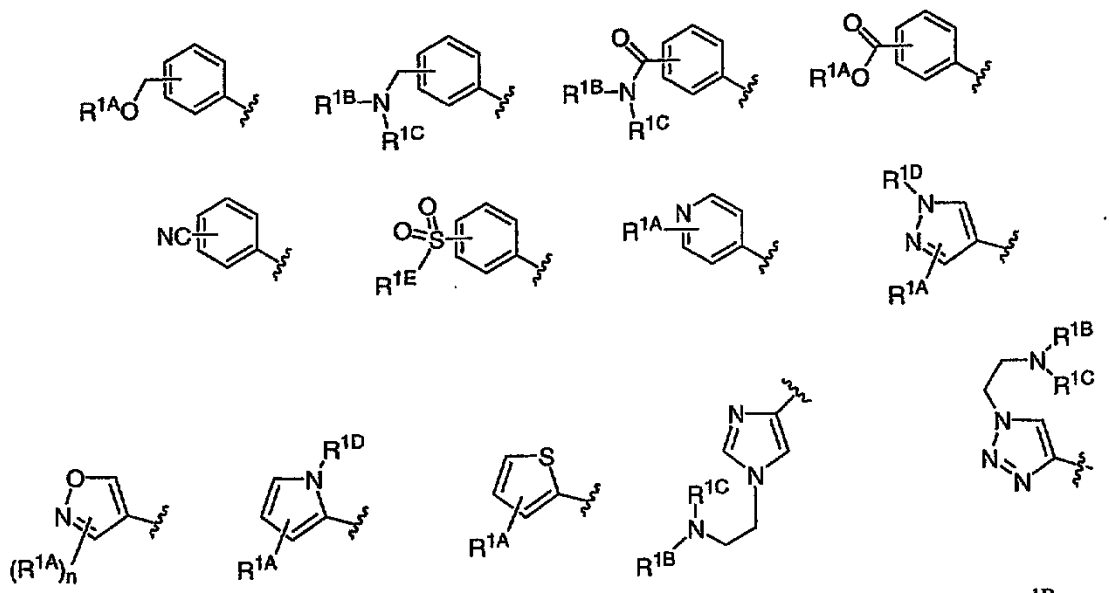
wherein each occurrence of R^{1A} is independently hydrogen, alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)heterocyclyl, -(alkyl)aryl, -(alkyl)heteroaryl, $-OR^{1B}$, $-SR^{1B}$, $-N(R^{1B})_2$, $-SO_2N(R^{1B})_2$, $-SO_2R^{1E}$,$-C(=O)N(R^{1B})_2$, halogen, -CN, $-NO_2$, $-C(=O)OR^{1B}$, $-N(R^{1B})C(=O)R^{1C}$ 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;

[0112] xliii) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is one of:



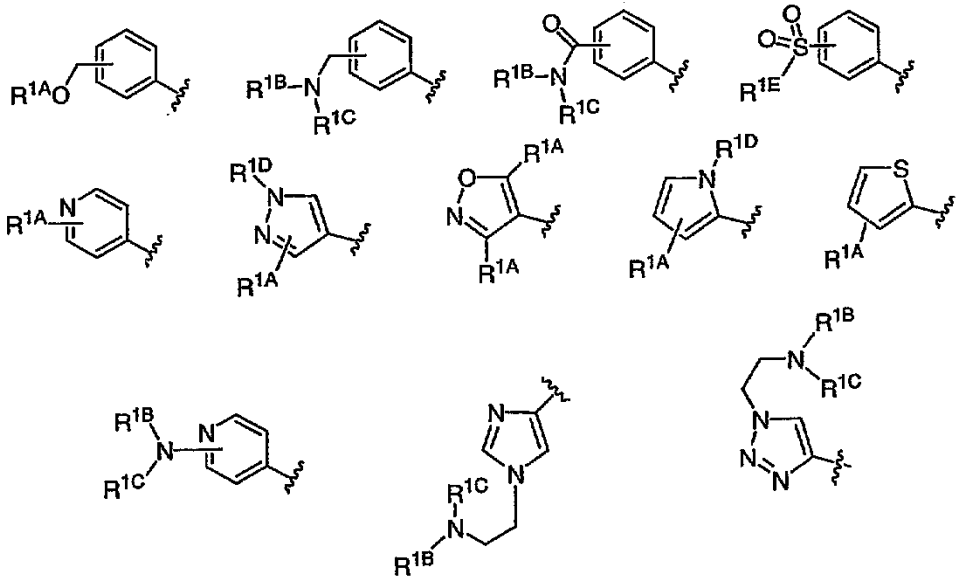
wherein n, R^{1A} and R^{1D} are as defined in xlii) above;

[0113] xliv) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is one of:



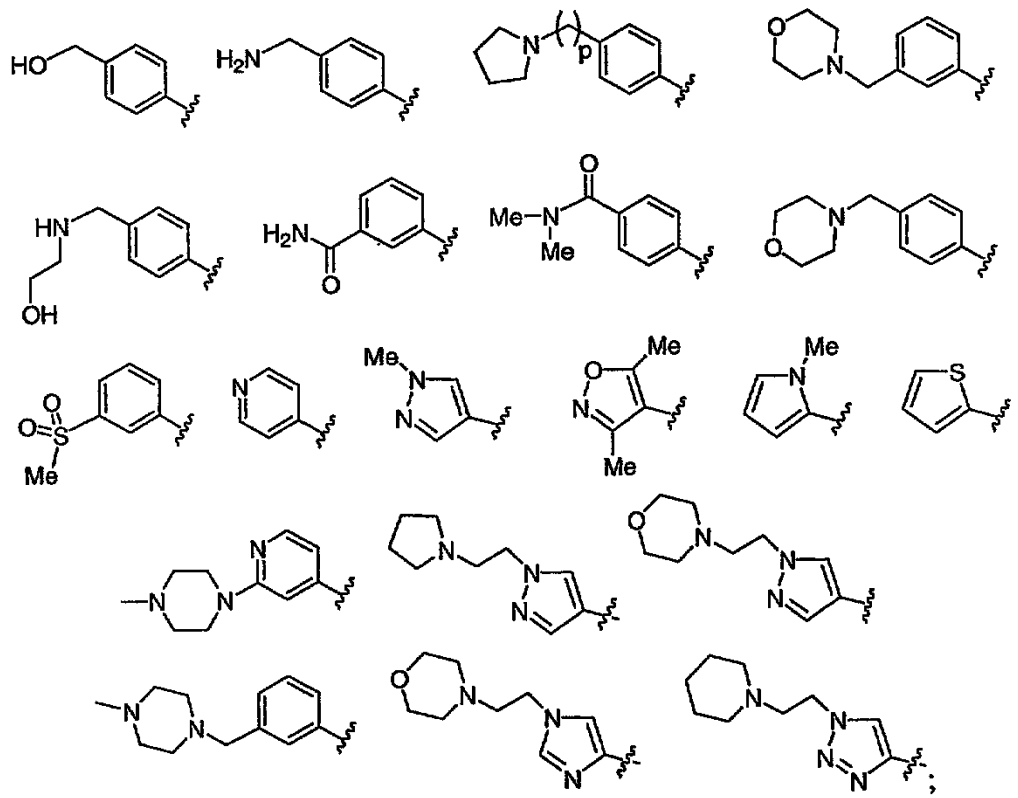
wherein n is 0-2; R^{1A} is hydrogen or lower alkyl; each occcurrence of R^{1B} and R^{1C} is independently hydrogen, lower alkyl, or R^{1B} and R^{1C}, taken together with the nitrogen atom to which they are attached, form a substituted or unsubstituted 5-6 membered heterocyclic moiety; R^{1D} is hydrogen,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

[0114] xlv) X^2 is S and X^1 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;

[0115] xlvi) X^2 is S and X^1 is $-C(R^{X1})-$; wherein R^{X1} is one of:



[0116] xlvii) L^1 is $-W^1$-Alk_1-; 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;

[0117] xlviii) L^1 is $-W^1$-Alk_1-; 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;

[0118] xlix) Compounds of subset xlviii) above wherein W^1 is S;

[0119] l) Compounds of subset xlviii) above wherein W^1 is O or NR^{W1};

[0120] li) L^1 is $-O\text{-}Alk_1\text{-}$; wherein Alk_1 is a substituted or unsubstituted C_2alkylene chain;

[0121] lii) L^1 is –O-cyclopropyl-;

[0122] liii) L^1 is $-O\text{-}CH_2CH_2\text{-}$;

[0123] liv) L^1 is $-NR^{W1}\text{-}Alk_1\text{-}$; wherein R^{W1} is hydrogen, lower alkyl, $C_{3\text{-}6}$cycloalkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; and Alk_1 is a substituted or unsubstituted $C_{2\text{-}6}$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;

[0124] lv) L^1 is $-NR^{W1}\text{-}Alk_1\text{-}$; wherein R^{W1} is hydrogen, lower alkyl or lower heteroalkyl; and Alk_1 is a substituted or unsubstituted C_2alkylene chain;

[0125] lvi) L^1 is –NH-cyclopropyl-;

[0126] lvii) L^1 is $-NH\text{-}CH_2CH_2\text{-}$;

[0127] lviii) L^1 is $-NH\text{-}CH_2CF_2\text{-}$;

[0128] lix) L^1 is $-NH\text{-}CH_2CH[(CH_2)_pOR^{W2}]\text{-}$; wherein p is 1 or 2 and R^{W2} is hydrogen or lower alkyl;

[0129] lx) L^1 is $-NH\text{-}CH_2CH(CH_2OH)\text{-}$;

[0130] lxi) L^1 is $-NH\text{-}CH_2CH(CH_2CH_2OH)\text{-}$;

[0131] lxii) L^1 is $-NR^{W1}\text{-}Alk_1\text{-}$; wherein R^{W1} is lower heteroalkyl; and Alk_1 is a substituted or unsubstituted C_2alkylene chain;

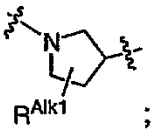
[0132] lxiii) L^1 is $-NR^{W1}\text{-}Alk_1\text{-}$; wherein R^{W1} is $-(CH_2)_2NR^{W2}R^{W3}$; Alk_1 is a substituted or unsubstituted C_2alkylene chain; and R^{W2} and R^{W3} are independently hydrogen or lower alkyl;

[0133] lxiv) L^1 is $-NR^{W1}\text{-}(CH_2)_2\text{-}$; wherein R^{W1} is $-(CH_2)_2NR^{W2}R^{W3}$; and R^{W2} and R^{W3} are independently hydrogen or lower alkyl;

[0134] lxv) L^1 is $-NR^{W1}\text{-}(CH_2)_2\text{-}$; wherein R^{W1} is $-(CH_2)_2NMe_2$;

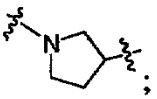
[0135] lxvi) L^1 is $-NR^{W1}\text{-}Alk_1\text{-}$; wherein R^{W1} together with a carbon atom present on Alk_1 forms an optionally substituted 5- to 6-membered heterocyclic moiety;

[0136] lxvii) L^1 has the structure:

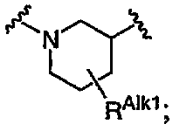


wherein R^{Alk1} is hydrogen, halohen, hydroxy, CN, nitro, lower alkyl, lower alkoxy, aryl, or heteroaryl;

[0137] lxviii) L^1 has the structure:

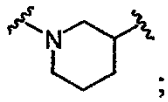


[0138] lxix) L^1 has the structure:



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

[0139] lxx) L^1 has the structure:



[0140] lxxi) L^1 is $-C(=O)NR^{W1}\text{-}Alk_1\text{-}$; wherein R^{W1} is hydrogen or lower alkyl; and Alk_1 is a substituted or unsubstituted C_1alkylene moiety;

[0141] lxxii) L^1 is $-C(=O)NH\text{-}CH_2\text{-}$;

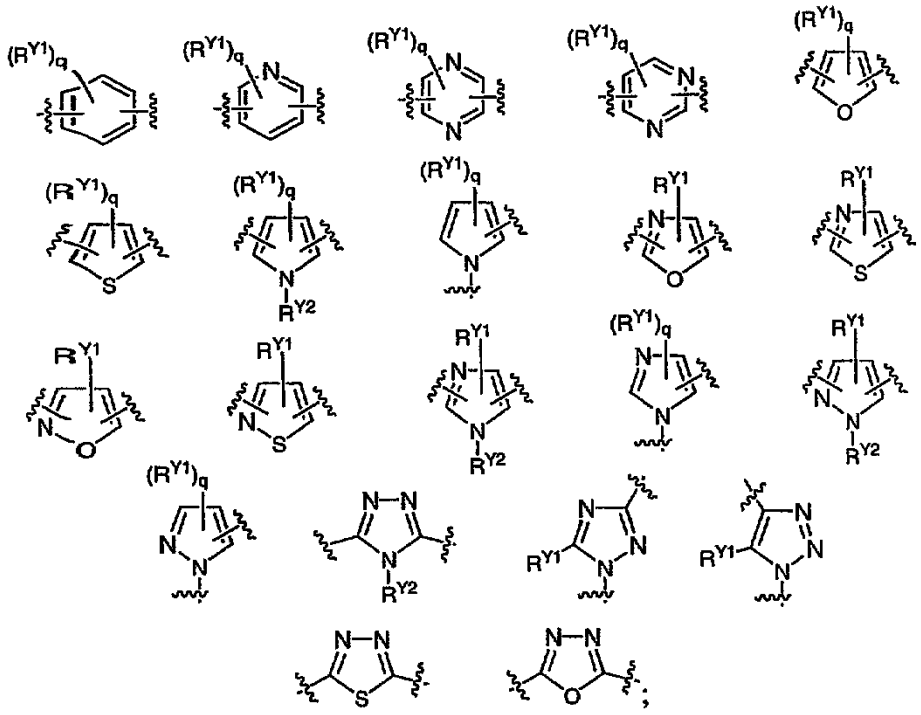
[0142] lxxiii) Y is a saturated or unsaturated cyclic ring system optionally comprising one or more heteroatoms selected from S, N and O;

[0143] lxxiv) Y is a saturated or unsaturated monocyclic cyclic ring system optionally comprising one or more heteroatoms selected from S, N and O;

[0144] lxxv) Y is a cycloalkyl, cycloalkenyl, heterocylic, aryl or heteroaryl moiety;

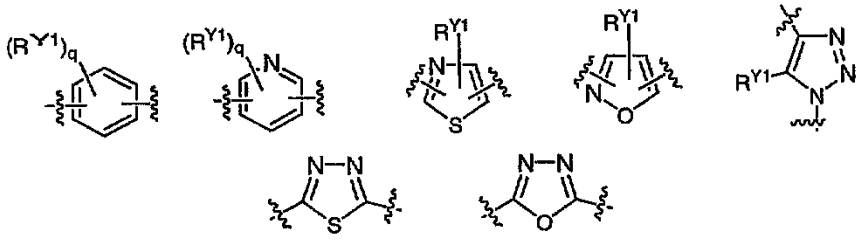
[0145] lxxvi) Y is a 5-6 membered cycloalkyl, 5-6 membered cycloalkenyl, 5-6 membered heterocylic, 6-membered aryl or 6-membered heteroaryl moiety;

[0146] lxxvii) Y is one of:



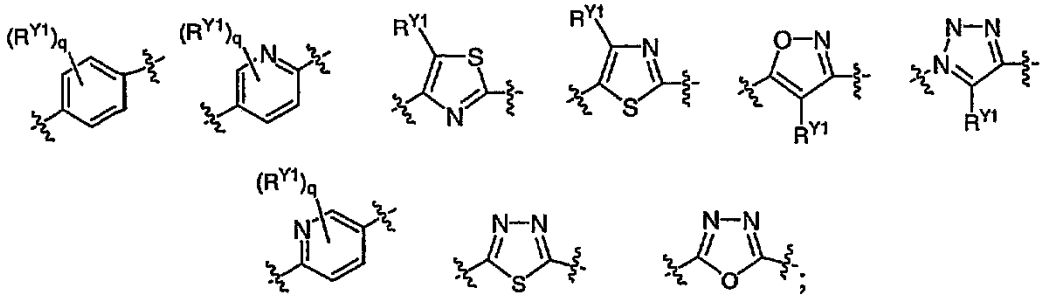
wherein q is an integer from 0 to 3; each occurrence of R^{Y1} is indenpendently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, -CN, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$,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

[0147] lxxviii) Y is one of:



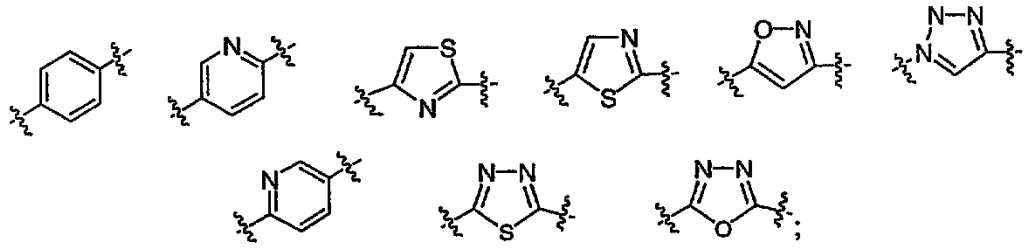
wherein q and R^{Y1} are as defined directly above;

[0148] lxxix) Y is one of:

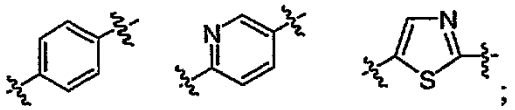


wherein q is 0-3; and R^{Y1} is hydrogen, halogen or lower alkyl;

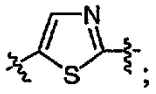
[0149] lxxx) Y is one of:



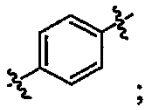
[0150] lxxxi) Y is one of:



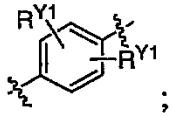
[0151] lxxxii) Y is:



[0152] lxxxii) Y is:

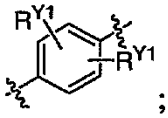


[0153] lxxxiii) Y is:



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

[0154] lxxxiv) Y is:



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

[0155] lxxxv) 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;

[0156] lxxxvi) 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;

[0157] lxxxvii) 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;

[0158] lxxxviii) 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;

[0159] lxxxix) 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;

[0160] xc) 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;

[0161] xci) L^2 is –NH-, -NHC(=O)-, -NHC(=O)O-, -NHC(=O)NH-, -CH_2-C(=O)NH- or –NHC(=O)$NHCH_2$-;

[0162] xcii) L^2 is -NH-;

[0163] xciii) L^2 is -NHC(=O)NH-;

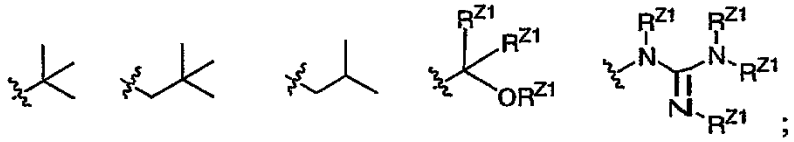
[0164] xciv) L^2 is -CH_2-C(=O)NH-;

[0165] xcv) L^2 is –NHC(=O)$NHCH_2$-;

[0166] xcvi) Z is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl or heteroaryl moiety;

[0167] xcvii) Z is a branched alkyl, alkenyl, alkynyl, heteroalkyl or heteroalkenyl moiety;

[0168] xcviii) Z is one of:

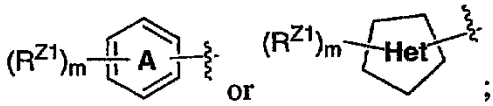


;

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

[0169] xcix) Z is a cycloalkyl, cycloalkenyl, heterocyclyl, aryl or heteroaryl moiety;

[0170] c) Z is cycloalkyl, cycloalkenyl, or a heterocyclyl, aryl or heteroaryl moiety having one of the structures:

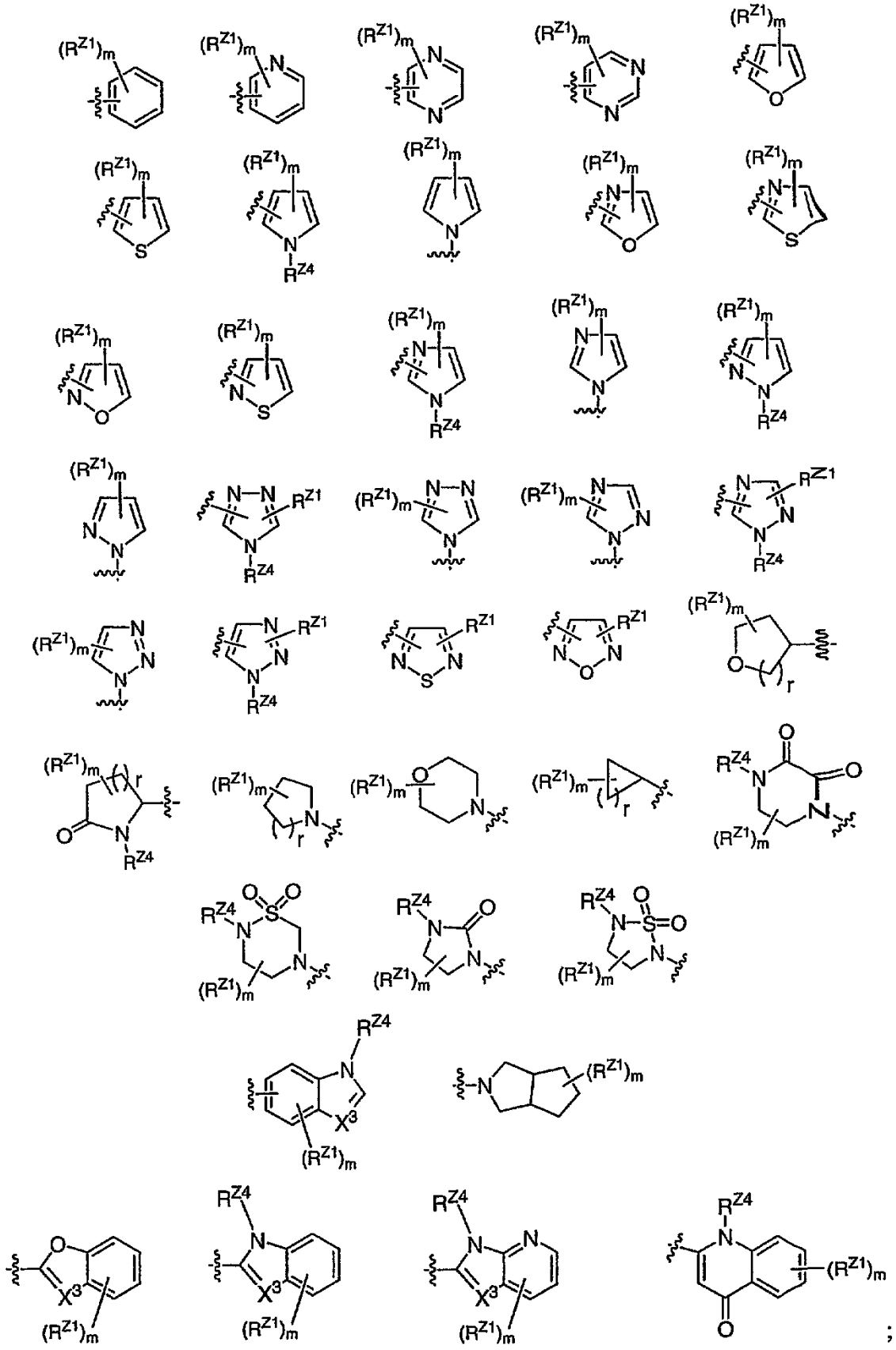


or ;

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;

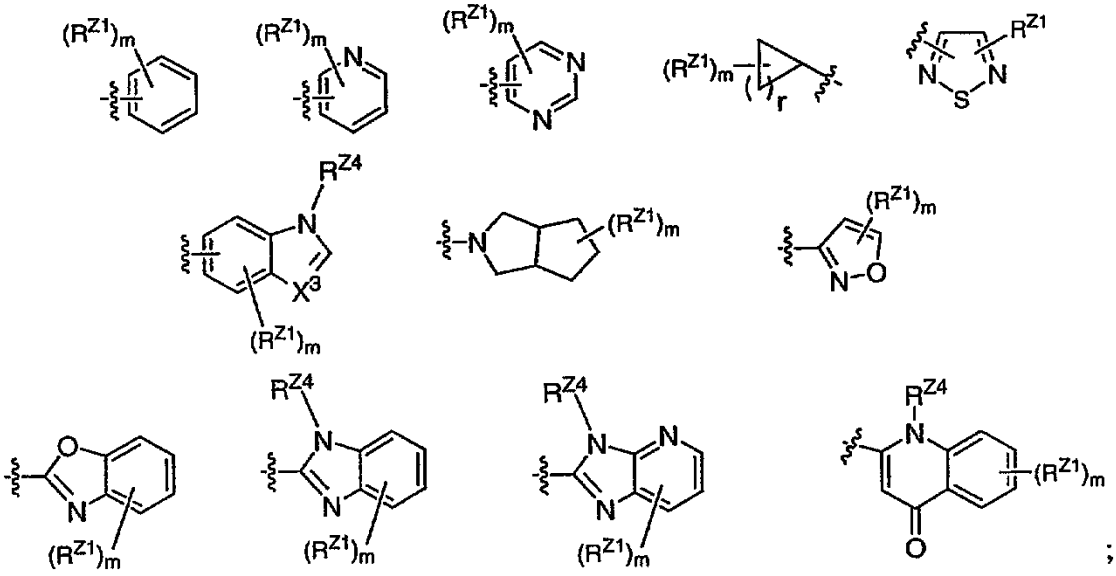
[0171] ci) Z is one of:



;

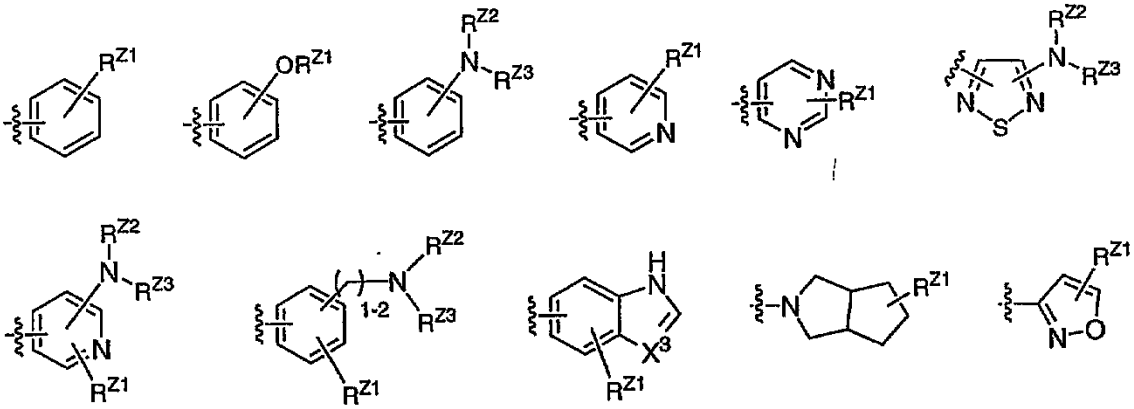
wherein m is an integer from 0 to 3; r is an integer from 1 to 4; X^3 is N or CR^{Z1}; each occurrence of R^{Z1} is indenpendently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Z2}$, $-SR^{Z2}$, $-NR^{Z2}R^{Z3}$, $-SO_2NR^{Z2}R^{Z3}$, $-SO_2R^{Z1}$, $-C(=O)NR^{Z2}R^{Z3}$, 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;

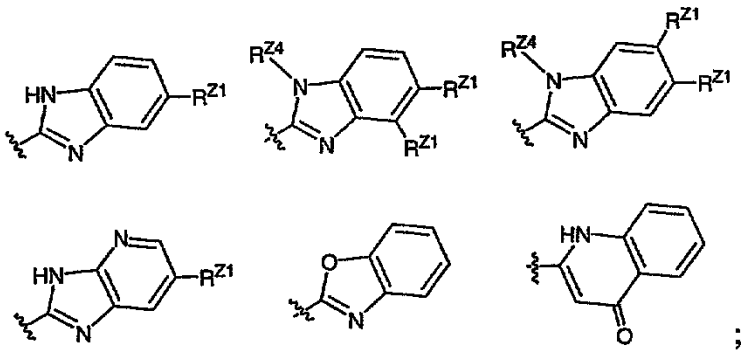
[0172] cii) Z is one of:



;

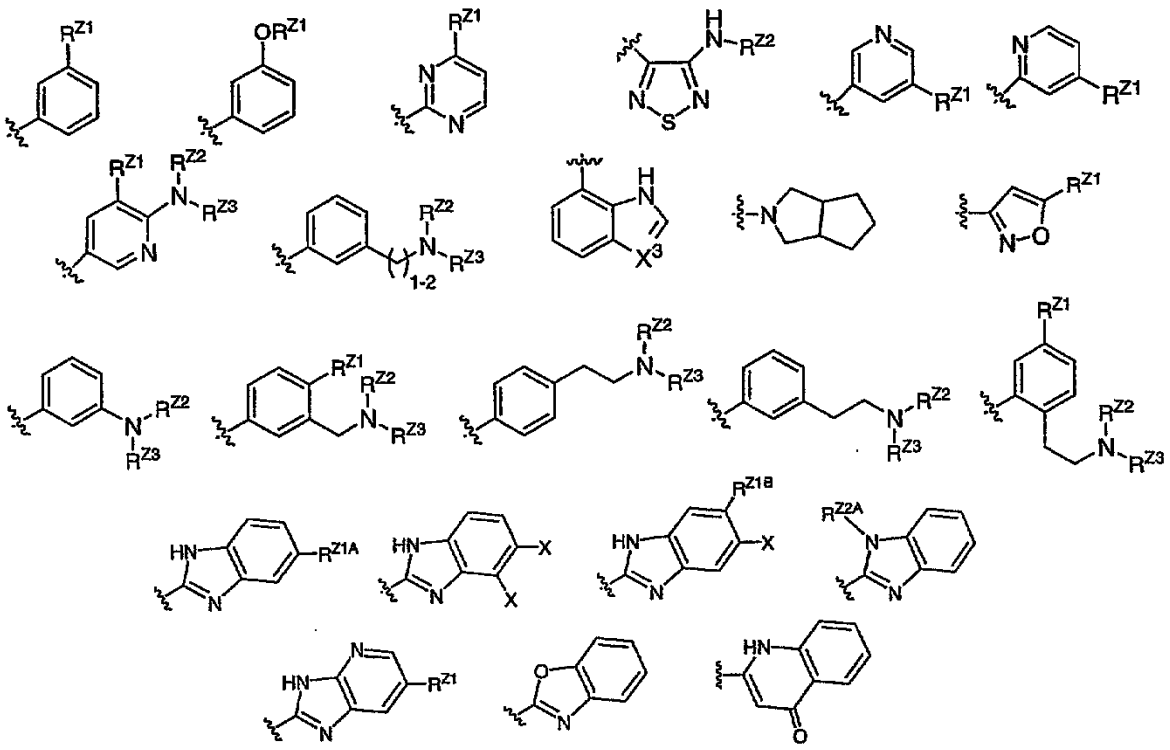
[0173] ciii) Z is one of:





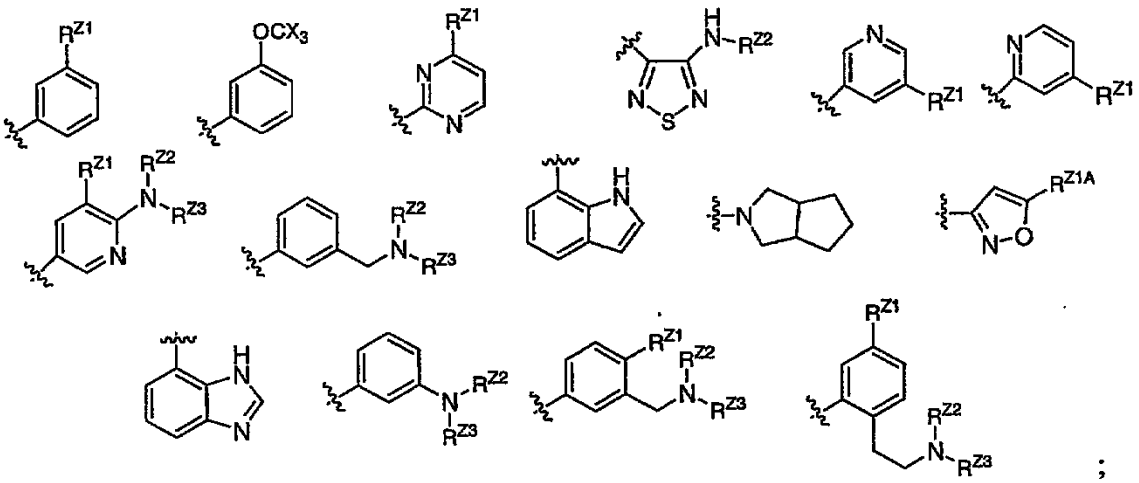
wherein X^3 is N or CR^{Z1}; R^{Z1} is hydrogen, halogen, lower alkyl, lower hydroxyalkyl or lower haloalkyl; R^{Z2} and R^{Z3} are independently hydrogen, lower alkyl, lower heteroalkyl, acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic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

[0174] civ) Z is one of:



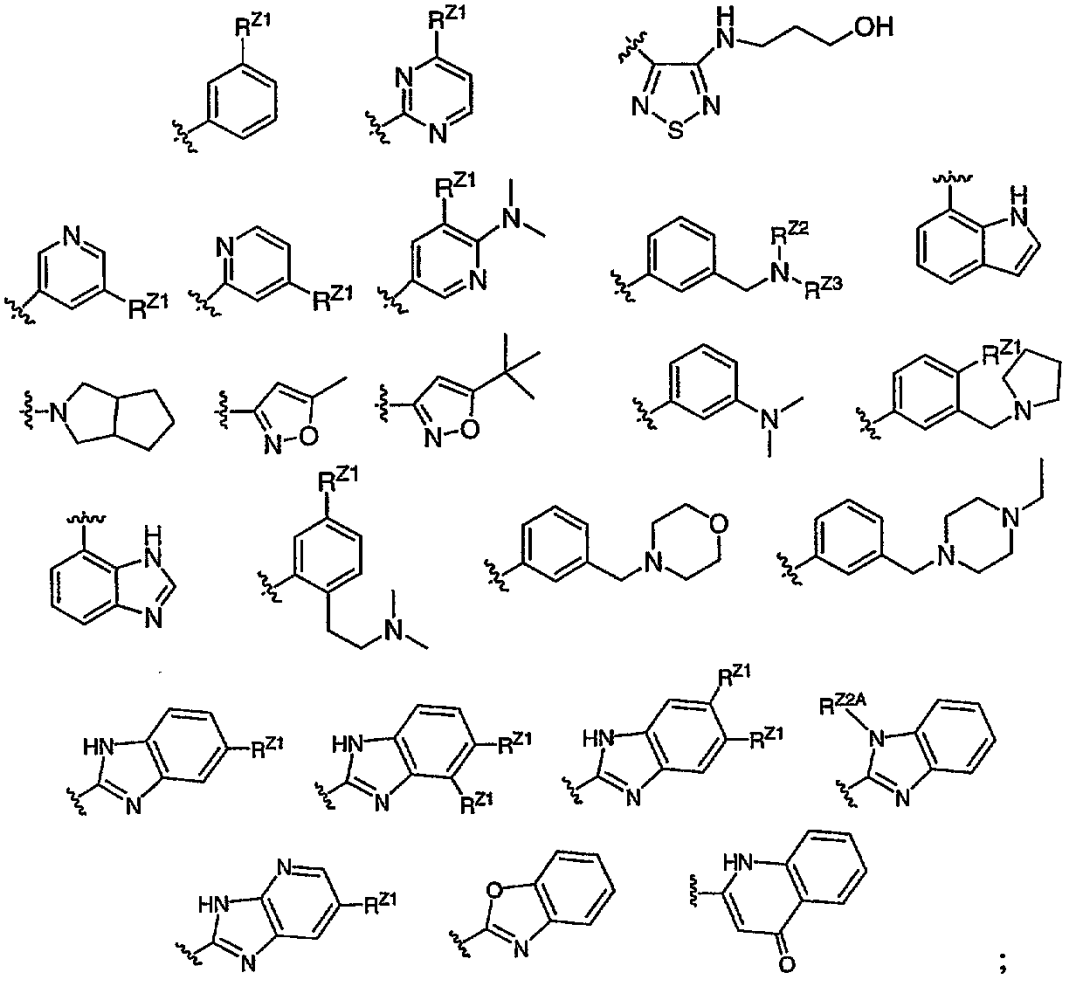
wherein X^3 is N or CR^{Z1}; R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl; and R^{Z2} and R^{Z3} are independently hydrogen, lower alkyl, lower heteroalkyl, acyl, or R^{Z2} and R^{Z3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring;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

[0175] cv) Z is one of:



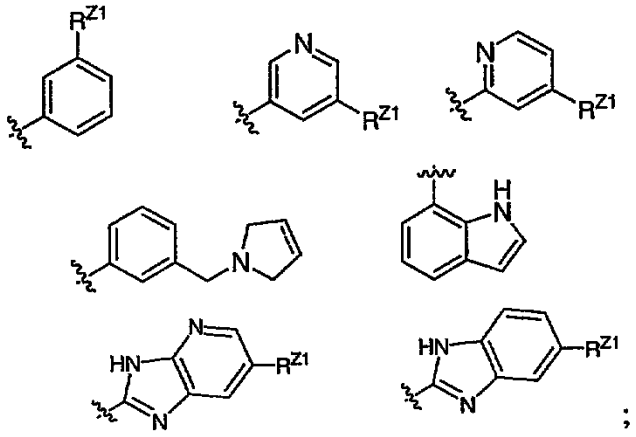
wherein X is halogen; R^{Z1A} is lower alkyl; R^{Z1} is halogen, lower alkyl or lower haloalkyl; and R^{Z2} and R^{Z3} are independently lower alkyl, or R^{Z2} and R^{Z3} taken together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring;

[0176] cvi) 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; and R^{Z2A} is hydrogen or methyl;

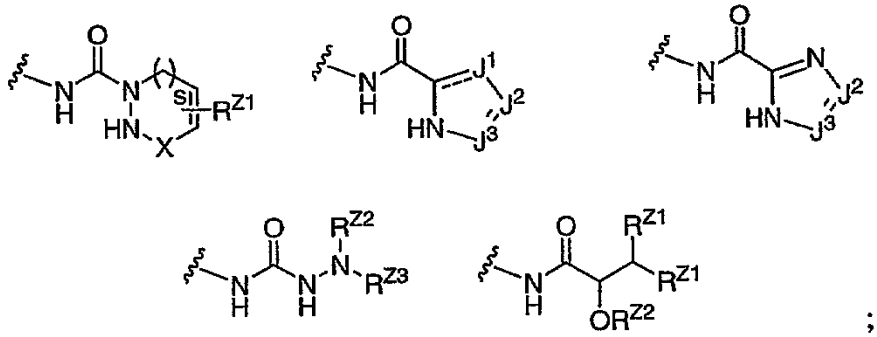
[0177] cvii) Z is one of:



;

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

[0178] cviii) $-L^2-Z$ together represent a moiety having one of the following structures:

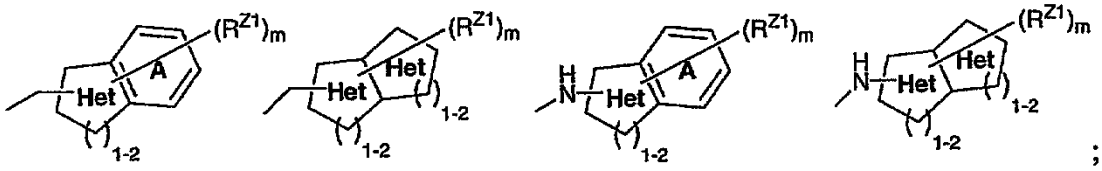


;

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;

[0179] cix) $-L^2-Z$ together represent $-CH_2$-Cy or –NH-Cy where Cy is an optionally substituted bicyclic heterocycle;

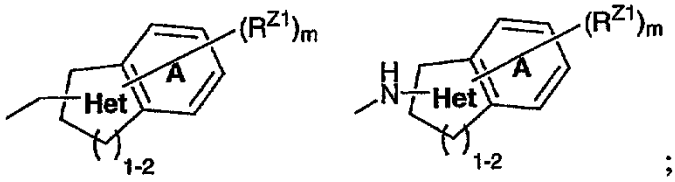
[0180] cx) $-L^2-Z$ together represent a moiety having one of the following structures:



;

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;

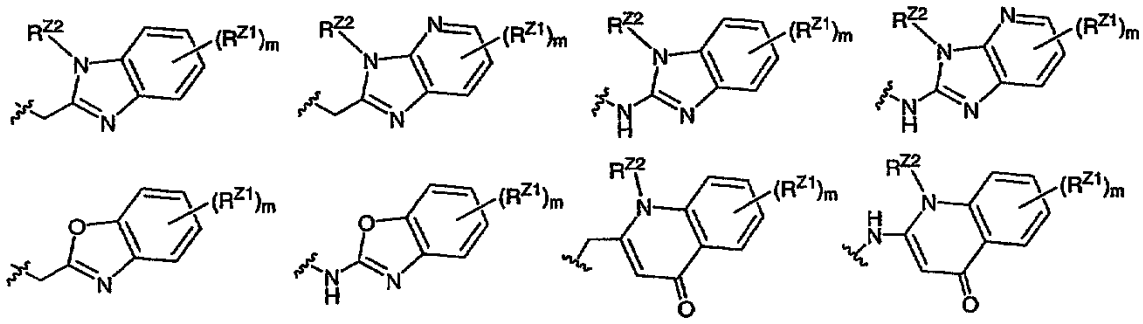
[0181] cxi) $-L^2-Z$ together represent a moiety having one of the following structures:



;

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;

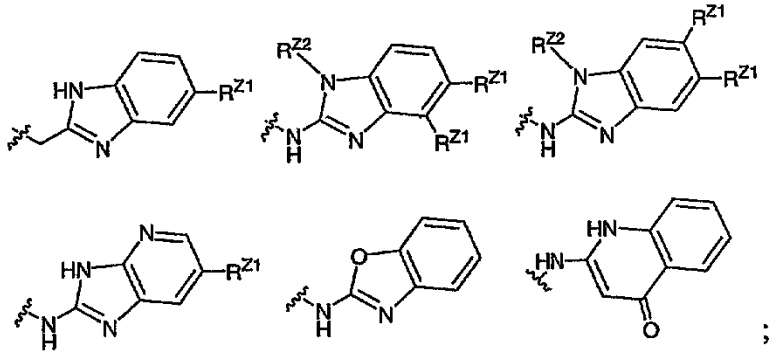
[0182] cxii) $-L^2-Z$ together represent a moiety having one of the following structures:



;

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;

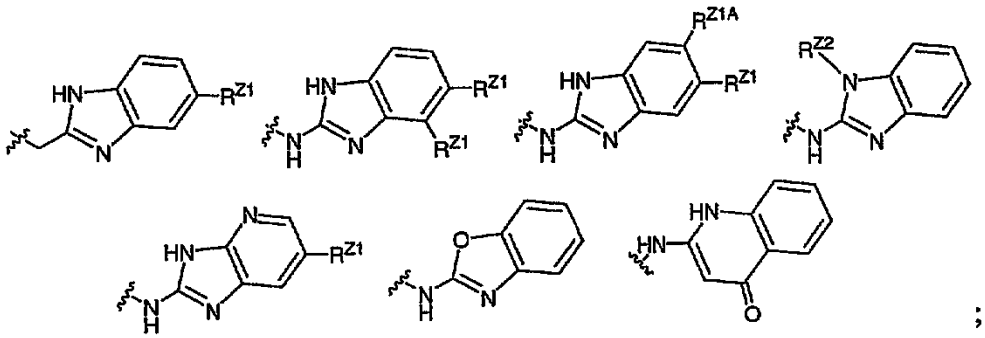
[0183] cxiii) $-L^2-Z$ together represent a moiety having one of the following structures:



;

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;

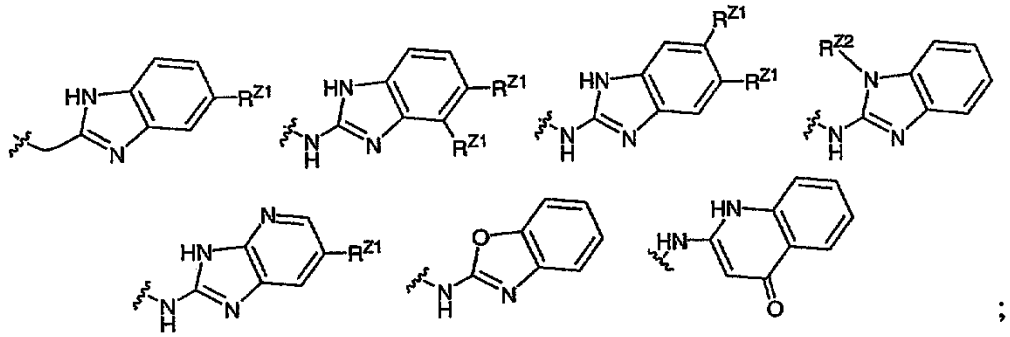
[0184] cxiv) $-L^2-Z$ together represent a moiety having one of the following structures:



;

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;

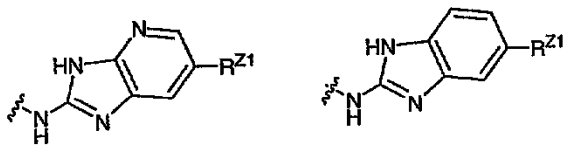
[0185] cxv) $-L^2-Z$ together represent a moiety having one of the following structures:



;

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

[0186] cxvi) $-L^2-Z$ together represent a moiety having one of the following structures:



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

[0187] 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.

[0188] The reader will also appreciate that any and all possible combinations of the variables described in i)- through cxvi) above (*e.g.*, R^1, 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^1, R^2, L^1, L^2, X^1, X^2, Y and Z, and other variables/substituents (*e.g.*, R^{X1}, R^{X2}, R^{Y1}, R^{Z1} etc.) as further defined for R^1, R^2, L^1, L^2, X^1, X^2, Y and Z, described in i)- through lii) above.

[0189] For example, an exemplary combination of variables described in i)- through cxvi) above includes those compounds of Formula I wherein:

$\mathbf{R^1}$ is H, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)aryl or -(heteroalkyl)heteroaryl;

$\mathbf{R^2}$ 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;

$\mathbf{X^1}$ is S;

$\mathbf{X^2}$ is $-C(R^{X2})-$; wherein R^{X2A} 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 $C_{1\text{-}6}$alkylene or $C_{2\text{-}6}$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;

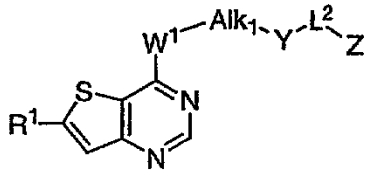
$\mathbf{L^2}$ is -C(=O)NR^{L2A}-, -OC(=O)NR^{L2A}-, -$NR^{L2A}NR^{L2B}$-, -$NR^{L2A}NR^{L2B}$C(=O)-, -NR^{L2A}C(=O)-, -$NR^{L2A}CO_2$-, -NR^{L2A}C(=O)NR^{L2B}-, -$NR^{L2A}SO_2$-, -SO_2NR^{L2A}-, -$NR^{L2A}SO_2NR^{L2B}$-, or a substituted or unsubstituted $C_{1\text{-}6}$alkylene or $C_{2\text{-}6}$alkenylene 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;

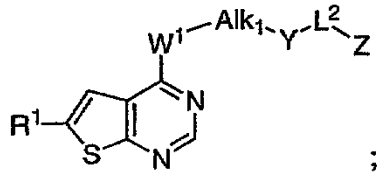
Z is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl or heteroaryl moiety.

[0190] Other exemplary combinations are illustrated by compounds of the following subgroups I through XVI:

[0191] **I. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**



or



;

(1) (2)

wherein R^1, 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

(i) R^1 is not Q^1, Q^2 or Q^3;

(ii) for compounds of formula (2), the following groups do not occur simultaneously as defined: R^1 is Q_5; Y and Z are independently optionally substituted aryl, carbocyle or 5-membered monocyclic heterocycle; Alk_1 is –N=CH-.

(iii) the following groups do not occur simultaneously as defined: Y and Z are each optionally substituted phenyl; L^2 is $-OCH_2-$ or $-OSO_2-$; W^1Alk_1 is–OCH(R)-, –OCH(R)-C_{1-6}alkylO- or –OCH(R)-C_{1-6}alkylC(=NR_x)- where R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl and R_x is H, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic; and R^1 is hydrogen, halogen or alkyl;

(iv) the following groups do not occur simultaneously as defined: W^1Alk_1 is –$NHCH_2CH_2-$ or $-OCH_2CH_2-$; Y is phenyl or L^2 is–C(R)=N-O-, wherein R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl; and R^1 is hydrogen, halogen or C_{1-4}alkyl;

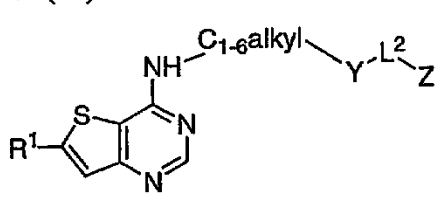
(v) the following groups do not occur simultaneously as defined: W^1Alk_1 is $-OCH_2-$, or $-N(R)CH_2-$, wherein R is H or C_{1-8}alkyl; Y is phenyl, or Z is a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl;

(vi) R^1 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; L^1 is $-NHC_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$heteroalkyl or $-OC_{1-6}$heteroalkyl; Y is cycloalkyl, aryl, heteroaryl or heterocyclyl; L^2-Z is $-X-R^x$ where X is –NR-, -C(=O)NH-, -NHC(=O)-, $-SO_2NH-$ or $-NHSO_2-$ and R^x is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl;

(vii) the following groups do not occur simultaneously as defined: L^1 is $-NR(CR^x)_{1-2}-$ or $-O(CR^x)_{1-2}-$ wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, OH, NH_2 or $-C_{1-4}$alkylNH; 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; L^2-Z is $-SO_2NHC_{3-8}$cycloalkyl, $-SO_2N(C_{3-8}cycloalkyl)_2$, $-C(=O)NHC_{3-8}$cycloalkyl or $-C(=O)N(C_{3-8}cycloalkyl)_2$; and

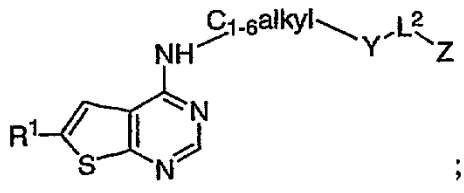
(viii) the following groups do not occur simultaneously as defined: R^1 is hydrogen, halogen, nitro or C_{1-4}alkyl; L^1 is $-NRC_{1-6}$alkyl- or $-OC_{1-6}$alkyl- wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}acyl; Y is phenyl; L^2–Z is a C_{1-12}alkyl saturated or unsaturated hydrocarbon chain optionally including -NR- and optionally substituted with haloC_{1-4}alkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{1-4}acyl, phenoxy, phenyl or phenylthio.

[0192] In certain embodiments, compounds of the invention have the structure (1^A) or (2^A) below:



(1^A)

or

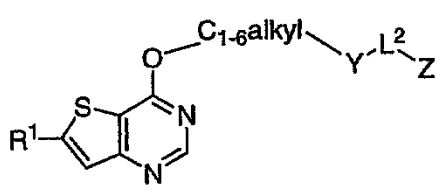


(2^A)

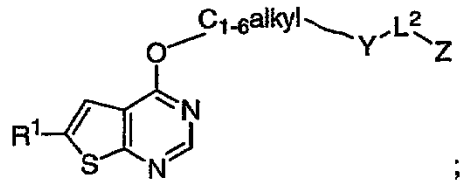
;

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

[0193] In certain embodiments, compounds of the invention have the structure (1^B) or (2^B) below:



or



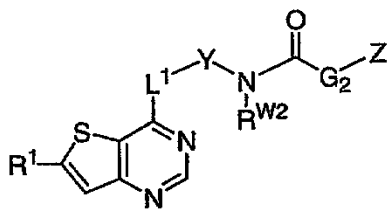
;

(1^B) (2^B)

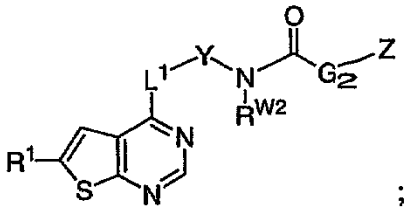
wherein the C_{1-6}alkyl moiety may be substittued or unsubstituted.

[0194] In certain embodiments, for compounds of formulae (1^A), (1^B), (2^A) and (2^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 $-CH_2CH_2-$.

[0195] II. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



or



;

(3) (4)

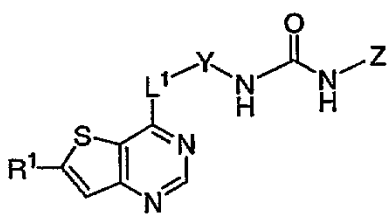
wherein R^1, L^1, Y and Z are as defined generally and in classes and subclasses herein; G_2 is absent, O or NR^{G2}; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

(i) R^1 is not Q^1, Q^2 or Q^3;

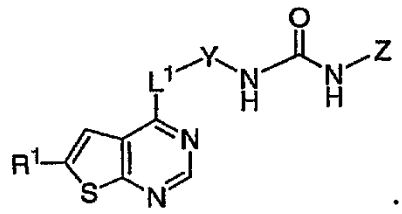
(ii) the following groups do not occur simultaneously as defined: G_2 is absent; L^1 is $-OCH_2-$, $-CH_2O-$, $-N(R)CH_2-$ or $-CH_2N(R)-$, wherein R is H or C_{1-8}alkyl; Y is phenyl; and Z is a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl; and

(iii) the following groups do not occur simultaneously as defined: R^1 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; L^1 is $-NHC_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$heteroalkyl or $-OC_{1-6}$heteroalkyl; Y is cycloalkyl, aryl, heteroaryl or heterocyclyl; G^2 is absent and Z is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl.

[0196] 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 the structure (3^A) or (4^A) below:

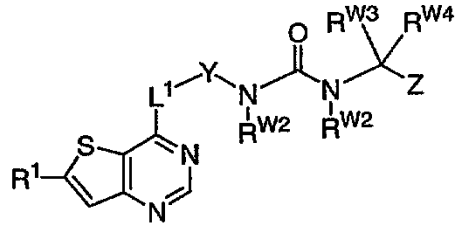


or

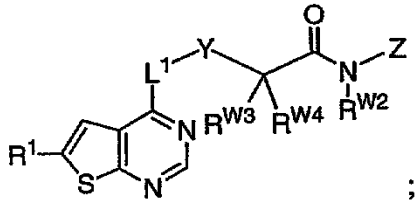


(3^A) (4^A)

[0197] III. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



or



;

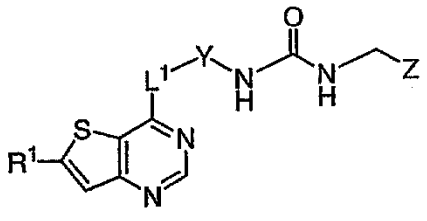
(5) (6)

wherein R^1, 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

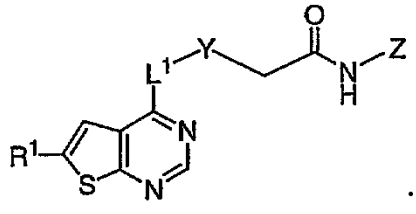
(i) R^1 is not Q^1, Q^2 or Q^3; and

(ii) the following groups do not occur simultaneously as defined: (R^{W3}, R^{W4}) is (H,H), (F,F) or (H, C_{1-4}alkyl); L^1 is $-OCH_2-$, $-CH_2O-$, $-N(R)CH_2-$ or $-CH_2N(R)-$, wherein R is H or C_{1-8}alkyl; Y is phenyl; and Z is a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl.

[0198] In certain embodiments, compounds of the invention have the structure (5^A) or (6^A) below:

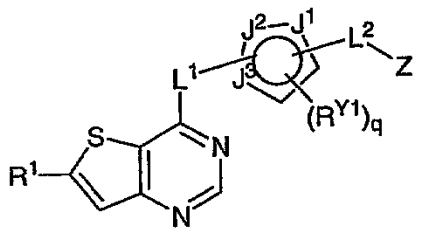


or

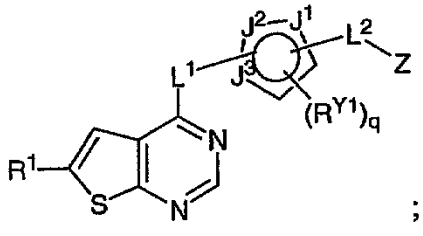


(5^A) (6^A)

[0199] IV. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



or



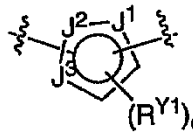
;

(7) (8)

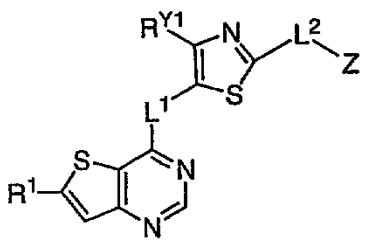
wherein q is an integer from 0-2; R^1, L^1, L^2 and Z are as defined generally and in classes and subclasses herein; and J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Y1}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{Y3}$, $-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

(i) R^1 is not Q^1, Q^2 or Q^3;

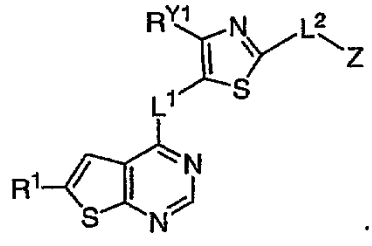
(ii) for compounds of formula (8), the following groups do not occur simultaneously as defined: R^1 is Q_5; Z is optionally substituted aryl, carbocyle or 5-membered monocyclic heterocycle; L^1 is -W–N=CH-, where W is O or NR, wherein R is H, C_{1-6}alk(en/yn)yl, C_{3-8}cycloalk(en)yl, aryl, hydroxyC_{1-6}alk(en/yn)yl, C_{3-8}cycloalk(en)yl-C_{1-6}alk(en/yn)yl or acyl.

(iii) the following groups do not occur simultaneously as defined: L^1 is $-NR(CR^x)_{1-2}-$ or $-O(CR^x)_{1-2}-$ wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, OH, NH_2 or $-C_{1-4}$alkylNH; and R^x is H or C_{1-4}alkyl;  is thienyl, furanyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl; L^2-Z is $-SO_2NHC_{3-8}$cycloalkyl, $-SO_2N(C_{3-8}cycloalkyl)_2$, $-C(=O)NHC_{3-8}$cycloalkyl or $-C(=O)N(C_{3-8}cycloalkyl)_2$.

[0200] In certain embodiments, compounds of the invention have the structure (7^A) or (8^A) below:

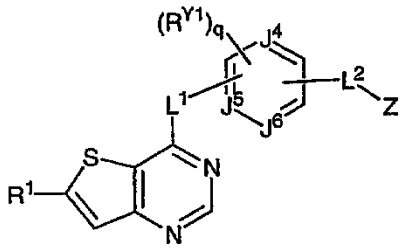


or

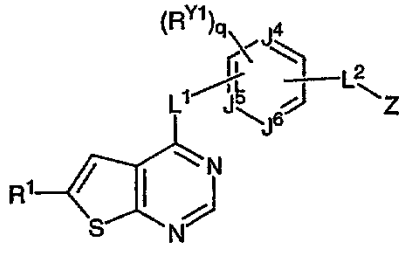


(7^A) (8^A)

[0201] V. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



or



(9) **(10)**

wherein q is an integer from 0-3; R^1, 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

(i) R^1 is not Q^1, Q^2 or Q^3;

(ii) the following groups do not occur simultaneously as defined: L^1 is $-OCH_2-$, $-CH_2O-$, $-N(R)CH_2-$ or $-CH_2N(R)-$, wherein R is H or C_{1-8}alkyl; J^4, J^5 and J^6 are each CR^{Y1}; and Z is a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl;

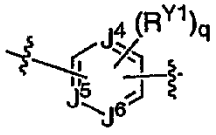
(iii) the following groups do not occur simultaneously as defined: J^4, J^5 and J^6 are each CH; L^1 is $-NHCH_2CH_2-$ or $-OCH_2CH_2-$; and L^2 is $-C(R)=N-O-$, wherein R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl; and R^1 is hydrogen, halogen or C_{1-4}alkyl.

(iv) the following groups do not occur simultaneously as defined: J^4, J^5 and J^6 are each CH; L^1 is $-OCH(R)-$, $-OCH(R)-C_{1-6}$alkylO- or $-OCH(R)-C_{1-6}$alkylC(=NR_x)- where R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl and R_x is H, aliphatic,

heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic; Z is optionally substituted phenyl; L^2 is $-OCH_2-$ or $-OSO_2-$; and R^1 is hydrogen, halogen or alkyl;

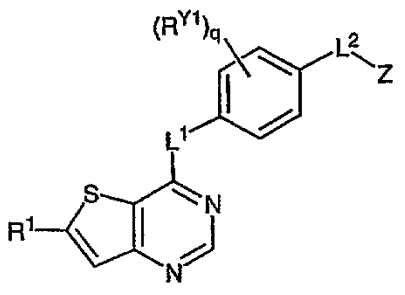
(v) for compounds of formula **(10)**, the following groups do not occur simultaneously as defined: R^1 is Q_5; J^4, J^5 and J^6 are each CR^{Y1}; Z is optionally substituted aryl, carbocyle or 5-membered monocyclic heterocycle; and L^1 is–W-N=CH- wherein W is O or NR, wherein R is H, C_{1-6}alk(en/yn)yl, C_{3-8}cycloalk(en)yl, aryl, hydroxyC_{1-6}alk(en/yn)yl, C_{3-8}cycloalk(en)yl-C_{1-6}alk(en/yn)yl or acyl;

(vi) the following groups do not occur simultaneously as defined: R^1 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; L^1 is $-NHC_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$heteroalkyl or $-OC_{1-6}$heteroalkyl; L^2-Z is $-X-R^x$ where X is –NR-, -C(=O)NH-, -NHC(=O)-, $-SO_2NH-$ or $-NHSO_2-$ and R^x is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl;

(vii) the following groups do not occur simultaneously as defined: L^1 is $-NR(CR^x)_{1-2}-$ or $-O(CR^x)_{1-2}-$ wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, OH, NH_2 or $-C_{1-4}$alkylNH; and R^x is H or C_{1-4}alkyl;  is phenyl, pyridyl, pyrimidyl or pyrazinyl; L^2-Z is $-SO_2NHC_{3-8}$cycloalkyl, $-SO_2N(C_{3-8}$cycloalkyl$)_2$, $-C(=O)NHC_{3-8}$cycloalkyl or $-C(=O)N(C_{3-8}$cycloalkyl$)_2$; and/or

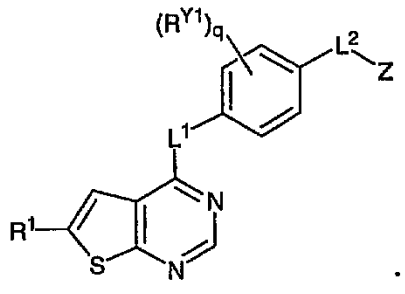
(ix) the following groups do not occur simultaneously as defined: R^1 is hydrogen, halogen, nitro or C_{1-4}alkyl; L^1 is $-NRC_{1-6}$alkyl- or $-OC_{1-6}$alkyl- wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}acyl; J^4, J^5 and J^6 are each CH; L^2–Z is a C_{1-12}alkyl saturated or unsaturated hydrocarbon chain optionally including -NR- and optionally substituted with haloC_{1-4}alkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{1-4}acyl, phenoxy, phenyl or phenylthio.

[0202] In certain embodiments, compounds of the invention have the structure (9^A) or (10^A) below:



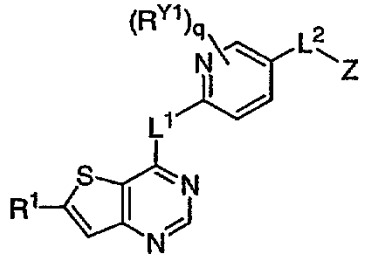
(9^A)

or



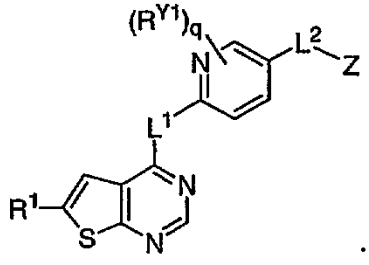
(10^A) .

[0203] In certain embodiments, compounds of the invention have the structure (9^B) or (10^B) below:



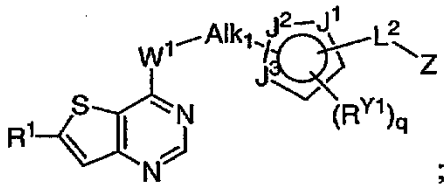
(9^B)

or



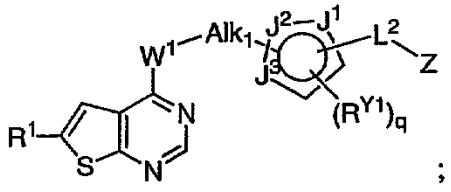
(10^B)

[0204] **VI. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**



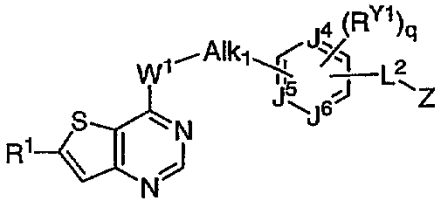
;

(11)



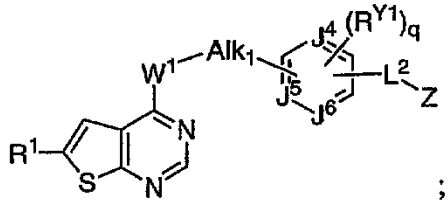
;

(12)



or

(13)



;

(14)

wherein R^1, 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

(i) R^1 is not Q^1, Q^2 or Q^3;

(ii) for compounds of formula **(12)**, the following groups do not occur simultaneously as defined: R^1 is Q_5; Z is optionally substituted aryl, carbocyle or 5-membered monocyclic heterocycle; Alk_1 is –N=CH-.

(iii) for compounds of formula **(14)**, the following groups do not occur simultaneously as defined: R^1 is Q_5; J^4, J^5 and J^6 are each CR^{Y1}; Z is optionally substituted aryl, carbocyle or 5-membered monocyclic heterocycle; Alk_1 is –N=CH-.

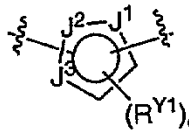
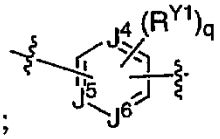
(iv) for compounds of formula **(13)** and **(14)**, the following groups do not occur simultaneously as defined: Z is optionally substituted phenyl; L^2 is $–OCH_2$- or $–OSO_2$-; W^1Alk_1 is–OCH(R)-, –OCH(R)-C_{1-6}alkylO- or –OCH(R)-C_{1-6}alkylC(=NR_x)- where R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl and R_x is H, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic; and R^1 is hydrogen, halogen or alkyl;

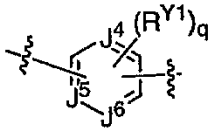
(v) for compounds of formula **(13)** and **(14)**, the following groups do not occur simultaneously as defined: W^1Alk_1 is $–NHCH_2CH_2$- or $–OCH_2CH_2$-; and L^2 is –C(R)=N-O-, wherein R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl; and R^1 is hydrogen, halogen or C_{1-4}alkyl;

(vi) for compounds of formula **(13)** and **(14)**, the following groups do not occur simultaneously as defined: W^1Alk_1 is $–OCH_2$-, or -N(R)CH_2-, wherein R is H or C_{1-8}alkyl; and Z is not a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl;

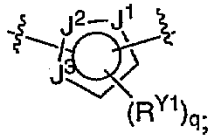
(vii) the following groups do not occur simultaneously as defined: R^1 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; W^1Alk_1 is $–NHC_{1-6}$alkyl, $–OC_{1-6}$alkyl, $–NHC_{1-6}$heteroalkyl or $–OC_{1-6}$heteroalkyl; L^2-Z is –X-R^x where X is –NR-, -C(=O)NH-, -NHC(=O)-, $-SO_2NH$- or $–NHSO_2$- and R^x is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl.

(viii) the following groups do not occur simultaneously as defined: W^1Alk_1 is $–NR(CR^x)_{1-2}$- or $–O(CR^x)_{1-2}$- wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, OH, NH_2

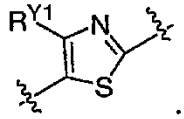
or $-C_{1-4}$alkylNH; and R^x is H or C_{1-4}alkyl;  is thienyl, furanyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl;  is phenyl, pyridyl, pyrimidyl or pyrazinyl; L^2-Z is $-SO_2NHC_{3-8}$cycloalkyl, $-SO_2N(C_{3-8}$cycloalkyl$)_2$, $-C(=O)NHC_{3-8}$cycloalkyl or $-C(=O)N(C_{3-8}$cycloalkyl$)_2$; and/or

(ix) the following groups do not occur simultaneously as defined: R^1 is hydrogen, halogen, nitro or C_{1-4}alkyl; W^1Alk_1 is $-NRC_{1-6}$alkyl- or $-OC_{1-6}$alkyl- wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}acyl;  is phenyl; L^2–Z is a C_{1-12}alkyl saturated or unsaturated hydrocarbon chain optionally including -NR- and optionally substituted with haloC_{1-4}alkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{1-4}acyl, phenoxy, phenyl or phenylthio.

[0205] In certain embodiments, in compounds of the formulae **(11)** and **(12)** the 5-membered ring having the structure:

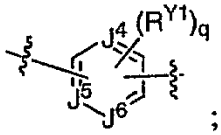


has the structure:



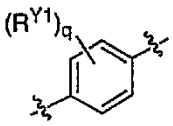
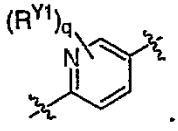
.

[0206] In certain embodiments, in compounds of the formulae **(13)** and **(14)** the 6-membered ring having the structure:



;

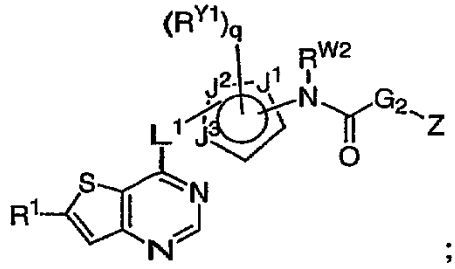
has one of the following structures:

.

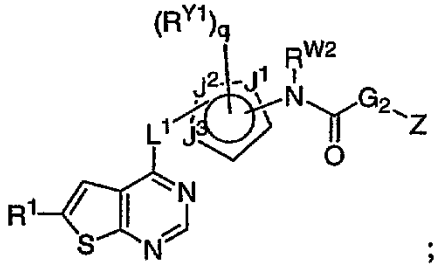
[0207] In certain embodiments, -W^1-Alk_1- is –NHC_{1-6}alkyl- or –OC_{1-6}alkyl-. In certain embodiments, -W^1-Alk_1- is –NHC_2alkyl- or –OC_2alkyl-. In certain embodiments, -W^1–Alk_1- is –$NHCH_2CH_2$-, –OCH_2CH_2- or –NH-$CH_2CH(CH_2OH)$-.

[0208] **VII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**



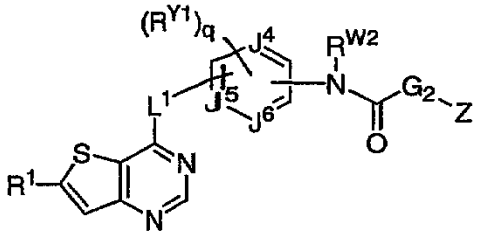
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(15)



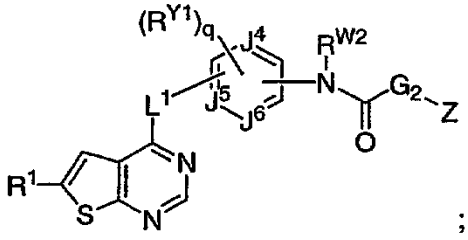
;

(16)



or

(17)



;

(18)

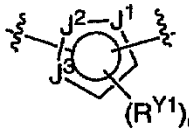
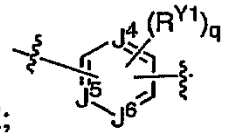
wherein R^1, L^1 and Z are as defined generally and in classes and subclasses herein; q is an integer from 0-3; J^1, J^2 and J^3 are independently O, S, N, NR^{Y1} or CR^{Yl}; J^4, J^5 and J^6 are independently N or CR^{Yl}; wherein each occurrence of R^{Y1} is independently hydrogen, alkyl, heteroalkyl, 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; 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

(i) R^1 is not Q^1, Q^2 or Q^3;

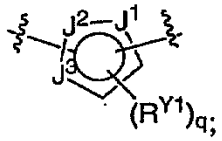
(ii) for compounds of formula **(16)** and **(18)**, the following groups do not occur simultaneously as defined: G_2 is absent; L^1 is $–OCH_2$-, $–CH_2O$-, -N(R)CH_2- or -

$CH_2N(R)$-, wherein R is H or C_{1-8}alkyl; and Z is a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl;

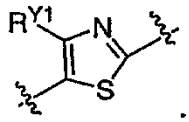
(iii) the following groups do not occur simultaneously as defined: G^2 is absent; R^1 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; L^1 is $-NHC_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$heteroalkyl or $-OC_{1-6}$heteroalkyl; and Z is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl; and/or

(iv) the following groups do not occur simultaneously as defined: G^2 is absent; L^1 is $-NR(CR^x)_{1-2}$- or $-O(CR^x)_{1-2}$- wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, OH, NH_2 or $-C_{1-4}$alkylNH; and R^x is H or C_{1-4}alkyl;  is thienyl, furanyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl;  is phenyl, pyridyl, pyrimidyl or pyrazinyl; R^{W2} is H or C_{3-8}cycloalkyl ; and Z is C_{3-8}cycloalkyl.

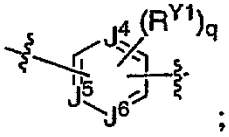
[0209] In certain embodiments, in compounds of the formulae **(15)** and **(16)** the 5-membered ring having the structure:



has the structure:

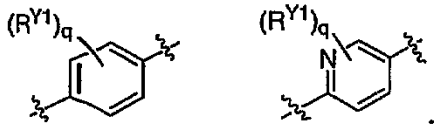


[0210] In certain embodiments, in compounds of the formulae **(17)** and **(18)** the 6-membered ring having the structure:



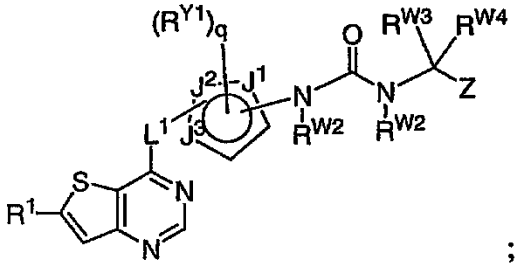
;

has one of the following structures:



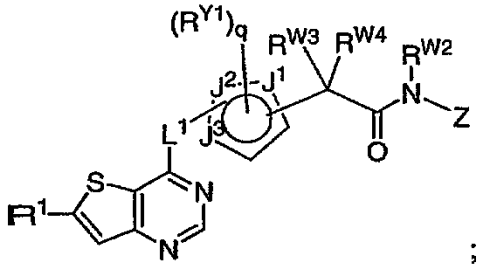
[0211] In certain embodiments, $-N(R^{W2})C(=O)G_2$- is $-NHC(=O)$-, $-NHC(=O)O$-, or $-NHC(=O)NH$-.

[0212] **VIII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**



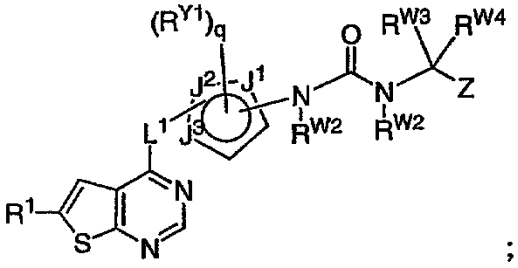
;

(19^A)



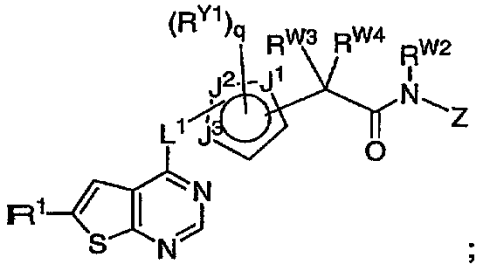
;

(20^A)



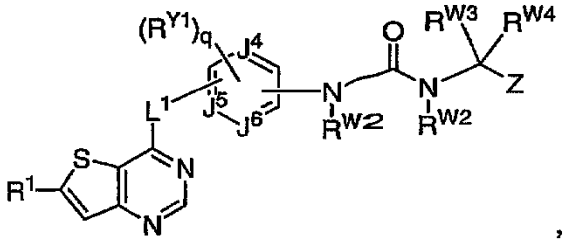
;

(19^B)

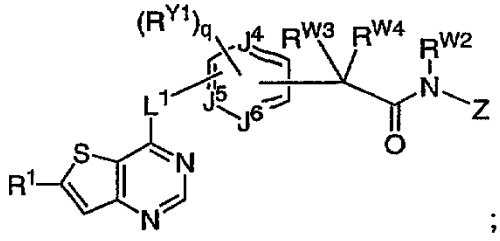


;

(20^B)



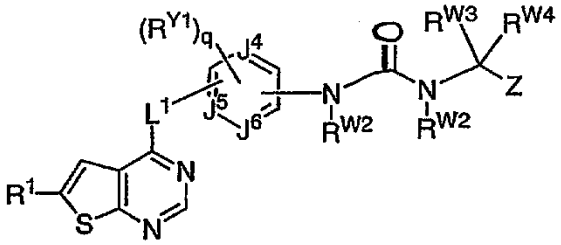
,



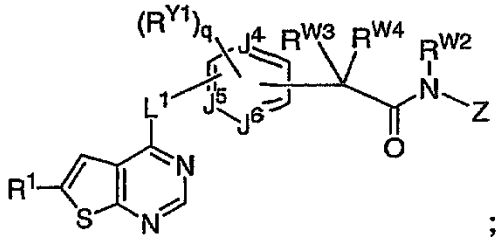
;

(21^A)

(22^A)



or



;

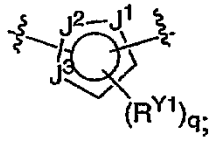
(21^B) (22^B)

wherein R^1, 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

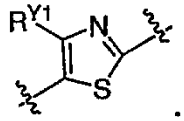
(i) R^1 is not Q^1, Q^2 or Q^3; and

(ii) for compounds of formula 20^{A-B} and 22^{A-B}, if (R^{W3}, R^{W4}) is (H,H), (F,F) or (H, C_{1-4}alkyl), then $-W^1-Alk_1-$ is not $-OCH_2-$ or $-N(R)CH_2-$, wherein R is H or C_{1-8}alkyl.

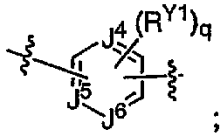
[0213] In certain embodiments, in compounds of the formulae **(19)** and **(20)** the 5-membered ring having the structure:



has the structure:

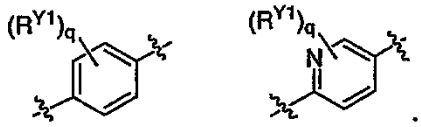


[0214] In certain embodiments, in compounds of the formulae **(21)** and **(22)** the 6-membered ring having the structure:



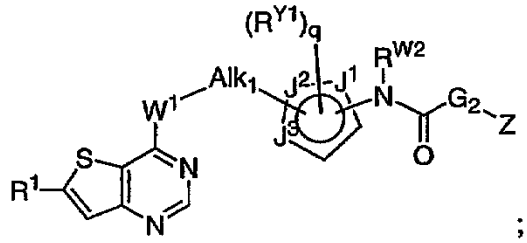
;

has one of the following structures:



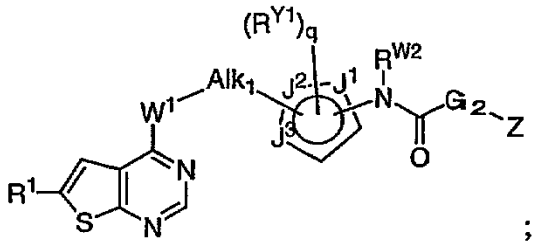
[0215] In certain embodiments, $-N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}-$ is $-NHC(=O)NHCH_2-$, and $-CR^{W3}R^{W4}C(=O)N(R^{W2})-$ is $-CH_2C(=O)NH-$.

[0216] IX. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



;

(23)



;

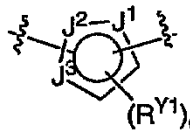
(24)

wherein R^1 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

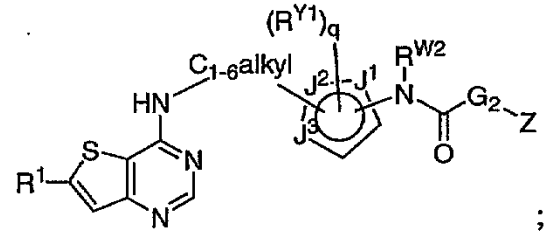
(i) R^1 is not Q^1, Q^2 or Q^3;

(ii) for compounds of formula (23) and (24), the following groups do not occur simultaneously as defined: G_2 is absent; L^1 is $-OCH_2-$, $-CH_2O-$, $-N(R)CH_2-$ or $-CH_2N(R)-$, wherein R is H or C_{1-8}alkyl; and Z is not a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl;

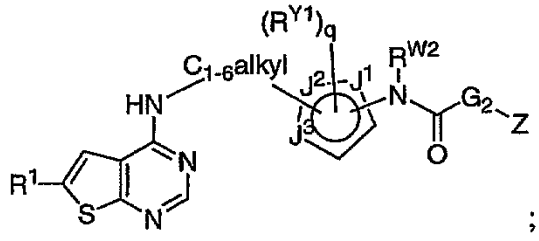
(iii) the following groups do not occur simultaneously as defined: G^2 is absent; R^1 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; W^1Alk_1 is $-NHC_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$heteroalkyl or $-OC_{1-6}$heteroalkyl; and Z is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl; and/or

(iv) the following groups do not occur simultaneously as defined: G^2 is absent; W^1Alk_1 is $-NR(CR^x)_{1-2}-$ or $-O(CR^x)_{1-2}-$ wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, OH, NH_2 or $-C_{1-4}$alkylNH; and R^x is H or C_{1-4}alkyl;  is thienyl, furanyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl; R^{W2} is H or C_{3-8}cycloalkyl ; and Z is C_{3-8}cycloalkyl.

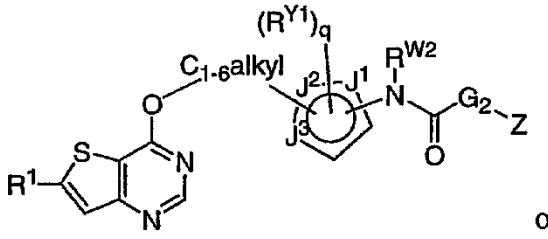
[0217] In certain embodiments, compounds of this class have the structure (23^A), (23^B), (24^A) or (24^B) below:



(23^A)

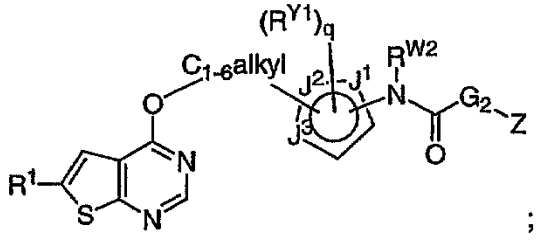


(23^A)



(24^B)

or



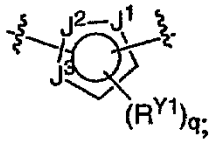
(24^B)

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

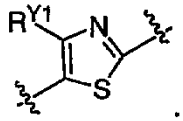
[0218] In certain embodiments, for compounds of formulae (23) and (24), $-W^1-Alk1-$ is $-NHC_2$alkyl- or $-OC_2$alkyl-. In certain embodiments, $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

[0219] In certain embodiments, for compounds of formulae (23), (24), (23^A), (23^B), (24^A) and (24^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 $-CH_2CH_2-$.

[0220] In certain embodiments, in compounds of the formulae (23), (24), (23^A), (23^B), (24^A) and (24^B) the 5-membered ring having the structure:

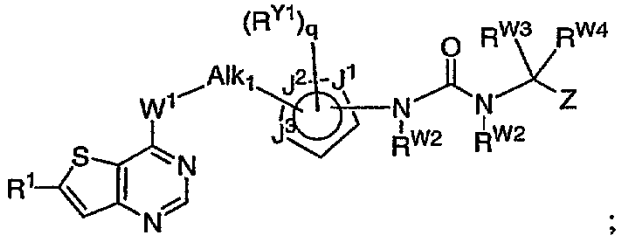


has the structure:

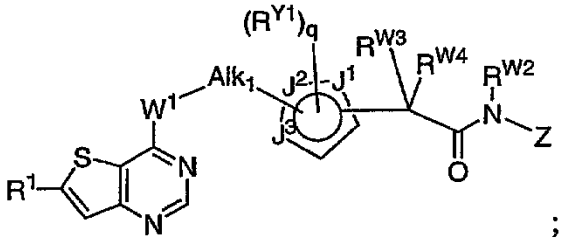


In certain embodiments, $-N(R^{W2})C(=O)G_2-$ is –NHC(=O)-, –NHC(=O)O-, or –NHC(=O)NH-.

[0221] X. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):

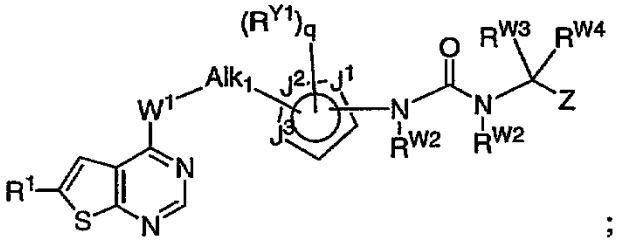


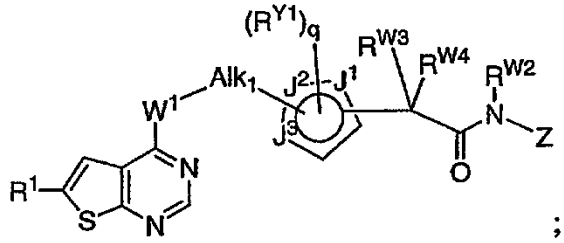
;



;

(25) (26)


;


;

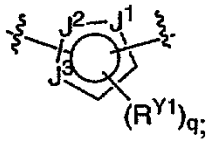
(27) (28)

wherein R^1 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

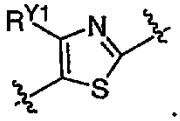
(i) R^1 is not Q^1, Q^2 or Q^3.

[0222] 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-$CH_2CH(CH_2OH)$-.

[0223] In certain embodiments, in compounds of the formulae (25), (26), (27) and (28), the 5-membered ring having the structure:

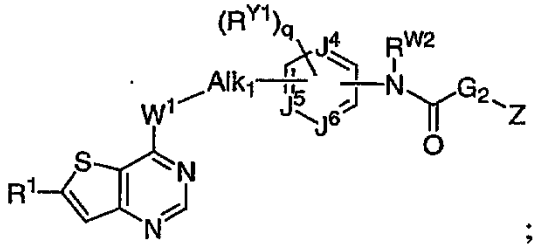


has the structure:



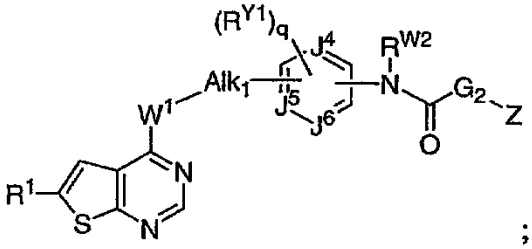
[0224] In certain embodiments, -$N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}$- is –$NHC(=O)NHCH_2$-, and -$CR^{W3}R^{W4}C(=O)N(R^{W2})$- is –$CH_2C(=O)NH$-.

[0225] **XI. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**



;

(29)



;

(30)

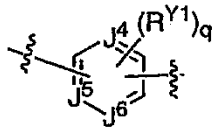
wherein R^1 and Z are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

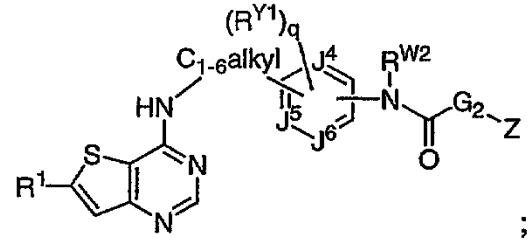
(i) R^1 is not Q^1, Q^2 or Q^3;

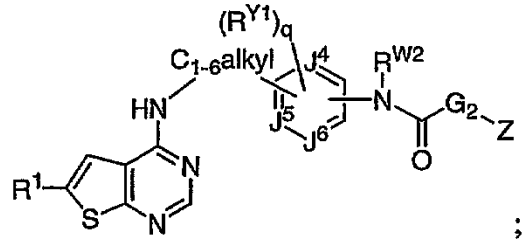
(ii) the following groups do not occur simultaneously as defined: G_2 is absent; W^1Alk_1 is $-OCH_2-$ or $-N(R)CH_2-$, wherein R is H or C_{1-8}alkyl; and Z is a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl;

(iii) the following groups do not occur simultaneously as defined: G^2 is absent; R^1 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; W^1Alk_1 is $-NHC_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$heteroalkyl or $-OC_{1-6}$heteroalkyl; and Z is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl; and/or

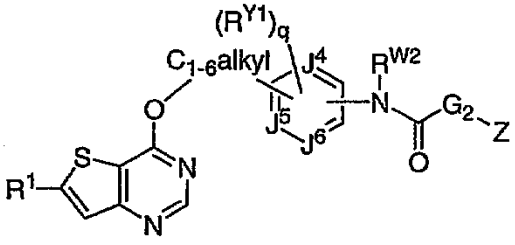
(iv) the following groups do not occur simultaneously as defined: G^2 is absent; W^1Alk_1 is $-NR(CR^x)_{1-2}-$ or $-O(CR^x)_{1-2}-$ wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, OH, NH_2 or $-C_{1-4}$alkylNH; and R^x is H or C_{1-4}alkyl;  is phenyl, pyridyl, pyrimidyl or pyrazinyl; R^{W2} is H or C_{3-8}cycloalkyl ; and Z is C_{3-8}cycloalkyl.

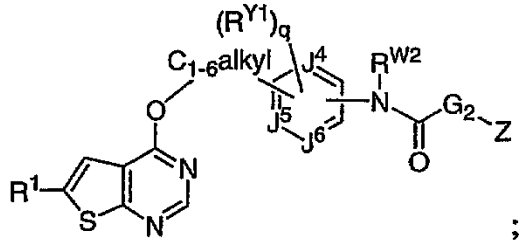
[0226] In certain embodiments, the compounds have the following structures:


;


;

(29^A) **(30^A)**


or


;

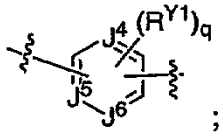
(29^B) (30^B)

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

[0227] In certain embodiments, for compounds of formulae **(XX)** and **(XXI)**, -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-$CH_2CH(CH_2OH)$-.

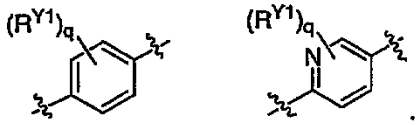
[0228] In certain embodiments, for compounds of formulae **(29)**, **(30)**, (29^A), (29^B), (30^A) and (30^B) the C_{1-6}alkyl moiety is a substituted or unsubstituted C_2alkyl moiety. In certain exemplary embodiments, the C_{1-6}alkyl moiety is -CH_2CH_2-.

[0229] In certain embodiments, in compounds of the formulae **(29)** and **(30)** the 6-membered ring having the structure:



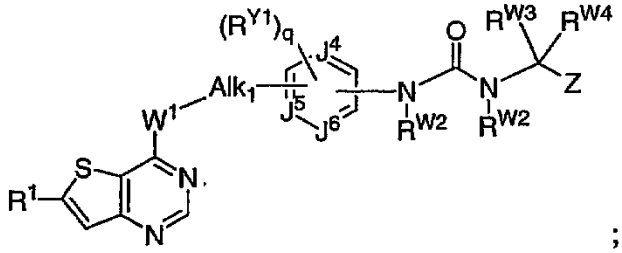
;

has one of the following structures:

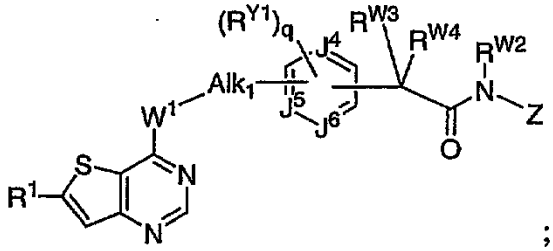


In certain embodiments, -$N(R^{W2})C(=O)G_2$- is –NHC(=O)-, –NHC(=O)O-, or –NHC(=O)NH-.

[0230] **XII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):**

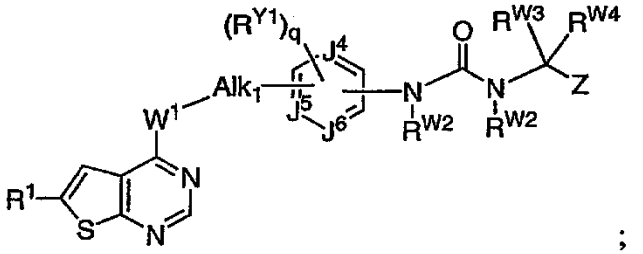


;

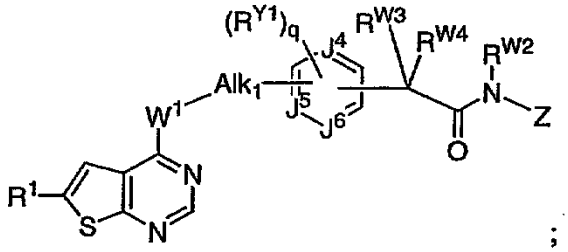


;

(31) **(32)**



;



;

(33) (34)

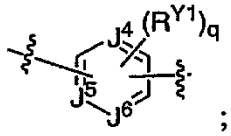
wherein R^1 and Z are as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

(i) R^1 is not Q^1, Q^2 or Q^3; and

(ii) for compounds of structure **(32)** or **(34)**, if (R^{W3}, R^{W4}) is (H,H), (F,F) or (H, C_{1-4}alkyl), then $-W^1-Alk_1-$ is not $-OCH_2-$ or $-N(R)CH_2-$, wherein R is H or C_{1-8}alkyl.

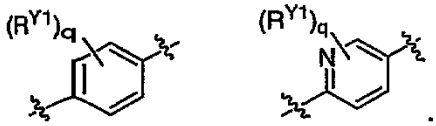
[0231] In certain embodiments, $-W^1-Alk_1-$ is $-NHC_{1-6}$alkyl- or $-OC_{1-6}$alkyl-. In certain embodiments, $-W^1-Alk_1-$ is $-NHC_2$alkyl- or $-OC_2$alkyl-. In certain embodiments, $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

[0232] In certain embodiments, in compounds of the formulae **(31)** - **(34)** the 6-membered ring having the structure:



;

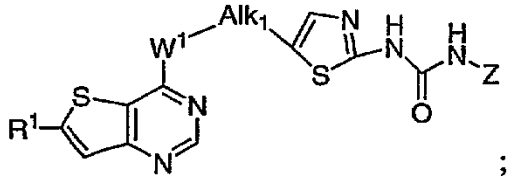
has one of the following structures:



[0233] In certain embodiments, $-N(R^{W2})C(=O)G_2-$ is $-NHC(=O)-$, $-NHC(=O)O-$, or $-NHC(=O)NH-$.

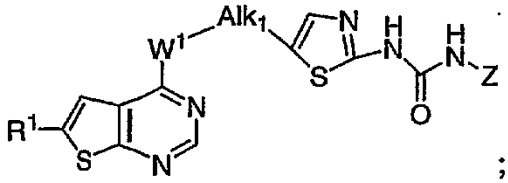
[0234] In certain embodiments, $-N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}-$ is $-NHC(=O)NHCH_2-$, and $-CR^{W3}R^{W4}C(=O)N(R^{W2})-$ is $-CH_2C(=O)NH-$.

[0235] XIII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



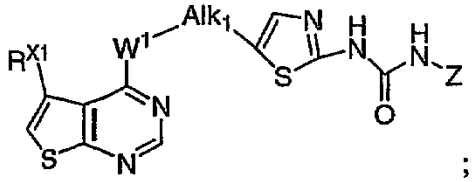
;

(35)



; or

(36)



;

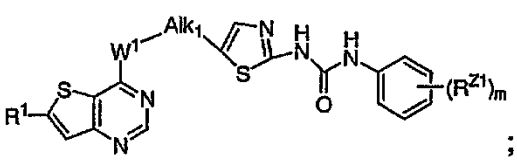
(37)

wherein R^1 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; each occurrence of R^{Z1} is indenpendently 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

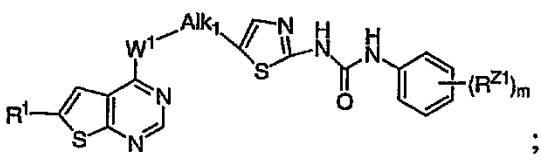
(i) neither R^1 nor R^{X1} is Q^1, Q^2 or Q^3.

In certain embodiments,$-W^1-Alk_1-$ is $-NH-C_{1-6}$alkyl- or $-O-C_{1-6}$alkyl-; wherein the C_{1-6}alkyl moiety may be substituted or unsubstituted. 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 $-NH-CH_2CH(CH_2OH)-$.

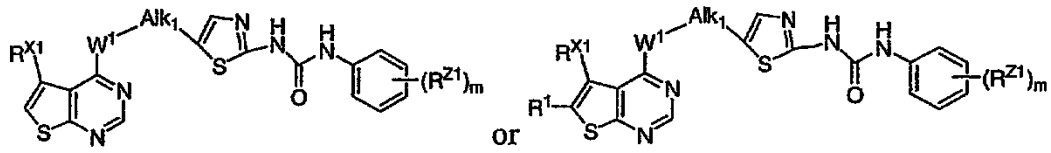
[0236] XIV. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



; (38)



; (39)



(40) (41)

wherein R^1 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 indenpendently 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

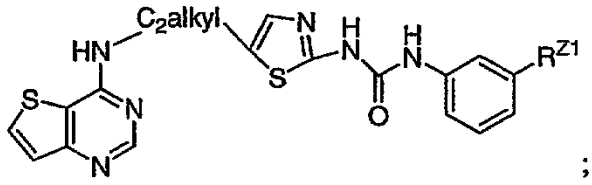
(i) neither R^1 nor R^{X1} is Q^1, Q^2 or Q^3.

[0237] In certain embodiments, for compounds of groups **XIII** and **XIV**, $-W^1-Alk_1-$ 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 $-NH-CH_2CH(CH_2OH)-$.

[0238] In certain embodiments, for compounds of groups **XIII** and **XIV**, R^1 is hydrogen, halogen, heterocyclyl, aryl or heteroaryl. In certain exemplary embodiments, R^1 is hydrogen.

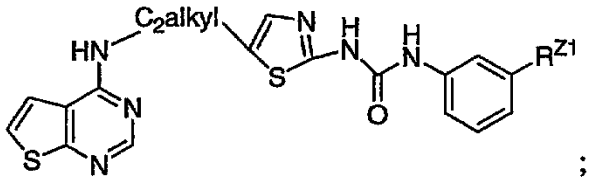
[0239] In certain embodiments, for compounds of group **XIV**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is halogen, lower alkyl or lower haloalkyl.

[0240] In certain embodiments, compounds of group **XIV** have the structure:



; or

(38^A)

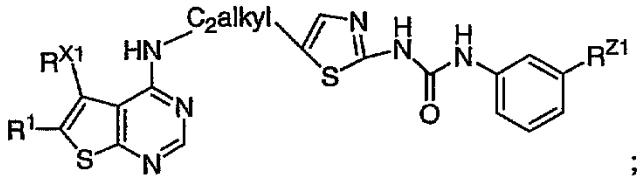


;

(39^A)

wherein 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 $-CF_3$.

[0241] In certain embodiments, compounds of group **XIV** have the structure:

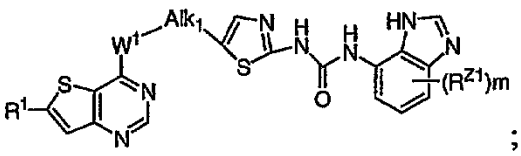


;

(41^A)

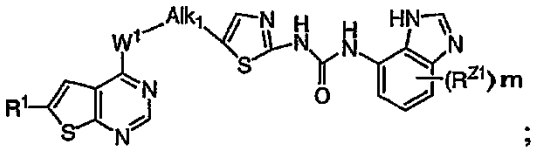
wherein R^1 is hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is halogen, lower alkyl or lower haloalkyl. In certain exemplary embodiments, R^1 is hydrogen, methyl, $-CO_2H$ or $-CO_2Me$; R^{X1} is hydrogen, methyl or thienyl; and R^{Z1} is Cl, F, methyl or $-CF_3$.

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



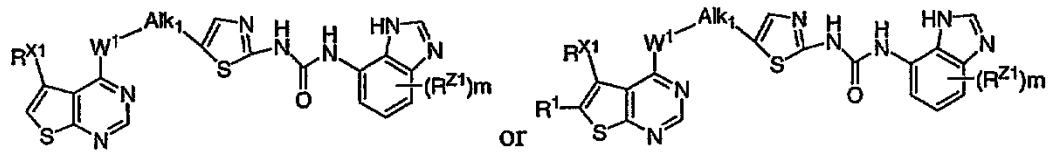
;

(42)



;

(43)



(44) (45)

wherein R^1 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 indenpendently 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

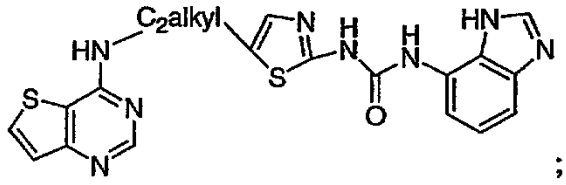
(i) neither R^1 nor R^{X1} is Q^1, Q^2 or Q^3.

[0243] 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, -W1-Alk1- is $-NHC_2$alkyl- or $-OC_2$alkyl-. In certain embodiments, $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

[0244] In certain embodiments, for compounds of group **XV**, R^1 is hydrogen, halogen, heterocyclyl, aryl or heteroaryl. In certain exemplary embodiments, R^1 is hydrogen.

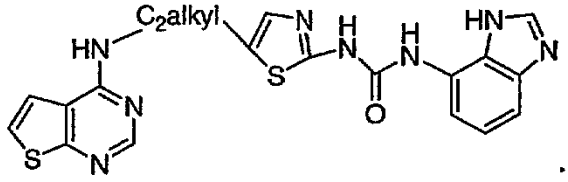
[0245] In certain embodiments, for compounds of group **XV**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 0.

[0246] In certain embodiments, compounds of group **XV** have the structure:



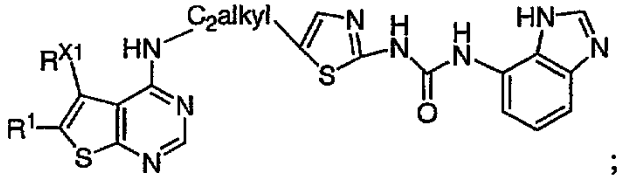
; or

(42^A)



(43^A)

[0247] In certain embodiments, compounds of group **XV** have the structure:

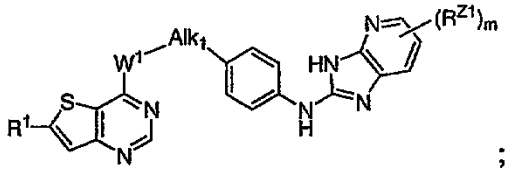


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(45^A)

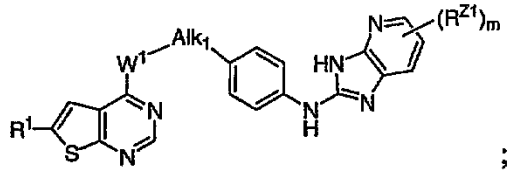
wherein R^1 is hydrogen, lower alkyl or $-CO_2R^{1A}$ where R^{1A} is hydrogen or lower alkyl; and R^{X1} is hydrogen, lower alkyl or heterocyclyl. In certain exemplary embodiments, R^1 is hydrogen, methyl, $-CO_2H$ or $-CO_2Me$; R^{X1} is hydrogen, methyl or thienyl.

[0248] XVI. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



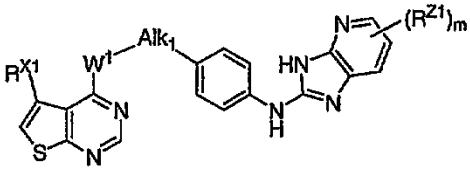
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(46)



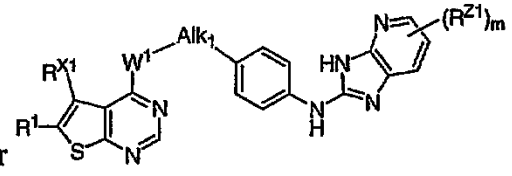
;

(47)



or

(48)



(49)

wherein R^1 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 indenpendently 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. In certain embodiments, the invention encompasses the compounds described directly above with the proviso that:

(i) neither R^1 nor R^{X1} is Q^1, Q^2 or Q^3; and

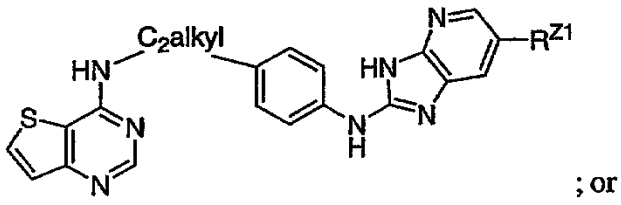
(ii) –W^1-Alk_1- is not –OCH_2- or -N(R)CH_2-, wherein R is H or C_{1-8}alkyl.

[0249] In certain embodiments, for compounds of group **XVI**, -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-$CH_2CH(CH_2OH)$-.

[0250] In certain embodiments, for compounds of group **XVI**, R^1 is hydrogen, halogen, heterocyclyl, aryl or heteroaryl. In certain exemplary embodiments, R^1 is hydrogen.

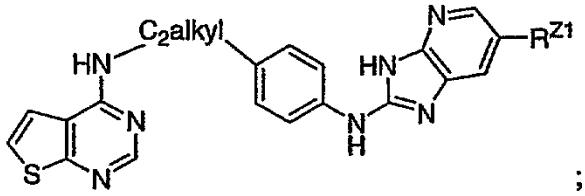
[0251] In certain embodiments, for compounds of group **XVI**, R^{Z1} is hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is Cl, F, methyl or –CF_3. In certain embodiments, m is 1 and R^{Z1} is lower haloalkyl. In certain embodiments, m is 1 and R^{Z1} is –CF_3.

[0252] In certain embodiments, compounds of group **XVI** have the structure:



; or

(46^A)

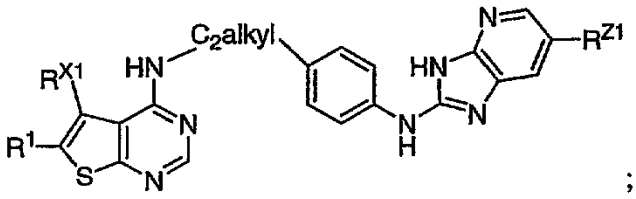


;

(47^A)

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

[0253] In certain embodiments, compounds of group **XVI** have the structure:

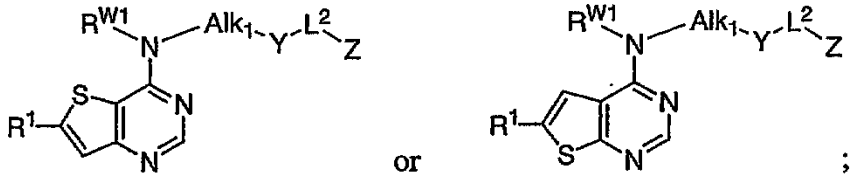


;

(49^A)

wherein R^1 is 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^1 is hydrogen, methyl, $-CO_2H$ or $-CO_2Me$; R^{X1} is hydrogen, methyl or thienyl; and R^{Z1} is Cl, F, methyl or $-CF_3$.

[0254] XVII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):

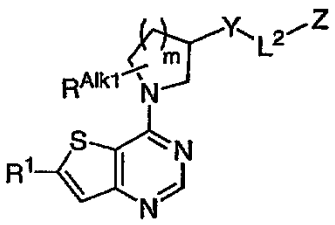


or ;

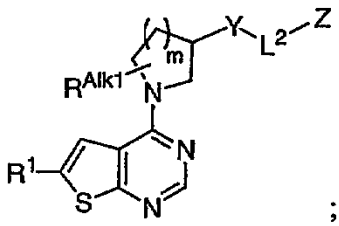
(50) **(51)**

wherein R^1, 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.

[0255] In certain embodiments, compounds of the invention have the structure (1^A) or (2^A) below:



or

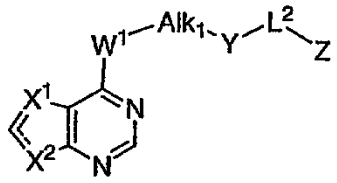


;

(50^A) (51^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.

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



(52)

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

one of X^1 and X^2 is S, the other is $-C(R^{X1})-$; wherein R^{X1} is hydrogen, halogen, cyano, nitro, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

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; or R^{W1} together with a carbon atom present on Alk_1 forms an optionally substituted 5- to 6-membered heterocyclic 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;

L^2 is $-NR^{W2}-$, $-N(R^{W2})C(=O)G_2-$, $-N(R^{W2})C(=O)N(R^{W2})CR^{W3}R^{W4}-$ or $-CR^{W3}R^{W4}C(=O)N(R^{W2})-$; wherein G_2 is absent, O or NR^{G2}; and R^{W2}, R^{W3}, R^{W4} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl;

Y is an optionally substituted phenyl or thiazolyl ring;

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

with the proviso that (a) R^{X1} is not 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); and

(b) in any one or more of the following groups, the recited variables do not occur simultaneously as defined:

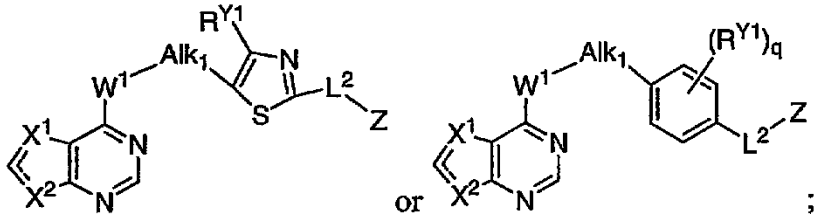
(i) $-W^1-Alk_1-$ is $-OCH_2-$ or $-N(R)CH_2-$, wherein R is H or C_{1-8}alkyl; Y is phenyl; and Z is a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl;

(ii) R^{X1} is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; $-W^1-Alk_1-$ is $-NHC_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$heteroalkyl or $-OC_{1-6}$heteroalkyl; L^2-Z is $-X-R^x$ where X is –NR- or -NHC(=O)-, and R^x is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl; and

(iii) one of X^1 and X^2 is S, the other is CR^{XA} wherein R^{XA} is hydrogen, C_{1-4}alkyl or phenyl optionally substituted with halogen, (halo)C_{1-4}alkyl or (halo)C_{1-4}alkoxy; $-W^1-Alk_1-$ is $-NRC_{1-6}$alkyl-, $-OC_{1-6}$alkyl- or $-SC_{1-6}$alkyl- wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}acyl; Y is phenyl; L^2–Z is a C_{1-12}alkyl saturated or unsaturated hydrocarbon chain including -NR- and optionally substituted with haloC_{1-4}alkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{1-4}acyl, phenoxy, phenyl or phenylthio.

[0257] In certain embodiments, $\mathbf{X^1}$ is S and $\mathbf{X^2}$ is CH. In certain embodiments, $\mathbf{X^1}$ is CH and $\mathbf{X^2}$ is S. In certain embodiments, $\mathbf{L^2}$ is NH, –NHC(=O)-, –NHC(=O)O-,–NHC(=O)NH-, –NHC(=O)NHCH$_2$-, or –CH$_2$C(=O)NH-.

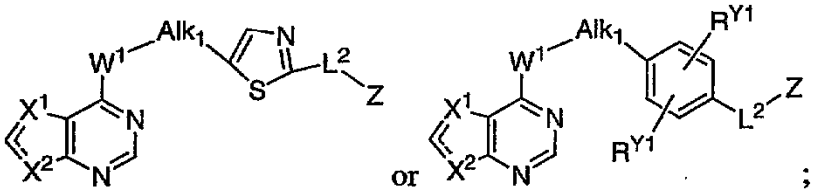
[0258] In certain embodiments, compounds of subgroup **XVIII** have the following structure:



(53) (54)

wherein q is 1-4; one of X^1 and X^2 is S and the other is –CH-; and 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.

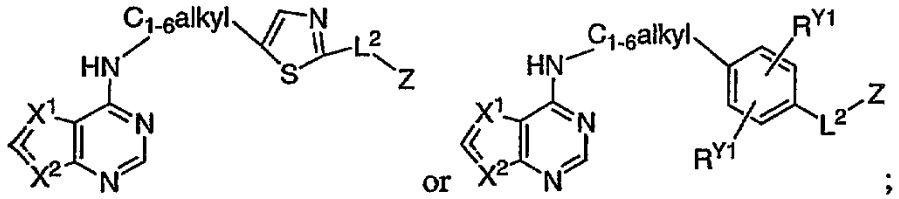
[0259] In certain embodiments, compounds of subgroup **XVIII** have the following structure:



(55) (56)

wherein W^1 is O or 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 C_{1-6}alkylene or C_{2-6}alkenylene moiety; and each occurrence of R^{Y1} is independently hydrogen, halogen or lower alkyl.

[0260] In certain embodiments, compounds of subgroup **XVIII** have the following structure:



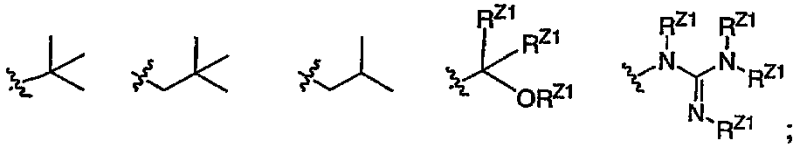
(57) (58)

wherein L^2 is NH, –NHC(=O)-, –NHC(=O)O-,–NHC(=O)NH-, –NHC(=O)$NHCH_2$-, or $–CH_2C(=O)NH$-.

[0261] In certain embodiments for compounds as described in subgroups **I-XVII** above, R^1 is hydrogen.

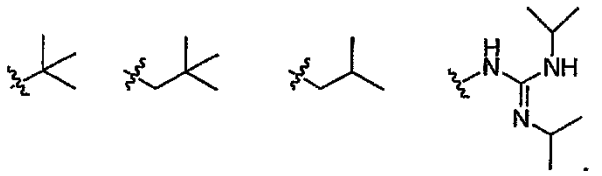
[0262] In certain embodiments, for compounds as described in subgroups **I-XVIII** above, R^{W1} together with a carbon atom present on Alk_1 forms an optionally substituted 5- to 6-membered heterocyclic ring.

[0263] In certain embodiments, for compounds as described in subgroups **I-XIII** and **XVII-XVIII** above, Z is a branched alkyl, alkenyl, alkynyl, heteroalkyl or heteroalkenyl moiety. In certain exemplary embodiments, Z has one of the following structures:



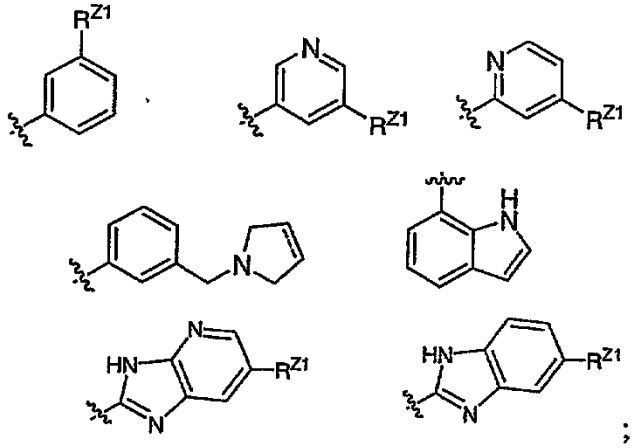
;

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:



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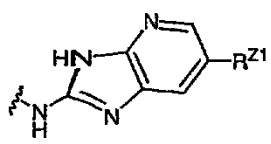
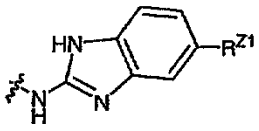
[0264] In certain embodiments, for compounds as described in subgroups **I-XIII** and **XVII-XVIII** above, Z is a cycloalkyl, cycloalkenyl, heterocyclyl, aryl or heteroaryl moiety. In certain exemplary embodiments, Z has one of the following structures:



;

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

[0265] In certain embodiments, for compounds as described in subgroups **I, IV-VI** and **XVII-XVIII** above, $-L^2-Z$ together represent a moiety having one of the following structures:

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

[0266] It will also be appreciated that for each of the subgroups **I-XVIII** described above, a variety of other subclasses are of special interest, including, but not limited to those classes described above i)- cxvi) and classes, subclasses and species of compounds described above and in the examples herein.

[0267] 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.

[0268] 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.

[0269] 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.

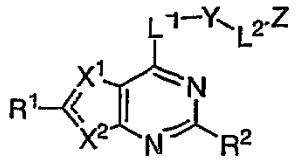
[0270] *2) Synthetic Overview:*

[0271] The practitioner has a a well-established literature of thienopyrimidine 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^1 and R^2 substituents and L^1, L^2, Y and Z moieties.

[0272] The various patent documents and other references cited herein provide helpful background information on preparing compounds similar to the inventive compounds described herein or relevant intermediates. Certain cited patent documents also contain information on formulation, uses, and administration of such compounds which may be of interest. For example, guidance may be found in U.S. Patent Nos.: 6,169,091; 5,227,387; 5,654,307 and 5,859,020; European Patent Application No.: EP 452002 and International Application Nos.: WO 97/09316, WO 01/32632 and WO 03/64428. Although U.S. Patent No.: 6,541,481 does not specifically disclose thienopyrimidines, the synthetic guidance provided therein may be adapted to generate compounds of the invention.

[0273] Moreover, the practitioner is directed to the specific guidance and examples provided in this document relating to various exemplary compounds and intermediates thereof.

[0274] As described above, the present invention provides novel compounds, specifically compounds having the following general structure:

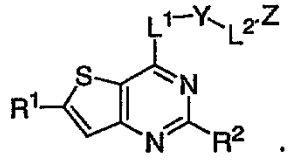


(I)

and pharmaceutically acceptable derivatives thereof;

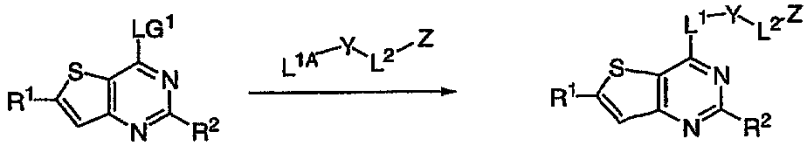
wherein R^1, R^2, X^1, X^2, L^1, L^2, Y and Z are as defined in classes and subclasess herein.

[0275] 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 thieno[3,2d]pyrimidines having the Formula (I^A):



(I^A)

[0276] In yet another aspect of the invention, methods for producing intermediates useful for the preparation of compounds of formulae (I) and (I^A) are provided, embodiments of said methods being depicted generally in Scheme A:

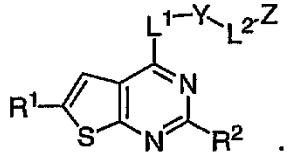


(1) (I^A)

Scheme A

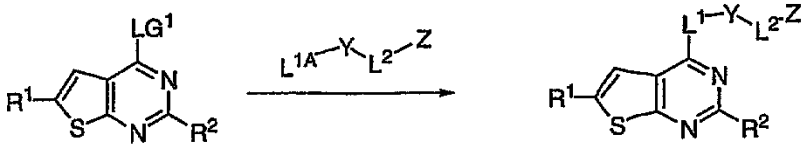
where LG^1 is a suitable leaving group and L^{1A} is adapted to displace LG^1 upon reaction with thieno[3,2d]pyrimidine (1).

[0277] In other embodiments, one class of compounds of special interest includes thieno[2,3d]pyrimidines having the Formula (I^B):



(I^B)

[0278] In yet another aspect of the invention, methods for producing intermediates useful for the preparation of compounds of formulae (I) and (I^B) are provided, embodiments of said methods being depicted generally in Scheme B:

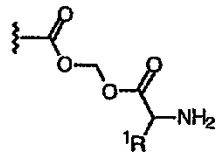


(1) (I^A)

Scheme B

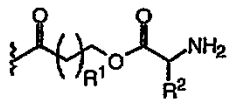
where LG^1 is a suitable leaving group and L^{1A} is adapted to displace LG^1 upon reaction with thieno[2,3d]pyrimidine (2).

[0279] 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:



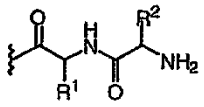
R^1 = all natural, unnatural amino acids

For the synthesis of the prodrug groups, see Borchardt, R. T. et. al., *J. Org. Chem. 1997, 43,* 3641-3652.



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.

[0280] 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.

[0281] **3) Pharmaceutical Compositions**

[0282] 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.

[0283] 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.

[0284] 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.

[0285] 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.

[0286] 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; 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.

[0287] *Uses of Compounds and Pharmaceutically acceptable compositions*

[0288] *Research Uses*

[0289] 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.

[0290] In certain exemplary embodiments, compounds of this invention were assayed for their ability to inhibit protein kinases, more specifically Aurora.

[0291] 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).

[0292] 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.

[0293] 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.

[0294] 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.

[0295] 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.

[0296] 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.

[0297] 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.

[0298] 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.

[0299] 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.

[0300] 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.

[0301] 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.

[0302] 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.

[0303] 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.

[0304] 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.

[0305] 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.

[0306] 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.

[0307] 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.

[0308] 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".

[0309] 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).

[0310] 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.

[0311] 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.

[0312] 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.

[0313] 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.

[0314] 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.

[0315] 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

[0316] 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

[0317] 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.

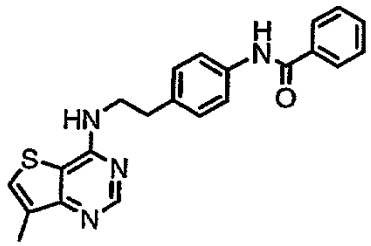
[0318] The following examples contain important additional information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and the equivalents thereof.

EXEMPLIFICATION

[0319] 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.

[0320] **Example 1**

[0321] This example describes the synthesis of



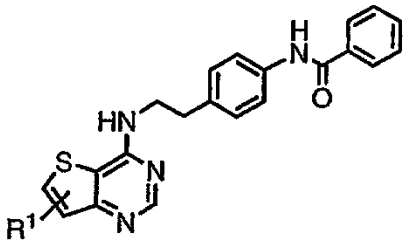
[0322] **Step1:** A solution of [2-(4-amino-phenyl)-ethyl]-carbamic acid tert-butyl ester (compound **1.1**; 1.0 mmol, prepared according to the procedure of Hah, J.M. et. al *J. Med. Chem 46*, **2003**, 1661) and triethylamine ("TEA"; 3.0 equivalents) in anhydrous tetrahydrofuran ("THF"; 5.0 mL) is treated with the dropwise addition of benzoyl chloride (1.1 equivalents) at 0 °C. After completion of the reaction, the mixture is partitioned between water and diethyl ether. The organic layer is separated, washed with 1.0 N HCl, saturated sodium bicarbonate, brine and dried. Purification by flash column chromatography on silica gel provides [2-(4-benzoylamino-phenyl)-ethyl]-carbamic acid tert-butyl ester (compound **1.2**).

[0323] **Step 2:** Compound **1.2** (1.0 mmol), is treated with anhydrous 4.0 N HCl in dioxane (25 mL) at 0 °C, stirred at room temperature for 2 hours and concentrated to dryness under reduced pressure. The crude amine salt, 4-chloro-7-methylthieno[3,2-d]pyrimidine (1.0 equiv.) and *N,N*-diisopropylethylamine ("DIEA"; 2.5 equivalents) is then heated in *n*-butanol (10 mL) at 135 °C for 2 hours. The reaction mixture is cooled and then partitioned between dichloromethane and water. The organic layer is separated, washed with brine, dried and concentrated under reduced pressure. The

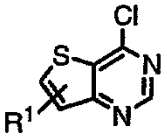
titled compound is precipitated from ethyl acetate ("EtOAc") and methanol ("MeOH") with hexanes.

[0324] Example 2

[0325] This example describes the synthesis of

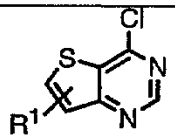
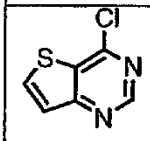
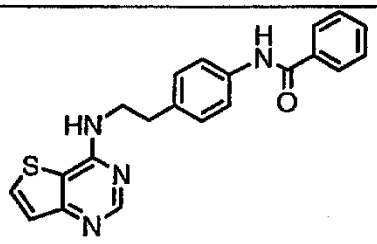
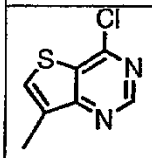
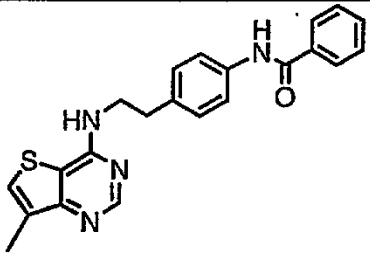
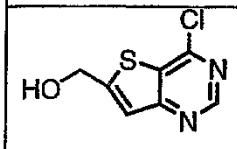
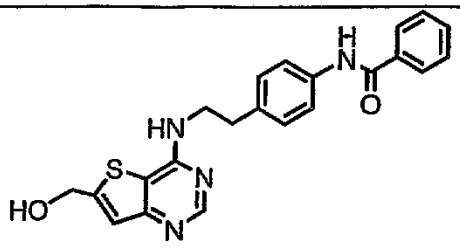


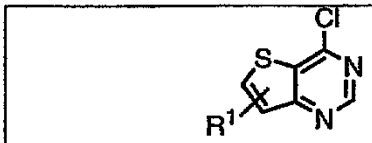
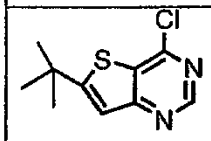
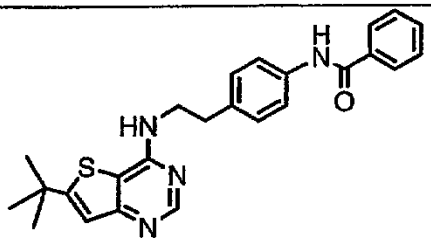
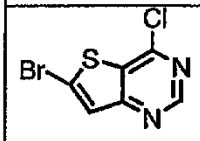
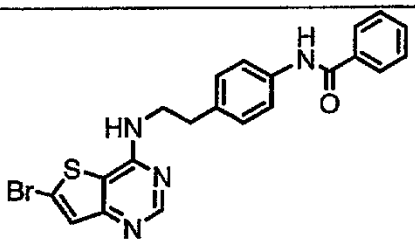
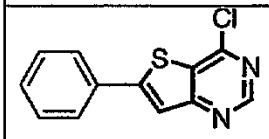
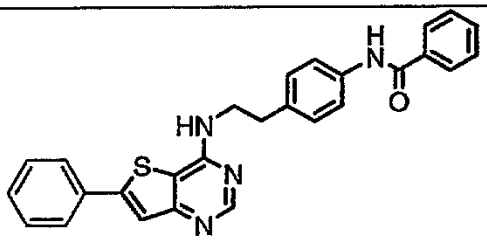
where R^1 is as described previously. These compounds are made according to the procedures of Example 1 except that



is used instead of 4-chloro-7-methylthieno[3,2-d]pyrimidine in step 2. Illustrative examples of R^1's are found throughout this disclosure as well as in Table 1.

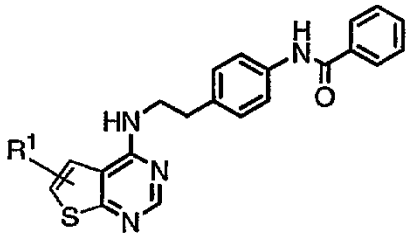
[0326] Table 1

	Final Compound
	
	
	

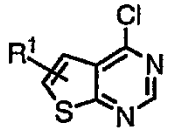
	Final Compound
	
	
	
	

[0327] **Example 3**

[0328] This example describes the synthesis of

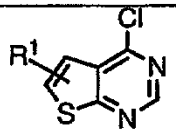
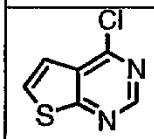
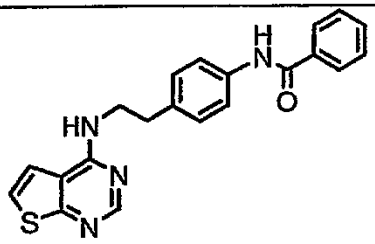
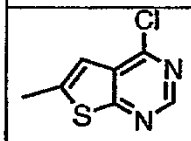
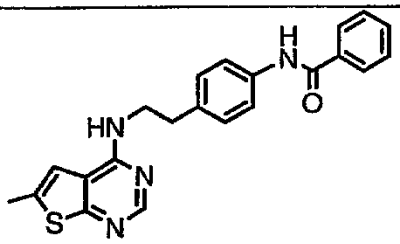
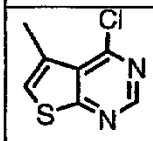
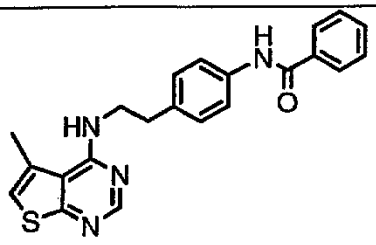


where R^1 is as described previously. These compounds are made according to the procedures of Example 1 except that



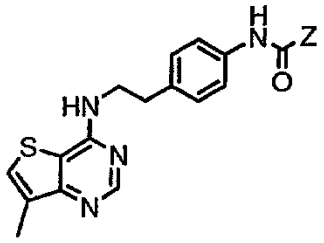
is used instead of 4-chloro-7-methylthieno[3,2-d]pyrimidine in step 2. Illustrative examples of R^1's are found throughout this disclosure as well as in Table 2.

[0329] **Table 2**

	Final Compound
	
	
	

[0330] **Example 4**

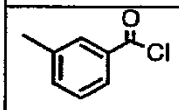
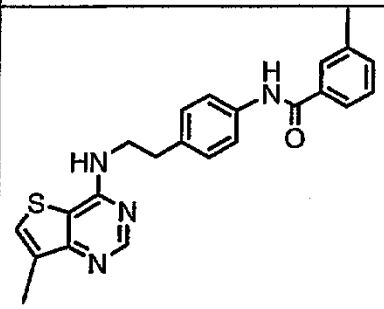
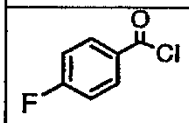
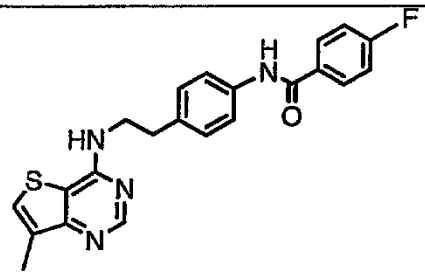
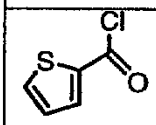
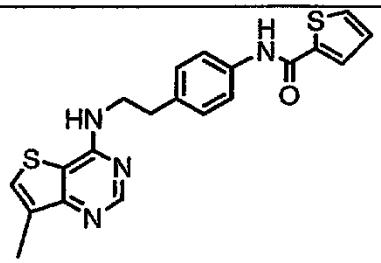
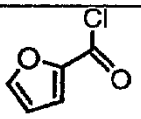
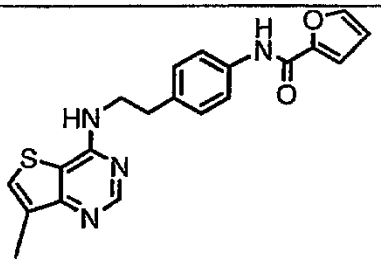
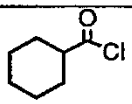
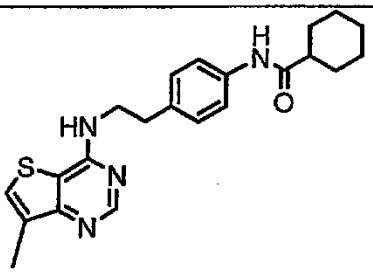
[0331] This example describes the synthesis of



where Z is as described previously. These compounds are made according to the procedures of Example 1 except that  is used instead of benzoyl chloride in step 1. Illustrative examples of Z's are found throughout this disclosure as well as in Table 3.

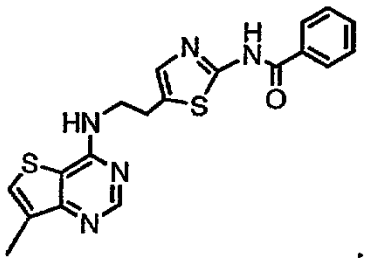
[0332] **Table 3**

	Final Compound

	Final Compound
	
	
	
	
	

[0333] **Example 5**

[0334] This example describes the synthesis of

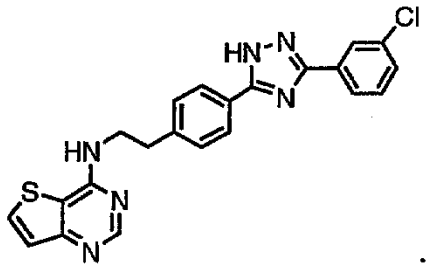


[0335] A solution of di-*tert*-butyl dicarbonate (0.5 equivalents) in anhydrous dioxane (3.0 mL) is added dropwise to a solution of 5-(2-amino-ethyl)-thiazol-2-ylamine (1.0 mmol, prepared according to the procedure of Eriks, J. C. et. al. *J. Med. Chem. 35,* **1992**, 3239) in anhydrous dioxane (3.0 mL) at room temperature. After completion of the reaction, the solvents are removed under reduced pressure and the desired product, [2-(2-amino-thiazol-5-yl)-ethyl]-carbamic acid tert-butyl ester (compound **5.1**), is purified by flash column chromatography on silica gel.

[0336] The titled compound is made according to the procedures of Example 1 except that compound **5.1** is used in step 1 instead of compound **1.1**.

[0337] **Example 6**

[0338] This example describes the synthesis of



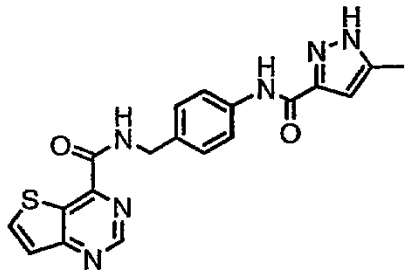
[0339] **Step 1:** 4-(2-Amino-ethyl)-benzonitrile (compound **6.1** (1.0 mmol), 4-chloro-thieno[3,2-d]pyrimidine (compound **6.2**; 1.0 equiv.) and DIEA (2.5 equivalents) is heated in *n*-butanol (10 mL) at 135 °C for 2 hours. The reaction mixture is cooled and then partitioned between dichloromethane and water. The organic layer is separated, washed with brine, dried and concentrated under reduced pressure. The desired product, 4-[2-(thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-benzonitrile (compound **5.3**), is precipitated from EtOAc with hexanes.

[0340] **Step 2:** Compound **6.3** is treated with sodium methoxide ("NaOMe") in MeOH according to a procedure found in Lipinski, C. A. et. al. *J. Med. Chem. 28,* **1985**, 1628 to yield 4-[2-(thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-benzimidic acid methyl ester (compound **6.4**).

[0341] **Step 3:** The titled compound is obtained by the reaction of compound **6.4** and 3-chloro-benzoic acid hydrazide by heating in MeOH.

[0342] **Example 7**

[0343] This example describes the synthesis of



[0344] **Step 1:** Compound **6.2** is reacted with potassium cyanide according to a procedure in Miyashita, A. et. al. (*Heterocycles 39,* **1994**, 345) to yield thieno[3,2-d]pyrimidine-4–carbonitrile (compound **7.1**).

[0345] **Step 2:** A solution of compound **7.1** (1.0 mmol) in concentrated HCl (20 mL) is stirred at 80 °C overnight. The reaction mixture is then cooled and evaporated to dryness under reduced pressure. The residue is dissolved in a saturated lithium hydroxide ("LiOH"_ solution (pH 9) and evaporated to dryness under reduced pressure. The residue is then dissolved in 10% aqueous HCl (pH 2), evaporated and dried under vacuum to provide thieno[3,2-d]pyrimidine-4-carboxylic acid (compound **7.2**).

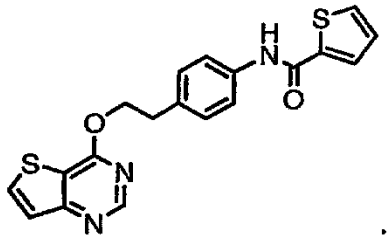
[0346] **Step 3:** To a solution of compound **7.2** (1.0 mmol) and 4-nitrobenzyl amine (1.0 mmol) in dichloromethane (5.0 mL) is added TEA (3.0 equivalents) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate ("HATU"; 1.1 equivalents). After completion of the reaction, the reaction is partitioned between EtOAc and water. The organic layer is separated, washed with 0.5 N HCl, saturated sodium bicarbonate, brine and dried. Purification by flash column chromatography on silica gel provides thieno[3,2-d]pyrimidine-4-carboxylic acid 4-nitro-benzylamide (compound **7.3**).

[0347] **Step 4:** Compound **7.3** (1.0 mmol) and Pd/C (10 w/w %, 60 mg) in MeOH-H_2O (12 mL) is stirred under a hydrogen atmosphere at room temperature until the reaction is complete. The catalyst is removed by filtration and the filtrate is evaporated to dryness under reduced pressure to provide thieno[3,2-d]pyrimidine-4-carboxylic acid 4-amino-benzylamide (compound **7.4**).

[0348] **Step 5:** To a solution of compound **7.4** (1.0 mmol) and 5-methyl-2H-pyrazole-3-carboxylic acid (1.0 mmol) in dichloromethane (5.0 mL) is added TEA (3.0 equiv.) and HATU (1.1 equiv.). After completion of the reaction, the reaction is partitioned between EtOAc and water. The organic layer is separated, washed with 0.5 N HCl, saturated sodium bicarbonate, brine and dried. Purification by flash column chromatography on silica gel provides the titled compound.

[0349] **Example 8**

[0350] This example describes the synthesis of

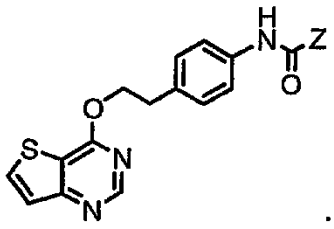


[0351] **Step 1:** 2-Thiophenecarbonyl chloride (1.1 equiv) is added dropwise to a solution of 2-(4-amino-phenyl)-ethanol (1.0 mmol) and TEA (3.0 equiv) in anhydrous THF (5.0 mL) at 0 °C. After completion of the reaction, the reaction mixture is poured into water and extracted with dichloromethane. The organic layer is separated, washed with saturated sodium bicarbonate, brine and dried. The desired product, thiophene-2-carboxylic acid [4-(2-hydroxy-ethyl)-phenyl]-amide (compound **8.1**) is purified by flash column chromatography on silica gel.

[0352] **Step 2:** To a solution of compound **8.1** (1.0 mmol) and compound **6.2** (1.0 equiv.) in anhydrous THF (8.0 mL) is added NaH (2.3 equiv.) at 0 °C. The reaction is warmed to room temperature and stirred overnight. Saturated ammonium chloride is added and the reaction mixture is extracted with EtOAc. The organic layer is separated, washed with brine, dried and concentrated under reduced pressure. The titled compound is precipitated from EtOAc with hexanes.

[0353] **Example 9**

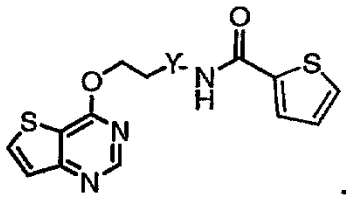
[0354] This example describes the synthesis of



where Z is as described previously. These compounds are made according to the procedures of Example 8 except that is used instead of 2-thiophenecarbonyl chloride in step 1. Illustrative examples of suitable Z are found throughout this disclosure as well as in Table 3.

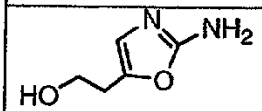
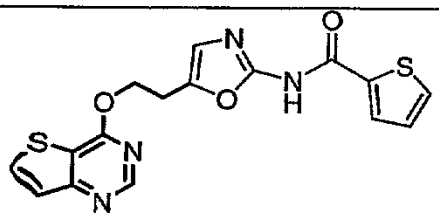
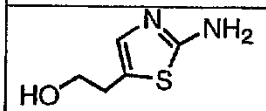
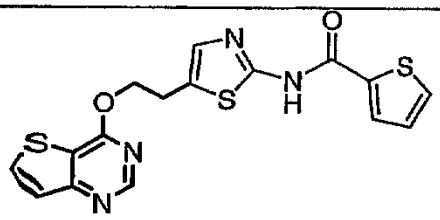
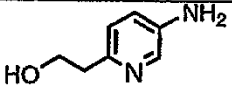
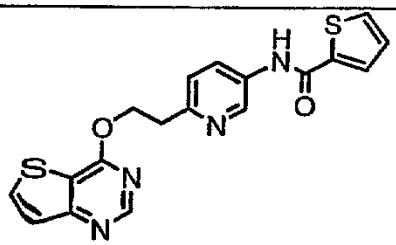
[0355] Example 10

[0356] This example describes the synthesis of



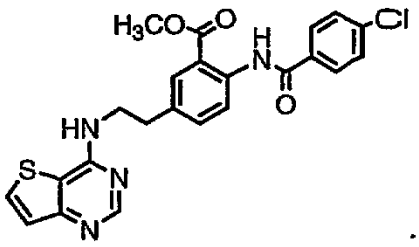
where Z is as described previously. These compounds are made according to the procedures of Example 8 except that $HO-(CH_2)_2-Y-NH_2$ is used instead of 2-(4-amino-phenyl)-ethanol in step 1. Illustrative examples of suitable Y's are found throughout this disclosure as well as in Table 4.

[0357] Table 4

$HO-(CH_2)_2-Y-NH_2$	Final Compound
	
	
	

[0358] Example 11

[0359] This example describes the synthesis of



[0360] **Step 1:** To a solution of 2-amino-5-methyl benzoic acid (1.0 mmol) dissolved in 10% MeOH in toluene (2.5 mL) is added dropwise trimethylsilyl-diazomethane (2.0 M in hexanes, 0.75 mL). The reaction mixture is stirred at room temperature for 1 hour and the solvent is removed under reduced pressure. The resulting methyl ester is dissolved in dichloromethane (3.0 mL) and then 4-chlorobenzoyl chloride (1.0 equivalent) and DIEA (1.0 equivalent) is added sequentially. The reaction mixture is stirred for 3 hours and the solvent is evaporated. The yellow residue is diluted with EtOAc, washed with 1 M $NaHSO_4$, brine, dried, filtered and concentrated under reduced pressure to provide 2-(4-chloro-benzoylamino)-5-methyl-benzoic acid methyl ester (compound **11.1**) which is used without purification in the next step.

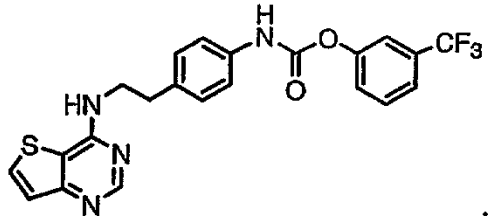
[0361] **Step 2:** To a solution of compound **11.1** (1.0 mmol) in benzene (2.0 mL) is added N-bromosuccinimide (1 equivalent) and benzoyl peroxide (0.33 equivalent). The reaction mixture is refluxed overnight under N_2. After cooling to room temperature, the solution is diluted with EtOAc, washed with H_2O, brine, dried, filtered and concentrated under reduced pressure. The crude product is purified by flash column chromatography on silica gel to provide 5-bromomethyl-2-(4-chloro-benzoylamino)-benzoic acid methyl ester (compound **11.2**).

[0362] **Step 3:** Potassium cyanide (1.0 equivalent) is added to a solution of compound **11.2** (1.0 mmol) in methyl sulfoxide ("DMSO"; 24 mL) and stirred for 2 hours at room temperature. The reaction mixture is diluted with EtOAc, washed with 1 M $NaHSO_4$, brine, filtered and evaporated under reduced pressure. The residue is purified by flash column chromatography on silica gel to provide the nitrile. T o a solution of the nitrile (1.0 mmol) dissolved in ethanol (5.0 mL) is added 4.0 N HCl in dioxane (0.25 mL) and catalytic Pd/C. The reaction mixture is subjected to hydrogenolysis at 50 psi for 12 hours. The solution is filtered over a pad of celite followed by careful rinsing with ethanol. The combined organic solution is concentrated under reduced pressure to provide 5–(2-amino-ethyl)-2-(4-chloro-benzoylamino)-benzoic acid methyl ester (compound **11.3**).

[0363] **Step 4:** Compound **11.3** (1.0 mmol), compound **6.2** (1.0 equivalent) and DIEA (2.5 equivalents) is heated in *n*-butanol (10 mL) at 135 °C for 2 hours. The reaction mixture is cooled and then partitioned between dichloromethane and water. The organic layer is separated, washed with brine, dried and concentrated under reduced pressure. The titled compound is precipitated from EtOAc with hexanes.

[0364] **Example 12**

[0365] This example describes the synthesis of

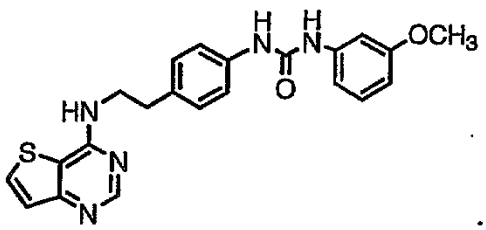


[0366] **Step 1:** A solution of 4-(2-amino-ethyl)-phenylamine (compound **12.1**; 0.1 mmol.), compound **6.2** (1.0 equivalent) and DIEA (2.5 equivalents) was heated in *n*-butanol (2 mL) at 135 °C for 2 hours. The reaction mixture was cooled and partitioned between dichloromethane and water. The organic layer was separated, washed with brine, dried and concentrated under reduced pressure to give crude [2-(4-amino-phenyl)-ethyl]-thieno[3,2-d]pyrimidin-4-yl-amine (compound **12.2**) which was used without purification for the next step.

[0367] **Step 2:** To a suspension of compound **12.2** (0.46 mmol) and TEA (2.5 equivalents) in anhydrous THF (3.0 mL) cooled to 0 °C was added 3-(trifluoromethyl)phenyl chloroformate (1.1 equivalents). The reaction was warmed to room temperature and after 45 minutes, water was added and the reaction extracted with EtOAc. The organic layer was separated, washed with brine, dried and concentrated under reduced pressure. Purification by reverse-phase HPLC (aqueous 0.1% trifluoroacetic acid ("TFA")/CH_3CN) provided the titled compound.

[0368] **Example 13**

[0369] This example describes the synthesis of



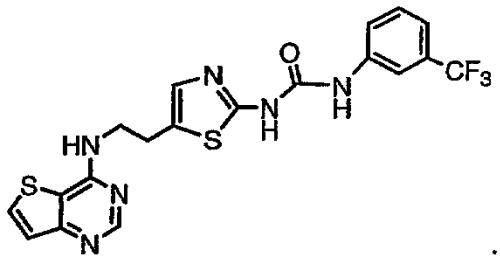
[0370] **Step 1:** 3-Methoxyphenyl isocyanate and compound **1.1** are reacted according to a procedure in Dhar, T. G. et. al. (*Bioorg. Med. Chem. Lett. 13,* **2003**,

3557) to yield (2-{4-[3-(3-Methoxy-phenyl)-ureido]-phenyl}-ethyl)-carbamic acid tert-butyl ester (compound **13.1**).

[0371] **Step 2:** Compound **13.1** (1.0 mmol) is treated with anhydrous 4.0 N HCl in dioxane (25 mL) at 0 °C, stirred at room temperature for 2 hours and concentrated to dryness under reduced pressure. The crude amine salt, compound **6.2** (1.0 equivalent) and DIEA (2.5 equivalents) is then heated in *n*-butanol (10 mL) at 135 °C for 2 hours. The reaction mixture is cooled and then partitioned between dichloromethane and water. The organic layer is separated, washed with brine, dried and concentrated under reduced pressure. The titled compound is precipitated from EtOAc with hexanes.

[0372] **Example 14**

[0373] This example describes the synthesis of



[0374] **Step 1:** [5-(2-Amino-ethyl)-thiazol-2-yl]-carbamic acid tert-butyl ester (compound **14.1**; 20.5 mmol), compound **6.2** (0.94 equivalent) and DIEA (1.0 equivalent) was heated in *N,N*-dimethylformamide ("DMF"; 75 mL) at 90 °C for 1.5 hours. The reaction mixture was cooled and diluted with EtOAc and water. The organic layer was separated, washed with brine, dried, concentrated and purified by flash column chromatography on silica gel to provide {5-[2-(thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-thiazol-2-yl}-carbamic acid tert-butyl ester (compound **14.2**) in 75% yield.

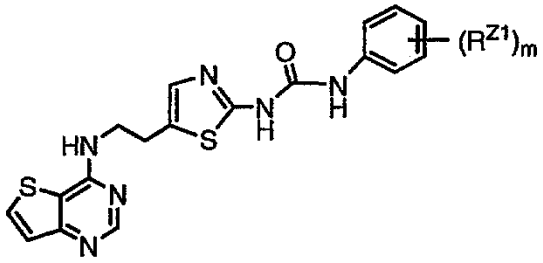
[0375] **Step 2:** To a solution of compound **14.2** (14.5 mmol) in 1,4-dioxane (30 mL) was added anhydrous HCl (20 mL of a 4 N solution in 1,4-dioxane) after stirring at room temperature for 2 hours the reaction was concentrated to dryness, diluted with water and the solution adjusted to pH 8 with saturated sodium bicarbonate. The slurry was extracted several times with EtOAc and the organic layers were combined, dried and concentrated to provide [2-(2-amino-thiazol-5-yl)-ethyl]-thieno[3,2-d]pyrimidin-4-yl-amine (compound **14.3**) in 88% yield.

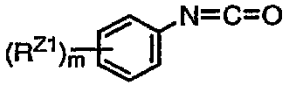
[0376] **Step 3:** To a suspension of compound **14.3** (10.8 mmol) in anhydrous benzene (75 mL) was added 3-trifluoromethylphenyl isocyanate (1.0 equivalent). The

reaction mixture was heated at 90°C for 1 hour, cooled and concentrated to give a solid that was washed with a mixture of dichloromethane and hexanes. The solid was treated with MeOH followed by the addition of1 N HCl and water. The solution was then sonicated and lyophilized to give a solid that was washed with ethanol and dried under vacuum to provide the HCl salt of the titled compound in 86% yield. Anal. Calcd for $C_{19}H_{16}N_6OS_2F_3Cl$: C, 45.55; H, 3.22; N, 16.78. Found: C, 45.56; H, 3.27; N, 16.75.

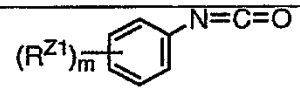
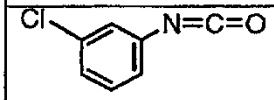
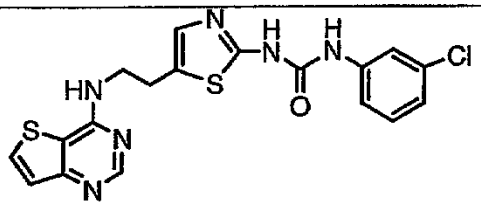
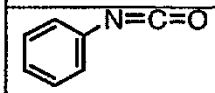
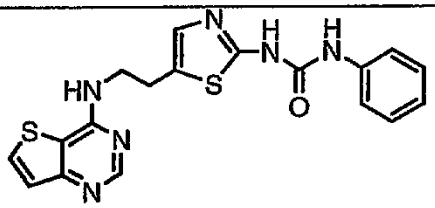
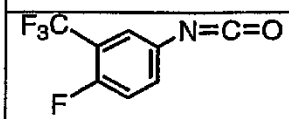
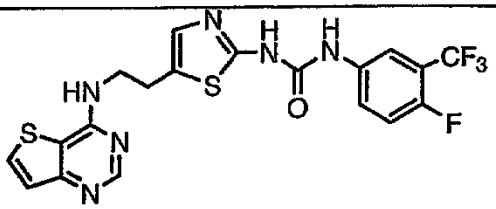
[0377] **Example 15**

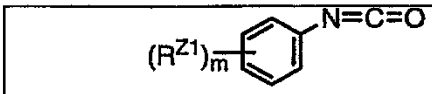
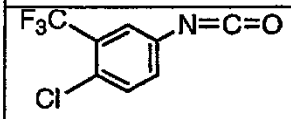
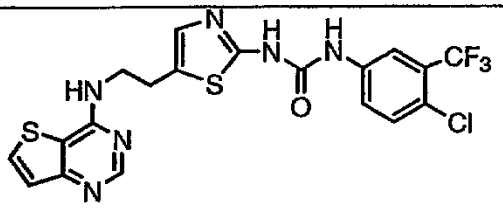
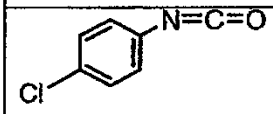
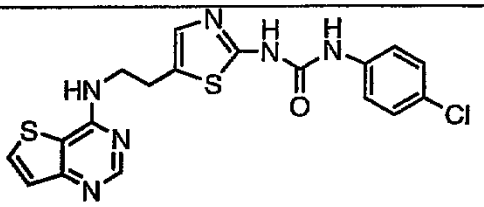
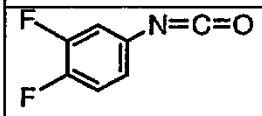
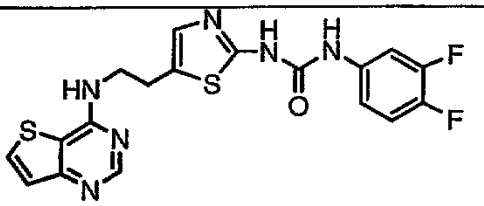
[0378] This example describes the synthesis of



where R^{Z1} and m are as described previously. These compounds are made according to the procedures of Example 14 except that  is used instead of 3-trifluromethylphenyl isocyanate in step 3. Illustrative examples of suitable R^{Z1}'s are found throughout this disclosure as well as in Table 5.

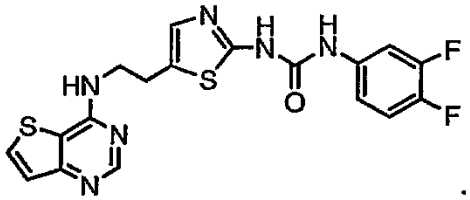
[0379] Table 5

	Final Compound
	
	
	

	Final Compound
	
	
	

[0380] **Example 16**

[0381] This example describes an alternate synthesis of



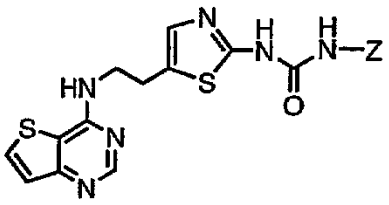
[0382] **Step 1:** To a suspension of compound **14.2** (23.7 mmol) in 1,4-dioxane (100 mL) was added HCl (70 mL of a 4.0 M in 1,4-dioxane) at 0 °C. The reaction was allowed to warm to room temperature, stirred for 2 hours and concentrated to dryness to give a tan solid. The crude solid was suspended in THF (200 mL) and cooled to 0 °C. Triethylamine (33 mL) was added followed by phenyl chloroformate (26.1 mmol). The reaction mixture was allowed to slowly warm to room temperature and stirred for 2 hours. Volatiles were removed under reduced pressure at room temperature, water was added and the solid collected by vacuum filtration. The solid was washed with ethyl ether and dried under vacuum to give {5-[2-(thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-thiazol-2-yl}-carbamic acid phenyl ester (compound **16.1**) in 80% yield as a tan solid.

[0383] **Step 2:** To a suspension of compound **16.1** (0.63 mmol) in DMSO (3.5 mL) was added 3,4-difluoroaniline (0.63 mmol) and 4-dimethylamino)pyridine

("DMAP"; catalytic amount or 1.0 equivalent). The reaction was heated in an 80 °C oil bath for 30 minutes, diluted with EtOAc and washed with water, 2.0 N NaOH, water, brine, dried and concentrated to give a solid. The solid was dissolved in hot EtOAc/MeOH and then hexanes/ethyl ether was added to precipitate the titled compound as a tan powder in 81% yield.

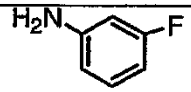
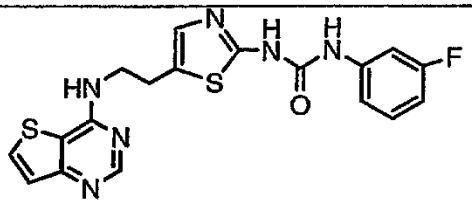
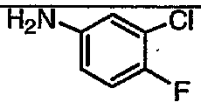
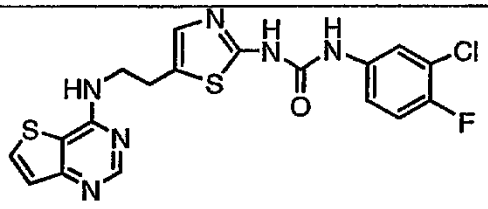
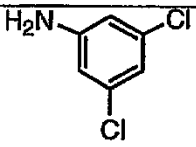
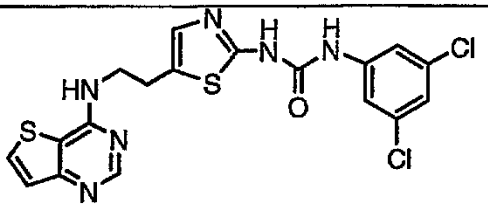
[0384] Example 17

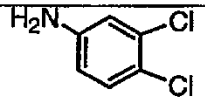
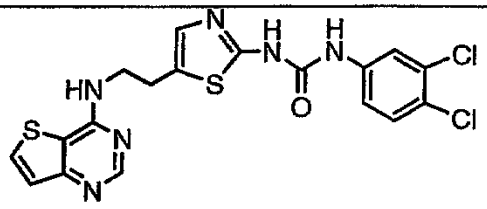
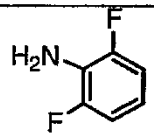
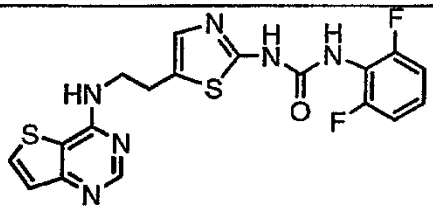
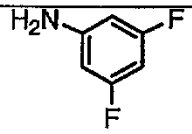
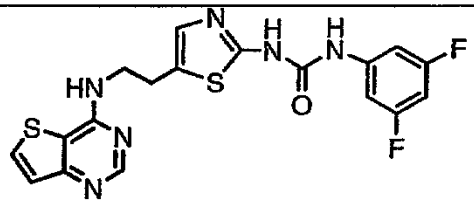
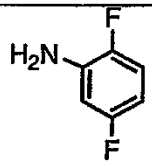
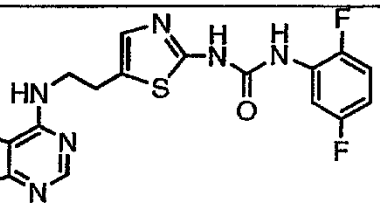
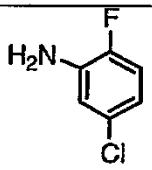
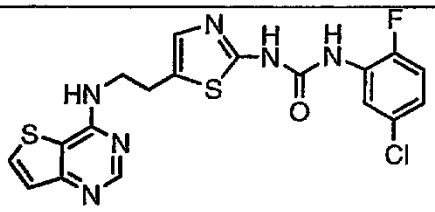
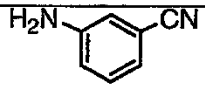
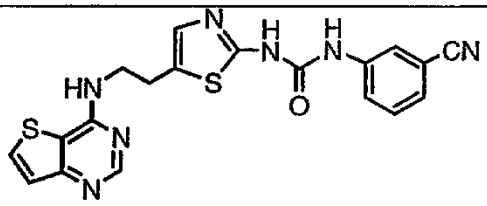
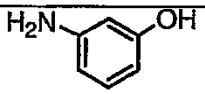
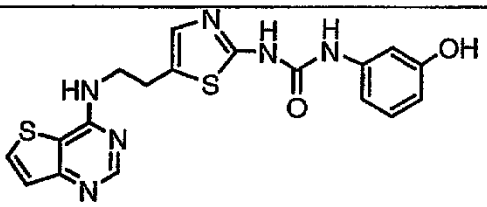
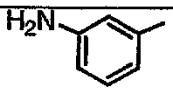
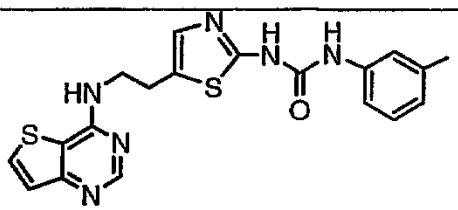
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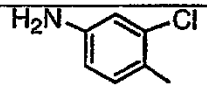
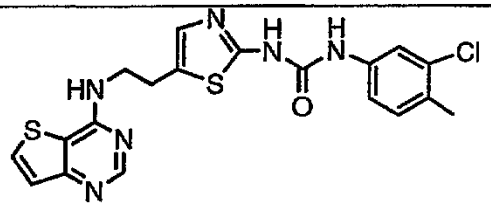
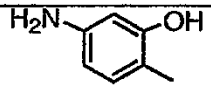
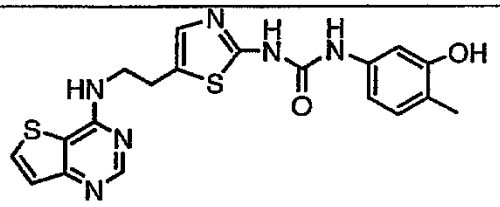
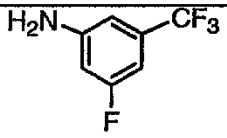
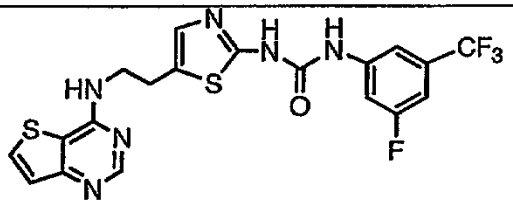
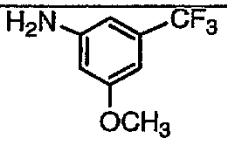
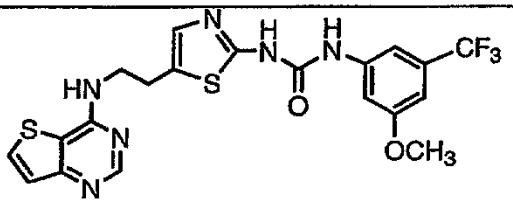
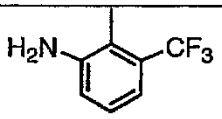
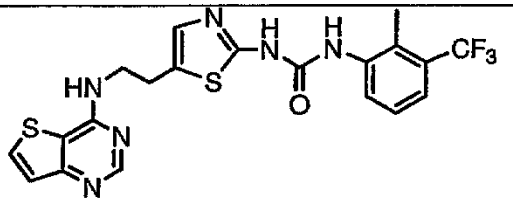
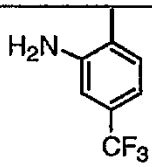
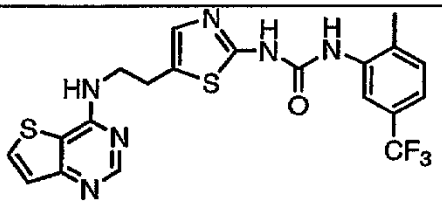
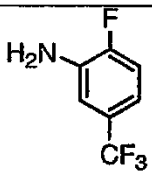
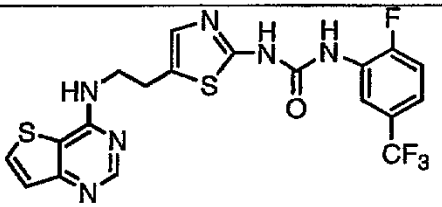
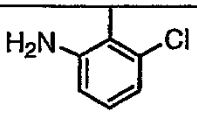
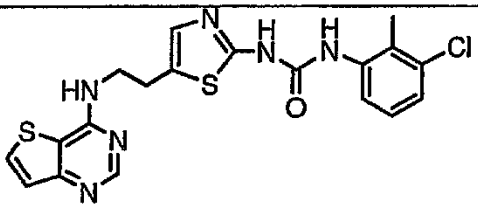


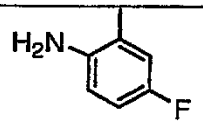
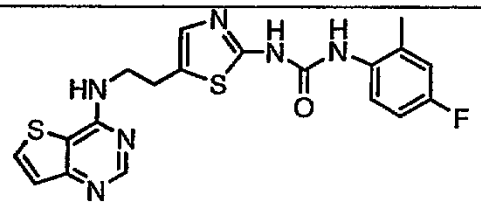
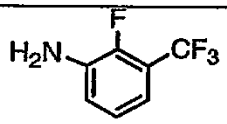
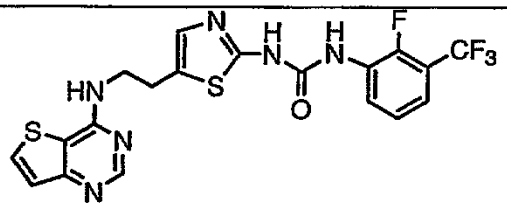
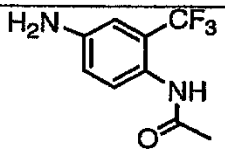
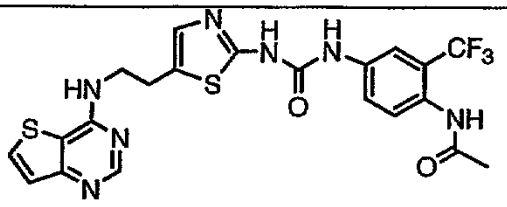
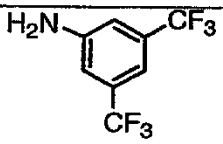
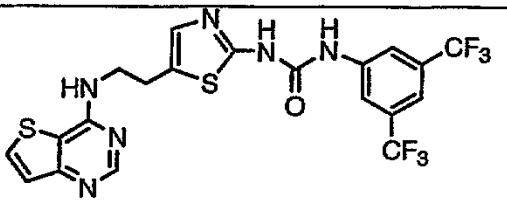
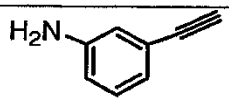
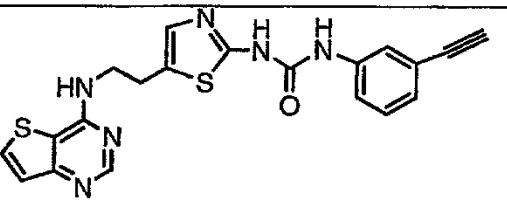
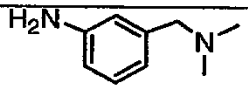
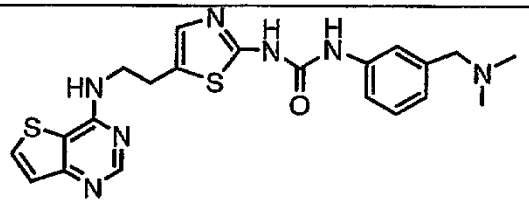
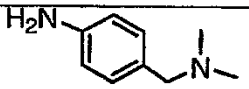
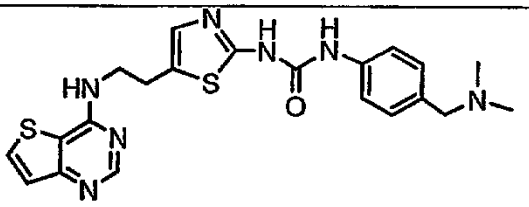
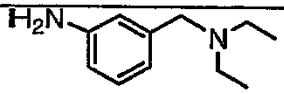
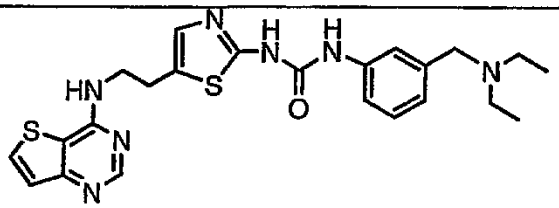
where Z is as described previously. These compounds are made according to Example 16 except that H_2NZ is used instead of 3,4-difluoroaniline in step 2. Illustrative examples of suitable Z's are found throughout this disclosure as well as in Table 6.

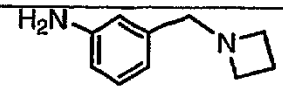
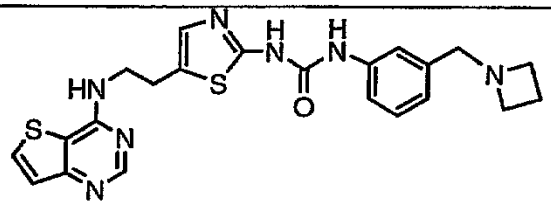
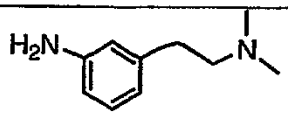
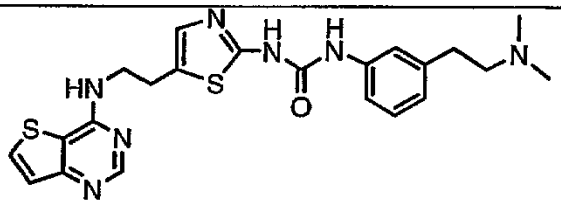
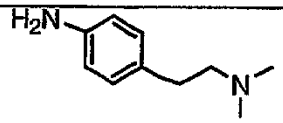
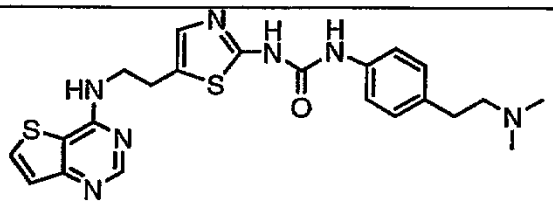
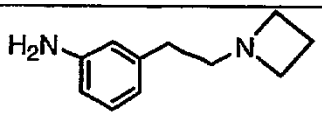
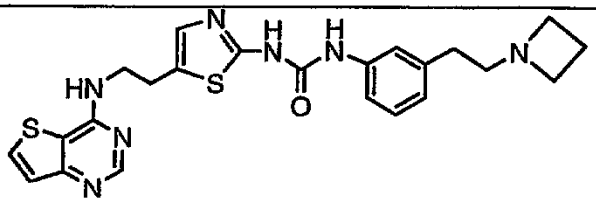
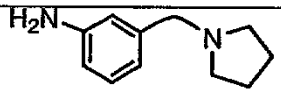
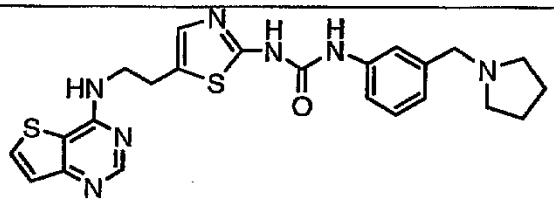
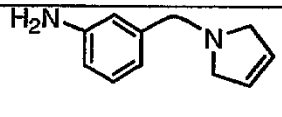
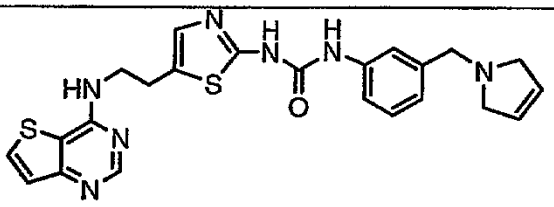
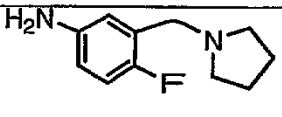
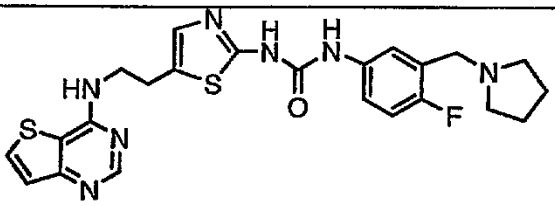
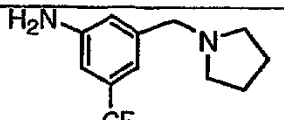
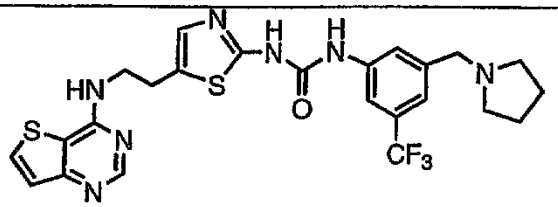
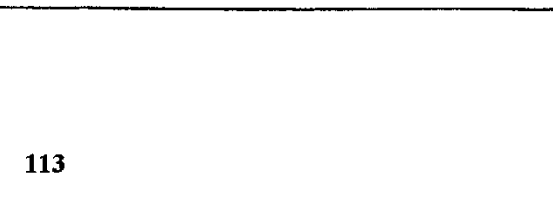
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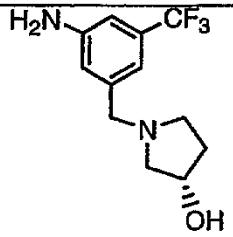
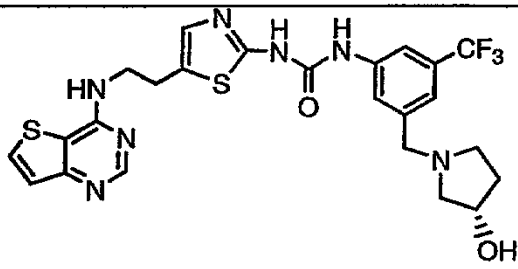
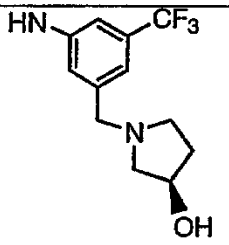
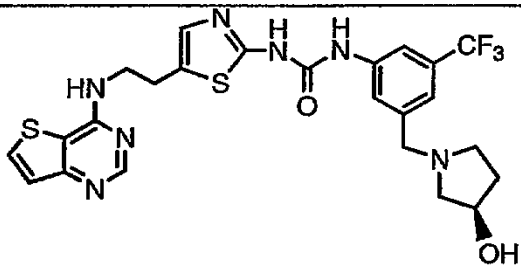
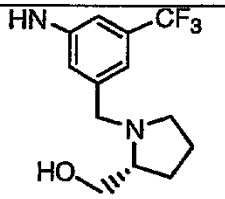
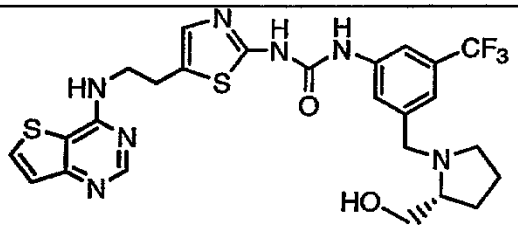
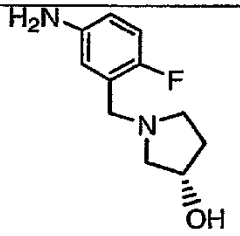
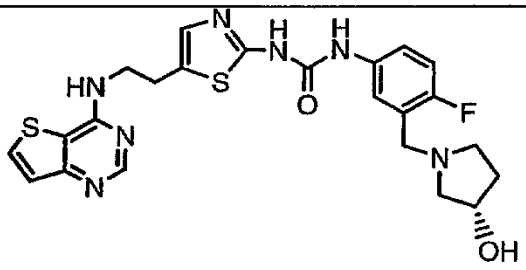
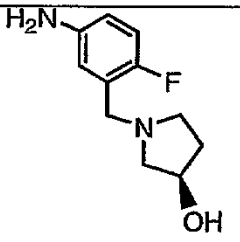
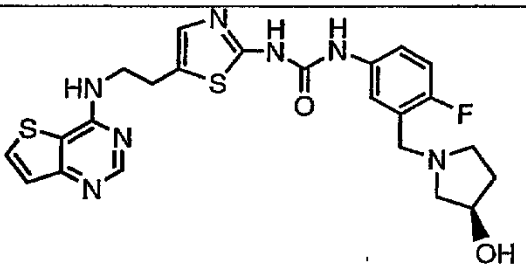
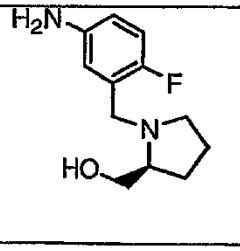
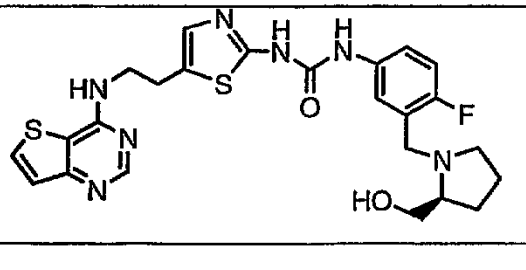
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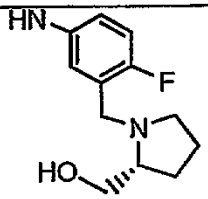
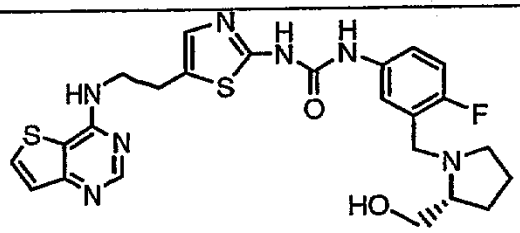
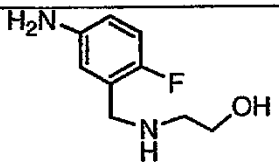
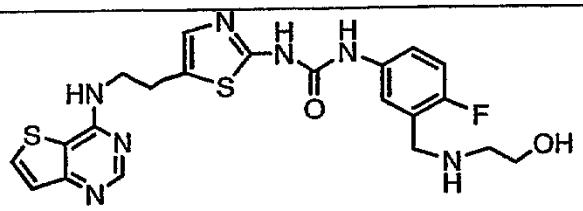
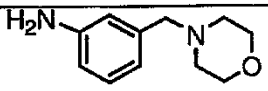
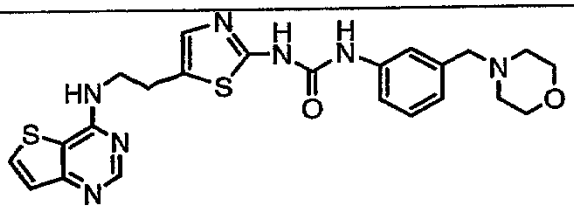
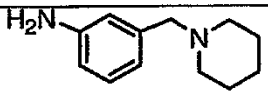
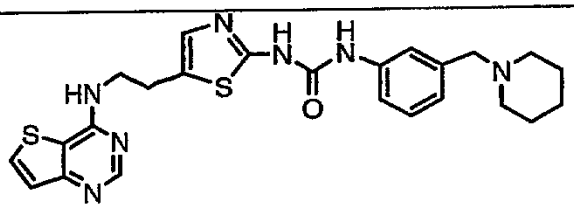
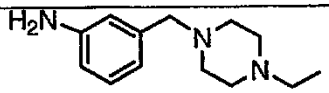
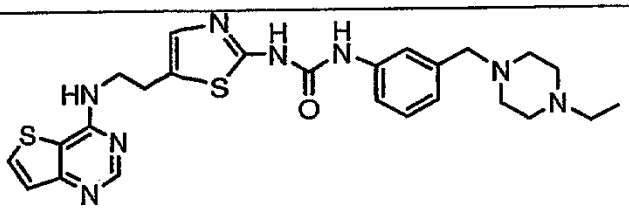
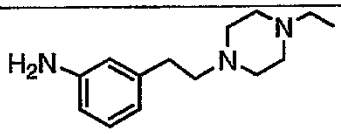
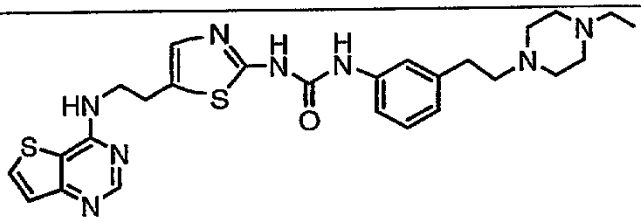
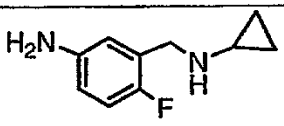
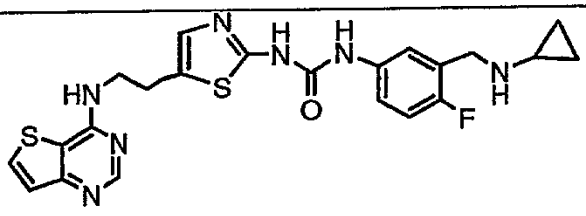
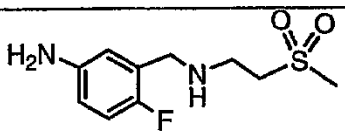
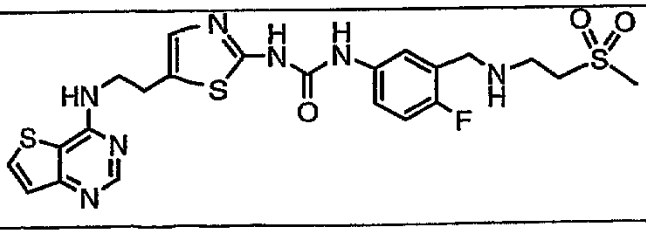
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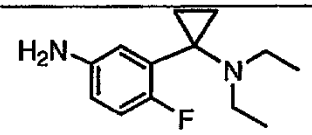
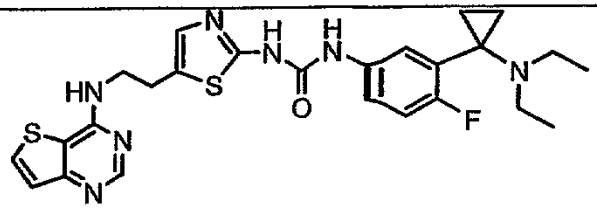
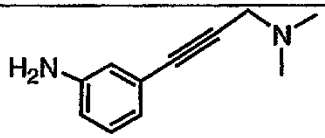
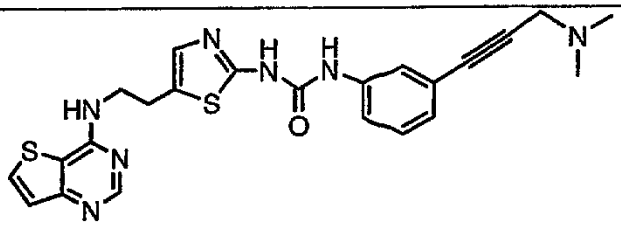
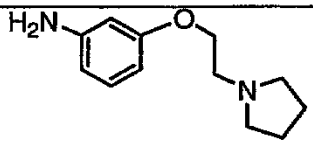
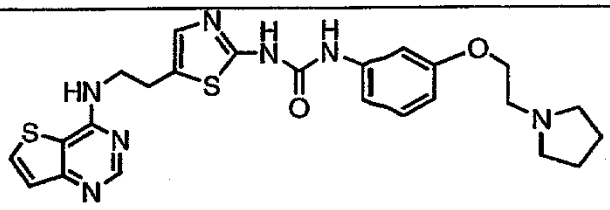
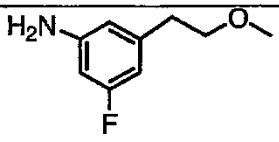
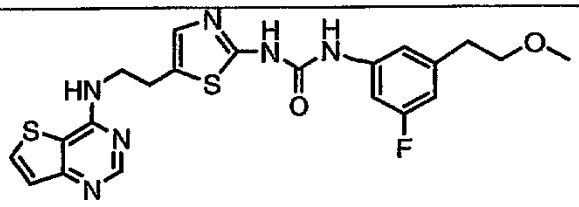
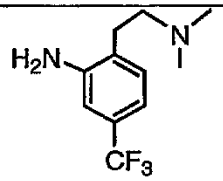
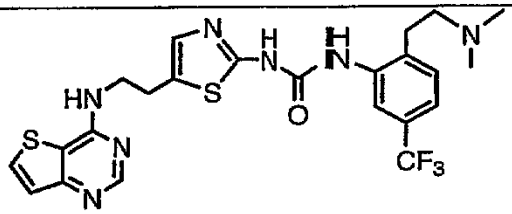
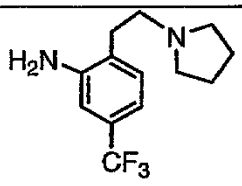
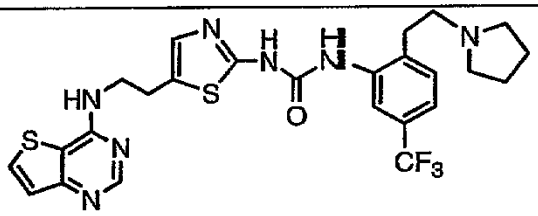
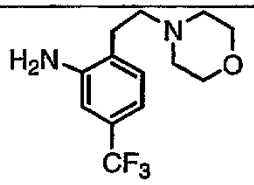
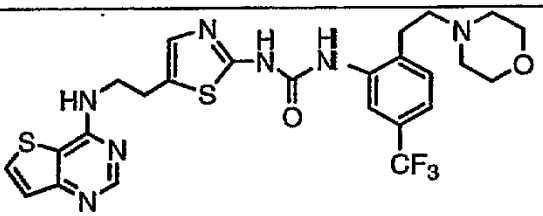
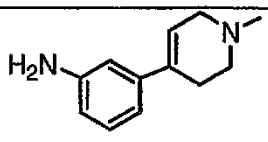
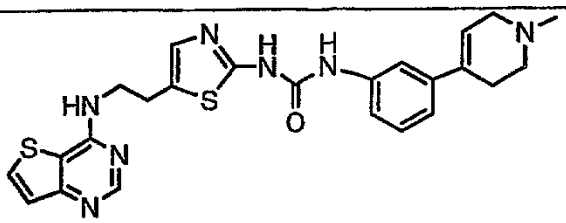
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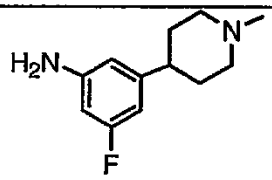
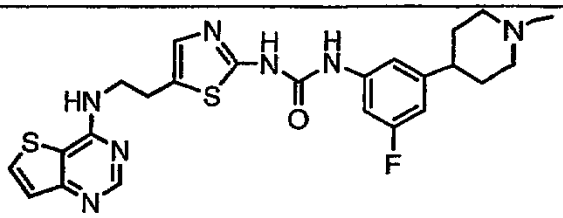
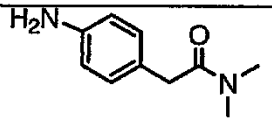
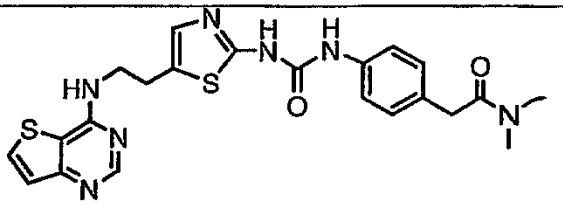
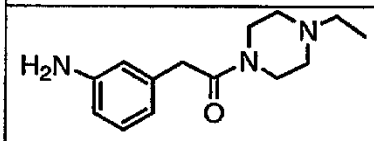
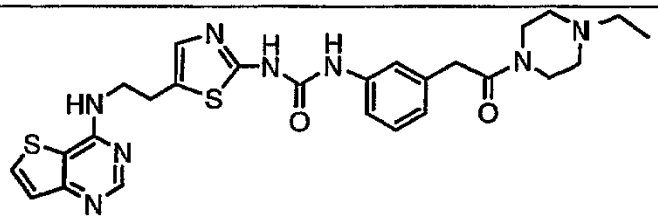
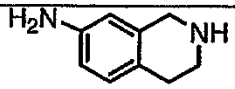
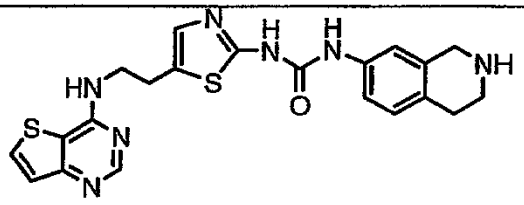
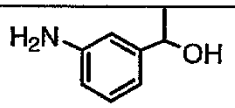
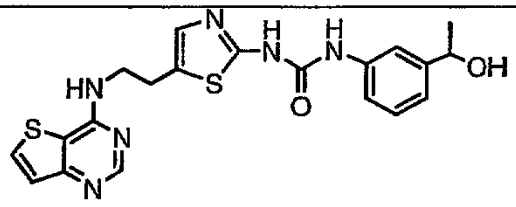
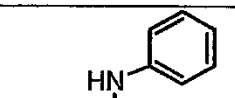
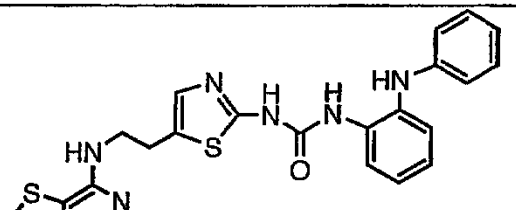
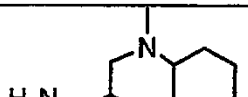
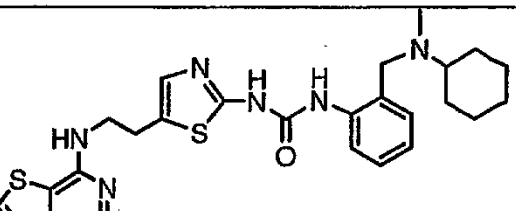
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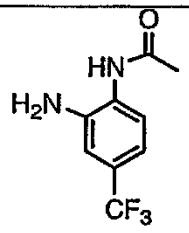
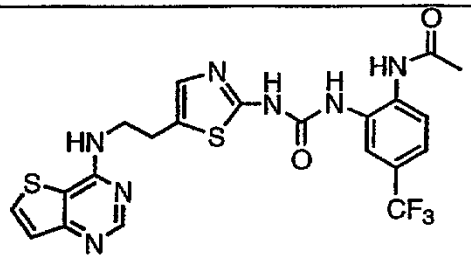
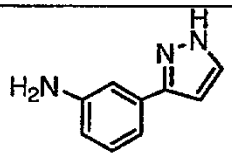
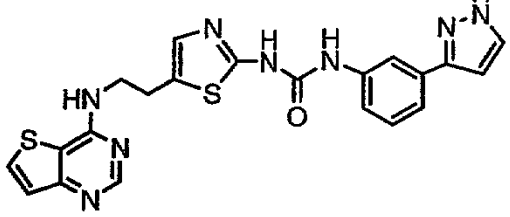
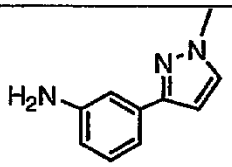
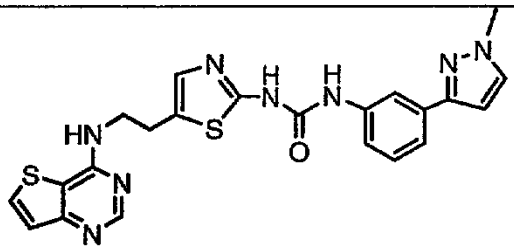
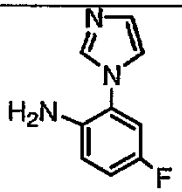
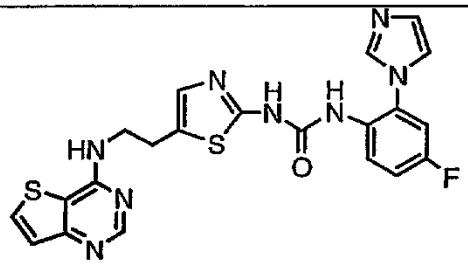
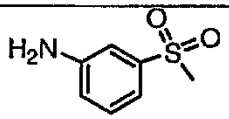
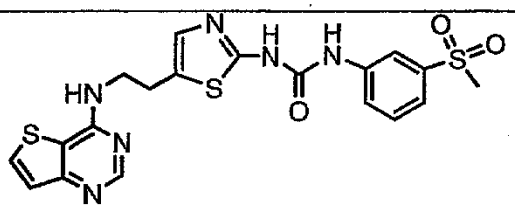
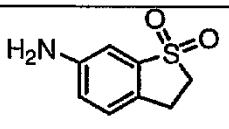
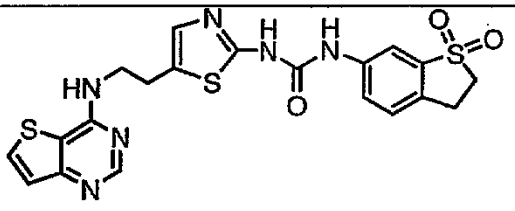
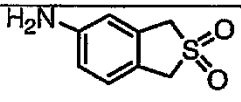
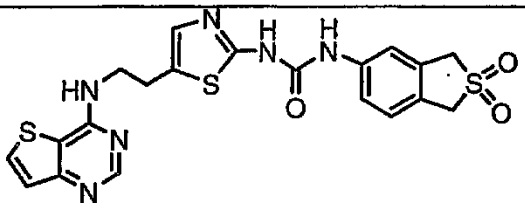
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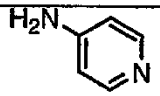
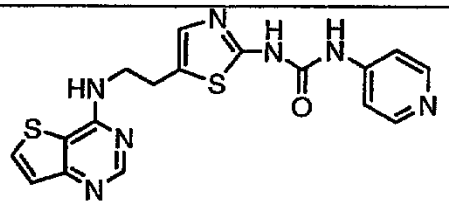
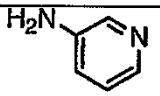
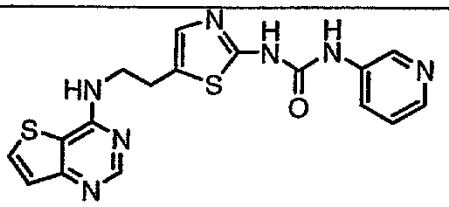
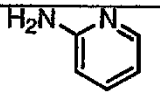
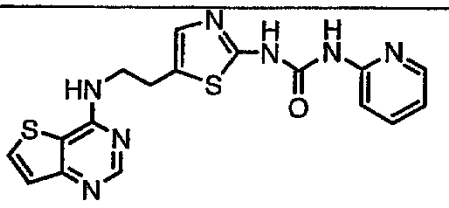
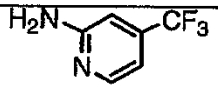
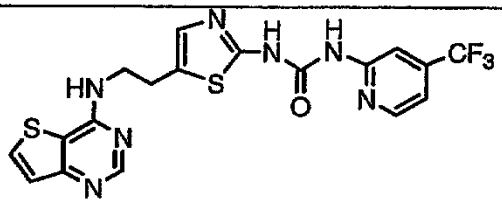
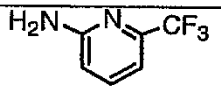
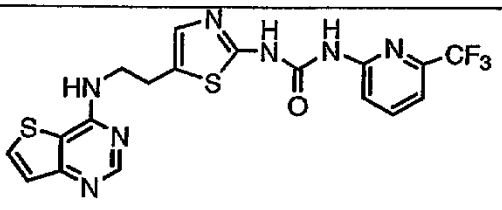
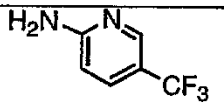
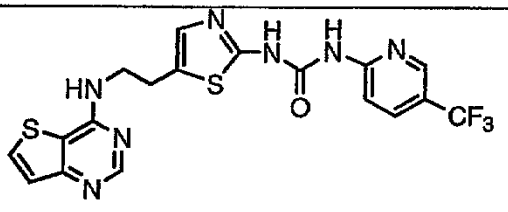
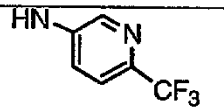
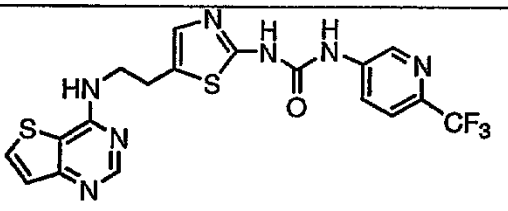
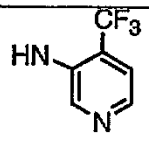
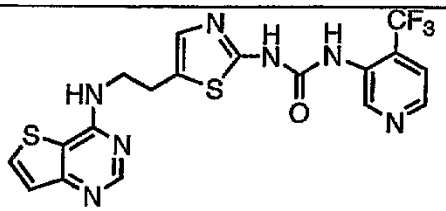
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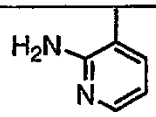
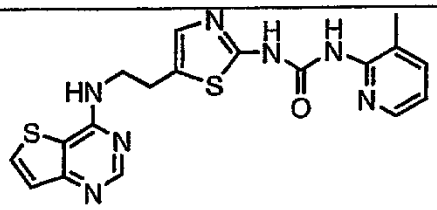
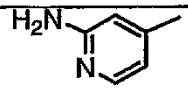
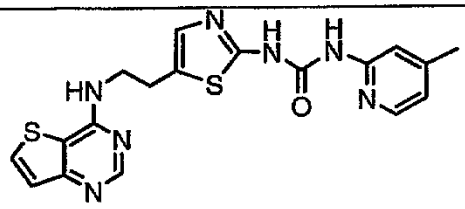
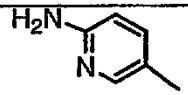
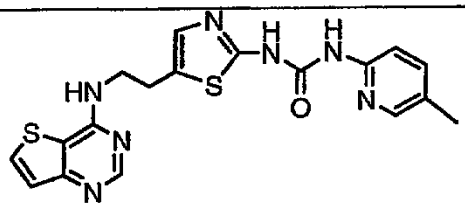
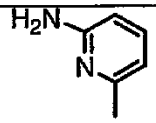
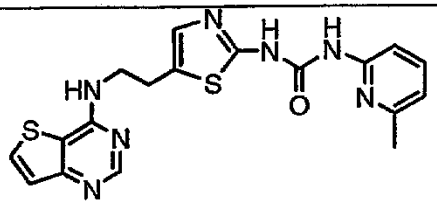
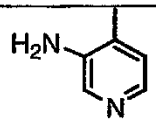
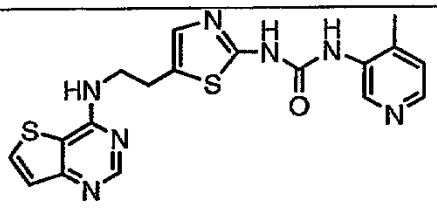
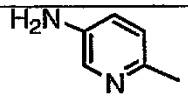
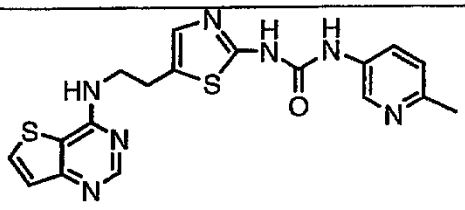
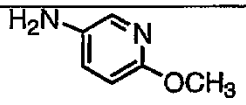
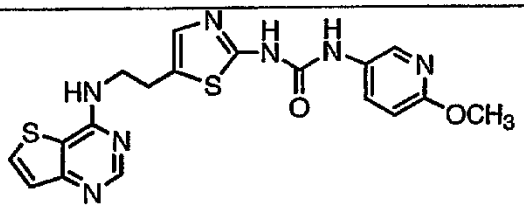
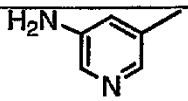
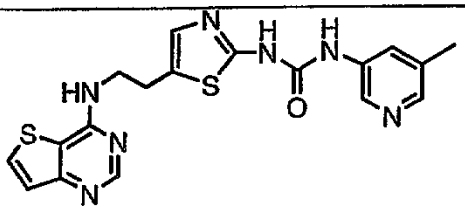
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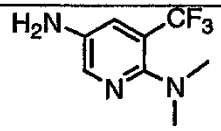
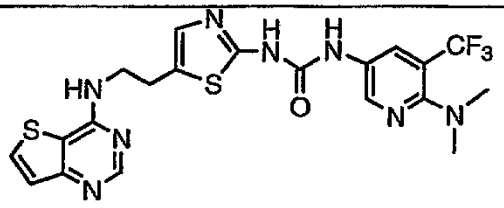
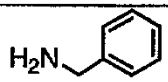
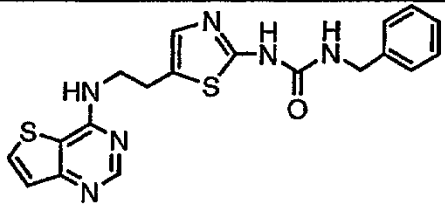
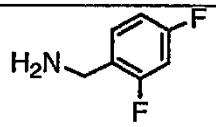
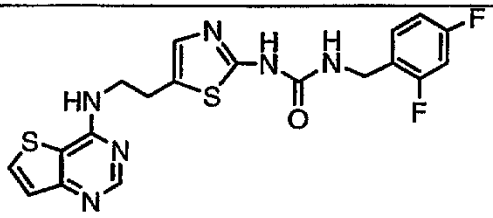
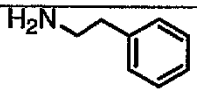
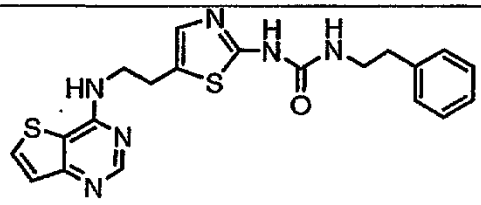
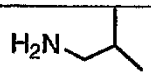
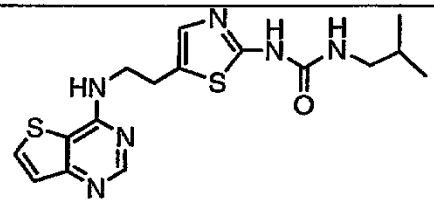
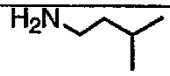
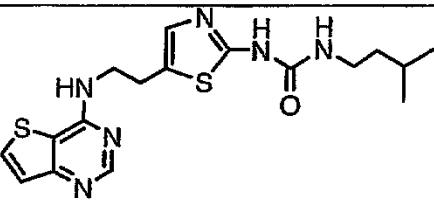
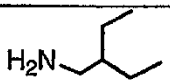
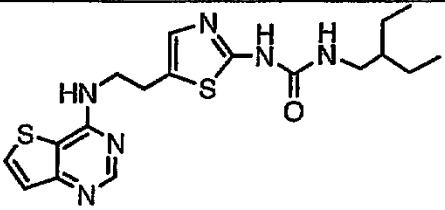
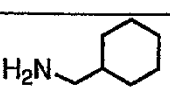
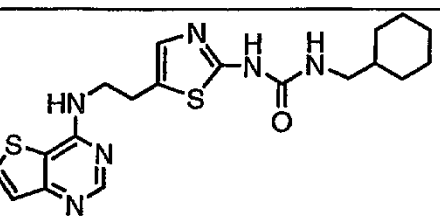
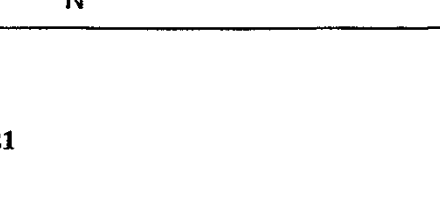
H_2NR	1. Final Compound
	
	
	
	
	
	
	
	

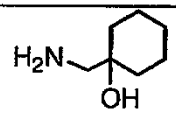
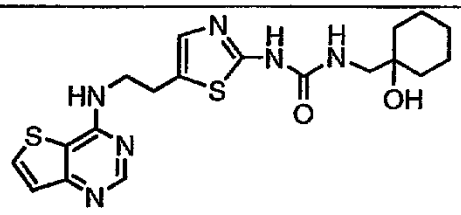
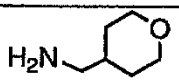
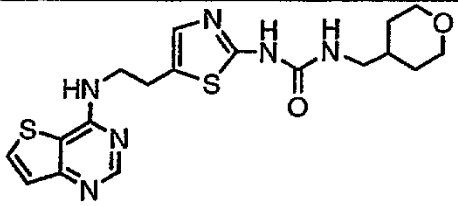
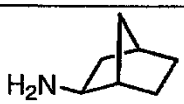
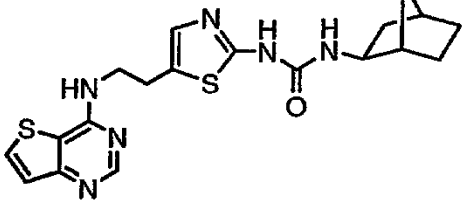
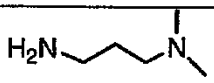
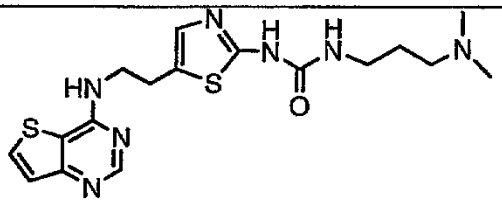
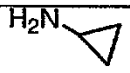
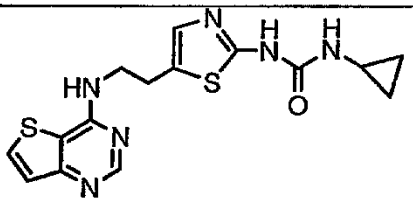
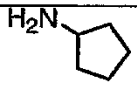
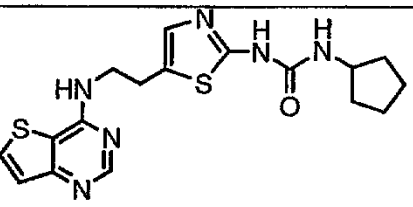
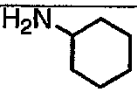
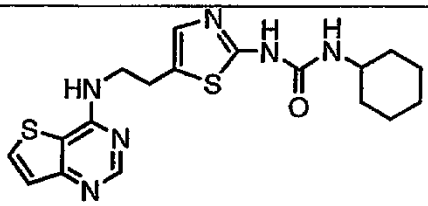
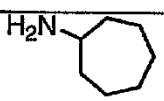
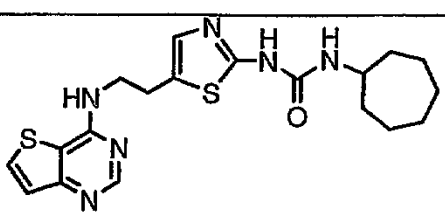
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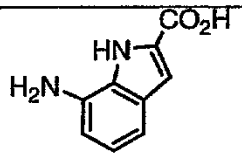
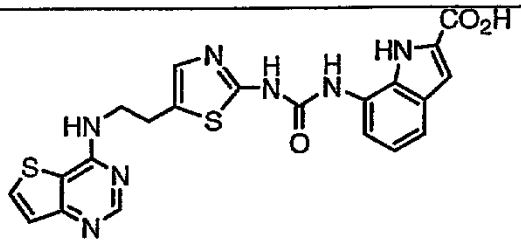
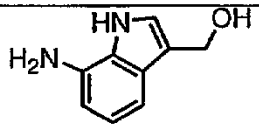
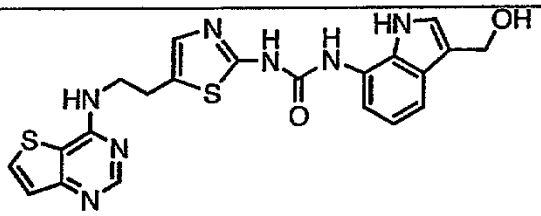
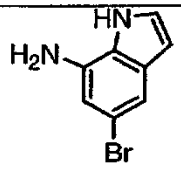
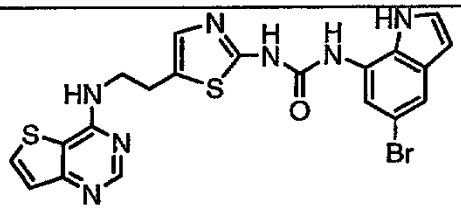
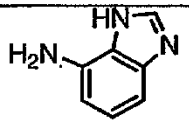
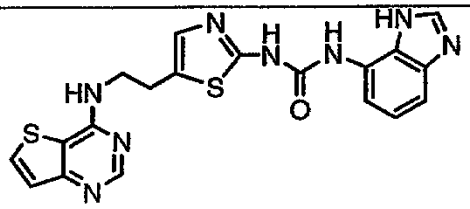
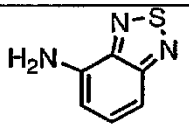
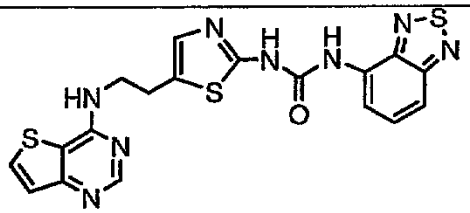
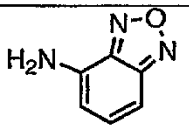
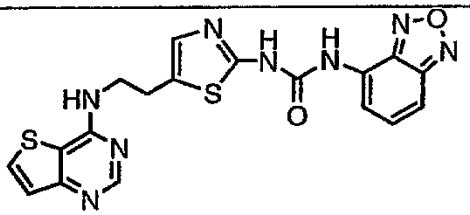
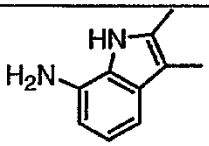
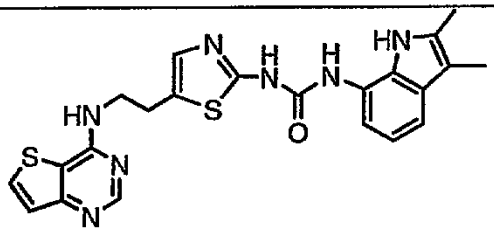
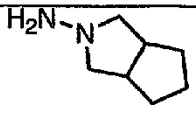
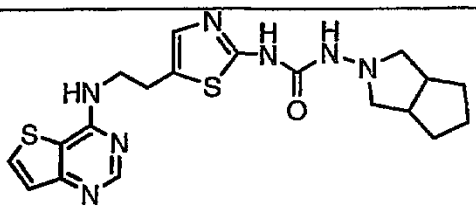
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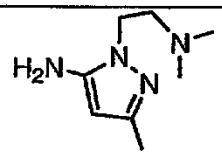
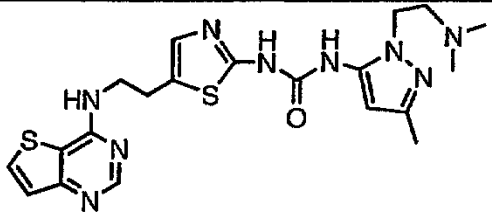
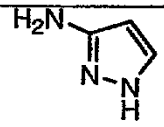
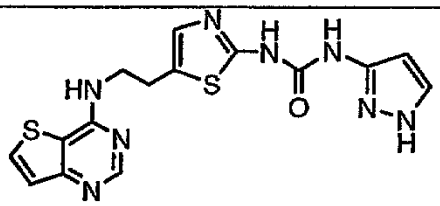
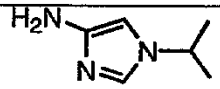
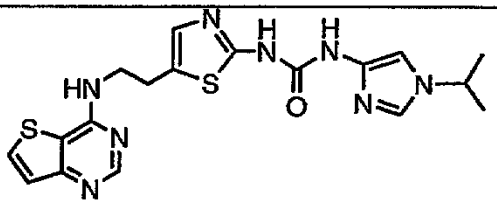
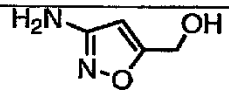
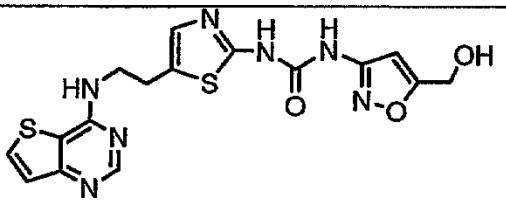
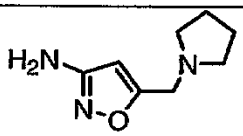
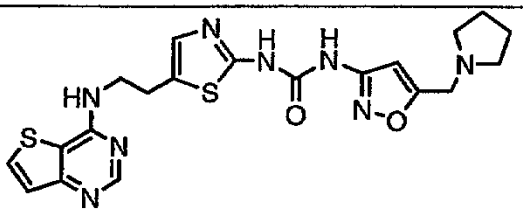
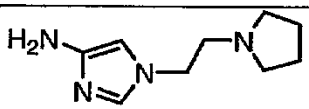
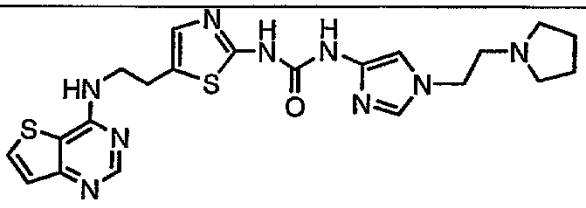
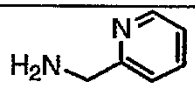
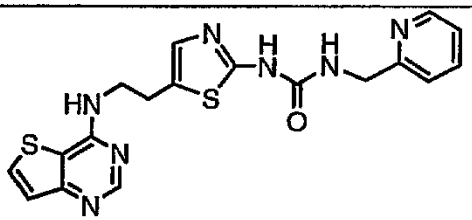
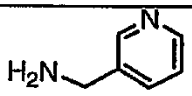
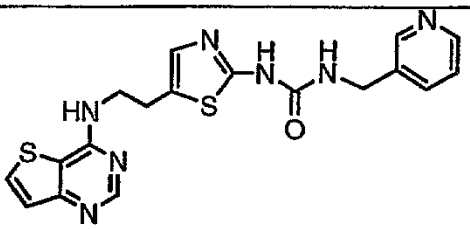
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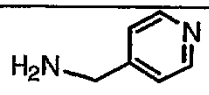
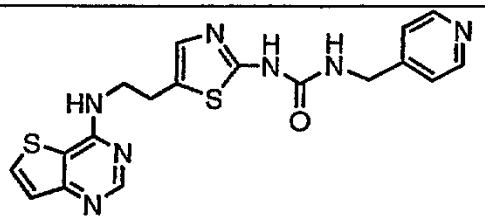
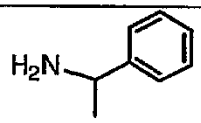
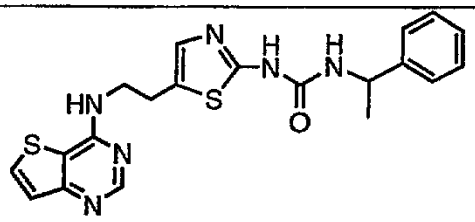
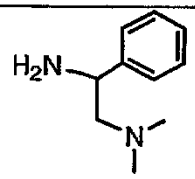
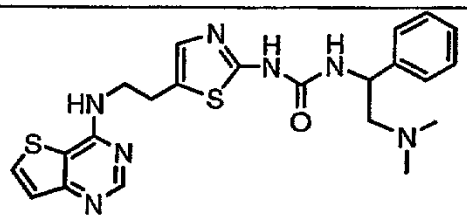
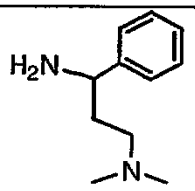
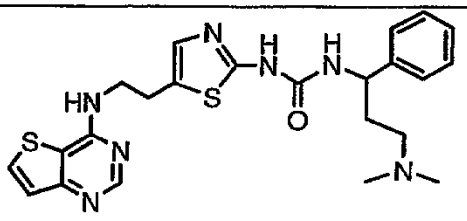
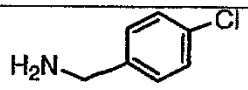
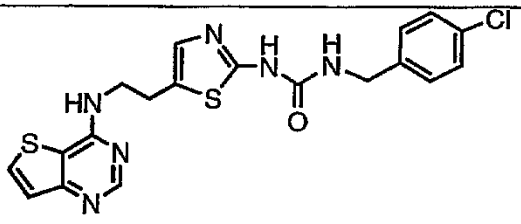
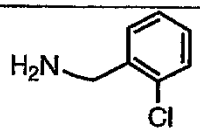
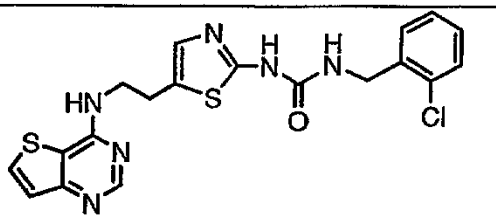
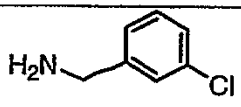
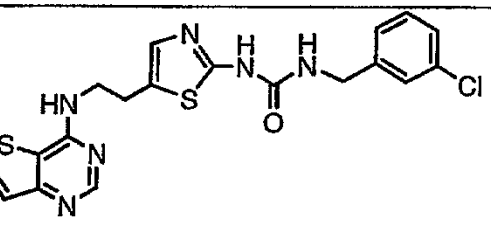
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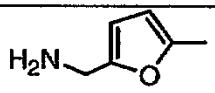
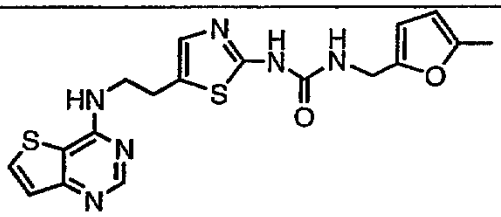
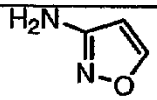
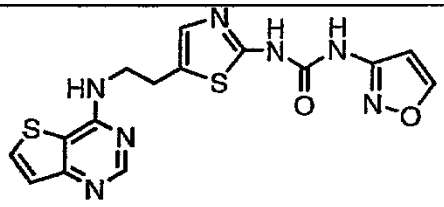
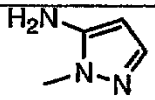
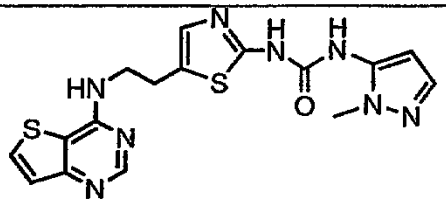
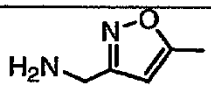
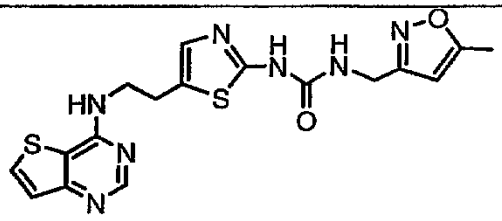
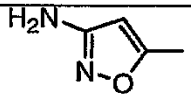
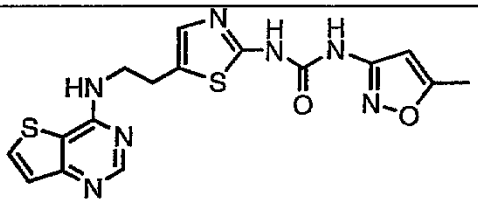
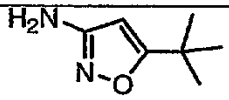
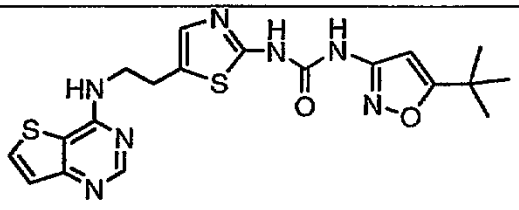
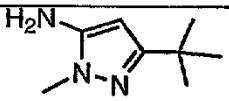
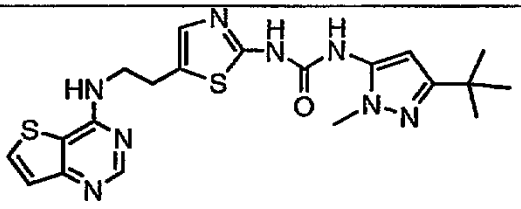
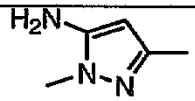
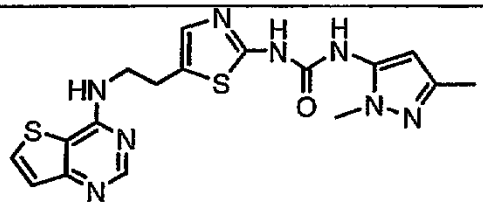
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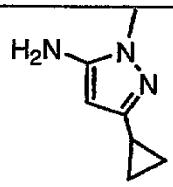
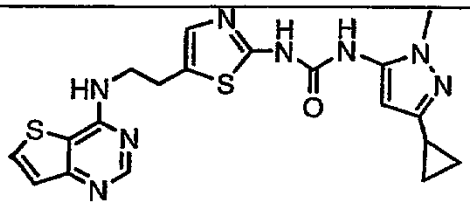
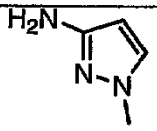
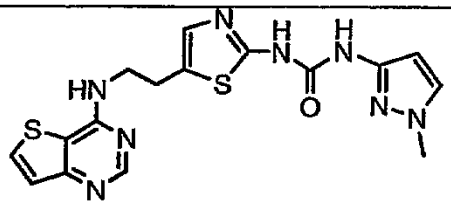
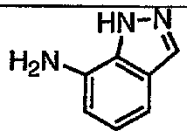
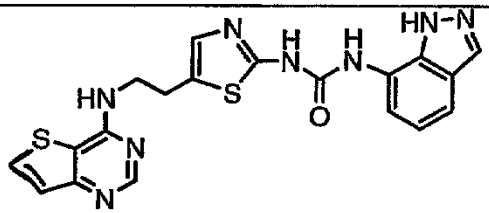
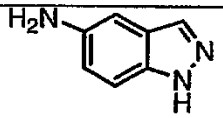
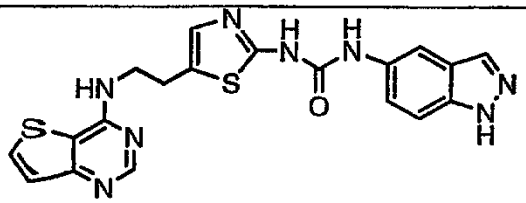
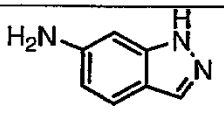
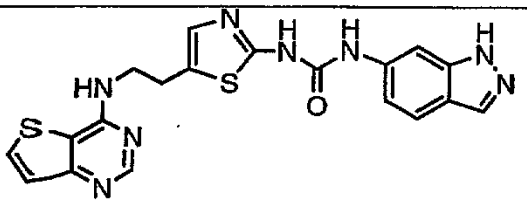
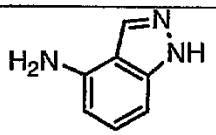
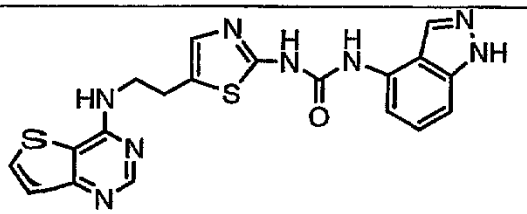
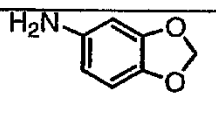
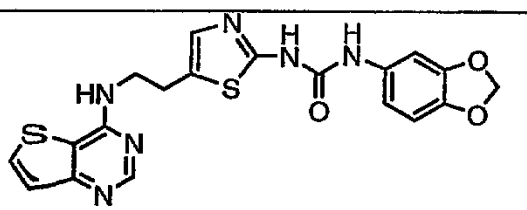
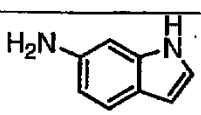
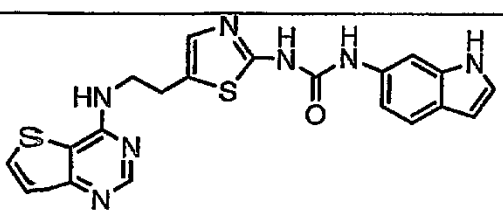
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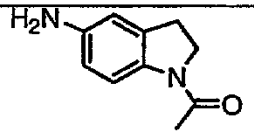
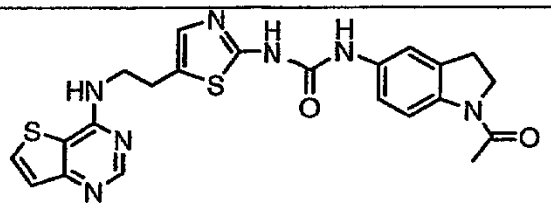
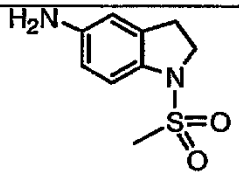
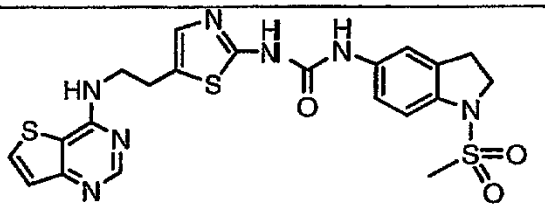
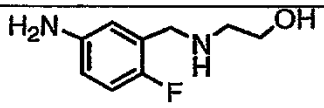
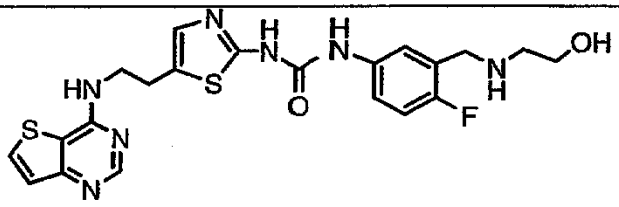
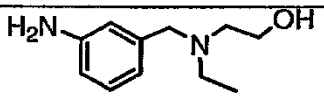
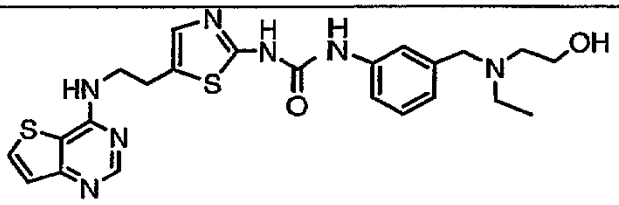
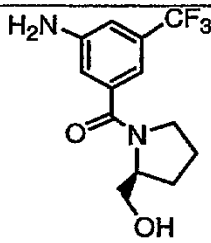
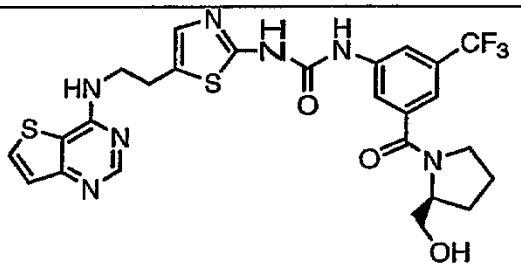
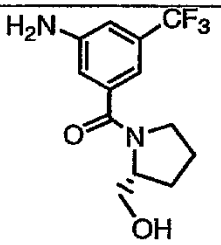
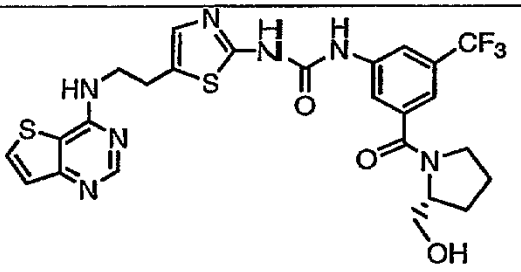
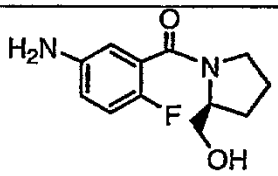
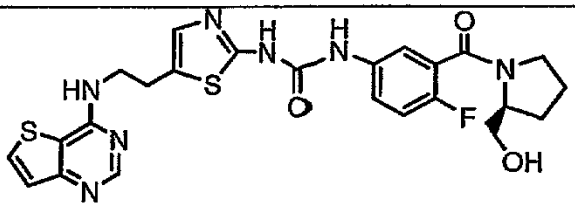
H_2NR	1. Final Compound
	
	
	
	
	
	
	
	

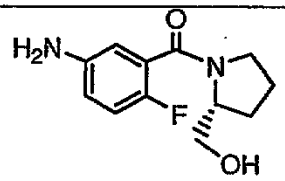
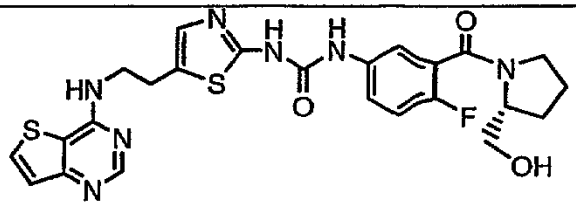
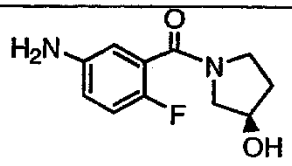
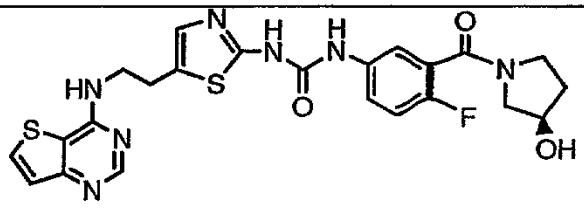
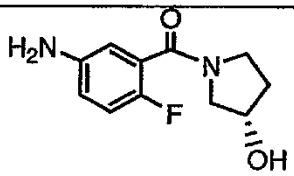
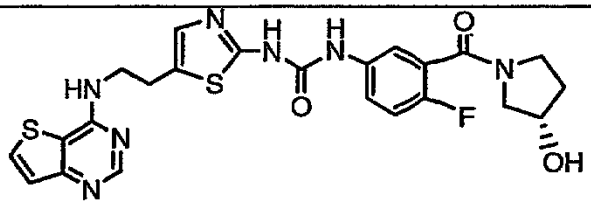
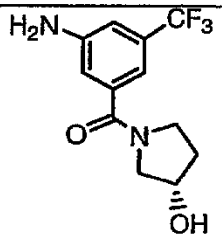
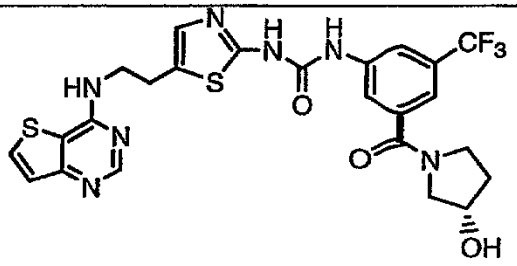
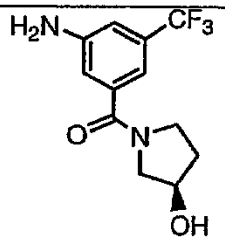
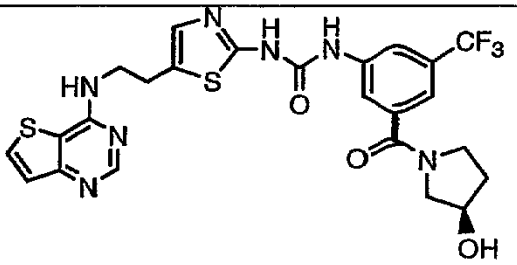
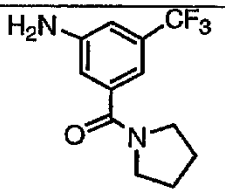
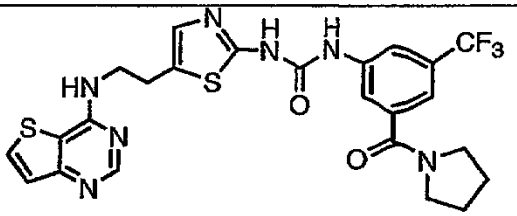
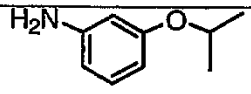
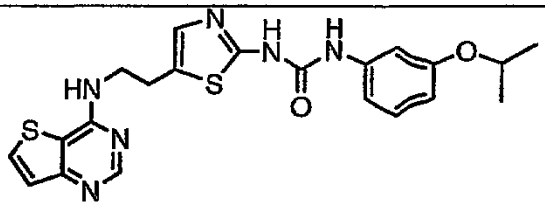
H_2NR	1. Final Compound
	
	
	
	
	
	
	
	

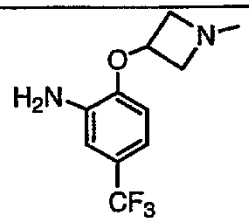
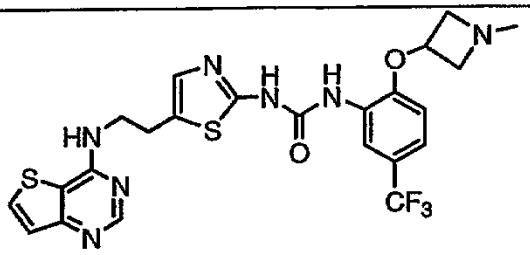
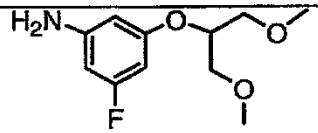
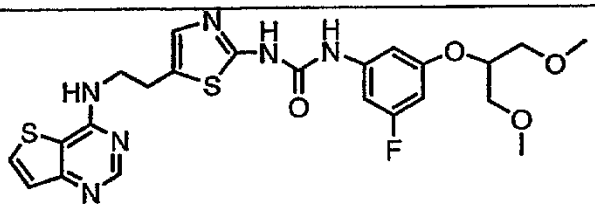
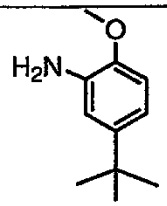
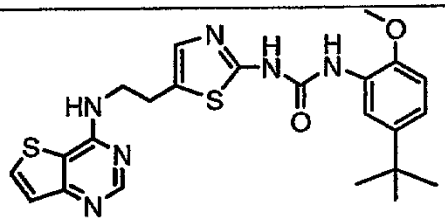
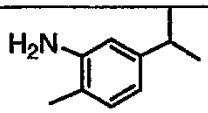
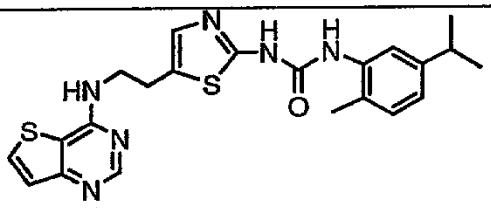
H_2NR	1. Final Compound
	
	
	
	
	
	
	

H_2NR	1. Final Compound
	
	
	
	
	
	
	
	

H_2NR	1. Final Compound
	
	
	
	
	
	
	
	

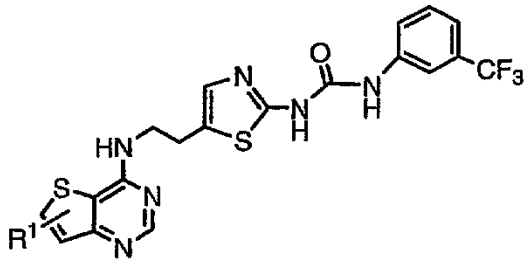
H_2NR	1. Final Compound
	
	
	
	
	
	
	

H_2NR	1. Final Compound
	
	
	
	
	
	
	

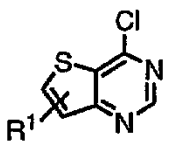
H_2NR	1. Final Compound
	
	
	
	

[0387] **Example 18**

[0388] This example describes the synthesis of



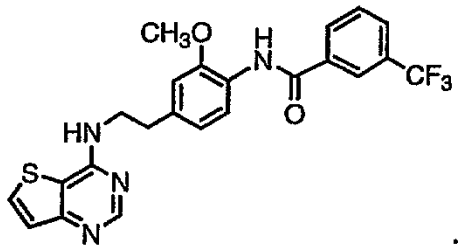
where R^1 is as described previously. These compounds are made according to the procedures of Example 18 except that



is used instead of 4-chloro-6-phenyl-thieno[3,2-d]pyrimidine in step 1. Illustrative examples of R^1's are found throughout this disclosure as well as in Table 1.

[0389] **Example 19**

[0390] This example describes the synthesis of



[0391] **Step 1:** (3-Methoxy-4-nitro-phenyl)-methanol (compound **19.1**; 2.78 mmol), THF(14.0 mL), PPh_3 (1.5 equivalents), and carbon tetrabromide (1.5 equivalents) are combined and stirred at room temperature for 2 hours. The reaction mixture was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel using a gradient of EtOAc/hexanes provided the corresponding bromide as a solid (87%). The resulting bromide (2.06 mmol) was added to DMSO (10 mL) and potassium cyanide (2.27 mmol), stirred at room temperature for 2.5 hours, hydrolyzed by the addition of 1.0 M HCl and then partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel using a gradient of EtOAc/hexanes provided (3-methoxy-4-nitro-phenyl)-acetonitrile (compound **19.2**) in 8%.

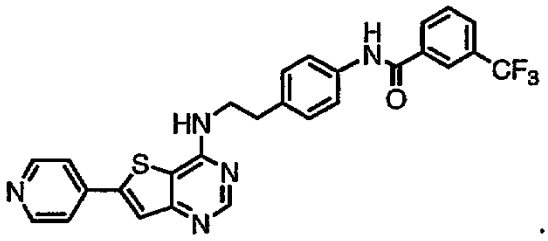
[0392] **Step 2:** Compound **19.2** (0.096 mmol), and catalytic Pd/C in EtOAc (2 mL) were placed under an atmosphere of hydrogen for 3 hours. The reaction mixture was filtered, concentrated and taken on crude to the next reaction. The crude compound (0.096 mmol), dichloromethane (0.5 mL), 3-(trifluoromethyl)benzoyl chloride (1.05 mmol) and DIEA (1.10 mmol) was stirred at room temperature for 10 minutes. Water was added after which the mixture partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel using a gradient of EtOAc/hexanes provided N-(4-cyanomethyl-2-methoxy-phenyl)-3-trifluoromethyl-benzamide (compound **19.3**) in 71%.

[0393] **Step 3:** Compound **19.3** (0.062 mmol), ethanol (1.5 mL), 4.0 M HCl/dioxane (1 equivalent) and catalytic Pd/C are placed under an atmosphere of hydrogen for 20 hours. The reaction mixture was filtered, concentrated and taken on crude to the next reaction. The crude compound (0.062 mmol), compound **6.2** (1.02

equiv), and DIEA (3.4 equiv.) was heated in *n*-butanol (0.52 mL) at 135 °C for 2 hours. The reaction mixture was cooled and then partitioned between dichlomethane and water. The organic layer was separated, washed with brine, dried, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel using a gradient of EtOAc/hexanes provided the titled compound as a pale yellow solid in 54%.

[0394] Example 20

[0395] This example describes the synthesis of



[0396] **Step 1:** A solution of compound **1.1** (1.0 mmol) and TEA (3.0 equiv.) in anhydrous THF (5.0 mL) was treated with the dropwise addition of 3-trifluoromethyl-benzoyl chloride (1.1 equivalents) at 0 °C. After completion of the reaction, the mixture was partitioned between water and diethyl ether. The organic layer was separated, washed with 1N HCl, saturated sodium bicarbonate, brine and dried. Purification by flash column chromatography on silica gel provided {2-[4-(3-trifluoromethyl-benzoylamino)-phenyl]-ethyl}-carbamic acid tert-butyl ester (compound **20.1**).

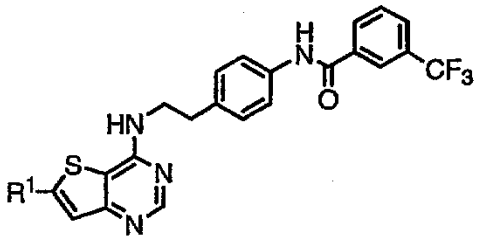
[0397] **Step 2:** Compound **20.1** (1.0 mmol) was treated with anhydrous 4.0 N HCl in dioxane (25 mL) at 0 °C, stirred at room temperature for 2 hours and concentrated to dryness under reduced pressure. The crude amine salt, 4-chloro-6-bromo thieno[3,2-d]pyrimidine (1.0 equivalent) and *N*, *N*-diisopropylethylamine (2.5 equivalents) was then heated in *n*-butanol (10 mL) at 135 °C for 2 hours. The reaction mixture was cooled and then partitioned between dichloromethane and water. The organic layer was separated, washed with brine, dried and concentrated under reduced pressure. The desired product, N-{4-[2-(6-bromo-thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-phenyl}-3-trifluoromethyl-benzamide (compound **20.2**), was then precipitated from EtOAc and hexanes to give a tan powder.

[0398] **Step 3:** Compound **20.2** (0.1 mmol), 4-pyridineboronic acid (3.0 equivalents), $Pd_2(dba)_3$ (16 mol%), $AsPh_3$ (30 mol%) and K_2HPO_4 (3.0 equivalents) in DMF (3.0 mL) and water (0.75 mL) was heated at 90 °C for 3 hours. The reaction

was cooled and after aqueous work-up and purification by flash column chromatography on silica gel, the titled compound is obtained.

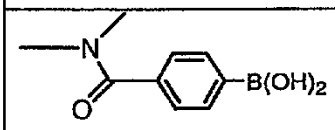
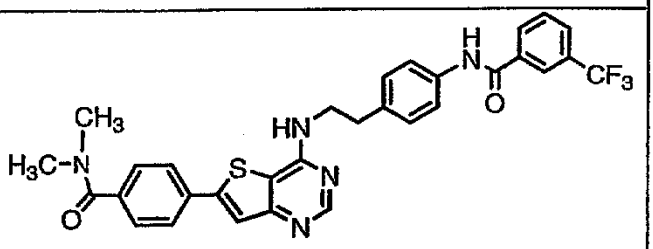
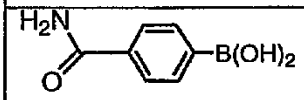
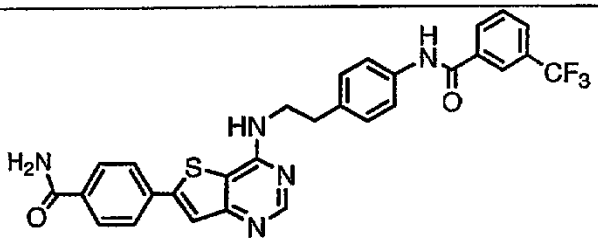
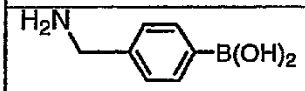
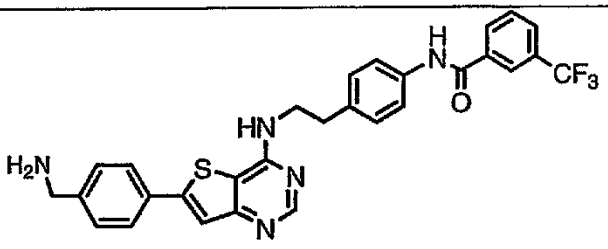
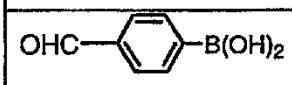
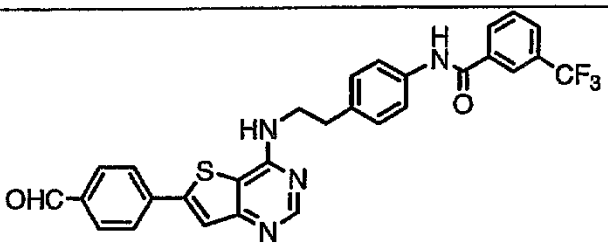
[0399] Example 21

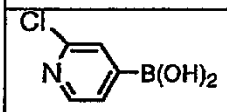
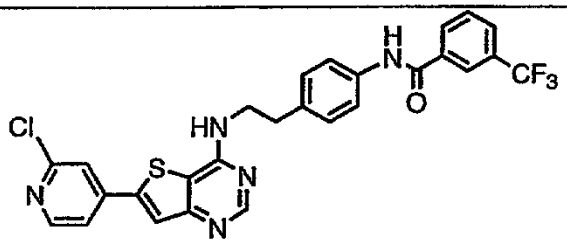
[0400] This example describes the synthesis of



where R^1 is as described previously. These compounds are made according to Example 20 except that $R^1B(OH)_2$ is used instead of 4-chloro-6-bromo thieno[3,2-d]pyrimidine in step 2. Illustrative examples of suitable R^1's are found throughout this disclosure as well as in Table 7.

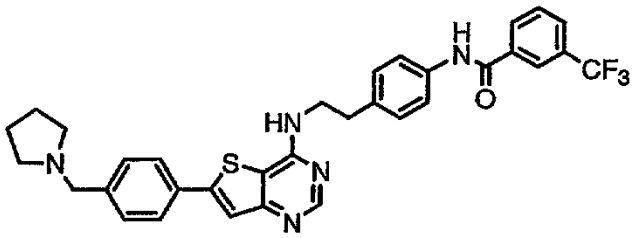
[0401] Table 7

$R^1B(OH)_2$	Final Compound
	
	
	
	

$R^1B(OH)_2$	Final Compound
	

[0402] **Example 22**

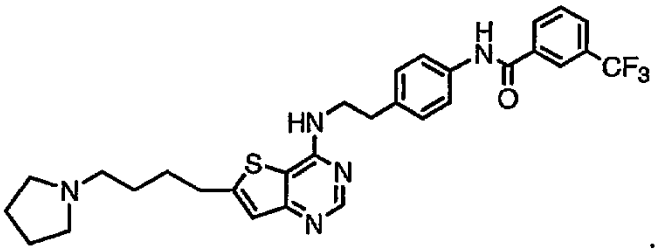
[0403] This example describes the synthesis of



[0404] **Step1:** N-(4-{2-[6-(4-Formyl-phenyl)-thieno[3,2-d]pyrimidin-4-ylamino]-ethyl}-phenyl)-3-trifluoromethyl-benzamide (compound **22.1**) was prepared as described in Example 21 using 4-formylphenylboronic acid.

[0405] **Step 2:** To a suspension of compound **22.1** (0.07 mmol) and pyrrolidine (5.0 equivalents) in ethanol (3.0 ml) and AcOH (0.5 mL) was added $NaCNBH_3$ (1.4 equiv.) at room temperature. After 2 hours the reaction mixture was partitioned between EtOAc and saturated sodium bicarbonate. The organic layer was separated, dried and concentrated under reduced pressure. Purification by preparative TLC provided the titled compound.

[0406] **Example 23**



[0407] **Step 1:** To a nitrogen purged solution of compound **20.2** (0.79 mmol), 3-butyn-1-ol (2.5 equivalents), $Pd(PhCN)_2Cl_2$ (0.2 equivalent) in piperidine was added CuI (0.5 equivalent) followed by stirring at room temperature for 3 hours. The reaction mixture was then subjected to an aqueous work-up and purified by flash column chromatography on silica gel to provide N-(4-{2-[6-(4-hydroxy-but-1-ynyl)-

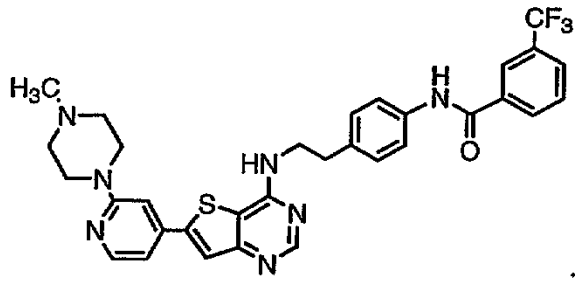
thieno[3,2-d]pyrimidin-4-ylamino]-ethyl}-phenyl)-3-trifluoromethyl-benzamide (compound **23.1**).

[0408] **Step 2:** To a solution of compound **23.1** (0.27 mmol) in dichloromethane was added sequentially TEA (3.0 equiv.) and methanesulfonyl chloride (2.5 equivalents). After stirring at room temperature for 2 hours, excess pyrrolidine (~ 5.0 equivalent) was added and the reaction was heated at 40 °C until starting material is consumed. The reaction was cooled, concentrated to dryness and purified by flash column chromatography on silica gel to provide N-(4-{2-[6-(4-pyrrolidin-1-yl-but-1-ynyl)-thieno[3,2-d]pyrimidin-4-ylamino]-ethyl}-phenyl)-3-trifluoromethyl-benzamide (compound **23.2**).

[0409] **Step 3:** A solution of compound **23.2** (0.06 mmol) and 10% palladium on carbon (0.11 equivalent) in MeOH was stirred under an atmosphere of hydrogen (via a balloon) until all starting material was consumed. The reaction mixture was filtered, concentrated to dryness and purified by flash column chromatography on silica gel to provide the titled compound.

[0410] **Example 24**

[0411] This example describes the synthesis of

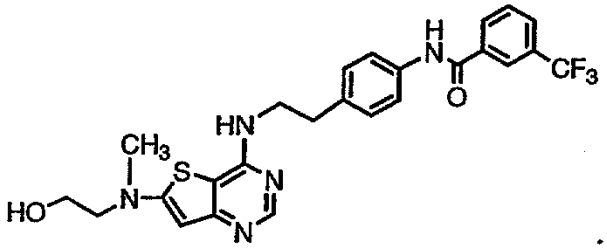


[0412] **Step 1:** N-(4-{2-[6-(2-Chloro-pyridin-4-yl)-thieno[3,2-d]pyrimidin-4-ylamino]-ethyl}-phenyl)-3-trifluoromethyl-benzamide (compound **21.1**) was prepared as described in Example 21 using 2-chloropyridine-4-boronic acid.

[0413] **Step 2:** A solution of compound **21.1** (0.036 mmol) and 1-methylpiperazine (10 equiv.) in 1-methyl-2-pyrrolidinone (2.0 mL) was heated overnight at 200 °C in a screw-top reaction vial. The reaction was cooled, concentrated and purified by preparative TLC to give the titled compound.

[0414] **Example 25**

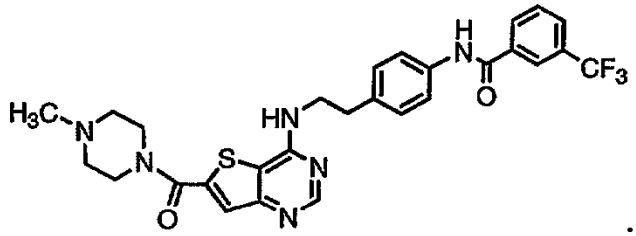
[0415] This example describes the synthesis of



[0416] To a flame-dried round-bottom flask containing compound **20.2** (0.19 mmol) was added DMSO (1.0 mL) followed by 2-(methylamino)-ethanol (0.96 mmol). The reaction was stirred under nitrogen at 150 °C overnight and then cooled to room temperature. Purification by reverse-phase HPLC (aqueous 0.1% TFA/ CH_3CN) provided the titled compound as an off-white powder (20 mg, 17 %).

[0417] **Example 26**

[0418] This example describes the synthesis of



[0419] **Step 1:** To a nitrogen purged solution of compound **20.2** (0.42 mmol), $Pd(AcO)_2$ (0.2 equivalent) and 1,3-bis(diphenylphosphino)propane ("Dppp"; 0.2 equivalent) in DMF (10.0 mL) and MeOH (2.0 mL) was added DIEA (4.1 equivalents). CO gas was bubbled through the reaction mixture for 20 minutes and the reaction was then stirred for 3.5 hours under a CO atmosphere (via a balloon) at 80 °C. After aqueous work-up and purification by flash column chromatography on silica gel, 4-{2-[4-(3-trifluoromethyl-benzoylamino)-phenyl]-ethylamino}-thieno[3,2-d]pyrimidine-6-carboxylic acid methyl ester (compound **26.1**) was obtained.

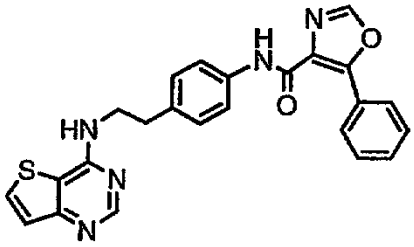
[0420] **Step 2:** To a solution of compound **26.1** (0.72 mmol) in THF (5.0 mL) was added aqueous 1.0 M LiOH (6.0 equivalents). The reaction mixture was stirred at 70 °C until all of the starting material was consumed. The reaction was cooled, neutralized with 10% HCl and concentrated to dryness under reduced pressure to provide 4-{2-[4-(3-trifluoromethyl-benzoylamino)-phenyl]-ethylamino}-thieno[3,2-d]pyrimidine-6-carboxylic acid (compound **26.2**).

[0421] **Step 3:** To a solution of compound **26.2** (0.08 mmol) in DMF (1.0 mL) was added 1-methylpiperazine (2.1 equivalents), DIEA (3.5 equivalents), DMAP (0.5 equivalent) and HATU (1.2 equivalents) at room temperature. After overnight

stirring followed by aqueous work-up, the titled compound was isolated after preparative TLC purification.

[0422] **Example 27**

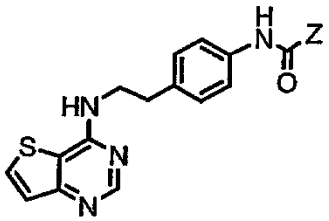
[0423] This example describes the synthesis of



[0424] To a solution of compound **12.2** (0.37 mmol) in DMF (3.0 mL) was added 5-phenyl-oxazole-4-carboxylic acid (1.0 equivalent), DIEA (3.4 equivalents), and HATU (1.1 equivalents). After overnight heating at 50 °C the reaction was directly subjected to purification by reverse-phase HPLC (aqueous 0.1% TFA/ CH_3CN) to provide the titled compound after lyophilization.

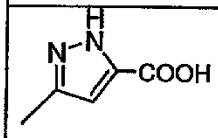
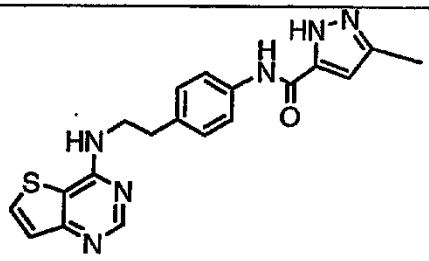
[0425] **Example 28**

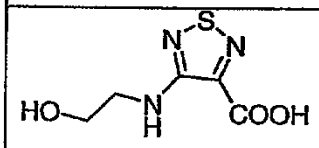
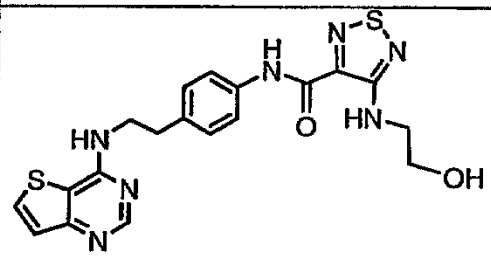
[0426] This example describes the synthesis of



where Z is as previously described. These compounds are made according to Example 27 except that ZCOOH is used instead of 5-phenyl-oxazole-4-carboxylic acid. Illustrative examples of suitable Z's are found throughout this disclosure as well as in Table 8.

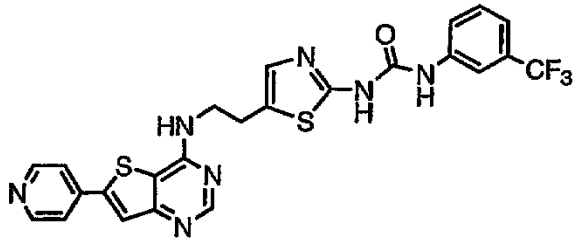
[0427] **Table 8**

ZCOOH	Final Compound
	

ZCOOH	Final Compound
	

[0428] **Example 29**

[0429] This example describes the synthesis of

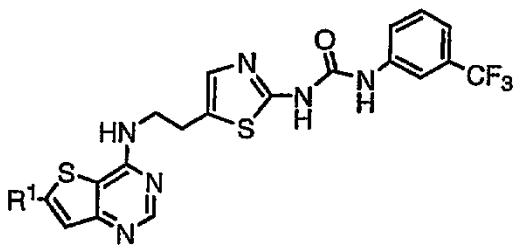


[0430] **Step 1:** A sealed Pyrex tube was charged, under nitrogen, with {5-[2-(6-bromo-thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-thiazol-2-yl}-carbamic acid tert-butyl ester (compound **29.1**; 0.2 mmol), 4-pyridineboronic acid (0.25 mmol), $PdCl_2(PPh_3)_2$ (0.04 mmol), 2M Na_2CO_3 (0.6 mmol), water (0.5mL), and DMF (1.5mL). The reaction mixture was heated subjected to microwave irradiation at 50 watts for 5 minutes at 100°C and then at 300 watts for 20 minutes at 120°C. After cooling, the reaction mixture was filtered and concentrated to provide crude [2-(2-amino-thiazol-5-yl)-ethyl]-(6-pyridin-4-yl-thieno[3,2-d]pyrimidin-4-yl)-amine (compound **29.2**) which was used in the next step without further purification.

[0431] **Step 2:** Compound **29.2** (0.15mmol) and 3-trifluoromethylphenyl isocyanate (0.2 mmol) was heated in acetonitrile (2 mL) at 70 °C for 4 hours. The reaction mixture was cooled, concentrated and purified by preparative TLC chromatography (5%MeOH in dichloromethane) to provide the titled compound.

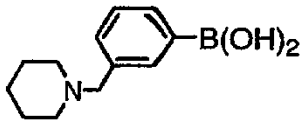
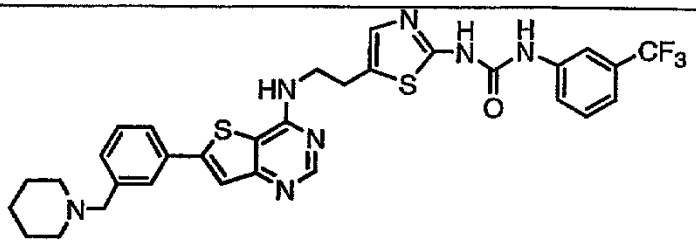
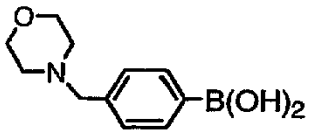
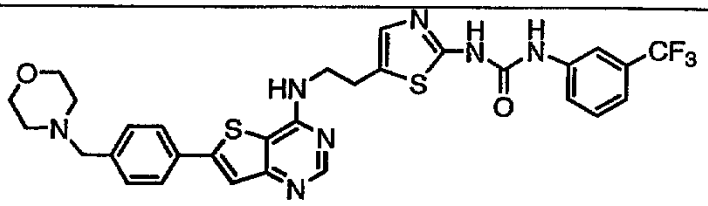
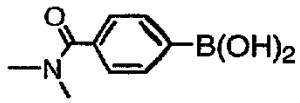
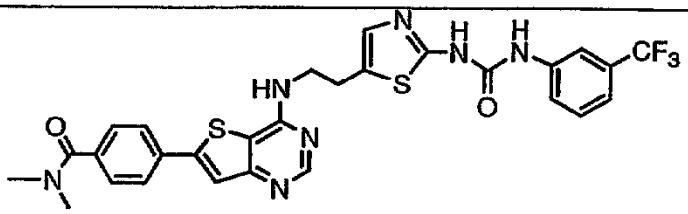
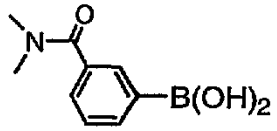
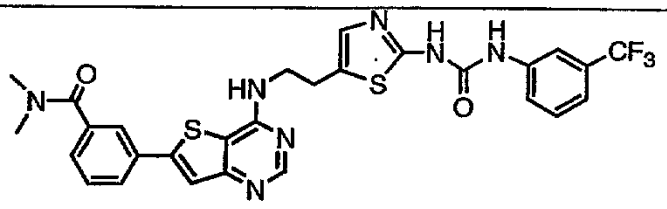
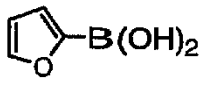
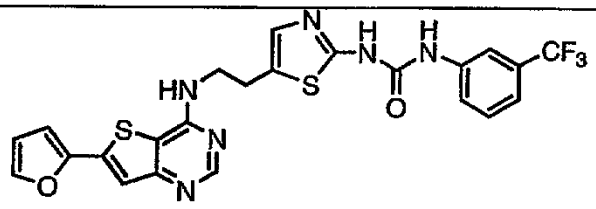
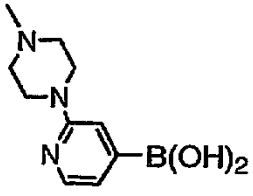
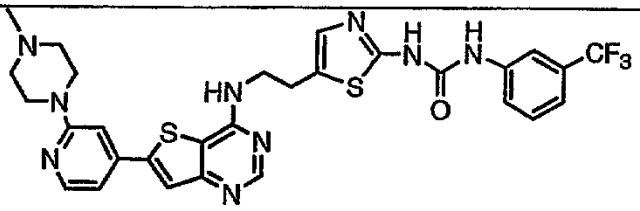
[0432] **Example 30**

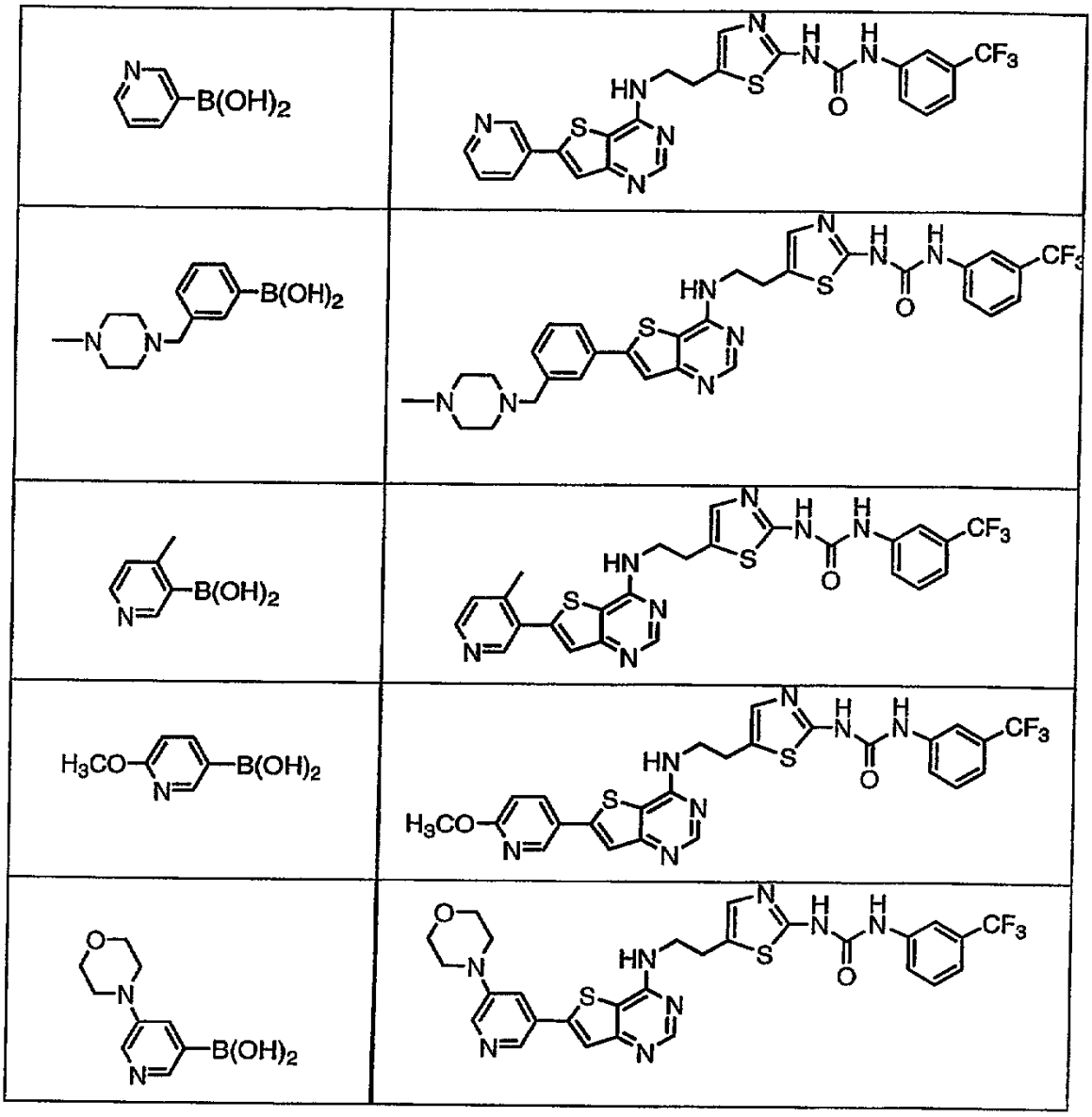
[0433] This example describes the synthesis of



where R^1 is as described previously. These compounds are made according to Example 29 except that $R^1B(OH)_2$ is used instead of 4-pyridineboronic acid in step 1. Illustrative examples of suitable R^1's are found throughout this disclosure as well as in Table 9.

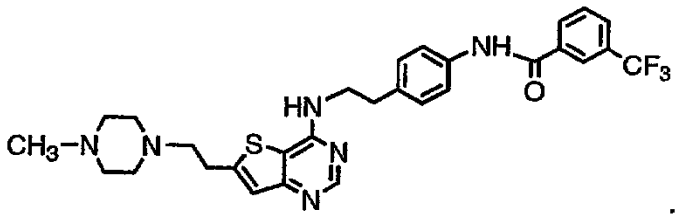
[0434] Table 9

$R^1B(OH)_2$	Final Compound
	
	
	
	
	
	



[0435] **Example 31**

[0436] This example describes the synthesis of



[0437] **Step 1:** Compound **26.1** is converted to the corresponding aldehyde via a two step reaction sequence. First, compound **26.1** is reduced to the alcohol with diisobutylaluminum hydride ("DIBAL") at -78°C. Second, after standard work-up and purification, the resulting alcohol is oxidized to N-{4-[2-(6-formyl-thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-phenyl}-3-trifluoromethyl-benzamide (compound

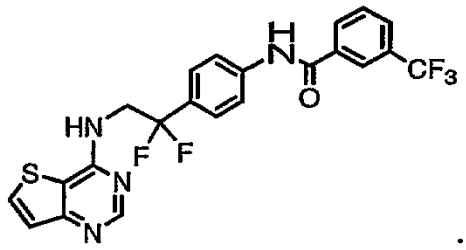
31.1) using pyridinium dichromate ("PDC") under standard conditions. Such transformations are found, for example, in Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents, Burke, S.D.; Danheiser, R.L., Ed.; John Wiley and Sons Inc: New York.

[0438] **Step 2:** Compound **31.1** is reacted with the ylide generated from (methoxymethyl)triphenylphosphonium chloride. The resulting product is then hydrolyzed with aqueous HCl to yield N-(4-{2-[6-(2-oxo-ethyl)-thieno[3,2-d]pyrimidin-4-ylamino]-ethyl}-phenyl)-3-trifluoromethyl-benzamide (compound **31.2**). Such a transformation is found, for example, in Stork, G. et.al. *J. Am. Chem. Soc.* **2001**, *123*, 3239.

[0439] **Step 3:** The titled compound is prepared according to Step 2 of Example 22 except for using compound **31.2** instead of compound **22.1** and for using 1-methylpiperazine instead of pyrrolidine.

[0440] **Example 32**

[0441] This example describes the synthesis of



[0442] **Step 1:** Difluoro-(4-nitro-phenyl)-acetic acid ethyl ester (compound **32.1**) is reacted according to Sato, K. et. al. *Chem. Pharm. Bull.* **1999**, *47*, 1013). Briefly, compound **32.1** and catalytic Pd/C in EtOAc are placed under an atmosphere of hydrogen for 3 hours. The reaction mixture is filtered, concentrated and taken on crude to the next reaction. The crude compound, dichloromethane , 3-(trifluoromethyl)benzoyl chloride and DIEA are stirred at room temperature for 10 minutes. Water is added after which the mixture partitioned between EtOAc and water. The organic layer is separated, washed with brine, dried, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel using a gradient of EtOAc/hexanes provides difluoro-[4-(3-trifluoromethyl-benzoylamino)-phenyl]-acetic acid ethyl ester (compound **32.2**).

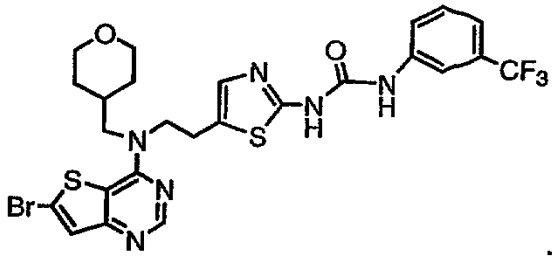
[0443] **Step 2:** Compound **32.2** is reduced with DIBAL at -78°C to the corresponding aldehyde according to a procedure found in Ishikawa, T. et. al. *J. Am. Chem. Soc.***2000**, *122*, 7633. The resulting aldehyde is then converted into N-[4-(2-

amino-1,1-difluoro-ethyl)-phenyl]-3-trifluoromethyl-benzamide (compound **32.3**) via reductive amination using NH_4OAc and $NaCNBH_3$ according to a procedure found in Aurelin, L. et. al. *J. Org. Chem.* **2003**, *68*, 2652.

[0444] **Step 3:** Compound **32.3**, compound **6.2** and DIEA are heated in n-butanol at 135 °C for 2 hours. The reaction mixture is cooled and then partitioned between dichloromethane and water. The organic layer is separated, washed with brine, dried, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel using a gardient of EtOAc/hexanes provides the titled compound.

[0445] **Example 33**

[0446] This example describes the synthesis of



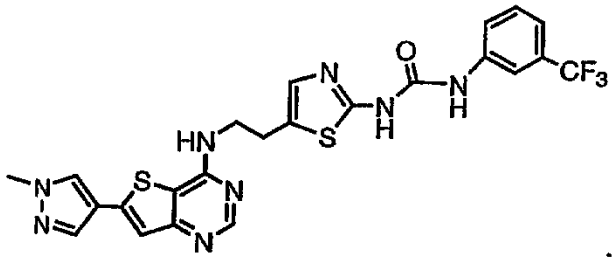
[0447] **Step 1:** A flask was charged with compound **14.1** (200 mg, 100 mol %), tetrahydro-pyran-4-carbaldehyde (100 mol %), and dichloroethane. To this was added $NaBH(OAc)_3$ (150 mol %) and the resulting slurry was stirred at room temperature for 2 hours. The solvents were removed in vacuo and the residue was re-suspended in EtOAc and H_2O. The organic layer was washed sequentially with saturated sodium bicarbonate, H_2O, and brine. The organic layers were combined, dried over Na_2SO_4, and concentrated to give (5-{2-[(tetrahydro-pyran-4-ylmethyl)-amino]-ethyl}-thiazol-2-yl)-carbamic acid tert-butyl ester (compound **33.1**) as an oil which was used in the next step without further purification.

[0448] **Step 2:** Compound **33.1**, *n*-butanol (2 mL), 6-bromo-4-chloro-[3,2-d]thienopyrimidine (100 mol %), and DIEA (500 mol %) was stirred for 2 hours at 100 °C and then concentrated in vacuo. The resulting oil was treated with 4N HCl in dioxane (10 mL) at room temperature for 1 hour. The reaction was concentrated to a solid and lixiviated three times with cold ether to provide [2-(2-amino-thiazol-5-yl)-ethyl]-(6-bromo-thieno[3,2-d]pyrimidin-4-yl)-(tetrahydro-pyran-4-ylmethyl)-amine (compound **33.2**) as a HCl salt which was used in the next step without further purification.

[0449] **Step 3:** Crude **33.2** was suspended in DMF (2 mL) and DIEA (1 mL). To this solution was added trifluoromethylphenyl isocyanate (120 mol%). The solution was stirred at room temperature for 5 minutes and then purified by reverse phase HPLC providing the titled compound. LCMS $[M+H]^+$ *m/z* 643.1

[0450] **Example 34**

[0451] This example describes the synthesis of

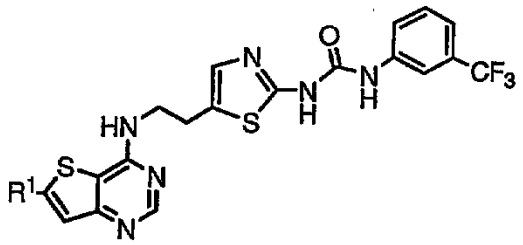


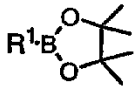
[0452] **Step 1:** 1-{5-[2-(6-Bromo-thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-thiazol-2-yl}-3-(3-trifluoromethyl-phenyl)-urea (compound **34.1**) was prepared according to Example 18 except that 6-bromo-4-chloro-[3,2-d]thienopyrimidine was used instead of 4-chloro-6-phenyl-thieno[3,2-d]pyrimidine in step 1.

[0453] **Step 2:** Compound **32.1** (100 mg, 100 mol %), 1-methyl–4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (46 mg, 120 mole %) and $PdCl_2(PPh_3)_2$ (20 mol %) was placed in a 100 mL reaction vial and to this was added DMF/H_2O (4:1, 4 mL) along with 2N Na_2CO_3 (1 mL). The vial was flushed with nitrogen, sealed and subjected to microwave irradiation (10 minutes, 300W, 100 °C). The contents were cooled, the solid precipitate was filtered and washed with cold ether and recrystallized from MeOH/ether to provide the titled compound. LCMS $[M+H]^+$ *m/z* 545.1

[0454] **Example 35**

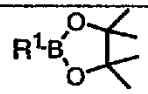
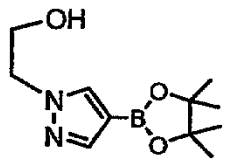
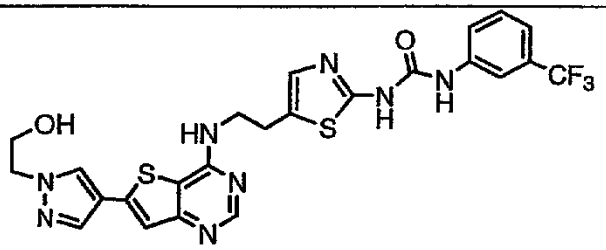
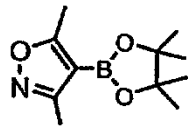
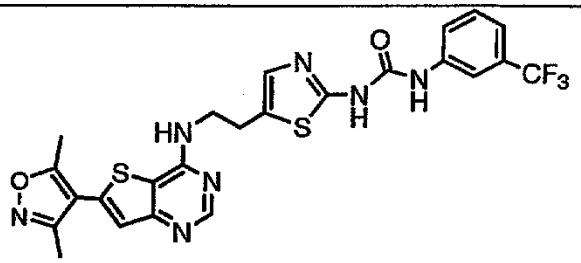
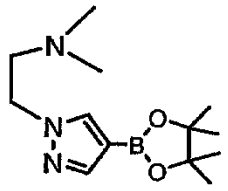
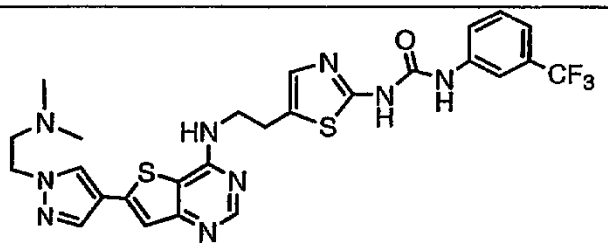
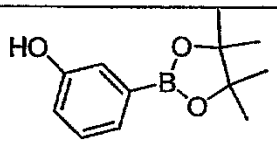
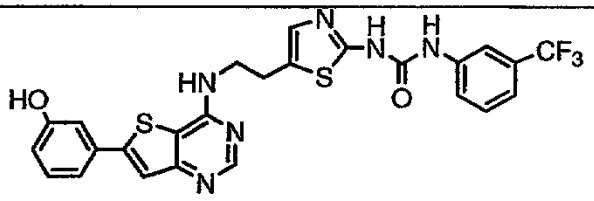
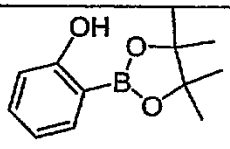
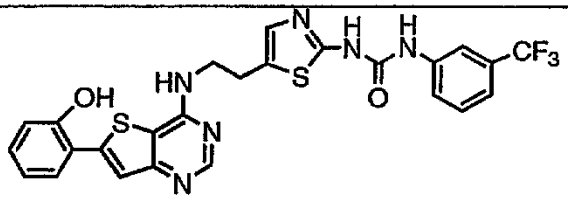
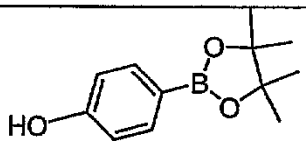
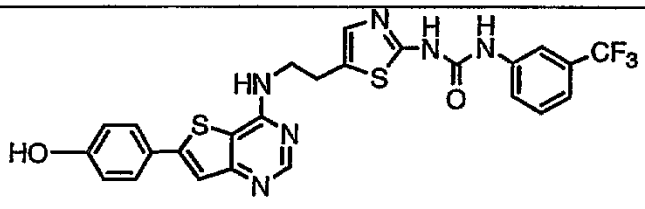
[0455] This example describes the synthesis of



where R^1 is as previously described. These compounds are made according to Example 34 except that  is used instead of 1-methyl-4-(4,4,5,5-tetramethyl-

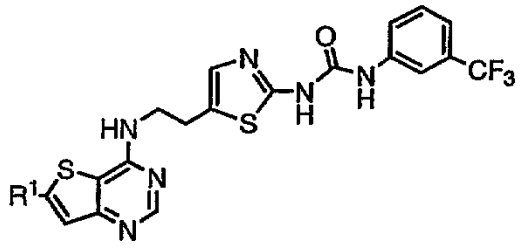
[1,3,2]dioxaborolan-2-yl)-1H-pyrazole in step 2. Illustrative examples of suitable R^1's are found throughout this disclosure as well as in Table 10.

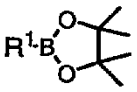
[0456] Table 10

	Final Compound
	
	
	
	
	
	

[0457] Example 36

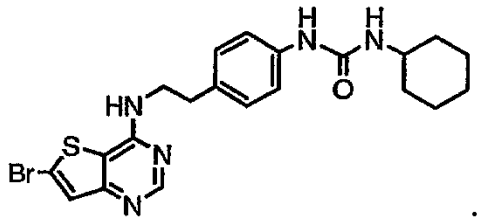
[0458] This example describes an alternate synthesis of



where R^1 is as previously described. Illustrative examples of suitable R^1's are found throughout this disclosure as well as in Table 10. These compounds are made according to Example 15 except that compound **34.1** and  are used instead of compound **20.2** and 4-pyridineboronic acid in step 3.

[0459] **Example 37**

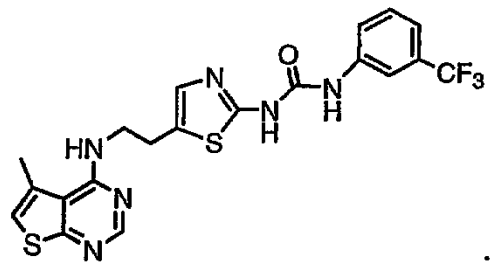
[0460] This example describes the synthesis of



[0461] [2-(4-Amino-phenyl)-ethyl]-(6-bromo-thieno[3,2-d]pyrimidin-4-yl)-amine (compound **37.1**; 75 mg, 100 mol %) was suspended in N-methyl-2-pyrrolidone (0.5 mL) and DIEA (150 uL, 400 mol %). To this solution was added cyclohexyl isocyanate (110 mol %). The reaction was heated at 95 °C for 1 hour, cooled and purified by reverse phase HPLC to provide the titled compound. LCMS $[M+H]^+$ *m/z* 474.2

[0462] **Example 38**

[0463] This example describes the synthesis of

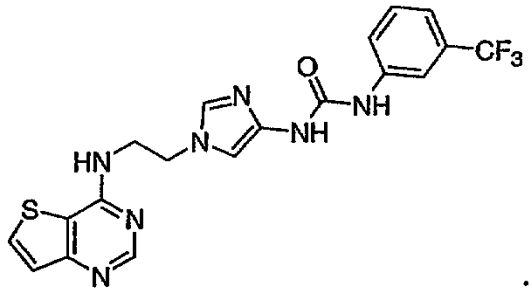


[0464] 1-[5-(2-Amino-ethyl)-thiazol-2-yl]-3-(3-trifluoromethyl-phenyl)-urea (compound **38.1**; 200 mg, 100 mol%), 5-methyl-4-chloro-[2,3-d]thienopyrimidine (112 mg, 100 mol %) and DIEA (500 mol %) in DMF (2 mL) was heated at 100 °C

for 15 min, cooled and purified by reverse phase HPLC to provide the titled compound. LCMS $[M+H]^+$ *m/z* 479.1

[0465] Example 39

[0466] This example describes the synthesis of



[0467] Step 1: A mixture of methanesulfonic acid 2-tert-butoxycarbonylamino-ethyl ester (compound **39.1**; 2.04 g, 8.53 mmol, prepared according to the procedure of Hey, M.P. *et. al J. Med. Chem* 37, **1994**, 381), 4-nitroimidazole (876 mg, 7.75 mmol), K_2CO_3 (1.18 g, 8.53 mmol), in DMF is stirred at 110 °C for 2 hours. After cooling to room temperature, the mixture is diluted with EtOAc and washed with water. The aqueous layer was extracted three times with EtOAc and the combined organic phases were dried (Na_2SO_4) and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 45 to 100% EtOAc in hexanes) to yield 634 mg (32%) of [2-(4-nitro-imidazol-1-yl)-ethyl]-carbamic acid tert-butyl ester (compound **39.2**) as a solid, ES (+) MS m/e =257 ($M+H^+$).

[0468] Step 2: A flask containing compound **39.2** (400mg, 1.56 mmol) and 10% (dry basis) palladium on activated carbon (~50% wet, Deguessa, 664 mg, ~0.312 mmol) in MeOH (6.0 mL) was sealed with a septum and purged with nitrogen followed by hydrogen. The mixture was stirred under hydrogen (balloon pressure) at ambient temperature for 3 hours. After completion of the reaction, the mixture was filtered through a plug of celite and concentrated. The residue was dried under high-vacuum to yield 353 mg (quantitative) of [2-(4-amino-imidazol-1-yl)-ethyl]-carbamic acid tert-butyl ester (compound **39.3**) as a solid, ES (+) MS m/e =227 ($M+H^+$).

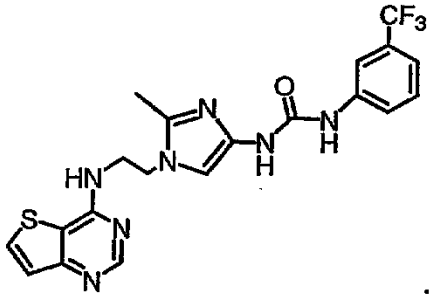
[0469] Step 3: To a solution of compound **39.3** in dichloromethane under nitrogen was added 3-trifluoromethylphenyl isocyanate dropwise. After about 0.1 hour, a white precipitate formed. The precipitate was filtered off, washed with dichloromethane and dried under high-vacuum to yield 485 mg (75%) of (2-{4-[3-(3-trifluoromethyl-phenyl)-ureido]-imidazol-1-yl}-ethyl)-carbamic acid tert-butyl ester (compound **39.4**) as a white solid, ES (+) MS m/e=414 ($M+H^+$).

[0470] **Step 4:** A mixture of compound **39.4** (485 mg, 1.17 mmol) and 4.0 N HCl in dioxane (10.0 mL) was stirred at room temperature for 0.25 hour. The solvent was then removed under reduced pressure and the residue was dried under high-vacuum to yield 410 mg (91%) of a HCl salt of 1-[1-(2-amino-ethyl)-1H-imidazol-4-yl]-3-(3-trifluoromethyl-phenyl)-urea (compound **39.5**) as a white solid, ES (+) MS m/e=314 ($M+H^+$).

[0471] **Step 5:** A mixture of compound **39.5** (309 mg, 0.800 mmol) and compound **6.2** (137 mg, 0.800 mmol) in DIEA/n-BuOH (1:1, 4.0 mL) was heated at 100 °C in a sealed tube behind a blast shield for 2 hours. After cooling to room temperature the mixture was concentrated under reduced pressure. The residue thus obtained was dried under high-vacuum and then purified by flash column chromatography on silica gel (0 to 10% MeOH in dichloromethane) to yield 222 mg (62%) of a solid, R_f 0.32 (10% MeOH in dichloromethane). ES (+) MS m/e =448 ($M+H^+$). This material was further purified on a C-18 column (10 g, 0 to 100% MeCN in aq. 0.01 N HCl). The fractions containing pure compound were pooled and lyophilized to yield 157 mg (38%) of the titled compound as a white solid. ES (+) MS m/e =448 ($M+H^+$).

[0472] **Example 40**

[0473] This example describes the synthesis of



[0474] **Step 1:** Compound **39.1** (2.0 g, 8.4 mmol) and 2-methyl-5-nitroimidazole (1.0 g, 8.4 mmol) in DMF (50 mL) were heated to 110 °C for 2 hours. The resulting reaction mixture was cooled to room temperature and diluted with water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography on silica gel using 40% EtOAc in hexanes to afford [2-(2-methyl-4-nitro-imidazol-1-yl)-ethyl]-carbamic acid tert-butyl ester (compound **40.1**; 0.44 g, 19%). ES (+) MS m/e = 271(M+1).

[0475] **Step 2:** 10 %wt Pd/C (0.17g 0.16 mmol) was added to a solution of compound **40.1** (0.44 g, 1.6 mmol) in MeOH (10 mL). The resulting reaction mixture was stirred under a hydrogen atmosphere (1 atm via a balloon). After 2 hours, the reaction mixture was filtered thru a plug of Celite and the resulting filtrate concentrated to provide [2-(4-amino-2-methyl-imidazol-1-yl)-ethyl]-carbamic acid tert-butyl ester (compound **40.2**; 0.3 g, 77%). ES (+) MS m/e = 241(M+1).

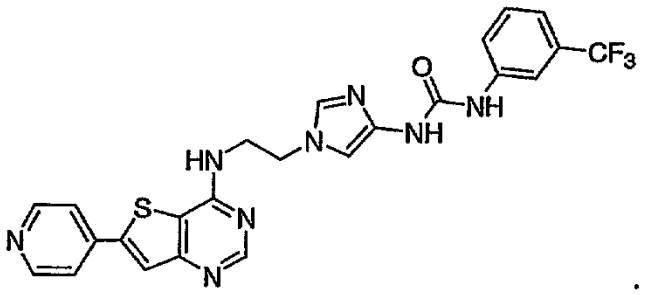
[0476] **Step 3:** 3-Trifluoromethylphenyl isocyanate (0.23 g, 1.2 mmol) was added to a solution of compound **40.2** (0.30 g, 1.2 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for 15 minutes, concentrated and purified by flash column chromatography on silica gel using EtOAc to provide (2-{2-methyl-4-[3-(3-trifluoromethyl-phenyl)-ureido]-imidazol-1-yl}-ethyl)-carbamic acid tert-butyl ester (compound **40.3**; 0.11 g, 21%). ES (+) MS m/e = 428(M+1).

[0477] **Step 4:** 4 N HCl in dioxanes (3 mL) was added to a solution of compound **40.3** (0.11 g, 0.26 mmol) in dichloromethane (3 mL). The reaction mixture stirred for 2 hours and concentrated to provide 1-[1-(2-amino-ethyl)-2-methyl-1H-imidazol-4-yl]-3-(3-trifluoromethyl-phenyl)-urea (compound **40.4**; 0.10g, 100%) as a HCl salt. ES (+) MS m/e = 328(M+1).

[0478] **Step 5:** 4-chloro-thieno[3,2-d]pyrimidine (0.040 g, 0.25 mmol) was added to a solution of compound **40.4** (0.094 g, 0.25mmol) and DIEA (0.13 mL, 0.94 mmol) in n-butanol (3 mL). The resulting reaction mixture was heated at 100 °C for 2 hours, cooled and concentrated to dryness. The resulting residue was purified by reverse phase HPLC to provide the titled compound (0.011 g, 10%). ES (+) MS m/e = 462(M+1).

[0479] **Example 41**

[0480] This example describes the synthesis of



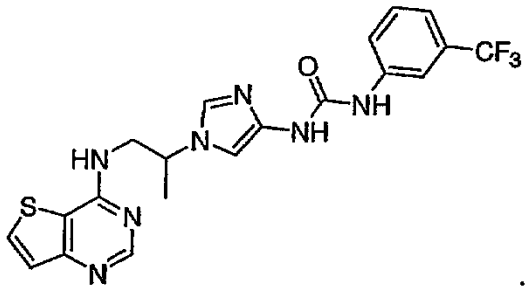
[0481] **Step 1:** A mixture of compound **39.5** (102 mg, 0.292 mmol) and 2-bromo-4-chloro-thieno[3,2-d]pyrimidine (73 mg, 0.292 mmol) in DIEA/*n*-butanol (1:1, 1.0 mL) was heated at 100 °C in a sealed tube behind a blast shield for 2 hours. After

cooling to room temperature the mixture was concentrated under reduced pressure. The residue thus obtained was dried under high-vacuum and then purified by preparative TLC (SiO_2, 10% MeOH in dichloromethane) to yield 80 mg (52%) of 1-{1-[2-(6-bromo-thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-1H-imidazol-4-yl}-3-(3-trifluoromethyl-phenyl)-urea (compound **41.1**) as a solid, R_f 0.34 (10% MeOH in dichloromethane). ES (+) MS m/e =528 ($M+H^+$).

[0482] **Step 2:** To a degassed mixture of compound **41.1** (119 mg, 0.226 mmol), 4-pyridine boronic acid 83 mg, 0.677 mmol), 0.8 mL aq. KH_2PO_4 (1.0 M, 0.8 mmol), in DMF at 100 °C was added Pd_2 (dba) $_3$ (21 mg, 0.0226 mmol) and triphenylarsine (17 mg, 0.0542 mmol). The resulting mixture was stirred at 100 °C under nitrogen for 6 hours. After cooling to room temperature, the mixture was partitioned between water and EtOAc and filtered through a plug of celite. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude residue was purified preparative TLC (SiO_2, 10% MeOH in dichloromethane) to yield a solid, R_f 0.27 (10% MeOH in dichloromethane). The solid was taken up in MeOH/dichloromethane and treated with 2.0 M HCl in ether. The resulting mixture was concentrated and the residue was lyophilized under high-vacuum to yield 15.3 mg of the titled compound as a white solid. ES (+) MS m/e =525 ($M+H^+$).

[0483] **Example 42**

[0484] This example describes the synthesis of



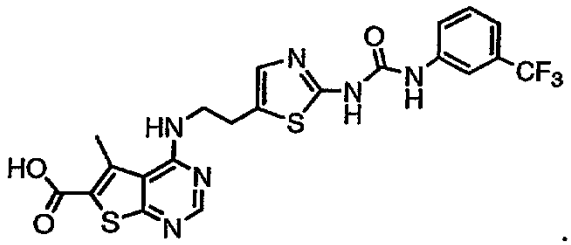
[0485] **Step 1:** To a mixture of 1-amino-propan-2-ol (compound **42.1**; 3.53 g, 47.0 mmol) and TEA (25 mL) in MeOH (35 mL) was slowly added a solution of di-tert-butyl dicarbonate (10.3 g, 47.0 mmol) in MeOH (15 mL). The resulting solution was stirred at room temperature over night. The mixture was then concentrated and the residue was dried under high-vacuum to yield 8.23 g (quantitative) of a clear oil. The oil thus obtained was dissolved in THF (100 mL) and treated with TEA (13.1 mL, 94.0 mmol). To the resulting solution was added methansulfonyl chloride

(0.3.82 mL, 49.3 mmol) dropwise at 0 °C under nitrogen. After 1 hour, the mixture was diluted with EtOAc and washed with aqueous 1 M HCl, aq sodium bicarbonate, and brine. The organic phase was dried (Na_2SO_4) and concentrated to yield 10.5 g (88%) of (compound **42.2**) as a clear oil which solidified upon standing, ES (+) MS m/e =254 ($M+H^+$).

[0486] **Step 2:** The titled compound was prepared according to Example 39 except that compound **42.2** was used instead of compound **39.1** in step 1.

[0487] **Example 43**

[0488] This example describes the synthesis of

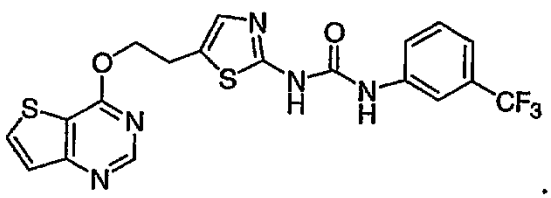


[0489] **Step 1:** A 20 mL vial was charged with 4-chloro-5-methyl-thieno[2,3-d]pyrimidine-6-carboxylic acid methyl ester (250 mg, 100 mol %), compound **38.1** (341 mg, 100 mole %), DIEA (1 mL) and DMF (2 mL). The resulting suspension was heated at 110 °C for 2 hours and cooled to room temperature. Concentration in vacuo provided 5-methyl-4-(2-{2-[3-(3-trifluoromethyl-phenyl)-ureido]-thiazol-5-yl}-ethylamino)-thieno[2,3-d]pyrimidine-6-carboxylic acid methyl ester; compound with methane (compound **43.1**) as a solid that was used in the next reaction without further purification. LCMS $[M+H]^+$ *m/z* 537.2

[0490] **Step 2:** A 20 mL vial was charged with compound **43.1** (100 mg), DMF (1 mL), and 2N NaOH (2 mL). The reaction was stirred at room temperature for 10 minutes and then purified by reverse phase HPLC (aqueous 0.1% CF_3COOH/MeCN gradient). The appropriate fractions were pooled, concentrated in vacuo to ~5 mL and lyophilized to dryness to provide the titled compound. LCMS $[M+H]^+$ *m/z* 523.1

[0491] **Example 44**

[0492] This example describes the synthesis of



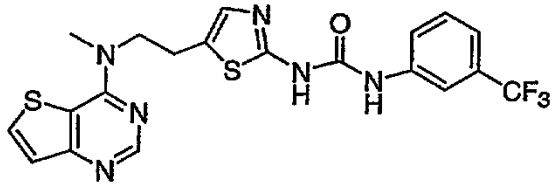
[0493] **Step 1:** To a solution of the HBr salt of (2-amino-thiazol-5-yl)-acetic acid methyl ester (compound **44.1**; 20 mmol) in DIEA (40 mmol) and DMF (100 mL) was added 3-trifluoromethylphenyl isocyanate (20 mmol) at room temperature. After overnight stirring, the reaction mixture was concentrated and purified by flash column chromatography on silica gel to provide {2-[3-(3-trifluoromethyl-phenyl)-ureido]-thiazol-5-yl}-acetic acid methyl ester (compound **44.2**) in 60% yield. EIMS (*m/z*): calcd. for $C_{14}H_{12}F_3N_3O_3S$ (M^+)+H 360.06, found 360.10.

[0494] **Step 2:** To a solution of compound **44.2** (10 mmol) in dry THF (50 mL) was added lithium aluminum hydride ("LAH"; 30 mmol; 1.0 M in THF) at room temperature. After stirring for 30 minutes, the reaction mixture was cooled and treated with the cautious addition of ice water. The solvent was removed, diluted with saturated sodium bicarbonate and extracted with EtOAc. The organic layers were combined, dried, concentrated and purified by flash column chromatography on silica gel to provide 1-[5-(2-hydroxy-ethyl)-thiazol-2-yl]-3-(3-trifluoromethyl-phenyl)-urea (compound **44.3**) in 95% yield. EIMS (*m/z*): calcd. for $C_{13}H_{12}F_3N_3O_2S$ (M^+)+H 332.06, found 332.10.

[0495] **Step 3:** To a solution of compound **44.3** (0.15 mmol) in dry DMF (2 mL) was added NaH (0.45 mmol, 60% oil dispersion) at room temperature and stirred for 30 minutes. Subsequently, 4-chlorothieno[3,-d]pyrimidine (0.15 mmol) was added and the resulting mixture was stirred at 60 °C for 1 hour and quenched by the addition of several drops of saturated ammonium chloride. The solvent was removed and the residue was purified by flash column chromatography on silica gel to provide the titled compound in 30% yield. EIMS (*m/z*): calcd. for $C_{19}H_{14}F_3N_5O_2S_2$ (M^+)+H 466.05, found 466.90.

[0496] **Example 45**

[0497] This example describes the synthesis of



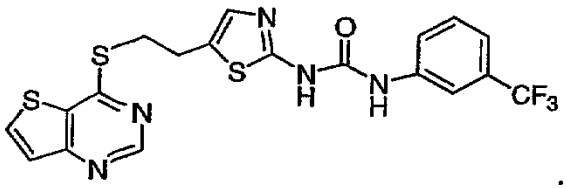
[0498] **Step 1:** A mixture of compound **44.2** (2.0 mmol) and anhydrous $MgCl_2$ (2.0 mmol) in methylamine (10 mL of a 2.0 M solution in THF) was stirred at room temperature for several hours. The mixture was concentrated, diluted with EtOAC and filtered. The filtrate was washed with brine, dried, concentrated and purified by

flash column chromatography on silica gel to provide the intermediate amide in 90% yield. EIMS (*m/z*): calcd. for $C_{14}H_{13}F_3N_4O_2S$ (M^+)+H 359.07, found 359.10. To a solution of the intermediate amide (1.0 mmol) in dry THF (5.0 mL) was added LAH (3.0 mmol, 1.0 M in THF) at room temperature. The resulting mixture was stirred at 60 °C for several hours, cooled to 0 °C and hydrolyzed with the addition of ice water. The mixture was concentrated, diluted with saturated sodium bicarbonate and extracted with EtOAc. The organic layer was then dried, concentrated and purified by flash column chromatography on silica gel to provide 1-[5-(2-methylamino-ethyl)-thiazol-2-yl]-3-(3-trifluoromethyl-phenyl)-urea (compound **45.1**) in 85% yield. EIMS (*m/z*): calcd. for $C_{14}H_{15}F_3N_4OS$ (M^+)+H 345.09, found 344.90.

[0499] **Step 2:** A mixture of compound **45.1** (0.15 mmol), compound **6.2** (0.15 mmol) and DIEA (0.15 mmol) in DMF (2.0 mL) was stirred at 100 °C for 2 hours. The solvent was removed and the residue purified by flash column chromatography on silica gel to provide the titled compound in 20% yield. EIMS (*m/z*): calcd. for $C_{20}H_{17}F_3N_6OS_2$ (M^+)+H 479.09, found 479.10.

[0500] **Example 46**

[0501] This example describes the synthesis of

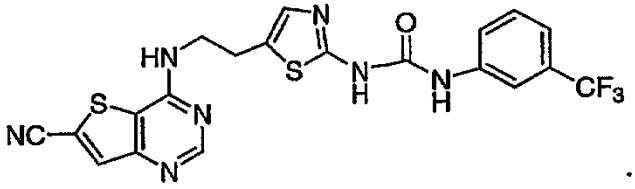


[0502] **Step 1:** To a solution of compound **44.3** (2.0 mmol) in dry dichlorormethane (10 mL) was added TEA (2.0 mmol) and tosyl chloride (2.2 mmol) at room temperature. The resulting mixture was stirred at room temperature for several hours, concentrated and purified by flash column chromatography on silica gel to provide the intermediate tosylate in 32% yield. EIMS (*m/z*): calcd. for $C_{20}H_{18}F_3N_3O_4S_2$ (M^+)+H 486.07, found 466.10. To a solution of the intermediate tosylate (0.5 mmol) in DMF (2.0 mL) was added potassium thioacetate (1.0 mmol) and the mixture was stirred at 90 °C for 2 hours. The solvent was removed and the residue was purified by flash column chromatography on silica gel to provide thioacetic acid S-(2-{2-[3-(3-trifluoromethyl-phenyl)-ureido]-thiazol-5-yl}-ethyl) ester (compound **46.1**) in 90% yield. EIMS (*m/z*): calcd. for $C_{15}H_{14}F_3N_3O_2S_2$ (M^+)+H 390.05, found 390.00.

[0503] **Step 2:** A mixture of compound **46_1** (0.15 mmol), compound **6.2** (0.15 mmol), and K_2CO_3 (0.16 mmol) in DMF (2.0 mL) was stirred at 90 °C for 1 hour. The solvent was removed and the residue purified by flash column chromatography on silica gel to provide the titled compound in 42% yield. EIMS (*m/z*): calcd. for $C_{19}H_{14}F_3N_5O_2S_3$ (M^+)+H 482.03, found 482.00.

[0504] **Example 47**

[0505] This example describes the synthesis of

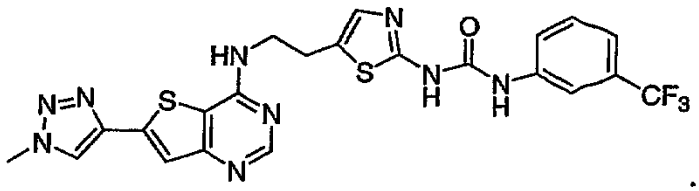


[0506] **Step 1:** To a suspension of compound **6.2** (5.0 mmol) in dry THF (25.0 mL) was added lithium diisopropylamide ("LDA"; 6.0 mmol; 2.0 M in heptane/THF/ethylbenzene) at -78 °C under an atmosphere of N_2. After stirring at -78 °C for 30 minutes, the mixture was transferred to a pre-cooled solution of TsCN (8.0 mmol) in dry THF (10 mL) at -78 °C. The resulting mixture was slowly warmed to room temperature and stirred for several hours. The reaction was quenched by the addition of several drops of saturated ammonium chloride and then concentrated. The residue was diluted with saturated sodium bicarbonate and extracted with EtOAc. The organic layers was dried, concentrated and purified by flash column chromatography on silica gel to provide 4-chloro-thieno[3,2-d]pyrimidine-6-carbonitrile c(compound **47.1**) in 20% yield. EIMS (*m/z*): calcd. for $C_7H_2CN_3S$ (M^+)+H 195.97, found 196.00.

[0507] **Step 2:** A mixture **47.1** (0.15 mmol), compound **38.1** (0.15 mmol) and DIEA (0.15 mmol) in DMF (2.0 mL) was stirred at 100 °C for 2 h. The solvent was removed and the residue purified by reverse phase HPLC (aqueous 0.1% CF_3COOH/MeCN gradient) to provide the titled compound in 40% yield. EIMS (*m/z*): calcd. for $C_{20}H_{14}F_3N_7OS_2$ (M^+)+H 490.07, found 490.90.

[0508] **Example 48**

[0509] This example describes the synthesis of



[0510] **Step 1:** A mixture of 6-bromo-4-chloro-thieno[3,2-d]pyrimidine (10.0 mmol), (trimethylsilyl)acetylene (12.0 mmol), $Pd(PhCN)_2Cl_2$,(1.0 mmol), CuI (1.0 mmol) and TEA (2.0 mmol) in dry THF (60.0 mL) was flushed with dry N_2 for several minutes and stirred at 60 °C for 30 minutes under an atmosphere of N_2. The solvent was removed and the residue purified by flash column chromatography on silica gel to provide 4-chloro-6-trimethylsilanylethynyl-thieno[3,2-d]pyrimidine (compound **48.1**) in 65% yield. EIMS (*m/z*): calcd. for $C_{11}H_{11}ClN_2SSi$ (M^+)+H 266.01, found 266.00.

[0511] **Step 2:** To a solution of compound **48.1** (5.0 mmol) in THF (50 mL) was tetrabutylammonium fluoride ("TBAF"; 5.0 mmol; 1.0 M in THF) at 0 °C. After stirring at 0 °C for 5 minutes, the reaction mixture was concentrated, diluted with EtOAc, washed with saturated sodium bicarbonate, brine and dried. The solvent was removed and the residue purified by flash column chromatography on silica gel to provide 4-chloro-6-ethynyl-thieno[3,2-d]pyrimidine (compound **48.2**) in 92% yield. EIMS (*m/z*): calcd. for $C_8H_3ClN_2S$ (M^+)+H 194.97, found 195.00

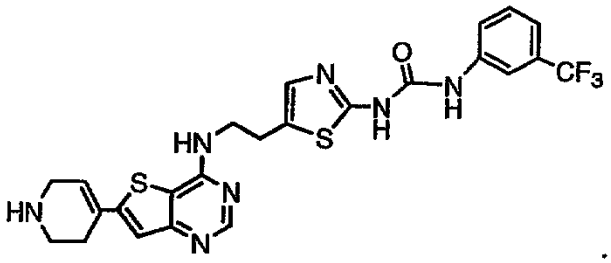
[0512] **Step 3:** A mixture of compound **48.2** (1.0 mmol), trimethylsilylmethyl azide (5.0 mmol), CuI (0.2 mmol), and DIEA (1.0 mmol) in DMF (10 mL) was stirred at room temperature for 24 hours. The solvent was removed and the residue was diluted with water and extracted with EtOAc. The organic layer was washed with dilute aqueous ammonium hydroxide, brine, dried, concentrated and purified by flash column chromatography to provide 4-chloro-6-(1-trimethylsilanylmethyl-1H-[1,2,3]triazol-4-yl)-thieno[3,2-d]pyrimidine (compound **48.3**) in 80% yield. EIMS (*m/z*): calcd. for $C_{12}H_{14}ClN_5SSi$ (M^+)+H 324.04, found 324.00.

[0513] **Step 4:** To a solution of compound **48.3** (0.5 mmol) in THF (10.0 mL) was added several drops of water and TBAF (0.55 mmol; 1.0 M in THF) at 0 °C. The resulting mixture was stirred at 0 °C for 15 minutes, concentrated and washed with hexanes. The white solid that formed was suspended in ice water (10 mL), filtered, washed with ice water and dried *in vacuo* to provide 4-chloro-6-(1-methyl-1H-[1,2,3]triazol-4-yl)-thieno[3,2-d]pyrimidine (compound **48.4**) in 95% yield. EIMS (*m/z*): calcd. for $C_9H_6ClN_5S$ (M^+)+H 252.00, found 252.00.

[0514] **Step 5:** A mixture of compound **48.4** (0.15 mmol), compound **38.1** (0.15 mmol) and DIEA (0.15 mmol) in DMF (2.0 mL) was stirred at 100 °C for 8 hours. The solvent was removed and the residue was purified by flash column chromatography on silica gel to provide the titled compound in 10% yield. EIMS (*m/z*): calcd. for $C_{22}H_{18}F_3N_9OS_2$ (M^+)+H 546.10, found 545.85.

[0515] **Example 49**

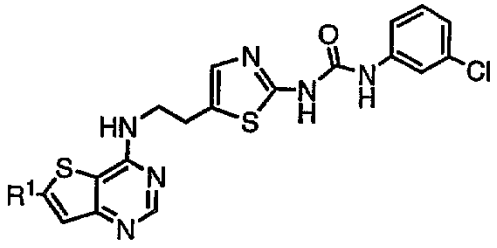
[0516] This example describes the synthesis of



[0517] A 100 mL vial was charged with compound **34.1** (125 mg, 100 mol %), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (86 mg, 120 mole %), and $PdCl_2(PPh_3)_2$ (33 mg, 20 mol %). To this was added DMF/H_2O (4:1, 1mL) along with 2N Na_2CO_3 (0.3 mL). The vial was flushed with nitrogen, sealed, and subjected to microwave irradiation (10 minutes, 300W, 100 °C). The contents were cooled and concentrated in vacuo. The resulting residue was purified by reverse phase HPLC (aqueous 0.1% CF_3COOH/MeCN gradient) resulting in a 1:1 mixture of 1-{5-[2-(thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-thiazol-2-yl}-3-(3-trifluoromethyl-phenyl)-urea; compound with 3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (compound **50.1**) and the titled compound. This mixture was dissolved in 4N HCl/dioxane (2 mL), stirred at room temperature for 15 minutes, and concentrated *in vacuo* to provide exclusively the HCl salt of the titled compound as a yellow powder LCMS $[M+H]^+$ *m/z* 546.1.

[0518] **Example 50**

[0519] This example describes the synthesis of

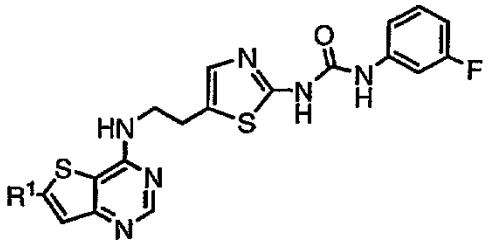


where R^1 is as described previously. These compounds are made according to Example 29 except that $R^1B(OH)_2$ is used instead of 4-pyridineboronic acid in step 1

and 3-chlorophenyl isocyanate is used instead of 3-trifluoromethylphenyl isocyanate in step 2. Illustrative examples of suitable R^1's are found throughout this disclosure as well as in Table 9.

[0520] Example 51

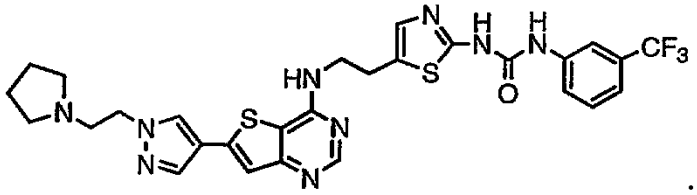
[0521] This example describes the synthesis of



where R^1 is as described previously. These compounds are made according to Example 29 except that $R^1B(OH)_2$ is used instead of 4-pyridineboronic acid in step 1 and 3-fluorophenyl isocyanate is used instead of 3-trifluoromethylphenyl isocyanate in step 2. Illustrative examples of suitable R^1's are found throughout this disclosure as well as in Table 9.

[0522] Example 52

[0523] This example describes the synthesis of



[0524] **Step 1:** To a flame dried flask was placed a suspension of compound **6.2** (5.92 mmol) in THF (50 mL). The reaction was cooled to –78 °C and a solution of LDA (3.25 mL of a 2.0 M solution in heptane/THF/ethyl benzene) was slowly added. After stirring for 30 minutes, a –78 °C, a solution of $(n\text{-Bu})_3SnCl$ (1.9 mL) in THF (50 mL) was added via cannula over a 20 minute period at –78 °C and stirred for 2 hours. The reaction was warmed to room temperature, hydrolyzed with saturated NH_4Cl, extracted with EtOAc, dried and concentrated. The crude product was purified by flash column chromatography on silica gel (1:1 hexanes/dichloromethane then 10% EtOAc/dichloromethane) to provide 4-chloro-6-tributylstannanyl-thieno[3,2-d]pyrimidine (compound **52.1**) in 92% yield.

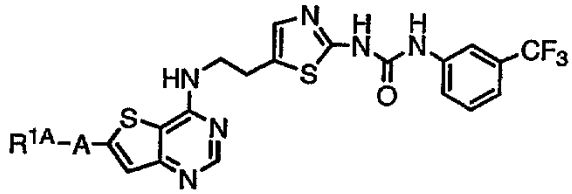
[0525] **Step 2:** Compound **52.1** (22.58 mmol) and 4-iodo-1-(2-pyrrolidin-1-yl-ethyl)-1H-pyrazole (22.32 mmol) was dissolved in DMF and degassed with nitrogen. To this was added $Pd_2(dba)_3$ (0.23 mmol), Ph_3As (0.46 mmol) and CuI (1.16 mmol).

The reaction mixture was heated at 80 °C for 6 hours, concentrated to dryness and purified by flash column chromatography on silica gel (10% MeOH in dichloromethane) to provide 4-chloro-6-[1-(2-pyrrolidin-1-yl-ethyl)-1H-pyrazol-4-yl]-thieno[3,2-d]pyrimidine (compound **52.2**).

[0526] **Step 3:** Compound **52.2** (3.04 mmol), compound **38.1** (3.03 mmol) and DIEA(6.88 mmol) in DMF (10 mL) was heated at 100 °C for 2 hours. The reaction mixture was concentrated to dryness and purified by column chromatography on C_{18} silica gel to provide the titled compound.

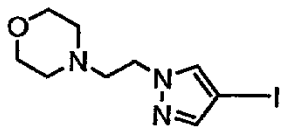
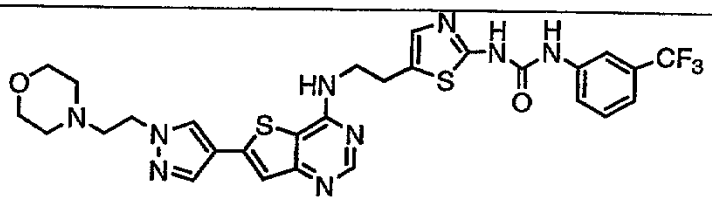
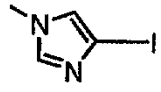
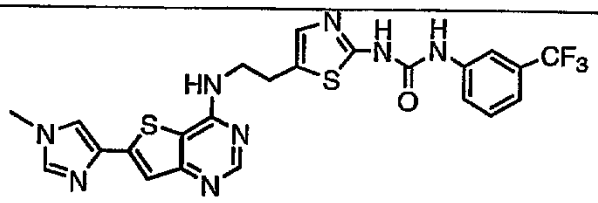
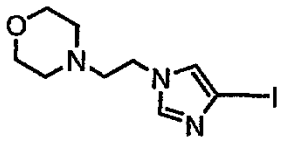
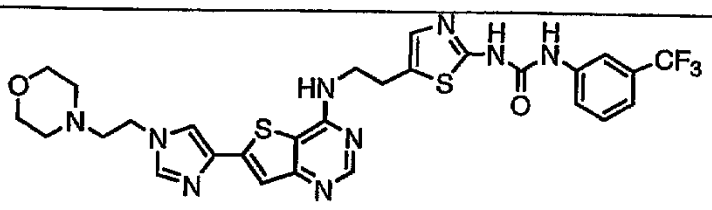
[0527] **Example 53**

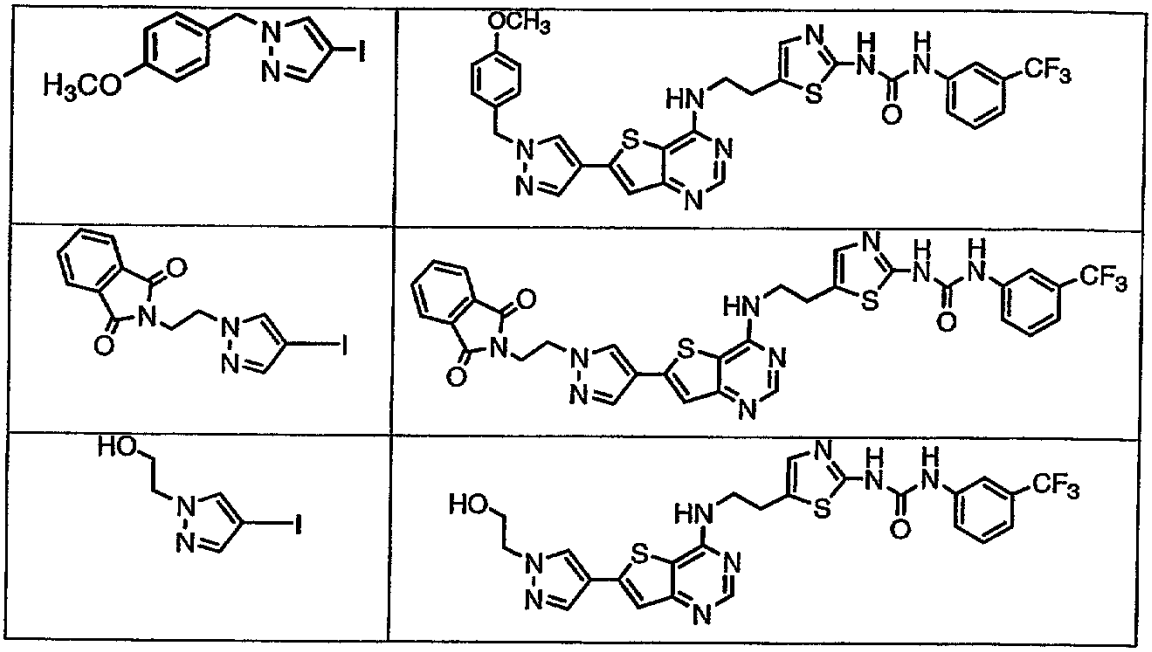
[0528] This example describes the synthesis of



where A and R^{1A} are as previously described. These compounds are made according to Example 52 except that R^{1A}-A-I is used instead of 4-iodo-1-(2-pyrrolidin-1-yl-ethyl)-1H-pyrazole in step 2. Illustrative examples of suitable R^{1A}'s and A's are found throughout this disclosure as well as in Table 11.

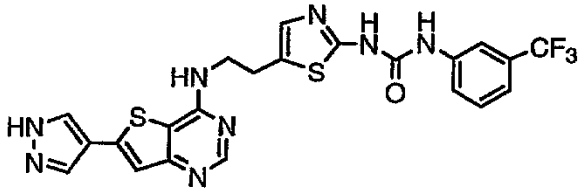
[0529] **Table 11**

R^{1A}-A-I	Final Compound
	
	
	



[0530] **Example 54**

[0531] This example describes the synthesis of

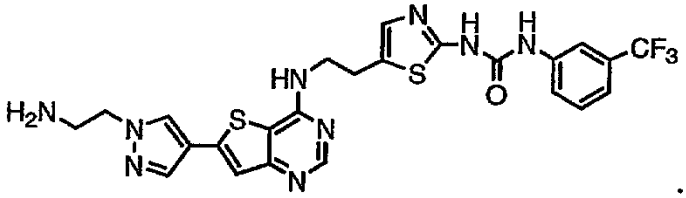


[0532] **Step 1:** 1-[5-(2-{6-[1-(4-Methoxy-benzyl)-1H-pyrazol-4-yl]-thieno[3,2-d]pyrimidin-4-ylamino}-ethyl)-thiazol-2-yl]-3-(3-trifluoromethyl-phenyl)-urea (compound **54.1**) is synthesized according to Example 53.

[0533] **Step 2:** Compound **54.1** (0.19 mmol) is heated at 60 °C in neat TFA for 8 hours. The reaction was evaporated to dryness and purified by column chromatography on C_{18} silica gel to provide the titled compound.

[0534] **Example 55**

[0535] This example describes the synthesis of

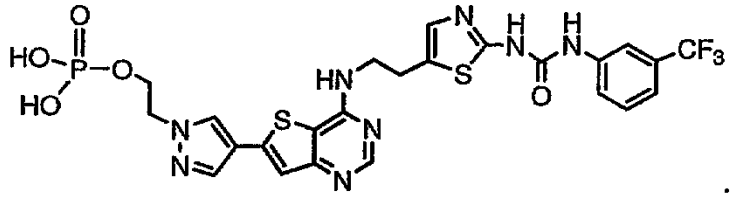


[0536] **Step 1:** 1-{5-[2-(6-{1-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-1H-pyrazol-4-yl}-thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-thiazol-2-yl}-3-(3-trifluoromethyl-phenyl)-urea (compound **55.1**) is synthesized according to Example 53.

[0537] **Step 2:** To a solution of compound **55.1** in ethanol was added hydrazine (22 equivalents) and the reaction mixture was heated at 60 °C for 2.5 hours. The reaction is concentrated to dryness and the residue purified by preparative TLC (10% 7.0 M NH_3/MeOH in dichloromethane) to provide the titled compound.

[0538] **Example 56**

[0539] This example describes the synthesis of

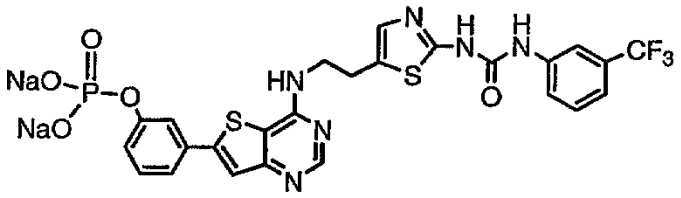


[0540] **Step 1:** 1-[5-(2-{6-[1-(2-Hydroxy-ethyl)-1H-pyrazol-4-yl]-thieno[3,2-d]pyrimidin-4-ylamino}-ethyl)-thiazol-2-yl]-3-(3-trifluoromethyl-phenyl)-urea (compound **56.1**) is synthesized according to Example 33 or Example 53.

[0541] **Step 2:** To a solution of compound **56.1** (0.17 mmol) in THF was added $POCl_3$ (10.9 mmol) at room temperature. After 2 hours, an additional equivalent of $POCl_3$ was added and the reaction was stirred for 4 hours. Water was added and the reaction mixture was stirred for an additional 1 hour. Volatiles were removed under reduced pressure and the residue purified by reverse phase HPLC to provide the titled compound along with recovered compound **56.1.**

[0542] **Example 57**

[0543] This example describes the synthesis of



[0544] **Step 1:** 1-(5-{2-[6-(3-Hydroxy-phenyl)-thieno[3,2-d]pyrimidin-4-ylamino]-ethyl}-thiazol-2-yl)-3-(3-trifluoromethyl-phenyl)-urea (compound **57.1**) was synthesized according to Example 35.

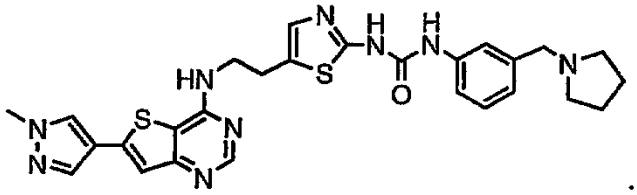
[0545] **Step 2:** To a solution of compound **57.1** (0.20 mmol) in THF (20 mL) was added 1-H-tetrazole (6.0 mL of a 3% w/w in CH_3CN). The reaction was purged with nitrogen and di-*tert*-butyl diethylphosphoramidite (1.06 mmol) was added. After stirring at room temperature for 3.5 hours, *tert*-butyl hydroperoxide (5 mL of 70% aqueous solution) was added. After stirring for 1 hour, the reaction was cooled to 0 °C followed by the addition of $NaHSO_3$ (15 mL of a 5% aqueous solution). After an

additional 1 hour, the reaction mixture was extracted with dichloromethane, washed with brine, dried and concentrated to give phosphoric acid di-tert-butyl ester 3-[4-(2-{2-[3-(3-trifluoromethyl-penta-2,4-dienyl)-ureido]-thiazol-5-yl}-ethylamino)-thieno[3,2-d]pyrimidin-6-yl]-phenyl ester (compound **57.2**)

[0546] **Step 3:** Crude compound **57.2** from the previous reaction was dissolved in dichloromethane and TFA (0.1 mL) was added. The reaction was stirred at room temperature overnight, concentrated to dryness and purified by reverse phase HPLC. The lyophilized product was washed with EtOAc to give a beige precipitate. The precipitate was stirred at room temperature with a suspension of ~2g of Dowex cation exchange resin (Na+ form) in water and CH_3CN for 2 hours. The resin was filtered and the filtrate lyophilized to give the titled compound.

[0547] **Example 58**

[0548] This example describes the synthesis of



[0549] **Step 1:** To a suspension of a HBr salt of 2-[2-(2-amino-thiazol-5-yl)-ethyl]-isoindole-1,3-dione (compound **58.1**; 1.42 mmol) in dichloromethane was added TEA (4.30 mmol) followed by the addition of phenyl chloroformate (1.43 mmol) at room temperature. After 2 hours, the reaction was concentrated to dryness to give a solid that was suspended in EtOAc, filtered, washed with additional EtOAc and dried under vacuum to provide {5-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-thiazol-2-yl}-carbamic acid phenyl ester (compound **58.2**, which is contaminated with triethyl amine salts) which was used in the next reaction without further purification.

[0550] **Step 2:** Compound **58.2** (0.64 mmol), 3-pyrrolidin-1-ylmethyl-phenylamine (0.64 mmol) and TEA (2.15 mmol) are dissolved in DMF and heated at 75 °C for 30 minutes. The reaction is concentrated to dryness and purified by flash column chromatography on silica gel (10% 7.0 M NH_3/MeOH in dichloromethane) to provide the desired urea. The urea was dissolved in ethanol and treated with hydrazine (0.06 mL) at 70 °C for 3 hours and concentrated. The residue is suspended and sonicated in dichloromethane, filtered and co-evaporated from MeOH/toluene

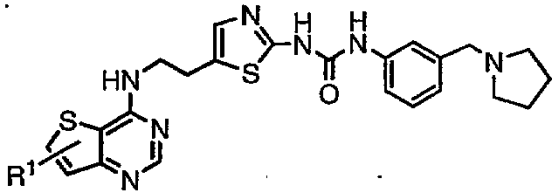
four times to provide 1-[5-(2-amino-ethyl)-thiazol-2-yl]-3-(3-pyrrolidin-1-ylmethyl-phenyl)-urea (compound **58.3**).

[0551] **Step 3:** A mixture of 6-bromo-4-chloro-thieno[3,2-d]pyrimidine (4.0 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (4.4 mmol), $Pd_2(dba)_3$ (0.8 mmol), Ph_3As (0.8 mmol) and K_2HPO_4(8.0 mmol) in a DMF (40 mL) and water (10 mL) are stirred at room temperature until the reaction was complete. The reaction is partitioned between EtOAc and water, washed with brine, dried, concentrated and purified by flash column chromatography on silica gel to give 4-chloro-6-(1-methyl-1H-pyrazol-4-yl)-thieno[3,2-d]pyrimidine (compound **58.4**).

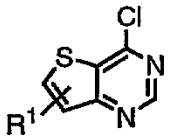
[0552] **Step 4:** Compound **58.3** (0.23 mmol), compound **58.4** (0.47 mmol) and DIEA (0.2 mL) in N,N-dimethylacetamide ("DMA") are heated at 110 °C for 5 hours. The reaction is concentrated to dryness and purified by flash column chromatography on silica gel (10% 7.0 M NH_3/MeOH in dichloromethane), and then is purified a second time by preparative TLC to afford the titled compound.

[0553] **Example 59**

[0554] This example describes the synthesis of



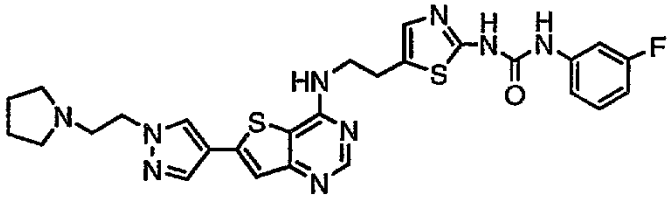
where R^1 is as described previously. These compounds are made according to the procedures of Example 58 except that



is used instead of compound **58.4** in step 4. Illustrative examples of R^1's are found throughout this disclosure as well as in Table 1.

[0555] **Example 60**

[0556] This example describes the synthesis of



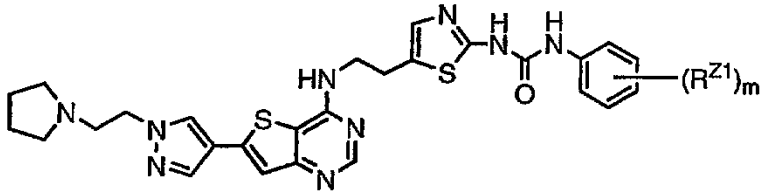
[0557] **Step 1:** A mixture of compound **58.1** (21.2 g) in dichloromethane (1.0 L), saturated $NaHCO_3$ (300 mL) and water (100 mL) was rapidly stirred until the organic layer became clear. The organic layer was separated and the aqueous layer was extracted with dichloromethane several times. The organic layers were combined, dried and concentrated to give the amine as a yellow solid. A portion of the amine (5.3 g) was dissolved in dichloromethane (80 mL) and treated with 3-fluorophenyl isocyante (2.5 mL) at room temperature with overnight stirring. The solid that formed was filtered, washed with dichloromethane and dried under vacuum to provide 1-{5-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-thiazol-2-yl}-3-(3-fluoro-phenyl)-urea (compound **60.1**; 2.6 g) as a colorless solid.

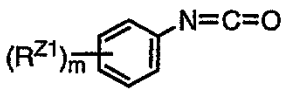
[0558] **Step 2:** To a suspension of compound **60.1** (2.6 g) in ethanol (64 mL) was added hydrazine (2.0 mL) and the reaction stirred at 65 °C for 4 hours. The solid that formed was filtered off and the filtrate was concentrated to give 1-[5-(2-amino-ethyl)-thiazol-2-yl]-3-(3-fluoro-phenyl)-urea (compound **60.2**; 1.6 g) as a yellow solid.

[0559] **Step 3:** A solution of compound **60.2** (1.48 mmol), compound **52.2** (1.67 mmol) and DIEA (3.44 mmol) in 1-methyl-2-pyrrolidinone ("NMP") was heated at 90 °C overnight. The reaction was cooled, diluted with EtOAc, washed with water, brine, dried and concentrated. The residue was purified by column chromatography to give the titled compound.

[0560] **Example 61**

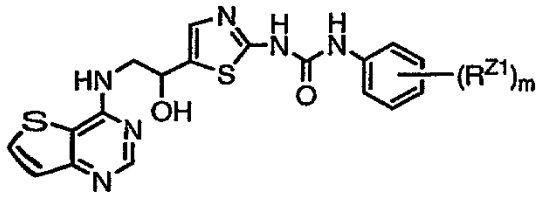
[0561] This example describes the synthesis of



where R^{Z1} and m are as described previously. These compounds are made according to the procedures of Example 60 except that  is used instead of 3-fluorophenyl isocyante in step 1. Illustrative examples of suitable R^{Z1}'s are found throughout this disclosure as well as in Table 5.

[0562] **Example 62**

[0563] This example describes the synthesis of



where R^{Z1} and m are as described previously.

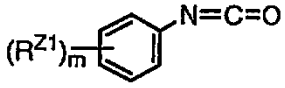
[0564] **Step 1:** To a suspension of 2-tert-butoxycarbonylamino-thiazole-5-carboxylic acid methyl ester (compound **62.1**; 21.7 mmol) in THF was slowly added LAH (25 mL of a 1.0 M solution in THF). After stirring for 1 hour at room temperature the reaction is cautiously hydrolyzed with the sequential addition of water (0.95 mL), 15% aqueous NaOH (0.95 mL) and additional water (2.85 mL). After stirring for 30 minutes the reaction is filtered through a pad of Celite and the filtrate is dried and concentrated to give (5-hydroxymethyl-thiazol-2-yl)-carbamic acid tert-butyl ester (compound **62.2**).

[0565] **Step 2:** To a solution of compound **62.2** (18.5 mmol) in dichloromethane is added molecular sieves (4.0 g) and PDC (39.0 mmol) at room temperature (THF is added to help dissolve the starting material). After 1.5 hours, an additional equivalent of PDC is added and the reaction is stirred for 5.5 hours. The reaction mixture is poured directly onto a silica gel column and is eluted with a gradient of 100% dichloromethane to 100% EtOAc. Fractions containing the desired product are pooled and concentrated to afford (5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (compound **62.3**).

[0566] **Step 3:** To a solution of compound **62.3** (4.5 mmol) in dichloromethane is added trimethylsilyl cyanide ("TMSCN"; 2.1 equivalents) and ZnI_2 (10% mol). After stirring at room temperature overnight, the reaction is concentrated under vacuum. The crude cyanohydrin is dissolved in THF and treated with AlH_3 (2.2 equivalents of a 0.5 M solution in THF). After stirring for 15 minutes, the reaction is quenched with the addition of saturated aqueous Na_2SO_4, is filtered through a pad of Celite, is dried and concentrated. Purification by flash column chromatography on silica gel (10% 7.0 M NH_3/MeOH in dichloromethane) provides [5-(2-amino-1-hydroxy-ethyl)-thiazol-2-yl]-carbamic acid tert-butyl ester (compound **62.4**).

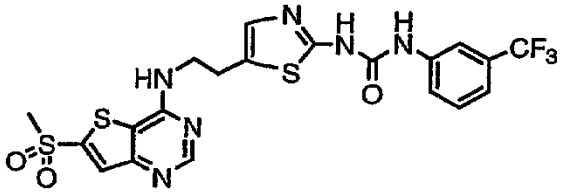
[0567] **Step 4:** Compound **62.4** (0.16 mmol), 4-chloro-thieno[3,2-d]pyrimidine (0.16 mmol.) and DIEA (0.28 mmol) is heated in DMA at 90 °C for 5 hours. The reaction mixture is cooled, concentrated and purified by preparative TLC (10%

MeOH in EtOAc) to afford {5-[1-hydroxy-2-(thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-thiazol-2-yl}-carbamic acid tert-butyl ester (compound **62.5**).

[0568] **Step 5:** To a solution of compound **62.5** (0.06 mmol) in dichloromethane is added anhydrous HCl (31 equivalents of a 4.0 M solution in 1,4-dioxane). After stirring for 1.5 hours at room temperature the reaction is concentrated to dryness to give a residue that is suspended in THF. To this suspension is added TEA (5.6 equivalents) and  (**1**.1 equivalents) and after stirring at room temperature for 1.5 hours, the reaction is concentrated and purified by preparative TLC (10% MeOH in EtOAc) to give titled compound. Illustrative examples of suitable R^{Z1}'s are found throughout this disclosure as well as in Table 5.

[0569] **Example 63**

[0570] This example describes the synthesis of



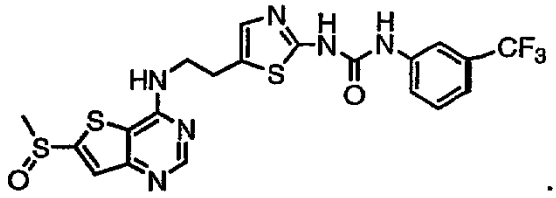
[0571] **Step 1:** To a suspension of compound **6.2** (5 mmol) in dry THF (25 mL) was added LDA (6 mmol, 2.0 M in heptane/THF/ethylbenzene) at –78 °C under an atmosphere of N_2. After stirring at –78 °C for 30 minutes, the mixture was transferred to a pre-cooled solution of methyl methanethiosulfonate (8 mmol) in of dry THF (10 mL) at -78^0C. The resulting mixture was slowly warmed to room temperature and stirred for 2 hours. The reaction was quenched by the addition of several portions of sat. aq. NH_4Cl, concentrated and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, dried and concentrated to give a residue that was purified by flash column chromatography on silica gel to give 4-chloro-6-methylsulfanyl-thieno[3,2-d]pyrimidine (compound **63.1**).

[0572] **Step 2:** A mixture of compound **63.1** (1 mmol) and 3-chloroperoxybenzoic acid ("*m*-CPBA";2 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 hours. The reaction mixture was then diluted with dichloromethane, washed with saturated aqueous $NaHCO_3$ several times, dried and concentrated to give a residue that was purified by flash column chromatography on silica gel to give 4-chloro-6-methanesulfonyl-thieno[3,2-d]pyrimidine (compound **63.2**).

[0573] **Step 3:** A mixture of compound **63.2** (0.2 mmol), compound **38.1** (0.2 mmol) and DIEA in DMF (2 mL) was heated at 100 °C for 2 hours. The reaction was concentrated to dryness and purified by reverse phase HPLC to provide the titled compound.

[0574] **Example 64**

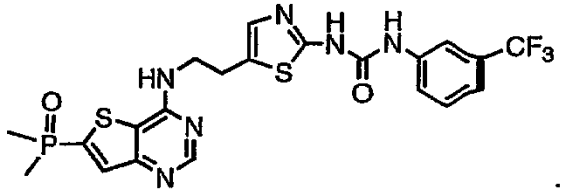
[0575] This example describes the synthesis of



[0576] This compound is made according to Example 63 except that only one equivalent of *m*-CPBA is used in step 2.

[0577] **Example 65**

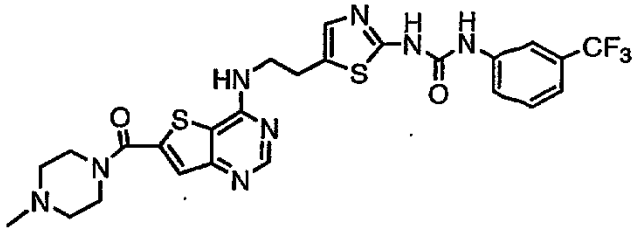
[0578] This example describes the synthesis of



[0579] This compound is made according to Example 63 except that dimethylphosphine chloride is used instead of methyl methanethiosulfonate in step 1.

[0580] **Example 66**

[0581] This example describes the synthesis of



[0582] **Step 1:** 4-(2-{2-[3-(3-Trifluoromethyl-phenyl)–ureido]-thiazol-5-yl}-ethylamino)-thieno[3,2-d]pyrimidine-6-carboxylic acid ethyl ester (compound **66.1**) is prepared according to Examnple 38 except that 4-chloro-thieno[3,2-d]pyrimidine-6-carboxylic acid ethyl ester is used instead of 5-methyl-4-chloro-[2,3-d]thienopyrimidine.

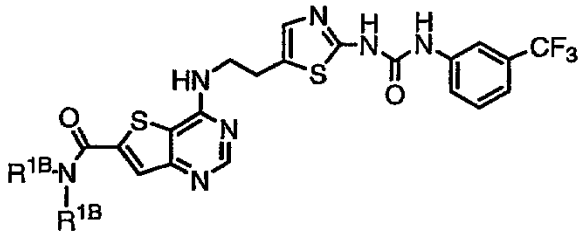
[0583] **Step 2:** A mixture of compound **66.1** (2 mmol) and $LiOH{\cdot}H_2O$ (4 mmol) in THF (20 mL) and H_2O (5 mL) was stirred at room temperature for 2 hours and then

neutralized with 1.0 N HCl (4 mL). The reaction was concentrated to dryness to give 4-(2-{2-[3-(3-trifluoromethyl-phenyl)-ureido]-thiazol-5-yl}-ethylamino)-thieno[3,2-d]pyrimidine-6-carboxylic acid (compound **66.2**) which is used without further purification in the next step.

[0584] **Step 3:** A mixture of compound **66.2** (0.05 mmol), 1-methylpiperazine (0.05 mmol), HATU (0.05 mmol) and DIEA (0.10 mmol) in DMF (1.0 mL) was stirred at room temperature overnight. The reaction was concentrated to dryness and purified by reverse phase HPLC to afford the titled compound.

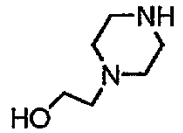
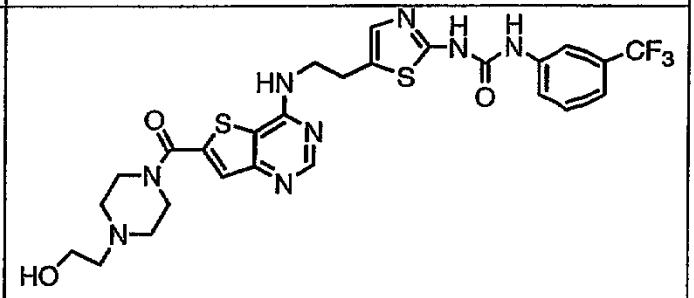
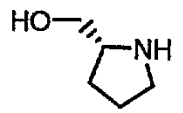
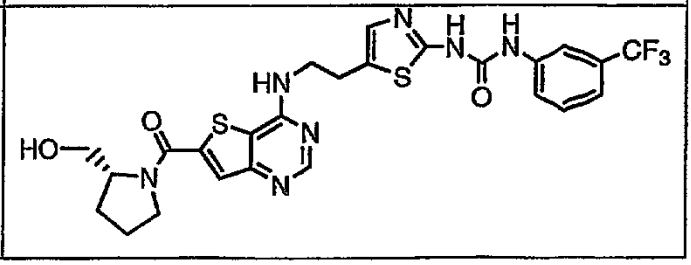
[0585] **Example 67**

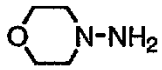
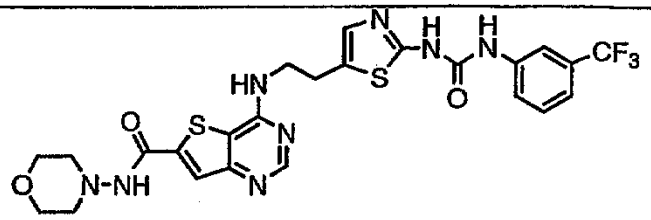
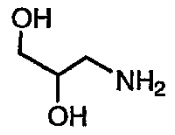
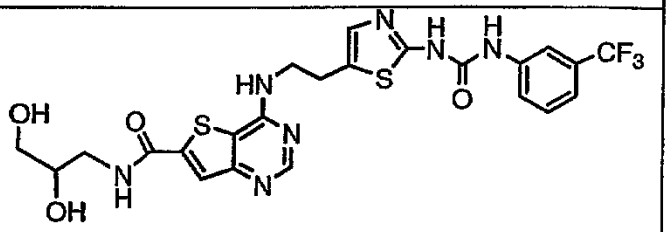
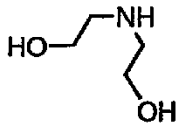
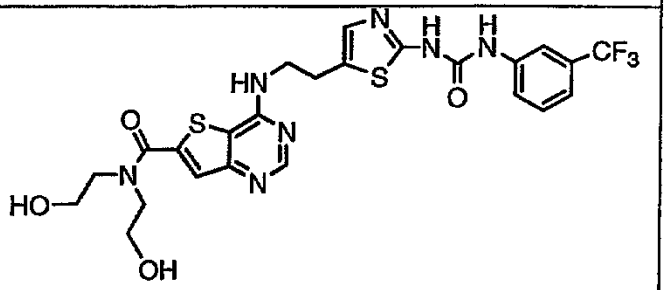
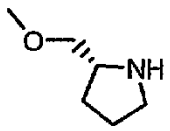
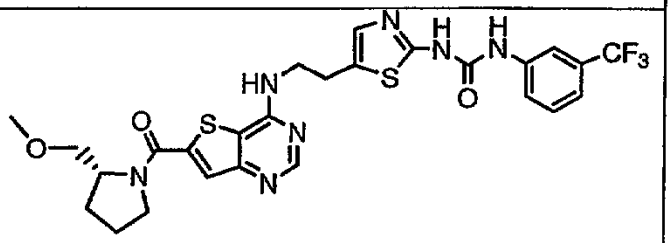
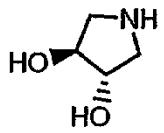
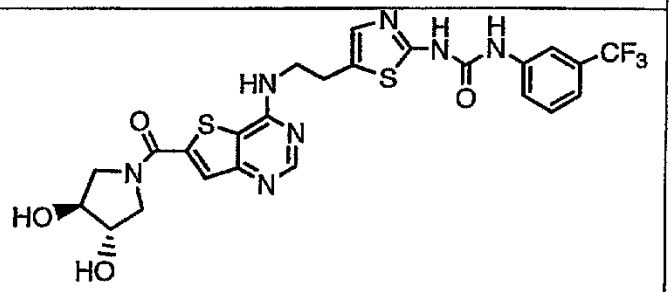
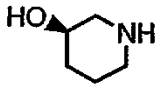
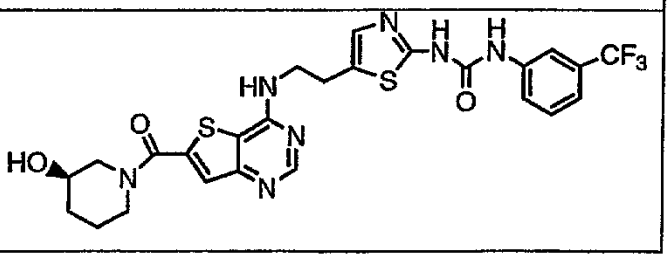
[0586] This example describes the synthesis of



where R^{1B}'s are as described previously. These compounds are made according to Example 66 except that $(R^{1B})_2N$ is used instead of 1-methylpiperazine in step 3. Illustrative examples of suitable $(R^{1B})_2N$'s are found throughout this disclosure as well as in Table 12.

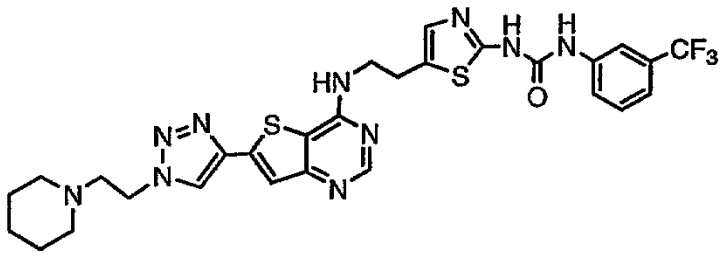
[0587] **Table 12**

$(R^{1B})_2N$	2. **Final Compound**
	
	

$(R^{1B})_2N$	2. **Final Compound**
	
	
	
	
	
	

[0588] **Example 68**

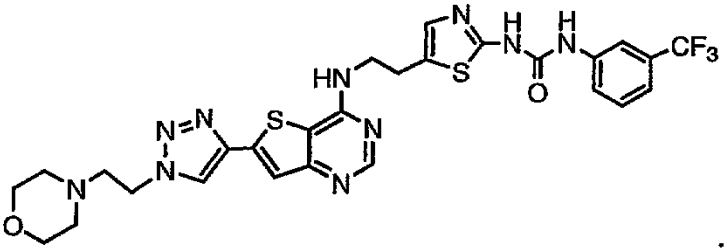
[0589] This example describes the synthesis of



[0590] A mixture of compound **48.2** (1.0 mmol), 1-(2-azido-ethyl)-piperidine (1.0 mmol), CuI (1.0 mmol) and DIEA (2.0 mmol) in DMF (10 mL) was stirred at room temperature for 2 h. Subsequently, compound **38.1** (1.0 mmoL) was added and the reaction was heated at 100 °C for 2 hours. The reaction was concentrated and the residue diluted with aqueous NH_4OH. The resulting suspension was filtered and washed with water and EtOAc. The solid was collected and dried under vacuum to provide the titled compound.

[0591] **Example 69**

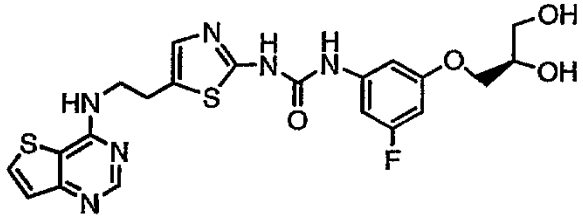
[0592] This example describes the synthesis of



[0593] This compound is made according to Example 68 except that 4-(2-azido-ethyl)-morpholine is used instead of 1-(2-azido-ethyl)-piperidine.

[0594] **Example 70**

[0595] This example describes the synthesis of



[0596] **Step 1:** To a solution of 3,5-difluoronitrobenzene (6.0 mmol) and (*S*)-(+)-2,2-dimethyl-1,3-dioxolan-4-methanol (7.5 mmol) in DMF (10 mL) is added NaH (2.3 equiv.) at room temperature. After stirring for 2 hours, saturated NH_4Cl is added and the reaction is extracted with EtOAc. The organic layer is separated, washed with brine, dried and concentrated to give a residue that was purified by preparative TLC (30% EtOAC in hexanes). The corresponding nitro compound thus obtained (1.0 mmol) is stirred at room temperature for 12 hours under a hydrogen atmosphere over

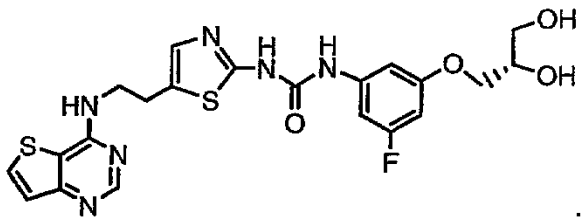
10% Pd/C (30 mg) in MeOH/EtOAc (15 mL). The reaction is filtered through a Celite pad and concentrated to dryness to provide 3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-fluoro-phenylamine (compound **70.1**) of sufficient purity to be used in the next step.

[0597] **Step 2:** A solution of compound **70.1** (1.0 mmol), compound **16.1** (1.0 mmol) and DMAP (1.0 mmol) in DMSO (10 mL) is heated at 90 °C for 30 minutes. The reaction is cooled, and partitioned between EtOAC and 1.0 N NaOH. The organic layer is separated, washed with brine, dried and concentrated to give a residue that was purified by preparative TLC (6% MeOH in dichoromethane) to provide 1-[3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-fluoro-phenyl]-3-{5-[2-(thieno[3,2-d]pyrimidin-4-ylamino)-ethyl]-thiazol-2-yl}-urea (compound **70.2**).

[0598] **Step 3:** To a solution of compound **70.2** (0.2 mmol) in MeOH (1.0 mL) and dichloromethane (1.0 mL) is added trifluoroacetic acid (5 equivalents). The reaction is stirred at room temperature for 12 hours and then directly purified by reverse phase HPLC to provide the titled compound.

[0599] **Example 71**

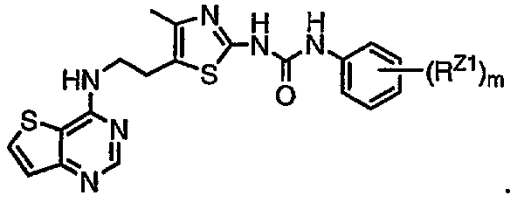
[0600] This example describes the synthesis of



[0601] This compound is made according to Example 70 except that from (*R*)-(-)-2,2-dimethyl-1,3-dioxolan-4-methanol is used instead of (*S*)-(+)-2,2-dimethyl-1,3-dioxolan-4-methanol in step 1.

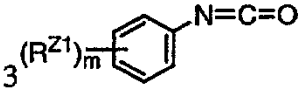
[0602] **Example 72**

[0603] This example describes the synthesis of



where R^{Z1} and m are as described previously.

[0604] **Step 1:** 2-[2-(2-Amino-4-methyl-thiazol-5-yl)-ethyl]-isoindole-1,3-dione is (compound **72.1**; 1.0 mmol) is prepared according to the procedure of Ericks, J. C.

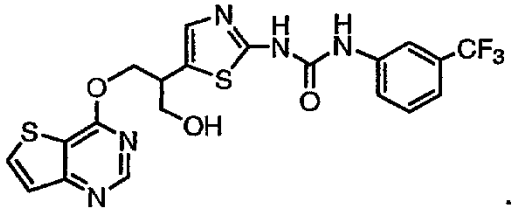
et al; *J. Med. Chem.* **1992**, 35, 3239. Compound **72.1** is refluxed with  (1 equivalent) in acetone (10 mL) for 30 minutes. The reaction is cooled to room temperature and the solvent is removed under reduced pressure. Trituration from dichloromethane and hexanes gives urea product (compound **72.2**).

[0605] **Step 2:** Compound **72.2** (0.7 mmol) is refluxed in EtOH (10 mL) with hydrazine (3 equivalents) for 2 hours. The reaction mixture is cooled to room temperature and the precipitate is filtered off and the filtrate concentrated to dryness to give the corresponding amine (compound **72.3**).

[0606] **Step 3:** To a solution of compound **72.3** (0.35 mmol) in DMF (1.0 mL) was added compound **6.2** (1 equivalent) and triethylamine (5 equivalents). The reaction is stirred at 90°C for 1 hour, cooled, diluted with EtOAc, washed with water, brine, dried and concentrated to provide the titled compound.

[0607] **Example 73**

[0608] This example describes the synthesis of



[0609] **Step 1:** A mixture of {2-[3-(3-trifluoromethyl-phenyl)-ureido]-thiazol-5-yl}-acetic acid methyl ester (4.17 mmol), paraformaldehyde (0.95 equiv.) and K_2CO_3 (0.95 equiv.) in DMSO (10.0 mL) was heated at 50 °C for 1.5 hours. The reaction was cooled, diluted with EtOAc, washed with water, dried and concentrated to give a residue that was purified by flash column chromatography on silica gel (0 to 6% MeOH in EtOAc) to provide 3-hydroxy-2-{2-[3-(3-trifluoromethyl-phenyl)-ureido]-thiazol-5-yl}-propionic acid methyl ester (compound **73.1**).

[0610] **Step 2:** To a mixture of compound **73.1** (1.67 mmol) and triethylamine (2.2 equivalent) in 1:1 dichloromethane/THF (12.0 mL) was added triisopropylsilyl trifluoromethanesulfonate (2.2 equivalents) dropwise at 0 °C. After complete consumption of the starting material (TLC 30% EtOAc in hexanes) the reaction mixture is diluted with EtOAc and washed with 0.5 N HCl, saturated sodium bicarbonate, dried and concentrated to give a residue that was purified by flash

column chromatography on silica gel (0 to 60% EtOAc in hexanes) to provide 2-{2-[3-(3-trifluoromethyl-phenyl)-ureido]-thiazol-5-yl}-3-triisopropylsilanyloxy-propionic acid methyl ester (compound **73.2**) as a foam.

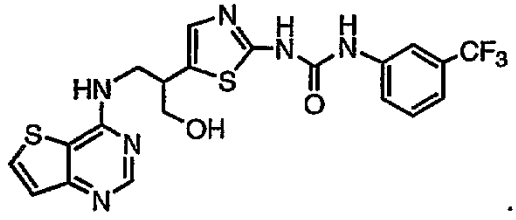
[0611] **Step 3:** To a solution of compound **73.2** (0.275 mmol) in THF (2.5 mL) was added LAH (0.275 mL of a 1.0 M solution in THF) dropwise at 0 °C. The reaction is allowed to warmed to room temperature and stirred until the starting material was consumed. The reaction is quenched by the dropwise addition of water and the reaction mixture was extracted with EtOAc. The combined organic layers were combined, dried and concentrated to give a residue that was purified by flash column chromatography (20 to 100% EtOAc in hexanes) to provide 1-[5-(2-hydroxy-1-triisopropylsilanyloxymethyl-ethyl)-thiazol-2-yl]-3-(3-trifluoromethyl-phenyl)-urea (compound **73.3**).

[0612] **Step 4:** To a suspension of NaH (0.12 mmol as a 60% oil dispersion) in THF (0.20 mL) was added a solution of compound **73.3** (0.04 mmol) in THF (1.0 mL) at room temperature. After stirring for 1 hour, 4-chlorothieno[3,2-d]pyrimidine (0.04 mmol) was added and the reaction mixture was heated at 60 °C for 1 hour. The reaction was cooled and quenched with the addition of saturated NH_4Cl. The reaction mixture was extracted with EtOAc, dried and concentrated to give a residue that was purified by preparative TLC (20% hexanes in EtOAc) to afford 1-{5-[2-(thieno[3,2-d]pyrimidin-4-yloxy)-1-triisopropylsilanyloxymethyl-ethyl]-thiazol-2-yl}-3-(3-trifluoromethyl-phenyl)-urea (compound **73.4**).

[0613] **Step 5:** To a solution of compound **73.4** (70 mg) in ethanol (4.0 mL) was added concentrated aqueous HCl (1.0 mL) and the reaction was stirred at room temperature overnight. The reaction is then diluted with water and methanol and directly purified by reverse phase HPLC. The fractions containing the desired product were pooled and lyophilized to afford the titled compound as a colorless solid.

[0614] **Example 74**

[0615] This example describes the synthesis of



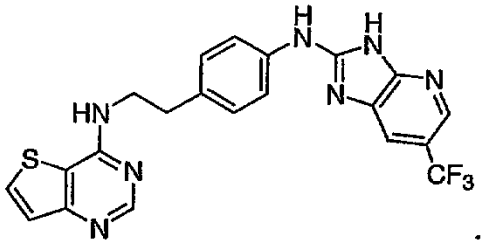
[0616] **Step 1:** Ammonia gas is bubbled through a solution of compound **73.1** (435 mg) in methanol (20.0 mL) for 10 minutes. The reaction vessel is then sealed and heated at 80 °C for 3 hours. The mixture is concentrated and the residue purified by preparative TLC to give 3-hydroxy-2-{2-[3-(3-trifluoromethyl-phenyl)-ureido]-thiazol-5-yl}-propionamide (compound **74.1**).

[0617] **Step 2:** To a solution of compound **74.1** (0.08 mmol) in THF (1.0 mL) is added LAH (0.24 mL of 1.0 M solution in THF) and the reaction mixture is heated at 50 °C for 4 hours. The reaction is quenched with the dropwise addition of saturated NH_4Cl, the volatiles are removed under reduced pressure and then extracted with EtOAc. The combined organic layers are filtered and concentrated to provide 1-[5-(2-amino-1-hydroxymethyl-ethyl)-thiazol-2-yl]-3-(3-trifluoromethyl-phenyl)-urea (compound **74.2**) of sufficient purity for use in the next step.

[0618] **Step 3:** A mixture of compound **74.2** (0.20 mmol), 4-chlorothieno[3,2-d]pyrimidine (0.20 mmol) and DIEA (1.0 mL) in *n*-butanol (1.0 mL) are heated at 110 °C for 2 hours. The reaction mixture is concentrated to dryness to give a residue that was purified by reverse phase HPLC. The product that is obtained was dissolved in methanol, treated with solid Na_2CO_3, filtered, concentrated and further purified by preparative TLC (10% methanol in dichloromethane) to afford the titled compound.

[0619] **Example 75**

[0620] This example describes the synthesis of



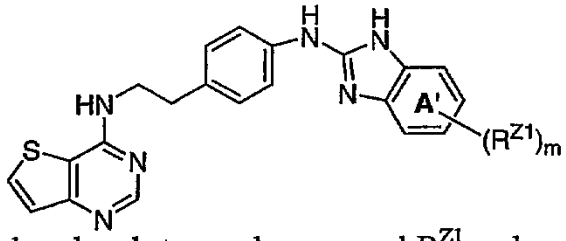
[0621] **Step 1:** A mixture of 4-nitrophenylethylamine (compound **75.1**; 20 mmol), compound **6.2** (20 mmol) and DIEA (20 mmol) in DMF (100 mL) was stirred at 100 °C for 4 hours. The reaction mixture was concentrated to dryness and diluted with 100 mL of water. The resulting suspension was filtered and the solid collected was washed with water and dried in *vacuo* to give the nitro-intermediate. To the nitro-intermediate was added zinc powder (100 mmol), saturated aqueous NH_4Cl (20 mL) and MeOH (100 mL) and the resulting mixture was stirred at 50 °C for 8 hours. The mixture was filtered through a short column of Celite®545 and washed with methanol. The filtrate was then concentrated and diluted with 50 mL of 0.1 N HCl.

The mixture was extracted with EtOAc several times and the aqueous phase was adjusted to pH 10 by the addition of 4N NaOH. Subsequently, the aqueous layer was back extracted with EtOAc. The organic layers were combined, dried and concentrated *in vacuo* to give [2-(4-amino-phenyl)-ethyl]-thieno[3,2-d]pyrimidin-4-yl-amine (compound **75.2**) in 80% yield. ^{1}H NMR (CD_3OD, 400MHz): δ 8.74 (s, 1H), 8.37 (d, *J*=5.4 Hz, 1H), 7.50 (d, *J*=5.4 Hz, 1H), 7.45 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=7.8 Hz, 2H), 4.00 (t, *J*=7.1, 2H), 3.11 (t, *J*=7.3 Hz, 2H) ppm; EIMS (*m/z*): 271.1 (M^++H).

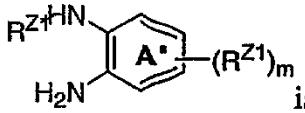
[0622] **Step 2:** A mixture of compound **1.2** (0.2 mmol) and thiocarbonyldiimidazole (0.2 mmol) in dry THF (2.0 mL) was stirred at room temperature for 30 minutes under an atmosphere of N_2. 5-Trifluoromethyl-pyridine-2,3-diamine (0.2 mmol) was added and the reaction stirred at room temperature until the reaction was deemed complete. The reaction mixture was then treated with *N,N'*-dicyclohexylcarbodiimide (0.2 mmol) and the resulting mixture was stirred at 40-60 °C for several hours. The solvent was removed and the residue was purified by preparative HPLC to give the titled compound. ^{1}H NMR (CD_3OD, 400MHz): δ 8.76 (s, 1H), 8.51 (s, 1H), 8.38 (s, 1H), 7.95 (s, 1H), 7.56 (d, *J*=7.3 Hz, 2H), 7.48 (s, 1H), 7.38 (d, *J*=6.4Hz, 2H), 4.03 (s, 2H), 3.09 (s, 2H) ppm; EIMS (*m/z*): 456.1 (M^++H).

[0623] **Example 76**

[0624] This compound describes the synthesis of

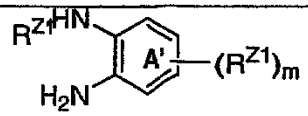
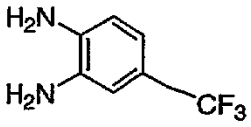
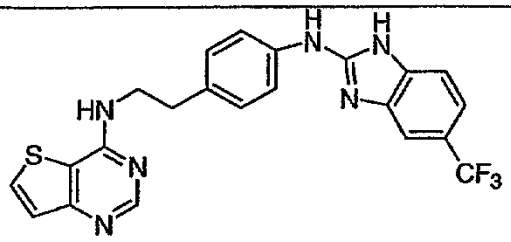
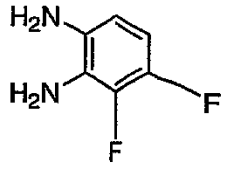
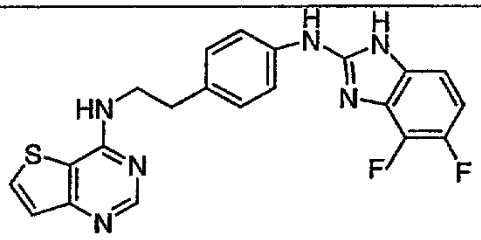
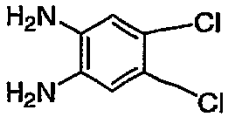
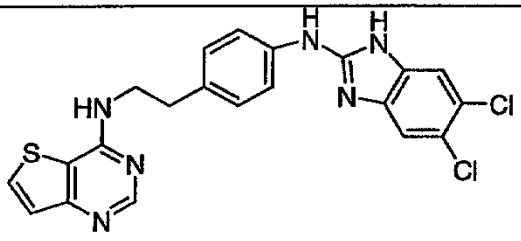
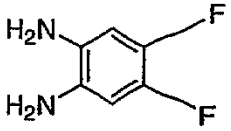
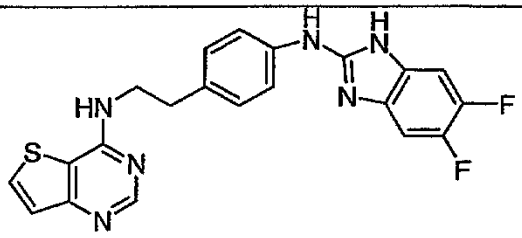
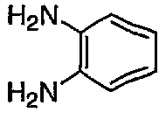
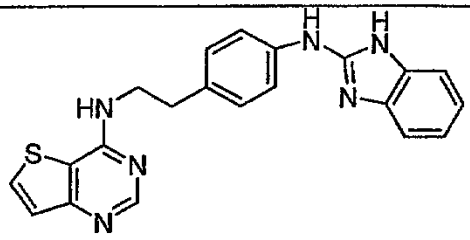
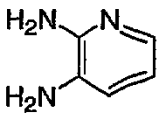
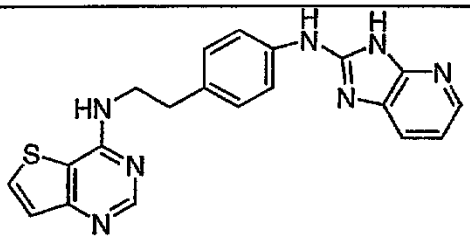
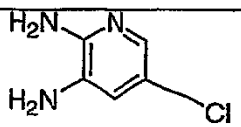
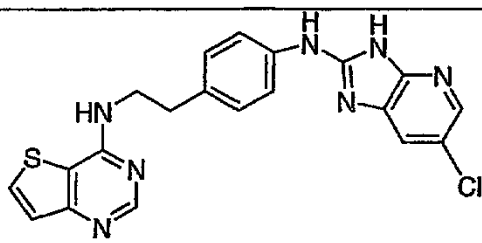


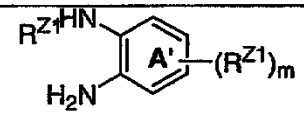
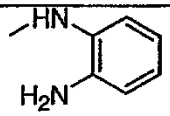
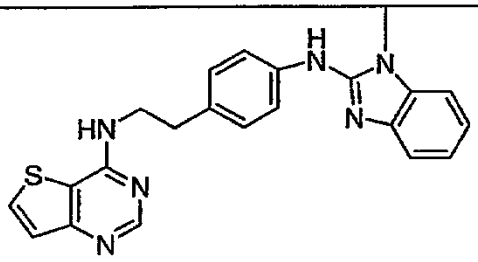
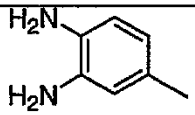
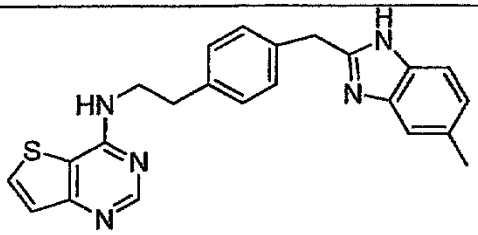
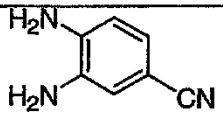
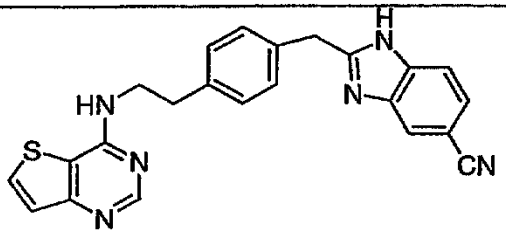
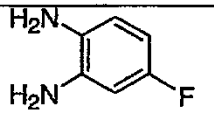
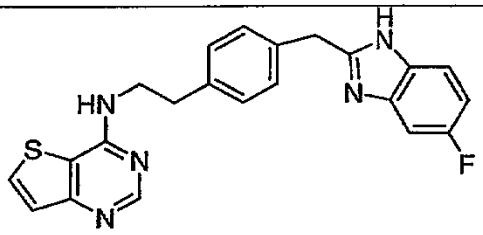
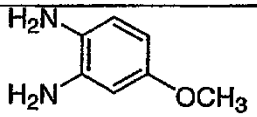
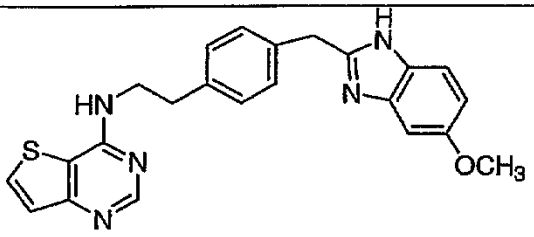
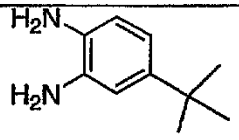
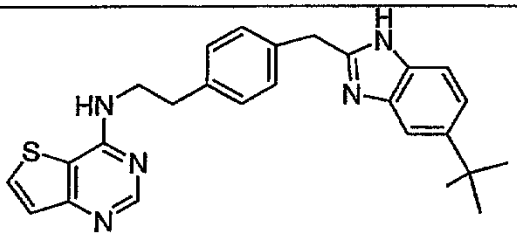
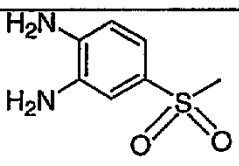
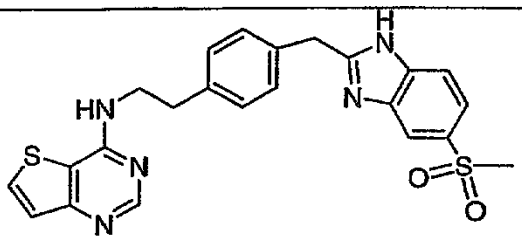
where A' is a 6-membered aryl or heteroaryl group and R^{Z1} and m are as previously described. These compounds are made according to Example 75 except that



is used instead of 5-trifluoromethyl-pyridine-2,3-diamine in step 2. Illustrative examples of suitable R^{Z1}'s are found throughout this disclosure as well as in Table 13.

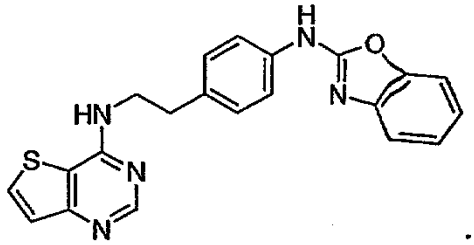
[0625] **Table 13**

	3. **Final Compound**
	
	
	
	
	
	
	

	3. **Final Compound**
	
	
	
	
	
	
	

[0626] **Example 77**

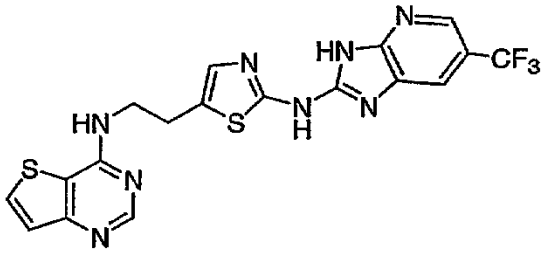
[0627] This example describes the synthesis of



[0628] A mixture of compound **75.2** (0.2 mmol), 2-chlorobenzoxazole (0.2 mmol), DIEA (0.4 mmol) and DMAP (0.02 mmol) in DMSO (2 mL) was stirred at 110 °C for several hours. The solvent was removed and the residue was purified by preparative HPLC to give the titled compound. ^{1}H NMR (CD_3OD, 400MHz): δ 8.74 (s, 1H), 8.38 (d, *J*=5.4 Hz, 1H), 7.58 (d, *J*=8.3 Hz, 2H), 7.48 (d, *J*=5.4 Hz, 1H), 7.39 (t, *J*=8.1 Hz, 2H), 7.28 (d, *J*=8.3 Hz, 2H), 7.23 (t, *J*=7.6 Hz, 1H), 7.14 (t, *J*=7.6 Hz, 1H), 4.03 (t, *J*=7.1 Hz, 2H), 3.05 (t, *J*=7.1 Hz, 2H) ppm; EIMS (*m/z*): 388.1 (M^++H).

[0629] **Example 78**

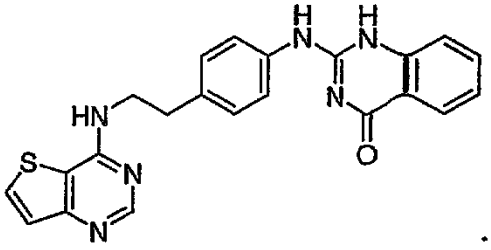
[0630] This example describes the synthesis of



[0631] This compound is prepared according to step 2 of Example 75 except that compound **14.3** is used instead of compound **75.2**. ^{1}H NMR (CD_3OD, 400MHz): δ 8.79 (s, 1H), 8.46 (s, 1H), 8.41 (d, *J*=5.9 Hz, 1H), 7.98 (s, 1H), 7.50 (d, *J*=5.4 Hz, 2H), 7.17 (s, 1H), 4.07 (t, *J*=6.8 Hz, 2H), 3.21 (t, *J*= 6.6 Hz, 2H) ppm; EIMS (*m/z*): 463.1 (M^++H).

[0632] **Example 79**

[0633] This example describes the synthesis of



[0634] **Step 1:** A solution of compound **1.1** (2.0 mmol) and thiocarbonyldiimidazole (2.0 mmol) in dry THF (10.0 mL) was stirred at room temperature for 30 minutes and then saturated with NH_3 (gas). The resulting mixture was stirred at room temperature for 10 minutes and concentrated to give a residue that was purified by preparative chromatography to give [2-(4-thioureido-phenyl)-ethyl]-carbamic acid tert-butyl ester (compound **79.2**) in 95% yield. ^{1}H NMR (CD_3OD, 400MHz): δ 7.25 (m, 4H), 3.26 (t, *J*=7.1 Hz, 2H), 2.76 (t, *J*=7.1 Hz, 2H), 1.43 (s, 9H) ppm; EIMS (*m/z*): 296.1 (M^++H).

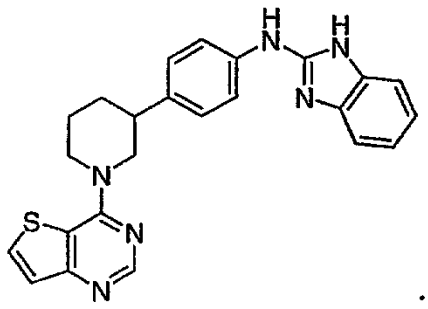
[0635] **Step 2:** A solution of compound **79.2** (1.5 mmol) and methyl iodide (6.0 mmol) in acetone (15.0 mL) was stirred at 40 °C overnight. The solvent was removed and the residue was dried *in vacuo* to give {2-[4-(2-methyl-isothioureido)-phenyl]-ethyl}-carbamic acid tert-butyl ester (compound **79.3**) in quantitative yield. ^{1}H NMR (CD_3OD, 400MHz): δ 7.40 (d, *J*=7.8 Hz, 2H), 7.28 (d, *J*=8.3 Hz, 2H), 3.30 (t, *J*=7.1 Hz, 2H), 2.82 (t, *J*=7.1 Hz, 2H), 2.73 (s, 3H) ppm; EIMS (*m/z*): 310.1 (M^++H).

[0636] **Step 3:** A mixture of compound **79.3** (1.5 mmol), isatoic anhydride (1.5 mmol), and Na_2CO_3 (3.0 mmol) in dioxane (15 mL) was stirred at 100 °C for 8 hours. The solvent was removed and the residue was diluted with 20 mL of water. Subsequently, the suspension was filtered and the white solid was washed sequentially with water and ether, and then dried *in vacuo* to give {2-[4-(4-oxo-1,4-dihydro-quinazolin-2-ylamino)-phenyl]-ethyl}-carbamic acid tert–butyl ester (compound **79.4**) in 52% yield. ^{1}H NMR (d^6-DMSO, 400MHz): δ 10.77 (s, 1H), 8.60 (s, 1H), 7.92 (d, *J*=7.3 Hz, 1H), 7.59 (m, 3H), 7.35 (d, *J*=8.3 Hz, 1H), 7.12-7.20 (m, 3H), 6.86 (s, 1H), 3.09 (t, *J*=7.1 Hz, 2H), 2.62 (t, *J*=7.1 Hz, 2H), 1.34 (s, 9H) ppm; EIMS (*m/z*): 381.2 (M^++H).

[0637] **Step 4:** A mixture of compound **79.4** (0.5 mmol) in anhydrous HCl in dioxane (5.0 mL of a 4.0 N solution in dioxane) was stirred at 60 °C for 1 hour. The solvent was removed and the residue dried *in vacuo* to give the amine intermediate. A mixture of this intermediate (0.2 mmol), compound **6.2** (0.2 mmol) and DIEA (1.0 mmol) was stirred at 100 °C for several hours. The solvent was removed and the residue was purified by preparative HPLC to give the titled compound. ^{1}H NMR (CD_3OD, 400MHz): δ 8.75 (s, 1H), 8.39 (d, *J*=4.9 Hz, 1H), 8.12 (d, *J*=8.3 Hz, 1H), 7.75 (t, *J*=7.8 Hz, 1H), 7.45-7.52 (m, 4H), 7.37-7.41 (m, 3H), 4.05 (t, *J*=7.1 Hz, 2H), 3.11 (t, *J*=7.1 Hz, 2H) ppm; EIMS (*m/z*): 415.1 (M^++H).

[0638] **Example 80**

[0639] This example describes the synthesis of



[0640] **Step 1:**

[0641] A mixture of 1.0 mmol of 3-(4-amino-phenyl)-piperidine-1-carboxylic acid tert-butyl ester and 1.0 mmol of thiocarbonyldiimidazole in 10 mL of dry THF was stirred at room temperature for 30 minutes under an atmosphere of N_2. After stirring with 1.0 mmol of diaminobenzene at room temperature for 30 minutes under an atmosphere of N_2, the reaction mixture was treated with 1.0 mmol of DCC and the resulting mixture was stirred at 60^{0}C for several hours. The solvent was removed and the residue was purified by preparative TLC to give 3-(4-amino-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (compound **80.1**) in 55% yield. EIMS (*m/z*): 393.2 (M^++H).

[0642] **Step 2:**

[0643] A mixture of 0.5 mmol of compound **80.1** in 10 mL of 4.0N HCl in dioxane was stirred at 60^{0}C for 1 h. The solvent was removed and the residue was dried *in vacuo* to give the free amine, (1H-benzoimidazol-2-yl)-(4-piperidin-3-yl-phenyl)-amine (compound **80.2**) in quantitative yield. EIMS (*m/z*): 293.1 (M^++H).

[0644] **Step 3:**

[0645] A mixture of 0.2 mmol of compound **6.2**, 0.2 mmol of compound **80.2**, and 1 mmol of DIEA was stirred at 100°C for several hours. The solvent was removed and the residue was purified by preparative HPLC to give the titled compound. ^{1}H NMR (CD_3OD, 400MHz): δ 8.72 (s, 1H), 8.46 (d, *J*=5.4 Hz, 1H), 7.57 (m, 3H), 7.49 (d, *J*=8.3 Hz, 2H), 7.43 (m, 2H), 7.34 (m, 2H), 5.16 (d, *J*=11.3 Hz, 2H), 3.58 (m, 2H), 3.10 (t, *J*=10.0 Hz, 1H), 2.04-2.17 (m, 3H), 1.92 (m, 1H) ppm; EIMS (*m/z*): 427.2 (M^++H).

[0646] Formulation of Compounds

[0647] 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.

[0648] Target Modulation studies.

[0649] Nu/nu mice were subcuntaneously injected into their hind flank with human HCT-116 cells and 50% Matrigel (Becton-Dickinson). Human HCT-116 tumors were then allowed to grow to 400 mm^3. The tumor bearing mice were then either given an administration of SPD or vehicle (Sigma-Aldrich) (orally, intravenously or intraperitoneally). At prescribed time points post dose, mice were anesthetized and blood taken via terminal cardiac puncture, and sacrificed. The HCT-116 tumors were excised from the mice, pulverized using liquid nitrogen-cooled mortar and pestle, and flash-frozen in liquid nitrogen. Tumor lysates were made from the pulverized samples by addition of lysis buffer.

[0650] For detection of response markers by Western blotting, the protein concentration of the lysates was determined by colorimetric detection. Twenty-five micrograms of protein was loaded per lane on an SDS-PAGE gel. Proteins were 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)

[0651] Maximum Tolerated Dose studies.

[0652] 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) were 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 were used. Animal weights were measured daily for 5 days and about every 3 days after that until the animal was removed from the study due to body weight loss of > 20% or any alterations in physiological function that would affect normal function. Clinical observations were performed throughout the study to note any toxicity and mice were monitored until the end of the study.

[0653] Efficacy studies.

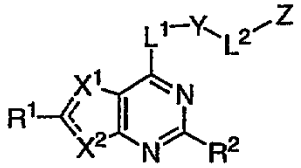
[0654] Nu/nu mice were subcuntaneously injected into their hind flank with human HCT-116 cells and 50% Matrigel (Becton-Dickinson). Human HCT-116 tumors were allowed to grow to 150-200 mm^3. The tumor bearing mice were then either given an administration of a test compound or a vehicle control. The tumor dimensions (length [l mm] and width [w mm]) were 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 were measured twice weekly until the animal was removed from the study, either because there was a body weight loss of greater than 20% or a tumor volume greater than 2000 mm^3. Clinical observations were performed throughout the study, which usually lasted for up to 70 days after the initial implantation of the tumor cells. Tumor volume increases were compared to negative (vehicle) and positive controls. Percentage tumor growth inhibition (TGI) was 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 was usually determined at defined times after the administration of the last dose of compound. Survival plots (Kaplan-Maier) were also performed to examine the pattern of survival.

[0655] 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.

CLAIMS

What is claimed is:

1. An isolated compound having the structure:



(I)

or pharmaceutically acceptable derivative thereof;

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

$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently hydrogen, halogen, cyano, nitro, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic moiety;

one of $\mathbf{X^1}$ and $\mathbf{X^2}$ is S, the other is $-C(R^{X1})-$; wherein 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;

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

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) L^1 is $-OCH_2-$, $-CH_2O-$, $-N(R)CH_2-$ or $-CH_2N(R)-$, wherein R is H or C_{1-8}alkyl; Y is phenyl; and Z is a 5-10-membered cycloalkyl, heterocyclyl, aryl or heteroaryl;

(ii) L^1-Y is $-NHCH_2CH_2$-phenyl or $-OCH_2CH_2$-phenyl; and L^2 is $-C(R)=N-O-$, wherein R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl; and R^1 and R^{X1} (or R^1 and R^{X2}, when X^1 is S) are independently hydrogen, halogen or C_{1-4}alkyl;

(iii) L^1 is $-OCH(R)-$, $-OCH(R)-C_{1-6}$alkylO- or $-OCH(R)-C_{1-6}$alkylC(=NR_x)- where R is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{3-6}cycloalkyl and R_x is H, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic or heteroaromatic; Y and Z are

each optionally substituted phenyl; and L^2 is $-OCH_2-$ or $-OSO_2-$; and R^1 and R^{X1} (or R^1 and R^{X2}, when X^1 is S) are independently hydrogen, halogen or alkyl;

(iv) X^1 is CR^{X1} wherein R^{X1} is Q_4; X^2 is S; R^1 is Q_5; Y and Z are independently optionally substituted aryl, carbocycle or 5-membered monocyclic heterocycle; and L^1 is–W-N=CH- wherein W is O or NR, wherein R is H, C_{1-6}alk(en/yn)yl, C_{3-8}cycloalk(en)yl, aryl, hydroxyC_{1-6}alk(en/yn)yl, C_{3-8}cycloalk(en)yl-C_{1-6}alk(en/yn)yl or acyl;

(v) neither R^1 nor R^{X1} (or neither R^1 nor R^{X2} , when X^1 is S) 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

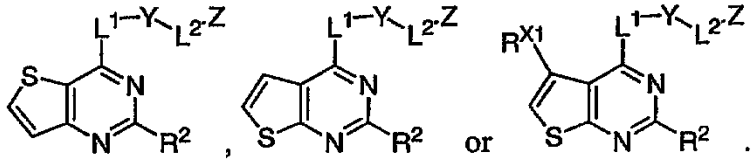
Q^3 is $-(CR^{1A}R^{1B})_tR^{1C}$, wherein t is an integer from 0 to 5 and the attachment point to R^{1C} is through a carbon atom of the R^{1C} group; wherein R^{1A} and R^{1B} are independently H or C_{1-6}alkyl; R^{1C} is an optionally substituted non-aromatic monocyclic ring, a fused or bridged bycyclic 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);

(vi) one of R^1 and R^{X1} (or one of R^1 and R^{X2}, when X^1 is S) is hydrogen, the other is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy; L^1 is $-NHC_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$heteroalkyl or $-OC_{1-6}$heteroalkyl; Y is cycloalkyl, aryl, heteroaryl or heterocyclyl; L^2-Z is $-X-R^x$ where X is –NR-, -C(=O)NH-, -NHC(=O)-, $-SO_2NH-$ or $-NHSO_2-$ and R^x is C_{3-10}cycloalkyl, morpholinyl, phenyl, phenylC_{1-4}alkyl or phenylC_{2-3}alkenyl;

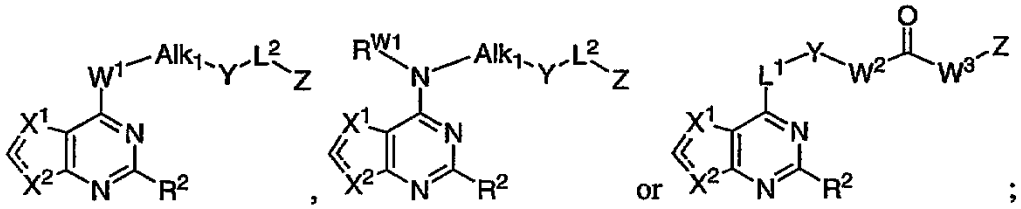
(vii) one of X^1 and X^2 is CH, the other is S; L^1 is $-NR(CR^x)_{1-2}-$ or $-O(CR^x)_{1-2}-$ wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, OH, NH_2 or $-C_{1-4}$alkylNH; and R^x is H or C_{1-4}alkyl; Y is phenyl, thienyl, furanyl, pyrrolyl, pyridyl, pyrimidyl, imidazolyl, pyrazinyl, oxazolyl, thiazolyl, naphthyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, isoquinolinyl or quinazolinyl; L^2-Z is $-SO_2NHC_{3-8}$cycloalkyl, $-SO_2N(C_{3-8}$cycloalkyl$)_2$, $-C(=O)NHC_{3-8}$cycloalkyl or $-C(=O)N(C_{3-8}$cycloalkyl$)_2$;

(viii) R^1 is hydrogen, halogen, nitro or C_{1-4}alkyl; one of X^1 and X^2 is S, the other is CR^{XA} wherein R^{XA} is hydrogen, C_{1-4}alkyl or phenyl optionally substituted with halogen, (halo)C_{1-4}alkyl or (halo)C_{1-4}alkoxy; L^1 is $-NRC_{1-6}$alkyl-, $-OC_{1-6}$alkyl- or $-SC_{1-6}$alkyl- wherein R is hydrogen, C_{1-4}alkyl, C_{1-4}acyl; Y is phenyl; L^2–Z is a C_{1-12}alkyl saturated or unsaturated hydrocarbon chain optionally including -NR- and optionally substituted with haloC_{1-4}alkoxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{1-4}acyl, phenoxy, phenyl or phenylthio.

4. The compound of claim 1 having the structure:

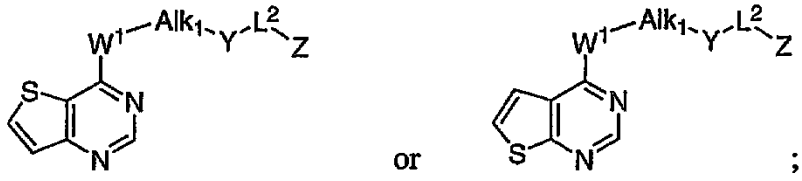


5. The compound of claim 1 having the structure:



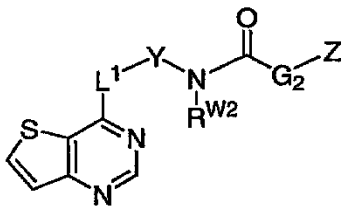
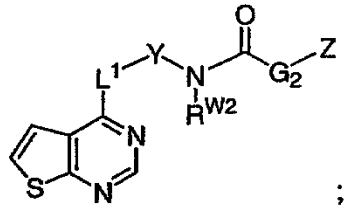
wherein W^1 is O or NR^{W1}, where R^{W1} is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aromatic, heteroaromatic, or acyl; and Alk_1 is a C_{1-6}alkylene or C_{2-6}alkenylene moiety; W^2 and W^3 are independently absent, O, NR^W, $CR^{W1}R^{W2}$ or $NR^WCR^{W1}R^{W2}$, where R^W 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.

6. The compound of claim 1 having the structure:



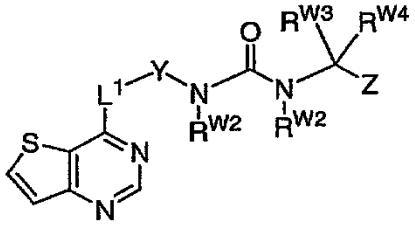
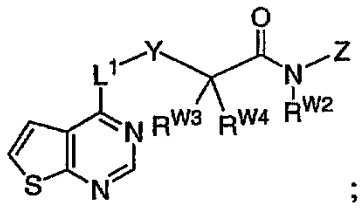
wherein L^2, Y and Z are as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; and Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent 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.

7. The compound of claim 1 having the structure:


or

;

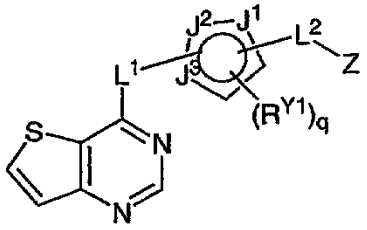
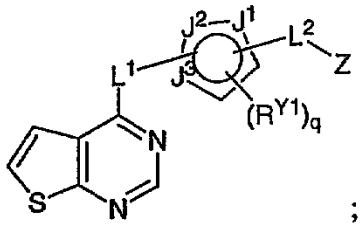
wherein L^1, Y and Z are as defined in claim 1; G_2 is absent, O or NR^{G2}; and R^{W2} and R^{G2} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

8. The compound of claim 1 having the structure:


or

;

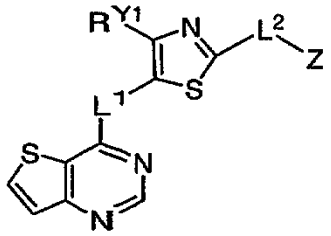
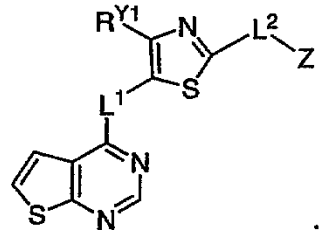
wherein L^1, Y and Z are as defined in claim 1; and R^{W2}, R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl or acyl.

9. The compound of claim 1 having the structure:

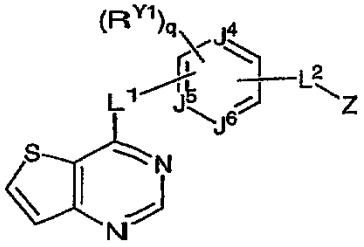
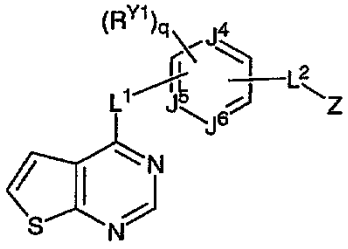

or

;

wherein q is an integer from 0-2; 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.

10. The compound of claim 8 having the structure:

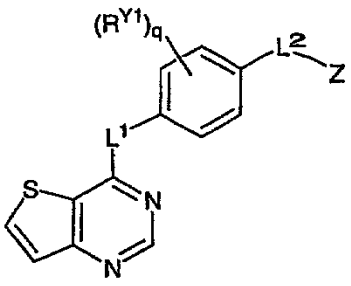
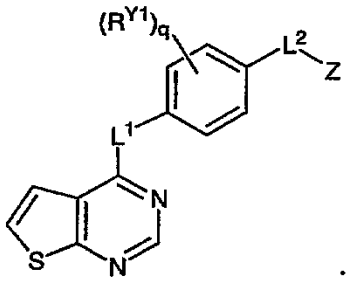

or

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11. The compound of claim 1 having the structure:

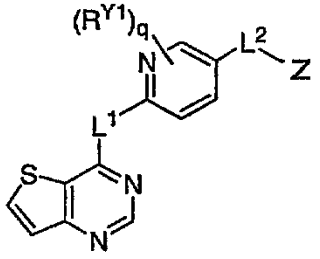
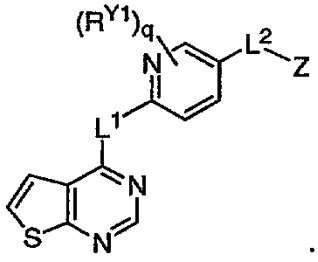

or


wherein q is an integer from 0-3; 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.

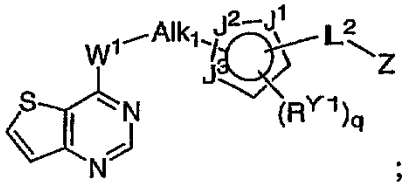
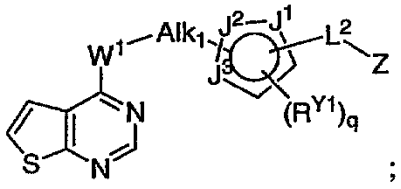
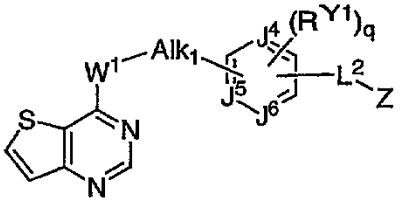
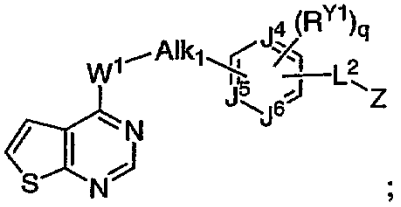
12. The compound of claim 11 having the structure:

13. The compound of claim 11 having the structure:

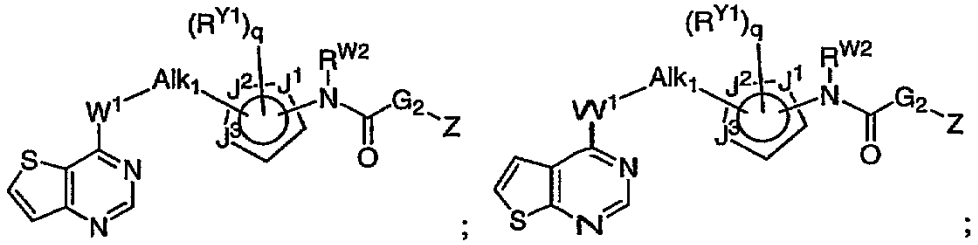
14. The compound of claim 1 having the structure:

wherein 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, $-OR^{Y3}$,

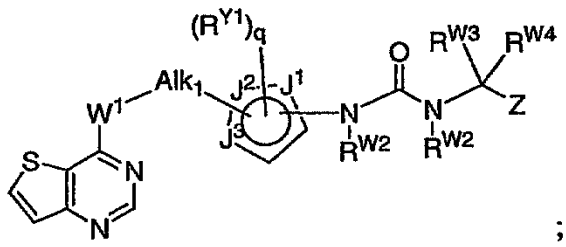
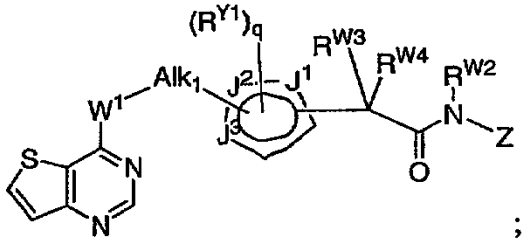
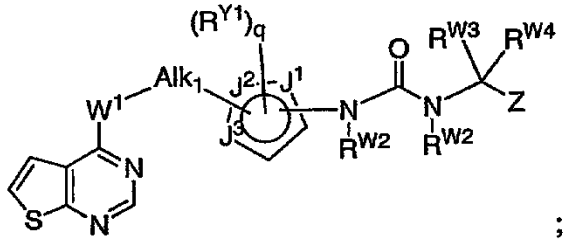
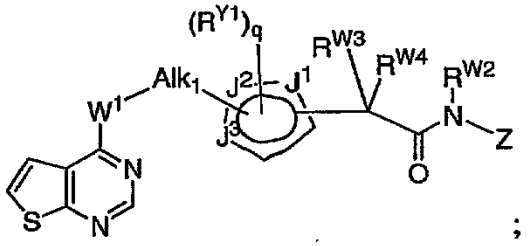
$-SR^{Y3}$, $-NR^{Y2}R^{Y3}$, $-SO_2NR^{Y2}R^{Y3}$, $-C(=O)NR^{Y2}R^{Y3}$, halogen, $-CN$, $-NO_2$, $-C(=O)OR^{Y3}$, $-N(R^{Y2})C(=O)R^{Y3}$, wherein each occcurrence of R^{Y2} and R^{Y3} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or 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.

15. The compound of claim 1 having the structure:



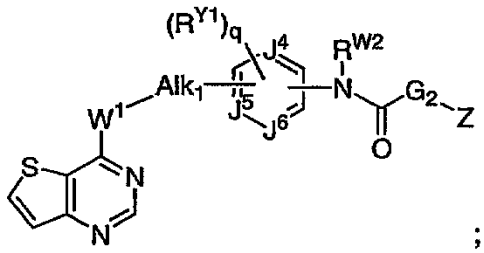
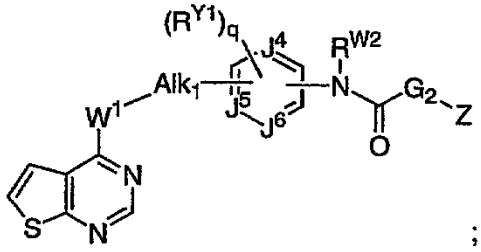
wherein Z is as defined generally and in classes and subclasses herein; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein 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.

16. The compound of claim 1 having the structure:


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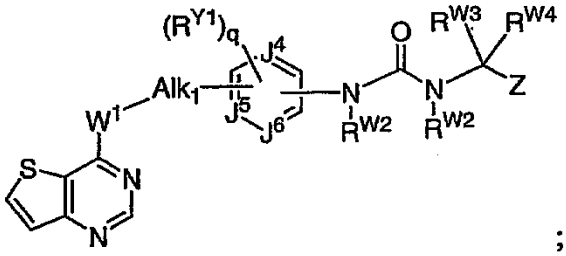
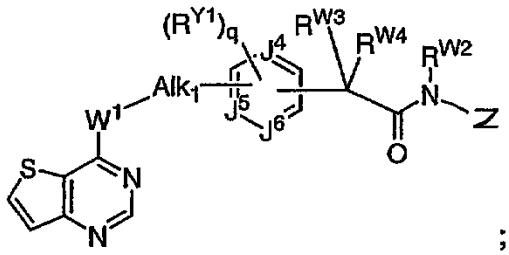
wherein Z is as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene units 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.

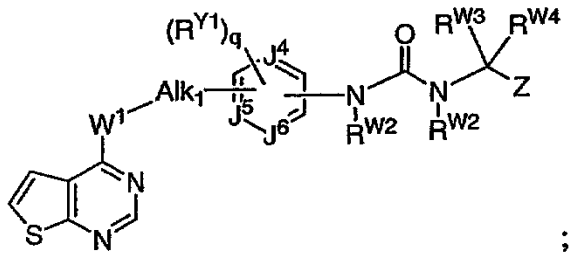
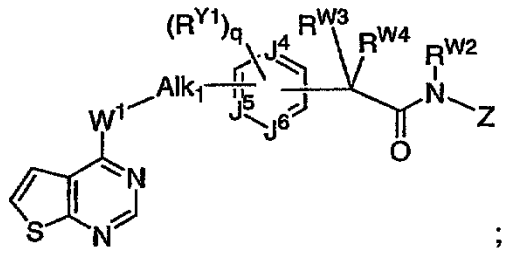
17. The compound of claim 1 having the structure:


;

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wherein Z is 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.

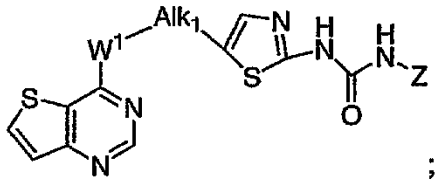
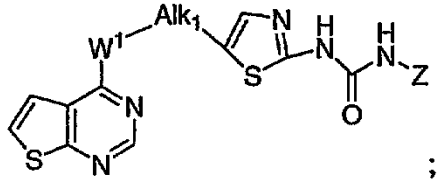
18. The compound of claim 1 having the structure:

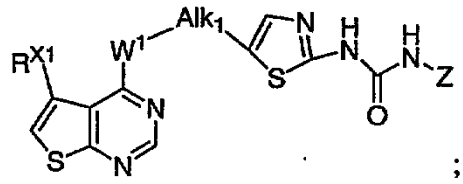

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wherein Z is as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene 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^{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; and R^{W2}, R^{W3} and R^{W4} are independently hydrogen, lower alkyl, lower heteroalkyl, heterocyclyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl.

19. The compound of claim 1 having the structure:

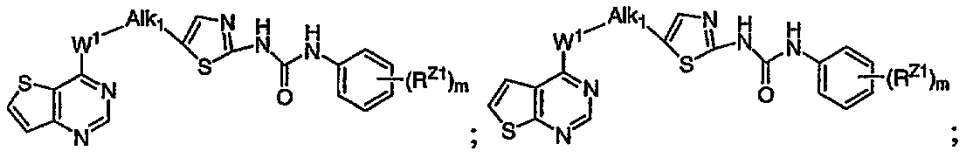

;

; or



;

wherein R^{X1} is 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 indenpendently 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.

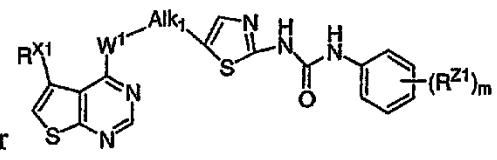
20. The compound of claim 1 having the structure:



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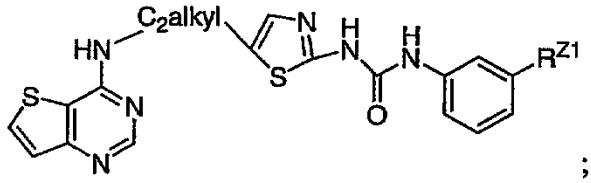
or



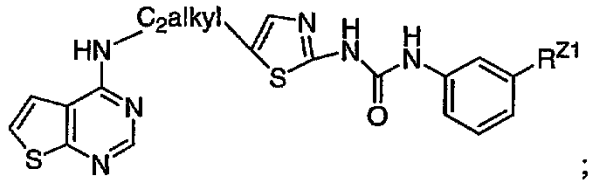
wherein R^{X1} is as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-}

$_6$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 indenpendently 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.

21. The compound of claim 21 having the structure:



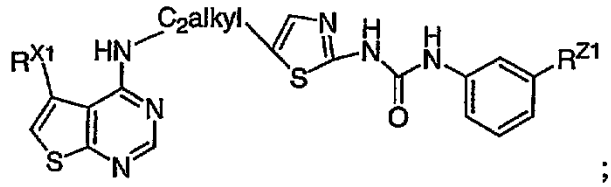
; or



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wherein R^{Z1} is halogen, lower alkyl or lower haloalkyl.

22. The compound of claim 21 having the structure:

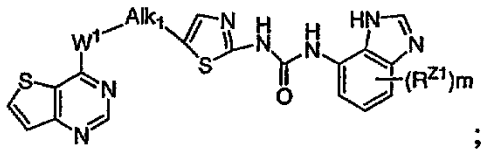
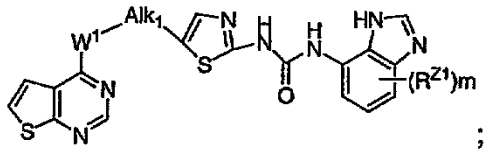


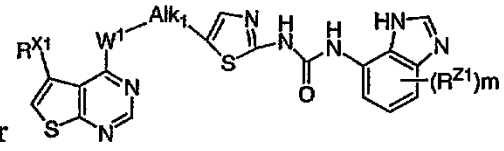
;

wherein R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is halogen, lower alkyl or lower haloalkyl.

23. The compound of claim 21 or 22 wherein R^{Z1} is Cl, F, methyl or $-CF_3$.

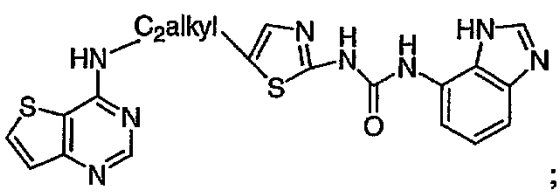
24. The compound of claim 1 having the structure:

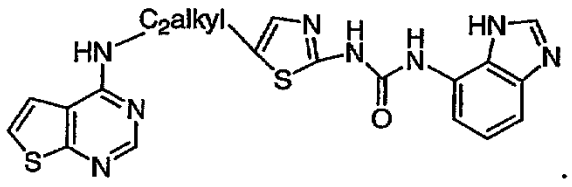

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or


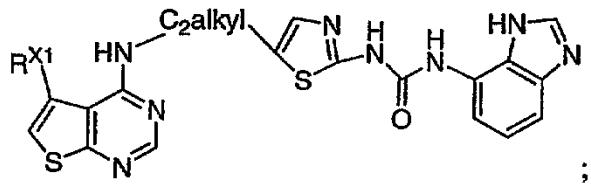
wherein R^{X1} is as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene 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 indenpendently 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.

25. The compound of claim 24 having the structure:


; or



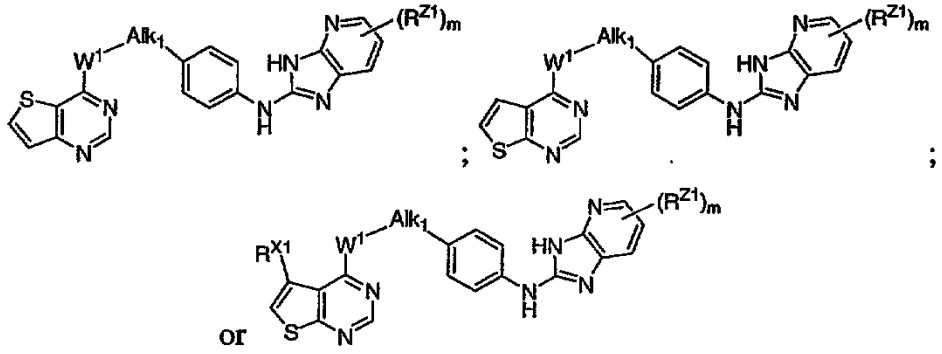
26. The compound of claim 24 having the structure:



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wherein R^{X1} is hydrogen, lower alkyl or heterocyclyl.

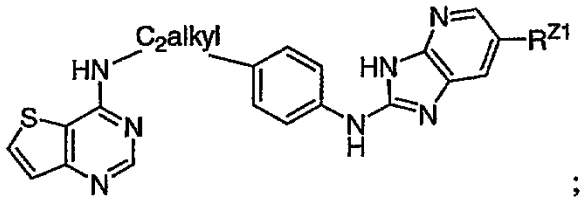
27. The compound of claim 1 having the structure:



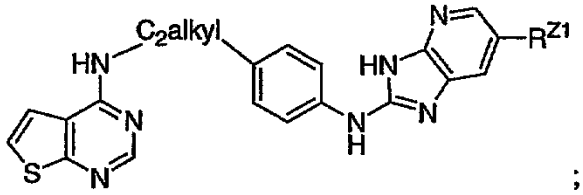
wherein R^{X1} is as defined in claim 1; W^1 is O or NR^{W1}, where R^{W1} is hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl, -(alkyl)heteroaryl or acyl; Alk_1 is a substituted or unsubstituted C_{1-6}alkylene or C_{2-6}alkenylene chain wherein up to two non-adjacent methylene 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 indenpendently 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.

28. The compound of claim 27 having the structure:



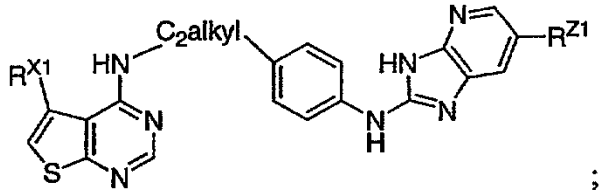
; or



;

wherein R^{Z1} is halogen, lower alkyl or lower haloalkyl.

29. The compound of claim 27 having the structure:

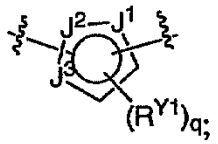


;

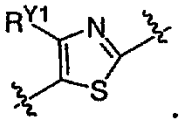
wherein R^{X1} is hydrogen, lower alkyl or heterocyclyl; and R^{Z1} is halogen, lower alkyl or lower haloalkyl.

30. The compound of claim 28 or 29 wherein R^{Z1} is Cl, F, methyl or $-CF_3$.

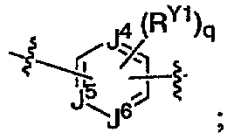
31. The compound of claim 14, 15 or 16 wherein the 5-membered ring having the structure:



has the following structure:

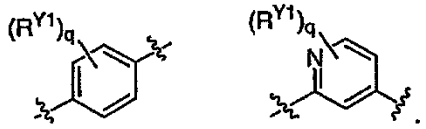


32. The compound of claim 14, 17 or 18 wherein the 6-membered ring having the structure:



;

has one of the following structures:



33. The compound of claim 6, 14, 15, 16, 17, 18 or 19 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 substittued or unsubstituted.

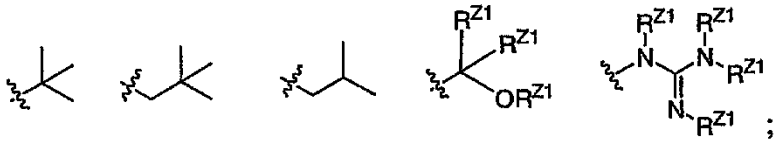
34. The compound of claim 33 wherein $-W^1-Alk_1-$ is $-NHCH_2CH_2-$, $-OCH_2CH_2-$ or $-NH-CH_2CH(CH_2OH)-$.

35. The compound of claim 7, 15 or 17 wherein $-N(R^{W2})C(=O)G_2-$ is $-NHC(=O)-$, $-NHC(=O)O-$, or $-NHC(=O)NH-$.

36. The compound of claim 35 wherein $-N(R^{W2})C(=O)G_2-$ is $-NHC(=O)NH-$.

37. The compound of claim 8, 16 or 18 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 $-CH_2C(=O)NH-$.

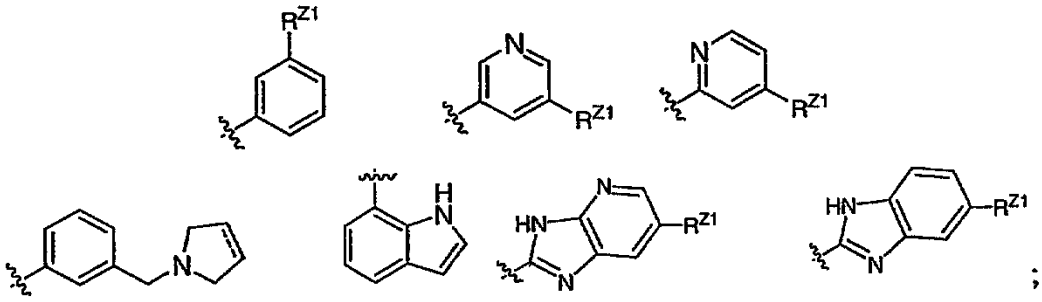
38. The compound of claim 1, wherein Z has one of the following structures:



;

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

39. The compound of claim 1, wherein Z has one of the following structures:



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

40. A composition comprising an effective amount of compound of any one of claims 1-39, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

41. The composition of claim 40, wherein the compound is in an amount to detectably inhibit Aurora protein kinase activity.

42. The composition of claim 40, 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.

43. 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 40; or

b) a compound of any one of claims 1-39.

44. The method of claim 43, wherein the method comprises inhibiting Aurora kinase activity.

45. 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 40; or

b) a compound of any one of claims 1-39.

46. The method according to claim 45, 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.