This invention describes novel pyrazole compounds of formula III:

![Chemical Structure](image)

wherein $Z^1$, $Z^2$, and $Z^3$ are as described in the specification; $Q$ is $\equiv S\equiv$, $\equiv O\equiv$, $\equiv N(R^4)\equiv$, or $\equiv CH(R^6)\equiv$; $R^1$ is T-Ring D, wherein Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclic or carbocyclic; and $R^2$ and $R^3$ are as described in the specification. The compounds are useful as protein kinase inhibitors, especially as inhibitors of Aurora-2 and GSK-3, for treating diseases such as cancer, diabetes and Alzheimer’s disease.
PYRAZOLE COMPOUNDS USEFUL AS PROTEIN KINASE INHIBITORS

RELATED APPLICATIONS


FIELD OF THE INVENTION

[0002] The present invention is in the field of medicinal chemistry and relates to compounds that are protein kinase inhibitors, compositions containing such compounds and methods of use. More particularly, this invention relates to compounds that are inhibitors of Aurora-2 protein kinase. The invention also relates to methods of treating diseases associated with protein kinases, especially diseases associated with Aurora-2, such as cancer.

BACKGROUND OF THE INVENTION

[0003] The search for new therapeutic agents has been greatly aided in recent years by better understanding of the structure of enzymes and other biomolecules associated with target diseases. One important class of enzymes that has been the subject of extensive study is the protein kinases.

[0004] Protein kinases mediate intracellular signal transduction. They do this by effecting a phosphoryl transfer from a nucleotide triphosphate to a protein acceptor that is involved in a signaling pathway. There are a number of kinases and pathways through which extracellular and other stimuli cause a variety of cellular responses to occur inside the cell. Examples of such stimuli include environmental and chemical stress signals (e.g., osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, H2O2), 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 effect 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 cell cycle.

[0005] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer’s disease or 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] Aurora-2 is a serine/threonine protein kinase that has been implicated in human cancer, such as colon, breast and other solid tumors. This kinase is believed to be involved in protein phosphorylation events that regulate the cell cycle. Specifically, Aurora-2 may play a role in controlling the accurate segregation of chromosomes during mitosis. Misregulation of the cell cycle can lead to cellular proliferation and other abnormalities. In human colon cancer tissue, the aurora-2 protein has been found to be overexpressed. See 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.

[0007] Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase comprised of a and isoforms that are each encoded by distinct genes [Coghlan et al., Chemistry & Biology, 7, 793-803 (2000); and Kim and Kimmel, Curr. Opinion Genetics Dev., 10, 508-514 (2000)]. GSK-3 has been implicated in various diseases including diabetes, Alzheimer’s disease, CNS disorders such as manic depressive disorder and neurodegenerative diseases, and cardiomyocyte hypertrophy [WO 95/65897; WO 00/38675; and Huq et al., J. Cell Biol. (2000) 151, 117]. These diseases may be acceded by, in the abnormal operation of certain cell signaling pathways in which GSK-3 plays a role. GSK-3 has been found to phosphorylate and deactivate the activity of a number of regulatory proteins. These proteins include glycogen synthase which is the rate limiting enzyme necessary for glycogen synthesis, the microtubule associated protein Tau, the gene transcription factor β-catenin, the translation initiation factor eIF2B, as well as ATP citrate lyase, axin, heat shock factor-1, c-Jun, c-Myc, c-Mycb, CREB, and CEPBP. These diverse protein targets implicate GSK-3 in many aspects of cellular metabolism, proliferation, differentiation and development.

[0008] In a GSK-3 mediated pathway that is relevant for the treatment of type II diabetes, insulin-induced signaling leads to cellular glucose uptake and glycogen synthesis. Along this pathway, GSK-3 is a negative regulator of the insulin-induced signal. Normally, the presence of insulin causes inhibition of GSK-3 mediated phosphorylation and deactivation of glycogen synthase. The inhibition of GSK-3 leads to increased glycogen synthesis and glucose uptake [Klein et al., PNAS, 93, 5455-9 (1996); Cross et al., Biochem. J., 303, 21-26 (1994); Cohen, Biochem. Soc. Trans., 21, 555-567 (1993); Massillon et al., Biochem J. 299, 123-128 (1994)]. However, in a diabetic patient where the insulin response is impaired, glycogen synthesis and glucose uptake fail to increase despite the presence of relatively high blood levels of insulin. This leads to abnormally high blood levels of glucose with acute and long term effects that may ultimately result in cardiovascular diseases, renal failure and blindness. In such patients, normal insulin-induced inhibition of GSK-3 fails to occur. It has also been reported that in patients with type II diabetes, GSK-3 is overexpressed [WO 00/38675]. Therapeutic inhibitors of GSK-3 are therefore potentially useful for treating diabetic patients suffering from an impaired response to insulin.

[0009] GSK-3 activity has also been associated with Alzheimer’s disease. This disease is characterized by the well-known β-amyloid peptide and the formation of intracellular neurofibrillary tangles. The neurofibrillary tangles contain hyperphosphorylated Tau protein where Tau is phosphorylated on abnormal sites. GSK-3 has been shown to phosphorylate these abnormal sites in cell and animal models. Furthermore, inhibition of GSK-3 has been shown to prevent hyperphosphorylation of Tau in cells [Lovestone et al., Current Biology 4, 1077-86 (1994); Brownlee et al., Neuronreport 8, 3251-55 (1997)]. Therefore, it is believed that GSK-3 activity may promote generation of the neurofibrillary tangles and the progression of Alzheimer’s disease.

[0010] Another substrate of GSK-3 is β-catenin which is degraded after phosphorylation by GSK-3. Reduced levels of β-catenin have been reported in schizophrenic patients and have also been associated with other diseases related to

[0011] As a result of the biological importance of GSK-3, there is current interest in therapeutically effective GSK-3 inhibitors. Small molecules that inhibit GSK-3 have recently been reported [WO 99/65897 (Chiron) and WO 00/38675 (SmithKline Beecham)].

[0012] For many of the aforementioned diseases associated with abnormal GSK-3 activity, other protein kinases have also been targeted for treating the same diseases. However, the various protein kinases often act through different biological pathways. For example, certain quinazolone derivatives have been reported recently as inhibitors of p38 kinase (WO 00/12497 to Scios). The compounds are reported to be useful for treating conditions characterized by enhanced p38-α activity and/or enhanced TGF-β activity. While p38 activity has been implicated in a wide variety of diseases, including diabetes, p38 kinase is not reported to be a constituent of an insulin signaling pathway that regulates glycogen synthesis or glucose uptake. Therefore, unlike GSK-3, p38 inhibition would not be expected to enhance glycogen synthesis and/or glucose uptake.

[0013] There is a continued need to find new therapeutic agents to treat human diseases. The protein kinases Aurora-2 and GSK-3 are especially attractive targets for the discovery of new therapeutics due to their important roles in cancer and diabetes, respectively.

**DESCRIPTION OF THE INVENTION**

[0014] It has now been found that compounds of this invention and pharmaceutical compositions thereof are effective as protein kinase inhibitors, particularly as inhibitors of Aurora-2. These compounds have the general formula I:

![Chemical Structure](image)

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

- Z to Z are as described below;
- Ring A is selected from the group consisting of:

![Chemical Structure](image)

[0015] R or R is T-R or L-Z-R;

[0016] R is Z-R or an optionally substituted group selected from C1-C6 aliphatic, C6-C10 aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms, or R and R are taken together to form a fused, optionally substituted 5-7 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur;

[0017] Q is selected from —N(R’)—, —O—, —S—, or —CH(R’)—;

[0018] R or R is T-(Ring D);

[0019] Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclic or carbocyclic, said heteroaryl or heterocyclic ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein each substitutable ring carbon of Ring D is independently substituted by oxo, T-R, or V-Z-R, and each substitutable ring nitrogen of Ring D is independently substituted by —R’;
T is a valence bond or a C<sub>1-4</sub> alkylidene chain, wherein when Q is —CH(R)—, a methylene unit of said C<sub>1-4</sub> alkylidene chain is optionally replaced by —O—, —S—, —N(R)<sub>2</sub>, —CO—, —CONH—, —NHCO—, —SO<sub>2</sub>—, —SO<sub>2</sub>NH—, —NHSO<sub>2</sub>—, —CO<sub>2</sub>—, —OC(O)—, —OC(O)NH— or —NHCO<sub>2</sub>—.

Z is a C<sub>1-4</sub> alkylidene chain.

L is —O—, —S—, —SO<sub>2</sub>—, —N(R)<sub>2</sub>, —SO—, —N(R)—, —N(R)CO, (optionally substituted Caliphatic), —N(R)N(R), —C=NN(R) —C=N OR, —N(R)CON(R), —N(R)SON(R), —N(R)SOR, or —OC(=O)N(R).

R<sup>2</sup> and R<sup>2</sup> are independently selected from —R, —T=W—R<sup>9</sup>, or R<sup>3</sup> and R<sup>2</sup> are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable ring carbon of said fused ring formed by R<sup>2</sup> and R<sup>2</sup> is independently substituted by halo, oxo, CN, NO<sub>2</sub>, R', or V—R<sup>9</sup>, and each substitutable ring nitrogen of said fused ring formed by R<sup>2</sup> and R<sup>2</sup> is independently substituted by R<sup>9</sup>.

R<sup>5</sup> is selected from —R, —halo, —OR, —(C=O)R, —CO<sub>2</sub>R, —COLOR, —COCH<sub>3</sub>OR, —NO<sub>2</sub>, —CN, —SO(O)R, —SO(OR), —SR, —N(R)<sup>2</sup>, —CON(R)<sup>2</sup>, —SO<sub>2</sub>N(R)<sup>2</sup>, —OC(O)OR—N(R)<sup>2</sup>CO, —N(R)<sup>2</sup>CO<sub>2</sub> (C<sub>1-6</sub> aliphatic), —N(R)<sup>2</sup>CON(R)<sup>2</sup>, —C=N(NR)<sup>2</sup>, —C=N—NR<sup>2</sup>, —N(R)<sup>2</sup>SO<sub>2</sub>N(R)<sup>2</sup>, or —OC(O)(R)<sup>2</sup>.

R<sup>8</sup> is selected from —R, —halo, —OR, —(C=O)R, —CO<sub>2</sub>R, —COLOR, —COCH<sub>3</sub>OR, —NO<sub>2</sub>, —CN, —SO(O)R, —SO(OR), —SR, —N(R)<sup>2</sup>, —CON(R)<sup>2</sup>, —SO<sub>2</sub>N(R)<sup>2</sup>, —OC(O)OR—N(R)<sup>2</sup>CO, —N(R)<sup>2</sup>CO<sub>2</sub> (C<sub>1-6</sub> aliphatic), —N(R)<sup>2</sup>CON(R)<sup>2</sup>, —C=N(NR)<sup>2</sup>, —C=N—NR<sup>2</sup>, —N(R)<sup>2</sup>SO<sub>2</sub>N(R)<sup>2</sup>, or —OC(O)(R)<sup>2</sup>.

R is independently selected from hydrogen or an optionally substituted group selected from C<sub>1-4</sub> aliphatic, C<sub>6-10</sub> aryl, a heteroaromatic ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms.

R is independently selected from —R<sup>3</sup>, —R<sup>4</sup> or —SO<sub>2</sub>R.<sup>2</sup>

R<sup>3</sup> is independently selected from —R<sup>5</sup>, —OR, —(C=O)R, —CO<sub>2</sub>R (optionally substituted C<sub>1-4</sub> aliphatic), —CON(R)<sup>2</sup>, or —SO<sub>2</sub>R.<sup>2</sup>

R<sup>5</sup> is independently selected from —R<sup>5</sup>, —OR, —(C=O)R, —CO<sub>2</sub>R, —COLOR, —COCH<sub>3</sub>OR, —NO<sub>2</sub>, —CN, —SO(O)R, —SO(OR), —SR, —N(R)<sup>2</sup>, —CON(R)<sup>2</sup>, —SO<sub>2</sub>N(R)<sup>2</sup>, —OC(O)OR—N(R)<sup>2</sup>CO, —N(R)<sup>2</sup>CO<sub>2</sub> (optionally substituted C<sub>1-6</sub> aliphatic), —N(R)<sup>2</sup>CON(R)<sup>2</sup>, —C=N(NR)<sup>2</sup>, —C=N—NR<sup>2</sup>, —N(R)<sup>2</sup>SO<sub>2</sub>N(R)<sup>2</sup>, or —OC(O)(R)<sup>2</sup>.

V is —O—, —S—, —SO<sub>2</sub>—, —N(R)<sub>2</sub>, —SO—, —N(R)—, —N(R)CO, (optionally substituted Caliphatic), —N(R)N(R), —N(R)CON(R), —N(R)SON(R), —N(R)SOR, or —OC(O)N(R).
The term “aryl” used alone or as part of a larger moiety as in “arylalkyl”, “arylalkoxyl”, or “arylalkylalkoxy” refers to aromatic ring groups having five to fourteen members, such as phenyl, benzyl, phenethyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. The term “aryloyl” also refers to rings that are optionally substituted. The term “aryl” may be used interchangeably with the term “aryl ring”. “Aryl” also includes fused polycyclic aromatic ring systems in which an aromatic ring is fused to one or more rings. Examples include 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term “aryl”, as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as in an indanyl, phenanthridinyl, or tetrahydroanthralophyl, where the radical or point of attachment is on the aromatic ring.

The term “heterocyclic”, “heterocyclyl”, or “heterocyclic” as used herein includes non-aromatic ring systems having five to fourteen members, preferably five to ten, in which one or more rings are carbons, preferably one or four, are each replaced by a heteroatom such as N, O, or S. Examples of heterocyclic rings include 3-1H-benzimidazol-2-one, (1-substituted)-2-oxo-benzimidazol-3-yl, 2-tetrahydropyranyl, 3-tetrahydrofuranyl, 2-tetrahydrofuranyl, 2-tetrahydropyranoyl, 4-tetrahydropyranoyl, 1,3-dioxolanyl, 1,2-dithioly, 1,2-dithioly, 2,5-dihydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrididinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazipidinyl, 1,4-diazolyl, 1,4-diazolyl, 2,5-dihydrothiophenyl, 1,4-diazolyl, benzoxanyl, benzopyrrolidinyl, benzoxazinyl, and benzothienyl. Also included within the scope of the term “heterocyclic” or “heterocyclyl”, as it is used herein, is a group in which a non-aromatic hetero atom-containing ring is fused to one or more aromatic or non-aromatic rings, such as in an indolyl, chroman, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the non-aromatic hetero atom-containing ring. The term “heterocyclic”, “heterocyclyl”, or “heterocyclic” whether saturated or partially unsaturated, also refers to rings that are optionally substituted.

The term “heteroaryl”, used alone or as part of a larger moiety as “heteroarylalkyl” or “heteroarylalkoxyl” refers to heterocyclic ring groups having five to fourteen members. Examples of heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyrindyl, 3-pyrindyl, 4-pyrindyl, 2-pyrindyl, 4-pyrindyl, 5-pyrindyl, 3-pyrindazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-triazolyl, 5-triazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzo furanyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzo oxazolyl, benzimidazolyl, isoquinolinyl, indazolyl, isoindolyl, acridinyl, or benzoisox azolyl. Also included within the scope of the term “heteroaryl”, as it is used herein, is a group in which a heterocyclic ring is fused to one or more aromatic or non aromatic rings where the radical or point of attachment is on the heterocyclic ring. Examples include tetrahydroquinolinyl, tetrahydroquinolinyl, and pyrido[3,4-d]pyrimidinyl. The term “heteroaryl” also refers to rings that are optionally substituted. The term “heteroaryl” may be used interchangeably with the term “heteroaryloyl” or the term “heteroaromatic”. An aryl (including aralkyl, aralkoxy, arylalkylalkoxy) and the like or heteroaryl (including heteroarylalkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Examples of suitable substituents on the unsubstituted carbon atom of an aryl, heteroaryl, aralkyl, or heteroarylalkyl group include a halogen, —R, —OR, —SR, 1,2-methylene-dioxy, 1,2-ethylenedioxy, protected OH (such as acyloxy), phenyl (Ph), substituted Ph, —O(Ph), substituted —O(Ph), —CH(Ph), substituted —CH(Ph), —CH₂(Ph), substituted —CH₂(Ph), —NO₂, —CN, —N(Ph)₂, —NR‘C(OR)₂, —NR‘C(O)(NR″)₂, —NR‘C(ONR″)₂, —NR‘C(O)R″, —NR‘C(O)NR″, —NR‘SO₂R″, —C(O)(OR)₂, —C(O)(ONR″)₂, —CO₂R, —C(O)(OR)₂, —C(O)(ONR″)₂, —CO₂(OR)₂, —S(O)R, —SO₂N(Ph)₂, —SO₂N(Ph)₂, —NR‘SO₂R″, —O(=S)(N(Ph)₂), —O(=N—H)—N(Ph)₂, —(CH₃)₂NHC(OR)₂, —(CH₃)₂NHC(O)(CH₃)V=R(R′)²; wherein R² is hydrogen, a substituted or unsubstituted aliphatic group, an unsubstituted heteroaryl or heterocyclic ring, phenyl (Ph), substituted Ph, —O(Ph), substituted —O(Ph), —CH₂(Ph), or substituted —CH₂(Ph); y is 0-6; and V is a linker group. Examples of substituents on the aliphatic group or the phenyl ring of R” include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarboxyloxy, dialkylaminocarboxyloxy, alkoxyl, nitro, cyano, carbonyl, alkoxy carbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents. Examples of suitable substituents on the saturated carbon of an aliphatic group or on a non-aromatic heterocyclic ring include those listed above for the unsubstituted carbon of an aryl or heteroaryl group and the following: —O, —S, —NHR, —NR′(R″)², —N—R, —NH(OR)², —NHCO₂(alkyl), —NHSO₃(alkyl), or —NR″*, wherein each R* is independently selected from hydrogen, an unsubstituted aliphatic group or a substituted aliphatic group. Examples of substituents on the aliphatic group include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarboxyloxy, dialkylaminocarboxyloxy, alkoxyl, nitro, cyano, carbonyl, alkoxy carbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

Suitable substituents on the nitrogen of a non-aromatic heterocyclic ring include —R, —N(R²)₂, —C(O)R, —CO₂R, —C(O)(OR)², —C(O)CH₂(OR)₂, —SO₂R, —SO₂N(Ph)², —C(=S)(N(Ph)₂), —C(=NH)—N(Ph)₂, and —NR′SO₂R; wherein R² is hydrogen, an aliphatic group, a substituted aliphatic group, phenyl (Ph), substituted Ph, —O(Ph), substituted —O(Pb), CH₃(Ph), substituted CH₃(Ph), or an unsubstituted heteroaryl or heterocyclic ring.
Examples of substituents on the aliphatic group or the phenyl ring include amino, alkylamino, dialkylamino, aminocarbonyl, haloxy, cyano, carbonyl, alkoxy carbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

[0046] The term “linker group” or “linker” means an organic moiety that connects two parts of a compound. Linkers are typically comprised of an atom such as oxygen or sulfur, a unit such as –NH–CH₂–, –C(O)–, –C(O)–NH–, or a chain of atoms, such as an alkylidene chain. The molecular mass of a linker is typically in the range of about 14 to 200, preferably in the range of 14 to 96 with a length of up to about six atoms. Examples of linkers include a saturated or unsaturated C₅₋₁₀ alkylidene chain which is optionally substituted, and wherein one or two saturated carbons of the chain are optionally replaced by –C(O)–, –C(O)C(O)–, –CONH–, –CONH–CONH–, –CO₂–, –OC(O)–, –NHCO₂–, –O–, –NHCONH–, –OC(O)NH–, –NHNH–, –NHCOC(O)–, –S–, –SO₂–, –SO₂–, –NH–, –SO₃–NH–, or –NHSO₃–.

[0047] The term “alkylidene chain” refers to an optionally substituted, straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation. The optional substituents are as described above for an aliphatic group.

[0048] A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0049] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0050] Compounds of formula I or salts thereof may be formulated into compositions. In a preferred embodiment, the composition is a pharmaceutical composition. In one embodiment, the composition comprises an amount of the protein kinase inhibitor effective to inhibit a protein kinase, particularly Aurora-2, in a biological sample or in a patient. In another embodiment, compounds of this invention and pharmaceutical compositions thereof, which comprise an amount of the protein kinase inhibitor effective to treat or prevent an Aurora-2-mediated condition and a pharmaceutically acceptable carrier, adjunct, or vehicle, may be formulated for administration to a patient.

[0051] Another aspect of this invention relates to a method of treating or preventing an Aurora-2-mediated disease with an Aurora-2 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

[0052] The term “Aurora-2-mediated condition” or “disease”, as used herein, means any disease or other deleterious condition in which Aurora is known to play a role. The term “Aurora-2-mediated condition” or “disease” also means those diseases or conditions that are alleviated by treatment with an Aurora-2 inhibitor. Such conditions include, without limitation, cancer. The term “cancer” includes, but is not limited to the following cancers: colon, breast, stomach, and ovarian.

[0053] Another aspect of the invention relates to inhibiting Aurora-2 activity in a biological sample, which method comprises contacting the biological sample with the Aurora-2 inhibitor of formula I, or a composition thereof.

[0054] Another aspect of this invention relates to a method of inhibiting Aurora-2 activity in a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

[0055] Another aspect of this invention relates to a method of treating or preventing a GSK-3-mediated disease with a GSK-3 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

[0056] The term “GSK-3-mediated condition” or “disease”, as used herein, means any disease or other deleterious condition or state in which GSK-3 is known to play a role. Such diseases or conditions include, without limitation, diabetes, Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, AIDS-associated dementia, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, repulsion/ischemia, and baldness.

[0057] One aspect of this invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof. This method is especially useful for diabetic patients. Another method relates to inhibiting the production of hyperphosphorylated tau protein, which is useful in halting or slowing the progression of Alzheimer’s disease. Another method relates to inhibiting the phosphorylation of β-catenin, which is useful for treating schizophrenia.

[0058] Another aspect of the invention relates to inhibiting GSK-3 activity in a biological sample, which method comprises contacting the biological sample with a GSK-3 inhibitor of formula I.

[0059] Another aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, which method comprises administering to the patient a compound of formula I or a composition comprising said compound.

[0060] The term “pharmaceutically acceptable carrier, adjunct, or vehicle” refers to a non-toxic carrier, adjunct, or vehicle that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.

[0061] The term “patient” includes human and veterinary subjects.

[0062] The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; preparations of an enzyme suitable for in vitro assay; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.
The amount effective to inhibit protein kinase, for example, Aurora-2 and GSK-3, is one that measurably inhibits the kinase activity where compared to the activity of the enzyme in the absence of an inhibitor. Any method may be used to determine inhibition, such as, for example, the Biological Testing Examples described below.

Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions 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, 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, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term “parenteral” as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intratrabecular, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butandiol. Among the acceptable vehicles and solvents that may be employed are water, Ringer’s solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including such as monoglycerides and diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethyleneated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

In addition to the compounds of this invention, pharmaceutically acceptable derivatives or prodrugs of the compounds of this invention may also be employed in compositions to treat or prevent the above-identified diseases or disorders.

A “pharmacologically acceptable derivative or prodrug” means any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitory active metabolite or residue thereof. Particularly favored derivatives or prodrugs are those that increase the bioavailability of the compounds of this inven-
When such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable prodrugs of the compounds of this invention include, without limitation, esters, amino acid esters, phosphate esters, metal salts and sulfonate esters.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginic, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, diglucuronate, doceylsulfate, ethanesulfonate, formate, fumarate, gluconate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyanilinesulfonate, lactate, maleate, maleonate, methanesulfonate, 2-naphtalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecenoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and N\(^{+}\)(C\(_{1-4}\) alkyl)\(_{2}\) salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The amount of the protein kinase inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the patient treated and the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01-100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of the inhibitor will also depend upon the particular compound in the composition.

Depending upon the particular protein kinase-mediated condition to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may be administered together with the inhibitors of this invention. For example, in the treatment of cancer other chemotherapeutic agents or other anti-proliferative agents may be combined with the Aurora-2 inhibitors of this invention to treat cancer. These agents include, without limitation, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

Other examples of agents the inhibitors of this invention may also be combined with include, without limitation, agents for treating diabetes such as insulin or insulin analogues, in injectable or inhalation form, glitazones, alpha glucosidase inhibitors, biguanides, insulin sensitizers, and sulfonyl ureas; 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 acetycholinesterase 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.

Those additional agents may be administered separately from the protein kinase inhibitor-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with the protein kinase inhibitor of this invention in a single composition.

Compounds of this invention may exist in alternative tautomeric forms, as in tautomers i and ii shown below. Unless otherwise indicated, the representation of either tautomer is meant to include the other.

Preferred R\(^{3}\) groups, when present, include hydrogen, alkyl- or dialkylamino, acetamido, or a C\(_{1-4}\) aliphatic group such as methyl, ethyl, cyclopropyl, or isopropyl.

Preferred R\(^{5}\) groups, when present, include Z-R\(^{5}\) or an optionally substituted group selected from C\(_{1-5}\) aliphatic, 5-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl, wherein Z is a methylene and R\(^{5}\) is --NR\(^{6}\)R\(^{7}\)--OR, or an optionally substituted group selected from C\(_{1-6}\) aliphatic, C\(_{6-10}\) aryl, a heteroary or a heterocyclic ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms. Preferred R\(^{5}\) groups include 5-6 membered heteroaryl or heterocyclic rings, such as 2-pyridyl, 4-pyridyl, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl; C\(_{1-6}\) aliphatic, such as methyl,
ethyl, cyclopropyl, isopropyl, or t-butyl; alkoxyalkylamino such as methoxyethylamino; alkoxyalkyl such as methoxymethyl or methoxymethyl; alkyl- or dialkylamino such as ethylamino or dimethylamino; alkyl- or dialkylaminooalkoxy such as dimethyaminopropoxy; acetamido; and optionally substituted phenyl such as phenyl or halo-substituted phenyl.

[R087] \( R^1 \) and \( R^2 \) may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carboxylic ring, wherein said fused ring is optionally substituted. These are exemplified in the following formula I compounds having a pyrazole-containing bicyclic ring system:

Another embodiment of this invention relates to compounds of formula II:

When the pyrazole ring system is monocyclic, preferred \( R^2 \) groups include hydrogen, \( -C(=O) \)aryl, \( -C(=O)N(=O) \)aryl, \( -C(=O)O \)aryl, \( -C(=O)S \)aryl, \( -C(=O)NR \)aryl, \( -C(=O)NR=O \)aryl, \( -C(=O)NR=NR \)aryl, \( -C(=O)NR=NR=O \)aryl, \( -C(=O)NR=NR=NR \)aryl, \( -C(=O)NR=NR=NR=O \)aryl, \( -C(=O)NR=NR=NR=NR \)aryl, \( -C(=O)NR=NR=NR=NR=O \)aryl, \( -C(=O)NR=NR=NR=NR=NR \)aryl, \( -C(=O)NR=NR=NR=NR=NR=O \)aryl, \( -C(=O)NR=NR=NR=NR=NR=NR \)aryl.

Preferred \( Q \) groups of formula I include —S—, —NH—, and —CH—. More preferred \( Q \) groups of formula I include —S— and —NH—.

Preferred substituents on the \( R^2/R^2 \) fused ring include one or more of the following: -halo, —(R^1)=CH—, —(R^1)=C(=O)NR—, —(R^1)=C(=O)NR=O—, —(R^1)=C(=O)NR=NR—, —(R^1)=C(=O)NR=NR=O—, —(R^1)=C(=O)NR=NR=NR—, —(R^1)=C(=O)NR=NR=NR=O—, —(R^1)=C(=O)NR=NR=NR=NR—, —(R^1)=C(=O)NR=NR=NR=NR=O—, —(R^1)=C(=O)NR=NR=NR=NR=NR—, —(R^1)=C(=O)NR=NR=NR=NR=NR=O—, —(R^1)=C(=O)NR=NR=NR=NR=NR=NR—;

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

[Z082] \( Z' \) is nitrogen or CR^8;

[R083] \( R^1 \) is \( Z-R^5 \) or an optionally substituted group selected from \( C_1-C_8 \) aliphatic, \( C_6-C_8 \) aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms, or \( R^1 \) and \( R^2 \) are taken together to form a fused, optionally substituted 5-7 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur;

[R084] \( Q \) is selected from —N(R^4)—, —O—, —S—, or —CH(R^4)—;

[R085] \( R^1 \) is \( T= \) (Ring D);

[R086] Ring \( D \) is a 5-7 membered monocyclic or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein each substitutable ring carbon of Ring \( D \) is independently substituted by oxo, \( T-R^5 \), or \( V--Z--R^5 \), and each substitutable ring nitrogen of Ring \( D \) is independently substituted by \( R^8 \);

[T087] \( T \) is a valence bond or a \( C_1-C_4 \) alkyldiene chain, wherein when \( Q = -CH(R^4)=- \), a methylene unit of said \( C_1-C_4 \) alkyldiene chain is optionally replaced by \( -O-- \), \( -S-- \), \( -N(R^4)-- \), \( -CO-- \), \( -CONH-- \), \( -NHCO-- \), \( -SO-- \), \( -SO_2-- \), \( -SO_2NH-- \), \( -NHCO_2-- \), \( -OC(=O)NH-- \), or \( -NHCO_2-- \);

[R088] \( Z \) is a \( C_1-C_4 \) alkyldiene chain;

[R089] \( L \) is \( -O-- \), \( -S-- \), \( -SO-- \), \( -SO_2-- \), \( -N(R^4)-- \), \( -CO-- \), \( -CONH-- \), \( -NHCO-- \), \( -SO-- \), \( -C(R^4)SO_2-- \), \( -C(R^4)SO_2NR(R^4)-- \), \( -C(R^4)NR_2-- \), \( -C(R^4)NR_2CO-- \), \( -C(R^4)NR_2CON(R^4)-- \), \( -N(R^4)NR_2-- \), \( -C(R^4)NR_2CON(R^4)-- \), \( -N(R^4)NR_2CON(R^4)-- \), \( -C(R^4)NR_2CON(R^4)-- \), \( -N(R^4)NR_2CON(R^4)-- \), \( -C(R^4)NR_2CON(R^4)-- \), \( -N(R^4)NR_2CON(R^4)-- \).

[R090] \( R^1 \) and \( R^2 \) are independently selected from \( -R \), \( -T-W--R^5 \), or \( R^2 \) and \( R^2 \) are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable ring carbon of said fused ring formed by \( R^1 \) and \( R^2 \) is independently substituted by halo, oxo, \( -CN-- \), \( -NO_2-- \), \( -O-- \), \( -V--R^6-- \), and each substitutable ring nitrogen of said ring formed by \( R^1 \) and \( R^2 \) is independently substituted by \( R^4 \),
[0101] R² is selected from —halo, —OR, —C(=O)R, —COOR, —COCHCOR, —NO₂, —CN, —S(O)R, —S(O)₂R, —SR, —N(R³)₂, —CON(R³)₂, —SO₂N(R⁴)₂, —OC(=O)R, —N(R³)COR, —N(R³)CO₂(C₆H₅) (optional substituted C₆H₅ aliphatic), —N(R³)N(R⁴)₂, —C=N(R³)N(R⁴)₂, —C=N—OR, —N(R³)CON(R³)₂, —N(R³)SO₂N(R⁴)₂, —N(R³)SO₂R, —OC(=O)N(R⁴)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;

[0102] each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;

[0103] each R² is independently selected from —R², —COR², —CO₂ optionally substituted C₁₋₆ aliphatic, —CON(R³)₂, or —SO₂R²;

[0104] each R³ is independently selected from —R, halo, —OR, —C(=O)R, —CO₂R, —COCHCOR, —NO₂, —CN, —S(O)R, —S(O)₂R, —SR, —N(R³)₂, —CON(R³)₂, —SO₂N(R⁴)₂, —OC(=O)R, —N(R³)COR, —N(R³)CO₂ (optional substituted C₁₋₆ aliphatic), —N(R³)N(R⁴)₂, —C=N—OR, —N(R³)CON(R³)₂, —N(R³)SO₂N(R⁴)₂, —N(R³)SO₂R, or —OC(=O)N(R⁴)²;

[0105] V is —O—, —S—, —SO—, —SO₂—, —N(R⁶)SO₂—, —SO₂N(R⁷)N(R⁸), —N(R³)R⁹, —CO—, —CON(R³)₂, —N(R⁴)CO₂(C₆H₅) (optional substituted C₆H₅ aliphatic), —N(R³)N(R⁴)₂, —C=N—N—, —N(R³)CON(R³)₂, —C=N—N—O—, —N(R³)SO₂N(R⁴)₂, —N(R³)SO₂R, or —C=N—N—O—;

[0106] W is —C(R⁵)O—, —C(R⁵)S—, —C(R⁵)SO—, —C(R⁵)SO₂—, —C(R⁵)SO₂N(R⁷)N(R⁸), —C(R⁵)N(R⁹)N(R³) (R⁹), —CO—, —CON(R³)₂, —N(R⁴)CO₂(C₆H₅) (optional substituted C₆H₅ aliphatic), —N(R³)N(R⁴)₂, —C=N—N—, —N(R³)CON(R³)₂, —C=N—N—O—, —N(R³)SO₂N(R⁴)₂, —N(R³)SO₂R, or —C=N—N—O—;

[0107] each R⁴ is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R⁴ groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclic or heteroary1 ring;

[0108] each R is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclic or heteroary1 ring; and

[0109] R³ is selected from —R, halo, —OR, —C(=O)R, —CO₂R, —COCHCOR, —NO₂, —CN, —S(O)R, —S(O)₂R, —SR, —N(R³)₂, —CON(R³)₂, —SO₂N(R⁴)₂, —OC(=O)R, —N(R³)COR, —N(R³)CO₂ (optional substituted C₁₋₆ aliphatic), —N(R³)N(R⁴)₂, —C=N—N—, —N(R³)CON(R³)₂, —C=N—N—O—, —N(R³)SO₂N(R⁴)₂, —N(R³)SO₂R, or —OC(=O)N(R⁴)₂; provided that when Q is —NH— and R⁴ and R⁸ are taken together to form a fused ring, R³ is other than a pyrazol-3-yl ring or a pyrazol-3-yl-containing bicyclic ring system.

[0110] Another embodiment of this invention relates to compounds of formula IIa:

[0111] R² is Z—R³ or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;

[0112] Q is selected from —N(R⁴)N(R⁵) —O—, —S—, or —CH(R⁸)R⁸; and

[0113] R¹ is T(Ring D);

[0114] Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclic or carbocyclic, said heterocyclic or heteroaryl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein each substitutable ring carbon of Ring D is independently substituted by oxo, T-R¹, or —V—Z—R², and each substitutable ring nitrogen of Ring D is independently substituted by —R³;

[0115] V is a valence bond or a C₁₋₆ alkylidene chain, wherein when Q is —CH(R⁸) —, a methylene unit of said C₁₋₆ alkylidene chain is optionally replaced by —O—, —S—, —N(R⁶) —, —CO—, —CONH—, —NHCOR—, —SO₂—, —SO₂NH—, —NH₂SO₂—, —CO₂—, —OC(O)—, —OC(O)NH—, or —NHCO₂—;

[0116] Z is a C₁₋₆ alkylidene chain;

[0117] L is —O—, —S—, —SO—, —SO₂—, —N(R⁶)SO₂—, —SO₂N(R⁷)N(R⁸), —N(R³)N(R⁹)N(R³) (R⁹), —CO—, —CON(R³)₂, —N(R⁴)CO₂(C₆H₅) (optional substituted C₆H₅ aliphatic), —N(R³)N(R⁴)₂, —C=N—N—, —N(R³)CON(R³)₂, —C=N—N—O—, —N(R³)SO₂N(R⁴)₂, —N(R³)SO₂R, —OC(=O)N(R⁴)₂, —C(N(R³)N(R⁹)N(R³) (R⁹), —C(R⁵)S—, —C(R⁵)SO₂—, —C(R⁵)SO₂N(R⁷)N(R⁸), —C(R⁵)N(R³)N(R⁹)N(R³) (R⁹), —C(R⁵)N(R⁴)SO₂N(R⁴)₂, —C(R⁵)N(R⁴)SO₂R, or —C(R⁵)N(R³)CON(R³)₂;

[0118] R² and R³ are independently selected from —R, —T—W—R³, or R² and R³ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 5-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable ring carbon of said fused ring formed by R² and R³ is independently substituted by halo, oxo, —CN, —NO₂, —R³, or —V—Z—R³, and each substitutable ring nitrogen of said ring formed by R² and R³ is independently substituted by R³;

[0119] R⁸ is selected from —halo, —OR, —C(=O)R, —CO₂R, —COCHCOR, —NO₂, —CN,
—S(O)R, —S(O)₂R, —SR, —N(R⁵)₂, —CON(R⁷), —CON(R⁷), —C=NN(R), —N≡N, —C≡N, —N(R)SON(R), —N(R)SOR, or —OC(=O)N(R)₂.

Each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₄ aliphatic, C₅₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms.

Each R' is independently selected from —R², —CO₂, optionally substituted C₁₋₄ aliphatic, —CON(R'), or —SO₂R².

Each R² is independently selected from —R, halo, —OR, —C(=O)OR, —CO₂R, —COCOR, —NO₂, —CN, —SO₂R, —SR, —N(R⁵)₂, —CON(R'), —SO₂N(R⁵)₂, —OC(=O)OR, —N(R)⁵COR, —N(R)⁵CO, —C=NOR, —C=NN(R), —N(R)⁵CON(R'), —N(R)⁵SO₃R², or —OC(=O)N(R)².

V is —O—, —S—, —SO₂—, —N(R⁵)—.

Each R is independently selected from hydrogen or an optionally substituted C₁₋₄ aliphatic group, or two R' groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclic or heteroaryl ring; and

Each R' is independently selected from hydrogen or an optionally substituted C₁₋₄ aliphatic group, or two R' groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-8 membered heterocyclic or heteroaryl ring.

Preferred R² groups of formula Ila include Z—R² or an optionally substituted group selected from C₁₋₄ aliphatic, 5-6 membered heterocyclic, phenyl, or 5-6 membered heteroaryl, wherein Z is a methylene and R² is —N(R)⁵₂ OR, or an optionally substituted group selected from C₁₋₄ aliphatic, C₅₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms.

Examples of preferred R² groups include 2-pyridyl, 4-pyridyl, pyrrolyl, pyridiny1, morpholino, piperaziny1, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkoxyalkylamino such as methoxyethylamino, alkoxyalkyl such as methoxymethyl or methoxyethyl, alkyl- or dialkylamino such as ethylamino or dimethylamino, alkyl- or dialkylamino such as dimethylaminopropylxoy, acetamido, optionally substituted phenyl such as phenyl or halo-substituted phenyl.

The R² and R²' groups of formula Ila may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbo cyclic ring. These are exemplified in the following formula Ila compounds having a pyrazole-containing bicyclic ring system:

Preferred substituents on the R²/R²' fused ring of formula Ila include one or more of the following: -halo, —N(R⁵)₂, —C₅₋₁₀ alkyl, —C₅₋₁₀ haloalkyl, —NO₂, —O(C₅₋₁₀ alkyl), —CO₂(C₅₋₁₀ alkyl), —CN, —SO₂(C₅₋₁₀ alkyl), —SO₂NH₂, —OC(=O)NH₂, —NH₂SO₂(C₅₋₁₀ alkyl), —NHC(O)(C₅₋₁₀ alkyl), —(C₅₋₁₀ alkyl) or —CO(C₅₋₁₀ alkyl), wherein the (C₅₋₁₀ alkyl) is a straight branched, or cyclic alkyl group. Preferably, the (C₅₋₁₀ alkyl) group is methyl.

When the pyrazole ring system of formula Ila is monocyclic, preferred R² groups include hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₄ aliphatic group. Examples of such preferred R² groups include H, methyl, ethyl, propyl, i-propyl, cyclopentyl, hydroxypyrrol, methoxypyrrol, and benzoxypyrrol. A preferred R² group is hydrogen.

When Ring D of formula Ila is monocyclic, preferred Ring D groups include phenyl, pyridyl, pyridazinyl, pyrimidinyl, and pyrazinyl.

When Ring D of formula Ila is bicyclic, preferred bicyclic Ring D groups include naphthyl, tetralydronaphthyl, indanyl, benzimidazolyl, quinolinyl, indoly1, isoindoly1, indolino1, benzo[b]furany1, benzo[b]biophenyl, indazolyl, benzo[b]hiazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, quinoxalinyl, 1,8-naphthyridinyl and isoquinolinyl.

On Ring D of formula Ila, preferred T—R' or V—Z—R² substituents include -halo, —CN, —NO₂, —N(R⁵)₂, optionally substituted C₁₋₄ aliphatic group, —OR, —C(=O)R, —CO₂R, —CONH(R'), —N(R)⁵COR, —N(R)⁵CO₂R, —SO₂N(R⁵), —N(R)⁵SO₂R, or —OC(=O)N(R)².

On Ring D of formula Ila, preferred T—R' or V—Z—R² substituents include -halo, —CN, —NO₂, —N(R⁵)₂, optionally substituted C₁₋₄ aliphatic group, —OR, —C(=O)R, —CO₂R, —CONH(R'), —N(R)⁵COR, —N(R)⁵CO₂R, —SO₂N(R⁵), —N(R)⁵SO₂R, or —OC(=O)N(R)².
or a 5-6 membered heterocyclic ring. More preferred R\textsuperscript{s} substituents include —Cl, —Br, —F, —CN, —CF\textsubscript{3}, —COOH, —CONHMe, —CONHe, —NH\textsubscript{2}, —NHAc, —NHSO\textsubscript{2}Me, —NHSO\textsubscript{2}Et, —NHSO\textsubscript{2}(n-propyl), —NHSO\textsubscript{2}(isopropyl), —NHCOEt, —NHCOCH\textsubscript{2}NHCHOH, —NHCOI\textsubscript{2}NCO\textsubscript{2}(tBu)CH\textsubscript{3}, —NHCOI\textsubscript{2}N(CH\textsubscript{2})\textsubscript{2}, —NHCOI\textsubscript{2}N(CH\textsubscript{2})\textsubscript{4}, —NHCOI\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}N(CH\textsubscript{2})\textsubscript{4}, 2, —NHCOI cyclicpropyl), —NHCO(isobutyl), —NHCOI morpholin-4-yl), —NHCOI CH\textsubscript{2}N(cphilic), —NHCOI CH\textsubscript{2}morpholin-4-yl), —NHCOI(tertbuty), —NH(C\textsubscript{1,4} aliphatic) such as —NHMe, —N(C\textsubscript{1,4} aliphatic) such as —NMMe\textsubscript{2}, OH, —O(C\textsubscript{1,4} aliphatic) such as —OCH\textsubscript{3}, C\textsubscript{1,4} aliphatic such as methyl, ethyl, cyclopropyl, isopropyl, or t-butyl, and —CO\textsubscript{2}(C\textsubscript{1,4} aliphatic).

Preferred formula Ila compounds have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R\textsuperscript{*} is Z—R\textsuperscript{2} or an optionally substituted group selected from C\textsubscript{1,6} aliphatic, 5-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl, wherein Z is a methylene and R\textsuperscript{2} is —N(R\textsuperscript{3}), —OR, or an optionally substituted group selected from C\textsubscript{1,6} aliphatic, C\textsubscript{6,10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

(b) R\textsuperscript{3} is T(Ring D), wherein T is a valence bond or a methylene unit;

(c) Ring D is a 5-7 membered monocyclic or an 8-10 membered bicyclic aryl or heteroaryl ring; and

(d) R\textsuperscript{3} is —R or —T—W—R\textsuperscript{*} and R\textsuperscript{4} is hydrogen, or R\textsuperscript{2} and R\textsuperscript{4} are taken together to form an optionally substituted benzo ring.

More preferred compounds of formula Ila have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R\textsuperscript{3} is an optionally substituted group selected from C\textsubscript{1,6} aliphatic, 5-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl;

(b) R\textsuperscript{3} is T(Ring D), wherein T is a valence bond and Q is —S—, —NH—, or —CH—;

(c) Ring D is a 5-6 membered monocyclic or an 8-10 membered bicyclic aryl or heteroaryl ring; and

(d) R\textsuperscript{3} is —R and R\textsuperscript{4} is hydrogen, wherein R is selected from hydrogen, C\textsubscript{1,6} aliphatic, phenyl, a 5-6 membered heteroaryl ring, or a 5-6 membered heterocyclyl ring.

Even more preferred compounds of formula Ila have one or more, and more preferably all, of the features selected from the group consisting of:

(a) R\textsuperscript{3} is selected from 2-pyridyl, 4-pyridyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkoxyalkylamino, alkoxyalkyl, alkyl- or dialkylamino, alkyl- or dialkylaminooalkoxy, acetamido, optionally substituted phenyl, or methoxyethyl;

(b) R\textsuperscript{3} is T(Ring D), wherein T is a valence bond and Ring D is a 5-6 membered aryl or heteroaryl ring, wherein Ring D is optionally substituted with one to two groups selected from —halo, —CN, —NO\textsubscript{2}, —N(R\textsuperscript{3}), optionally substituted C\textsubscript{1,6} aliphatic group, —OR, —CO\textsubscript{2}R, —CONH(R\textsuperscript{3}), —N(R\textsuperscript{3})COR, —N(R\textsuperscript{3})SO\textsubscript{2}R, —N(R\textsuperscript{3})COCH\textsubscript{2}CH\textsubscript{2}N(R\textsuperscript{3}), and Q is —S— or —NH—; and

(c) R\textsuperscript{3} is hydrogen or a substituted or unsubstituted C\textsubscript{1,6} aliphatic, and L is —O—, —S—, or —NH—.

Representative compounds of formula Ila are shown below in Table 1.
Another embodiment of this invention relates to compounds of formula IIb:

![Chemical structure of IIb]

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

- \( R' \) is \( Z \) or \( R'' \) or an optionally substituted group selected from \( C_{1,4} \) aliphatic, \( C_{6,10} \) aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms, or \( R' \) and \( R'' \) are taken together to form a fused, optionally substituted 5-7 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur;

- \( Q \) is selected from \( -N(R')^{+} \), \( -O^{-} \), \( -S^{-} \), or \( -CH(\text{R}^{6})^{-} \);

- \( R^{1} \) is \( T \)-(Ring D);

- Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclic or carbocyclic, said heteroaryl or heterocyclic ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein each substitutable ring carbon of Ring D is independently substituted by \( \text{o xo, } T \)-\( R^{2} \), or \( V- \)\( Z-R^{3} \), and each substitutable ring nitrogen of Ring D is independently substituted by \( -R^{4} \);

- \( T \) is a valence bond or a \( C_{1,4} \) alkylidene chain, wherein when \( Q \) is \(-CH(\text{R}^{6})^{-}\), a methylene unit of said \( C_{1,4} \) alkylidene chain is optionally replaced by \(-O- \), \(-S- \), \(-N(\text{R}^{7})- \), \(-\text{CO-} \), \(-\text{CONH-} \), \(-\text{NHCO-} \), \(-\text{SO}_{2}- \), \(-\text{SO}_{2}\text{NH-} \), \(-\text{NHISO}_{2}- \), \(-\text{CO}_{2}- \), \(-\text{OC(O)-} \), \(-\text{OC(O)NH-} \), or \(-\text{NHCISO}_{2}- \);

- \( Z \) is a \( C_{1,4} \) alkylidene chain;

- \( \text{L is }-O-\), \(-S-\), \(-SO_{2}\), \(-SO_{2}N(\text{R}^{7})-\), \(-N(\text{R}^{7})-\), \(-\text{CO-}\), \(-\text{CO}(\text{O})-\), \(-\text{N(\text{R}^{7})CO(O)}-\), \(-\text{N(\text{R}^{7})CON(\text{R}^{6})-} \), \(-\text{N(\text{R}^{7})SO}_{2}\text{N(\text{R}^{7})-} \), \(-\text{N(\text{R}^{7})N(\text{R}^{7})-} \), \(-\text{CO}(\text{O})N(\text{R}^{6})-\), \(-\text{OC(O)N(\text{R}^{6})-} \), \(-\text{C(R')O-} \), \(-\text{C(R')SO}_{2}S- \), \(-\text{C(R')SO}_{2}N(\text{R}^{7})- \), \(-\text{C(R')-} \), \(-\text{C(R')N(\text{R}^{7})C(O)-} \), \(-\text{C(R')N(\text{R}^{7})CON(\text{R}^{6})-} \), \(-\text{C(R')N(\text{R}^{7})C(O)-} \), \(-\text{C(R')N(\text{R}^{7})CON(\text{R}^{6})-} \), \(-\text{C(R')CN(\text{R}^{7})CON(\text{R}^{6})-} \).

- \( R^{2} \) and \( R^{2} \) are independently selected from \(-\text{R-} \), \(-T-W-\text{R}^{6} \), or \(-\text{R}^{2} \) and \( R^{2} \) are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable ring carbon of said fused ring formed by \( R^{2} \) and \( R^{2} \) is independently substituted by halo, \( \text{o xo, } -\text{CN, } -\text{NO}_{2} \), \(-R^{2} \), or \(-V-R^{2} \), and each substi-
tutable ring nitrogen of said ring formed by $R^2$ and $R^2$ is independently substituted by $R^3$;

**[0167]** $R^2$ is selected from halo, —OR, —C(=O)OR, —CO$_2$R, —COCOR, —COCH$_2$COR, —NO$_2$, —CN, —S(O)$_2$R, —SO$_2$R, —SR, —N(R)$^2$CON(R)$^2$, —N(R)$^2$CON(R)$^2$, —N(R)$^2$SO$_2$N(R)$^2$, —N(R)$^2$SO$_2$R, —OC(=O)N(R)$^2$, or —N(R)$^2$CON(R)$^2$; or an optionally substituted group selected from C$_1$-6 aliphatic, C$_6$-11 aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;

**[0168]** each $R$ is independently selected from hydrogen or an optionally substituted group selected from C$_1$-6 aliphatic, C$_6$-11 aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;

**[0169]** each $R^4$ is independently selected from $R^3$, —OR, —CO$_2$ (optionally substituted C$_1$-6 aliphatic), —CON(R)$^2$, or —SO$_2$R;

**[0170]** each $R^5$ is independently selected from —R, halo, —OR, —C(=O)OR, —CO$_2$R, —COCOR, —NO$_2$, —CN, —S(O)$_2$R, —SO$_2$R, —SR, —N(R)$^2$CON(R)$^2$, —N(R)$^2$CON(R)$^2$, —N(R)$^2$SO$_2$N(R)$^2$, —N(R)$^2$SO$_2$R, —OC(=O)N(R)$^2$, or —N(R)$^2$CON(R)$^2$; or an optionally substituted group selected from C$_1$-6 aliphatic, —N(R)$^2$N(R)$^2$, —N(R)$^2$CON(R)$^2$, or —N(R)$^2$CON(R)$^2$; or an optionally substituted group selected from C$_1$-6 aliphatic, —N(R)$^2$N(R)$^2$, or —N(R)$^2$CON(R)$^2$;

**[0171]** $V$ is —O—, —S—, —SO$_2$—, —N(R)$^2$SO$_2$N(R)$^2$, —N(R)$^2$CON(R)$^2$, —N(R)$^2$SO$_2$N(R)$^2$, —N(R)$^2$CON(R)$^2$, —N(R)$^2$SO$_2$N(R)$^2$, or —N(R)$^2$CON(R)$^2$;

**[0172]** $W$ is —C(R)$^2$O—, —C(R)$^2$S—, —C(R)$^2$SO$_2$N(R)$^2$, —C(R)$^2$SO$_2$N(R)$^2$, —C(R)$^2$OCON(R)$^2$, —C(R)$^2$OC(=O)N(R)$^2$, —C(R)$^2$OC(=O)N(R)$^2$, —C(R)$^2$OC(=O)N(R)$^2$, —C(R)$^2$OCON(R)$^2$, —C(R)$^2$OC(=O)N(R)$^2$, or —C(R)$^2$OC(=O)N(R)$^2$; or an optionally substituted group selected from C$_1$-6 aliphatic, —N(R)$^2$N(R)$^2$, —N(R)$^2$CON(R)$^2$, or —N(R)$^2$CON(R)$^2$;

**[0173]** each $R^6$ is independently selected from hydrogen or an optionally substituted C$_1$-6 aliphatic group, or two R groups on the same nitrogen atom are taken together as a 5-6 membered heterocycle or heteroaryl ring; and

**[0174]** each $R^7$ is independently selected from hydrogen or an optionally substituted C$_1$-6 aliphatic group, or two R groups on the same nitrogen atom are taken together as a 5-6 membered heterocycle or heteroaryl ring; and

**[0175]** $R^5$ is selected from —R, halo, —OR, —C(=O)OR, —CO$_2$R, —COCOR, —NO$_2$, —CN, —S(O)$_2$R, —SO$_2$R, —SR, —N(R)$^2$CON(R)$^2$, —N(R)$^2$CON(R)$^2$, —N(R)$^2$SO$_2$N(R)$^2$, —N(R)$^2$SO$_2$R, —OC(=O)N(R)$^2$, —N(R)$^2$CON(R)$^2$, —N(R)$^2$CON(R)$^2$, —N(R)$^2$SO$_2$N(R)$^2$, —N(R)$^2$SO$_2$R, or —OC(=O)N(R)$^2$; provided that when Q is —NH$_2$ and $R^3$ and $R^4$ are taken together to form a fused ring, $R^1$ is other than a pyrazol-3-yl ring or a pyrazol-3-yl-containing bicyclic ring system.

**[0176]** Preferred $R^7$ groups of formula IIb include Z—R$^7$ or an optionally substituted group selected from C$_1$-6 aliphatic, 5-6 membered heterocycle, phenyl, or 5-6 membered heteroaryl, wherein Z is a methylene and R$^7$ is —N(R)$^4$CON(R)$^4$, —OR, or an optionally substituted group selected from C$_1$-6 aliphatic, C$_6$-11 aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms.

**[0177]** Examples of preferred R$^7$ groups include 2-pyridyl, 4-pyridyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkylalkylamino such as methoxyethylamino, alkoyalkyl such as methoxymethyl or methoxyethyl, alkyl or dialkylamino such as ethylamino or dimethylamino, alkyl- or dialkylaminooxoxyl such as dimethylaminopropoxyl, acetamido, optionally substituted phenyl such as phenyl or halo-substituted phenyl.

**[0178]** The R$^2$ and R$^2$ groups of formula IIb may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring. Preferred fused rings include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carboxycycle ring. These are exemplified in the following formula IIb compounds having a pyrazole-containing bicyclic ring system:

![Chemical Structure](image_url)

**[0179]** Preferred substituents on the R$^2$/R$^2$ fused ring of formula IIb include one or more of the following: —halo, —N(R)$^4$CON(R)$^4$, —C$_1$-4 alkyl, —C$_1$-4 haloalkyl, —NO$_2$, —O(C$_1$-4 alkyl), —CO$_2$ (C$_1$-4 alkyl), —CN, —SO$_2$ (C$_1$-4 alkyl), —SO$_2$NH$_2$, —OC(O)NH$_2$, —NH$_2$SO$_2$ (C$_1$-4 alkyl), —NHC(O)(C$_1$-4 alkyl), —C(=O)NH$_2$, and —CO(C$_1$-4 alkyl), wherein the (C$_1$-4 alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C$_1$-4 alkyl) group is methyl.

**[0180]** When the pyrazole ring system of formula IIb is monocyclic, preferred R$^2$ groups include hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C$_1$-6 aliphatic group. Examples of such preferred R$^2$ groups include H, methyl, ethyl, propyl, 1-propyl, cyclopentyl, hydroxypropyl, methoxypropyl, and benzyloxypropyl. A preferred R$^2$ group is hydrogen.

**[0181]** When Ring D of formula IIb is monocyclic, preferred Ring D groups include phenyl, pyridyl, pyridazinyl, pyrimidinyl, and pyrazinyl.
When Ring D of formula IIb is bicyclic, preferred bicyclic Ring D groups include naphthyl, tetrahydrobenzothiazolyl, indanyl, benzimidazolyl, quinolinyl, indolyl, isoindolyl, indoliny, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzothiazolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxazolyl, 1,8-naphthyridinyl and isooquinolyl.

On Ring D of formula IIb, preferred T-R'R or V-Z—R' substituents include -halo, —CN, —NO2, —N(R')2, optionally substituted C1-6 aliphatic group, —OR, —C(O)R, —CO2R, —CONH(R'), —N(R')COR, —N(R')CO2R, —SO2N(R')2, —N(R')SO2R, —N(R')COC(NR')2, —N(R')CH(NR')2, and —N(R') COCH2CH2N(R')2, wherein R is selected from hydrogen, C1-4 aliphatic, phenyl, or a 5-6 membered heteroaryl ring, or a 5-6 membered heterocyclic ring. More preferred R' substituents include —Cl, —Br, —F, —CN, —CF3, —COOH, —CONHMe, —CONHet, —NH2, —NHAc, —NHSO3Me, —NHSO3Et, —NHSO3(n-propyl), —NHSO2(allyl), —NHCOEt, —NHCOCH2NHCH3, —NHCOCH2NC(O)CH2CH3, —NHCOCH2CH2NC(O)CH2CH3, —NHCO(chloro), —NHCO(isobutyryl), —NH COCH2(morpholin-4-yl), —NHCOCH2(morpholin-4-yl), —NHCOCH2CH2NHC(O)CH2CH3, —NHCO2(t-butyl), —NH(C1-4 aliphatic) such as —NHMe, —N(C1-4 aliphatic) such as —NMethyl, —OH, —O(C1-4 aliphatic) such as —OMe, —C1-4 aliphatic such as methyl, ethyl, cyclopropyl, isopropyl, or t-butyl, and —C(O)2(—C1-4 aliphatic).

When R' and R'3 are taken together to form a fused ring, preferred rings formed by R' and R'3 include 5-6 membered unsaturated or partially unsaturated rings having 0-2 heteroatoms. More preferred fused rings formed by R' and R'3 include benzofuran and pyrido.

Preferred R'3 groups of formula IIb, when present, include R, OR, and N(R')2. Examples of preferred R'3 include methyl, ethyl, NH2, NH2CH2CH2NH, NH2CH2CH2CH2NH, NH2CH2CH2CH2O (piperidin-1-yl)CH2CH2O, and NH2CH2CH2O.

Preferred formula IIb compounds have one or more, and more preferably all, of the features selected from the group consisting of:

- (a) R' is Z—R'3 or an optionally substituted group selected from C1-6 aliphatic, 5-6 membered heterocyclic, phenyl, or 5-6 membered heteroaryl, wherein Z is a methylene and R'3 is —N(R')2, —OR, or an optionally substituted group selected from C1-6 aliphatic, C1-6 aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;
- (b) R' is T-(Ring D), wherein T is a valence bond or a methylene unit;
- (c) Ring D is a 5-7 membered monocyclic or an 8-10 membered bicyclic aryl or heteroaryl ring, and
- (d) R'3 is —R or —T—W—R'3 and R' is hydrogen, or R' and R'3 are taken together to form an optionally substituted benzo ring.

More preferred compounds of formula IIb have one or more, and more preferably all, of the features selected from the group consisting of:

- (a) R'3 is an optionally substituted group selected from C1-6 aliphatic, 5-6 membered heterocyclic, phenyl, or 5-6 membered heteroaryl;
- (b) R' is T-(Ring D), wherein T is a valence bond, and Q is —S—, —NH—, or —CH2—.
In another embodiment, this invention provides a composition comprising a compound of formula IIb and a pharmaceutically acceptable carrier.

Another aspect of this invention relates to a method of treating or preventing an Aurora-2-mediated disease with an Aurora-2 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula IIb or a pharmaceutical composition thereof.

Another aspect of this invention relates to a method of inhibiting Aurora-2 activity in a patient, which method comprises administering to the patient a compound of formula IIb or a pharmaceutical composition thereof.

Another aspect of this invention relates to a method of inhibiting a GSK-3-mediated disease with a GSK-3 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula IIb or a pharmaceutical composition thereof.

One aspect of this invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound of formula IIb or a pharmaceutical composition thereof. This method is especially useful for diabetic patients. Another method relates to inhibiting the production of hyperphosphorylated tau protein, which is useful in halting or slowing the progression of Alzheimer’s disease. Another method relates to inhibiting the phosphorylation of β-catenin, which is useful for treating schizophrenia.

Another aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, which method comprises administering to the patient a compound of formula IIb or a pharmaceutical composition thereof.

Another method relates to inhibiting Aurora-2 or GSK-3 activity in a biological sample, which method comprises contacting the biological sample with the Aurora-2 or GSK-3 inhibitor of formula IIb, or a pharmaceutical composition thereof, in an amount effective to inhibit Aurora-2 or GSK-3.

Each of the aforementioned methods directed to the inhibition of Aurora-2 or GSK-3, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula IIb, as described above.

Another embodiment of this invention relates to compounds of formula III:

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

- $Z^1$ is nitrogen or CR, $Z^2$ is nitrogen or CH, and $Z^3$ is nitrogen or CR, provided that one of $Z^2$ and $Z^3$ is nitrogen;
- $R^1$ is T-$R^3$ or L-$Z^2$-$R^1$;
- $Q$ is selected from $-\text{C}(=\text{O})\text{R}$, $-\text{O}$, $-\text{S}$, or $-\text{CH}(=\text{O})\text{R}$;
- $R^2$ is T-(Ring D);
- $\text{Ring D}$ is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, het-
erocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein each substitutable ring carbon of Ring D is independently substituted by oxo, T-R^2, or V=Z−R^2, and each substitutable ring nitrogen of Ring D is independently substituted by —R^2;
preferred substituents on the formula III R²/R' fused ring include one or more of the following: -halo, 
-N(R²)₂, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -NO₂, -O(C₁₋₄ alkyl), -CO₂ (C₁₋₄ alkyl), -CN, -SO₂ (C₁₋₄ alkyl), 
-SO₂ NH₂, -OC(O)NH₂, -NH₂SO₂ (C₁₋₄ alkyl), -NHC (C₁₋₄ alkyl), -C(O)NH₂, and -CO₂ (C₁₋₄ alkyl), wherein 
the (C₁₋₄ alkyl) is a straight, branched, or cyclic alkyl group. Preferably, the (C₁₋₄ alkyl) group is methyl.

When the pyrazole ring system of formula III is monocylic, preferred R² groups include hydrogen or a 
substituted or unsubstituted group selected from aryl, heteroaryl, or a C₁₋₆ aliphatic group. Examples of such preferred R² 
groups include H, methyl, ethyl, propyl, t-propyl, cyclopentyl, hydroxypyropyl, methoxypropyl, and benzoxypoxypropyl. A preferred R² 
group is hydrogen.

When Ring D of formula III is monocylic, preferred Ring D groups include phenyl, pyridyl, pyridazinyl, pyrimidinyl, and pyrazinyl.

When Ring D of formula III is bicyclic, preferred bicyclic Ring D groups include naphthyl, tetrahydro-naphthyl, 
indanyl, benzimidazolyl, quinolinyl, indolyl, isoindolyl, indolyl, benzof[b]naphthyl, benzof[b]pyridinyl, indazolyl, 
benzothiazolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl and isooquinolinyl.

On Ring D of formula III, preferred T-R² or V-Z-
R² substituents include -halo, -CN, -NO₂, -N(R²)₂, optionally 
substituted C₁₋₆ aliphatic group, -OR, -CO₂R, -CON(R²)₂, -OC(O)R², -N(R²)₂COR, 
-N(R²)₂CO₂R, -SO₂N(R²)₂, -N(R²)₂SO₂R, -N(R²)₂CO₂CH₂N(R²)₂, 
-N(R²)₂CO₂CH₂N(CH₂)₂N(R²)₂, and -N(R²)₂CO₂CH₂N(CH₂)₂N(R²)₂, wherein R is selected from hydrog 
C₁₋₆ aliphatic, phenyl, a 5-6 membered heteroaryl ring, 
or a 5-6 membered heterocyclic ring. More preferred R² 
substituents include -Cl, -Br, -F, -CN, -CF₃, 
-COOH, -CONHMe, -CONH₂, -NH₂, -NHAc, 
-NHSO₃Me, -NHSO₃Et, -NHSO₃(n-propyl), -NHSO₃ 
(isopropyl), -NHOEt, -NHOCH₂CH₃, 
-NHCOCH₂N(CH₃)₂, -NHCOCH₂NH₂, -NHCOCH₂N(CH₃)₂, 
-NHCOCH₂NH₂, -NHCOCH₂N(CH₃)₂, 
-NHCOCH₂N(CH₃)₂, -NHCOCH₂NH₂, and 
-NHCOCH₂N(CH₃)₂, wherein R is selected from hydrog 
C₁₋₆ aliphatic such as -NHMe, -N(C₁₋₆ aliphatic)₂ such as -NMe₂, OH, -O(C₁₋₆ aliphatic) such as 
-OMe, C₁₋₆ aliphatic such as methyl, ethyl, cyclopentyl, 
isobutyl, or t-butyl, and -CO₂ (C₁₋₆ aliphatic).

Preferred compounds of formula IIIa, IIIb, IIIc, or 
IIId have one or more, and more preferably all, of the features 
selected from the group consisting of:

(a) R² is hydrogen, alkyl- or dialkylamino, aceta 
mino, or a C₁₋₄ aliphatic group;

(b) R² is T-(Ring D), wherein T is a valence bond 
or a methylene unit;

(c) Ring D is a 5-7 membered monocylic or an 
8-10 membered bicyclic aryl or heteroaryl ring; and

(d) R² is -R or -T-W-R² is hydrogen, or 
R² and R² are taken together to form an optionally 
substituted benzo ring.

More preferred compounds of formula IIIa, IIIb, 
IIIc, or IIId have one or more, and more preferably all, of the features 
selected from the group consisting of:

(a) R² is T-(Ring D), wherein T is a valence bond, 
and Q is -S-, -NH-, or -CH₂-;

(b) Ring D is a 5-6 membered monocylic or an 
8-10 membered bicyclic aryl or heteroaryl ring; and
(c) $R^2$ is $-R$ and $R^2$ is hydrogen, wherein $R$ is selected from hydrogen, C$_{1-6}$ aliphatic, phenyl, a 5-6 membered heteroaryl ring, or a 5-6 membered heterocyclic ring.

Even more preferred compounds of formula IIIa, IIIb, IIIc, or IIId have one or more, and more preferably all, of the features selected from the group consisting of:

(a) $R^1$ is hydrogen, methyl, ethyl, propyl, cyclopropyl, isopropyl, methyamino or acetimido;

(b) $R^1$ is T-(Ring D), wherein T is a valence bond and Ring D is a 5-6 membered aryl or heteroaryl ring, wherein Ring D is optionally substituted with one to two groups selected from -halo, -CN, -NO$_2$, -N(R$^4$)$_2$, optionally substituted C$_{1-6}$ aliphatic group, -OR, -CO$_2$R, -CON(R$^4$)$_2$, -OCO(R$^4$)$_2$, -N(R$^4$)COR, -N(R$^4$)SO$_2$R, -N(R$^4$)COCH$_2$CH$_2$N(R$^4$)$_2$, or -N(R$^4$)COCH$_2$CH$_2$N(R$^4$)$_2$, and Q is $-S-$ or $-N\tilde{\mathrm{H}}-$; and

(c) $R^2$ is hydrogen or a substituted or unsubstituted C$_{1-6}$-aliphatic.

Representative compounds of formula III are shown below in Table 3.

### Table 3

III-1

III-2

III-3

III-4

III-5

III-6

III-7
[0251] In another embodiment, this invention provides a composition comprising a compound of formula III and a pharmaceutically acceptable carrier.

[0252] Another aspect of this invention relates to a method of treating or preventing an Aurora-2-mediated disease with an Aurora-2 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula III or a pharmaceutical composition thereof.

[0253] Another aspect of this invention relates to a method of inhibiting Aurora-2 activity in a patient, which method comprises administering to the patient a compound of formula III or a composition comprising said compound.

[0254] Another aspect of this invention relates to a method of treating or preventing a GSK-3-mediated disease with a GSK-3 inhibitor, which method comprises administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula III or a pharmaceutical composition thereof.

[0255] One aspect of this invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound of formula III or a pharmaceutical composition thereof. This method is especially useful for diabetic patients. Another method relates to inhibiting the production of hyperphosphorylated Tau protein, which is useful in halting or slowing the progression of Alzheimer’s disease. Another method relates to inhibiting the phosphorylation of β-catenin, which is useful for treating schizophrenia.

[0256] Another aspect of this invention relates to a method of inhibiting GSK-3 activity in a patient, which method comprises administering to the patient a compound of formula III or a composition comprising said compound.

[0257] Another method relates to inhibiting Aurora-2 or GSK-3 activity in a biological sample, which method comprises contacting the biological sample with the Aurora-2 or GSK-3 inhibitor of formula III, or a pharmaceutical composition thereof, in an amount effective to inhibit Aurora-2 or GSK-3.

[0258] Each of the aforementioned methods directed to the inhibition of Aurora-2 or GSK-3, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula III as described above.

[0259] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general Schemes I-VII.

[0260] Scheme I above shows a general route for the preparation of compounds of formula Ib. The dichloro intermediate 1 (prepared using methods similar to those reported in J. Indian Chem. Soc., 61, 690-693 (1984) or in J. Med. Chem., 37, 3828-3833 (1994)) is sequentially reacted with two nucleophiles: R'-QH to displace the chloride at position 4 to afford intermediate 2; and then 2 is treated with an aminopyrazole (or aminooxazole) to displace the chloride at position 2, using procedures similar to those described in J. Med. Chem., 38, 14, 2763-2773, (1995) to afford compounds of formula Ib.
Scheme II above shows a general route for the preparation of compounds of formula IIb wherein Q is an N, O or S linker and R² is a group attached to the pyrimidine core via a heteroatom. Starting material 4,6-dihydroxy-2-methylsulfanylpyrimidine (4) is prepared using procedures similar to those reported in J. Med. Chem., 27, 12, 1621-1629 (1984). Chlorination of 4 with POCI₃ affords the dichloride intermediate 5. The two chlorides of 5 are sequentially displaced with the appropriate R¹-QH, to afford compound 6, and then with R²—H (amine, alcohol, or thiol) to afford compound 7 using procedures similar to those reported in U.S. Pat. No. 2,585,906. Alternatively, the order of displacement may be reversed by first displacing with R²—H and then with R¹-QH. The methyl sulfinyl group of compound 7 is then oxidized (for example, with ozone) to afford compound 8 and the resulting methylsulfonyl is finally displaced with the amino moiety of aminopyrazole (or aminomidazole) by methods substantially similar to those described above for Scheme 1 step (b) to afford compounds of formula IIb.
Scheme III above shows a general route for the preparation of compounds of formula IIa. The three chlorides of starting material 8 are sequentially displaced with (a) the amino moiety of aminopyrazole (or aminoidazole) to afford compound 9, (b) the R¹-QH group to afford compound 10, and (c) R²-H (amine, alcohol, or thiol) using procedures similar to the ones reported in J. Indian Chem. Soc., 53, 207-208, (1976) to afford compounds of formula IIa. These three steps can also be performed in different order to afford compounds of formula IIa.

[0263] Scheme IV above shows a general route for the preparation of compounds of formula IIIa. Treatment of 11 with aminopyrazole (or aminoidazole) to provide 12 may be performed in a manner similar to that described in Heterocycles, 51, 5, 1999, 1035-1050. The intermediate 13 is obtained by displacement with R¹-QH in a manner similar to that described in Farmaco. Ed. Sci., 27, 1972, 591-600. For the preparation of compounds of formula IIIa where Rx is hydrogen, the chlorine may be removed by reduction. Alternatively, for the preparation of compounds of formula IIIa where Rx is other than hydrogen, the chlorine may be displaced by methods known to those skilled in the art to afford compounds with a variety of R² substituents.
Scheme V above shows a general route for the preparation of the compounds of formula IIIb. Displacement of the bromide with R1-QH to afford compound 15 may be performed in a manner similar to that described in Heterocycles, 51, 5, 1999, 1035-1050. Displacement of the chlorines may be carried out sequentially as described above.

Scheme VI

Scheme VI above shows a general route for the preparation of the compounds of formulae IIIc and IIId. The displacement with aminopyrazole (or aminoisoxazole) followed by the displacement with R1-QH may be performed in a manner similar to that described in Indian J. Chem. Sect. B, 29, 5, 1990, 435-439.

In order that the invention described herein may be more fully understood, the following examples are set forth.

**BIOLOGICAL TESTING**

The activity of the compounds as protein kinase inhibitors 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 the activated protein kinase. Alternate in vitro assays quantitate the ability of the inhibitor to bind to the protein kinase. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/protein kinase 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 the protein kinase bound to known radioligands.

**Biological Testing Example 1**

**K<sub>i</sub> Determination for the Inhibition of GSK-3**

Compounds are screened for their ability to inhibit GSK-3β (AA 1-420) activity using a standard coupled enzyme system (Fox et al. (1998) Protein Sci. 7, 2249). Reactions are carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM MgCl<sub>2</sub>, 25 mM NaCl, 300 μM NADH, 1 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay are 20 μM ATP (Sigma Chemicals, St Louis, Mo.) and 300 μM peptide (HSSPHEKQ(O<sub>2</sub>H)<sub>3</sub>EDEEE, American Peptide, Sunnyvale, Calif.). Reactions are carried out at 30° C. and 20 nM GSK-3β. Final concentrations of the components of the coupled enzyme system are 2.5 mM phospho-enolpyruvate, 300 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase.

**Biological Testing Example 2**

**K<sub>i</sub> Determination for the Inhibition of Aurora-2**

Compounds are screened in the following manner for their ability to inhibit Aurora-2 using a standard coupled enzyme assay (Fox et al. (1998) Protein Sci 7, 2249).

To an assay stock buffer solution containing 0.1M HEPES 7.5, 10 mM MgCl<sub>2</sub>, 1 mM DTT, 25 mM NaCl, 2.5 mM phosphoenolpyruvate, 300 mM NADH, 30 mg/ml pyruvate kinase, 10 mg/ml lactate dehydrogenase, 40 mM ATP, and 800 μM peptide (LRRASLG, American Peptide, Sunnyvale, Calif.) is added a DMSO solution of a compound of the present invention to a final concentration of 30 μM. The resulting mixture is incubated at 30° C. for 10 min. The
reaction is initiated by the addition of 10 μL of Aurora-2 stock solution to give a final concentration of 70 nM in the assay. The rates of reaction are obtained by monitoring absorbance at 340 nm over a 5 minute read time at 30° C using a BioRad Ultramark plate reader (Hercules, Calif.). The Kᵢ values are determined from the rate data as a function of inhibitor concentration.

While we have presented a number of embodiments of this invention, it is apparent that our basic construction can be altered to provide other embodiments which 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 which have been represented by way of example.

We claim:

1-26 (canceled)

27. A compound of formula IIa:

IIa

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

R' is Z—R² or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₅ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;

Q is selected from —N(R')₂, —O—, —S—, or —CH (R')₂;

R² is T-(Ring D);

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclic or carbocyclic, said heteroaryl or heterocyclic ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein each substitutable ring carbon of Ring D is independently substituted by oxo, T-R², or V—Z—R², and each substitutable ring nitrogen of Ring D is independently substituted by —R²;

T is a valence bond or a C₁₋₄ alkylidene chain, wherein when Q is —CH(R')₂, a methylene unit of said C₁₋₄ alkylidene chain is optionally replaced by —O—,

—S—, —N(R')₂, —CO—, —CONH—, —NHCO—,

—SO₂—, —SO₃H—, —NH₂SO₂—, —CO₂—,

—OC (O)—, —OC(O)NH—, or —NHCO₂—;

Z is a C₁₋₄ alkylidene chain;

L is —O—, —S—, —SO₂—, —SO₃H—, —N(R')₂SO₂—,

—SO₂N(R')₂—, —N(R')₂—, —CO₂—,

—N(R')₂CO—, —N(R')₂CON(R')₂—, —N(R')₂CON (O)R—,

—(O)N(R')₂—, —(O)CON(R')₂—, —(O)CON(R')₂—,

—C(O)N(R')₂—, —C(O)CON(R')₂—, —C(O)CON(R')₂—,

—C(O)SO₂N(R')₂—, —C(O)SO₃H—, —C(O)CON (O)R—,

—C(O)SO₂N(R')₂—, —C(O)SO₃H—, —C(O)CON (O)R—;

R²₁ and R²₂ are independently selected from —R²₁, T-W—R²₂, or R²₂ and R² are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable ring carbon of said fused ring formed by R²₁ and R²₂ is independently substituted by halo, oxo, —CN,

—NO₂—, —R¹, or —V—R², and each substitutable ring nitrogen of said ring formed by R²₁ and R²₂ is independently substituted by R²₂;

R² is selected from -halo, —OR, —C(=O)R, —CO₂R,

—COCH₃COR, —NO₂, —CN, —SO₂R, —SR, —N(R')₂, —CON(R')₂, —SO₃H(R')₂,

—OC(=O)OR, —N(R')₂COR, —N(R')₂CO₂ (C₁₋₆ aliphatic),

—N(R')₂CON(R')₂, —C=NN(R')₂, —C=NR₁—OR, —N(R')₂CON(R')₂, —N(R')₂SO₂N(R')₂, —N(R')₂,

—OC(=O)N(R')₂, or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₅ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;

each R is independently selected from hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₅ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;

each R² is independently selected from —R²₁, —COR², —CO₂ (optionally substituted C₁₋₆ aliphatic), —CON (R')₂, or —SO₂R;

each R²₂ is independently selected from —OR, —C(=O)R, —NO₂, —CN, —SO₂R, —SR, —N(R')₂, —CON(R')₂, —SO₃H(R')₂, —OC(=O)OR, —N(R')₂COR, —N(R')₂CO₂ (C₁₋₆ aliphatic),

—N(R')₂CON(R')₂, —C=NN(R')₂, —C=NR₁—OR, —N(R')₂CON(R')₂, —N(R')₂SO₂N(R')₂, —N(R')₂SO₃H(R')₂, —OC(=O)N(R')₂, or —N(R')₂;

V is —O—, —S—, —SO₂—, —SO₃H—, —N(R')₂SO₂—,

—SO₂N(R')₂—, —N(R')₂—, —CO₂—,

—N(R')₂CO—, —N(R')₂CON(R')₂—, —N(R')₂CON (O)R—,

—(O)N(R')₂—, —(O)CON(R')₂—, —(O)CON(R')₂—,

—C(O)N(R')₂—, —C(O)CON(R')₂—, —C(O)CON(R')₂—,

—C(O)SO₂N(R')₂—, —C(O)SO₃H—, —C(O)CON (O)R—,

—C(O)SO₂N(R')₂—, —C(O)SO₃H—, —C(O)CON (O)R—;

W is —C(R')₂O—, —C(R')₂S—, —C(R')₂SO₂—,

—C(R')₂SO₂—, —C(R')₂CON(R')₂—, —C(R')₂N (R')₂CO₂—,

—C(R')₂CO₂—, —C(R')₂CON(R')₂—, —C(R')₂OC(O)N (R')₂—, —C(R')₂N(R')₂CO₂—, —C(R')₂N(R')₂CON (R')₂—,

—C(R')₂—N—O—, —C(R')₂N(R')₂CON(R')₂—, —C(R')₂N(R')₂CON(R')₂—, or —CON(R')₂—;

each R² is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R² groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclic or heteroaryl ring; and

each R² is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group, or two R² on
the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclic or heteroaryl ring.

28. The compound of claim 27, wherein R⁴ is independently selected from Z—R⁴ or an optionally substituted group selected from C₁₋₆ aliphatic, 5-6 membered heterocyclic, phenyl, or 5-6 membered heteroaryl, wherein Z is a methylene and R⁴ is —N(R⁴)₂, —OR, or an optionally substituted group selected from C₁₋₆ aliphatic, C₆₋₁₀ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms.

29. The compound of claim 28, wherein R⁴ is independently selected from 2-pyridyl, 4-pyridyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, methyl, ethyl, cyclopropyl, isopropyl, t-butyl, alkoxyalkylamino such as methoxyethylamino, alkoxyalkyl such as methoxymethyl or methoxyethyl, alkyl- or dialkylamino such as ethylamino or dimethylamino, alkyl- or dialkylaminooalkoxy such as dimethylaminopropoxy, acetamido, optionally substituted phenyl such as phenyl or halo-substituted phenyl.

30. The compound of claim 27, wherein R² and R² may be taken together to form a fused ring, thus providing a bicyclic ring system containing a pyrazole ring.

31. The compound of claim 30, wherein the fused ring include benzo, pyrido, pyrimido, and a partially unsaturated 6-membered carbocycle ring.

32. The compound of claim 27, wherein R² and R² taken together form a pyrazole-containing bicyclic ring system independently selected from:

33. The compound of claim 32, wherein the R²/R² fused ring of formula IIb include one or more substituents selected from: -halo, —N(R⁴)₂, —C₁₋₆ alkyl, —C₁₋₆ halonalkyl, —NO₂, —O(C₁₋₆ alkyl), —CO₂(C₁₋₆ alkyl), —CN, —SO₂(C₁₋₆ alkyl), —SO₂(CH₃)₂, —OC(O)NH₂, —NH₂SO₂(C₁₋₆ alkyl), —NHC(O)(C₁₋₆ alkyl), —C(O)NH₂, and —CO(C₁₋₆ alkyl), wherein the (C₁₋₆ alkyl) is a straight, branched, or cyclic alkyl group.

34. The compound of claim 33, wherein the (C₁₋₆ alkyl) group is methyl.

35. The compound of claim 27, wherein Ring D of is a monocyclic ring.

36. The compound of claim 35, wherein Ring D is independently selected from phenyl, pyridyl, pyridazinyl, pyrimidinyl, and pyrazinyl.

37. The compound of claim 27, selected from:

IIa-1

IIa-5

IIa-6

IIa-7
5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms, or \( R' \) and \( R^8 \) are taken together to form a fused, optionally substituted 5-7 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur;

Q is selected from \( -N(R'^8)-, -O-, -S-, \) or \( -CH(R^8)-; \)

\( R' \) is \( -(\text{Ring D}); \)

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclic or carbocyclic, said heteroaryl or heterocyclic ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein each substitutable ring carbon of Ring D is independently substituted by oxo, \( T-R^5 \), or \( V-Z-R^3 \), and each substitutable ring nitrogen of Ring D is independently substituted by \( -R^6; \)

\( T \) is a valence bond or a \( C_{1-4} \) alkylidene chain, wherein when Q is \( -CH(R^6)- \), a methylene unit of said \( C_{1-4} \) alkylidene chain is optionally replaced by \( -O- \), \( -S- \), \( -N(R'^8)- \), \( -CO- \), \( -CONH- \), \( -NHCO- \), \( -SO_2- \), \( -SO_2NH- \), \( -NSO_2- \), \( -CO_2- \), \( -OC(O)- \), \( -OC(O)NH- \), or \( -NHCO_2-; \)

Z is a \( C_{1-4} \) alkylidene chain;

\( L \) is \( -O- \), \( -S- \), \( -SO_2- \), \( -N(R'^8)SO_2- \), \( -SO_3N(R'^8)- \), \( -N(R'^8)SO_3- \), \( -N(R'^8)COO- \), \( -N(R'^8)OCO- \), \( -N(R'^8)CON(R'^8)- \), \( -N(R'^8)N(R'^8)- \), \( -OCOCR(N'^8)- \), \( -COCR(N'^8)- \), \( -CR(N'^8)S- \), \( -CR(N'^8)SO_2- \), \( -CR(N'^8)SO_3- \), \( -CR(N'^8)CON(R'^8)- \), \( -CR(N'^8)CON(R'^8)- \), \( -C(N'^8)S- \), \( -C(N'^8)SO_2- \), \( -C(N'^8)SO_3- \), \( -C(N'^8)CON(R'^8)- \), \( -C(N'^8)CON(R'^8)- \), \( -CR(N'^8)N(R'^8)- \), \( -C(N'^8)N(R'^8)- \), \( -CR(N'^8)N(R'^8)- \), \( -C(N'^8)N(R'^8)SO_2N(R'^8)- \), or \( -C(N'^8)N(R'^8)CON(R'^8)-; \)

\( R^2 \) and \( R^7 \) are independently selected from \( -R, -(\text{T-W})-R^5 \), or \( R^2 \) and \( R^7 \) are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable ring carbon of said fused ring formed by \( R^2 \) and \( R^7 \) is independently substituted by oxo, halo, \( -CN, -NO_2, -R^7 \), or \( -V-R^3 \), and each substitutable ring nitrogen of said ring formed by \( R^2 \) and \( R^7 \) is independently substituted by \( R^6; \)

\( R'^8 \) is selected from \( -(\text{halo}), -(\text{OR}), -(\text{COOR}), -(\text{COCH}_2\text{COR}), -(\text{NO}_2), -(\text{CN}), -(\text{SO}_2\text{R}), -(\text{SR}), -(\text{N(R'^8)CO}), -(\text{N(R'^8)CON(R'^8)}), -(\text{N(R'^8)CON(R'^8)}), -(\text{N(R'^8)CON(R'^8)}), -(\text{N(R'^8)CON(R'^8)}), -(\text{SO}_3\text{R}), -(\text{SO}_3\text{R}), -(\text{R'^8}) \), or an optionally substituted group selected from \( C_{1-6} \) aliphatic, \( C_{6-10} \) aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms,

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

\( R^7 \) is \( Z=R'^8 \) or an optionally substituted group selected from \( C_{1-6} \) aliphatic, \( C_{6-10} \) aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclic ring having 5-10 ring atoms;
The compound of claim 38, wherein Ring D is a monocyclic ring independently selected from phenyl, pyridyl, pyridazinyl, pyrimidinyl, and pyrazinyl.

The compound of claim 38, wherein Ring D is a bicyclic ring independently selected from naphthyl, tetrahydronapthyl, indanyl, benzimidazolyl, quinolinyl, indolyl, isoindolyl, indoliny, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzothiazolyl, cyananilinyl, phthalazinyl, quinazolyl, quinoxalinyl, 1,8-naphthyridinyl and isoquinolinyl.

The compound of claim 38, wherein R and R' are taken together to form a fused ring independently selected from a 5-6 membered unsaturated or partially unsaturated rings having 0-2 heteroatoms.

The compound of claim 44, wherein the fused ring formed by R and R' include benzo, cyclohexo, and pyrido.

The compound of claim 1 selected from:

- The compound of claim 38, wherein Ring D is a monocyclic ring independently selected from phenyl, pyridyl, pyridazinyl, pyrimidinyl, and pyrazinyl.
- The compound of claim 38, wherein Ring D is a bicyclic ring independently selected from naphthyl, tetrahydronapthyl, indanyl, benzimidazolyl, quinolinyl, indolyl, isoindolyl, indoliny, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzothiazolyl, cyananilinyl, phthalazinyl, quinazolyl, quinoxalinyl, 1,8-naphthyridinyl and isoquinolinyl.
- The compound of claim 38, wherein R and R' are taken together to form a fused ring independently selected from a 5-6 membered unsaturated or partially unsaturated rings having 0-2 heteroatoms.
- The compound of claim 44, wherein the fused ring formed by R and R' include benzo, cyclohexo, and pyrido.
- The compound of claim 1 selected from:
continued

Ilb-9

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