Title: THIENO-[2,3-D]PYRIMIDINE AND THIENO-PYRID AZINE COMPOUNDS AND METHODS OF USE

Abstract: The present invention comprises a new class of compounds useful for the prophylaxis and treatment of protein kinase mediated diseases, including inflammation and related conditions. The compounds have a general Formula (I), wherein A₁, A₂, B, R² and R³ are defined herein. The invention also comprises pharmaceutical compositions including one or more compounds of Formula (I), uses of such compounds and compositions for treatment of kinase mediated diseases including rheumatoid arthritis, psoriasis and other inflammation disorders, as well as intermediates and processes useful for the preparation of compounds of Formula (I).
THTENO-[2,3-d]PYRIMIDINE AND THIENO-PYRIDAZINE COMPOUNDS AND
METHODS OF USE
This application claims the benefit of U.S. Provisional Application No. 60/793,950, filed April 21, 2006 of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION
Protein kinases represent a large family of enzymes, which catalyze the phosphorylation of target protein substrates. The phosphorylation is usually a transfer reaction of a phosphate group from ATP to the protein substrate. Common points of attachment for the phosphate group to the protein substrate include, for example, a tyrosine, serine or threonine residue. For example, protein tyrosine kinases (PTKs) are enzymes, which catalyze the phosphorylation of specific tyrosine residues in cellular proteins. Examples of kinases in the protein kinase family include, without limitation, abl, Akt, bcr-abl, Blk, Brk, Btk, c-kit, c-Met, c-src, c-fms, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf, CSFIR, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFRI, Fgr, flt-1, Fps, Frk, Fyn, Hck, IGF-IR, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PQC, PKC, PYK2, ros, tie, tie2, TRK, Yes, and Zap70. Due to their activity in numerous cellular processes, protein kinases have emerged as important therapeutic targets.

Protein kinases play a central role in the regulation and maintenance of a wide variety of cellular processes and cellular function. For example, kinase activity acts as molecular switches regulating inflammatory cytokine production via various pathways. Uncontrolled or excessive cytokine production has been observed in many disease states, and particularly in those related to inflammation.
The p38 protein kinase has been reported to be involved in the regulation of inflammatory cytokines. Interleukin-1 (IL-1) and Tumor Necrosis Factor α (TNF-α) are pro-inflammatory cytokines secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli (e.g., lipopolysaccharide - LPS) or external cellular stress (e.g., osmotic shock and peroxide).

Elevated levels of TNF-α over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; Reiter's syndrome; type II diabetes; bone resorption diseases; graft vs. host reaction; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. HIV-I, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster are also exacerbated by TNF-α.

TNF-α has been reported to play a role in head trauma, stroke, and ischemia. For instance, in animal models of head trauma (rat), TNF-α levels increased in the contused hemisphere (Shohami et al., J. Cereb. Blood Flow Metab. 14:615 (1994)). In a rat model of ischemia wherein the middle cerebral artery was occluded, the levels of TNF-α mRNA of TNF-α increased (Feurstein et al., Neurosci. Lett. 164:125 (1993)). Administration of TNF-α into the rat cortex has been reported to result in significant neutrophil accumulation in capillaries and adherence in small blood vessels. TNF-α promotes the infiltration of other cytokines (IL-1p, IL-6) and also chemokines, which promote neutrophil infiltration into the infarct area (Feurstein, Stroke, 25:1481 (1994)).

TNF-α appears to play a role in promoting certain viral life cycles and disease states associated therewith. For instance, TNF-α secreted by monocytes induced elevated levels of HIV expression in a chronically infected T cell clone (Clouse et al., J. Immunol., 142:431 (1989)). Lahdevirta et al., (Am. J. Med., 85:289 (1988)) discussed the role of TNF-α in the HTV associated states of cachexia and muscle degradation.

TNF-α is upstream in the cytokine cascade of inflammation. As a result, elevated levels of TNF-α may lead to elevated levels of other inflammatory and proinflammatory cytokines, such as BL-I, IL-6, and IL-8.
Elevated levels of IL-1 over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; ulcerative colitis; anaphylaxis; muscle degeneration; cachexia; Reiter's syndrome; type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; sepsis; septic shock; and toxic shock syndrome. Viruses sensitive to TNF-α inhibition, e.g., HIV-1, HIV-2, HIV-3, are also affected by DL-1.

TNF-α and IL-1 appear to play a role in pancreatic β-cell destruction and diabetes. Pancreatic β-cells produce insulin which helps mediate blood glucose homeostasis. Deterioration of pancreatic β-cells often accompanies type I diabetes. Pancreatic β-cell functional abnormalities may occur in patients with type II diabetes. Type II diabetes is characterized by a functional resistance to insulin. Further, type II diabetes is also often accompanied by elevated levels of plasma glucagon and increased rates of hepatic glucose production. Glucagon is a regulatory hormone that attenuates liver gluconeogenesis inhibition by insulin. Glucagon receptors have been found in the liver, kidney and adipose tissue. Thus glucagon antagonists are useful for attenuating plasma glucose levels (WO 97/16442, incorporated herein by reference in its entirety). By antagonizing the glucagon receptors, it is thought that insulin responsiveness in the liver will improve, thereby decreasing gluconeogenesis and lowering the rate of hepatic glucose production.

In rheumatoid arthritis models in animals, multiple intra-articular injections of IL-1 have led to an acute and destructive form of arthritis (Chandrasekhar et al., Clinical Immunol Immunopathol., 55:382 (1990)). In studies using cultured rheumatoid synovial cells, IL-1 is a more potent inducer of stromelysin than is TNF-α (Firestein, Am. J. Pathol., 140:1309 (1992)). At sites of local injection, neutrophil, lymphocyte, and monocyte emigration has been observed. The emigration is attributed to the induction of chemokines (e.g., IL-8), and the up-regulation of adhesion molecules (Dinarello, Eur. Cytokine Netw., 5:517-531 (1994)).

IL-1 also appears to play a role in promoting certain viral life cycles. For example, cytoMne-induced increase of HTV expression in a chronically infected macrophage line has been associated with a concomitant and selective increase in IL-I production (Folks et al., J. Immunol., 136:40 (1986)). Beutler et al. (J. Immunol.,
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In rheumatoid arthritis, both EL-I and TNF-α induce synoviocytes and chondrocytes to produce collagenase and neutral proteases, which leads to tissue destruction within the arthritic joints. In a model of arthritis (collagen-induced arthritis (CIA) in rats and mice), intra-articular administration of TNF-α either prior to or after the induction of CIA led to an accelerated onset of arthritis and a more severe course of the disease (Brahn et al., Lymphokine Cytokine Res., 11:253 (1992); and Cooper, Clin. Exp. Immunol., 898:244 (1992)).

IL-8 has been implicated in exacerbating and/or causing many disease states in which massive neutrophil infiltration into sites of inflammation or injury (e.g., ischemia) is mediated by the chemotactic nature of IL-8, including, but not limited to, the following: asthma, inflammatory bowel disease, psoriasis, adult respiratory distress syndrome, cardiac and renal reperfusion injury, thrombosis and glomerulonephritis. In addition to the chemotaxis effect on neutrophils, IL-8 also has the ability to activate neutrophils. Thus, reduction in IL-8 levels may lead to diminished neutrophil infiltration.

Several approaches have been taken to block the effect of TNF-α. One approach involves using soluble receptors for TNF-α (e.g., TNFR-55 or TNFR-75), which have demonstrated efficacy in animal models of TNF-α-mediated disease states. A second approach to neutralizing TNF-α using a monoclonal antibody specific to TNF-α, cA2, has demonstrated improvement in swollen joint count in a Phase II human trial of rheumatoid arthritis (Feldmann et al., Immunological Reviews, 195-223 (1995)). These approaches block the effects of TNF-α and IL-I by either protein sequestration or receptor antagonism.

Yet another approach to block the effect of TNF-α has been to modulate the activity of the p38 kinase enzyme. For example, the PCT publication, WO 04/010995, published on February 05, 2004, describes fused heteroaryl derivatives for use as P38 kinase inhibitors in the treatment of L.A. rheumatoid arthritis; PCT publication, WO 2005/009937, published on February 03, 2005, describes 5-membered heterocycle-based P38 kinase inhibitors; U.S. Patent No. 6,635,644, issued October 21, 2003, describes fused nitrogen-containing bicyclic ring systems as P38 inhibitors; and U.S. Patent No. 6,794,380, issued September 21, 2004, describes amide derivatives as P38 inhibitors.
BRBEF DESCRIPTION OF THE INVENTION

The present invention provides a new class of compounds useful in the prophylaxis and treatment of inflammatory diseases, such as TNF-α, IL-1β, IL-6 and/or EL-8 mediated diseases, as well as pain and diabetes. Accordingly, the invention also comprises pharmaceutical compositions comprising the compounds, methods for the prophylaxis and treatment of TNF-α, IL-1β, IL-6 and/or IL-8 mediated diseases, such as inflammatory, pain and diabetes diseases, using the compounds and compositions of the invention, and intermediates and processes useful for the preparation of the compounds of the invention.

The compounds provided by the invention, including stereoisomers, tautomers, solvates, pharmaceutically acceptable salts, derivatives or prodrugs thereof, are defined by general Formula I

\[
\text{I}
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wherein \( A_1, A_2, B, R_2 \) and \( R_3 \) are as described below. The invention also provides procedures for making compounds of Formula I, and intermediates useful in such procedures.

The compounds provided by the invention are capable of modulating kinase enzymes such as p38 kinase. To this end, the invention further provides for the use of these compounds for therapeutic, prophylactic, acute and/or chronic treatment of kinase mediated diseases, such as those described herein.

The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All patents and other publications recited herein are hereby incorporated by reference in their entirety.
DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the invention, the compounds, including stereoisomers, tautomers, solvates, pharmaceutically acceptable salts, derivatives or prodrugs thereof, are defined by general Formula I:

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or stereoisomer, tautomer, solvate, pharmaceutically acceptable salt, derivative or prodrug thereof, wherein

\[
\begin{align*}
\text{wherein } 0, 1 \text{ or } 2; \\
R^1 &\text{ is } -(CR^7R^8)_nX \text{ or } -(CR^7R^8)_nX, \text{ wherein } n = 0, 1 \text{ or } 2 \text{ and } X \text{ is absent, } NR^7R^8, \\
\text{NR}^7R^8, OR^7, SR^7, OR^8, SR^8, C(O)R^7, OC(O)R^7, COOR^7, C(O)R^8, OC(O)R^8, COOR^8, \\
\text{C(O)NR}^7R^8, C(S)NR^7R^8, \text{NR}^7C(O)R^7, \text{NR}^7C(O)R^7, \text{NR}^7C(S)NR^7R^8, \\
\text{NR}^7(COOR^7), \text{OC(O)NR}^7R^8, \text{C(O)NR}^7R^8, \text{C(S)NR}^7R^8, \text{NR}^7C(O)R^8, \text{NR}^7C(S)R^8, \\
\text{NR}^7(C(O)NR^7R^8, \text{NR}^7C(S)NR^7R^8, \text{NR}^7(COOR^7), \text{OC(O)NR}^7R^8, \text{S(O)}_2R^7, \text{S(O)}_2NR^7R^8, \\
\text{NR}^7S(O)_2NR^7R^8, \text{NR}^7S(O)_2R^7, \text{S(O)}_2R^8, \text{S(O)}_2NR^7R^8, \text{NR}^7S(O)_2NR^7R^8, \text{NR}^7S(O)_2R^8 \text{ or a } \\
\text{a 5-8 membered monocyclic or } 6-12 \text{ membered bicyclic ring system, said ring system } \\
\text{formed of carbon atoms optionally including } 1-3 \text{ heteroatoms if monocyclic or } 1-6 \\
\text{heteroatoms if bicyclic, said heteroatoms selected from } \text{O, N, S, wherein said ring } \\
\text{system is optionally substituted independently with one or more substituents of } R^5, R^8 \text{ or } \\
\text{R}^9; \\
\text{R}^2 \text{ is H, halo, haloalkyl, NO}_2, \text{CN, OR}^7, \text{SR}^7, \text{NR}^7R^8, \text{C(O)R}^7, \text{COOR}^7, \\
\text{C(O)NR}^7R^7, \text{C(O)NR}^7R^8, \text{NR}^7C(O)R^7, \text{NR}^7C(O)R^7, \text{NR}^7C(O)NR^7R^8, \\
\text{NR}^7C(O)NR^7R^8, \text{OC(O)NR}^7R^8, \text{S(O)}_2R^7, \text{S(O)}_2NR^7R^8, \text{S(O)}_2NR^7R^8, \\
\text{NR}^7S(O)_2R^7, \text{NR}^7S(O)_2R^8, \text{C}_{1-8}-\text{alkyl, } \text{C}_{2-10}-\text{alkenyl, } \text{C}_{2-10}-\text{alkynyl, } \text{Cs-} \text{cycloalkyl or } \text{Gn-} \text{cycloalkenyl, each of the } \\
\text{C}_{1-8}-\text{alkyl, } \text{C}_{2-10}-\text{alkenyl, } \text{C}_{2-10}-\text{alkynyl, } \text{C}_{3-10}-\text{cycloalkyl and } \text{Gn-} \text{cycloalkenyl optionally comprising} 
\end{align*}
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1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R^8 or R^9;

R^3 is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, wherein said ring system is substituted independently with one or more substituents of R^{10}, R^{16}, NR^{10}R^{10}, NR^{10}R^{11}, OR^{10}, SR^{10}, OR^{11}, SR^{11}, C(O)R^{10}, C(S)R^{10}, C(NCN)R^{10}, C(O)R^{11}, C(S)R^{11}, C(NCN)R^{11}, C(O)C(O)R^{10}, OC(O)R^{10}, COOR^{9}, C(O)SR^{10}, C(O)C(O)R^{11}, OC(O)R^{11}, COOR^{11}, C(O)SR^{11}, C(O)NR^{0}R^{10}, C(S)NR^{0}R^{10}, C(O)NR^{0}R^{11}, C(S)NR^{0}R^{11}, OC(O)NR^{0}R^{11}, NR^{0}C(O)R^{0}, NR^{0}C(O)R^{11}, NR^{0}C(S)R^{0}, NR^{0}C(S)R^{11}, NR^{0}C(O)NR^{0}R^{10}, NR^{0}C(S)NR^{0}R^{10}, NR^{0}C(S)NR^{0}R^{11}, NR^{0}(COOR)^{9}, NR^{0}(COOR)^{11}, NR^{0}C(O)C(O)R^{0}, NR^{0}C(O)C(O)R^{11}, NR^{0}C(O)C(O)NR^{0}R^{11}, S(O)_{2}R^{10}, S(O)_{2}R^{11}, S(O)_{2}NR^{0}R^{10}, S(O)_{2}NR^{0}R^{11}, NR^{0}S(O)_{2}R^{10}, NR^{0}S(O)_{2}R^{11};

R^4 is H, halo, haloalkyl, NO_{2}, CN, SR^{7}, OR^{7}, C(O)R^{7}, COOR^{7}, OC(O)R^{7}, NR^{7}R^{7}, NR^{7}R^{8}, C(O)NR^{7}R^{7}, C(O)NR^{7}R^{8}, NR^{7}C(O)R^{7}, NR^{7}C(O)R^{8}, NR^{7}C(O)NR^{7}R^{8}, S(O)_{2}NR^{7}R^{8}, NR^{7}S(O)_{2}NR^{7}R^{8}, NR^{7}S(O)_{2}NR^{7}R^{8}, d_{io-alkyl}, C_{2-10}alkenyl, C_{2-10}alkynyl, Cs-ion-cycloalkyl or C^o-cycloalkenyl, each of the Ci-io-alkyl, C_{2-3}io-alkenyl, C_{2-3}io-alkynyl, Cs-ion-cycloalkyl and C_{4-10}io-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R^8 or R^9;

R^3 is H, CN or Ci_{io-alkyl}, C_{2-3}io-alkenyl, C_{2-3}io-alkynyl, Ca-io-cycloalkyl or C_{4-10}io-cycloalkenyl, each of the Ci-o-alkyl, C_{2-3}io-alkenyl, C_{2-3}io-alkynyl, Cs-ion-cycloalkyl and C_{4-10}io-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R^8 or R^9;

R^6 is H, CN or Cl_i-o-alkyl, C_{2-3}io-alkenyl, C_{2-3}io-alkynyl, Ca-io-cycloalkyl or C_{4-10}io-cycloalkenyl, each of the Ci.io-alkyl, C_{2-3}io-alkenyl, C_{2-3}io-alkynyl, C_{3-5}io-cycloalkyl and C_{4-10}io-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R^8 or R^9;

R^7 is H, Ci-io-alkyl, C_{2-3}io-alkenyl, C_{2-3}io-alkynyl, Cs-io-cycloalkyl or C_{4-10}io-cycloalkenyl, each of the Ci.io-alkyl, C_{2-3}io-alkenyl, C_{2-3}io-alkynyl, C_{3-5}io-cycloalkyl and C_{4-10}io-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of NR^{8}R^{9}, NR^{9}R^{9}, OR^{8}, SR^{8}, OR^{9}, SR^{9}, C(O)R^{8}, OC(O)R^{8}, COOR^{8}, C(O)R^{9}, OC(O)R^{9}, COOR^{9}, C(O)NR^{8}R^{9}, C(O)NR^{9}R^{9}.
NR^9C(O)R^8, NR^9C(O)R^9, NR^9C(O)NR^9R^9, NR^9C(O)NR^8R^9, NR^9(COO^8R), NR^9(COO^9R),
OC(O)NR^9R^8, OC(O)NR^9R^9, S(O)NR^9R^8, S(O)NR^9R^9, S(O)NR^8R^9, S(O)NR^9R^8,
NR^9S(O)NR^9R^8, NR^9S(O)NR^9R^9, NR^9S(O)NR^8R^9, NR^9S(O)NR^9R^8, NR^9S(O)NR^9R^9,
NR^9S(O)NR^8R^9, OC(O)NR^9R^8, S(O)NR^9R^8, S(O)NR^9R^9, NR^9S(O)NR^8R^9, NR^9S(O)NR^9R^8,
NR^9S(O)NR^9R^9, or a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12
membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and
wherein each ring of said ring system is optionally substituted independently with 1-5
substituents of R^9, oxo, NR^9R^9, OR^9, SR^9, C(O)R^9, COOR^9, C(O)NR^9R^9, NR^9C(O)R^9,
NR^9C(O)NR^9R^9, OC(O)NR^9R^9, S(O)NR^9R^8, S(O)NR^9R^9, NR^9S(O)NR^8R^9, NR^9S(O)NR^9R^8,
or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms including
1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3
substituents of R^9;

alternatively, R^7 and R^8 taken together form a saturated or partially or fully
unsaturated 5-6 membered monocyclic or 7-10 membered bicyclic ring of carbon atoms
optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally
substituted independently with 1-5 substituents of R^9;

R^9 is H, halo, haloalkyl, CN, OH, NO_2, NH_2, acetyl, oxo, Ci-io-alkyl, C_{2;10^-}
alkenyl, C_{2;io-alkynyl}, Qs-io-cycloalkyl, C^io-cycloalkenyl, C^io-alkylamino-, C_{1;10^-}
dialkylamino-, Ci-io-alkoxy, C_{io-thioalkoxy} or a saturated or partially or fully
unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered
tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3
heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic,
said heteroatoms selected from O, N, or S, wherein each of the Ci-io-alkyl, C_{io-alkenyl},
C_{io-alkynyl}, C_{1;io^-cycloalkyl}, G_{io-cycloalkenyl}, Ci-io-alkylamino-, Cuo-dialkylamino-,
Ci-io-alkoxy, Ci_{io-thioalkoxy} and each ring of said ring system is optionally substituted
independently with 1-3 substituents of halo, haloalkyl, CN, NO_2, NH_2, OH, oxo, methyl,
methoxyl, ethyl, ethoxy, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-
butyl, methylamine, dimethyamine, ethylamine, diethylamine, propylamine,
isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R^{10} is H, halo, haloalkyl, CN, NO_2, C_{Mio^-alkyl}, C_{2;io^-alkenyl}, C_{2;io^-alkynyl}, C_{3;10^-}
cycloalkyl or C_{4;1io^-cycloalkenyl}, each of the Ci_{1io^-alkyl}, C_{2;io^-alkenyl}, C_{2;io^-alkynyl}, C_{3;10^-}
cycloalkyl and Gno-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N,
O and S and optionally substituted with one or more substituents of R^{11}, R^{12} or R^{16},
NR^{11}R^{12}, NR^{22}R^{12}, OR^{11}, OR^{12}, SR^{12}, C(O)R^{11}, OC(O)R^{11}, COOR^{11}, C(O)R^{12},
OC(O)R^{12}, COOR^{12}, C(O)NR^{11}R^{12}, NR^{11}C(O)R^{11}, C(O)NR^{12}R^{12}, NR^{12}C(O)R^{12},
NR^{13}C(O)NR^{11}R^{12}, NR^{13}C(O)NR^{12}R^{12}, NR^{12}(COOR^{11}), NR^{12}(COOR^{12}), OC(O)NR^{13}R^{12},
OC(O)NR^{12}R^{12}, S(O)_{2}R^{11}, S(O)_{2}R^{12}, S(O)_{2}NR^{11}R^{12}, S(O)_{2}NR^{12}R^{12}, NR^{12}S(O)_{2}NR^{14}R^{12},
NR^{13}S(O)_{2}NR^{12}R^{12}, NR^{12}S(O)_{2}R^{11} \lor NR^{13}S(O)_{2}R^{12};

R^{11} is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12
membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and
wherein each ring of said ring system is optionally substituted independently with 1-5
substituents of R^{12}, R^{13}, R^{14} or R^{16};

alternatively, R^{10} and R^{11} taken together form a partially or fully saturated or
unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms
selected from O, N, or S, and the ring optionally substituted independently with 1-5
substituents of R^{12}, R^{13}, R^{14} or R^{16};

R^{12} is H, Ci.iQ-alkyl, C_{2,10}-alkenyl, C_{2,10}-alkynyl, C_{4,10}\text{-cycloalkenyl}, Cuio-alkylamino-, Ci.io-alkylamino-, Cj.io-alkoxyl or Ci.io-thioalkyl, each
of which is optionally substituted independently with 1-5 substituents of R^{13}, R^{14}, R^{15} or
R^{16};

R^{13} is NR^{14}R^{15}, NR^{15}R^{14}, OR^{14}, OR^{15}; SR^{14}, OR^{15}; SR^{15}, C(O)R^{14}, OC(O)R^{14}, COOR^{14},
C(O)R^{15}, OC(O)R^{15}, COOR^{15}, C(O)NR^{14}R^{15}, C(O)NR^{15}R^{14}, NR^{14}C(O)R^{14}, NR^{15}C(O)R^{14},
NR^{14}C(O)R^{15}, NR^{15}C(O)R^{15}, NR^{14}C(O)NR^{14}R^{15}, NR^{15}C(O)NR^{15}R^{14}, NR^{14}(COOR^{14}),
NR^{15}(COOR^{15}), OC(O)NR^{14}R^{15}, OC(O)NR^{15}R^{14}, S(O)_{2}R^{14}, S(O)_{2}R^{15}, S(O)_{2}NR^{14}R^{15},
S(O)_{2}NR^{15}R^{14}, S(O)_{2}NR^{14}R^{15}, NR^{14}S(O)_{2}NR^{14}R^{15}, NR^{15}S(O)_{2}NR^{14}R^{15}, NR^{14}S(O)_{2}R^{14} \lor NR^{15}S(O)_{2}R^{15}.

R^{14} is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12
membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and
wherein each ring of said ring system is optionally substituted independently with 1-5
substituents of R^{15} or R^{16};

R^{15} is H or Ci.io-alkyl, C_{2,10}-alkenyl, C_{2,10}-alkynyl, Cs.io-cycloalkyl, C_{4,10}\text{-}
cycloalkenyl, Ci.io-alkylamino-, Ci.io-dialkylamino-, Ci.io-alkoxyl or Ci.io-thioalkoxyl,
each of which is optionally substituted independently with 1-5 substituents of R^{16}; and
R^6 is H, halo, haloalkyl, CN, OH, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

In another embodiment, the compounds provided herewith, or stereoisomers, tautomers, solvates, pharmaceutically acceptable salts, derivatives or prodrugs thereof, are generally defined by Formula II

\[
\begin{align*}
\text{Ais CR}^4 \text{ or N;} \\
R^2 \text{ is H, halo, haloalkyl, NO}_2, \text{CN, OR}^7, \text{SR}^7, \text{NR}^7\text{R}^7, \text{C(O)R}^7, \text{COOR}^7, \\
\text{C(O)NR}^7\text{R}^7, \text{C(O)NR}^7\text{R}^7, \text{NR}^7\text{C(O)R}^7, \text{NR}^7\text{C(O)C(O)R}^7, \text{NR}^7\text{C(O)NR}^7\text{R}^7, \text{NR}^7\text{C(O)NR}^7\text{R}^7, \\
\text{NR}^7\text{S(O)}_2\text{R}^7, \text{OC(O)NR}^7\text{R}^7, \text{S(O)}_2\text{R}^7, \text{S(O)}_2\text{NR}^7\text{R}^7, \text{S(O)}_2\text{NR}^7\text{R}^7, \\
\text{NR}^7\text{S(O)}_2\text{R}^7, \text{NR}^7\text{S(O)}_2\text{R}^7, \text{C}_{4-10}\text{-alkyl, C}_{2-6}\text{-alkenyl, C}_{2-6}\text{-alkynyl, Cs-iso-cycloalkyl or} \\
\text{C}_{1-6}\text{-cycloalkenyl, each of the Cs-iso-alkyl, C}_{2-6}\text{-iso-alkenyl, C}_{2-6}\text{-iso-alkynyl, Qio-iso-cycloalkyl} \\
\text{and C}_{4-6}\text{-iso-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S} \\
\text{and optionally substituted with one or more substituents of R}^7 \text{ or R}^9; \\
R^3 \text{ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12} \\
\text{membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of} \\
\text{carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if} \\
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S,}
wherein said ring system is substituted independently with one or more substituents of
R 3, R 10, R 16, NR 10 R 10, OR 10, SR 10, C(O)R 10, C(S)R 10, C(NC)R 10,
C(O)R 11, C(S)R 11, C(NC)R 11, C(O)C(O)R 10, OC(O)R 10, COOR 10, C(O)SR 11,
C(O)C(O)R 11, OC(O)R 11, COOR 11, C(O)SR 11, C(O)NR 10 R 10, C(S)NR 10 R 10, C(O)NR 11,
C(S)NR 11, R 10 R 11, C(O)C(O)R 11, OR 10 R 11, C(O)NR 11, NR 10 C(O)R 11, NR 10 C(S)R 11,
NR 10 C(O)NR 10 R 10, NR 10 C(S)NR 10 R 10, NR 10 C(S)NR 10 R 11, NR 10 C(S)NR 11,
NR 10 (COOR 10), NR 10 (COOR 11), NR 10 C(S)C(O)R 10, NR 10 C(S)C(O)R 11,
NR 10 C(S)C(O)N 10 R 11, S(O) 2 R 10, S(O) 2 R 11, S(O) 2 NR 10 R 10, S(O) 2 NR 10 R 11,
NR 10 S(O) 2 NR 10 R 11, NR 10 S(O) 2 R 10 Or NR 10 S(O) 2 R 11, provided that at least one substituent
on R 3 is NR 10 R 10, NR 10 R 11, C(O)R 10, OC(O)R 10, COOR 10, C(O)R 11, OC(O)R 11, COOR 11,
C(O)SR 10, C(O)SR 11, C(O)NR 10 R 10, C(S)NR 10 R 10, C(O)NR 10 R 11, C(S)NR 10 R 11,
NR 10 C(O)R 10, NR 10 C(S)R 10, NR 10 C(S)R 11, NR 10 C(S)R 11, NR 10 C(O)NR 10 R 10,
NR 10 C(O)NR 10 R 11, NR 10 C(S)NR 10 R 10, NR 10 C(S)NR 10 R 11, NR 10 (COOR 10),
NR 10 (COOR 11), OC(O)NR 10 R 11, S(O) 2 R 10, S(O) 2 R 11, S(O) 2 NR 10 R 10, S(O) 2 NR 10 R 11,
NR 10 S(O) 2 NR 10 R 11, NR 10 S(O) 2 R 10 or NR 10 S(O) 2 R 11;  
R 4 is H or is absent;  
R 5 is H, halo, haloalkyl, NO 2, CN, SR 7a, OR 7a, C(O)R 7a, COOR 7a, OC(O)R 7a,
NR 7a R 7a, NR 7a R 7a, C(O)NR 7a R 7a, C(O)NR 7a R 7b, NR 7a C(O)R 7a, NR 7a C(O)R 8,
NR 7a C(O)R 8, S(O)NR 7a R 7a, S(O) 2 NR 7a R 7b, NR 7a S(O)NR 7a R 7b, NR 7a S(O) 2 NR 7a R 7b, Ci
3-alkyl, C 2-halo-alkenyl, C 2,1 halo-alkenyl, C 2,1 cycloalkenyl or Gno-cycloalkenyl, each of the Ci.
3-alkyl, C 2-halo-alkenyl, C 2,1 halo-alkenyl, C 2,1 cycloalkenyl and Gno-cycloalkenyl optionally
comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or
more substituents of R 8 or R 9;  
R 6 is H, CN or Ci.1o-alkenyl, C 2,1o-alkenyl, C 2,1o-cycloalkenyl or C 4,10-
cycloalkenyl, each of the Ci.1o-alkenyl, C 2,1o-alkenyl, C 2,1o-cycloalkenyl and C 4,10-
cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and
optionally substituted with one or more substituents of R 8 or R 9;  
alternatively, R 5and R 6 taken together with the carbon or nitrogen atom to which
they are attached form a saturated or partially or fully unsaturated 5-6 membered
monocyclic or 7-10 membered bicyclic heterocyclic ring optionally including 1-3
additional heteroatoms selected from O, N, or S, and optionally substituted independently
with 1-5 substituents of R 8 or R 9;  
R 7a is H, Ci.1o-alkyl, C 2,1o-alkenyl, C 2,1o-alkenyl, Cs.1o-cycloalkyl, C 4,1o-
cycloalkenyl or partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-
12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, each of the C1-10-alkyl, C2-10-alkenyl, C2-10-alkynyl, C4-10-cycloalkyl, C4-10-cycloalkenyl and partially or fully saturated 5-6 membered heterocyclic optionally substituted with one or more substituents OIR89, NR9R99, OR98, SR98, O(C)R98, C(O)R99, OC(O)R99, R9C(O)R99, NR9C(O)R99, COOR99, C(O)NR9R99, C(O)NR9R99, NR9C(O)NR9R99, NR9C(O)NR9R99, NR9(COOR99), NR9(COOR99), OC(O)NR9R99, OC(O)NR9R99, S(O)2R89, S(O)2NR9R99, S(O)2R99, S(O)2NR9R99, NR9S(O)2NR9R99, NR9S(O)2NR9R99, NR9S(O)2R89, NR9S(O)2R99, NR9S(O)2R99, or R89;

R7b is H or C1-10-alkyl;

alternatively, R7a and R7b taken together with the nitrogen atom to which they are attached form a saturated or partially or fully unsaturated 5-6 membered monocyclic or 7-10 membered bicyclic heterocyclic ring optionally including 1-3 additional heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents OIR79 or R79;

R8 is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of R9, oxo, NR9R99, OR98, SR98, C(O)R99, COOR99, C(O)NR9R99, NR9C(O)R99, OC(O)NR9R99, S(O)2R99, S(O)2NR9R99, NR9S(O)2R99, or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R9;

R9 is H, halo, haloalkyl, CN, OH, NO2, NH2, oxo, acetyl, C1-10-alkenyl, C2-10-alkynyl, C2-10-cycloalkyl, C2-10-cycloalkenyl, C1-10-dialkylamino-, C1-10-dialkylamino-, Q-10-alkoxy, C1-10-thioalkoxy or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, wherein each of the d1-10-alkyl, C2-10-alkenyl, C2-10-alkynyl, C2-10-cycloalkyl, C1-10-cycloalkenyl, C1-10-cycloalkenyl, C1-10-dialkylamino-, C1-10-dialkylamino-, C1-10-thioalkoxy and ring of said ring system is optionally substituted
independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, o xo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyI, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R₁₀ is H, halo, haloalkyl, CN, NO₂, Ci-oalkyl, C₂-i₀alkenyl, C₃-i₀alkynyl, C₃-i₁0⁺
cycloalkyl or C₄-i₀-cycloalkenyl, each of the Ci-oalkyl, C₂-i₀alkenyl, C₂-i₀alkynyl, C₃-i₀⁺
cycloalkyl and Gno-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R₁¹, R₁² or R₁⁶, NR₁²R₁², OR₁¹, OR₁², SR₁², C(O)R₁¹, OC(O)R₁¹, COOR₁¹, C(O)R₁², OC(O)R₁², COOR₁², C(O)NR₁²R₁², NR₁²C(O)R₁², NR₁²C(O)NR₁²R₁², NR₁²(COOR₁²), NR₁²(COOR₁²), OC(O)NR₁²R₁², OR₁²(COOR₁²), OC(O)NR₁²R₁², S(O)₂R₁², S(O)₂R₁², S(O)₂NR₁²R₁², S(O)₂NR₁²R₁², NR₁²S(O)₂NR₁²R₁², NR₁²S(O)₂R₁², NR₁²S(O)₂R₁², NR₁²S(O)₂R₁², OR₁²NR₁²S(O)₂R₁²;

R₁¹ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12
membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-5 heteroatoms if
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and
wherein each ring of said ring system is optionally substituted independently with 1-5
substituents of R₁², R₁³, R₁⁴ or R₁⁶;

alternatively, R₁⁰ and R₁¹ taken together form a partially or fully saturated or
unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms
selected from O, N, or S, and the ring optionally substituted independently with 1-5
substituents of R₁², R₁³, R₁⁴ or R₁⁶;

R₁² is H, Cu-oalkyl, C₂-oalkenyl, C₂-oalkynyl, C₃-i₀-cycloalkyl, C₄-i₁₀⁺
cycloalkenyl, C₁-oalkylamino-, Ci-o-dialkylamino-, C₁-i₀-alkoxy or Ci-o-thioalkyl, each
of which is optionally substituted independently with 1-5 substituents of R₁³, R₁⁴, R₁⁵ or
R₁⁶;

R₁³ is NR₁⁴R₁⁵, NR₁⁵R₁⁵, OR₁⁴, OR₁⁵; SR₁⁵, C(O)R₁⁴, OC(O)R₁⁴, COOR₁⁴, C(O)R₁⁵, OC(O)R₁⁵, COOR₁⁵, C(O)NR₁⁴R₁⁵, C(O)NR₁⁵R₁⁵, NR₁⁴C(O)R₁⁴, NR₁⁵C(O)R₁⁴, NR₁⁴C(O)R₁⁵, NR₁⁵C(O)R₁⁵, NR₁⁴(COOR₁⁴), NR₁⁵(COOR₁⁵), OC(O)NR₁⁴R₁⁵, OC(O)NR₁⁵R₁⁵, S(O)₂R₁⁴, S(O)₂R₁⁵, S(O)₂NR₁⁴R₁⁵, S(O)₂NR₁⁵R₁⁵, S(O)₂R₁⁴R₁⁵, S(O)₂R₁⁵R₁⁵, NR₁⁴S(O)₂R₁⁴ or NR₁⁵S(O)₂R₁⁵;

R₁⁴ is a partially or fully saturated or unsaturated 5-8 membered or a saturated or
partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14
membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of \( R^{15} \) or \( R^{16} \);

\[
R^{15} = H \text{ or } \text{Ci.10-alkyl, C}_2\text{-io-alkenyl, C}_2\text{-io-alkynyl, C}_3\text{-io-cycloalkyl, C}_4\text{-io-cycloalkenyl, Ci.10-alkylamino-, Ci.10-dialkylamino-, C}_1\text{-io-alkoxyl or Ci.10-thioalkoxyl, each of which is optionally substituted independently with 1-5 substituents of } R^{16}; \]

\[
R^{16} = \text{H, halo, haloalkyl, CN, OH, NO}_2, \text{NH}_2, \text{OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO}_2, \text{NH}_2, \text{OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.}
\]

In another embodiment, the compounds of Formula I include N as A\(^1\) and CR\(^1\) as A\(^2\), in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include N as A\(^2\) and CR\(^1\) as A\(^1\), in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include B as a direct bond, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include \(-\text{CR}^5\text{R}^6^m\) as B, wherein m is 0, 1 or 2, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include \(-\text{C}(=\text{O})^p\) as B, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include \(-\text{N}(\text{R}^6)^q\) as B, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include \(-\text{O}^r\) as B, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include \(-\text{S}(=\text{O})^s\) as B, wherein m is 0, 1 or 2, in conjunction with any of the above or below embodiments.
In another embodiment, the compounds of Formula I include -C(R^7 R^8)nX or -C(R^7 R^8)X as R^1, wherein n is 0, 1 or 2 and X is NR^7 R^7, NR^7 R^8, OR^7, SR^7, OR^8; SR^8, C(O)R^7, OC(O)R^7, COOR^7, C(O)R^8, OC(O)R^8, COOR^8, C(O)NR^7 R^7, C(S)NR^7 R^7, NR^7 C(O)R^7, NR^7 C(S)R^7, NR^7 C(O)NR^7 R^7, NR^7 C(S)NR^7 R^7, NR^7 (COOR^7), OC(O)NR^7 R^7, C(O)NR^7 R^8, C(S)NR^7 R^8, NR^7 C(O)R^8, NR^7 C(S)R^8, NR^7 C(O)NR^7 R^8, NR^7 C(S)NR^7 R^8, NR^7 (COOR^8), OC(O)NR^7 R^8, S(O)NR^7 R^8, S(O)_2 NR^7 R^8, NR^7 S(O)NR^7 R^8, NR^7 S(O)_2 R^8, S(O)NR^7 R^8, S(O)_2 NR^7 R^8, NR^7 S(O)NR^7 R^8, NR^7 S(O)_2 R^8, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include a 5-8 membered monocyclic or 6-12 membered bicyclic ring system as R^1, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, wherein said ring system is optionally substituted independently with one or more substituents of R^5, R^8 or R^9, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I or II include H, halo, haloalkyl, NO_2, CN_3 OR^7, SR^7, NR^7 R^8, C(O)R^7, C_{10-11}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, Ca-i-o-cycloalkyl or Gno-cycloalkenyl as R^2, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I or II include COOR^7, C(O)NR^7 R^7, C(O)NR^7 R^8, NR^7 C(O)R^7, NR^7 C(S)R^7, NR^7 C(O)NR^7 R^7, NR^7 C(S)NR^7 R^7, OC(O)NR^7 R^8, S(O)_2 R^7, S(O)_2 NR^7 R^7, S(O)_2 NR^7 R^8, NR^7 S(O)_2 R^7 ORNR^7 S(O)_2 R^8 as R^2, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I or \pi include H or Ca-i-o-alkyl as R^2, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I optionally include one or more substituents of R^10, R^11, R^10, NR^10 R^10, NR^10 R^11, OR^10, SR^10, OR^11, SR^11, C(O)R^10, C(S)R^10, C(NCN)R^10, C(O)R^11, C(S)R^11, C(NCN)R^11, C(O)C(O)R^10, OC(O)R^10, COOR^10, C(O)SR^10, C(O)C(O)R^11, OC(O)R^11, COOR^11, C(O)SR^11, C(O)NR^10 R^10, C(S)NR^10 R^10, C(O)NR^10 R^11, C(S)NR^10 R^11, OC(O)NR^10 R^11, NR^10 C(O)R^10, NR^10 C(O)R^11, NR^10 C(S)R^10, NR^10 C(S)R^11, NR^10 C(O)NR^10 R^10, NR^10 C(O)NR^10 R^11, NR^10 C(S)NR^10 R^10, NR^10 C(S)NR^10 R^11, NR^10 (COOR^10), NR^10 (COOR^11), NR^10 C(O)C(O)R^10, NR^10 C(O)C(O)R^11, NR^10 C(O)C(O)NR^10 R^11, S(O)_2 R^10, S(O)_2 R^11, S(O)_2 NR^10 R^10.
S(O)_2NR^{10}R^{11}, NR^{10}S(O)_2NR^{10}R^{11}, NR^{10}S(O)_2R^{10}OrNR^{10}S(O)_2R^{11} on R^3, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula
\[
\pi \quad \text{include at least one substituent} \quad \text{OfNR}^{10}R^{10}, \text{NR}^{10}R^{11}, S(O)_2R^{10}, S(O)_2R^{11}, C(O)NR^{10}R^{10},
\]
\[
C(S)NR^{10}R^{10}, C(O)NR^{10}R^{11}, C(S)NR^{10}R^{11}, NR^{10}C(O)R^{10}, NR^{10}C(S)R^{10}, NR^{10}C(O)R^{11},
\]
\[
NR^{10}C(S)R^{10}, NR^{10}C(O)NR^{10}R^{10}, NR^{10}C(O)NR^{10}R^{11}, NR^{10}C(S)NR^{10}R^{10},
\]
\[
NR^{10}C(S)NR^{10}R^{11}, S(O)_2NR^{10}R^{10}, S(O)_2NR^{10}R^{11}, NR^{10}S(O)_2NR^{10}R^{11}, \text{NR}^{10}S(O)_2R^{10} \text{or}
\]
\[
NR^{10}S(O)_2R^{11} \text{on R}^3, \text{in conjunction with any of the above or below embodiments.}
\]

In another embodiment, the compounds of Formula I or II include two substituents on R^3, a first substituent OfNR^{10}R^{10}, NR^{10}R^{11}, S(O)_2R^{10},
\]
\[
S(O)_2R^{11}, C(O)NR^{10}R^{10}, C(O)NR^{10}R^{11}, NR^{10}C(O)R^{10}, NR^{10}C(O)NR^{10}R^{10},
\]
\[
NR^{10}C(O)NR^{10}R^{11}, S(O)_2NR^{10}R^{10}, S(O)_2NR^{10}R^{11}, NR^{10}S(O)_2NR^{10}R^{11}, NR^{10}S(O)_2R^{10} \text{or}
\]
\[
NR^{10}S(O)_2R^{11} \text{and a second substituent of R}^{16}, \text{in conjunction with any of the above or below embodiments.}
\]

In another embodiment, the compounds of Formula I or II include phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrollyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyln, dibenzofuranyln, benzothiophenyl, benzoxazolyl, benzopyrazolyl, benzisoxazolyl, benzothiazolyl or benzimidazolyl R^3, each of which has one substituent OfNR^{10}R^{10}, NR^{10}R^{11}, C(O)R^{10},
\]
\[
OC(O)R^{10}, COOR^{10}, C(O)R^{11}, OC(O)R^{11}, COOR^{11}, C(O)SR^{10}, C(O)SR^{11}, C(O)NR^{10}R^{10},
\]
\[
C(S)NR^{10}R^{10}, C(O)NR^{10}R^{11}, C(S)NR^{10}R^{11}, NR^{10}C(O)R^{10}, NR^{10}C(S)R^{10}, NR^{10}C(O)R^{11},
\]
\[
NR^{10}C(S)R^{11}, NR^{10}C(O)NR^{10}R^{10}, NR^{10}C(O)NR^{10}R^{11}, NR^{10}C(S)NR^{10}R^{10},
\]
\[
NR^{10}C(S)NR^{10}R^{11}, NR^{10}COOR^{10}, NR^{10}COOR^{11}, OC(O)NR^{10}R^{11}, S(O)_2R^{11},
\]
\[
S(O)_2NR^{10}R^{10}, S(O)_2NR^{10}R^{11}, NR^{10}S(O)_2NR^{10}R^{11}, NR^{10}S(O)_2R^{10}OrNR^{10}S(O)_2R^{11}, \text{and 1-3}
\]
\[
\text{optional substituents of R}^{10}, R^{11}, R^{16}, NR^{10}R^{10}, NR^{10}R^{11}, OR^{10}, SR^{10}, OR^{11}, SR^{11},
\]
\[
C(O)R^{10}, C(S)R^{10}, C(NCN)R^{10}, C(O)R^{11}, C(S)R^{11}, C(NCN)R^{11}, C(O)C(O)R^{10}, OC(O)R^{10},
\]
\[
COOR^{10}, C(O)SR^{10}, C(O)C(O)R^{11}, OC(O)R^{11}, COOR^{11}, C(O)SR^{11}, C(O)NR^{10}R^{10},
\]
\[
C(S)NR^{10}R^{10}, C(O)NR^{10}R^{11}, C(S)NR^{10}R^{11}, OC(O)NR^{10}R^{11}, NR^{10}C(O)R^{10}, NR^{10}C(O)R^{11},
\]
\[
NR^{10}C(S)R^{10}, NR^{10}C(S)R^{11}, NR^{10}C(O)NR^{10}R^{10}, NR^{10}C(O)NR^{10}R^{11}, NR^{10}C(S)NR^{10}R^{10},
\]
\[
NR^{10}C(S)NR^{10}R^{11}, NR^{10}COOR^{10}, NR^{10}COOR^{11}, NR^{10}C(O)C(O)R^{10}, NR^{10}C(O)C(O)R^{11},
\]
\[
NR^{10}C(O)C(O)R^{12}, NR^{10}C(O)C(O)NR^{10}R^{11}, S(O)_2R^{10}, S(O)_2R^{11}, S(O)_2NR^{10}R^{10},
\]
\[
S(O)_2NR^{10}R^{11}, NR^{10}S(O)_2NR^{10}R^{11}, NR^{10}S(O)_2R^{10}OrNR^{10}S(O)_2R^{11}, \text{in conjunction with any of the above or below embodiments.}
\]
In another embodiment, the compounds of Formula I or II include one substituent
of NR 1 R 10 , N R 1 R 11 , C(O)NR 10 R 10 , C(S)NR 10 R 10 , C(O)NR 10 R 10 , C(S)NR 10 R 10 ,
NR 10 C(O)R 10 , NR 10 C(S)R 10 , NR 10 C(O)R 11 , NR 10 C(S)R 11 , NR 10 C(O)(O)R 10 ,
NR 10 C(S)NR 10 R 10 , NR 10 C(S)NR 10 R 11 , S(O) 2 NR 10 R 10 , S(O) 2 NR 10 R 11 ,
NR 10 S(O) 2 NR 10 R 11 , NR 10 S(O) 2 R 10 OrNR 10 S(O) 2 R 11 and 0-3 substituents of R 16 , on R 4 .

In another embodiment, the compounds of Formula I or II include H, halo,
haloalkyl, NO 2 , CN, NR 7 R 7 , NR 7 R 8 , OR 7 ; SR 7 , C(O)R 7 , Ci 10 -alkyl, C 2 ,io-alkenyl, C 2 ,io-alkynyl,
C 3 ,io-cycloalkyl or G 4 ,io-cycloalkenyl as R 4 , in conjunction with any of the above
or below embodiments.

In another embodiment, the compounds of Formula I include OC(O)R 7 , COOR 7 ,
C(O)NR 7 R 7 , C(O)NR 7 R 8 , NR 7 C(O)R 7 , NR 7 C(O)R 8 , NR 7 C(O)NR 8 R 8 , NR 7 (COOR 7 ),
OC(O)NR 7 R 8 , S(O) 2 R 7 , S(O) 2 NR 7 R 8 , NR 7 S(O) 2 NR 7 R 8 , NR 7 S(O) 2 R 7 , NR 7 S(O) 2 R 7 as R 4 ,
in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I or

II include H or C 1 ,io-alkyl as R 4 , in conjunction with any of the above or below
embrdiments.

In another embodiment, the compounds of Formula I include N as A 1 , CR 1 as A 2 ,
and phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl,
quinoxalinyl, isoquinoxalinyl, thiophenyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl,
thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl,
dihydrobenzofuranyl, benzothiophenyl, benzisoxazolyl, benzopyrazolyl, benzothiazolyl
or benzimidazolyl as R 3 , in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I
include NR 7 R 7 , NR 7 R 8 , OR 7 , SR 7 , OR 8 , SR 8 , C(O)R 7 , C(O)R 8 , C(O)NR 7 R 7 , C(S)NR 7 R 7 ,
NR 7 C(O)R 7 , NR 7 C(S)R 7 , NR 7 C(S)NR 7 R 7 , NR 7 (COOR 7 ), C(O)NR 7 R 8 ,
C(S)NR 7 R 8 , NR 7 C(O)R 8 , NR 7 C(S)R 8 , NR 7 C(S)NR 7 R 8 , NR 7 (COOR 8 ),
S(O) 2 NR 7 R 7 , NR 7 S(O) 2 NR 7 R 8 , NR 7 S(O) 2 R 7 , S(O) 2 NR 7 R 8 , NR 7 S(O) 2 NR 7 R 8 , NR 7 S(O) 2 R 8
or a ring system selected from phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl,
isoquinolinyl, quinoxalinyl, isoquinoxalinyl, thiophenyl, furyl, pyrrolyl, pyrazolyl,
imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl,
benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl,
oxazolyl, isoaxazolyl, thiazolyl, pyrazolyl, morpholinyl, piperidinyl, piperazinyl,
pyranol, dioxazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyloheptyl as
R 4 in conjunction with any of the above or below embodiments, wherein said ring system
is optionally substituted independently with 1-5 substituents of R^7, R^8, R^9, oxo, OR^7, SR^7, C(O)R^7, NR^7R^7, NR^7R^8, OR^8, SR^8, C(O)R^8, COOR^7, OC(O)R^7, COOR^8, OC(O)R^8, C(O)NR^7R^7, C(O)NR^7R^8, NR^7C(O)R^7, NR^7C(O)R^8, NR^7C(O)NR^7R^7, NR^7C(O)NR^7R^8, S(O)^2NR^7R^7, S(O)^2NR^8R^7, NR^7S(O)^2NR^7R^7 or NR^7S(O)^2NR^8R^8.

In another embodiment, there are provided compounds of Formula I wherein A^1 is CR^1;

A^2 is N;
B is a direct bond;

R^1 is -(CR^7R^8)^n^ where wherein n is 1 or 2, NR^7R^7, NR^7R^8, OR^7; SR^7, OR^8, SR^8, C(O)R^7, C(O)R^8, C(O)NR^7R^7, C(S)NR^7R^7, NR^7C(O)R^7, NR^7C(O)NR^7R^7, NR^7C(S)NR^7R^8, C(S)NR^7R^8, C(O)NR^7R^8, NR^7C(O)R^8, NR^7C(S)R^8, NR^7C(O)NR^7R^8, NR^7C(S)NR^7R^8, NR^7(COOR^8), S(O)^2NR^7R^7, NR^7S(O)^2NR^7R^7, NR^7S(O)^2R^7, S(O)^2NR^8R^8, NR^7S(O)^2R^8, NR^7S(O)^2NR^8R^8, NR^7S(O)^2R^8 or a ring system selected from phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoxazolonyln, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzisoxazolyl, benzopyrazolyl, benzknidazolyl, tetrahydrofuran, pyrroldinyl, oxazolinyln, isoxazolinyln, thiazolinyln, pyrazinyl, oxazolyl, pyridinyl, tetrahydrofuranyl, dihydrobenzofuran, isoquinolynyl, pyrimidinyl, tetrahydrofuran, dihydrobenzofuran, benzothiophenyl, benzoxazolynyl, benzopyrazolyl, benzothiazolyn, benzimidazolyn, said

R^2 is H or C,-o-alkyl;

R^3 is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuran, benzothiophenyl, benzoxazolynyl, benzopyrazolyl, benzothiazolyn, benzimidazolyn, said

R^3 substituted with one substituent of NR^0R^10, NR^0R^11, C(O)R^10R^10, C(S)NR^10R^10, C(O)NR^10R^11, C(S)NR^10R^11, NR^10(C(O)R^10, NR^10C(S)R^10, NR^10(C)NR^10R^11, NR^10C(S)R^11, NR^0C(O)NR^0R^10, NR^0C(O)NR^0R^11, NR^0C(S)NR^0R^10, NR^0C(S)NR^0R^11, S(O)^2NR^0R^10, S(O)^2NR^0R^11, NR^0S(O)^2NR^0R^11, NR^0S(O)^2R^10 OrNR^0S(O)^2R^11 and 0-3 substituents of R^16;
\( R^4 \) is H or C\(_{10}\)-alkyl;
\( R^5 \) is H or C\(_{20}\)-alkyl;
\( R^6 \) is H or C\(_{30}\)-alkyl;
\( R^7 \) is H, C\(_{10}\)-alkyl, C\(_{20}\)-io-alkenyl, C\(_{20}\)-io-alkynyl or Cs\(_{10}\)-cycloalkyl, each of the C.

\( R^8 \) is phenyl, napthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzisoxazolyl, benzoimidazolyl, benzoxazolinyl, furoxan, benzopyrrol, benzotriazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, pyranyl, dioxazolinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of which is optionally substituted independently with \( 1-5 \) substituents of R\(_9\) oxo, NR\(_9\) R\(_9\), OR\(_9\), SR\(_9\), C(O)R\(_9\), COOR\(_9\), C(O)NR\(_9\), NR\(_9\)C(O)R\(_9\), NR\(_9\)C(O)NR\(_9\), NR\(_9\)C(O)NR\(_9\), NR\(_9\)C(O)R\(_9\), OR\(_9\), SR\(_9\), C(O)R\(_9\), COOR\(_9\), C(O)NR\(_9\), NR\(_9\)C(O)R\(_9\), NR\(_9\)C(O)NR\(_9\), NR\(_9\)C(O)R\(_9\), or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R\(_9\);

alternatively, R\(_7\) and R\(_8\) taken together form a saturated or partially or fully unsaturated 5-6 membered monocyclic or 7-10 membered bicyclic ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R\(_9\);

R\(_9\) is H, halo, haloalkyl, CN, OH, NO\(_2\), NH\(_2\), acetyl, Q.io-alkyl, C\(_{20}\)-io-alkenyl, C\(_{20}\)-io-alkynyl, C\(_{30}\)-io-cycloalkenyl, C\(_{io}\)-alkylamino-, C\(_{io}\)-dioalkylamino-.
l-o-cycloalkenyl, Ci.10-alkylarnino-, Cuio-dialkylamino-, Ci.10-alkoxyl, Ci.10-thioalkoxyl
and ring of said ring system is optionally substituted independently with 1-5 substituents
of halo, haloalkyl, CN, NO2, NH2, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl,
propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine,
dimethalamine, ethylamine, diethalamine, propylamine, isopropylamine, dipropylamine,
diisopropylamine, benzyl or phenyl;

R10 is H, halo, haloalkyl, CN, NO2, C10H11-alkyl, C2-alo-alkenyl or Cs-alo-cycloalkyl,
each of the C3-alo-alkyl, C2-alo-alkenyl, and Cs-alo-cycloalkyl optionally comprising 1-4
heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of
R11, R12 or R16, NR1R2, NR1R2S(O)2NR1R2, OR1, SR11, OR12, SR12, C(O)R11, OC(O)R1,
COOR11, C(O)R12, OC(O)R12, COOR12, C(O)NR1R12, NR12C(O)R11, C(O)NR1R12R12,
NR12C(O)R12, NR12C(O)NR1R12, NR12(COOR12), NR12(COOR12), OC(O)NR1R12,
OC(O)NR1R12, S(O)2R11, S(O)2R12, S(O)2NR1R12, S(O)2NR1R12R12, NR12S(O)2NR1R12,
NR12S(O)2NR12R12, NR12S(O)2R12, NR12S(O)2R12, NR12S(O)2R12 or NR12S(O)2R12;

R11 is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl,
quinazolinyl, isoquinazolinyl, thiophenyl, fiiry1, pyrrole, imidazoy1, triazol, thiazolyl,
oxazolyl, isoazoxoy1, isothiazoy1, indolyl, isoindolyl, benzofurany1, benzothiophenyl,
benzimidazoy1, tetrahydrofuranyl, pyrrolidiny1, oxazoliny1, isoazoxoliny1, thiazoliny1,
pyrazoliny1, morpholinyl, piperidinyl, piperezinyl, pyrany1, diozoxinyl, cyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of which is optionally
substituted independently with 1-5 substituents of R12, R14 or R16;

alternatively, R10 and R11 taken together form a partially or fully saturated or
unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms
selected from O, N, or S, and the ring optionally substituted independently with 1-5
substituents of R12, R13, R14 or R16;

R12 is H, Ci.10-alkyl, C2-1o-alkenynyl, C2-1o-alkynyl, C3-1o-cycloalkyl, C4-10-
cycloalkenyl, Ci.10-alkylarnino-, Ci.10-cycloalkylamino-, Ci.10-alkoxyl or Ci.10-thioalkoxyl,
each of which is optionally substituted independently with 1-3 substituents of R13, R14, R15
or R16;

R13 is NR14R15, NR15R15, OR14; SR14, OR15; SR15, C(O)R14, OC(O)R14, COOR14,
C(O)R15, OC(O)R15, COOR15, C(O)NR14R15, C(O)NR15R15, NR14C(O)R14, NR15C(O)R14,
NR14C(O)R15, NR15C(O)R15, NR15C(O)NR14R15, NR15C(O)NR15R15, NR15(COOR14),
NR15(COOR15), OC(O)NR14R15, OC(O)NR15R15, S(O)2R14, S(O)2R15, S(O)2NR14R15,
S(O)2NR15R15, NR14S(O)2NR14R15, NR15S(O)2NR15R15, NR14S(O)2R14 OrNR15S(O)2R15;
R$_{14}$ is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzo[fi]ranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, pyrazinyl, pyranyl, dioxozinyl, cyclobutyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of which is optionally substituted independently with 1-3 substituents of R$_{15}$ or R$_{16}$;

R$_{15}$ is H or Ci.io-alkyl, C$_2$ io-alkenyl, C$_3$ io-alkynyl, Cs-io-cycloalkynyl, C4-10-cycloalkenyl, Ci-io-alkylamino-, Ci-io-dialklyamino-, Ci.io-alkoxyl or Ci.io-thioalkoxyl, each of which is optionally substituted independently with 1-3 substituents of R$_{16}$; and

R$_{16}$ is H, halo, haloalkyl, CN, OH, NO$_2$, NH$_2$, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO$_2$, NH$_2$, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

In another embodiment, the compounds of Formula I include compounds wherein

R$_1$ is NR$_{R_1}$R$_{R_2}$, NR$_{R_4}$R$_{R_5}$, C(O)R$_{R_6}$, C(O)NR$_{R_7}$R$_{R_8}$, C(O)NR$_{R_7}$R$_{R_8}$, NR$_{R_4}$C(O)R$_{R_6}$, S(O)$_2$NR$_{R_7}$R$_{R_8}$, NR$_{R_4}$S(O)$_2$R$_{R_8}$, or a ring system selected from phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzo[fi]ranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, pyrazinyl, pyranyl, dioxozinyl, cyclobutyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, wherein the ring system is optionally substituted independently with 1-3 substituents of R$_{R_1}$, R$_{R_2}$, oxo, OR$_{R_7}$, SR$_{R_7}$, C(O)R$_{R_7}$, NR$_{R_4}$R$_{R_7}$, NR$_{R_4}$R$_{R_8}$, OR$_{R_8}$, SR$_{R_8}$, C(O)R$_{R_8}$, COOR$_{R_7}$, OC(O)R$_{R_7}$, COOR$_{R_8}$, OC(O)R$_{R_8}$, C(O)NR$_{R_7}$, C(O)NR$_{R_7}$R$_{R_8}$, NR$_{R_4}$C(O)R$_{R_8}$, NR$_{R_4}$C(O)NR$_{R_7}$R$_{R_8}$, NR$_{R_4}$C(O)NR$_{R_7}$R$_{R_8}$, S(O)$_2$NR$_{R_7}$R$_{R_8}$, S(O)$_2$NR$_{R_7}$R$_{R_8}$, NR$_{R_4}$S(O)$_2$NR$_{R_7}$R$_{R_8}$ or NR$_{R_4}$S(O)$_2$NR$_{R_7}$R$_{R_8}$; and

R$_{2}$ is H.
R³ is

wherein

one of A⁶ and A⁷ is CR³a and the other of A⁶ and A⁷ is CR³b or N;
each of A⁵, A⁸, A⁹, A¹⁰ and A¹¹ is, independently, CR³b or N;
X² is CR³a;
each of X¹, X³ and X⁴ is, independently, CR³b or N;
Y¹ is CR³aR³c, NR³c, O or S;
Y² is CR³aR³b or NR³a; and

Z is CH or N;
R³a IsNR⁰R¹⁰, NR⁰R¹¹, C(O)NR⁰R¹⁰, C(O)NR⁰R¹¹, NR⁰C(O)R¹⁰,
NR⁰C(O)R¹¹, NR⁰C(O)NR⁰R¹⁰, NR⁰C(O)NR⁰R¹¹, S(O)₂NR⁰R¹⁰,
S(O)₂NR⁰R¹¹, NR¹⁰S(O)₂NR⁰R¹¹, NR¹⁰S(O)₂R⁰ Or NR¹⁰S(O)₂R¹¹;
R³b is H₂ halo, haloalkyl, CN, NO₂, NH₂, C₁⁰-alkyl, C₂⁰-alkenyl, C₃⁰-cycloalkyl; and

alkynyl or C₃-i₀-cycloalkyl; and
\(-23-\)

\[ R^{3} \text{ is } H, \text{CN or } C_{10}-\text{alkyl}; \]

\[ R^{4} \text{ is } H; \]

\[ R^{5} \text{ is } H; \]

\[ R^{6} \text{ is } H; \]

\[ R^{7} \text{ is } \text{H, } \text{Cl,io-alkenyl, } C_{2,io-alkenyl} \text{ or } C_{3,6}-\text{CyClOalicyl, each of the } \text{Ci-to-alkyl, } C_{2,io-alkenyl} \text{ and } C_{3,6}-\text{cycloalkyl } \text{optionally substituted with 1-3 substituents } O\text{NR}^{8}R^{9}, \text{NR}^{8}\text{R}^{9}, \text{OR}^{8}, \text{SR}^{8}, \text{OR}^{9}, \text{SR}^{9}, \text{C(O)R}^{8}, \text{OC(O)R}^{8}, \text{COOR}^{8}, \text{C(O)R}^{9}, \text{OC(O)R}^{9}, \text{COOR}^{9}, \]

\[ \text{C(O)NR}^{8}R^{9}, \text{C(O)NR}^{8}\text{R}^{9}, \text{NR}^{8}\text{C(O)R}^{8}, \text{NR}^{8}\text{C(O)R}^{9}, \text{NR}^{8}\text{C(O)NR}^{8}\text{R}^{9}, \text{NR}^{8}\text{C(O)NR}^{8}\text{R}^{9}, \]

\[ \text{NR}^{8}(\text{COOR}^{8}), \text{NR}^{8}(\text{COOR}^{9}), \text{OC(O)NR}^{8}\text{R}^{9}, \text{OC(O)NR}^{8}\text{R}^{9}, \text{S(O)}_{2}\text{R}^{8}, \text{S(O)}_{2}\text{NR}^{8}\text{R}^{9}, \]

\[ \text{S(O)}_{2}\text{R}^{8}, \text{S(O)}_{2}\text{NR}^{8}\text{R}^{9}, \text{NR}^{8}\text{S(O)}_{2}\text{R}^{8}, \text{NR}^{8}\text{S(O)}_{2}\text{R}^{8}, \text{R}^{8} \text{ or } R^{9}; \]

\[ R^{8} \text{ is phenyl, naphthyl, pyridil, pyrimidil, quinolinil, isoquinolinil, quinazolinil, thiophenil, furyl, pyrrolyl, imidazolil, triazolil, thiazolil, oxazolil, isoxazolil, isothiazolil, indolil, isoindolil, benzofuranyl, benzo thiophenil, benzimidazolil, tetrahydrofuranyl, pyrrolidinil, oxazolinil, isoxazolinil, thiazolinil, pyrazolinil, morpholinil, piperidinil, piperazinil, pyranyl, dioxozinil, cyclopropyl, cyclobutyl, cyclpentyl, cyclohexyl and cycloheptyl, each of which is optionally substituted independently with 1-3 substituents of } R^{9}, \text{oxo, } \text{NR}^{8}\text{R}^{9}, \text{OR}^{9}, \text{SR}^{9}, \text{C(O)R}^{9}, \text{COOR}^{9}, \text{C(O)NR}^{8}\text{R}^{9}, \text{NR}^{8}\text{C(O)R}^{8}, \text{NR}^{8}\text{C(O)NR}^{8}\text{R}^{9}, \text{OC(O)NR}^{8}\text{R}^{9}, \text{S(O)}_{2}\text{R}^{9}, \text{S(O)}_{2}\text{NR}^{8}\text{R}^{9}, \]

\[ \text{NR}^{8}\text{S(O)}_{2}\text{R}^{9}, \text{or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from } O, N, \text{or } S, \text{and optionally substituted independently with 1-3 substituents of } R^{9}; \]

\[ \text{alternatively, } R^{7} \text{ and } R^{8} \text{ taken together form a saturated or partially or fully unsaturated 5-6 membered monocyclic or 7-10 membered bicyclic ring of carbon atoms} \]

\[ \text{optionally including 1-3 heteroatoms selected from } O, N, \text{or } S, \text{and the ring optionally substituted independently with 1-3 substituents of } R^{9}; \]

\[ R^{9} \text{ is } H, \text{halo, haloalkyl, } \text{CN, OH, NO}_{2}, \text{NH}_{2}, \text{acetyl, } \text{Ci}_{10}-\text{alkyl, } C_{2,io-alkenyl}, C_{3,io-cycloalkyl}, C_{4,io-cycloalkenyl}, \text{Ci/io-al kylamino-, } \text{Ci/io-dialkylamino-, } Q_{i0-alkoxyl, } C_{1,io-thioalkoxyl} \text{ or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from } O, N, \text{or } S, \text{wherein each of the } \text{Ci/io-alkyl, } C_{2,io-alkenyl, } C_{2,io-cycloalkyl, } Q_{i0-alkoxyl, } C_{4,io-cycloalkenyl, } \text{Ci/io-al kylamino-, } C_{10}-\text{dialkylamino-, } C_{M0-alkoxyl, } C_{1,io-thioalkoxyl} \]
and ring of said ring system is optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxy, ethyl, ethoxy, propyl, propoxy, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R² is H, halo, haloalkyl, CN, NO₂, d-io-alkyl, C₂-i₀-alkenyl or C₃-i₀-Cycloalkyl, each of the C₂-i₀-alkenyl, C₂-i₀-cycloalkyl and Ca-o-cycloalkyl optionally substituted with 1-3 substituents of R¹₁, R¹₂, R¹₆, NR¹¹R¹₂, NR¹²R¹₂, OR¹₁, SR¹₁, OR¹₂, SR¹², C(O)R¹², OC(O)R¹₁, COOR¹₁, C(O)R¹₂, OC(O)R¹₂, COOR¹₂, C(O)NR¹¹R¹₂, NR¹²C(O)R¹₁, C(O)NR¹²R¹₂, NR¹²C(O)NR¹¹R¹₂, NR¹²C(O)NR¹¹R₁₂, NR¹²(COOR¹₁), NR¹²(COOR¹₂), OC(O)NR¹¹R¹₂, OC(O)NR¹²R¹₆, S(O)₂R¹₁, S(O)₂R¹₂, S(O)₂N(R)R¹₂, S(O)₂R¹₂, S(O)₂R¹₁, S(O)₂R¹₂, S(O)₂NR¹¹R¹₂, S(O)₂NR¹²R¹₂, S(O)₂R¹₁, S(O)₂R¹₂, NR¹²S(O)₂R¹₁, NR¹²S(O)₂R¹₂, NR¹²S(O)₂R¹₁, NR¹²S(O)₂R¹₂, NR¹²S(O)₂R¹₁, ORNR¹²S(O)₂R¹₂; and

R¹¹ is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, pyranyl, dioxazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of which is optionally substituted independently with 1-3 substituents of R¹₂, R¹₃ or R¹⁰.

In another embodiment, the compounds are generally defined by Formula I or II above, wherein R³ is
wherein

one of A\textsubscript{6} and A\textsubscript{7} is CR\textsubscript{3a} and the other of A\textsubscript{6} and A\textsubscript{7} is CR\textsubscript{3b} or N;

each of A\textsubscript{5}, A\textsubscript{8}, A\textsubscript{9}, A\textsubscript{10} and A\textsubscript{11} is, independently, CR\textsubscript{3b} or N;

X\textsubscript{2} is CR\textsubscript{3a};

each of X\textsubscript{1}, X\textsubscript{3} and X\textsubscript{4} is, independently, CR\textsubscript{3b} or N;

Y\textsubscript{1} is CR\textsuperscript{30}R\textsuperscript{3c}, NR\textsuperscript{3c}, O or S;

Y\textsubscript{2} is CR\textsuperscript{30}R\textsuperscript{3b} or NR\textsuperscript{3a}; and

Z is CH or N;

R\textsuperscript{3a} is NR\textsuperscript{10}R\textsuperscript{10}, NR\textsuperscript{10}R\textsuperscript{11}, C(O)NR\textsuperscript{10}R\textsuperscript{10}, C(O)NR\textsuperscript{10}R\textsuperscript{11}, NR\textsuperscript{10}C(O)R\textsuperscript{10},

NR\textsuperscript{10}C(O)R\textsuperscript{11}, NR\textsuperscript{10}C(O)NR\textsuperscript{10}R\textsuperscript{10}, NR\textsuperscript{10}C(O)NR\textsuperscript{10}R\textsuperscript{11}, S(O)\textsubscript{2}NR\textsuperscript{10}R\textsuperscript{10},

S(O)\textsubscript{2}NR\textsuperscript{10}R\textsuperscript{11}, NR\textsuperscript{10}S(O)\textsubscript{2}NR\textsuperscript{10}R\textsuperscript{11}, NR\textsuperscript{10}S(O)\textsubscript{2}R\textsuperscript{10} Or NR\textsuperscript{10}S(O)\textsubscript{2}R\textsuperscript{11};
R\textsuperscript{3b} is H, halo, haloalkyl, CN, NO\textsubscript{2}, NH\textsubscript{2}, C\textsubscript{1-10}-alkyl, C\textsubscript{2-10}-alkynyl or Cs-10-cycloalkyl; and

R\textsuperscript{3c} is H, CN or Ci-10-alkyl, in conjunction with any of

the above or below embodiments of compounds of Formula I or II.

In another embodiment, the compounds are generally defined by Formula I or II above, wherein R\textsuperscript{3} is

\begin{align*}
\text{R}\textsuperscript{3b} &= \text{H, halo, haloalkyl, CN, NO}\textsubscript{2}, \text{NH}\textsubscript{2}, \text{C}\textsubscript{1-10}-\text{alkyl, C}\textsubscript{2-10}-\text{alkynyl or Cs-10-cycloalkyl}; \\
\text{R}\textsuperscript{3c} &= \text{H, CN or Ci-10-alkyl, in conjunction with any of the above or below embodiments of compounds of Formula I or II.}
\end{align*}

In another embodiment, the compounds are generally defined by Formula I or II above, wherein R\textsuperscript{3} is

\begin{align*}
\text{R}\textsuperscript{3b} &= \text{H, halo, haloalkyl, CN, NO}\textsubscript{2}, \text{NH}\textsubscript{2}, \text{C}\textsubscript{1-10}-\text{alkyl, C}\textsubscript{2-10}-\text{alkynyl or Cs-10-cycloalkyl}; \\
\text{R}\textsuperscript{3c} &= \text{H, halo, haloalkyl, CN, NO}\textsubscript{2}, \text{NH}\textsubscript{2}, \text{C}\textsubscript{1-10}-\text{alkyl, C}\textsubscript{2-10}-\text{alkynyl or Cs-10-cycloalkyl}; \\
\text{R}\textsuperscript{3d} &= \text{H, halo, haloalkyl, CN, NO}\textsubscript{2}, \text{NH}\textsubscript{2}, \text{C}\textsubscript{1-10}-\text{alkyl, C}\textsubscript{2-10}-\text{alkynyl or Cs-10-cycloalkyl}; \\
\text{R}\textsuperscript{3e} &= \text{H, halo, haloalkyl, CN, NO}\textsubscript{2}, \text{NH}\textsubscript{2}, \text{C}\textsubscript{1-10}-\text{alkyl, C}\textsubscript{2-10}-\text{alkynyl or Cs-10-cycloalkyl};
\end{align*}

wherein

\begin{align*}
\text{each of A}^{5}, \text{A}^{6}, \text{and A}^{7} &= \text{independently, CR}\textsuperscript{3b} \text{or N}; \\
\text{A}^{8} &= \text{CR}\textsuperscript{3c} \text{orN; and} \\
\text{A}^{9} &= \text{CR}\textsuperscript{3d} \text{orN;} \\
\text{Y}^{1} &= \text{O or S;} \\
\text{Y}^{2} &= \text{NR}^{3a}; \\
\text{R}\textsuperscript{3a} &= \text{NR}\textsuperscript{10}R^{10}, \text{NR}\textsuperscript{10}R^{11}, \text{C(O)NR}\textsuperscript{10}R^{10}, \text{C(O)NR}\textsuperscript{10}R^{11}, \text{NR}\textsuperscript{10}C(O)R^{10}, \\
\text{SR}^{10}R^{11}, \text{NR}\textsuperscript{10}C(O)NR\textsuperscript{10}R^{10}, \text{NR}\textsuperscript{10}C(O)NR\textsuperscript{10}R^{11}, \text{S(O)NR}\textsuperscript{10}R^{10}, \\
\text{S(O)NR}\textsuperscript{10}R^{11}, \text{NR}\textsuperscript{10}S(O)\textsuperscript{2}NR\textsuperscript{10}R^{10}, \text{NR}\textsuperscript{10}S(O)\textsuperscript{2}NR\textsuperscript{10}R^{11}, \text{OzNR}\textsuperscript{10}S(O)\textsuperscript{2}R^{10}; \\
\text{R}\textsuperscript{3b} &= \text{H, halo, haloalkyl, CN, NO}\textsubscript{2}, \text{NH}\textsubscript{2}, \text{C}_{1-10}-\text{alkyl, C}_{2-10}-\text{alkynyl or Cs-10-cycloalkyl}; \\
\text{R}\textsuperscript{3c} &= \text{H, halo, haloalkyl, CN, NO}\textsubscript{2}, \text{NH}\textsubscript{2}, \text{C}_{1-10}-\text{alkyl, C}_{2-10}-\text{alkynyl or Cs-10-cycloalkyl};
\end{align*}
R\(^{3d}\) is H, halo, haloalkyl, CN, NO\(_2\), NH\(_2\), Cl, alkyl, C\(_2\)io-alkenyl, C\(_2\)io-alkynyl or Cs.io-cycloalkyl; and alternatively, R\(^{3c}\) and R\(^{3d}\) taken together with the atoms to which they are attached form a phenyl or tetrahydrofuran ring system, optionally substituted with 1-3 substituents of halo, haloalkyl, CN, NO\(_2\), NH\(_2\), Cno-alkyl, C\(_2\)io-alkenyl, C\(_2\)io-alkynyl or Cs-io-cycloalkyl, in conjunction with any of the above or below embodiments of compounds of Formula I or \(\pi\).

In another embodiment, the compounds of Formula \(\pi\) include R\(^{5}\) and R\(^{6}\), taken together with the nitrogen to which they are attached, forming a saturated or partially or fully unsaturated 5-6 membered monocyclic or 7-10 membered bicyclic heterocyclic ring optionally including 1-3 additional heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of R\(^{8}\) or R\(^{9}\), in conjunction with any of the above or below embodiments of compounds of Formula \(\pi\).

In another embodiment, the compounds of Formula II include R\(^{5}\) and R\(^{6}\), taken together with the nitrogen to which they are attached, forming a heterocyclic ring selected from pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl and piperazinyl, wherein said ring is optionally substituted independently with 1-3 substituents of R\(^{8}\) or R\(^{9}\), in conjunction with any of the above or below embodiments of compounds of Formula \(\pi\).

In yet another embodiment, the compounds of Formula I or II include the examples described hereinbelow.

**DEFINITIONS**

The following definitions should assist in understanding the invention described herein.

The terms "agonist" and "agonistic" when used herein refer to or describe a molecule which is capable of, directly or indirectly, substantially inducing, promoting or enhancing biological activity of a biological molecule, such as an enzyme or receptor, including Tie-2 and Lck.

The term "comprising" is meant to be open ended, including the indicated components), but not excluding other elements.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.
The term "C₅alkyl", when used either alone or within other terms such as "haloalkyl" and "alkylamino", embraces linear or branched radicals having α to β number of carbon atoms (such as Ci-C₁⁰). The term "alkyl" radicals include "lower alky!" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, penty1, isoamyl, hexyl and the like. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl.

The term "alkenyl", when used alone or in combination, embraces linear or branched radicals having at least one carbon-carbon double bond in a moiety having between two and ten carbon atoms. Included within alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms and, for example, those radicals having two to about four carbon atoms. Examples of alkenyl radicals include, without limitation, ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations, as appreciated by those of ordinary skill in the art.

The term "alkynyl", when used alone or in combination, denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to ten carbon atoms. Examples of alkynyl radicals include "lower alkynyl" radicals having two to about six carbon atoms and, for example, lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include, without limitation, ethynyl, propynyl (propargyl), butynyl, and the like.

The term "alkoxy" or "alkoxyl", when used alone or in combination, embraces linear or branched oxygen-containing radicals each having alkyl portions of one or more carbon atoms. The term alkoxy radicals include "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoroisopropoxy.

The term "aryl", when used alone or in combination, means a carbocyclic aromatic moiety containing one, two or even three rings wherein such rings may be attached together in a fused manner. Every ring of an "aryl" ring system need not be aromatic, and the ring(s) fused to the aromatic ring may be partially or fully unsaturated and include one or more heteroatoms selected from nitrogen, oxygen and sulfur. Thus, the
term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, dihydrobenzafuranyl, anthracenyl, indanyl, benzodioxazinyl, and the like. Unless otherwise specified, the "aryl" group may be substituted, such as with 1 to 5 substituents including lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino, and the like. Phenyl substituted with \(-0-CH_2-O\) or \(-0-CH_2-CH_2-O\) forms an aryl benzodioxolyl substituent.

The term "carbocyclic", also referred to herein as "cycloalkyl", when used alone or in combination, means a partially or fully saturated ring moiety containing one ("monocyclic"), two ("bicyclic") or even three ("tricyclic") rings wherein such rings may be attached together in a fused manner and formed from carbon atoms. Examples of saturated carbocyclic radicals include saturated 3 to 6-membered monocyclic groups such as cyclopropane, cyclobutane, cyclopentane and cyclohexane and partially saturated monocyclic groups such as cyclopentene, cyclohexene or cyclohexadiene. The partially saturated groups are also encompassed in the term "cycloalkenyl" as defined below.

The terms "ring" and "ring system" refer to a ring comprising the delineated number of atoms, the atoms being carbon or, where indicated, a heteroatom such as nitrogen, oxygen or sulfur. Where the number of atoms is not delineated, such as a "monocyclic ring system" or a "bicyclic ring system", the numbers of atoms are 5-8 for a monocyclic and 6-12 for a bicyclic ring. The ring itself, as well as any substituents thereon, may be attached at any atom that allows a stable compound to be formed. The term "nonaromatic" ring or ring system refers to the fact that at least one, but not necessarily all, rings in a bicyclic or tricyclic ring system is nonaromatic.

The terms "partially or fully saturated or unsaturated" and "saturated or partially or fully unsaturated" with respect to each individual ring, refer to the ring either as fully aromatic (fully unsaturated), partially aromatic (or partially saturated) or fully saturated (containing no double or triple bonds therein). If not specified as such, then it is contemplated that each ring (monocyclic) in a ring system (if bicyclic or tricyclic) may either be fully aromatic, partially aromatic or fully saturated, and optionally substituted with up to 5 substituents.

The term "cycloalkenyl", when used alone or in combination, means a partially or fully saturated cycloalkyl containing one, two or even three rings in a structure having at least one carbon-carbon double bond in the structure. Examples of cycloalkenyl groups include \(C_3-C_6\) rings, such as compounds including, without limitation, cyclopropene, cyclobutene, cyclopentene and cyclohexene. The term also includes carbocyclic groups.
having two or more carbon-carbon double bonds such as "cycloalkyldienyl" compounds. Examples of cycloalkyldienyl groups include, without limitation, cyclopentadiene and cycloheptadiene.

The term "halo", when used alone or in combination, means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl", when used alone or in combination, embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. For example, this term includes monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals such as a perhaloalkyl. A monohaloalkyl radical, for example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms and, for example, lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoroalkyl, difluoroalkyl, trifluoroalkyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

"Perfluoroalkyl", as used herein, refers to alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentfluoroethyl.

The term "heteroaryl", as used herein, either alone or in combination, means a fully unsaturated (aromatic) ring moiety formed from carbon atoms and having one or more heteroatoms selected from nitrogen, oxygen and sulfur. The ring moiety or ring system may contain one ("monocyclic"), two ("bicyclic") or even three ("tricyclic") rings wherein such rings are attached together in a fused manner. Every ring of a "heteroaryl" ring system need not be aromatic, and the ring(s) fused thereto (to the heteroaromatic ring) may be partially or fully saturated and optionally include one or more heteroatoms selected from nitrogen, oxygen and sulfur. The term "heteroaryl" does not include rings having ring members of -O-O-, -O-S- or -S-S-.

Examples of unsaturated heteroaryl radicals, include unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, including for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl] and tetrazole; unsaturated 7- to 10-membered heterobicycyl groups containing 1 to 4 nitrogen atoms, including for example, quinolyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, aza-quinazolinyl, and the like; unsaturated 5- to 6-membered
heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-
fiiry1, benzofuryl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a
sulfur atom, for example, 2-thienyl, 3-thienyl, benzothienyl, etc.; unsaturated 5- to 6-
membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen
atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-
oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group
containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl,
isothiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term "heterocyclic", when used alone or in combination, means a partially or
fully saturated ring moiety containing one, two or even three rings wherein such rings
may be attached together in a fused manner, formed from carbon atoms and including one
or more heteroatoms selected from N, O or S. Examples of saturated heterocyclic radicals
include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen
atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3
to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3
nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group
containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of
partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranly, dihydrosulfur,
dihydrofurly and dihydrothiazoyl.

The term "heterocycle" also embraces radicals where heterocyclic radicals are
fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing
1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizynyl, benzimidazolyl,
quionolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-
b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms
and 1 to 3 nitrogen atoms [e.g. benzoazolyl, benzoazaloyl]; unsaturated condensed
heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g.,
benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated
condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl,
benzothenyl, 2,3-dihydro-benzo[1,4]dioxinly and dihydrobenzofuryl]. Examples of
heterocyclic radicals include five to ten membered fused or unfused radicals.

Examples of partially saturated and saturated heterocycly1 include, without
limitation, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl,
morpholinyl, tetrahydropyranly, thiazolidinyl, dihydrothietyl, 2,3-dihydro-
benzo[1,4]dioxanly, indoliny1, isoindoliny1, dihydrobenzothienyl, dihydrobenzofuryl,
isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-
tetrahydro-quinolyl. 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-
triazolo[3,4-a]isoquinolyn, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-
dihydro-1H-1 λ-benzo[d]isothiazol-6-yI, dihydropyranyl, dihydrofuryl and
dihydrothiazolyl, and the like.

The term "alkylamino" includes "N-
alkylamino" where amino radicals are independently substituted with one alkyl radical. Preferred alkylamino radicals are "lower alkylamino" radicals having one to six carbon atoms. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Examples of such lower alkylamino radicals include N-methylamino, and N-ethylamino, N-propylamino, N-isopropylamino and the like.

The term "dialkylamino" includes "N, N-
dialkylamino" where amino radicals are independently substituted with two alkyl radicals. Preferred alkylamino radicals are "lower alkylamino" radicals having one to six carbon atoms. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Examples of such lower alkylamino radicals include N,N-dimethylamino, N,N-diethylamino, and the like.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -CO₂H.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -(C=O)-.

The term "aminocarbonyl" denotes an amide group of the formula -C(=O)NH₂-.

The terms "alkythio" and "thioalkoxy" embrace radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkythio" is methylthio, (CH₃S-).

The term "haloalkythio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "haloalkythio" is trifluoromethylthio.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. Examples of aminoalkyl radicals include "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminoburyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.
The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. Examples of alkylaminoalkyl radicals include "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. Examples of alkylaminoalkoxy radicals include "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminooethoxy, N,N-dimethylaminooethoxy, N,N-diethylaminooethoxy and the like.

The term "Formula I" includes any sub formulas, such as Formula II. Similarly, the term "Formula II" includes any sub formulas.

The term "pharmaceutically-acceptable" when used with reference to a compound of Formulas I or II is intended to refer to a form of the compound that is safe for administration. For example, a free base, a salt form, a solvate, a hydrate, a prodrug or derivative form of a compound of Formula I or of Formula II, which has been approved for mammalian use, via oral ingestion or any other route of administration, by a governing body or regulatory agency, such as the Food and Drug Administration (FDA) of the United States, is pharmaceutically acceptable.

Included in the compounds of Formulas I and II are the pharmaceutically acceptable salt forms of the free-base compounds. The term "pharmaceutically-acceptable salts" embraces salts, commonly used to form alkali metal salts and to form addition salts of free acids or free bases, which have been approved by a regulatory agency. As appreciated by those of ordinary skill in the art, salts may be formed from ionic associations, charge-charge interactions, covalent bonding, complexation, coordination, etc. The nature of the salt is not critical, provided that it is pharmaceutically acceptable.

Suitable pharmaceutically acceptable acid addition salts of compounds of Formulas I and II may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, hydrofluoric, nitric, carbonic, sulfonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, aroylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include, without limitation, formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic,
benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pahloic), πiethanesulfonic, ethane'sulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic; toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric; camphorsulfonic, digluconic, cyclopentane propionic, dodșeysulfonic, glucohʃptanoic, glyceroxophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, thiocyanic, undecanoic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I and II include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including, without limitation, primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, disopropylethylamine and trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of Formulas I or II. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid (HCl), hydrobromic acid (HBr), citric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, stearic and salicylic acid, pamoic acid, gluconic acid, ethanesulfonic acid, methanesulfonic acid (MSA), benzenesulfonic acid (BSA), toluenesulfonic acid, tartaric acid, fumaric acid, medronic acid, napsylic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals such as sodium, potassium, calcium or magnesium, or with organic bases.

Additional examples of such salts can be found in Berge et al., J. Pharm. Sci., 66:1 (1977). Conventional methods may be used to form the salts: For example, a phosphate salt of a compound of the invention may be made by combining the desired
compound free base in a desired solvent, or combination of solvents, with phosphoric acid in a desired stoichiometric amount, at a desired temperature, typically under heat (depending upon the boiling point of the solvent). The salt can be precipitated upon cooling (slow or fast) and may crystallize (i.e., if crystalline in nature), as appreciated by those of ordinary skill in the art. Further, hemi-, mono-, di, tri- and poly-salt forms of the compounds of the present invention are also contemplated herein. Similarly, hemi-, mono-, di, tri- and poly-hydrated forms of the compounds, salts and derivatives thereof, are also contemplated herein.

The term "derivative" is broadly construed herein, and intended to encompass any salt of a compound of this invention, any ester of a compound of this invention, or any other compound, which upon administration to a patient is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to the ability to modulate a kinase enzyme.

The term "pharmaceutically-acceptable derivative" as used herein, denotes a derivative, which is pharmaceutically acceptable.

The term "prodrug", as used herein, denotes a compound which upon administration to a subject or patient is capable of providing (directly or indirectly) a compound of this invention. Examples of prodrugs would include esterified or hydroxylated compounds where the ester or hydroxyl groups would cleave in vivo, such as in the gut, to produce a compound according to Formula I. A "pharmaceutically-acceptable prodrug" as used herein, denotes a prodrug, which is pharmaceutically acceptable. Pharmaceutically acceptable modifications to the compounds of Formula I are readily appreciated by those of ordinary skill in the art.

The compound(s) of Formula I or π may be used to treat a subject by administering the compound(s) as a pharmaceutical composition. To this end, the compound(s) can be combined with one or more carriers, diluents or adjuvants to form a suitable composition, which is described in more detail herein.

The term "carrier", as used herein, denotes any pharmaceutically acceptable additive, excipient, adjuvant, or other suitable ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration purposes. "Diluent" and "adjuvant" are defined hereinafter.

The terms "treat", "treating," "treatment," and "therapy" as used herein refer to therapy, including without limitation, curative therapy, prophylactic therapy, and preventative therapy. Prophylactic treatment generally constitutes either preventing the
onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals.

The phrase "effective dosage amount" is intended to quantify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

The term "leaving groups" (also denoted as "LG") generally refer to groups that are displaceable by a nucleophile. Such leaving groups are known in the art. Examples of leaving groups include, but are not limited to, halides (e.g., I, Br, F, Cl), sulfonates (e.g., mesylate, tosylate), sulfides (e.g., SCH₂), N-hydroxsuccinimide, N-hydroxybenzotriazole, and the like. Nucleophiles are species that are capable of attacking a molecule at the point of attachment of the leaving group causing displacement of the leaving group. Nucleophiles are known in the art. Examples of nucleophilic groups include, but are not limited to, amines, thiols, alcohols, Grignard reagents, anionic species (e.g., alkoxides, amides, carbanions) and the like.

GENERAL SYNTHETIC PROCEDURES

The present invention further comprises procedures for the preparation of compounds of Formulas I and II.

The compounds of Formulas I and II can be synthesized according to the procedures described in the following Schemes 1-5, wherein the substituents are as defined for Formulas I and II, above, except where further noted.

The following list of abbreviations used throughout the specification represent the following and should assist in understanding the invention:

ACN, MeCN - acetonitrile
AgNO₃ - silver nitrate
BSA - bovine serum albumin
BOP - benzotriazol-1-yl-oxy
CDI - carbonyldiimidazole
Cs₂CO₃ - cesium carbonate
CHCl₃ - chloroform
CH₂Cl₂, DCM - dichloromethane, methylene chloride
DCC - dicyclohexylcarbodiimide
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>1,3-diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DIEA, (JPr)(_2)NEt</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>EDC</td>
<td>1-(3-dimethylaminopropyl)-3-ethylcarbodiimide</td>
</tr>
<tr>
<td>Et(_2)O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>FBS</td>
<td>fetal bovine serum</td>
</tr>
<tr>
<td>G, gm</td>
<td>gram</td>
</tr>
<tr>
<td>h, hr</td>
<td>hour</td>
</tr>
<tr>
<td>H(_2)</td>
<td>hydrogen</td>
</tr>
<tr>
<td>H(_2)O</td>
<td>water</td>
</tr>
<tr>
<td>HATU</td>
<td>O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate</td>
</tr>
<tr>
<td>HBr</td>
<td>hydrobromic acid</td>
</tr>
<tr>
<td>HCl</td>
<td>hydrochloric acid</td>
</tr>
<tr>
<td>HOBT</td>
<td>1-hydroxybenzotriazole hydrate</td>
</tr>
<tr>
<td>HOAc</td>
<td>acetic acid</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>IPA, IpOH</td>
<td>isopropyl alcohol</td>
</tr>
<tr>
<td>K(_2)CO(_3)</td>
<td>potassium carbonate</td>
</tr>
<tr>
<td>KI</td>
<td>potassium iodide</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>MgSO(_4)</td>
<td>magnesium sulfate</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrum</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>N(_2)</td>
<td>nitrogen</td>
</tr>
<tr>
<td>NaCNBH(_3)</td>
<td>sodium cyanoborohydride</td>
</tr>
<tr>
<td>Na(_2)CO(_3)</td>
<td>sodium carbonate</td>
</tr>
<tr>
<td>NaHCO(_3)</td>
<td>sodium bicarbonate</td>
</tr>
<tr>
<td>NaH</td>
<td>sodium hydride</td>
</tr>
<tr>
<td>NaOCH(_3)</td>
<td>sodium methoxide</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>NaOH</td>
<td>sodium hydroxide</td>
</tr>
<tr>
<td>Na$_2$SO$_4$</td>
<td>sodium sulfate</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NH$_4$Gl</td>
<td>ammonium chloride</td>
</tr>
<tr>
<td>NH$_4$OH</td>
<td>ammonium hydroxide</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methylpyrrolidinone</td>
</tr>
<tr>
<td>P(M)U$_3$</td>
<td>tri(tert-buryl)phosphine</td>
</tr>
<tr>
<td>PBS</td>
<td>phosphate buffered saline</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>Pd(PPh$_3$)$_4$</td>
<td>palladium(0)triphenylphosphine</td>
</tr>
<tr>
<td></td>
<td>tetrakis</td>
</tr>
<tr>
<td>Pd(dppf)Cl$_2$</td>
<td>palladium^1,1-bis(diphenylphosphinoferrocene)</td>
</tr>
<tr>
<td></td>
<td>π chloride</td>
</tr>
<tr>
<td>Pd(PhCN)$_2$Cl$_2$</td>
<td>palladium di-cyanophenyl dichloride</td>
</tr>
<tr>
<td>Pd(OAc)$_2$</td>
<td>palladium acetate</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$</td>
<td>bis(dibenzyldieneacetone) palladium</td>
</tr>
<tr>
<td>PyBop</td>
<td>benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium</td>
</tr>
<tr>
<td></td>
<td>hexafluorophosphate</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>TBTU</td>
<td>O-benzotriazol-1-yl-N,N,N%N'-tetramethyluronium</td>
</tr>
<tr>
<td></td>
<td>tetrafluoroborate</td>
</tr>
<tr>
<td>TEA, Et$_3$N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet light</td>
</tr>
</tbody>
</table>
A thieno-[2,3-d]pyrimidine compound 13 (wherein A² is N, A¹ is CR¹ and "L" is a linker "B" as designated in Formula I) can be prepared according to the method generally described in Scheme 1 (also referred to herein as Method A). As shown, a 1,4-dithiol-2,5-diol 1 can be reacted with an optionally substituted cyanoacetamide 2 in the presence of a suitable base and solvent to generate an amino-thiophene carboxamide 3. Compound 3 can be treated with an ethyl xanthate salt, such as potassium ethyl xanthate, in the presence of heat and a suitable solvent to generate the corresponding dihydrothieno-[2,3-d]pyrimidinone 4. The thiocarbonyl of compound 4 can then be converted to the corresponding thio-methyl compound 5 by treatment with methyl iodide. The carbonyl of the pyrimidine ring can then be converted to the corresponding chloride 6 by treatment with a suitable chloride source, such as phosphorus oxychloride (POCl₃), as shown in scheme 1 above. The methylsulfide compound 6 can be oxidized up to the corresponding sulfone 7 with a suitable oxidizing reagent, such as oxone as shown above. The chloro-pyrimidine 7 can be reduced to the corresponding des-chloro-pyrimidine 8 using a suitable reducing agent, such as by hydrogenation with a suitable catalyst, such as a suitable palladium catalyst, as shown. The methylsulfonl moiety of compound 8 can now be reacted with a suitable compound 9 containing a nucleophilic species, such as an oxygen, nitrogen, sulfur or carbon nucleophile, to afford the desirably R'-substituted pyrimidine compound 10. For example, the nucleophile (R¹) may be a nitrogen, oxygen or sulfur nucleophile (R¹ = -NHR⁷ or ⁸, -OR⁷ or ⁸ or -SR⁷ or ⁸), which can displace the
sulfonyl of the pyrimidine in the presence of a suitable base by conventional methods, as appreciated by those skilled in the art. Heat may or may not be required to effect the transformation depending upon the particular substrates involved. Suitable nucleophiles are discussed in more detail in scheme S, as well as in the examples set forth below.

Compound 10 can be converted to the corresponding bromide 11, by treatment with a suitable source of bromine under suitable conditions, such as Br₂ or N-bromosuccinimide (commonly referred to as NBS) in the presence of suitable solvent to form the bromide adduct 11.

The bromide intermediate 11 can be reacted with a suitable boronic acid 12, in the presence of a suitable catalyst in a Suzuki-type reaction, to form the desired compound 13. Formation of compound 13 may require heat, up to and including reflux temperatures depending on the particular solvent and concentration, as appreciated by those skilled in the art.

The Suzuki method is a reaction using a borane reagent, such as a dioxaborolane intermediate 12 (also described in scheme 3 below as a borane B-A intermediate 8), and a suitable leaving group containing reagent, such as the bromide compound 11 (Br is a leaving group "LG", which may also be other halogens, such as an I). As appreciated to one of ordinary skill in the art, Suzuki reactions also utilize a palladium catalyst. Suitable palladium catalysts include Pd(PPh₃)₄, Pd(OAc)₂ or Pd(dpdpf)Cl₂. Where LG is a halide, the halide may be an iodide, a bromide or even a chloride (chloro-pyridyl or chloropicolinyl) B rings undergo Suzuki reactions in the presence of Palladium(OAc)₂. Other LGs are also suitable. For example, Suzuki couplings are known to occur with a sulfonate, such as trifluoromethanesulfonate, as the leaving group.

The Suzuki reaction conditions may vary. For example, Suzuki reactions are generally run in the presence of a suitable base such as a carbonate base, bicarbonate or an acetate base, in a suitable solvent such as toluene, acetonitrile, DMF or an aqueous-organic solvent combination or a biphasic system of solvents. Further, the reaction may require heat depending upon the particular pyrimidine 11 and/or boronic acid 12, as appreciated by those skilled in the art. In addition, where R³ is an aromatic moiety, such as phenyl, the reaction may be complete in a short period of time with heat.

Further, the boronic acid 12 may be any suitable desired boronic acid having the general formula (RO)₂B-R³ (where "B" is absent or a direct bond — see formula II) or (RO)₂B-"B"-R³ (where "B" is a spacer such as an -(CR₅R₆)₉₂-, -C(=O) -, -N(R) -, -O- or -S(=O)₂- ) as defined in Formula I. The boronic acid may also be a cyclic boronate (as
shown). In this fashion, desired R₃ groups such as aryl or heteroaryl R₃ groups, can be installed into the pyriiridiñe (or phthalazine, not shown) core 11. The desired boronic acid compounds 12 may generally be made as illustrated in scheme 6 below.

Other known metal coupling chemistry, such Stille, Kumada, Negishi coupling methods, and the like, may be employed to couple pyrimidines 11 (or phthalazines, see scheme 2) to desired cyclic R₃-substituted moieties.

**Scheme 2**

A thieno-pyridazine compound 21 (wherein A₁ is N, A² is CR¹ and "L" is a linker "B" as designated in Formula I) can be prepared according to the method generally described in Scheme 2 above (also referred to herein as Method B). As shown, a bromo-tert-butyl thiophene carboxamide 15 can be made by successively reacting a thiophene carboxylic acid 1 with a sulfonyl chloride followed by t-butyl amine. The bromide of compound 15 can be replaced with a suitable or desired -B-R₃ moiety or simply an R₃ (where "B" is absent or a direct bond, as in compounds of formula II) group using a desired boronic acid 16 in a Suzuki-type coupling procedure, as described above in scheme 1, to provide the intermediate 17. Formylation of compound 17 can be accomplished in the presence of a suitable base, such as a strong lithium base, followed by treatment with DMF to generate the corresponding formyl compound 18. Compound 18 can be treated with hydrazine in the presence of a suitable acid, such as HOAc, to generate the corresponding thieno-pyridazinone 19. The carbonyl of the pyridazinone ring can then be converted to the corresponding chloride 20 by treatment with a suitable chloride source, such as phosphorus oxychloride (POCl₃), as shown in scheme 1 above. The chloride of the chloro-pyridazine 20 can be displaced with a suitable nucleophilic
species 9, as described in scheme 1 above, to afford the desirably \( R^1 \)-substituted thieno-
pyridazine compound 21.

**Scheme 3**

A thieno-pyridazine compound 28 (wherein \( A^1 \) is N, \( A^2 \) is CR\(^1\) and "B" is a direct
bond) can be prepared according to the method generally described in Scheme 3 above
(also referred to herein as Method C). As shown, an aldehyde-chloro-tert-butyl thiophene
carboxamide 23 can be made by successively reacting a chloro-tert-butyl thiophene
carboxamide 22 with a strong lithium base, followed by treatment with DMF, as
described in scheme 2 above. The chloride of compound 23 can be replaced with a
suitable or desired -B-R\(^3\) moiety or simply an acid-substituted R\(^3\) group (a desirably
substituted benzoic acid wherein \( n \) is 0-5 as shown in scheme 3 above, where "B" is
absent or a direct bond) using a desired boronic acid 24 in a Suzuki-type coupling
procedure, as described above in scheme 1, to provide the coupled adduct 25. Treatment
of compound 25 with hydrazine followed by conversion of the carbonyl of the
corresponding thieno-pyridazinone 26 to the corresponding chloride intermediate (not
shown) can be made using the methods described above in Scheme 2. The carboxylic acid
group of the phenyl ring of the transitional chloride intermediate can be coupled to a
suitable micleophilic species, such as a desired amine, as illustrated, to afford the
desirably chloro-R³-substituted thieno-pyridazine compound 27. Other suitable linker groups on R³ can be made using the methods described in Scheme 5 below. Compound 27 can then be reacted using a Suzuki-type reaction to afford desired R'-substituted thieno-pyridazine compounds 28.

Alternatively, an amino-substituted thieno-pyridazine compound 30 can be prepared according to the method generally described in Scheme 4 above (also referred to herein as Method D). As shown, chloro-B-R³-substituted thieno-phthalazine compound 29 can then be reacted using a desirably substituted amino R¹ group in the presence of a suitable base, such as N,N-diisopropylamine and the like, with heat to afford the desired amino-substituted thieno-pyridazine compounds 30.
R₃ ring systems, generally designated in scheme 5 as the "B ring", may be substituted with various substitutions as specified herein. For example, the substitution may be a linker, such as amino, carboxyl, sulfonyle, amidoo, and urea linker, as defined herein in Formulas I and π, connecting various substitutions, including R¹⁰ groups and R¹¹ ring systems (generally designated herein as the "A" ring) to the R₃ ring ("B" ring in scheme 5 above). This linker may be attached by various coupling methods as described.
in Scheme 5. Each of the nine sub-schemes, numbered 1-9 above and described below, utilize the following meanings for \((R)_n^X, X, \text{Nu}^-, E^+\) and \(m\): \((R)_n\) refers to \(n\) number of \(R^{10}\), \(R^{11}\) and \(R^{16}\) substitutions wherein \(n\) is an integer from 0-9; \(X\) refers generally to a "leaving group" such as a halide (bromine, chlorine, iodine or fluorine), alkylsulfonate and other known groups (also see definitions herein); \(\text{Nu}^-\) refers generally to a nucleophilic species such as a primary or secondary amine, an oxygen, a sulfur or an anionic carbon species — examples of nucleophiles include, without limitation, amines, hydroxides, alkoxides and the like; \(E^+\) refers generally to an electrophilic species, such as the carbon atom of a carbonyl, which is susceptible to nucleophilic attack or readily eliminates — examples of suitable electrophilic carbonyl species include, without limitation, acid halides, mixed anhydrides, aldehydes, carbamoyl-chlorides, sulfonyl chlorides, acids activated with activating reagents such as TBTU, HBTU, HATU, HOBT, BOP, PyBOP and carbodiimides (DCC, EDC, CDI and the like), and other electrophilic species including halides, isocyanates, daizionium ions and the like; and \(m\) is either 0 or 1.

The coupling of ring B to A, as shown as products in sub-schemes 1-9, can be brought about using various conventional methods to link ring B and A together. For example, an amide or a sulfonamide linkage, as shown in sub-schemes 2 and 4, and 7 and 9 where the \(\text{Nu}^-\) is an amine, respectively, can be made utilizing an amine on either the B or A groups and an acid chloride or sulfonyl chloride on the other of either the B or A groups. The reaction proceeds generally in the presence of a suitable solvent and/or base. Suitable solvents include, without limitation, generally non-nucleophilic, anhydrous solvents such as toluene, \(\text{CH}_2\text{Cl}_2\), THF, DMF, DMSO, N,N-dimethylacetamide and the like, including solvent combinations thereof. The solvent may range in polarity, as appreciated by those skilled in the art. Suitable bases include, for example, tertiary amine bases such as DIEA, TEA, carbonate bases such as \(\text{Na}_2\text{CO}_3\), \(\text{K}_2\text{CO}_3\), \(\text{Cs}_2\text{CO}_3\), hydrides such as \(\text{NaH}, \text{KH}\), borohydrides, cyanoborohydrides and the like, alkoxides such as \(\text{NaOCH}_3\), and the like. The base itself may also serve as a solvent. The reaction may optionally be run neat, i.e., without any base and/or solvent. These coupling reactions are generally fast and conversion occurs typically in ambient conditions. However, depending upon the particular substrate, such reactions may require heat, as appreciated by those skilled in the art.

Similarly, carbamates as illustrated in sub-schemes 5 and 1 where \(\text{Nu}^-\) is an amine, anhydrides as illustrated in sub-scheme 1 where \(\text{Nu}^-\) is an oxygen, reverse amides as generally illustrated in sub-scheme 8 where \(\text{Nu}^-\) is an amine and \(E^+\) is an acid chloride,
ureas as illustrated in sub-scheme 3, thioamides and thioureas where the respective carbonyl oxygen is a sulfur, thiocarbamates where the respective carbonyl oxygen and/or carbamate oxygen is a sulfur, and the like. While the above methods are so described, they are not exhaustive, and other methods for linking groups A and B together may be utilized as appreciated by those skilled in the art.

Although sub-schemes 1-9 are illustrated as having the nucleophilic and electrophilic coupling groups, such as the amino group and acid chloride groups illustrated in sub-scheme 2, directly attached to the substrate, either the A group or B ring, in question, the invention is not so limited. It is contemplated herein that these nucleophilic and/or electrophilic coupling groups may be tethered from their respective ring. For example, the amine group on the B ring, and/or the acid halide group on the A group or ring, as illustrated in sub-scheme 2, may be removed from direct attachment to the ring by a one or more atom spacer, such as by a methylene, ethylene spacer or the like. As appreciated by those skilled in the art, such spacer may or may not affect the coupling reactions described above, and accordingly, such reaction conditions may need to be modified to effect the desired transformation.

The coupling methods described in sub-schemes 1-9 of scheme 5 are also applicable for coupling desired A groups or rings to desired substituted phthalazine benzoic acids (scheme 3) to synthesize desired compounds of Formulas I and II. For example, a desirably substituted phthalazine benzoic acid may be reacted with a desirably substituted primary or secondary amine, such as an NHR or NHR1 group in the presence of a suitable solvent and a known coupling reagent, such as TBTU, HATU, CDI or others, to prepare the desired A-B amide bond, and the final compound of Formulas I or II.

Note that the B-A moiety illustrated in scheme 5 is connected through a linker "L". "L" may be any linker generally defined by the R3 substitutions in Formulas I and II, and particularly, it includes, without limitation, an amide, a urea, a thiourea, a thioamide, a carbamate, an anhydride, a sulfonamide and the like, allowing for spacer atoms either between ring B and L and/or between ring or group A and L, as described in Scheme 5 above.

To enhance the understanding and appreciation of the present invention, the following specific examples (starting reagents, intermediates and compounds of Formulas I and II) are set forth. It should be appreciated that the above general methods and specific examples below are merely for exemplification purposes only and are not to be construed
as limiting the scope of this invention in any manner. In addition, compounds of Formulas I and π may be made by alternative methods, possibly utilizing alternative synthetic intermediates and reagents. The following analytical methods were used to purify and/or characterize the compounds, and intermediates, described in the examples below.

5

Analytical methods:

Unless otherwise indicated, all HPLC analyses were run on a Agilent Model 1100 system with an Agilent Technologies Zorbax SB-C₈ (5 µ) reverse phase column (4.6 x 150 mm; Part no. 883975-906) run at 30 °C with a flow rate of about 1.50 mL/min. The mobile phase used solvent A (H₂O/0.1% TFA) and solvent B (ACN/0.1% TFA) with a 11 min gradient from 5% to 100% ACN. The gradient was followed by a 2 min. return to 5% ACN and about a 2.5 min. re-equilibration (flush).

LC-MS Method:

Samples were run on an Agilent model-1100 LC-MSD system with an Agilent Technologies XDB-C₈ (3.5 µ) reverse phase column (4.6 x 75 mm) at 30 °C. The flow rate was constant and ranged from about 0.75 mL/min to about 1.0 mL/min.

The mobile phase used a mixture of solvent A (H₂O/0.1% HOAc) and solvent B (ACN/0.1% HOAc) with a 9 min time period for a gradient from 10% to 90% solvent B. The gradient was followed by a 0.5 min period to return to 10% solvent B and a 2.5 min 10% solvent B re-equilibration (flush) of the column.
Preparative HPLC Method:

Where indicated, compounds of interest were purified via reverse phase HPLC using a Gilson workstation utilizing one of the following two columns and methods:
(A) Using a 50 x 100 mm column (Waters, Exterra, C18, 5 microns) at 50 mL/min. The mobile phase used was a mixture of solvent A (H₂O/10 mM ammonium carbonate at pH about 10, adjusted with cone. NH₄OH) and solvent B (85:15 ACN/water, 10 mM ammonium carbonate at pH of about 10 adjusted with cone. NH₄OH). Each purification run utilized a 10 minute gradient from 40% to 100% solvent B followed by a 5 minute flow of 100% solvent B. The gradient was followed by a 2 min return to 40% solvent B.
(B) Using a 20 x 50 mm column at 20 mL/min. The mobile phase used was a mixture of solvent A (H₂O/0.1% TFA) and solvent B (ACN/0.1% TFA) with a 10 min gradient from 5% to 100% solvent B. The gradient is followed by a 2 min return to 5% ACN.

Proton NMR Spectra:

Unless otherwise indicated, all ¹H NMR spectra were run on a Varian series Mercury 300 MHz instrument or a Broker series 400 MHz instrument. Where so characterized, all observed protons are reported as parts-per-million (ppm) downfield from tetramethylsilane (TMS) or other internal reference in the appropriate solvent indicated.

Mass Spectra (MS)

Unless otherwise indicated, all mass spectral data for starting materials, intermediates and/or exemplary compounds are reported as mass/charge (m/z), having an (TvH-H⁺) molecular ion. The molecular ion reported was obtained by electrospray detection method. Compounds having an isotopic atom, such as bromine and the like, are reported according to the detected isotopic pattern, as appreciated by those skilled in the art.

Example 1 (Method A)

Synthesis of N-Cyclopropyl-4-methyl-3-(2-(2-morpholinoethyl)thieno[2,3-d]pyrimidin-6-yl)benzamide

Step CaV 2-Aminothiophene-3-carboxamide

1,4-Dithiane-2,5-diol (50 g, 328 mmol), and cyanoacetamide (55.2 g, 657 mmol) were added to a mixture of MeOH (150 mL), water (9 mL) and TEA (6.5 g, 50 mmol). The
resulting mixture was heated at about 35-40 °C for 30 minutes while stirring, and then heated to about 50-60 °C for an additional 30 minutes with stirring. The reaction mixture was then cooled to RT and poured into a mixture of ice (70 g)/water (200 mL). A fine precipitate formed upon addition, which was filtered and dried overnight to give (66.7 g) of the title compound. MS (ES+): 143 (M+H)⁺.

Step (b): 2-Thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one

2-Aminothiophene-3-carboxamide (13 g, 92 mmol) and potassium ethylxanthate (48 g, 275 mmol) were mixed together and added to DMF (300 mL). The resulting mixture was heated to 150 °C for 6 hrs, then cooled to RT and concentrated on the rotovap under reduced pressure at 90 °C. The residue was diluted with 300 mL of aqueous citric acid (5%) and cooled to 0 °C and stirred for 30 min. The tan powder was filtered and dried overnight to give (11.5 g) of the title compound MS (ES+): 185 (M+H)⁺.

Step (c): 2-(Methylthio)thieno[2,3-d]pyrimidin-4(3H)-one

To a solution of 2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one (28 g, 152 mmol) and 1N aqueous NaOH (600 mL) at RT was added methyl iodide (11 mL, 182 mmol). The resulting mixture was stirred vigorously for 2 hrs. The reaction mixture was cooled to 0 °C and acetic acid about (100 mL) was added until the mixture was at a pH of about 4.5. A fine precipitate was filtered and dried overnight to afford the title compound as a fine tan powder (27 g). MS (ES+): 199 (M+H)⁺.

Step (d): 4-Chloro-2-fmethylthio)thieno[2,3-d]pyrimidine

To a 3 L round bottom was added 2-(methylthio)thieno[2,3-d]pyrimidin-4(3H)-one (29 g, 146 mmol), POCl₃ (224 g, 1463 mmol), and the resulting mixture was heated to reflux for 1 hour. The reaction mixture was concentrated under reduced pressure at 50 °C. The residue was diluted with EtOAc (500 mL) at 0 °C. Saturated sodium bicarbonate (400 mL) was added slowly. The resulting mixture was stirred vigorously at 0 °C for 1 hr and the layers were separated. Saturated sodium bicarbonate (400 mL) was added to the organic layer at 0 °C slowly. The resulting mixture was stirred vigorously at 0 °C for 20 min and the layers were separated. Brine (400 mL) was added to the organic layer and stirred for five minutes and the layers were again separated. The organic layer was dried over MgSO₄, filtered and concentrated to afford the title compound (25 g) MS (ES+): 217 (M+H)⁺.

Step (e): 4-Chloro-2-fmethylsulfonylthieno[2,3-d]pyrimidine
To 1L round-bottom flask was added 4-chloro-2-(methythio) thieno[2,3-c]pyrimidine (35.0 g, 162 mmol), THF (300 mL). The solution was stirred at 0°C and treated dropwise with a solution of OXONE (209 g, 339 mmol) in water (350 mL). The resulting mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc (500 mL) and water (300 mL). Separated the layers, the aqueous layer was extracted with EtOAc (3 x 300 mL). Organic layers were combined, washed with brine (2 x 300 mL), dried over MgSO₄, filtered and concentrated to provide the title compound (0.910 g). MS (ES+): 345 (M+H)+.

Step (g): 2-(2-methylsulfonyl)thieno[2,3-c]pyrimidine

To 500 mL round-bottom flask was added 4-chloro-2-(methylsulfonyl)thieno[2,3-c]pyrimidine (15 g, 60 mmol), ethyl alcohol (300 mL), nitrogen gas was bubbled for 5 minutes. To this solution was added 10% palladium on activated charcoal (15 g). To the resulting mixture was bubbled hydrogen gas over night. The reaction mixture was filtered through Celite. The filtrate was concentrated to give the title compound (11.0 g). MS (ES+): 215 (M+H)+.

Step (f): 2-(2-morpholinoethyl) thieno[2,3-c]pyrimidine

A solution of 2-(methylsulfonyl)thieno[2,3-c]pyrimidine (1.0 g, 4.67 mmol), 4-(2-aminoethyl)morpholine (1.8 g, 14.02 mmol), and 1-methyl-2-pyrrolidinone (1.5 mL) was heated to 100°C overnight. The reaction mixture was cooled to RT and diluted with EtOAc (200 mL)/water (75 mL). The layers were separated, and the organic layer was washed successively with water (4 x 75 mL) and brine (1 x 75 mL). The organic layer was then dried over MgSO₄, filtered and concentrated to give (1.2 g) of the crude product. The crude product was adsorbed onto a plug of silica gel and chromatographed through a Redi-Sep pre-packed silica gel column (40 g), eluting with a gradient of 5% to 95% MeOH in DCM to provide the title compound (1.02 g) MS (ES+): 265 (M+H)+.

Step (h): 6-Bromo-2-(2-morpholinoethyl)thieno[2,3-c]pyrimidine

To a solution of 2-(2-morpholinoethyl)thieno[2,3-c]pyrimidine (1.0 g, 3.79 mmol) in DCM (50 mL) at 0°C was added a solution of bromine (1.2 eq) in DCM (3 mL) dropwise. The resulting solution was stirred at 0°C for 30 min. The reaction mixture was quenched with saturated solution of NH₄Cl. The layers were separated, and the aqueous layer was extracted with DCM (3 x 25 mL). Organic layers were combined, washed with brine (2 x 30 mL), dried over MgSO₄, filtered and concentrated to provide the title compound (0.910 g). MS (ES+): 345 (M+H)+.
Step (T): N-Cyclopropyl-4-methyl-3-<2-morpholinoethyl)thieno[2,3-f]pyridazin-2-ylbenzamide

A 5 ml glass microwave reaction vessel was charged with 6-bromo-2-(2-morpholinoethyl)thieno[2,3-f]pyrimidine (0.200 g, 0.582 mmol), N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3-2-dioxaborolan-2-<Obenzamide (0.135 g, 0.582 mmol), cesium fluoride (0.277 g, 1.75 mmol), tetrakis(triphenylphosphine)palladium(0) (0.046 g, 0.040 mmol), 1,4-dioxane (1 mL, 57 mmol) and water (1 mL). The reaction mixture was heated in a Smith Synthesizer microwave reactor (Personal Chemistry, Inc., Upssala, Sweden) at 150 °C for 20 min. The reaction mixture was diluted with EtOAc and filtered through Celite®. The organic solutions were evaporated under reduced pressure. The crude residue was suspended in DCM and washed with saturated sodium bicarbonate (1 x 25 mL) followed by brine (1 x 25 mL), water (1 x 25 mL) and dried over MgSCV. The organic solutions were evaporated under reduced pressure and the residue was adsorbed onto a plug of silica gel and chromatographed through a Redi-Sep pre-packed silica gel column (40 g), eluting with a gradient of 5% to 95% MeOH in DCM to provide the title compound (0.095 g) MS (ES+): 438 (M+H)^+.

**Example 2 (Method B)**

**Synthesis of V-cyclopropyl-4-methyl-3-(7-morpholinothieno[2,3-f]pyridazin-2-yl)benezamide**

Step (a): 5-Bromo-2-methyl-4-(t-butylthiophene-2-carboxamide

A mixture of 5-bromothiophene-2-carboxylic acid (10.0 g, 48 mmol) and thionyl chloride (3.5 ml, 48 mmol) was boiled under reflux for 3 hrs. Excess of thionyl chloride was removed by distillation under reduced pressure. The residue was taken up in DCM (30 ml) and a solution of t/t-butylamine (7.0 g, 96 mmol) in DCM (30 ml) was added with stirring, the temperature of the mixture being kept below 10 °C. The resulting solution was stirred at 25 °C for 12 hrs, washed with water (3 x 20 ml) and dried over MgSO_4_. The combined washings were basified to pH 1 with 5M KOH(aq) and extracted with DCM (3 x 100 ml) and dried over MgSO_4_. The combined organic solutions were evaporated under reduced pressure to give the crude product (12.5 g). Recrystallization from (C_6H_5)_2ZCHCl_2 gave the pure amide (10.5 g) as a white solid. MS (ES+): 263 (M+H)^+.
Step (b): N-tert-butyl-S-fcyclopropylcarbamoylV^-methylphenyDthiopheneV^-carboxamide

A 15 ml glass microwave reaction vessel was charged with 5-Bvomo-N-tert-
butylthiophene-2-carboxamide (1.5 g, 5.7 mmol), N-cyclopropyl-4-methyl-3-(4,4,5,5-
tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (1.7 g, 5.7 mmol), cesium fluoride (0.63 g, 17 mmol), tetrakis(triphenylphosphine)palladium(0) (0.46 g, 0.40 mmol), 1,4-dioxane (4 ml, 57 mmol) and water (4 ml). The reaction mixture was heated in a Smith
Synthesizer microwave reactor (Personal Chemistry, Inc., Upssala, Sweden) at 150 °C for
20 min. The reaction mixture was diluted with EtOAc and filtered through Celite and the
Celite was washed with DCM. The combined organic solutions were evaporated under
reduced pressure. The crude residue was suspended in DCM and washed with saturated
sodium bicarbonate followed by brine, water and dried over MgSO₄. The organic
solutions were evaporated under reduced pressure and the crude product was adsorbed
onto a plug of silica gel and chromatographed through a Redi-Sep pre-packed silica gel
column (40 g), eluting with a gradient of 5% to 95% MeOH in DCM to provide N-tert-
butyl-5-(5-(cyclopropylcarbamoyl)-2-methylphenyl) thiophene-2-carboxamide (1.2 g).
MS (ES+): 357 (M+H)+.

Step (c): N-γt-butyl-5-f5-(cyclopropylcarbamoyl)π-2-methylphenylV3-formylthiophene-
2-carboxamide

In 150 mL round-bottom flask equipped with a stir bar, under N₂, was added N-tert-butyl
5-(5-(cyclopropylcarbamoyl)-2-methylphenyl)thiophene-2-carboxamide (1.2 g, 3.4
mmol) followed by anhydrous THF (100 mL). The solution was cooled down to –78 °C
and butyllithium, (2.2 ml, 30 mmol) was added dropwise over 5 min. The mixture was
stirred at –78 °C for 0.5 hrs and was added DMF (0.780 ml, 10 mmol). The mixture was
stirred at –78 °C for 0.5 hr, quenched with saturated solution of NH₄Cl and then allowed
to warm up to room temperature. The reaction then diluted with EtOAc (100 ml) and the
layers were separated and the aqueous layer was extracted with EtOAc (3 X 50 ml) and
the combined organic solution was washed with brine, water and dried over MgSO₄. The
organic solutions were evaporated under reduced pressure and the crude product was
adsorbed onto a plug of silica gel and chromatographed through a Redi-Sep pre-packed
silica gel column (40 g), eluting with a gradient of 5% to 95% MeOH in DCM to provide
N-fcr/-butyl-5-(5-(cyclopropylcarbamoyl)>2-methylphenyl)-3-formylthiophene-2-
carboxamide (1.01 g). MS (ES+): 385 (M+H)+
Step (d): \(N\)-Cyclopropyl-4-methyl-3-(7-oxo-6,7-dihydrothieno[2,3-\(d\)]pyridazin-2-\(y\))benzamide
A 5 ml glass microwave reaction vessel was charged with \(N\)-fer/-butyl-5-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-3-fo \(n\)ylthiophene-2-carboxamide (0.350 g, 0.910 mmol), glacial acetic acid (2.63 ml, 45.5 mmol), hydrazine (0.0875 g, 2.73 mmol). The reaction mixture was heated in a Smith Synthesizer microwave reactor (Personal Chemistry, Inc., Upssala, Sweden) at 150 °C for 20 min. The crude was concentrated and azotropically dried with toluene, the residue was partitioned between water and DCM, and the aqueous layer was extracted with DCM (2 X 25 ml). Combined organic solution was washed with saturated solution of NaHCO\(_3\) (aq), and dried over MgSO\(_4\). The organic solutions were evaporated under reduced pressure and the crude product was adsorbed onto a plug of silica gel and chromatographed through a Redi-Sep pre-packed silica gel column (40 g), eluting with a gradient of 5% to 95% MeOH in DCM to provide \(N\)-Cyclopropyl-4-methyl-3-(7-oxo-6,7-dihydrothieno[2,3-\(d\)]pyridazin-2-\(y\))benzamide (0.110 g) MS (ES+): 328 (M+H)+

Step (e): 3-(7-Chlorothieno[2,3-\(d\)]-N-cyclopropyl-4-methylbenzamide
Heat a mixture of \(N\)-Cyclopropyl-4-methyl-3-(7-oxo-6,7-dihydrothieno[2,3-\(d\)]pyridazin-2-\(y\))benzamide (0.102 g, 0.312 mmol) POCl\(_3\) (10 mL) at 90 °C for 2 hrs. The reaction mixture was evaporated under reduced pressure and to the crude product was added ice (50 g) followed by careful addition of saturated solution of NaHCO\(_3\) (aq) extract with EtOAc, and dried over MgSO\(_4\). The organic solutions were evaporated under reduced pressure to provide 3-(7-chlorothieno[2,3-\(d\)]/pyridazin-2-\(y\))-\(N\)-cyclopropyl-4-methylbenzamide (0.056 g) MS (ES+): 345 (M+H)+.

Step (f): \(N\)-Cyclopropyl-4-methyl-3-(7-morpholinothieno[2,3-\(d\)]pyridazin-2-\(y\))benzamide
A 2.5 ml glass microwave reaction vessel was charged with 3-(7-chlorothie\(n\)o[2,3-\(t\)lpyridazm-2-X]-\(N\)-cyclopropyl-4-methylbenzamide (0.020 g, 0.058 mmol), acetonitrile (1 ml), morpholine (0.015 g, 0.17 mmol). The reaction mixture was heated in a Smith Synthesizer microwave reactor (Personal Chemistry, Inc., Upssala, Sweden) at 150 °C for 50 min. The solvent was evaporated under reduced pressure and the crude product was adsorbed onto a plug of silica gel and chromatographed through a Redi-Sep pre-packed silica gel column (12 g), eluting with a gradient of 5% to 95% MeOH in DCM to provide
JV-cyclopropyl-4-methyl-3-(7-naorpholinothieno [2,3-α]pyridazin-2-y)benzamide (0.016 g) MS (ES+): 395 (M+H)+.

Example 3 (Method C)

Synthesis of JV-cyclopropyl-3-(7-(3-fluoro-2-methoxyphenyl)thieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide

Step (a): JV-fer/-butyl-5-chloro-3-formylthiophene-2-carboxamide

A 1-L three-neck flask was charged with N-tert-butyl-S-chlorothiophene^-carboxamide (10.0 g, 45.9 mmol) and thoroughly flushed with nitrogen gas. The flask was charged with THF (400 ml) by cannulation, then cooled to -75 °C. tert-butyllithium, 1.7 m solution in pentane (68.4 ml, 116 mmol) was added by syringe pump over 45 min, keeping the temperature less than -70 °C. After stirring at -70 °C for 90 min, the reaction was gradually warmed to -60 °C and stirred for 1 hr. The mixture was again cooled to -75 °C and DMF (14.2 ml, 184 mmol) was added dropwise, ensuring the temperature remained below -70 °C. The mixture was stirred at -75 °C for 1 hr. The reaction was quenched with 200 ml sat. aq. NH₄Cl, then allowed to warm to RT. Water was added to the solution to dissolve solids and the mixture was extracted with EtOAc (3X). The combined organics were dried over Na₂SO₄, filtered and concentrated to give the title compound as a tan solid (11.6 g.). MS (ESI, pos. ion) m/z: 246 (M+). 10

Step (b): 3-(5-(fer/-butylcarbamoyl)M-fo πnythiophen-2-vB^-melhylbenzoic acid

A mixture of N-/er/-butyl-5-chloro-3-formylthiophene-2-carboxamide (2.40 g, 9.77 mmol), 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (3.07 g, 11.7 mmol), Pd(PPh₃)₂Cl₂ (0.343 g, 0.488 mmol, Strem), and sodium carbonate (3.11 g, 29.3 mmol) in DME:EtOH:H₂O = 7:2:3 (36 ml) was heated to 80 °C for 8 hrs. After cooling to RT, the mixture was diluted with sat. aq. NH₄Cl and extracted with EtOAc (3X). The combined organics were dried over Na₂SO₄, filtered and concentrated over SiO₂. Column chromatography (MeOHZCH₂Cl₂ = 0->2%) gave the desired product. Yield: 2.31 g.

Step (c): 4-methyl-3-(7-oxo-6,7-dihydrothienor2,3-dljpyridazin-2-yl)benzoic acid

A solution of 3-(5-(fer/-butylcarbamoyl)-4-formylthiophen-2-yl)-4-methylbenzoic acid (2.30 g, 6.7 mmol) in acetic acid (20 ml) was treated with hydrazine (0.73 ml, 20 mmol) and heated to 110 °C for 8 hrs. After cooling to RT the volatiles were removed in vacuo. The residue was recrystallized from MeOH. Yield: 1.01 g. MS (ESI, pos. ion) m/z: 287 (M+). 20

- 54 -
Step (d): 3-7-chlorothieno[2,3-d]pyridazin-2-yl-N-cyclopropyl-4-methylbenzamide

A mixture of 4-methyl-3-(7-oxo-6,7-dihydrothieno[2,3-d]pyridazin-2-yl)benzoic acid (1.01 g, 3.53 mmol) and phosphorus oxychloride (30.0 ml, 322 mmol) was heated to 105 °C for 4 hrs. After cooling to RT, the volatiles were removed in vacuo. The residue was re-dissolved in DCM (50 ml) and treated with TEA (1.49 ml, 10.6 mmol) and dropwise with cyclopropylamine (0.746 ml, 10.6 mmol). The mixture was diluted with 1 M KHSO₄ and extracted with CCl₄ (3X). The combined organics were dried over Na₂SO₄, filtered and concentrated over SiO₂. Column chromatography (MeOH:CH₂Cl₂ = 0→2%) afforded the desired product. Yield: 0.92 g. MS (ESI, pos. ion) m/z: 344 (M+1).

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Step Te): N-cyclopropyl-3-fluoro-^-methoxyphenyl-thieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide

A mixture of S^-chlorothienoP^-dlpyridazin^-yO- N-cyclopropyl-M-methylbenzamide (90 mg, 0.26 mmol), 3-fluoro-2-methoxyphenylboronic acid (67 mg, 0.39 mmol), Pd(PPh₃)₂Cl₂ (18 mg, 0.03 mmol), and sodium carbonate (83 mg, 0.78 mmol) in a mixture of DME, ethanol and H₂O (7:2:3, 2 ml) was heated to 150 °C for 15 min in the Emrys Optimizer® microwave. The mixture was diluted with MeOH and concentrated over SiO₂. Column chromatography (MeOH:CH₂Cl₂ = 0→2%) afforded the desired product. Yield: 59 mg. MS (ESI, pos. ion) m/z: 434 (M+1).

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Example 4

Synthesis of 3-(7-chlorothieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide

A mixture of 4-methyl-3-(7-oxo-6,7-dihydrothieno[2,3-d]pyridazin-2-yl)benzoic acid (1.00 g, 3.49 mmol) and phosphorus oxychloride (15.0 ml, 161 mmol), was heated to 105 °C for 2 hrs. The mixture was concentrated in vacuo. The residue was dissolved in CH₂Cl₂ and treated with anhydrous ammonia gas at 0 °C for 30 min. The mixture was diluted with sat aq. NaHCO₃ and extracted with 25% i-PrOHCHCl₃ (3X). The combined organics were dried over Na₂SO₄, filtered and concentrated over SiO₂. Column chromatography (MeOH:CH₂Cl₂ = 0→3%) afforded the title compound. MS (ESI, pos. ion) m/z: 304 (M+1).
Example 5

Synthesis of 7-V-cyclopentyl-4-methyl-3-(7-((5)-3-methylmorpholino)thieno[2,3-d]pyridazin-2-yl)benzamide

A mixture of 3-(7-chlorothieno[2,3-d]pyridazin-2-yl)-N-cyclopentyl-4-methylbenzamide (90 mg, 262 µmol) and (S)-3-methylmorpholine (79 mg, 785 µmol) in NMP (2 ml) was heated to 165 °C for 48 hrs. The mixture was cooled to RT, diluted with H₂O and filtered. The solids were washed with H₂O and air-dried. The residue was purified with reverse-phase chromatography (Phenomenex Synergi 4m Max RP 80 A column, 150X21 mm, 20 ml/min, 10-95% CH₃CN/H₂O, 0.1% TFA, 10.5 min gradient) to afford the title compound. MS (ESI, pos. ion) m/z: 409 (M+).

Example 6

Synthesis of V-cyclopentyl-4-methyl-3-(7-(3-oxopiperazin-1-yl)thieno[2,3-d]pyridazin-2-yl)benzamide

The title compound was prepared by a method similar to that described in Example 2. 3-(7-chlorothieno[2,3-d]pyridazin-2-yl)-N-cyclopentyl-4-methylbenzamide (100 mg, 291 µmol), piperazin-2-one (44 mg, 436 µmol) and diisopropylethylamine (152 µl, 873 µmol) were combined in NMP (2 ml) and heated to 180 °C for 18 hrs. The mixture was cooled to RT, diluted with H₂O and filtered. The solids were washed with H₂O and air-dried. Both the solid and solution were collected, dissolved in DMSO and purified with reverse-phase chromatography (Phenomenex Synergi 4m Max RP 80 A column, 150X21 mm, 20 ml/min, 10-95% CH₃CN/H₂O, 0.1% TFA, 10.5 min gradient). The residue was purified with reverse-phase chromatography (Phenomenex Synergi 4m Max RP 80 A column, 150X21 mm, 20 ml/min, 10-95% CH₃CN/H₂O, 0.1% TFA, 10.5 min gradient) to afford the title compound. MS (ESI, pos. ion) m/z: 408 (M+).

The following compounds in Table 1 are further examples of compounds of Formulas I and π, and were prepared by procedures analogous to those described in the Example which correlates to the method indicated.

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<th>Ex. No.</th>
<th>Compound Name</th>
<th>Mass Spec Obtained</th>
<th>Method</th>
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<tr>
<td>7</td>
<td>N-cyclopentyl-3-(2-((3-diethylamino)propyl)amino)thieno[2,3-d]pyrimidin-6-yl)-4-methylbenzamide</td>
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<td>-----------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>16</td>
<td>( \text{N-cyclopropyl-4-methyl-3-((1-(2,2,2-trifluoroethyl)-3-piperidinyl)methyl)amino} \text{thieno[2,3-d]pyrimidin-6-yl} \text{benzamide} )</td>
<td>403</td>
<td>A</td>
</tr>
<tr>
<td>17</td>
<td>( \text{N-cyclopropyl-4-methyl-3-(2-((3-(4-morpholinyl)propyl)amino)thieno[2,3-d]pyrimidin-6-yl)benzamide} )</td>
<td>451</td>
<td>A</td>
</tr>
<tr>
<td>18</td>
<td>( \text{3-(2-((3-(dimethylamino)-2,2-dimethylpropyl)amino)thieno[2,3-d]pyrimidin-6-yl)-4-methylbenzamide} )</td>
<td>397</td>
<td>A</td>
</tr>
<tr>
<td>19</td>
<td>( \text{3-(2-((3-(dimethylamino)-2,2-dimethylpropyl)amino)thieno[2,3-d]pyrimidin-6-yl)-N,4-dimethylbenzamide} )</td>
<td>411</td>
<td>A</td>
</tr>
<tr>
<td>20</td>
<td>( \text{N-cyclopropyl-3-(7-hydroxythieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide} )</td>
<td>326</td>
<td>B</td>
</tr>
<tr>
<td>21</td>
<td>( \text{3-(7-chlorothieno[2,3-d]pyridazin-2-yl)-N-cyclopropyl-4-methylbenzamide} )</td>
<td>345</td>
<td>B</td>
</tr>
<tr>
<td>22</td>
<td>( \text{N-cyclopropyl-3-(7-(4-fluoro-2-methylphenyl)thieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide} )</td>
<td>418</td>
<td>C</td>
</tr>
<tr>
<td>23</td>
<td>( \text{N-cyclopropyl-4-methyl-3-(7-(2-(methylxy)-3-pyridinyl)thieno[2,3-d]pyridazin-2-yl)benzamide} )</td>
<td>417</td>
<td>C</td>
</tr>
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</table>
The following compounds in Tables 2 and 3 and Examples thereafter are additional representative examples of compounds of Formula I and π, as provided by the present invention.

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<tr>
<th></th>
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<th>MW</th>
<th></th>
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<td>25</td>
<td>N-cyclopropyl-4-methyl-3-(7-(2-(methyloxy)phenyl)thieno[2,3-d]pyridazin-2-yl)benzamide</td>
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</tr>
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<td>N-cyclopropyl-3-(7-(2,4-difluorophenyl)thieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide</td>
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<td>27</td>
<td>3-(7-(4-fluoro-2-methylphenyl)thieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide</td>
<td>378</td>
<td>C</td>
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</tbody>
</table>

![Diagram](image-url)

Table 2

The following compounds in Tables 2 and 3 and Examples thereafter are additional representative examples of compounds of Formula I and π, as provided by the present invention.
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<thead>
<tr>
<th>Ex. No.</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>L</th>
<th>( R^{10} ) or ( R^{11} )</th>
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<td>4-morpholiny</td>
<td>2-CH₃ phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
</tr>
<tr>
<td>29</td>
<td>1-piperaziny</td>
<td>4-CH₃ phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
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<td>phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
</tr>
<tr>
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<td>cyclohexyl-N-</td>
<td>6-CH₃ phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
</tr>
<tr>
<td>32</td>
<td>morpholine-(CH₂)₂-N-</td>
<td>2-OCH₃ phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
</tr>
<tr>
<td>33</td>
<td>(CH₃)₂N-(CH₂)₃-N-</td>
<td>4-OCH₃ phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
</tr>
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<td>34</td>
<td>(C₂H₅)₂N-(CH₂)₃-N-</td>
<td>phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
</tr>
<tr>
<td>35</td>
<td>3-OH-1-pyrrolidiny</td>
<td>6-OCH₃ phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
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<td>m-C(O)NH-</td>
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<td>Methyl or cyclopropyl</td>
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<td>H</td>
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<td>Methyl or cyclopropyl</td>
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<td>Methyl or cyclopropyl</td>
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<tr>
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<td>Ex. No.</td>
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<td>R&lt;sup&gt;3&lt;/sup&gt;</td>
<td>L</td>
<td>R&lt;sup&gt;10&lt;/sup&gt; or R&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>--------------</td>
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<td>-----------------------------</td>
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<td>1-piperidinyl</td>
<td>phenyl</td>
<td>H</td>
<td>m-C(O)NH-ethyl</td>
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<tr>
<td>52</td>
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<td>6-CH&lt;sub&gt;3&lt;/sub&gt;-phenyl</td>
<td>H</td>
<td>m-C(O)NH-ethyl</td>
<td>ethyl</td>
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<tr>
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<td>morpholine-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-N-</td>
<td>2-OCH&lt;sub&gt;3&lt;/sub&gt;-phenyl</td>
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<td>m-C(O)NH-ethyl</td>
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<tr>
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<td>m-C(O)NH-ethyl</td>
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<td>H</td>
<td>m-C(O)NH-ethyl</td>
<td>ethyl</td>
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<tr>
<td>58</td>
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<td>m-C(O)NH-propyl</td>
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<td>H</td>
<td>m-C(O)NH-propyl</td>
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</tr>
<tr>
<td>75</td>
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<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;-phenyl</td>
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<td>m-C(O)NH-propyl</td>
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<td>76</td>
<td>(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;N-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-N-</td>
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<td>H</td>
<td>m-C(O)NH-propyl</td>
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<td>m-C(O)NH-propyl</td>
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### Table 3

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<th>Ex. No.</th>
<th>R¹</th>
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<th>R³</th>
<th>L</th>
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<td>3-amido-1-pyrrolidinyl</td>
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<tr>
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<td>3-amido-1-piperidinyl</td>
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<td>CH₃</td>
<td>m-C(O)NH-</td>
<td>cyclopropyl</td>
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</table>

![Diagram](image)
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<thead>
<tr>
<th>Ex. No.</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>L</th>
<th>R⁰ or R¹</th>
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<td>Methyl or cyclopropyl</td>
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<td>Methyl or cyclopropyl</td>
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<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
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<td>99</td>
<td>3-OH-1-pyrrolidinyl</td>
<td>6-OCH₃-phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
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<td>6-OCH₃-phenyl</td>
<td>H</td>
<td>m-C(O)NH-</td>
<td>Methyl or cyclopropyl</td>
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</tr>
</tbody>
</table>
and compounds of Examples 165-167

wherein X is CH₂, NH, O or S, and R is H, 2,4-difluoro, 2-methyl-4-fluoro, and 2-pyridyl substitutions on the phenyl ring.
While the examples described above provide processes for synthesizing compounds of Formulas I and π, other methods may be utilized to prepare such compounds. Methods involving the use of protecting groups may be used. Particularly, if one or more functional groups, for example carboxy, hydroxy, amino, or mercapto groups, are or need to be protected in preparing the compounds of the invention, because they are not intended to take part in a specific reaction or chemical transformation, various known conventional protecting groups may be used. For example, protecting groups typically utilized in the synthesis of natural and synthetic compounds, including peptides, nucleic acids, derivatives thereof and sugars, having multiple reactive centers, chiral centers and other sites potentially susceptible to the reaction reagents and/or conditions, may be used.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they readily lend themselves, i.e. without undesired secondary reactions, to removal, typically accomplished by solvolysis, reduction, photolysis or other methods of removal such as by enzyme activity, under conditions analogous to physiological conditions. It should also be appreciated that the protecting groups should not be present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions described herein.

Salts of a compound of the invention having a salt-forming group may be prepared in a conventional manner or manner known to persons skilled in the art. For example, acid addition salts of compounds of the invention may be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide) may also be converted into a salt with one acid molecule per compound (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a solid under a high vacuum at elevated temperature, for example from 50 °C to 170 °C, one molecule of the acid being expelled per molecule of the compound.

Acid salts can usually be converted to free-base compounds, e.g. by treating the salt with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogen carbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide. Exemplary salt forms and their preparation are described herein in the Definition section of the application.

All synthetic procedures described herein can be carried out under known reaction conditions, advantageously under those described herein, either in the absence or in the presence (usually) of solvents or diluents. As appreciated by those of ordinary skill in the art, the solvents should be inert with respect to, and should be able to dissolve, the starting materials and other reagents used. Solvents should be able to partially or wholly solubilize the reactants in the absence or presence of catalysts, condensing agents or neutralizing agents, for example ion exchangers, typically cation exchangers for example in the H⁺ form. The ability of the solvent to allow and/or influence the progress or rate of the reaction is generally dependant on the type and properties of the solvent(s), the reaction conditions including temperature, pressure, atmospheric conditions such as in an inert atmosphere under argon or nitrogen, and concentration, and of the reactants themselves.

Suitable solvents for conducting reactions to synthesize compounds of the invention include, without limitation, water; esters, including lower alkyl-lower alkanoates, e.g., EtOAc; ethers including aliphatic ethers, e.g., Et₂O and ethylene glycol dimethylether or cyclic ethers, e.g., THF; liquid aromatic hydrocarbons, including benzene, toluene and xylene; alcohols, including MeOH, EtOH, 1-propanol, EPOH, n- and t-butanol; nitriles including CH₃CN; halogenated hydrocarbons, including CH₂Cl₂, CHCl₃ and CCl₄; acid amides including DMF; sulfoxides, including DMSO; bases, including heterocyclic nitrogen bases, e.g. pyridine; carboxylic acids, including lower
alkanecarboxylic acids, e.g., AcOH; inorganic acids including HCl, HBr, HF, H₂SO₄ and the like; carboxylic acid anhydrides, including lower alkane acid anhydrides, e.g., acetic anhydride; cyclic, linear, or branched hydrocarbons, including cyclohexane, hexane, pentane, isopentane and the like, and mixtures of these solvents, such as purely organic solvent combinations, or water-containing solvent combinations e.g., aqueous solutions. These solvents and solvent mixtures may also be used in "working-up" the reaction as well as in processing the reaction and/or isolating the reaction produces, such as in chromatography.

The invention further encompasses "intermediate" compounds, including structures produced from the synthetic procedures described, whether isolated or not, prior to obtaining the finally desired compound. Structures resulting from carrying out steps from a transient starting material, structures resulting from divergence from the described method(s) at any stage, and structures forming starting materials under the reaction conditions are all "intermediates" included in the invention. Further, structures produced by using starting materials in the form of a reactive derivative or salt, or produced by a compound obtainable by means of the process according to the invention and structures resulting from processing the compounds of the invention in situ are also within the scope of the invention.

New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the subject of this invention. In select embodiments, such starting materials are used and reaction conditions so selected as to obtain the desired compound(s).

Starting materials of the invention, are either known, commercially available, or can be synthesized in analogy to or according to methods that are known in the art. Many starting materials may be prepared according to known processes and, in particular, can be prepared using processes described in the examples. In synthesizing starting materials, functional groups may be protected with suitable protecting groups when necessary. Protecting groups, their introduction and removal are described above.

Compounds of the present invention can possess, in general, one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric,
dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

All such isomeric forms of these compounds including racemates, racemic mixtures, scalemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures are included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms. The invention expressly includes all tautomeric forms of the compounds described herein.

The compounds may also occur in cis- or trans- or E- or Z- double bond isomeric forms. All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

Substituents on ring moieties (e.g., phenyl, thienyl, etc.) may be attached to specific atoms, whereby they are intended to be fixed to that atom, or they may be drawn unattached to a specific atom, whereby they are intended to be attached at any available atom that is not already substituted by an atom other than H (hydrogen).

The compounds of this invention may contain heterocyclic ring systems attached to another ring system. Such heterocyclic ring systems may be attached through a carbon atom or a heteroatom in the ring system.

Alternatively, a compound of any of the formulas described herein may be synthesized according to any of the procedures described herein. In the procedures described herein, the steps may be performed in an alternate order and may be preceded, or followed, by additional protection/deprotection steps as necessary. The procedures may further use appropriate reaction conditions, including inert solvents, additional
reagents, such as bases (e.g., LDA, DDEA, pyridine, K$_2$CO$_3$, and the like), catalysts, and salt forms of the above. The intermediates may be isolated or carried on in situ, with or without purification. Purification methods are known in the art and include, for example, crystallization, chromatography (liquid and gas phase, and the like), extraction, distillation, trituration, reverse phase HPLC and the like. Reactions conditions such as temperature, duration, pressure, and atmosphere (inert gas, ambient) are known in the art and may be adjusted as appropriate for the reaction.

As can be appreciated by the skilled artisan, the above synthetic schemes are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the inhibitor compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser’s Reagents for Organic Synthesis, John Wiley and Sons (1994); A. Katritzky and A. Pozharski, Handbook of Heterocyclic Chemistry, 2nd edition (2001); M. Bodanszky, A. Bodanszky, The Practice of Peptide Synthesis, Springer-Verlag, Berlin Heidelberg (1984); J. Seyden-Penne, Reductions by the Alumino- and Borohydrides in Organic Synthesis, 2nd edition, Wiley-VCH, (1997); and L. Paquette, editor, Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995).

Accordingly, in one embodiment, the present invention provides a method of making a compound of Formula I or II, the method comprising the step of reacting a compound 7
where \( \pi A^1, A^2, R^1 \) and \( R^2 \) are as defined herein and \( X \) is a halogen, with a boronic acid having a general formula \((RO^B-R^3)\) to make a compound of Formula I or \( \pi \).

The compounds of the invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. By way of example, a compound of the invention may be modified to incorporate a hydrophobic group or "greasy" moiety in an attempt to enhance the passage of the compound through a hydrophobic membrane, such as a cell wall.

These detailed descriptions fall within the scope, and serve to exemplify, the above-described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention.

Although the pharmacological properties of the compounds of the invention (Formulas I and \( U \)) vary with structural change, in general, activity possessed by compounds of Formulas I and \( \pi \) may be demonstrated both in vitro as well as \( \textit{in vivo} \). Particularly, the pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological in vitro assays. The following exemplified pharmacological assays have been carried out with the compounds according to the invention. Compounds of the invention were found to inhibit the activity of various kinase enzymes, including, without limitation, p38 receptor kinase at doses less than 25 \( \mu M \).

**BIOLOGICAL EVALUATION**

The following assays were used to characterize the ability of compounds of the invention to inhibit the production of TNF-\( \alpha \) and IL-1-\( \beta \). The second assay can be used to measure the inhibition of TNF-\( \alpha \) and/or EL-1-\( \beta \) in mice after oral administration of the test compounds.

**Lipopolysaccharide-activated monocyte TNF production assay**
Isolation of monocytes

Test compounds were evaluated in vitro for the ability to inhibit the production of TNF by monocytes activated with bacterial lipopolysaccharide (LPS). Fresh residual source leukocytes (a byproduct of plateletpheresis) were obtained from a local blood bank, and peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation on Ficol-Paque Plus (Pharmacia). PBMCs were suspended at 2 x 10^6/mL in DMEM supplemented to contain 2% FCS, 10 mM, 0.3 mg/mL glutamate, 100 U/mL penicillin G and 100 mg/mL streptomycin sulfate (complete media). Cells were plated into Falcon flat bottom, 96 well culture plates (200 µL/well) and cultured overnight at 37°C and 6% CO₂. Non-adherent cells were removed by washing with 200 µL/well of fresh medium. Wells containing adherent cells (~ 70% monocytes) were replenished with 100 µL of fresh medium.

Preparation of test compound stock solutions

Test compounds were dissolved in DMZ. Compound stock solutions were prepared to an initial concentration of 10 - 50 µM. Stocks were diluted initially to 20 — 200 µM in complete media. Nine two-fold serial dilutions of each compound were then prepared in complete medium.

Treatment of cells with test compounds and activation of TNF production with lipopolysaccharide

One hundred microliters of each test compound dilution were added to microtiter wells containing adherent monocytes and 100 µL complete medium. Monocytes were cultured with test compounds for 60 min at which time 25 µL of complete medium containing 30 ng/mL lipopolysaccharide from E. coli K532 were added to each well. Cells were cultured an additional 4 hrs. Culture supernatants were then removed and TNF presence in the supernatants was quantified using an ELISA.

TNFELISA

Flat bottom, 96 well Corning High Binding ELISA plates were coated overnight (4°C) with 150 µL/well of 3 µg/mL murine anti-human TNF-α MAb (R&D Systems #MAB210). Wells were then blocked for 1 h at room temperature with 200 µL/well of CaC₂-free ELISA buffer supplemented to contain 20 mg/mL BSA (standard ELISA buffer: 20 mM, 150 mM NaCl, 2 mM CaCl₂, 0.15 mM thimerosal, pH 7.4). Plates were washed and replenished with 100 µL of test supernatants (diluted 1:3) or standards. Standards consisted of eleven 1.5-fold serial dilutions from a stock of 1 ng/mL.
recombinant human TNF (R&D Systems). Plates were incubated at room temperature for 1 hr on orbital shaker (300 rpm), washed and replenished with 100 µL/well of 0.5 µg/mL goat anti-human TNF-α (R&D systems #AB-210-NA) biotinylated at a 4:1 ratio. Plates were incubated for 40 min, washed and replenished with 100 µL/well of alkaline phosphatase-conjugated streptavidin (Jackson ImmunoResearch #016-050-084) at 0.02 µg/mL. Plates were incubated 30 min, washed and replenished with 200 µL/well of 1 mg/mL of p-nitrophenyl phosphate. After 30 min, plates were read at 405 nm on a Vmax plate reader.

Data analysis

Standard curve data were fit to a second order polynomial and unknown TNF-α concentrations determined from their OD by solving this equation for concentration. TNF concentrations were then plotted vs. test compound concentration using a second order polynomial. This equation was then used to calculate the concentration of test compounds causing a 50% reduction in TNF production.

Compounds of the invention can also be shown to inhibit LPS-induced release of IL-1β, TL-6 and/or IL-8 from monocytes by measuring concentrations of IL-1β, TL-6 and/or IL-8 by methods well known to those skilled in the art. In a similar manner to the above described assay involving the LPS induced release of TNF-α from monocytes, compounds of this invention can also be shown to inhibit LPS induced release of IL-1β, IL-6 and/or IL-8 from monocytes by measuring concentrations of IL-1β, IL-6 and/or IL-8 by methods well known to those skilled in the art. Thus, the compounds of the invention may lower elevated levels of TNF-α, BL-I, DL-6, and IL-8 levels. Reducing elevated levels of these inflammatory cytokines to basal levels or below is favorable in controlling, slowing progression, and alleviating many disease states. All of the compounds are useful in the methods of treating disease states in which TNF-α, IL-1β, IL-6, and IL-8 play a role to the full extent of the definition of TNF-α-mediated diseases described herein.

Lipopolysaccharide-activated TtIF1 Cell TNF production assay

THP1 cells are resuspended in fresh THP1 media (RPMI 1640, 10% heat-inactivated FBS, IXPGS, IXNEAA, plus 30 µM βME) at a concentration of 1E6/mL. One hundred microliters of cells per well are plated in a polystyrene 96-well tissue
culture. One microgram per mL of bacterial LPS is prepared in THPl media and is transferred to the wells. Test compounds are dissolved in 100% DMSO and are serially diluted 3 fold in a polypropylene 96-well-microtiter plate (drug plate). HI control and LO control wells contain only DMSO. One microliter of test compound from the drug plate followed by 10 µL of LPS are transferred to the cell plate. The treated cells are induced to synthesize and secrete TNF-α at 37 °C for 3 hrs. Forty microliters of conditioned media are transferred to a 96-well polypropylene plate containing 110 µL of ECL buffer (50mM Tris-HCl pH 8.0, 100 mM NaCl, 0.05% Tween 20, 0.05% NaN 3 and 1%FBS) supplemented with 0.44nM MAB610 monoclonal Ab (R&D Systems), 0.34nM ruthenylated AF210NA polyclonal Ab (R&D Systems) and 44µg/mL sheep anti-mouse M280 Dynabeads (Dynal). After a 2 hr incubation at room temperature with shaking, the reaction is read on the ECL M8 Instrument (IGEN Inc.). A low voltage is applied to the ruthenylated TNF-α immune complexes, which in the presence of TPA (the active component in Origlo), results in a cyclical redox reaction generating light at 620nM. The amount of secreted TNF-α in the presence of compound compared with that in the presence of DMSO vehicle alone (HI control) is calculated using the formula: % control (POC) = (cpd - average LO)/(average HI - average LO)* 100. Data (consisting of POC and inhibitor concentration in µM) is fitted to a 4-parameter equation (y = A + ((B-A)/(1 + ((x/C)^D)))), where A is the minimum y (POC) value, B is the maximum y (POC), C is the x (cpd concentration) at the point of inflection and D is the slope factor) using a Levenburg-Marquardt non-linear regression algorithm.

Inhibition of LPS-Induced TNF-α production in mice
Male DBA/1LACJ mice are dosed with vehicle or test compounds in a vehicle (the vehicle consisting of 0.5% tragacanth in 0.03 N HCl) 30 min prior to lipopolysaccharide (2 mg/Kg, I.V.) injection. Ninety minutes after LPS injection, blood is collected and the serum is analyzed by ELISA for TNF-α levels.

Compounds of the invention may be shown to have anti-inflammatory properties in animal models of inflammation, including carageenan paw edema, collagen induced arthritis and adjuvant arthritis, such as the carageenan paw edema model (C. A. Winter et al Proc.: Soc. Exp. Biol. Med., 111:544 (1962); K. F. Swingle, in R. A. Scherrer and M. W. Whitehouse, Eds., Anti-inflammatory Agents, Chemistry and Pharmacology,

Of the compounds tested, the compounds of Examples 1-3 and 5-27 exhibited activities in the monocyte assay (LPS induced TNF release) with IC$_{50}$ values of 5 µM or less. Of the compounds tested, the compounds of Examples 2, 5, 8, 11-13, 15, 17-20 and 24-26 exhibited activities in the monocyte assay (LPS induced TNF release) with IC$_{10}$ values of 1.0 µM or less.

INDICATIONS

Accordingly, compounds of the invention are useful for, but not limited to, the prevention or treatment of inflammation, cancer and related diseases. The compounds of the invention have kinase modulatory activity in general, and kinase inhibitory activity in particular. In one embodiment of the invention, there is provided a method of treating a disorder related to a protein kinase enzyme in a subject, the method comprising administering to the subject an effective dosage amount of a compound of a compound of Formulas I or II. In another embodiment, the kinase enzyme is p38.

To this end, the compounds of the invention would be useful as anti-inflammatory agents in treating inflammation, or to minimize deleterious effects of p38.

Based on the ability to modulate p38 kinase impacting pro-inflammatory cytokine production, the compounds of the invention are also useful in treatment and therapy of p38 related and/or cytokine-mediated diseases. Particularly, these compounds can be used for the treatment of rheumatoid arthritis, Paget's disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HTV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection, or any combination thereof, in a subject.

An example of an inflammation related disorder is (a) synovial inflammation, for example, synovitis, including any of the particular forms of synovitis, in particular bursal synovitis and purulent synovitis, as far as it is not crystal-induced. Such synovial
inflammation may for example, be consequential to or associated with disease, e.g. arthritis, e.g. osteoarthritis, rhéumatoid arthritis or arthritis deformans. The present invention is further applicable to the systemic treatment of inflammation, e.g. inflammatory diseases or conditions, of the joints or locomotor apparatus in the region of the tendon insertions and tendon sheaths. Such inflammation may be, for example, consequential to or associated with disease or further (in a broader sense of the invention) with surgical intervention, including, in particular conditions such as insertion endopathy, myofasciale syndrome and tendomyosis. The present invention is further applicable to the treatment of inflammation, e.g. inflammatory disease or condition, of connective tissues including dermatomyositis and myositis.

The compounds of the invention can also be used as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy or macular degeneration.

The compounds of the invention are also useful in the treatment of diabetic conditions such as diabetic retinopathy and microangiopathy.

The present invention also provides methods for the treatment of protein tyrosine kinase-associated disorders, comprising the step of administering to a subject in need thereof at least one compound of the Formula I or of Formula II in an amount effective therefor. Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

Use of the compound(s) of the present invention in treating protein tyrosine kinase-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as:

The present invention also provides for a method for treating the aforementioned disorders such as atopic dermatitis by administration of a therapeutically effective amount of a compound of the present invention, which is an inhibitor of protein tyrosine kinase, to a patient, whether or not in need of such treatment.
In yet another embodiment, the compounds are useful for decreasing the level of,
or lowering plasma concentrations of, one or more of TNF-α, BL-1β, TL-6 and IL-8 in a
subject, generally a mammal and typically a human.

In yet another embodiment, the compounds are useful for treating a pain disorder,
in a subject, which is typically a human by administering to the subject an effective
dosage amount of a compound according to Formulas I or II.

In yet another embodiment, the compounds are useful for decreasing
prostaglandin production in a subject, which is typically a human, by administering to the
subject an effective dosage amount of a compound according to Formulas I or II.

Besides being useful for human treatment, these compounds are useful for
veterinary treatment of companion animals, exotic animals and farm animals, including
mammals, rodents, and the like. For example, animals including horses, dogs, and cats
may be treated with compounds provided by the invention.

FORMULATIONS AND METHOD OF USE

Treatment of diseases and disorders herein is intended to also include therapeutic
administration of a compound of the invention, or a pharmaceutical salt thereof, or a
pharmaceutical composition of either to a subject (i.e., an animal, preferably a mammal,
most preferably a human) which may be in need of preventative treatment, such as, for
eexample, for pain, inflammation and the like. Treatment also encompasses prophylactic
administration of a compound of the invention, or a pharmaceutical salt thereof, or a
pharmaceutical composition of either to a subject (i.e., an animal, preferably a mammal,
most preferably a human). Generally, the subject is initially diagnosed by a licensed
physician and/or authorized medical practitioner, and a regimen for prophylactic and/or
therapeutic treatment via administration of the compound(s) or compositions of the
invention is suggested, recommended or prescribed.

The amount of compound(s) which is/are administered and the dosage regimen
for treating TNF-α, IL-1, IL-6, and IL-8 mediated diseases, cancer, and/or hyperglycemia
with the compounds and/or compositions of this invention depends on a variety of
factors, including the age, weight, sex and medical condition of the subject, the type of
disease, the severity of the disease, the route and frequency of administration, and the
particular compound employed. Thus, the dosage regimen may vary widely, but can be
determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg,
advantageously between about 0.01 and about 50 mg/kg, more advantageously about 0.01 and about 30 mg/kg, even more advantageously between about 0.1 and about 10 mg/kg, and even more advantageously between about 0.25 and about 1 mg/kg body weight may be appropriate, and should be useful for all methods of use disclosed herein. The daily dose can be administered in one to four doses per day.

While it may be possible to administer a compound of the invention alone, in the methods described, the compound administered normally will be present as an active ingredient in a pharmaceutical composition. Thus, in another embodiment of the invention, there is provided a pharmaceutical composition comprising a compound of this invention in combination with a pharmaceutically acceptable carrier, which includes diluents, excipients, adjuvants and the like (collectively referred to herein as "carrier" materials) as described herein, and, if desired, other active ingredients. A pharmaceutical composition of the invention may comprise an effective amount of a compound of the invention or an effective dosage amount of a compound of the invention. An effective dosage amount of a compound of the invention includes an amount less than, equal to or greater than an effective amount of the compound; for example, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are required to administer an effective amount of the compound, or alternatively, a multi-dose pharmaceutical composition, such as powders, liquids and the like, in which an effective amount of the compound is administered by administering a portion of the composition.

The compound(s) of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, advantageously
from about 1 to 500 mg, and typically from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods and practices.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants or "excipients" appropriate to the indicated route of administration. If orally administered on a per dose basis, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, t alc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, to form the final formulation. For example, the active compound(s) and excipient(s) may be tableted or encapsulated by known and accepted methods for convenient administration. Examples of suitable formulations include, without limitation, pills, tablets, soft and hard-shell gel capsules, troches, orally-dissolvable forms and delayed or controlled-release formulations thereof.

Particularly, capsule or tablet formulations may contain one or more controlled-release agents, such as hydroxypropylmethyl cellulose, as a dispersion with the active compound(s).

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, ointments, creams, pastes, suspensions and the like) and drops suitable for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include
a compound, which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include DMSO and related analogs.

The compounds of this invention can also be administered by transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier, which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base, which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include, for example, Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl olate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.
Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol), cosolvent solubilization (ie. propylene glycol) or micellar solubilization (ie. Tween 80).

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 synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions
may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

Accordingly; in yet another embodiment of the present invention, there is provided a method of manufacturing a medicament, the method comprising combining an amount of a compound according to Formulas I or II with a pharmaceutically acceptable carrier to manufacture the medicament.

In yet another embodiment, there is provided a method of manufacturing a medicament for the treatment of inflammation, the method comprising combining an amount of a compound according to Formulas I or II with a pharmaceutically acceptable carrier to manufacture the medicament.

COMBINATIONS

While the compounds of the invention can be dosed or administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or in conjunction with other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered simultaneously or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of TNF-α, IL-1, IL-6, and EL-8 mediated diseases, cancer, and/or hyperglycemia.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formulas I and II may also be administered sequentially with known anti-inflammatory agents when a combination formulation is inappropriate. The invention is not limited in the sequence of
administration; compounds of the invention may be administered either prior to,
simultaneous with or after administration of the known anti-inflammatory agent.

The compounds of the invention may also be used in co-therapies with other therapeutic agents, including p38 inhibitors and CDK inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, NSAID’s, SOD mimics or $\alpha\beta$3 inhibitors.

The foregoing description is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds, compositions and methods. Variations and changes, which are obvious to one skilled in the art, are intended to be within the scope and nature of the invention, as defined in the appended claims. From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. All patents and other publications recited herein are hereby incorporated by reference in their entireties.
What is claimed is:
1. A compound of Formula I:

```
  A1               A2
  /\                /\ 
  |    \            |    \ 
  H    C          N   C
  \    /          /    \ 
   \  /          /    / 
    \\         /     \ 
     S   F     R1   R2
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or stereoisomer, tautomer, solvate, pharmaceutically acceptable salt, derivative or prodrug thereof, wherein

one of A\(^1\) and A\(^2\) is CR\(^1\) and the other of A\(^1\) and A\(^2\) is N;

B is a direct bond, \((-\text{CR}^4 \text{R}^5)\)_m, \(-\text{C} (=\text{O})\)_, \(-\text{N}(\text{R}^6)_2\)_, -O-, or \(-\text{S}(=\text{O})\)_m, wherein m is

0, 1 or 2;

R\(^1\) is \((-\text{CR}^7 \text{R}^8\)_nX or \(-\text{CR}^7 \text{R}^8\)_nX, wherein n is 0, 1 or 2 and X is absent, NR\(^7\)R\(^8\), NR\(^7\)R\(^8\), OR\(^7\), OR\(^8\), OR\(^8\), C(O)R\(^7\), OC(O)R\(^7\), COOR\(^7\), C(O)R\(^8\), OC(O)R\(^8\), COOR\(^8\), C(O)NR\(^7\)R\(^8\), C(S)NR\(^7\)R\(^8\), NR\(^7\)C(O)R\(^8\), NR\(^7\)C(O)NR\(^7\)R\(^8\), NR\(^7\)C(S)NR\(^7\)R\(^8\),

NR\(^7\)(COOR\(^7\)), OC(O)NR\(^7\)R\(^8\), C(O)NR\(^7\)R\(^8\), C(S)NR\(^7\)R\(^8\), NR\(^7\)C(O)R\(^8\), NR\(^7\)C(S)R\(^8\),

NR\(^7\)C(O)NR\(^7\)R\(^8\), NR\(^7\)C(S)NR\(^7\)R\(^8\), NR\(^7\)(COOR\(^8\)), OC(O)NR\(^7\)R\(^8\), S(O)\(_2\)R\(^7\), S(O)\(_2\)NR\(^7\)R\(^8\),

NR\(^7\)S(O)\(_2\)NR\(^7\)R\(^8\), NR\(^7\)S(O)\(_2\)NR\(^7\)R\(^8\), NR\(^7\)S(O)\(_2\)NR\(^7\)R\(^8\), NR\(^7\)S(O)\(_2\)R\(^8\),

or a 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic. said heteroatoms selected from O, N, or S, wherein said ring system is optionally substituted independently with one or more substituents of R\(^7\), R\(^8\) or R\(^9\);

R\(^2\) is H, halo, haloalkyl, NO\(_2\), CN, OR\(^7\), OR\(^8\), OR\(^8\), C(O)R\(^7\), OC(O)R\(^7\), C(O)NR\(^7\)R\(^8\), NR\(^7\)C(O)R\(^7\), NR\(^7\)C(O)NR\(^7\)R\(^8\), NR\(^7\)C(O)NR\(^7\)R\(^8\),

OC(O)NR\(^7\)R\(^8\), S(O)\(_2\)R\(^7\), S(O)\(_2\)NR\(^7\)R\(^8\), S(O)\(_2\)NR\(^7\)R\(^8\), NR\(^7\)S(O)\(_2\)R\(^7\), NR\(^7\)S(O)\(_2\)R\(^8\), C\(_{10}\)-alkyl,

c_{1o}\)-alkenyl, c\(_{10}\)-alkynyl, C\(_{2-10}\)Cycloalkyl or Gnom-cycloalkenyl, each of the Ci.o-alkyl, C\(_{2-10}\)-alkenyl, C\(_{2-10}\)-alkynyl, C\(_{3-10}\)-cycloalkyl and Q.io-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R\(^8\) or R\(^9\);
R³ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S,

wherein said ring system is substituted independently with one or more substituents of R¹⁰, R¹², R¹⁶, N⁰R¹⁰, N⁰R¹¹, OR¹⁰, SR¹⁰, OR¹¹, SR¹¹, C(O)R¹⁰, C(S)R¹⁰, C(NCN)R¹⁰, C(O)R¹¹, C(S)R¹¹, C(NCN)R¹¹, C(O)C(O)R¹⁰, OC(O)R¹⁰, COOR¹⁰, C(OSR¹⁰, C(O)C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(OSR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, OC(O)NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹⁰, NR¹⁰C(S)R¹¹,

NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹⁰, NR¹⁰C(S)NR¹⁰R¹¹,

NR¹⁰(COOR¹⁰), NR¹⁰(COOR¹¹), NR¹⁰(CO(CO)R), NR¹⁰C(O)(C(O)R), NR¹⁰C(O)(C(O)R),

NR¹⁰(C(O)C(O)NR¹⁰R¹⁰, S(O)₂R¹⁰, S(O)₂R¹¹, S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹,

NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰, OrNR¹⁰S(O)₂R¹¹;

R⁴ is H, halo, haloalkyl, NO₂, CN, SR², OR², C(O)R², COOR², OC(O)R², NR²R²,

NR³R⁸, C(O)NR³R⁸, C(O)NR³R⁸, NR³C(O)R³, NR³C(O)R³, NR³C(O)NR³R³, S(O)NR³R³,

S(O)₂NR³R³, NR²S(O)₂NR³R³, NR²S(O)₂NR³R³, C₄–₉–alkyl, C₂–₉–alkynyl, C₃–io–cycloalkyl or C₄–io–cycloalkenyl, each of the Cuio-alkyl, C₂–io–alkynyl, Cs–io–cycloalkenyl and Gno–cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R⁵ or R⁶;


OC(O)NR\textsubscript{8}R\textsubscript{9}, OC(O)NR\textsubscript{9}R\textsubscript{9}, S(O)\textsubscript{2}NR\textsubscript{8}R\textsubscript{9}, S(O)\textsubscript{2}R\textsubscript{9}, S(O)\textsubscript{2}NR\textsubscript{9}R\textsubscript{9},
NR\textsubscript{8}S(O)\textsubscript{2}NR\textsubscript{8}R\textsubscript{9}, NR\textsubscript{8}S(O)\textsubscript{2}NR\textsubscript{9}R\textsubscript{9}, NR\textsubscript{9}S(O)\textsubscript{2}R\textsubscript{8}, NR\textsubscript{8}S(O)\textsubscript{2}R\textsubscript{9}, R\textsubscript{8} or R\textsubscript{9};

R\textsubscript{8} is a partially or fully saturated or unsaturated 5-8 membered monocyclic; 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of R\textsubscript{9}, oxo, NR\textsubscript{8}R\textsubscript{9}, OR\textsubscript{9}, SR\textsubscript{9}, C(O)R\textsubscript{9}, COOR\textsubscript{9}, C(O)NR\textsubscript{8}R\textsubscript{9}, NR\textsubscript{8}C(O)R\textsubscript{9}, NR\textsubscript{9}C(O)NR\textsubscript{8}R\textsubscript{9}, OC(O)NR\textsubscript{8}R\textsubscript{9}, S(O)\textsubscript{2}R\textsubscript{8}, S(O)\textsubscript{2}NR\textsubscript{8}R\textsubscript{9}, NR\textsubscript{8}S(O)\textsubscript{2}R\textsubscript{9}, or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R\textsubscript{9};

alternatively, R\textsubscript{7} and R\textsubscript{8} taken together form a saturated or partially or fully unsaturated 5-6 membered monocyclic or 7-10 membered bicyclic ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R\textsubscript{9};

R\textsubscript{9} is H, halo, haloalkyl, CN, OH, NO\textsubscript{2}, NH\textsubscript{2}, acetyl, oxo, Ci.io-alkyl, C\textsubscript{2}-\textsubscript{6} alkenyl, C\textsubscript{2}-\textsubscript{io}-alkynyl, Cs-io-cycloalkyl, C\textsubscript{4}-\textsubscript{io-cycloalkenyl}, Ci.io-alkylamino-, C\textsubscript{1}-io-dialkylamino-, Ci.io-alkoxyl, Ci.io-thioalkoxyl or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, wherein each of the C\textsubscript{i}-io-alkyl, C\textsubscript{2}-io-alkenyl, C\textsubscript{2}-io-alkynyl, Cs-io-cycloalkyl, Gno-cycloalkenyl, Ci.io-alkylamino-, C\textsubscript{1}-io-dialkylamino-, Ci.io-alkoxyl, Ci.io-thioalkoxyl and each ring of said ring system is optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO\textsubscript{2}, NH\textsubscript{2}, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tertbutyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R\textsubscript{10} is H, halo, haloaalkyl, CN, NO\textsubscript{2}, C\textsubscript{1}-\textsubscript{io-alkyl}, C\textsubscript{2}-\textsubscript{io-alkenyl}, C\textsubscript{2}-\textsubscript{io-alkynyl}, C\textsubscript{3}-io-cycloalkyl or C\textsubscript{4}-io-cycloalkenyl, each of the Ci-io-alkyl, C\textsubscript{2}-io-alkenyl, C\textsubscript{2}-io-alkynyl, C\textsubscript{3}-io-cycloalkyl and C\textsubscript{4}-io-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R\textsubscript{11}, R\textsubscript{12} or R\textsubscript{16}, NR\textsubscript{11}R\textsubscript{12}, NR\textsubscript{12}R\textsubscript{12}, OR\textsubscript{11}, SR\textsubscript{11}, OR\textsubscript{12}, SR\textsubscript{12}, C(O)R\textsubscript{11}, OC(O)R\textsubscript{11}, COOR\textsubscript{11}, C(O)R\textsubscript{12},
R\textsuperscript{11} is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12
membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and
wherein each ring of said ring system is optionally substituted independently with 1-5
substituents of R\textsuperscript{12}, R\textsuperscript{13}, R\textsuperscript{14} or R\textsuperscript{16};

alternatively, R\textsuperscript{10} and R\textsuperscript{11} taken together form a partially or fully saturated or
unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms
selected from O, N, or S, and the ring optionally substituted independently with 1-5
substituents of R\textsuperscript{12}, R\textsuperscript{13}, R\textsuperscript{14} or R\textsuperscript{16};

R\textsuperscript{12} is H, C\textsubscript{1-3}-alkyl, C\textsubscript{2-10}-alkenyl, C\textsubscript{2-10}-alkynyl, C\textsubscript{2-10}-
cycloalkenyl, Ci-carbalkylmino-, Ci-carbalkyloxy or Ci-thioalkyl, each of
which is optionally substituted independently with 1-5 substituents of R\textsuperscript{13}, R\textsuperscript{14}, R\textsuperscript{15} or
R\textsuperscript{16};

R\textsuperscript{13} is NR\textsuperscript{14}R\textsuperscript{15}, NR\textsuperscript{15}R\textsuperscript{16}, OR\textsuperscript{14}; SR\textsuperscript{14}, OR\textsuperscript{15};
SR\textsuperscript{15}, C(O)R\textsuperscript{14}, OC(O)R\textsuperscript{14}, COOR\textsuperscript{14},

C(O)R\textsuperscript{15}, OC(O)R\textsuperscript{15}, COOR\textsuperscript{15}, C(O)NR\textsuperscript{14}R\textsuperscript{15}, C(O)NR\textsuperscript{15}R\textsuperscript{16},
NR\textsuperscript{14}C(O)R\textsuperscript{15}, NR\textsuperscript{15}C(O)R\textsuperscript{16}, NR\textsuperscript{14}C(O)NR\textsuperscript{15}R\textsuperscript{16},
NR\textsuperscript{15}C(O)NR\textsuperscript{15}R\textsuperscript{16}, NR\textsuperscript{14}(COOR\textsuperscript{15}),
NR\textsuperscript{15}(COOR\textsuperscript{15}), OC(O)NR\textsuperscript{14}R\textsuperscript{15}, OC(O)NR\textsuperscript{15}R\textsuperscript{16},
S(O)\textsubscript{2}R\textsuperscript{14}, S(O)\textsubscript{2}R\textsuperscript{15}, S(O)\textsubscript{2}NR\textsuperscript{14}R\textsuperscript{15},
S(O)\textsubscript{2}NR\textsuperscript{15}R\textsuperscript{16}, S(O)\textsubscript{2}NR\textsubscript{14}R\textsubscript{15},
NR\textsuperscript{14}S(O)\textsubscript{2}R\textsuperscript{14}, OR\textsuperscript{14}S(O)\textsubscript{2}R\textsuperscript{15};

R\textsuperscript{14} is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12
membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and
wherein each ring of said ring system is optionally substituted independently with 1-5
substituents of R\textsuperscript{15} or R\textsuperscript{16};

R\textsuperscript{15} is H or d-alkyl, C\textsubscript{2-10}-alkynyl, C\textsubscript{2-10}-alkynyl, Cs-carbalkylmino, C\textsubscript{4-10}-
cycloalkenyl, Ci-carbalkylmino-, Ci-carbalkyloxy or Ci-thioalkyl, each of
which is optionally substituted independently with 1-5 substituents of R\textsuperscript{16}; and

R\textsuperscript{16} is H\textsubscript{3}, halo, haloalkyl, CN, OH, NO\textsubscript{2}, NH\textsubscript{2}, OH, methyl, methoxy, ethyl,
ethoxyl, propyl, propoxyl, isopropyl, butyl, isobutyl, tert-butyl, methyaminio,
dimethylaminob, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, cyclopropyl; cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

2. The compound of Claim 1 wherein A¹ is CR¹ and A² is N.

3. The compound of Claim 1 wherein A² is CR² and A¹ is N.

4. The compound of Claim 1 wherein B is -C(=O)-, -N(R⁵)-, -O-, or -S(O)m-, wherein m is 0, 1 or 2.

5. The compound of Claim 1 wherein B is a direct bond.

6. The compound of Claim 1 wherein R³ is phenyl, naphthyl, pyrindyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, benzisoxazolyl, benzopyrazolyl, benzo(thiazolyl or benzimidazolyl, each of which is optionally substituted as defined in claim 1.

7. The compound of Claim 1 wherein at least one substituent on R³ is NR¹⁰R¹⁰, NR¹⁰R¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹¹, NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹¹, S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹.

8. The compound of Claim 1 wherein B is a direct bond; -CR¹⁰R¹⁰, wherein n is 1 or 2, NR⁷R⁷, NR⁷R⁸, OR⁷, SR⁷, OR⁸, SR⁸, C(O)R⁷, C(O)R⁸, C(O)NR⁷R⁷, C(S)NR⁷R⁷, NR⁷C(O)R⁷, NR⁷C(S)R⁷, NR⁷C(O)NR⁷R⁷.
NR^7C(S)NR^7R^7, NR^7(COOR^7), C(O)NR^7R^7, C(S)NR^7R^7, NR^7C(O)R^7, NR^7C(S)R^7, NR^7C(O)NR^7R^7, NR^7C(S)NR^7R^7, C(O)NR^7R^7, S(O)_2NR^7R^7, NR^7S(O)_2NR^7R^7, NR^7S(O)_2R^7, S(O)_2NR^7R^8, NR^7S(O)_2NR^7R^8, NR^7S(O)_2R^8 or a ring system selected from phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, benzoxazolyl, benzopyrazolyl, benzothiazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, piperaizinyl, pyrany1, dioxazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, wherein said ring system is optionally substituted independently with 1-3 substituents of R^7, R^8, R^9, oxo, OR^7, SR^7, C(O)R^7, NR^7R^7, NR^7R^8, OR^8, SR^8, C(O)R^8, COOR^7, OC(O)R^7, COOR^8, OC(O)R^8, C(O)NR^7R^7, C(O)NR^7R^8, NR^7C(O)R^7, NR^7C(O)NR^7R^7, NR^7C(O)NR^7R^8, S(O)_2NR^7R^7, S(O)_2NR^7R^8, NR^7S(O)_2NR^7R^7 or NR^7S(O)_2NR^7R^8.

R^2 is H or Ci.io-alkyl;

R^3 is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzo furanyl, dihydrobenzofuranyl, benzothiophenyl, benzoxazolyl, benzopyrazolyl, benzothiazolyl or benzimidazolyl, said R^3 substituted with one substituent of NR^9R^10, NR^10R^11, C(O)NR^9R^10, C(S)NR^9R^10, C(O)NR^10R^11, C(S)NR^10R^11, NR^9C(O)R^10, NR^9C(S)R^10, NR^10C(O)R^11, NR^10C(S)R^11, NR^10C(O)NR^9R^10, NR^10C(O)NR^10R^11, NR^10C(S)NR^9R^10, NR^10C(S)NR^10R^11, S(O)_2NR^9R^10, S(O)_2NR^10R^11, NR^10S(O)_2NR^9R^10 or NR^10S(O)_2NR^10R^11 and 0-3 substituents of R^16;

R^4 is Hor C_10H_16-alkyl;

R^5 is H or Ci-io-alkyl;

R^6 is H or C_10H_16-alkyl;

R^7 is H, C_10H_16-alkyl, C_2H_5-alkenyl, C_2H_5-alkynyl or C_3H_7-0-cycloalkyl, each of the Ci.

10-alkyl, C_2H_5-alkenyl and C_2H_5-alkynyl and C_3H_7-0-cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of NR^8R^9, NR^9R^9, OR^8, SR^8, OR^8, SR^8, C(O)R^8, OC(O)R^8, COOR^8, C(O)R^9, COOR^9, C(O)NR^8R^8, C(O)NR^9R^9, NR^9C(O)R^8, NR^9C(O)R^9, NR^9C(O)NR^8R^9, NR^9C(O)NR^9R^9, NR^9(OCOOR^8), NR^9(OCOOR^9), OC(O)NR^8R^9, OC(O)NR^9R^9, S(O)_2R^8.
S(O)₂NR₈R₉, S(O)₂R₉S(O)₂R₉, NR₉S(O)₂NR₉R₉, NR₉S(O)₂NR₉R₉, NR₉S(O)₂R₈, NR₉S(O)₂R₉, R₈ or R₉;

R₈ is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, moβ holınyl, piperidinyl, piperezinyl, pyranyl, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of which is optionally substituted independently with 1,3-sıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtıtı티
C(O)R_{12}, OC(O)R_{12}, COOR_{12}, C(O)NR_{12}R_{11}, NR_{12}C(O)R_{11}, C(O)NR_{12}R_{12}, NR_{12}C(O)R_{12},
NR_{12}C(O)NR_{12}R_{11}, NR_{12}C(O)NR_{12}R_{12}, NR_{12}(COOR_{11}), OC(O)NR_{12}R_{11},
OC(O)NR_{12}R_{12}, CO(O)NR_{11}R_{12}, OC(O)NR_{11}R_{12}, CO(O)NR_{11}R_{12}, CO(O)NR_{11}R_{12},
S(O)_{2}NR_{12}R_{11}, S(O)_{2}NR_{12}R_{12}, S(O)_{2}NR_{12}R_{11}, S(O)_{2}NR_{12}R_{12}, NR_{12}S(O)_{2}NR_{11}R_{12},
NR_{12}S(O)_{2}NR_{12}R_{11}, NR_{12}S(O)_{2}R_{12}, NR_{12}S(O)_{2}R_{12}, NR_{12}S(O)_{2}R_{12}, NR_{12}S(O)_{2}R_{12};

R_{11} is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinoliny1, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, oxazolyl, isoazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoazolinyl, thiazolinyl, pyrazolyl, morpholony1, piperidinyl, pyranyl, dioxazinyl, cyclopenty1, cyclobuty1, cyclopentyl, cyclohexyl and cyclohepty1, each of which is optionally substituted independently with 1-3 substituents of R_{12}, R_{13}, R_{14} or R_{15};

alternatively, R_{10} and R_{11} taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R_{12}, R_{13}, R_{14} or R_{15};

R_{12} is H, Ci-i0-alkeny1, C_{2}i-i0-alkeny1, C_{3}i-i0-cycloalkyl, Q-to-cycloalkeny1, Ci-i0-alkylamino-, Ci-i0-dialkylamino-, C_{1}i-i0-alkoxy1 or Ci-i0-thioalky1, each of which is optionally substituted independently with 1-3 substituents of R_{13}, R_{14}, R_{15} or R_{16};

R_{13} is NR_{14}R_{15}, NR_{16}R_{15}, OR_{14}; SR_{14}, OR_{15}; SR_{15}, C(O)R_{14}, OC(O)R_{14}, COOR_{14},
C(O)R_{15}, OC(O)R_{15}, COOR_{15}, C(O)NR_{15}R_{14}, C(O)NR_{15}R_{14}, NR_{14}C(O)R_{15},
NR_{14}C(O)R_{15}, NR_{15}C(O)R_{14}, NR_{15}C(O)R_{14}, NR_{15}C(O)NR_{15}R_{15}, NR_{15}C(O)NR_{15}R_{15},
NR_{15}(COOR_{15}), NR_{15}(COOR_{15}), OC(O)NR_{14}R_{15}, OC(O)NR_{14}R_{15}, S(O)_{2}R_{14}, S(O)_{2}R_{14}, S(O)_{2}NR_{14}R_{15},
S(O)_{2}NR_{14}R_{15}, NR_{15}S(O)_{2}NR_{14}R_{15}, NR_{15}S(O)_{2}NR_{15}R_{15}, NR_{15}S(O)_{2}R_{14} OR_{15}S(O)_{2}R_{15};

R_{14} is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinoliny1, isoquinoliny1, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, oxazolyl, isoazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoazolinyl, thiazolinyl, pyrazolyl, morpholiny1, piperidinyl, pyranyl, dioxazinyl, cyclopenty1, cyclobuty1, cyclopentyl, cyclohexyl and cyclohepty1, each of which is optionally substituted independently with 1-3 substituents of R_{15} or R_{16};

R_{15} is H or. Ci-i0-alkyl, C_{2}i-i0-alkeny1, C_{2}i-i0-alkeny1, C_{3}i-i0-cycloalkyl, C_{4}i-i0-
cycloalkeny1, Ci-i0-alkylamino-, C_{1}i0-dialkylamino-, Ci-i0-alkoxy1 or Ci-i0-thioalkoxy1, each of which is optionally substituted independently with 1-3 substituents of R_{16}; and
R is H, halo, haloalkyl, CN, OH, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxy, propyl, p-tert-butyl, isopropyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

9. The compound of Claim 8 wherein

R is NR²R⁷, NR²R⁸, C(O)R⁷, C(O)R⁸, C(O)NR²R⁷, C(O)NR²R⁸, NR²C(O)R⁷, NR²C(O)R⁸, S(O)₂NR²R⁷, S(O)₂NR²R⁸, NR²S(O)₂R⁷, NR²S(O)₂R⁸ or a ring selected from phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, pyranylis, dioxazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, wherein the ring is optionally substituted independently with 1-3 substituents of R⁷, R⁸, oxo, OR⁷, SR⁷, C(O)R⁷, NR²R⁷, NR²R⁸, OR⁸, SR⁸, C(O)R⁸, COOR⁷, OC(O)R⁷, COOR⁸, OC(O)R⁸, C(O)NR²R⁷, C(O)NR²R⁸, NR²C(O)R⁷, NR²C(O)R⁸, NR²C(O)NR²R⁷, NR²C(O)NR²R⁸, S(O)₂NR²R⁷, S(O)₂NR²R⁸, NR²S(O)₂NR²R⁷ or NR²S(O)₂NR²R⁸;

R² is H;
R³ is
wherein
one of A₆ and A₇ is CR₃a and the other of A₆ and A₇ is CR₃b or N;
each of A₅, A₈, A₉, A₁₀ and A₁₁ is, independently, CR₃b or N;
X² is CR₃a;
each of X¹, X³ and X⁴ is, independently, CR₃b or N;
Y¹ is CR₃bR₃c, NR₃c, O or S;
Y² is CR₃bR₃b or NR₃a; and
Z is CH or N;
R₃a is NR₁₀R₁₀, NR₁₀R₁₁, C(O)NR₁₀R₁₀, C(O)NR₁₀R₁¹, NR₁₀C(O)R₁₀,
NR₁₀C(O)R₁¹, NR₁₀C(O)NR₁₀R₁⁰, NR₁₀C(O)NR₁₀R₁¹, S(O)₂NR₁₀R₁₀,
S(O)₂NR₁₀R₁¹, NR₁₀S(O)₂NR₁⁰, NR₁₀S(O)₂R₁⁰ Or NR₁₀S(O)₂R₁¹;
- 94 -

R^3b is H, halo, haloalkyl, CN, NO_2, NH_2, C_{M-alkyl}, C_{2-io-alkeny}, C_{2-0-alkoxy} or C_3-cycloalkyl; and

R^3b is H, CN or C_{-10}-alkyl;

R^4 is H;

R^5 is H;

R^6 is H;

R^7 is H, C_{i-o-alkyl}, C_{2-i-0}-alkeny or C_{3-al-Calkyl}, each of the C_{i-o-alkyl}, C_{2-10}-alkeny and C_{e-cycloalkyl} optionally substituted with 1-3 substituents OiNR^8 R^9, NR^8 R^9, OR^8, SR^8, OR^9, SR^9, C(O)R^8, OC(O)R^8, COOR^8, C(O)R^9, OC(O)R^9, COOR^9, or R^9;

C(O)NR^8 R^9, C(O)NR^9 R^9, NR^9 C(O)R^8, NR^9 C(O)R^9, NR^9 C(O)NR^8 R^9, NR^9 C(O)NR^9 R^9, NR^9 (COOR^8), NR^9 (COOR^9), OC(O)NR^8 R^9, OC(O)NR^9 R^9, S(O)_2 R^8, S(O)_2 NR^8 R^9, S(O)_2 R^9, S(O)_2 NR^9 R^9, S(O)_2 NR^9 R^9, NR^9 S(O)NR^9 R^9, NR^9 S(O)_2 NR^9 R^9, NR^9 S(O)_2 NR^9 R^9, or R^9;

R^8 is phenyl, naphthyl, pyridyl, pyrimidyl, quinolinyl, isoquinolinyl, quinazolinyl, thiophene pyr, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzo(b)thiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolydiny, oxazoliny, isoxazoliny, thiazoliny, pyrazoliny, morpholinyl, piperidiny, piperaziny, pyranyl, dioxaziny, cyclopropyl, cyclobutyl, cyclo pentyl, cyclohexyl and cycloheptyl, each of which is optionally substituted independently with 1-3 substituents of R^9;

20 alternatively, R^7 and R^8 taken together form a saturated or partially or fully unsaturated 5-6 membered monocyclic or 7-10 membered bicyclic ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R^9;

25 R^9 is H, halo, haloalkyl, CN, OH, NO_2, NH_2, acetyl, C_{-10}-alkyl, C_{2-i-0}-alkeny, C_{-10}-alkynyl, C_{-i-o-cycloalkyl}, C_{-i-o-cycloalkenyl}, Cl-i-o-alkylamino-, Cl-i-o-dialkylamino-, Cl_i-o-alkoxyl, Cl_i-thioalkoxyl or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O,
N, or S, wherein each of the C$_{1-10}$-alkyl, C$_{2-10}$-alkenyl, C$_{2-10}$-alkynyl, C$_{5-10}$-cycloalkyl, C$_{5-10}$-cycloalkenyl, C$_{5-10}$-cycloalkynyl, C$_{5-10}$-alkylamino-, C$_{5-10}$-dialkylamino-, C$_{5-10}$-alkoxy, C$_{5-10}$-thioalkoxy and ring of said ring system is optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO$_2$, NH$_2$, OH, oxo, methyl, methoxy, ethyl, ethoxy, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, disopropylamine, benzyl or phenyl;

R$^{10}$ is H, halo, haloalkyl, CN, NO$_2$, C$_{4-10}$-alkyl, C$_{2-10}$-alkenyl or C$_{3-10}$-cycloalkyl, each of the C$_{4-10}$-alkyl, C$_{2-10}$-alkenyl, and C$_{5-10}$-cycloalkyl optionally substituted with 1-3 substituents of R$^{11}$, R$^{12}$, R$^{16}$, NR$^{11}$R$^{12}$, NR$^{12}$R$^{13}$, OR$^{11}$, OR$^{12}$, SR$^{11}$, SR$^{12}$, C(O)R$^{11}$, OC(O)R$^{11}$, COOR$^{11}$, C(O)R$^{12}$, OC(O)R$^{12}$, COOR$^{12}$, C(O)NR$^{11}$R$^{12}$, NR$^{12}$C(O)R$^{11}$, C(O)NR$^{12}$R$^{13}$, NR$^{13}$C(O)NR$^{11}$R$^{12}$, NR$^{12}$C(O)NR$^{13}$R$^{12}$, NR$^{12}$C(O)NR$^{12}$R$^{13}$, COOR$^{12}$, COOR$^{13}$, OC(O)NR$^{11}$R$^{12}$, OC(O)NR$^{13}$R$^{12}$, S(O)$_2$R$^{11}$, S(O)$_2$R$^{12}$, S(O)$_2$NR$^{11}$R$^{12}$, S(O)$_2$NR$^{13}$R$^{12}$, NR$^{12}$S(O)$_2$NR$^{11}$R$^{12}$, NR$^{12}$S(O)$_2$NR$^{13}$R$^{12}$, NR$^{12}$S(O)$_2$S(O)$_2$R$^{11}$, NR$^{12}$S(O)$_2$S(O)$_2$R$^{12}$, NR$^{12}$S(O)$_2$R$^{13}$R$^{12}$; and

R$^{11}$ is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinoliny1, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrroldinyl, oxazolinyl, isoazolinyl, thiazolinyl, pyrazolyl, morpholinyl, piperidinyl, piperazinyl, pyranyl, dioxazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of which is optionally substituted independently with 1-3 substituents of R$^{12}$, R$^{13}$ or R$^{16}$.

10. The compound of Claim 9 wherein

R$^3$ is
wherein
each of A5, A6, and A7 is, independently, CR3b or N;
A8 is CR3c or N; and
A9 is CR3d or N;
Y1 is O or S;
Y2 is NR3a;
R3b is NR10R10, NR10R11, C(O)NR10R10, C(O)NR10R11, NR10C(O)R10,
NR10C(O)R11, NR10C(O)NR10R10, NR10C(O)NR10R11, S(O)2NR10R10,
S(O)2NR10R11, NR10S(O)2NR10R11, NR10S(O)2R10 OrNR10S(O)2R11;
R3c is H, halo, haloalkyl, CN, NO2, NH2, C1-10-alkyl, C2,io-alkenyl, C2,io-alkynyl or Ca-io-cycloalkyl;
R3d is H, halo, haloalkyl, CN, NO2, NH2, C1-10-alkyl, C2,io-alkenyl, C2,io-alkynyl or C3,io-cycloalkyl;
alternatively, R3c and R3d taken together with the atoms to which they are
attached form a phenyl or tetrahydrofuranyl ring system, optionally substituted
with 1-3 substituents of halo, haloalkyl, CN, NO2, NH2, C1-10-alkyl, C2,io-alkenyl,
C2,io-alkynyl or Ca-io-cycloalkyl;
11. The compound of Claim 9 wherein wherein A₁ is CR₁ and A₂ is N.

12. The compound of Claim 9 wherein wherein A₁ is N and A₂ is CR₁.

13. A compound of Formula I!

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{N} \\
\text{A} \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\text{R}_5 \\
\text{R}_6
\end{array}
\]

or stereoisomer, tautomer, solvate, pharmaceutically acceptable salt, derivative or prodrug thereof, wherein

A is CR³ or N;

R² is H, halo, haloalkyl, NO₂, CN, OR⁷, SR⁷, NR⁷R²⁷, C(O)R⁷, COOR⁷,

C(O)NR⁷R²⁷, C(O)NR⁷R²⁷, NR⁷R²⁷C(O)R⁷, NR⁷C(O)R⁷R²⁷, NR⁷C(O)NR⁷R²⁷R²⁷,

NR⁷C(O)NR⁷R²⁷, OC(O)NR⁷R²⁷, S(O)₂R²⁷, S(O)₂NR⁷R²⁷, S(O)₂SR⁷R²⁷,

NR⁷S(O)₂R²⁷, NR⁷S(O)₂R²⁷, C₅₋₈-alkyl, C₂₋₄-alkenyl, C₃₋₁₀-cycloalkyl or
C₈₋₁₀-cycloalkenyl, each of the C₁₋₄-alkyl, C₂₋₄-alkenyl, C₃₋₁₀-Cycloalkyl

and Q-to-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S
and optionally substituted with one or more substituents of R⁷ or R⁹;

R³ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12
membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S,
wherein said ring system is substituted independently with one or more substituents of
R¹⁰, R¹¹, R¹⁶, NR¹⁰R¹⁰, NR¹⁰R¹¹, OR¹⁰, SR¹⁰, OR¹¹, SR¹¹, C(O)R¹⁰, C(S)R¹⁰, C(CN)R¹⁰,
C(O)R¹¹, C(S)R¹¹, C(NCN)R¹¹, C(O)C(O)R¹⁰, OC(O)R¹⁰, COOR¹⁰, C(O)SR¹⁰,
C(O)C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)SR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹,
C(S)NR¹⁰R¹¹, OC(O)NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹⁰, NR¹⁰C(S)R¹¹,
NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹⁰, NR¹⁰C(S)NR¹⁰R¹¹,
NR¹⁰(COOR¹⁰), NR¹⁰(COOR¹⁰), NR¹⁰(C(O)C(O)R¹⁰, NR¹⁰C(O)C(O)R¹¹,
NR¹⁰C(O)C(O)NR¹⁰R¹¹, S(O)₂R¹⁰, S(O)₂R¹¹, S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹,
NR¹⁰S(O)₂R¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or NR¹⁰S(O)₂R¹¹, provided that at least one substituent
on R³ is NR¹⁰R¹, NR¹⁰R¹¹, C(O)R¹⁰, OC(O)R¹⁰, COOR¹⁰, C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(OSR¹⁰, C(OSR¹¹, C(ONR¹⁰R¹⁰, C(ONR¹⁰R¹¹, C(ONSIR¹⁰R¹⁰, C(ONSIR¹⁰R¹¹, C(ONSIR¹⁰R¹³, NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹¹, NR¹⁰C(O)R¹², NR¹⁰C(S)R¹², NR¹⁰C(O)R¹³, NR¹⁰C(S)R¹³, NR¹⁰(OCOR¹⁰),
5 NR¹⁰(COOR¹¹), OC(O)NR¹⁰R¹¹, S(O)₂R¹⁰, S(O)₂R¹¹, S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or NR¹⁰S(O)₂R¹¹;
R⁴ is H or is absent;
R⁵ is H, halo, haloalkyl, NO₂, CN, SR⁷a, OR⁷a, C(O)R⁷a, COOR⁷a, OC(O)R⁷a, NR⁷aR⁷a, NR⁷aR⁷b, C(O)NR⁷aR⁷b, C(O)NR⁷aR⁷c, NR⁷aC(O)R⁷a, NR⁷aC(O)R⁸,
10 NR⁷aC(O)NR⁷bR⁸, S(O)NR⁷bR⁸γb, S(O)₂NR⁷bR⁸γb, NR⁷bS(O)NR⁷bR⁷b, NR⁷bS(O)NR⁷bR⁷b, Cγb₁₀-alkyl, C₂γb₁₀-alkenyl, G₂γb₁₀-alkenyl, C₅₆γb-o-cycloalkyl or Gno-cycloalkenyl, each of the C₂γb₁₀-alkenyl, C₂γb₁₀-alkenyl, C₅₆γb-o-cycloalkyl and C₄γb₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R⁸ or R⁹;
R⁶ is H, CN or Cno-alkyl, C₂γb₁₀-alkenyl, C₂γb₁₀-alkenyl, Ca-i-o-cycloalkyl or C₄γb₁₀-cycloalkenyl, each of the Ca-i-o-alkenyl, C₂γb₁₀-alkenyl, C₂γb₁₀-alkenyl, C₃γb-o-cycloalkyl and C₄γb₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R⁸ or R⁹;
alternatively, R⁵ and R⁶ taken together with the carbon or nitrogen atom to which they are attached form a saturated or partially or fully unsaturated 5-6 membered monocyclic or 7-10 membered bicyclic heterocyclic ring optionally including 1-3 additional heteroatoms selected from O, N or S; and optionally substituted independently with 1-5 substituents of R⁸OrR⁹;
R⁷a is H, Cno-alkyl, C₂γb₁₀-alkenyl, C₂γb₁₀-alkenyl, G₂γb₁₀-cycloalkyl, G₁⁴γb-
25 cycloalkenyl or partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, each of the Cγb₁⁴-alkyl, C₂γb₁⁴-alkenyl, C₂γb₁⁴-alkenyl, C₃γb₁⁴-cycloalkenyl, Gwo-cycloalkenyl and optionally or fully saturated 5-6 membered heterocyclic
optionally substituted with one or more substituents OfNR³R⁹, NR³R⁹, OR⁸, SR⁸, OR⁹, SR⁸, C(O)R⁸, OC(O)R⁸, COOR⁸, C(O)R⁹, OC(O)R⁹, COOR⁹, C(O)NR³R⁹, C(O)NR³R⁹,
30 NR³C(O)R⁸, NR³C(O)R⁹, NR³(C)NR³R⁹, NR³C(O)NR³R⁹, NR³C(O)NR³R⁹, NR³(C)NR³R⁹, NR³(C)NR³R⁹, OC(O)NR³R⁹, OC(O)NR³R⁹, S(O)₂R⁸, S(O)₂NR³R⁹, S(O)₂R⁹, S(O)₂NR³R⁹, NR³S(O)₂NR³R⁹, NR³S(O)₂NR³R⁹, NR³S(O)₂R⁸, NR³S(O)₂R⁹, R⁸ or R⁹;
R₇ᵇ is H or C₁₋₁₀-alkyl;
alternatively, R₇ᵃ and R₇ᵇ taken together with the nitrogen atom to which they are
attached form a saturated or partially or fully unsaturated 5-6 membered monocyclic or 7-
10 membered bicyclic heterocyclic ring optionally including 1-3 additional heteroatoms
selected from O, N, or S, and optionally substituted independently with 1-5 substituents
of R₈ or R₀;
R₈ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12
membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O₂, N, or S, and
wherein each ring of said ring system is optionally substituted independently with 1-5
substituents of R₉, oxo, NR₉R₉, OR₉, SR₉, C(O)R₉, COOR₉, C(O)NR₉R₉, NR₉C(O)R₉,
NR₉C(O)NR₉R₉, OC(O)NR₉R₉, S(O)₂R₉, S(O)₂NR₉R₉, NR₉S(O)₂R₉, or a partially or fully
saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3
heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3
substituents of R₉;
R₉ is H, halo, haloalkyl, CN, NO₂, NH₂, oxo, acetyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl,
C₂₋₁₀-alkynyl, Ca-io-cycloalkyl, Cwo-cycloalkenyl, Ci.io-alkylamino-, C₁₋₁₀
dialkylamino-, Ci.io-alkoxyl, Ci.io-thioalkoxyl or a saturated or partially or fully
unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered
tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3
heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, wherein each of the C₁-io-alkyl, C₂₋₁₀-alkenyl,
C₂₋₁₀-alkynyl, Cs₉-o-cycloalkyl, Cn-o-cycloalkenyl, Ci.io-alkylamino-, Ci.io-dialkylamino-,
Ci.io-alkoxyl, Q-io-thioalkoxyl and ring of said ring system is optionally substituted
independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl,
methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-
butyl, methylamine, dimethyamine, ethylamine, diethylamine, propylamine,
isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;
R₁₀ is H, halo, haloalkyl, CN, NO₂, Ci.io-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-
cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the Ci.io-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-
cycloalkyl and Cn-o-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N,
O and S and optionally substituted with one or more substituents of R₁₁, R₁₂ or R₁⁶,
NR₁₁R₁₂, NR₁₂R₁₁, OR₁₁, OR₁₂, SR₁₁, SR₁₂, C(O)R₁₁, OC(O)R₁₁, COOR₁₁, C(O)R₁₂,
- 100 -

OC(O)R_{12}, COOR_{12}, C(O)NR_{12}^1R_{12}^1, NR_{12}^2C(O)R_{11}^1, C(O)NR_{12}^1R_{12}^2, NR_{12}^2C(O)R_{12}^2,
NR_{12}^2C(O)NR_{11}^1R_{12}^1, NR_{12}^2C(O)NR_{11}^1R_{12}^2, NR_{12}^2(COOR_{11}^1), NR_{12}^2(COOR_{12}^1), OC(O)NR_{11}^1R_{12}^1,
OC(O)NR_{11}^1R_{12}^2, S(O)_{2}^1R_{11}^1, S(O)_{2}^1R_{12}^1, S(O)_{2}^1NR_{11}^1R_{12}^1, S(O)_{2}^1NR_{11}^1R_{12}^2,
NR_{12}^2S(O)_{2}NR_{12}^1R_{12}^2, NR_{12}^2S(O)_{2}NR_{12}^1R_{12}^2, NR_{12}^2S(O)_{2}NR_{12}^1R_{12}^2, ORNR_{12}^2S(O)_{2}R_{12}^2;

R_{11}^2 is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12
membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if
bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and
wherein each ring of said ring system is optionally substituted independently with 1-5
substituents of R_{12}^2, R_{13}^1, R_{14}^1 or R_{16}^1;

alternatively, R_{10}^1 and R_{11}^1 taken together form a partially or fully saturated or
unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms
selected from O, N, or S, and the ring optionally substituted independently with 1-5
substituents of R_{12}^2, R_{13}^1, R_{14}^1 or R_{16}^1;

-R_{12}^2 is H, Ci-i0-alkyl, C_{2_1-i0}-alkenyl, C_{2_1-i0}-alkynyl, C_{3_1-i0}-Cyclonaryl, C_{4_1-i0}-
cycloalkenyl, Ci-i0-alkylamino-, Ci-i0-dialkylamino-, Ci-i0-alkoxyI or Ci-i0-thioalkyl, each
of which is optionally substituted independently with 1-5 substituents of R_{13}^1, R_{14}^1, R_{15}^1 or
R_{16}^1;

-R_{13}^1 is NR_{14}^1R_{15}^1, NR_{14}^1R_{15}^1, OR_{14}^1, SR_{14}^1, OR_{15}^1; SR_{15}^1, C(O)R_{14}^1, OC(O)R_{14}^1, COOR_{14}^1.

C(O)R_{15}^1, OC(O)R_{15}^1, COOR_{15}^1, C(O)NR_{14}^1R_{15}^1, C(O)NR_{14}^1R_{15}^1, NR_{14}^1C(O)R_{14}^1, NR_{15}^1C(O)R_{14}^1,
NR_{14}^1C(O)R_{15}^1, NR_{15}^1C(O)R_{15}^1, NR_{15}^1C(O)NR_{14}^1R_{15}^1, NR_{15}^1C(O)NR_{14}^1R_{15}^1, NR_{15}^1(COOR_{14}^1),
NR_{15}^1(COOR_{15}^1), OC(O)NR_{14}^1R_{15}^1, OC(O)NR_{14}^1R_{15}^1, S(O)_{2}^1R_{14}^1, S(O)_{2}^1R_{15}^1, S(O)_{2}^1NR_{14}^1R_{15}^1,
S(O)_{2}^1NR_{15}^1R_{15}^1, NR_{14}^1S(O)_{2}NR_{14}^1R_{15}^1, NR_{15}^1S(O)_{2}NR_{14}^1R_{15}^1, NR_{14}^1S(O)_{2}R_{14}^1 or NR_{15}^1S(O)_{2}R_{15}^1;

R_{14}^1 is a partially or fully saturated or unsaturated 5-8 membered or a saturated or
partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14
membered tricyclic ring system, said ring system formed of carbon atoms optionally
including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms
if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring
system is optionally substituted independently with 1-5 substituents of R_{15}^1 or R_{16}^1;

-R_{15}^1 is H or d.io-alkyl, C_{2_1-i0}-alkenyl, C_{2_1-i0}-alkynyl, C_{2_1-i0}-cycloalkenyl, C_{4_1-i0}-
cycloalkenyl, Ci-i0-alkylamino-, Ci-i0-dialkylamino-, Ci-i0-alkoxyI or Ci-i0-thioalkoxyI, each
of which is optionally substituted independently with 1-5 substituents of R_{16}^1; and

-R_{16}^1 is H, halo, haloalkyl, CN, OH, NO_{2}, NH_{2}, OH, methyl, methoxyl, ethyl,
ethoxyl, propyl, propoxyl, isopropyl, butyl, isobutyl, tert-butyl, methylanino,
dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, cyclopentyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propanoyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, berityl or phenyl.

14. The compound of Claim 13 wherein A is N and R³ is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzo(b)thiophenyl, benzoxazolyl, benzopyrazolyl, benzothiazolyl or benzimidazolyl, each of which is optionally substituted as defined in claim 10.

15. The compound of Claim 13 wherein A is CR⁴ and R³ is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, thiophenyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzo(b)thiophenyl, benzoxazolyl, benzopyrazolyl, benzothiazolyl or benzimidazolyl, each of which is optionally substituted as defined in claim 10.

16. The compound of Claim 13 wherein R² is H or C₆H₅-alkyl and R⁵ and R⁶ taken together with the carbon atom or nitrogen to which they are attached form a saturated or partially or fully unsaturated 5-6 membered monocyclic or 7-10 membered bicyclic heterocyclic ring optionally including 1-3 additional heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of R⁸ or R⁹.

17. The compound of Claim 13 wherein said at least one substituent on R³ is NR¹⁰R¹¹, NR¹⁰R¹¹, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, S(O)₂NR¹⁰R¹¹, S(O)₂NR¹⁰R¹¹, S(O)₂NR¹⁰R¹¹, S(O)₂NR¹⁰R¹¹, S(O)₂NR¹⁰R¹¹, S(O)₂NR¹⁰R¹¹, S(O)₂NR¹⁰R¹¹, S(O)₂NR¹⁰R¹¹, S(O)₂NR¹⁰R¹¹,
18. The compound of Claim 13 wherein
R^3 is

wherein
one of A^6 and A^7 is CR^3a and the other of A^6 and A^7 is CR^3b or N;
each of A^5, A^8, A^9, A^10 and A^u is, independently, CR^3b or N;
X^2 is CR^3a;
each of X^1, X^3 and X^4 is, independently, CR^3b or N;
Y^1 is CR^3bR^3c, NR^30, 0 or S;
Y^2 is CR^3bR^3b or NR^3a; and
Z is CH or N;
- 103 -

wherein \( R_{3a} \) is \( NR_{10}R_{10}, NR_{10}R_{11}, C(O)NR_{10}R_{10}, C(O)NR_{10}R_{11}, \)
\( NR_{10}C(O)R_{10}, NR_{10}C(O)R_{11}, NR_{10}C(O)NR_{10}R_{10}, NR_{10}C(O)NR_{10}R_{11}, \)
\( S(O)NR_{10}R_{10}, S(O)NR_{10}R_{11}, NR_{10}S(O)NR_{10}R_{11}, NR_{10}S(O)R_{10}, \)
\( NR_{10}S(O)_{2}R_{11}; \)
\( R_{3b} \) is \( H, \) halo, haloalkyl, \( CN, NO_{2}, NH_{2}, C_{i-o}-alkyl, C_{2-i0}-alkenyl, C_{2-j0}-alkynyl \)
or \( C_{2-o,cycloalkyl}; \)
\( R_{3c} \) is \( H, \) CN or \( C_{wo}-alkyl. \)

19. The compound of Claim 18 wherein

\[ R_{3} = \]

\[
\begin{array}{c}
\text{A}_5 \text{A}_6 \text{A}_7 \\
\text{R}_{3a} \\
\end{array}
\]

\[
\begin{array}{c}
\text{A}_5 \text{A}_6 \\
\text{R}_{3a} \text{R}_{3b} \\
\end{array}
\]

\[
\begin{array}{c}
\text{A}_5 \text{A}_6 \text{A}_7 \\
\text{R}_{3c} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Y}_1 \text{Y}_2 \\
\text{R}_{3a} \text{R}_{3b} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Y}_1 \text{Y}_2 \\
\text{R}_{3c} \text{R}_{3b} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Y}_1 \text{Y}_2 \\
\text{R}_{3c} \text{R}_{3b} \\
\end{array}
\]

wherein

- each of \( A_{5}, A_{6}, \) and \( A_{7} \) is, independently, \( CR_{3b} \) or \( N; \)
- \( A_{5} \) is \( CR_{3c} \) or \( N; \)
- \( A_{6} \) is \( CR_{3d} \) or \( N; \)
- \( Y_{1} \) is \( O \) or \( S; \)
- \( Y_{2} \) is \( NR_{3d}; \)

wherein \( R_{3a} \) is \( NR_{10}R_{10}, NR_{10}R_{11}, C(O)NR_{10}R_{10}, C(O)NR_{10}R_{11}, \)
\( NR_{10}C(O)R_{10}, NR_{10}C(O)R_{11}, NR_{10}C(O)NR_{10}R_{10}, NR_{10}C(O)NR_{10}R_{11}, \)
\( S(O)NR_{10}R_{10}, S(O)NR_{10}R_{11}, NR_{10}S(O)NR_{10}R_{11}, NR_{10}S(O)R_{10}, \)
or \( NR_{10}S(O)_{2}R_{11}; \)
\( R_{3b} \) is \( H, \) halo, haloalkyl, \( CN, NO_{2}, NH_{2}, C_{i-o}-alkyl, C_{2-i0}-alkenyl, C_{2-j0}-alkynyl \)
or \( C_{2-o,cycloalkyl}; \)
- 104 -

R\(^{30}\) is H, halo, haloalkyl, CN, NO\(_2\), NH\(_2\), C\(_{1-10}\)-alkyl, C\(_{2-10}\)-alkynyl or Cs-io-cycloalkyl;

R\(^{3c}\) is H, halo, haloalkyl, CN, NO\(_2\), NH\(_2\), C\(_{1-10}\)-alkyl, C\(_{2-10}\)-alkenyl, C\(_{2-10}\)-alkynyl or Cs-io-cycloalkyl; and

R\(^{3d}\) is H, halo, haloalkyl, CN, NO\(_2\), NH\(_2\), C\(_{1-10}\)-alkyl, C\(_{2-10}\)-alkenyl, C\(_{2-10}\)-alkynyl or Cs-io-cycloalkyl;

alternatively, R\(^{3c}\) and R\(^{3d}\) taken together with the atoms to which they are attached form a phenyl or tetrahydrofuranyl ring system, optionally substituted with 1-3 substituents of halo, haloalkyl, CN, NO\(_2\), NH\(_2\), C\(_{1-10}\)-alkenyl, C\(_{2-10}\)-alkynyl or Cs-io-cycloalkyl.

20. The compound of Claim 13 wherein

A is CR\(^4\) or N;

R\(^2\) is H or C\(_{1-10}\)-alkyl;

R\(^3\) is
wherein

one of A\textsuperscript{6} and A\textsuperscript{7} is \textit{CR}\textsuperscript{3a} and the other of A\textsuperscript{6} and A\textsuperscript{7} is \textit{CR}\textsuperscript{3b} or N;

each of A\textsuperscript{5}, A\textsuperscript{8}, A\textsuperscript{9}, A\textsuperscript{10} and A\textsuperscript{11} is, independently, \textit{CR}\textsuperscript{3b} or N;

X\textsuperscript{2} is \textit{CR}\textsuperscript{3a};

each of X\textsuperscript{1}, X\textsuperscript{3} and X\textsuperscript{4} is, independently, \textit{CR}\textsuperscript{3b} or N;

Y\textsuperscript{1} is \textit{CR}\textsuperscript{3b}R\textsuperscript{3c}, NR\textsuperscript{3c}, O or S;

Y\textsuperscript{2} is \textit{CR}\textsuperscript{3a}R\textsuperscript{3b} or NR\textsuperscript{3c};

Z is CH or N;

wherein R\textsuperscript{3a} is NR\textsuperscript{10}R\textsuperscript{10}, NR\textsuperscript{10}R\textsuperscript{11}, C(O)NR\textsuperscript{10}R\textsuperscript{10}, C(O)NR\textsuperscript{10}R\textsuperscript{11}, NR\textsuperscript{10}C(O)R\textsuperscript{10}, NR\textsuperscript{10}C(O)R\textsuperscript{11}, NR\textsuperscript{10}C(O)NR\textsuperscript{10}R\textsuperscript{10}, NR\textsuperscript{10}C(O)NR\textsuperscript{10}R\textsuperscript{11}, S(O)\textsuperscript{2}NR\textsuperscript{10}R\textsuperscript{10}, S(O)\textsuperscript{2}NR\textsuperscript{10}R\textsuperscript{11}, NR\textsuperscript{10}S(O)\textsuperscript{2}NR\textsuperscript{10}R\textsuperscript{11}, NR\textsuperscript{10}S(O)\textsuperscript{2}R\textsuperscript{10} or NR\textsuperscript{10}S(O)\textsuperscript{2}R\textsuperscript{11};

R\textsuperscript{3b} is H, halo, haloalkyl, CN, NO\textsubscript{2}, NH\textsubscript{2}, C\textsubscript{i}-alkyl, C\textsubscript{2}-alkenyl,

\textit{alkynyl or Ca-io-cycloalkyl};

R\textsuperscript{3c} is H, halo, haloalkyl, CN, NO\textsubscript{2}, NH\textsubscript{2}, C\textsubscript{i}-alkyl, C\textsubscript{2}-alkenyl,

\textit{C\textsubscript{2}-alkynyl or Cs-io-cycloalkyl}; and

R\textsuperscript{3d} is H, halo, haloalkyl, CN, NO\textsubscript{2}, NH\textsubscript{2}, C\textsubscript{i}-alkyl, C\textsubscript{2}-alkenyl,

\textit{C\textsubscript{2}-alkynyl or Ca.io-cycloalkyl};

R\textsuperscript{4} is absent;

R\textsuperscript{5} and R\textsuperscript{6} taken together with the carbon or nitrogen atom to which they are attached form a ring selected from phenyl, pyridine, pyrimidine, pyridazine, pyrazole,
imidazole, pyrrolidine, oxazoline, isoxazoline, thiazoline, pyrazoline, morpholine,
piperidine and piperazine, wherein said ring is optionally substituted independently with 1-5 substituents of R^8 or R^9;

R^{7b} is H, Ci-io-alkyl, C_{3-6}-cycloalkyl, or partially or fully saturated 5-6 membered heterocyclic, each of the Ci.io-alkyl, C_{3-6}-cycloalkyl and partially or fully saturated 5-6 membered heterocyclic optionally substituted with one or more substituents of NR^8R^9, NR^8R^9, OR^8, SR^8, OR^9, SR^9, C(O)R^8, OC(O)R^8, COOR^8, C(O)R^9, OC(O)R^9, COOR^9, C(O)NR^8R^9, C(O)NR^8R^9, NR^8C(O)R^8, NR^8C(O)NR^8R^9, NR^8C(O)NR^8R^9, NR^8(COOR^8), NR^8(COOR^9), OC(O)NR^8R^9, OC(O)NR^8R^9, S(O)R^8, S(O)NR^8R^9, S(O)NR^8R^9, S(O)NR^8R^9, NR^8S(O)NR^8R^9, NR^8S(O)NR^8R^9, NR^8S(O)NR^8R^9, R^8 or R^9;

R^{7b} is H or Ci., o'-alkyl;
alternatively, R^{7b} and R^{7b} taken together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl and piperazinyl, wherein said ring is optionally substituted independently with 1-3 substituents of R^8 or R^9;

R^8 is phenyl, naphthyl, pyridyl, pyrimidyl, quinolinyl, isoquinolinyl, quinazolinyl, thiophenyl, fiiryyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, dioxazolyl, cyclopentyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of which is optionally substituted independently with 1-3 substituents of R^9, oxo, NR^9R^9, OR^9, SR^9, C(O)R^9, COOR^9, C(O)NR^9R^9, NR^9C(O)R^9, NR^9C(O)NR^9R^9, OC(O)NR^9R^9, S(O)R^9, S(O)NR^9R^9, S(O)NR^9R^9, NR^9S(O)NR^9R^9, or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R^9;

R^9 is H, halo, haloalkyl, CN, OH, NO_2, NH_2, acetyl, C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{2-10}-alkynyl, C_{3-10}-alkyl, C_{3-10}-alkenyl, C_{3-10}-alkynyl, C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{2-10}-alkynyl, C_{3-10}-alkyl, C_{3-10}-alkenyl, C_{3-10}-alkynyl, C_{3-10}-alkyl, C_{3-10}-alkenyl, C_{3-10}-alkynamino, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-; C_{1-10}-alkylamino-, C_{1-10}-alkylamino-, C_{1-10}-alkylamino-,
cycloalkyl, Ci-io-alkylamino-, Ci-io-dialkylamino-, Ci/io-alkoxyl, Ci/io-thioalkoxyl and ring system optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO\textsubscript{2}, NH\textsubscript{2}, OH, oxo, methyl, methoxy, ethyl, ethoxy, propyl, propoxy, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethyamine, ethylamine, diethylamino, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

\[ R^{10} \text{ is } H, \text{ halo}, \text{ haloalkyl, } CN, \text{ NO\textsubscript{2}}, \text{ Ci-i\textsubscript{o}-alkyl, } C_{2-10}\text{-alkenyl or } C_{3-10}\text{-CyCIOalkyl, each of the Ci-i-k-alkyl, } C_{2-10}\text{-alkenyl, and } Cs^0\text{-cycloalkyl optionally substituted with 1-3 substituents of } R^{11}, R^{12}, R^{16}, NR^{11}R^{12}, NR^{12}R^{12}, OR^{11}, SR^{12}, OR^{12}, SR^{11}, C(O)R^{11}, OC(O)R^{11}, COOR^{11}, C(O)R^{11}, COOR^{11}, C(O)NR^{11}R^{12}, NR^{12}C(O)R^{11}, C(O)NR^{12}R^{12}, NR^{12}C(O)NR^{12}R^{12}, NR^{12}(COOR^{12}), NR^{12}(COOR^{12}), OC(O)NR^{11}R^{12}, OC(O)NR^{12}R^{12}, S(O)_{2}R^{11}, S(O)_{2}R^{11}, S(O)_{2}NR^{11}R^{12}, S(O)_{2}NR^{12}R^{12}, NR^{12}S(O)_{2}R^{11}, NR^{12}S(O)_{2}R^{12}, NR^{12}(S(O)_{2})_{2}R^{11}, NR^{12}(S(O)_{2})_{2}R^{12}; \]

\[ R^{11} \text{ is phenyl, naphthyl, pyridyl, pyrimidyl, triazinyl, quinoliny1, isoquinoliny1, quinazoliny1, isoquinazoliny1, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuryl, pyrrolidiny1, oxazoliny1, isoxazoliny1, thiazoliny1, pyrazoliny1, morpholinyl, piperidiny1, piperazinyl, pyranyl, dioxoazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of which is optionally substituted independently with 1-3 substituents of } R^{12}, R^{13} \text{ or } R^{16}. \]

Alternatively, } R^{10} \text{ and } R^{11} \text{ taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of } R^{12}, R^{13} \text{, or } R^{16}; \]

\[ R^{12} \text{ is } H, \text{ Ci-i-alkyl, } C_{2-10}\text{-alkenyl, } C_{2-10}\text{-alkenyl, } C_{4-10}\text{-cycloalkenyl, } C_{4-10}\text{-alkylamino-, } C_{4-10}\text{-dialkylamino-, } C_{4-10}\text{-alkoxyl or } C_{4-10}\text{-thioalkoxyl, each of which is optionally substituted independently with 1-3 substituents of } R^{13}, R^{14}, R^{15} \text{ or } R^{16}; \]

\[ R^{13} \text{ is } NR^{14}R^{15}, NR^{15}R^{15}, OR^{14}; SR^{14}, OR^{15}; SR^{15}, C(O)R^{14}, OC(O)R^{14}, COOR^{14}, C(O)R^{15}, OC(O)R^{15}, COOR^{15}, C(O)NR^{14}R^{15}, C(O)NR^{15}R^{15}, C(O)NR^{14}R^{14}, NR^{16}C(O)R^{14}, NR^{14}C(O)R^{15}, NR^{15}C(O)R^{15}, NR^{15}C(O)NR^{14}R^{15}, NR^{15}C(O)NR^{15}R^{15}, NR^{15}(COOR^{14}), NR^{15}(COOR^{15}), OC(O)NR^{14}R^{15}, OC(O)NR^{15}R^{15}, S(O)_{2}R^{14}, S(O)_{2}R^{15}, S(O)_{2}NR^{14}R^{15}, S(O)_{2}NR^{15}R^{15}, NR^{14}S(O)_{2}R^{14}, NR^{15}S(O)_{2}R^{15}, NR^{14}S(O)_{2}R^{14} OrNR^{15}S(O)_{2}R^{15}; \]
R\textsuperscript{16} is a partially or fully saturated or unsaturated 5-8 membered or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-3 substituents of R\textsuperscript{15} or R\textsuperscript{16};

R\textsuperscript{15} is H or Ci.io-alkyl, C\textsubscript{2}-io-alkenyl, C\textsubscript{2}-io-alkynyl, Ca-io-cycloalkyl, Gno-cycloalkenyl, Ci.io-alkylamino-, Q-io-dialkylamino-, Ci.io-alkoxyl or Ci.io-thioalkoxyl, each of which is optionally substituted independently with 1-3 substituents of R\textsuperscript{16}; and

R\textsuperscript{16} is H, halo, haloalkyl, CN, OH, NO\textsubscript{2}, NH\textsubscript{2}, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, o xo, acetyl, benzyl or a ring system selected from phenyl, pyridyl, thiophenyl, furyl, tetrahydrofurfuryl, pyrolyl, pyrazolyl, thieno-pyrazolyl, imidazolyl, triazolyl, thiazolyl, thiadiazolyl, ben佐thiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazoxyzol, isoxazolyl, isothiazolyl, indolyl, azaindolyl, isoindolyl, indazolyl, benzofuranyl, ben佐thiophenyl, benzimidazolyl, pyrroldinyl, pyrazolinyl, mφ holiny, piperidinyl, pipеразинyl, cyclopropyl, cyclobutyl, azetidinyl, cyclopentyl and cyclohexyl, said ring system optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO\textsubscript{2}, NH\textsubscript{2}, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

21. The compound of Claim 1, and pharmaceutically acceptable salts thereof, selected from:

TsT-cyclopropyl-S-(2-((3-(diethy lamino)propyl)amino)thieno[2,3-d]pyrimidin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(2-((3-(dimethylamino)-2,2-dimethylpropyl)amino)thieno[2,3-d]pyrrimidin-6-yl)-4-methylbenzamide;

N-ethyl-4-methyl-3-(2-((2-(4-morpholinyl)ethyl)amino)thieno[2,3-d]pyrimidin-6-yl)benzamide;

4-methyl-3-(2-((2-(4-morpholinyl)ethyl)amino)thieno[2,3-d]pyrimidin-6-yl)benzoic acid;

3-(2-((2-amino-2-methylpropyl)amino)thieno[2,3-d]pyrimidin-6-yl)-N-cyclopropyl-4-methylbenzamide;
- 109 -

1. N-cyclopropyl-4-methyl-3-(2-((tetrahydro-2-furanylmethyl)amino)thieno[2,3-d]pyrimidin-6-yl)benzamide;
2. N-cyclopropyl-4-methyl-3-(2-(((3R)-6-oxo-3-piperidinyl)amino)thieno[2,3-d]pyrimidin-6-yl)benzamide;
3. 1,1-dimethylethyl 3-(((6-(5-((cyclopropylamino)carbonyl)-2-methylphenyl)thieno[2,3-d]pyrimidin-2-yl)amino)methyl)-l-piperidinecarboxylate;
4. N-cyclopropyl-4-methyl-3-(2-((3-(piperidinylmethyl)amino)thieno[2,3-d]pyrimidin-6-yl)benzamide;
5. N-cyclopropyl-4-methyl-3-(2-(((l-(2,2,2-trifluoroethyl)-3-piperidinyl)methyl)amino)thieno[2,3-d]pyrimidin-6-yl)benzamide;
6. N-cyclopropyl-4-methyl-3-(2-((3-(4-morpholinyl)propyl)amino)thieno[2,3-d]pyrimidin-6-yl)benzamide;
7. 3-(2-((3-(dimethylamino)-2,2-dimethylpropyl)amino)thieno[2,3-d]pyrimidin-6-yl)-4-methylbenzamide;
8. N-cyclopropyl-3-(7-hydroxythieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide;
9. 3-(7-chlorothieno[2,3-d]pyridazin-2-yl)-N-cyclopropyl-4-methylbenzamide;
10. N-cyclopropyl-3-(7-(4-fluoro-2-methylphenyl)thieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide;
11. N-cyclopropyl-4-methyl-3-(7-(2-(methoxy)-3-pyridinyl)thieno[2,3-d]pyridazin-2-yl)benzamide;
12. N-cyclopropyl-4-methyl-3-(7-(2-methylphenyl)thieno[2,3-d]pyridazin-2-yl)benzamide;
13. N-cyclopropyl-4-methyl-3-(7-(2-(methylo>N-cyclopropyl-3-(7-(2,4-difluorophenyl)thieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide;
14. 3-(7-(4-fluoro-2-methylphenyl)thieno[2,3-d]pyridazin-2-yl)-4-methylbenzamide.

22. A medicament comprising a compound according to any of Claims 1-21 and a pharmaceutically acceptable carrier.

23. The manufacture of the medicament of claim 22 for the treatment of inflammation.

25. Use of the medicament of Claim 22 for the treatment of Paget's disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, adult respiratory distress syndrome (ARDS), Crohn's disease, allergic rhinitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-I, HTV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection or a combination thereof in a subject.

26. The medicament of Claim 22 to lower plasma concentrations of TNF-a, HL-I, BL-6, IL-8 or a combination thereof in a subject.

27. Use of the medicament of Claim 22 for the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis or a combination thereof in a subject.


29. Use of the medicament of Claim 22 for the treatment of ankylosing spondylitis, inflammatory bowel disease, inflammatory pain, ulcerative colitis, asthma, chronic obstructive pulmonary disease, myelodisplastic syndrome, endotoxic shock, chronic Hepatitis C or a combination thereof in a subject.