SUBSTITUTED INDAZOLYL(INDOLYL)MALEIMIDE DERIVATIVES AS KINASE INHIBITORS

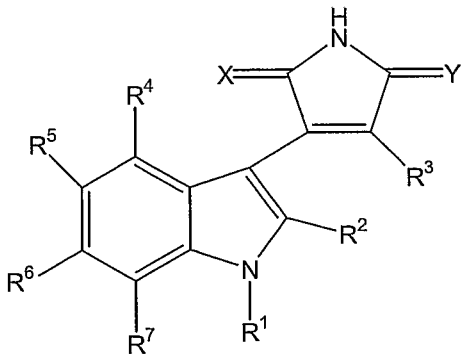
This application claims benefit of provisional patent application Serial No. 60/478,516 filed June 13, 2003 hereby incorporated by reference herein.

FIELD OF THE INVENTION

This invention is directed to certain novel compounds, methods for producing them and methods for treating or ameliorating a kinase or dual-kinase mediated disorder. More particularly, this invention is directed to indazolyl-substituted pyrroline compounds useful as selective kinase or dual-kinase inhibitors, methods for producing such compounds and methods for treating or ameliorating a kinase or dual-kinase mediated disorder.

BACKGROUND OF THE INVENTION

United States Patent 5,057,614 to Davis, et. al., describes substituted pyrrole compounds of formula I:



wherein R^1 signifies hydrogen, alkyl, aryl (limited to phenyl), aralkyl (limited to phenylalkyl), alkoxyalkyl, hydroxyalkyl, haloalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, trialkylaminoalkyl, aminoalkylaminoalkyl, azidoalkyl, acylaminoalkyl, acylthioalkyl, alkylsulphonylaminoalkyl, arylsulphonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, alkylsulphinylalkyl, alkylsulphonylalkyl, alkylsulphonyloxyalkyl, alkylcarbonyloxyalkyl, cyanoalkyl, amidinoalkyl, isothiocyanatoalkyl,

glucopyranosyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, hydroxyalkylthioalkyl, mercaptoalkylthioalkyl, arylthioalkyl or carboxyalkylthioalkyl or a group of the formula

$-(CH_2)_n$-W-Het, (a) $-(CH_2)_n$-T-C(=V)-Z, (b)

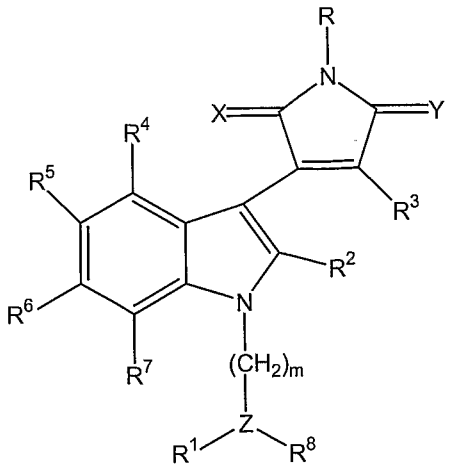
$-(CH_2)_n$-NH-C(=O)-Im, or (c) $-(CH_2)_n$-NH-C(=NH)-Ar (d)

in which Het signifies a heterocyclyl group, W signifies NH, S or a bond, T signifies NH or S, V signifies O, S, NH, NNO_2, NCN OR $CHNO_2$, Z signifies alkylthio, amino, monoalkylamino or dialkylamino, Im signifies 1-imidazolyl, Ar signifies aryl, and n stands for 2-6; R^2 signifies hydrogen, alkyl, aralkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, acylaminoalkyl, alkylsulphonylaminoalkyl, arylsulphonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylthio or alkylsulphinyl; R^3 signifies a carbocyclic or heterocyclic aromatic group; R^4, R^5, R^6 and R^7 each independently signify hydrogen, halogen, hydroxy, alkoxy, aryloxy, haloalkyl, nitro, amino, acylamino, monoalkylamino, dialkylamino, alkylthio, alkylsulphinyl or alkylsulphonyl; and one of X and Y signifies O and the other signifies O, S, (H,OH) or (H,H); with the proviso that R^1 has a significance different from hydrogen when R^2 signifies hydrogen, R^3 signifies 3-indolyl or 6-hydroxy-3-indolyl, R^4, R^5 and R^7 each signify hydrogen, R^6 signifies hydrogen or hydroxy and X and Y both signify O and when R^2 signifies hydrogen, R^3 signifies 3-indolyl, R^4, R^5, R^6 and R^7 each signify hydrogen, X signifies (H,H) and Y signifies O; as well as pharmaceutically acceptable salts of acidic compounds of formula I with bases and of basic compounds of formula I with acids, as therapeutically active substances for the use in control or prevention of inflammatory, immunological, bronchopulmonary and cardiovascular disorders.

The novel compounds of the present invention are structurally unlike those disclosed by the Davis 5,057,614 patent. In particular, the Davis 5,057,614 patent discloses indolyl substituted pyrrole compounds of formula I

which may be further substituted on the R^3 position with a carbocyclic or heterocyclic aromatic group. The carbocyclic aromatic group denoted by R^3 can be a monocyclic or polycyclic group, preferably a monocyclic or bicyclic group, i.e. phenyl or naphthyl, which can be substituted or unsubstituted, for example, with one or more, preferably one to three, substituents selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, monoalkylamino, dialkylamino, alkylthio, alkylsulphinyl and alkylsulphonyl. Unlike compounds of the present invention, examples of carbocyclic aromatic groups denoted in the Davis '614 patent by R^3 are phenyl, 2-, 3-, or 4-chlorophenyl, 3-bromophenyl, 2- or 3-methylphenyl, 2,5-dimethylphenyl, 4-methoxyphenyl, 2- or 3-trifluoromethylphenyl, 2-, 3-, or 4-nitrophenyl, 3-, or 4-aminophenyl, 4-methylthiophenyl, 4-methylsulphinylphenyl, 4-methylsulphonylphenyl and 1-, or 2-naphthyl. The heterocyclic aromatic group denoted by R^3 can be a 5- or 6-membered heterocyclic aromatic group which can optionally carry a fused benzene ring and which can be substituted or unsubstituted, for example, with one or more, preferably one to three, substituents selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, mono- or dialkylamino, alkylthio, alkylsulphinyl and alkylsulphonyl. Unlike compounds of the present invention, examples of heterocyclic aromatic groups denoted in the Davis '614 patent by R^3 are 2-, or 3-thienyl, 3-benzothienyl, 1-methyl-2-pyrrolyl, 1-benzimidazolyl, 3-indolyl, 1- or 2-methyl-3-indolyl, 1-methoxymethyl-3-indolyl, 1-(1-methoxyethyl)-3-indolyl, 1-(2-hydroxypropyl)-3-indolyl, 1-(4-hydroxybutyl)-3-indolyl, 1-[1-(2-hydroxyethylthio)ethyl]-3-indolyl, 1-[1-(2-mercaptoethylthio)ethyl]-3-indolyl, 1-(1-phenylthioethyl)-3-indolyl, 1-[1-(carboxymethylthio)ethyl]-3-indolyl and 1-benzyl-3-indolyl.

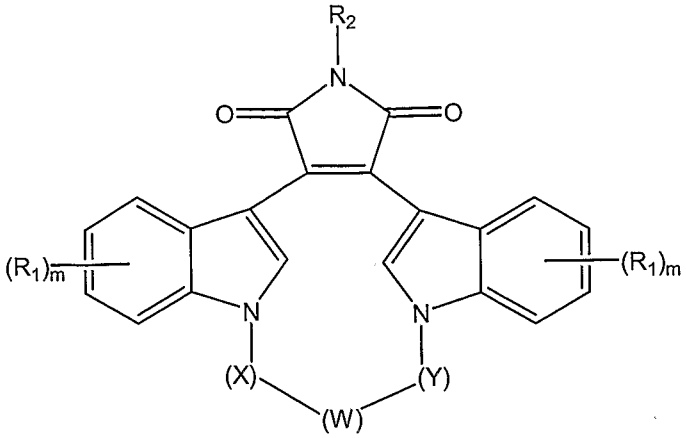
United States Patent 5,721,245 to Davis, et. al., describes substituted 4-[3-indolyl]-1H-pyrrolone compounds of formula I:



wherein R is hydrogen or hydroxy, R^1 and R^2 taken together are a group of the formula $-(CH_2)_n-$ and R^7 is hydrogen or R^1 and R^7 taken together are a group of the formula $-(CH_2)_n-$ and R^2 is hydrogen; R^3 is an aryl or aromatic heterocyclic group; R^4, R^5 and R^6 each independently are hydrogen, halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, alkylthio, alkylsulfinyl or alkylsulfonyl; R^8 is a group of the formula $-(CH_2)_p-R^9$ or $-(CH_2)_q-R^{10}$; R^9 is hydrogen, alkylcarbonyl, aminoalkylcarbonyl, cyano, amidino, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, aminocarbonyl or aminothiocarbonyl; R^{10} is hydroxy, alkoxy, halogen, amino, monoalkylamino, dialkylamino, trialkylamino, azido, acylamino, alkylsulfonylamino, arylsulfonylamino, alkylthio, alkoxycarbonylamino, aminoacylamino, aminocarbonylamino, isothiocyanato, alkylcarbonyloxy, alkylsulfonyloxy or arylsulfonyloxy, a 5- or 6-membered saturated nitrogen-containing heterocycle attached via the nitrogen atom or a group of the formula -U-C(V)-W; U is S or NH; V is NH, NNO_2, NCN, $CHNO_2$; W is amino, monoalkylamino or dialkylamino; one of X and Y is O and the other is O or (H,H); Z is CH or N; m, p and q are, independently, an integer from 0 to 5, and n is an integer from 1 to 5, with the proviso that q and m are, independently, 2 to 5 when Z is N; as well as pharmaceutically acceptable salts of acidic compounds of formula I with bases and of basic compounds of formula I with acids, as therapeutically active substances for use in control or prevention of inflammatory, immunological, bronchopulmonary and cardiovascular disorders.

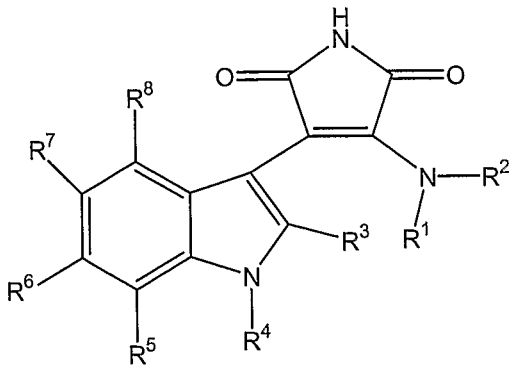
The novel compounds of the present invention are structurally unlike those disclosed by the Davis 5,721,245 patent. In particular, the Davis 5,721,245 patent discloses 4-[3-indolyl]-1H-pyrrolone compounds of formula I which may be further substituted on the R^3 position with an aryl or aromatic heterocyclic group. The term "aryl", alone or in combination denotes a monocyclic or polycyclic group, preferably a monocyclic or bicyclic group, for example, phenyl or naphthyl, which can be substituted or unsubstituted, for example, with one or more, preferably one to three, substituents selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, alkylthio, alkylsulfinyl and alkylsulfonyl. Unlike compounds of the present invention, examples of such aryl groups in the Davis '245 patent are phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 2-methylphenyl, 3-methylphenyl, 2,5-dimethylphenyl, 4-methoxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 3-aminophenyl, 4-aminophenyl, 4-methylthiophenyl, 4-methylsulfinylphenyl, 4-methylsulfonylphenyl, 1-naphthyl, 2-naphthyl and the like. The term "aromatic heterocyclic" means a 5- or 6-membered heterocyclic aromatic group which can optionally carry a fused benzene ring and which can be substituted or unsubstituted, for example, with one or more, preferably one to three, substituents selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, alkylthio, alkylsulfinyl and alkylsulfonyl. Unlike compounds of the present invention, examples of such heterocyclic groups in the Davis '245 patent are 2-thienyl, 3-thienyl, 3-benzothienyl, 3-benzofuranyl, 2-pyrrolyl, 3-indolyl and the like which can be unsubstituted or substituted in the manner indicated. The 5- or 6-membered saturated nitrogen containing heterocycle attached via the nitrogen atom can contain an additional nitrogen or oxygen or a sulfur atom, examples of such heterocycles are pyrrolidino, piperidino, piperazino, morpholino and thiomorpholino.

United States Patent 5,624,949 to Heath, Jr., et. al., describes bis-indolemaleimide derivatives of the formula:



wherein W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_m$O-, -heterocycle-, -heterocycle-$(CH_2)_m$O-, -fused bicyclic-, -fused bicyclic-$(CH_2)_m$O-, -NR_3-, -NOR_3-, -CONH- or -NHCO-; X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together, X, Y and W combine to form $(CH_2)_n$-AA-; R_1 is independently hydrogen, halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR_4R_5 or -NHCO(C_1-C_4)alkyl; R_2 is hydrogen, CH_3CO-, NH_2 or hydroxy; R_3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), -$CONR_4R_5$, -C(C=NH)NH_2, -SO(C_1-C_4 alkyl), -$SO_2(NR_4R_5)$ or -SO_2(C_1-C_4 alkyl); R_4 and R_5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring; AA is an amino acid residue; m is independently 0, 1, 2 or 3; and n is independently 2, 3, 4 or 5 as protein kinase C (PKC) inhibitors and as selective PKCβ-I and PKCβ-II inhibitors.

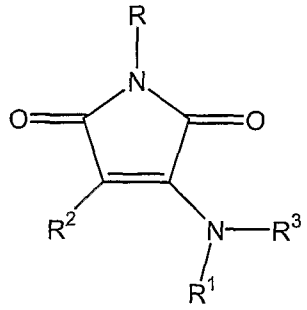
Patent application WO 00/06564 discloses disubstituted maleimide compounds of Formula (I):



wherein R^1 represents hydrogen or alkyl; R^2 represents aryl, cycloalkyl or a

heterocycle; R^3, R^5, R^6, R^7 and R^8 represent each hydrogen, halogen, hydroxy, amino, alkyl or alkoxy; and R^4 is W, or R^4 and R^3 or R^4 and R^5 may form together a ring substituted by W thereon; wherein W represents $-(CH_2)_l-(Y)_m-(CH_2)_n-Z$ as PKCβ inhibitors.

Patent application WO 00/21927 describes 3-amino-4-arymaleimide compounds having formula (I):



or a pharmaceutically acceptable derivative thereof, wherein: R is hydrogen, alkyl, aryl or aralkyl; R^1 is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl; R^2 is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl; R^3 is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or, R^1 and R^3 together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocyclic ring and a method for the treatment of conditions associated with a need for inhibition of GSK-3, such as diabetes, dementias such as Alzheimer's disease and manic depression.

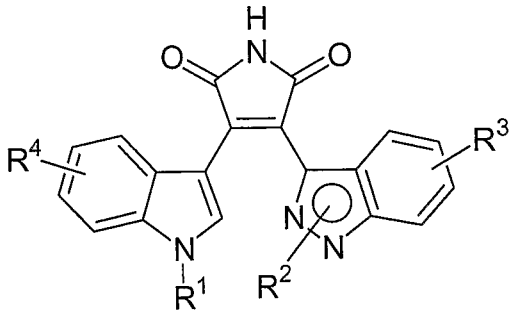
The indazolyl-substituted pyrroline compounds of the present invention have not been heretofore disclosed.

Accordingly, it is an object of the present invention to provide indazolyl-substituted pyrroline compounds useful as a kinase or dual-kinase inhibitor (in particular, a kinase selected from protein kinase C or glycogen synthase kinase-3; and, more particularly, a kinase selected from protein kinase C α,

protein kinase C β (e.g. protein kinase C β-I and protein kinase C β-II), protein kinase C γ or glycogen synthase kinase-3β), methods for their production and methods for treating or ameliorating a kinase or dual-kinase mediated disorder.

SUMMARY OF THE INVENTION

The present invention is directed to indazolyl-substituted pyrroline compounds of Formula (I)



Formula (I)

wherein

R^1 is selected from the group consisting of:

hydrogen,

C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{3-8} cycloalkyl {wherein alkyl, alkenyl, alkynyl and C_{3-8} cycloalkyl are optionally substituted with one to two substituents independently selected from the group consisting of

-O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-OH, -O-(C_{1-8})alkyl-O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-NH_2, -O-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -O-(C_{1-8})alkyl-S-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-NH_2, -O-(C_{1-8})alkyl-SO_2-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-N[(C_{1-8})alkyl]$_2$, -O-C(O)H, -O-C(O)-(C_{1-8})alkyl, -O-C(O)-NH_2, -O-C(O)-NH-(C_{1-8})alkyl, -O-C(O)-N[(C_{1-8})alkyl]$_2$, -O-(C_{1-8})alkyl-C(O)H, -O-(C_{1-8})alkyl-C(O)-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-CO_2H,

-O-(C_{1-8})alkyl-C(O)-O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-C(O)-NH_2, -O-(C_{1-8})alkyl-C(O)-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-C(O)-N[(C_{1-8})alkyl]$_2$, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-S-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-OH, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-NH_2, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -S-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-OH, -(C_{1-8})alkyl-O-(C_{1-8})alkyl, -(C_{1-8})alkyl-NH_2, -(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -(C_{1-8})alkyl-S-(C_{1-8})alkyl, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, -C(N)-NH_2, aryl and aryl(C_{1-8})alkyl (wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-8}alkyl, C_{1-8}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-8}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl, (halo)$_{1-3}$(C_{1-8})alkoxy, hydroxy, hydroxy(C_{1-8})alkyl and nitro)), cyano, (halo)$_{1-3}$, hydroxy, nitro, oxo, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-8}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl, (halo)$_{1-3}$(C_{1-8})alkoxy, hydroxy, hydroxy(C_{1-8})alkyl and nitro)},

-C(O)-(C_{1-8})alkyl, -C(O)-aryl, -C(O)-O-(C_{1-8})alkyl, -C(O)-O-aryl, -C(O)-NH-(C_{1-8})alkyl, -C(O)-NH-aryl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-aryl,

heterocyclyl, aryl and heteroaryl {wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, -C(O)H, -C(O)-(C_{1-8})alkyl, $-CO_2H$, -C(O)-O-(C_{1-8})alkyl, $-C(O)-NH_2$, $-C(NH)-NH_2$, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, $-SO_2$-(C_{1-8})alkyl, $-SO_2-NH_2$, $-SO_2$-NH-(C_{1-8})alkyl, $-SO_2$-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, $-C(O)-NH_2$, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, $-SO_2$-(C_{1-8})alkyl, $-SO_2-NH_2$, $-SO_2$-NH-(C_{1-8})alkyl, $-SO_2$-N[(C_{1-8})alkyl]$_2$ and $-C(NH)-NH_2$), amino-(C_{1-8})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, $-C(O)-NH_2$, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, $-SO_2$-(C_{1-8})alkyl, $-SO_2-NH_2$, $-SO_2$-NH-(C_{1-8})alkyl, $-SO_2$-N[(C_{1-8})alkyl]$_2$ and $-C(NH)-NH_2$), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl-, (halo)$_{1-3}$(C_{1-8})alkoxy-, hydroxy, hydroxy(C_{1-8})alkyl, nitro, aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl};

R^2 is selected from the group consisting of -C_{1-8}alkyl-Z, -C_{2-8}alkenyl-Z and -C_{2-8}alkynyl-Z; wherein the -C_{1-8}alkyl, -C_{2-8}alkenyl and -C_{2-8}alkynyl is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4})alkylamino, C_{1-4}alkyl, C_{1-4}alkoxy, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy and hydroxy(C_{1-4})alkyl;

Z is a 5 to 6 member monocyclic heteroaryl ring having from 2 to 4 heteroatoms containing at least one carbon atom and at least one nitrogen atom; wherein Z optionally is substituted with R^5;

R^5 is 1 to 2 substituents attached to a carbon or nitrogen atom of Z and each

substitute is independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH(C_{1-8}alkyl), -C(O)-N(C_{1-8})alkyl)$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-8}alkyl), -SO_2-N(C_{1-8}alkyl)$_2$, -(C_{1-8})alkyl-NH_2, -(C_{1-8})alkyl-NH(C_{1-8}alkyl), -(C_{1-8})alkyl-N(C_{1-8}alkyl)$_2$, -(C_{1-8})alkyl-(halo)$_{1-3}$, -(C_{1-8})alkyl-OH, -aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl;

with the proviso that, when R^5 is attached to a carbon atom, R^5 is further selected from the group consisting of -C_{1-8}alkoxy, -(C_{1-8})alkoxy-(halo)$_{1-3}$, -SH, -S-(C_{1-8})alkyl, -N-R^6, cyano, halo, hydroxy, and nitro;

R^6 is 1 to 2 substituents independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, - C_{3-8}cycloalkyl, -C(O)H, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-8}alkyl), -C(O)-N(C_{1-8}alkyl)$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-8}alkyl), -SO_2-N(C_{1-8}alkyl)$_2$, -C(N)-NH_2, -C(N)-NH(C_{1-8}alkyl) and -C(N)-N(C_{1-8}alkyl)$_2$;

R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-8})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and

-C(NH)-NH_2), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl-, (halo)$_{1-3}$(C_{1-8})alkoxy-, hydroxy, hydroxy(C_{1-8})alkyl-, nitro, aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl;

and pharmaceutically acceptable salts thereof.

The present invention is directed to indazolyl-substituted pyrroline compounds useful as a selective kinase or dual-kinase inhibitor; in particular, a kinase selected from protein kinase C or glycogen synthase kinase-3; and, more particularly, a kinase selected from protein kinase C α, protein kinase C β (e.g. protein kinase C βI and protein kinase C β-II), protein kinase C γ or glycogen synthase kinase-3β.

The present invention is also directed to methods for producing the instant indazolyl-substituted pyrroline compounds and pharmaceutical compositions and medicaments thereof.

The present invention is further directed to methods for treating or ameliorating a kinase or dual-kinase mediated disorder. In particular, the method of the present invention is directed to treating or ameliorating a kinase or dual-kinase mediated disorder such as, but not limited to, cardiovascular diseases, diabetes, diabetes-associated disorders, inflammatory diseases, immunological disorders, dermatological disorders, oncological disorders and CNS disorders.

DETAILED DESCRIPTION OF THE INVENTION

Preferred embodiments of the present invention include compounds of Formula (I) wherein, R^1 isselected from the group consisting of:

hydrogen,

C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl and C_{3-8} cycloalkyl {wherein alkyl, alkenyl,

alkynyl and C_{3-8} cycloalkyl are optionally substituted with one to two substituents independently selected from the group consisting of -O-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-OH, -O-(C_{1-4})alkyl-O-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-NH_2, -O-(C_{1-4})alkyl-NH-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-N[(C_{1-4})alkyl]$_2$, -O-(C_{1-4})alkyl-S-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-SO_2-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-SO_2-NH_2, -O-(C_{1-4})alkyl-SO_2-NH-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-SO_2-N[(C_{1-4})alkyl]$_2$, -O-C(O)H, -O-C(O)-(C_{1-4})alkyl, -O-C(O)-NH_2, -O-C(O)-NH-(C_{1-4})alkyl, -O-C(O)-N[(C_{1-4})alkyl]$_2$, -O-(C_{1-4})alkyl-C(O)H, -O-(C_{1-4})alkyl-C(O)-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-CO_2H, -O-(C_{1-4})alkyl-C(O)-O-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-C(O)-NH_2, -O-(C_{1-4})alkyl-C(O)-NH-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-C(O)-N[(C_{1-4})alkyl]$_2$, -C(O)H, -C(O)-(C_{1-4})alkyl, -CO_2H, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SH, -S-(C_{1-4})alkyl, -S-(C_{1-4})alkyl-S-(C_{1-4})alkyl, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl-OH, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl-NH_2, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl-NH-(C_{1-4})alkyl, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl-N[(C_{1-4})alkyl]$_2$, -S-(C_{1-4})alkyl-NH-(C_{1-4})alkyl, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, -(C_{1-4})alkyl-OH, -(C_{1-4})alkyl-O-(C_{1-4})alkyl, -(C_{1-4})alkyl-NH_2, -(C_{1-4})alkyl-NH-(C_{1-4})alkyl, -(C_{1-4})alkyl-N[(C_{1-4})alkyl]$_2$, -(C_{1-4})alkyl-S-(C_{1-4})alkyl, -C(O)-(C_{1-4})alkyl, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$, -C(N)-NH_2, aryl and aryl(C_{1-4})alkyl (wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-4}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy, hydroxy, hydroxy(C_{1-4})alkyl and nitro)), cyano, (halo)$_{1-3}$, hydroxy, nitro, oxo, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one

to three substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-4}alkyl), cyano, halo, $(halo)_{1-3}(C_{1-4})$alkyl, $(halo)_{1-3}(C_{1-4})$alkoxy, hydroxy, hydroxy(C_{1-4})alkyl and nitro)},

$-C(O)-(C_{1-4})$alkyl, -C(O)-aryl, $-C(O)-O-(C_{1-4})$alkyl, -C(O)-O-aryl, $-C(O)-NH-(C_{1-4})$alkyl, -C(O)-NH-aryl, $-C(O)-N[(C_{1-4})alkyl]_2$, $-SO_2-(C_{1-4})$alkyl, $-SO_2$-aryl,

heterocyclyl, aryl and heteroaryl {wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, -C(O)H, $-C(O)-(C_{1-4})$alkyl, $-CO_2H$, $-C(O)-O-(C_{1-4})$alkyl, $-C(O)-NH_2$, $-C(NH)-NH_2$, $-C(O)-NH-(C_{1-4})$alkyl, $-C(O)-N[(C_{1-4})alkyl]_2$, -SH, $-S-(C_{1-4})$alkyl, $-SO_2-(C_{1-4})$alkyl, $-SO_2-NH_2$, $-SO_2-NH-(C_{1-4})$alkyl, $-SO_2-N[(C_{1-4})alkyl]_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, $-(C_{1-4})alkyl-NH_2$, $-C(O)-(C_{1-4})$alkyl, $-C(O)-O-(C_{1-4})$alkyl, $-C(O)-NH_2$, $-C(O)-NH-(C_{1-4})$alkyl, $-C(O)-N[(C_{1-4})alkyl]_2$, $-SO_2-(C_{1-4})$alkyl, $-SO_2-NH_2$, $-SO_2-NH-(C_{1-4})$alkyl, $-SO_2-N[(C_{1-4})alkyl]_2$ and $-C(NH)-NH_2$), amino-(C_{1-4})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, $-(C_{1-4})alkyl-NH_2$, $-C(O)-(C_{1-4})$alkyl, $-C(O)-O-(C_{1-4})$alkyl, $-C(O)-NH_2$, $-C(O)-NH-(C_{1-4})$alkyl, $-C(O)-N[(C_{1-4})alkyl]_2$, $-SO_2-(C_{1-4})$alkyl, $-SO_2-NH_2$, $-SO_2-NH-(C_{1-4})$alkyl, $-SO_2-N[(C_{1-4})alkyl]_2$ and $-C(NH)-NH_2$), cyano, halo, $(halo)_{1-3}(C_{1-4})$alkyl, $(halo)_{1-3}(C_{1-4})$alkoxy, hydroxy, hydroxy(C_{1-4})alkyl, nitro, aryl, $-(C_{1-4})$alkyl-aryl, heteroaryl and $-(C_{1-4})$alkyl-heteroaryl}.

More preferably, R^1 is selected from the group consisting of:

hydrogen,

C_{1-4}alkyl, C_{2-4}alkenyl {wherein alkyl is substituted with one to two substituents

independently selected from the group consisting of -O-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-OH, -O-(C_{1-4})alkyl-NH-(C_{1-4})alkyl, -O-C(O)-(C_{1-4})alkyl, -C(O)H, $-CO_2H$, -C(O)-O-(C_{1-4})alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, -(C_{1-4})alkyl-OH, -C(O)-O-(C_{1-4})alkyl and aryl(C_{1-4})alkyl), hydroxy, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkyl and halo)},

aryl and heteroaryl {wherein aryl and heteroaryl are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, $-CO_2H$, -C(O)-O-(C_{1-4})alkyl, $-C(O)-NH_2$, -C(NH)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy, hydroxy, hydroxy(C_{1-4})alkyl, aryl and heteroaryl}.

Preferred embodiments of the present invention include compounds of Formula (I) wherein, R^1 is selected from the group consisting of hydrogen,

C_{1-4}alkyl, C_{2-4}alkenyl {wherein alkyl is substituted with one to two substituents independently selected from the group consisting of -O-(C_{1-4})alkyl-NH-(C_{1-4})alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4}alkyl), hydroxy, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkyl and halo)},

aryl and heteroaryl {wherein aryl and heteroaryl are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, $-CO_2H$, -C(O)-O-(C_{1-4})alkyl, $-C(O)-NH_2$, -C(NH)-NH_2,

-C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy, hydroxy, hydroxy(C_{1-4})alkyl, aryl and heteroaryl}.

More preferably, R^1 is selected from the group consisting of hydrogen,

C_{1-4}alkyl, C_{2-3}alkenyl {wherein alkyl is substituted with one to two substituents independently selected from the group consisting of -O-(C_{1-4})alkyl-NH-(C_{1-4})alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4}alkyl), hydroxy, pyrrolidinyl, morpholinyl, piperazinyl (wherein piperazinyl is optionally substituted with methyl), phenyl, naphthalenyl, benzo[b]thienyl and quinolinyl (wherein phenyl and benzo[b]thienyl are optionally substituted with one to two chloro substituents)},

phenyl, naphthalenyl, furyl, thienyl, pyridinyl, pyrimidinyl, benzo[b]thienyl, quinolinyl and isoquinolinyl (wherein phenyl, naphthalenyl and pyridinyl are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halo and hydroxy; and, wherein phenyl is optionally substituted with one substituent selected from the group consisting of phenyl and thienyl).

For the sake of clarity, when R^2 is alkynyl-Z, the unsaturated bond(s) in the alkynyl will not be directly linked to a nitrogen atom on Z or the indazolyl of Formula I.

Preferred embodiments of the present invention include compounds of Formula (I) wherein, R^2 is selected from the group consisting of:

-C_{1-4}alkyl-Z, -C_{2-4}alkenyl-Z and -C_{2-4}alkynyl-Z; wherein the -C_{1-4}alkyl, -

C_{2-4}alkeny and -C_{2-4}alkynyl is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4})alkylamino, C_{1-4}alkyl, C_{1-4}alkoxy, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy and hydroxy(C_{1-4})alkyl.

More preferably, R^2 is selected from the group consisting of:
-C_{1-4}alkyl-Z wherein the -C_{1-4}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4})alkylamino, C_{1-4}alkyl, C_{1-4}alkoxy, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy and hydroxy(C_{1-4})alkyl.

Preferred embodiments of the present invention include compounds of Formula I wherein Z is a 5 to 6 member monocyclic heteroaryl ring having from 2 to 4 heteroatoms containing at least one carbon atom and at least one nitrogen atom selected from the group consisting of pyrazine, pyrimidine, imidazol, pyridazine, triazine, furazan, isoxazole, isothiazole, thiazole, isothiazole, triazole, oxatriazole and tetrazole.

Most preferably Z is selected from the group consisting of imidazol, triazole, oxatriazole and tetrazole.

Most preferably Z is selected from the group consisting of oxatriazole and tetrazole.

Preferred embodiments of the present invention include compounds of Formula I wherein R^5 is 1 to 2 substituents attached to a carbon or nitrogen atom of Z and each substitute is independently selected from the group consisting of hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -C(O)H, -C(O)-(C_{1-4})alkyl, -CO_2H, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH(C_{1-4}alkyl), -C(O)-N(C_{1-4})alkyl)$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-4}alkyl), -SO_2-N(C_{1-4}alkyl)$_2$, -(C_{1-4})alkyl-NH_2,

-(C_{1-4})alkyl-NH(C_{1-4}alkyl), -(C_{1-4})alkyl- N(C_{1-4}alkyl)$_2$, -(C_{1-4})alkyl-(halo)$_{1-3}$, -(C_{1-4})alkyl-OH, -aryl, -(C_{1-4})alkyl-aryl, heteroaryl and -(C_{1-4})alkyl-heteroaryl; with the proviso that, when R^5 is attached to a carbon atom, R^5 is further selected from the group consisting of -C_{1-4}alkoxy, -(C_{1-4})alkoxy-(halo)$_{1-3}$, -SH, -S-(C_{1-4})alkyl, -N-R^6, cyano, halo, hydroxy, and nitro.

More preferably R^5 is 1 to 2 substituents attached to a carbon or nitrogen atom of Z and each substitute is independently selected from the group consisting of -C_{1-4}alkyl, -C_{2-4}alkenyl, -(C_{1-4})alkyl-NH_2, -(C_{1-4})alkyl-NH(C_{1-4}alkyl), -(C_{1-4})alkyl- N(C_{1-4}alkyl)$_2$, -(C_{1-4})alkyl-(halo)$_{1-3}$, -(C_{1-4})alkyl-OH, -(C_{1-4})alkyl-aryl, heteroaryl and -(C_{1-4})alkyl-heteroaryl; with the proviso that, when R^5 is attached to a carbon atom, R^5 is further selected from the group consisting of -C_{1-4}alkoxy, -(C_{1-4})alkoxy-(halo)$_{1-3}$, -S-(C_{1-4})alkyl, -N-R^6, halo, and hydroxy.

Most preferably R^5 is -C_{1-4}alkyl.

Preferred embodiments of the present invention include compounds of Formula I wherein R^6 is 1 to 2 substituents independently selected from the group consisting of hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -C_{3-4}cycloalkyl, -C(O)H, -C(O)-(C_{1-4})alkyl, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-4}alkyl), -C(O)-N(C_{1-4}alkyl)$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-4}alkyl), -SO_2-N(C_{1-4}alkyl)$_2$, -C(N)-NH_2, -C(N)-NH(C_{1-4}alkyl) and -C(N)-N(C_{1-4}alkyl)$_2$.

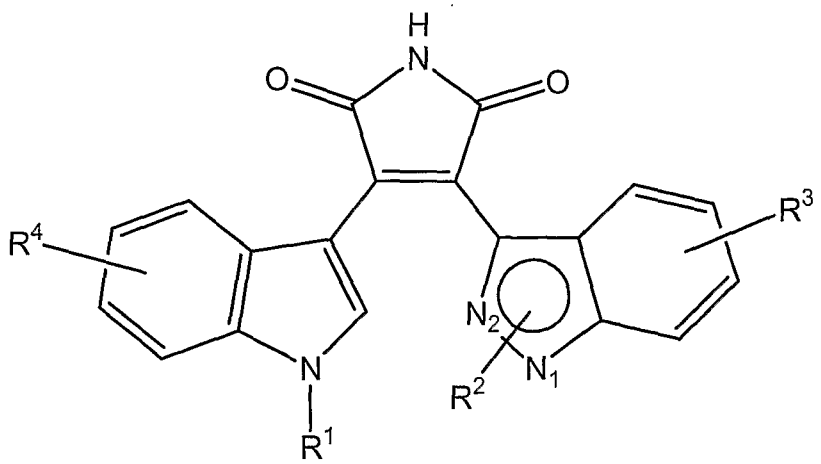
Preferred embodiments of the present invention include compounds of Formula (I) wherein, R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, -C(O)H, -C(O)-(C_{1-4})alkyl, -CO_2H, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SH, -S-(C_{1-4})alkyl, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen,

C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, -(C_{1-4})alkyl-NH_2, -C(O)-(C_{1-4})alkyl, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-4})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, -(C_{1-4})alkyl-NH_2, -C(O)-(C_{1-4})alkyl, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$ and -C(NH)-NH_2), cyano, halo, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy, hydroxy, hydroxy(C_{1-4})alkyl, nitro, aryl, -(C_{1-4})alkyl-aryl, heteroaryl and -(C_{1-4})alkyl-heteroaryl.

More preferably, R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, cyano and halogen.

Most preferably, R^3 and R^4 are independently selected from the group consisting of hydrogen, methyl, methoxy, cyano and chloro.

Exemplified compounds of Formula (I) include compounds selected from Formula (Ia) (N1 and N2 for the R^2 substituent indicate that R^2 is attached to the N1- or N2-position of the indazole ring, respectively):



Formula (Ia)

	No.	R^1	R^2	R^3	R^4	ES-MS m/z (MH^+)
	1	Me	N1-[imidazol-1-yl$(CH_2)_3$]	H	5-Cl;	485
	2	Me	N1-[triazol-1-yl$(CH_2)_3$]	H	5-Cl;	486
681140	3	Me	N1-[tetrazol-2-yl$(CH_2)_3$]	H	5-Cl;	487
681142	4	Me	N1-[tetrazol-1-yl$(CH_2)_3$]	H	5-Cl;	487
18018338	5	2-naphthyl	N1-[tetrazol-2-yl$(CH_2)_3$]	H	H;	565
18018351	6	2-naphthyl	N1-[tetrazol-1-yl$(CH_2)_3$]	H	H;	565
18024656	7	3-pyridinyl	N1-[tetrazol-2-yl$(CH_2)_3$]	H	H;	516
18024799	8	3-pyridinyl	N1-[tetrazol-1-yl$(CH_2)_3$]	H	H;	516
19410859	9	Me	N1-[5-Me-tetrazol-2-yl$(CH_2)_3$]	H	5-Cl;	501
19410872	10	Me	N1-[5-Me-tetrazol-1-yl$(CH_2)_3$]	H	5-Cl;	501
25757173	11	Me	N1-[tetrazol-5-yl$(CH_2)_2$]	H	5-Cl;	473
25901889	12	3-pyridinyl	N1-[tetrazol-5-yl$(CH_2)_2$]	H	5-Cl;	536

and pharmaceutically acceptable salts thereof.

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." FDA approved pharmaceutically acceptable salt forms (*Ref. International J. Pharm.* **1986**, 33, 201-217; *J. Pharm. Sci.*, **1977**, Jan, 66(1), p1)

include pharmaceutically acceptable acidic/anionic or basic/cationic salts. Pharmaceutically acceptable acidic/anionic salts include, and are not limited to acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphospate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate and triethiodide. Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, benzathine, calcium, chloroprocaine, choline, diethanolamine, ethylenediamine, lithium, magnesium, meglumine, potassium, procaine, sodium and zinc. Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Organic or inorganic acids also include, and are not limited to, hydriodic, perchloric, sulfuric, phosphoric, propionic, glycolic, methanesulfonic, hydroxyethanesulfonic, oxalic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, saccharinic or trifluoroacetic acid.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form or individual enantiomers may be prepared by standard techniques known to those skilled in the art, for example, by enantiospecific synthesis or resolution, formation of diastereomeric pairs by salt formation with an optically active acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents and such solvates are also intended to be encompassed within the scope of this invention.

Unless specified otherwise, the term "alkyl" refers to a saturated straight or branched chain consisting solely of 1-8 hydrogen substituted carbon atoms; preferably, 1-6 hydrogen substituted carbon atoms; and, most preferably, 1-4 hydrogen substituted carbon atoms. The term "alkenyl" refers to a partially unsaturated straight or branched chain consisting solely of 2-8 hydrogen substituted carbon atoms that contains at least one double bond. The term "alkynyl" refers to a partially unsaturated straight or branched chain consisting solely of 2-8 hydrogen substituted carbon atoms that contains at least one triple bond. The term "alkoxy" refers to –O-alkyl, where alkyl is as defined *supra.* The term "hydroxyalkyl" refers to radicals wherein the alkyl chain terminates with a hydroxy radical of the formula HO-alkyl, where alkyl is as defined *supra.* Alkyl, alkenyl and alkynyl chains are optionally substituted within the alkyl chain or on a terminal carbon atom.

The term "cycloalkyl" refers to a saturated or partially unsaturated monocyclic alkyl ring consisting of 3-8 hydrogen substituted carbon atoms or a saturated or partially unsaturated bicyclic ring consisting of 9 or 10 hydrogen substituted carbon atoms. Examples include, and are not limited to, cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "heterocyclyl" as used herein refers to an unsubstituted or substituted stable three to seven member monocyclic saturated or partially unsaturated ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O or S, or a stable eight to eleven member bicyclic saturated or partially saturated ring system which consists of carbon atoms and from one to four heteroatoms selected from N, O, or S. In either the monocyclic or bicyclic rings the nitrogen or sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. Preferred are saturated or partially unsaturated rings having five or six members of which at least one member is a N, O or S atom and which optionally contains one additional N, O or S atoms; saturated or partially unsaturated bicyclic rings

having nine or ten members of which at least one member is a N, O or S atom and which optionally contains one or two additional N, O or S atoms; wherein said nine or ten member bicyclic rings may have one aromatic ring and one nonaromatic ring. In another embodiment of this invention the previously defined heterocyclyl have as the additional heteroatom N, wherein at most two nitrogens atoms are adjacent. Examples include, and are not limited to, pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, thiazolidinyl, piperidinyl, morpholinyl or piperazinyl.

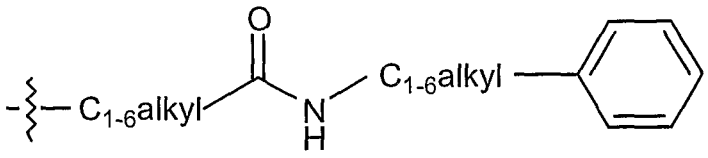
The term "aryl" refers to an aromatic monocyclic ring containing carbon and hydrogen, such as a carbon ring containing 6 carbon atom with hydrogen atoms substituted thereon, an aromatic bicyclic ring system containing 10 carbon atoms with hydrogen substituted thereon or an aromatic tricyclic ring system containing 14 carbon atoms with hydrogen atoms substituted thereon. Also included within the scope of the definition of aryl are bicyclic and tricyclic ring systems (containing carbon and hydrogen) wherein only one of the rings is aromatic such as tetrahydronaphthalene and indane. The hydrogen atoms on the monocyclic, bicyclic and tricyclic rings may be replaced with other groups or subsitutents as indicated. Examples include, and are not limited to, phenyl, naphthalenyl or anthracenyl.

The term "heteroaryl" as used herein represents an unsubstituted or substituted stable five or six member monocyclic heteroaromatic ring system or an unsubstituted or substituted stable nine or ten member bicyclic heteroaromatic ring system and unsubstituted or substituted stable twelve to fourteen member tricyclic ring systems which consists of carbon atoms and from one to four heteroatoms selected from N, O or S, and wherein the nitrogen heteroatom of any of these heteroaryls may optionally be oxidized, or may optionally be quaternized. Preferred heteroaryl are aromatic monocyclic rings containing five members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms; an aromatic monocyclic ring having six members of which one, two or three

members are a N atoms; an aromatic bicyclic ring having nine members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms; an aromatic bicyclic ring having ten members of which of which one, two, three or four members are N atoms; or, an aromatic tricyclic ring system containing 13 members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms. In another embodiment of this invention, the previously defined heteroaryls have as the additional heteroatom N, wherein at most four nitrogens atoms are adjacent. Examples include, and are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, oxatriazole, tetrazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazine, indolyl, indazolyl, benzo(*b*)thienyl, quinolinyl, isoquinolinyl or quinazolinyl.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (*e.g.*, aralkyl, alkylamino) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C_1-C_6) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

Under standard nomenclature rules used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. Thus, for example, a "phenylC_{1-6}alkylamidoC_{1-6}alkyl" substituent refers to a group of the formula:



A substituent's point of attachment may also be indicated by a dashed line to indicate the point(s) of attachment, followed by the adjacent functionality and ending with the terminal functionality such as, for example, _-(C_{1-6})alkyl-

C(O)NH-(C_{1-6})alkyl-phenyl.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

An embodiment of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. Illustrative of the invention is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. Further illustrative of the present invention are pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The compounds of the present invention are selective kinase or dual-kinase inhibitors useful in a method for treating or ameliorating a kinase or dual-kinase mediated disorder. In particular, the kinase is selected from protein kinase C or glycogen synthase kinase-3. More particularly, the kinase is selected from protein kinase C α, protein kinase C β-II, protein kinase C γ or glycogen synthase kinase-3β.

Protein Kinase C Isoforms

Protein kinase C is known to play a key role in intracellular signal transduction (cell-cell signaling), gene expression and in the control of cell differentiation and growth. The PKC family is composed of twelve isoforms that are further classified into 3 subfamilies: the calcium dependent classical PKC isoforms alpha (α), beta-I (β-I), beta-II (β-II) and gamma (γ); the calcium independent PKC isoforms delta (δ), epsilon (ε), eta (η), theta (θ) and mu (μ); and, the atypical PKC isoforms zeta (ζ), lambda (λ) and iota (ι).

Certain disease states tend to be associated with elevation of particular PKC isoforms. The PKC isoforms exhibit distinct tissue distribution, subcellular localization and activation-dependent cofactors. For example, the α and β isoforms of PKC are selectively induced in vascular cells stimulated with agonists such as vascular endothelial growth factor (VEGF) (P. Xia, et al., *J. Clin. Invest.*, **1996**, *98*, 2018) and have been implicated in cellular growth, differentiation, and vascular permeability (H. Ishii, et al., *J. Mol. Med.*, **1998**, *76*, 21). The elevated blood glucose levels found in diabetes leads to an isoform-specific elevation of the β-II isoform in vascular tissues (Inoguchi, et al., *Proc. Natl. Acad. Sci. USA*, **1992**, *89*, 11059-11065). A diabetes-linked elevation of the β isoform in human platelets has been correlated with their altered response to agonists (Bastyr III, E. J. and Lu, J., *Diabetes*, **1993**, *42*, (Suppl. 1) 97A). The human vitamin D receptor has been shown to be selectively phosphorylated by PKCβ. This phosphorylation has been linked to alterations in the functioning of the receptor (Hsieh, et al., *Proc. Natl. Acad. Sci. USA*, **1991**, *88*, 9315-9319; Hsieh, et al., *J. Biol. Chem.*, **1993**, *268*, 15118-15126). In addition, the work has shown that the β-II isoform is responsible for erythroleukemia cell proliferation while the α isoform is involved in megakaryocyte differentiation in these same cells (Murray, et al., *J. Biol. Chem.*, **1993**, *268*, 15847-15853).

Cardiovascular Diseases

PKC activity plays an important role in cardiovascular diseases. Increased PKC activity in the vasculature has been shown to cause increased vasoconstriction and hypertension (Bilder, G. E., et al., *J. Pharmacol. Exp. Ther.*, **1990**, 252, 526-530). PKC inhibitors block agonist-induced smooth muscle cell proliferation (Matsumoto, H. and Sasaki, Y., *Biochem. Biophys. Res. Commun.*, **1989**, *158*, 105-109). PKC β triggers events leading to induction of Egr-1 (Early Growth Factor-1) and tissue factor under hypoxic conditions (as part of the oxygen deprivation-mediated pathway for triggering procoagulant events) (Yan, S-F, et al., *J. Biol. Chem.*, **2000**, *275*, 16, 11921-11928). PKC β is suggested as a mediator for production of PAI-1 (Plaminogen Activator Inhibitor-1) and is implicated in the development of thrombosis and atherosclerosis (Ren, S, et al., *Am. J. Physiol.*, **2000**, *278*, (4, Pt. 1), E656-E662). PKC inhibitors are useful in treating cardiovascular ischemia and improving cardiac function following ischemia (Muid, R. E., et al., *FEBS Lett.*, **1990**, 293, 169-172; Sonoki,, H. et al., *Kokyu-To Junkan*, **1989**, *37*, 669-674). Elevated PKC levels have been correlated with an increased platelet function response to agonists (Bastyr III, E. J. and Lu, J., *Diabetes*, **1993**, *42*, (Suppl. 1) 97A). PKC has been implicated in the biochemical pathway in the platelet-activating factor (PAF) modulation of microvascular permeability (Kobayashi, et al., *Amer. Phys. Soc.*, **1994**, H1214- H1220). PKC inhibitors affect agonist-induced aggregation in platelets (Toullec, D., et al., *J. Biol. Chem.*, **1991**, *266*, 15771-15781). Accordingly, PKC inhibitors may be indicated for use in treating cardiovascular disease, ischemia, thrombotic conditions, atherosclerosis and restenosis.

Diabetes

Excessive activity of PKC has been linked to insulin signaling defects and therefore to the insulin resistance seen in Type II diabetes (Karasik, A., et al., *J. Biol. Chem.*, **1990**, *265*, 10226-10231; Chen, K. S., et al., *Trans. Assoc. Am. Physicians*, **1991**, *104*, 206-212; Chin, J. E., et al., *J. Biol. Chem.*, **1993**, *268*, 6338-6347).

Diabetes-Associated Disorders

Studies have demonstrated an increase in PKC activity in tissues known to be susceptible to diabetic complications when exposed to hyperglycemic conditions (Lee, T-S., et al., *J. Clin. Invest.*, **1989**, *83*, 90-94; Lee, T-S., et al., *Proc. Natl. Acad. Sci. USA*, **1989**, *86*, 5141-5145; Craven, P. A. and DeRubertis, F. R., *J. Clin. Invest.*, **1989**, *87*, 1667-1675; Wolf, B. A., et al., *J. Clin. Invest.*, **1991**, *87*, 31- 38; Tesfamariam, B., et al., *J. Clin. Invest.*, **1991**, *87*, 1643-1648). For example, activation of the PKC-β-II isoform plays an important role in diabetic vascular complications such as retinopathy (Ishii, H., et al., *Science*, **1996**, *272*, 728-731) and PKCβ has been implicated in development of the cardiac hypertrophy associated with heart failure (X. Gu, et al., *Circ. Res.*, **1994**, *75*, 926; R. H. Strasser, et al., *Circulation*, **1996**, *94*, I551). Overexpression of cardiac PKCβII in transgenic mice caused cardiomyopathy involving hypertrophy, fibrosis and decreased left ventricular function (H. Wakasaki, et al., *Proc. Natl. Acad. Sci. USA*, **1997**, *94*, 9320).

Inflammatory Diseases

PKC inhibitors block inflammatory responses such as the neutrophil oxidative burst, CD3 down-regulation in T-lymphocytes and phorbol-induced paw edema (Twoemy, B., et al., *Biochem. Biophys. Res. Commun.*, **1990**, *171*, 1087-1092; Mulqueen, M. J., et al. *Agents Actions,* **1992**, *37*, 85-89). PKC β has an essential role in the degranulation of bone marrow-derived mast cells, thus affecting cell capacity to produce IL-6 (Interleukin-6) (Nechushtan, H., et al., *Blood,* **2000** (March), *95*, 5, 1752-1757). PKC plays a role in enhanced ASM (Airway Smooth Muscle) cell growth in rat models of two potential risks for asthma: hyperresponsiveness to contractile agonists and to growth stimuli (Ren, S, et al., *Am. J. Physiol.*, **2000**, *278*, (4, Pt. 1), E656-E662). PKC β-1 overexpression augments an increase in endothelial permeability, suggesting an important function in the regulation of the endothelial barrier (Nagpala, P.G., et al., *J. Cell Physiol.*, **1996**, *2*, 249-55). PKC β mediates activation of

neutrophil NADPH oxidase by PMA and by stimulation of Fcγ receptors in neutrophils (Dekker, L.V., et al., *Biochem. J.*, **2000**, *347*, 285-289). Thus, PKC inhibitors may be indicated for use in treating inflammation and asthma.

Immunological Disorders

PKC may be useful in treating or ameliorating certain immunological disorders. While one study suggests that HCMV (Human Cytomegalovirus) inhibition is not correlated with PKC inhibition (Slater, M.J., et al., *Biorg. & Med. Chem.*, **1999**, *7*, 1067-1074), another study showed that the PKC signal transduction pathway synergistically interacted with the cAMP-dependent PKA pathway to activate or increase HIV-1 transcription and viral replication and was abrogated with a PKC inhibitor (Rabbi, M.F., et al., *Virology*, **1998** (June 5), *245*, 2, 257-69). Therefore, an immunological disorder may be treated or ameliorated as a function of the affected underlying pathway's response to up- or down-regulation of PKC.

PKC β deficiency also results in an immunodeficiency characterized by impaired humoral immune responses and a reduced B cell response, similar to X-linked immunodeficiency in mice, playing an important role in antigen receptor-mediated signal transduction (Leitges, M., et al., *Science (Wash., D.C.)*, **1996**, *273*, 5276, 788-789). Accordingly, transplant tissue rejection may be ameliorated or prevented by suppressing the immune response using a PKC β inhibitor.

Dermatological Disorders

Abnormal activity of PKC has been linked to dermatological disorders characterized by abnormal proliferation of keratinocytes, such as psoriasis (Horn, F., et al., *J. Invest. Dermatol.*, **1987**, *88*, 220-222; Raynaud, F. and Evain-Brion, D., *Br. J. Dermatol.*, **1991**, *124*, 542-546). PKC inhibitors have been shown to inhibit keratinocyte proliferation in a dose-dependent manner (Hegemann, L., et al., *Arch. Dermatol. Res.*, **1991**, *283*, 456-460; Bollag, W. B., et al., *J. Invest. Dermatol.*, **1993**, *100*, 240-246).

Oncological Disorders

PKC activity has been associated with cell growth, tumor promotion and cancer (Rotenberg, S. A. and Weinstein, I. B., *Biochem. Mol. Aspects Sel. Cancer*, **1991**, *1*, 25-73; Ahmad, et al., *Molecular Pharmacology*, **1993**, *43*, 858-862); PKC inhibitors are known to be effective in preventing tumor growth in animals (Meyer, T., et al., *Int. J. Cancer,* **1989**, *43*, 851-856; Akinagaka, S., et al., *Cancer Res.*, **1991**, *51*, 4888-4892). PKC β-1 and β-2 expression in differentiated HD3 colon carcinoma cells blocked their differentiation, enabling them to proliferate in response to basic FGF (Fibroblast Growth Factor) like undifferentiated cells, increasing their growth rate and activating several MBP (Myelin-Basic Protein) kinases, including p57 MAP (Mitogen-Activated Protein) kinase (Sauma, S., et al., *Cell Growth Differ.,* **1996**, *7*, 5, 587-94). PKC α inhibitors, having an additive therapeutic effect in combination with other anti-cancer agents, inhibited the growth of lymphocytic leukemia cells (Konig, A., et al., *Blood,* **1997**, *90*, 10, Suppl. 1 Pt. 2). PKC inhibitors enhanced MMC (Mitomycin-C) induced apoptosis in a time-dependent fashion in a gastric cancer cell-line, potentially indicating use as agents for chemotherapy-induced apoptosis (Danso, D., et al., *Proc. Am. Assoc. Cancer Res.,* **1997**, *38*, 88 Meet., 92). Therefore, PKC inhibitors may be indicated for use in ameliorating cell and tumor growth, in treating or ameliorating cancers (such as leukemia or colon cancer) and as adjuncts to chemotherapy.

PKC α (by enhancing cell migration) may mediate some proangiogenic effects of PKC activation while PKC δ may direct antiangiogenic effects of overall PKC activation (by inhibiting cell growth and proliferation) in capillary endothelial cells, thus regulating endothelial proliferation and angiogenesis (Harrington, E.O., et al., *J. Biol. Chem.,* **1997**, *272*, 11, 7390-7397). PKC inhibitors inhibit cell growth and induce apoptosis in human glioblastoma cell lines, inhibit the growth of human astrocytoma xenografts and act as radiation sensitizers in glioblastoma cell lines (Begemann, M., et al., *Anticancer Res. (Greece),* **1998** (Jul-Aug), *18*, 4A, 2275-82). PKC inhibitors, in combination

with other anti-cancer agents, are radiation and chemosensitizers useful in cancer therapy (Teicher, B.A., et al., *Proc. Am. Assoc. Cancer Res.,* **1998**, *39*, 89 Meet., 384). PKC β inhibitors (by blocking the MAP kinase signal transduction pathways for VEGF (Vascular Endothelial Growth Factor) and bFGF (basic Fibrinogen Growth Factor) in endothelial cells), in a combination regimen with other anti-cancer agents, have an anti-angiogenic and antitumor effect in a human T98G glioblastoma multiforme xenograft model (Teicher, B.A., et al., *Clinical Cancer Research,* **2001** (March), *7*, 634-640). Accordingly, PKC inhibitors may be indicated for use in ameliorating angiogenesis and in treating or ameliorating cancers (such as breast, brain, kidney, bladder, ovarian or colon cancers) and as adjuncts to chemotherapy and radiation therapy.

Central Nervous System Disorders

PKC activity plays a central role in the functioning of the central nervous system (CNS) (Huang, K. P., *Trends Neurosci.,* **1989**, *12*, 425-432) and PKC is implicated in Alzheimer's disease (Shimohama, S., et al., *Neurology,* **1993**, *43*, 1407-1413) and inhibitors have been shown to prevent the damage seen in focal and central ischemic brain injury and brain edema (Hara, H., et al., *J. Cereb. Blood Flow Metab.,* **1990**, 10, 646-653; Shibata, S., et al., *Brain Res.,* **1992**, 594, 290-294). Accordingly, PKC inhibitors may be indicated for use in treating Alzheimer's disease and in treating neurotraumatic and ischemia-related diseases.

The long-term increase in PKC γ (as a component of the phosphoinositide 2nd messenger system) and muscarinic acetylcholine receptor expression in an amygdala-kindled rat model has been associated with epilepsy, serving as a basis for the rat's permanent state of hyperexcitability (Beldhuis, H.J.A., et al., *Neuroscience,* **1993**, *55*, 4, 965-73). Therefore, PKC inhibitors may be indicated for use in treating epilepsy.

The subcellular changes in content of the PKC γ and PKC β-II isoenzymes for animals in an *in-vivo* thermal hyperalgesia model suggests that

peripheral nerve injury contributes to the development of persistent pain (Miletic, V., et al., *Neurosci. Lett.*, **2000**, *288*, 3, 199-202). Mice lacking PKC γ display normal responses to acute pain stimuli, but almost completely fail to develop a neuropathic pain syndrome after partial sciatic nerve section (Chen, C., et al., *Science (Wash., D.C.)*, **1997**, *278*, 5336, 279-283). PKC modulation may thus be indicated for use in treating chronic pain and neuropathic pain.

PKC has demonstrated a role in the pathology of conditions such as, but not limited to, cardiovascular diseases, diabetes, diabetes-associated disorders, inflammatory diseases, immunological disorders, dermatological disorders, oncological disorders and central nervous system disorders.

Glycogen Synthase Kinase-3

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase composed of two isoforms (α and β) which are encoded by distinct genes. GSK-3 is one of several protein kinases which phosphorylate glycogen synthase (GS) (Embi, et al., *Eur. J. Biochem*, **1980**, *107*, 519-527). The α and β isoforms have a monomeric structure of 49 and 47kD respectively and are both found in mammalian cells. Both isoforms phosphorylate muscle glycogen synthase (Cross, et al., *Biochemical Journal*, **1994**, *303*, 21-26) and these two isoforms show good homology between species (human and rabbit GSK-3α are 96% identical).

Diabetes

Type II diabetes (or Non-Insulin Dependent Diabetes Mellitus, NIDDM) is a multifactorial disease. Hyperglycemia is due to insulin resistance in the liver, muscle and other tissues coupled with inadequate or defective secretion of insulin from pancreatic islets. Skeletal muscle is the major site for insulin-stimulated glucose uptake and in this tissue glucose removed from the circulation is either metabolised through glycolysis and the TCA (tricarboxylic acid) cycle or stored as glycogen. Muscle glycogen deposition plays the more important role in glucose homeostasis and Type II diabetic subjects have

defective muscle glycogen storage. The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of glycogen synthase (Villar-Palasi C. and Larner J., *Biochim. Biophys. Acta*, **1960**, *39*, 171-173, Parker P.J., et al., *Eur. J. Biochem.*, **1983**, *130*, 227-234, and Cohen P., *Biochem. Soc. Trans.*, **1993**, *21*, 555-567). The phosphorylation and dephosphorylation of GS are mediated by specific kinases and phosphatases. GSK-3 is responsible for phosphorylation and deactivation of GS, while glycogen bound protein phosphatase 1 (PP1G) dephosphorylates and activates GS. Insulin both inactivates GSK-3 and activates PP1G (Srivastava A.K. and Pandey S.K., *Mol. and Cellular Biochem.*, **1998**, *182*, 135-141).

Studies suggest that an increase in GSK-3 activity might be important in Type II diabetic muscle (Chen, et al., *Diabetes*, **1994**, *43*, 1234-1241). Overexpression of GSK-3β and constitutively active GSK-3β (S9A, S9e) mutants in HEK-293 cells resulted in suppression of glycogen synthase activity (Eldar-Finkelman, et al., *PNAS*, **1996**, *93*, 10228-10233) and overexpression of GSK-3β in CHO cells, expressing both insulin receptor and insulin receptor substrate 1 (IRS-1) resulted in impairment of insulin action (Eldar-Finkelman and Krebs, *PNAS*, **1997**, *94*, 9660-9664). Recent evidence for the involvement of elevated GSK-3 activity and the development of insulin resistance and Type II diabetes in adipose tissue has emerged from studies undertaken in diabetes and obesity prone C57BL/6J mice (Eldar-Finkelman, et al., *Diabetes*, **1999**, *48*, 1662-1666).

Dermatological Disorders

The finding that transient β-catenin stabilization may play a role in hair development (Gat, et al., *Cell*, **1998**, *95*, 605-614) suggests that GSK-3 inhibitors could also be used in the treatment of baldness.

Inflammatory Diseases

Studies on fibroblasts from the GSK-3β knockout mouse indicate that

inhibition of GSK-3 may be useful in treating inflammatory disorders or diseases through the negative regulation of NFkB activity (Hoeflich K. P., et al., *Nature*, **2000**, *406*, 86-90).

Central Nervous System Disorders

In addition to modulation of glycogen synthase activity, GSK-3 also plays an important role in the CNS disorders. GSK-3 inhibitors may be of value as neuroprotectants in the treatment of acute stroke and other neurotraumatic injuries (Pap and Cooper, *J. Biol. Chem.*, **1998**, *273*, 19929-19932). Lithium, a low mM inhibitor of GSK-3, has been shown to protect cerebellar granule neurons from death (D'Mello, et al., *Exp. Cell Res.*, **1994**, *211*, 332-338) and chronic lithium treatment has demonstrable efficacy in the middle cerebral artery occlusion model of stroke in rodents (Nonaka and Chuang, *Neuroreport*, **1998**, *9(9)*, 2081-2084).

Tau and β-catenin, two known *in vivo* substrates of GSK-3, are of direct relevance in consideration of further aspects of the value of GSK-3 inhibitors in relation to treatment of chronic neurodegenerative conditions. Tau hyperphosphorylation is an early event in neurodegenerative conditions such as Alzheimer's disease and is postulated to promote microtubule disassembly. Lithium has been reported to reduce the phosphorylation of tau, enhance the binding of tau to microtubules and promote microtubule assembly through direct and reversible inhibition of GSK-3 (Hong M. et al *J. Biol. Chem.*, **1997**, *272(40)*, 25326-32). β-catenin is phosphorylated by GSK-3 as part of a tripartite axin protein complex resulting in β-catenin degradation (Ikeda, et al., *EMBO J.*, **1998**, *17*, 1371-1384). Inhibition of GSK-3 activity is involved in the stabilization of catenin hence promotes β-catenin-LEF-1/TCF transcriptional activity (Eastman, Grosschedl, *Curr. Opin. Cell Biol.*, **1999**, *11*, 233). Studies have also suggested that GSK-3 inhibitors may also be of value in treatment of schizophrenia (Cotter D., et al. *Neuroreport*, **1998**, *9*, 1379-1383; Lijam N., et al., *Cell*, **1997**, *90*, 895-905) and manic depression (Manji, et al., *J. Clin.*

Psychiatry, **1999**, *60*, (Suppl 2) 27-39 for review).

Accordingly, compounds found useful as GSK-3 inhibitors could have further therapeutic utility in the treatment of diabetes, dermatological disorders, inflammatory diseases and central nervous system disorders.

Embodiments of the method of the present invention include a method for treating or ameliorating a kinase or dual-kinase mediated disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an instant compound or pharmaceutical composition thereof. The therapeutically effective amount of the compounds of Formula (I) exemplified in such a method is from about 0.001 mg/kg/day to about 300 mg/kg/day.

Embodiments of the present invention include the use of a compound of Formula (I) for the preparation of a medicament for treating or ameliorating a kinase or dual-kinase mediated disorder in a subject in need thereof.

In accordance with the methods of the present invention, an individual compound of the present invention or a pharmaceutical composition thereof can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

Embodiments of the present method include a compound or pharmaceutical composition thereof advantageously co-administered in combination with other agents for treating or ameliorating a kinase or dual-kinase mediated disorder. For example, in the treatment of diabetes, especially Type II diabetes, a compound of Formula (I) or pharmaceutical composition thereof may be used in combination with other agents, especially

insulin or antidiabetic agents including, but not limited to, insulin secretagogues (such as sulphonylureas), insulin sensitizers including, but not limited to, glitazone insulin sensitizers (such as thiazolidinediones) or biguanides or α glucosidase inhibitors.

The combination product comprises co-administration of a compound of Formula (I) or pharmaceutical composition thereof and an additional agent for treating or ameliorating a kinase or dual-kinase mediated disorder, the sequential administration of a compound of Formula (I) or pharmaceutical composition thereof and an additional agent for treating or ameliorating a kinase or dual-kinase mediated disorder, administration of a pharmaceutical composition containing a compound of Formula (I) or pharmaceutical composition thereof and an additional agent for treating or ameliorating a kinase or dual-kinase mediated disorder or the essentially simultaneous administration of a separate pharmaceutical composition containing a compound of Formula (I) or pharmaceutical composition thereof and a separate pharmaceutical composition containing an additional agent for treating or ameliorating a kinase or dual-kinase mediated disorder.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

The ubiquitous nature of the PKC and GSK isoforms and their important roles in physiology provide incentive to produce highly selective PKC and GSK inhibitors. Given the evidence demonstrating linkage of certain isoforms to

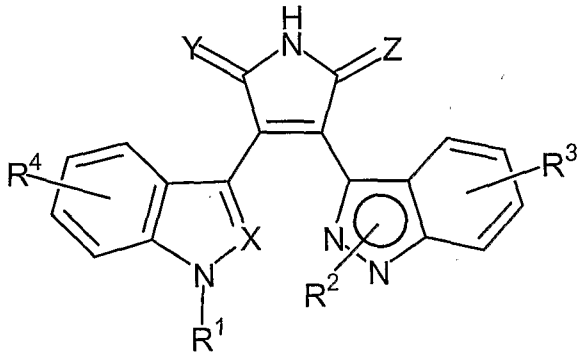
disease states, it is reasonable to assume that inhibitory compounds that are selective to one or two PKC isoforms or to a GSK isoform relative to the other PKC and GSK isoforms and other protein kinases are superior therapeutic agents. Such compounds should demonstrate greater efficacy and lower toxicity by virtue of their specificity. Accordingly, it will be appreciated by one skilled in the art that a compound of Formula (I) is therapeutically effective for certain kinase or dual-kinase mediated disorders based on the modulation of the disorder by selective kinase or dual-kinase inhibition. The usefulness of a compound of Formula (I) as a selective kinase or dual-kinase inhibitor can be determined according to the methods disclosed herein and the scope of such use includes use in one or more kinase or dual-kinase mediated disorders.

Therefore, the term "kinase or dual-kinase mediated disorders" as used herein, includes, and is not limited to, cardiovascular diseases, diabetes, diabetes-associated disorders, inflammatory diseases, immunological disorders, dermatological disorders, oncological disorders and CNS disorders.

Cardiovascular diseases include, and are not limited to, acute stroke, heart failure, cardiovascular ischemia, thrombosis, atherosclerosis, hypertension, restenosis, retinopathy of prematurity or age-related macular degeneration. Diabetes includes insulin dependent diabetes or Type II non-insulin dependent diabetes mellitus. Diabetes-associated disorders include, and are not limited to, impaired glucose tolerance, diabetic retinopathy, proliferative retinopathy, retinal vein occlusion, macular edema, cardiomyopathy, nephropathy or neuropathy. Inflammatory diseases include, and are not limited to, vascular permeability, inflammation, asthma, rheumatoid arthritis or osteoarthritis. Immunological disorders include, and are not limited to, transplant tissue rejection, HIV-1 or immunological disorders treated or ameliorated by PKC modulation. Dermatological disorders include, and are not limited to, psoriasis, hair loss or baldness. Oncological disorders include, and are not limited to, cancers or tumor growth (such as breast, brain, kidney, bladder, ovarian or colon cancer or leukemia), proliferative angiopathy and

angiogenesis; and, includes use for compounds of Formula (I) as an adjunct to chemotherapy and radiation therapy. CNS disorders include, and are not limited to, chronic pain, neuropathic pain, epilepsy, chronic neurodegenerative conditions (such as dementia or Alzheimer's disease), mood disorders (such as schizophrenia), manic depression or neurotraumatic, cognitive decline and ischemia-related diseases {as a result of head trauma (from acute ischemic stroke, injury or surgery) or transient ischemic stroke (from coronary bypass surgery or other transient ischemic conditions)}.

In another embodiment of a method of treating or ameliorating a disorder selected from the group consisting of diabetes-associated disorders, dermatological disorders, oncological disorders and central nervous system disorders comprising administering to a subject in need of treatment a therapeutically effective amount of a compound of Formula (I):



Formula (I)

wherein

R^1 is selected from the group consisting of:

hydrogen,

C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{3-8} cycloalkyl {wherein alkyl, alkenyl, alkynyl and C_{3-8} cycloalkyl are optionally substituted with one to two substituents independently selected from the group consisting of -O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-OH, -O-(C_{1-8})alkyl-O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-NH_2, -O-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -O-(C_{1-8})alkyl-S-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-NH_2, -O-(C_{1-8})alkyl-SO_2-NH-(C_{1-8})alkyl,

-O-(C_{1-8})alkyl-SO_2-N[(C_{1-8})alkyl]$_2$, -O-C(O)H, -O-C(O)-(C_{1-8})alkyl, -O-C(O)-NH_2, -O-C(O)-NH-(C_{1-8})alkyl, -O-C(O)-N[(C_{1-8})alkyl]$_2$, -O-(C_{1-8})alkyl-C(O)H, -O-(C_{1-8})alkyl-C(O)-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-CO_2H, -O-(C_{1-8})alkyl-C(O)-O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-C(O)-NH_2, -O-(C_{1-8})alkyl-C(O)-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-C(O)-N[(C_{1-8})alkyl]$_2$, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-S-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-OH, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-NH_2, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -S-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-OH, -(C_{1-8})alkyl-O-(C_{1-8})alkyl, -(C_{1-8})alkyl-NH_2, -(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -(C_{1-8})alkyl-S-(C_{1-8})alkyl, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, -C(N)-NH_2, aryl and aryl(C_{1-8})alkyl (wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-8}alkyl, C_{1-8}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-8}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl, (halo)$_{1-3}$(C_{1-8})alkoxy, hydroxy, hydroxy(C_{1-8})alkyl and nitro)), cyano, (halo)$_{1-3}$, hydroxy, nitro, oxo, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-8}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl, (halo)$_{1-3}$(C_{1-8})alkoxy, hydroxy, hydroxy(C_{1-8})alkyl and nitro)},

-C(O)-(C_{1-8})alkyl, -C(O)-aryl, -C(O)-O-(C_{1-8})alkyl, -C(O)-O-aryl, -C(O)-NH-(C_{1-8})alkyl, -C(O)-NH-aryl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-aryl,

aryl and heteroaryl {wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-8})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl-, (halo)$_{1-3}$(C_{1-8})alkoxy-, hydroxy, hydroxy(C_{1-8})alkyl, nitro, aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl};

R^2 is selected from the group consisting of -C_{1-8}alkyl-Z, -C_{2-8}alkenyl-Z and -C_{2-8}alkynyl-Z; wherein the -C_{1-8}alkyl, -C_{2-8}alkenyl and -C_{2-8}alkynyl is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4})alkylamino, C_{1-4}alkyl, C_{1-4}alkoxy, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy and hydroxy(C_{1-4})alkyl;

Z is a 5 to 6 member monocyclic heteroaryl ring having from 2 to 4

heteroatoms containing at least one carbon atom and at least one nitrogen atom; wherein Z optionally is substituted with R^5;

R^5 is 1 to 2 substituents attached to a carbon or nitrogen atom of Z and each substitute is independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH(C_{1-8}alkyl), -C(O)-N(C_{1-8})alkyl)$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-8}alkyl), -SO_2-N(C_{1-8}alkyl)$_2$, -(C_{1-8})alkyl-NH_2, -(C_{1-8})alkyl-NH(C_{1-8}alkyl), -(C_{1-8})alkyl-N(C_{1-8}alkyl)$_2$, -(C_{1-8})alkyl-(halo)$_{1-3}$, -(C_{1-8})alkyl-OH, -aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl;

with the proviso that, when R^5 is attached to a carbon atom, R^5 is further selected from the group consisting of -C_{1-8}alkoxy, -(C_{1-8})alkoxy-(halo)$_{1-3}$, -SH, -S-(C_{1-8})alkyl, -N-R^6, cyano, halo, hydroxy, and nitro;

R^6 is 1 to 2 substituents independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, - C_{3-8}cycloalkyl, -C(O)H, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-8}alkyl), -C(O)-N(C_{1-8}alkyl)$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-8}alkyl), -SO_2-N(C_{1-8}alkyl)$_2$, -C(N)-NH_2, -C(N)-NH(C_{1-8}alkyl) and -C(N)-N(C_{1-8}alkyl)$_2$;

R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-8})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen,

C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl-, (halo)$_{1-3}$(C_{1-8})alkoxy-, hydroxy, hydroxy(C_{1-8})alkyl-, nitro, aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl;

and pharmaceutically acceptable salts thereof.

A compound may be administered to a subject in need of treatment by any conventional route of administration including, but not limited to oral, nasal, sublingual, ocular, transdermal, rectal, vaginal and parenteral (i.e. subcutaneous, intramuscular, intradermal, intravenous etc.).

To prepare the pharmaceutical compositions of this invention, one or more compounds of Formula (I) or salt thereof as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral). Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in The Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

Methods of formulating pharmaceutical compositions have been described in numerous publications such as Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, Volumes 1-3, edited by Lieberman, et al.; Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1-2, edited by Avis, et al.; and Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1-2, edited by Lieberman, et al.; published by Marcel Dekker, Inc.

In preparing a pharmaceutical composition of the present invention in liquid dosage form for oral, topical and parenteral administration, any of the usual pharmaceutical media or excipients may be employed. Thus, for liquid dosage forms, such as suspensions (i.e. colloids, emulsions and dispersions) and solutions, suitable carriers and additives include but are not limited to pharmaceutically acceptable wetting agents, dispersants, flocculation agents, thickeners, pH control agents (i.e. buffers), osmotic agents, coloring agents, flavors, fragrances, preservatives (i.e. to control microbial growth, etc.) and a liquid vehicle may be employed. Not all of the components listed above will be required for each liquid dosage form.

In solid oral preparations such as, for example, powders, granules, capsules, caplets, gelcaps, pills and tablets (each including immediate release, timed release and sustained release formulations), suitable carriers and additives include but are not limited to diluents, granulating agents, lubricants, binders, glidants, disintegrating agents and the like. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated, gelatin coated, film coated or enteric coated by standard techniques.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 0.001 mg to about 300 mg (preferably, from about 0.01 mg to about 100 mg; and, more preferably, from about 0.1 mg to about 30 mg) and may be given at a dosage of from about 0.001 mg/kg/day to about 300 mg/kg/day (preferably, from about 0.01 mg/kg/day to about 100 mg/kg/day; and, more preferably, from about 0.1 mg/kg/day to about 30 mg/kg/day).

Preferably, in the method for treating or ameliorating a kinase or dual-kinase mediated disorder described in the present invention and using any of the compounds as defined herein, the dosage form will contain a pharmaceutically acceptable carrier containing between about 0.01 mg and 100 mg; and, more preferably, between about 5 mg and 50 mg of the compound; and, may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, lozenges, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories for administration by oral, intranasal, sublingual, intraocular, transdermal, parenteral, rectal, vaginal, inhalation or insufflation means. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection.

For preparing solid pharmaceutical compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as diluents, binders, adhesives, disintegrants, lubricants, antiadherents and glidants. Suitable diluents include, but are not limited to, starch (i.e. corn, wheat, or potato starch, which may be hydrolized), lactose (granulated, spray dried or anhydrous), sucrose, sucrose-based diluents (confectioner's sugar; sucrose plus about 7 to 10 weight percent invert sugar; sucrose plus about 3 weight percent modified dextrins; sucrose plus invert sugar, about 4 weight percent invert sugar, about 0.1 to 0.2 weight percent cornstarch and magnesium stearate), dextrose, inositol, mannitol, sorbitol, microcrystalline cellulose (i.e. AVICEL ™ microcrystalline cellulose

available from FMC Corp.), dicalcium phosphate, calcium sulfate dihydrate, calcium lactate trihydrate and the like. Suitable binders and adhesives include, but are not limited to acacia gum, guar gum, tragacanth gum, sucrose, gelatin, glucose, starch, and cellulosics (i.e. methylcellulose, sodium carboxymethycellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, and the like), water soluble or dispersible binders (i.e. alginic acid and salts thereof, magnesium aluminum silicate, hydroxyethylcellulose (i.e. TYLOSE ™ available from Hoechst Celanese), polyethylene glycol, polysaccharide acids, bentonites, polyvinylpyrrolidone, polymethacrylates and pregelatinized starch) and the like. Suitable disintegrants include, but are not limited to, starches (corn, potato, etc.), sodium starch glycolates, pregelatinized starches, clays (magnesium aluminum silicate), celluloses (such as crosslinked sodium carboxymethylcellulose and microcrystalline cellulose), alginates, pregelatinized starches (i.e. corn starch, etc.), gums (i.e. agar, guar, locust bean, karaya, pectin and tragacanth gum), cross-linked polyvinylpyrrolidone and the like. Suitable lubricants and antiadherents include, but are not limited to, stearates (magnesium, calcium and sodium), stearic acid, talc waxes, stearowet, boric acid, sodium chloride, DL-leucine, carbowax 4000, carbowax 6000, sodium oleate, sodium benzoate, sodium acetate, sodium lauryl sulfate, magnesium lauryl sulfate and the like. Suitable glidants include, but are not limited to, talc, cornstarch, silica (i.e. CAB-O-SIL ™ silica available from Cabot, SYLOID ™ silica available from W.R. Grace/Davison and AEROSIL ™ silica available from Degussa) and the like. Sweeteners and flavorants may be added to chewable solid dosage forms to improve the palatability of the oral dosage form. Additionally, colorants and coatings may be added or applied to the solid dosage form for ease of identification of the drug or for aesthetic purposes. These carriers are formulated with the pharmaceutical active to provide an accurate, appropriate dose of the pharmaceutical active with a therapeutic release profile.

Generally these carriers are mixed with the pharmaceutical active to form a solid preformulation composition containing a homogeneous mixture of

the pharmaceutical active of the present invention, or a pharmaceutically acceptable salt thereof. Generally the preformulation will be formed by one of three common methods: (a) wet granulation, (b) dry granulation and (c)dry blending. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from about 0.1 mg to about 500 mg of the active ingredient of the present invention. The tablets or pills containing the novel compositions may also be formulated in multilayer tablets or pills to provide a sustained or provide dual-release products. For example, a dual release tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric materials such as shellac, cellulose acetate (i.e. cellulose acetate phthalate), polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, methacrylate and ethylacrylate copolymers, methacrylate and methyl methacrylate copolymers and the like. Sustained release tablets may also be made by film coating or wet granulation using slightly soluble or insoluble substances in solution (which for a wet granulation acts as the binding agents) or low melting solids a molten form (which in a wet granulation may incorporate the active ingredient). These materials include natural and synthetic polymers waxes, hydrogenated oils, fatty acids and alcohols (i.e. beeswax, carnauba wax, cetyl alcohol, cetylstearyl alcohol and the like), esters of fatty acids metallic soaps and other acceptable materials that can be used to granulate, coat, entrap or otherwise limit the solubility of an active ingredient to achieve a prolonged or sustained release product.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, but are not limited to aqueous solutions, suitably flavored syrups, aqueous or oil suspensions and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable suspending agents for aqueous suspensions, include synthetic and natural gums such as, acacia, agar, alginate (i.e. propylene alginate, sodium alginate and the like), guar, karaya, locust bean, pectin, tragacanth and xanthan gum, cellulosics such as sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose and combinations thereof, synthetic polymers such as polyvinyl pyrrolidone, carbomer (i.e. carboxypolymethylene) and polyethylene glycol; clays such as bentonite, hectorite, attapulgite or sepiolite; and other pharmaceutically acceptable suspending agents such as lecithin, gelatin or the like. Suitable surfactants include but are not limited to sodium docusate, sodium lauryl sulfate, polysorbate, octoxynol-9, nonoxynol-10, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polyoxamer 188, polyoxamer 235 and combinations thereof. Suitable deflocculating or dispersing agent include pharmaceutical grade lecithins. Suitable flocculating agent include but are not limited to simple neutral electrolytes (i.e. sodium chloride, potassium, chloride and the like), highly charged insoluble polymers and polyelectrolyte species, water soluble divalent or trivalent ions (i.e. calcium salts, alums or sulfates, citrates and phosphates (which can be used jointly in formulations as pH buffers and flocculating agents). Suitable preservatives include but are not limited to parabens (i.e. methyl, ethyl, *n*-propyl and *n*-butyl), sorbic acid, thimerosal, quaternary ammonium salts, benzyl alcohol, benzoic acid, chlorhexidine gluconate, phenylethanol and the like. There are many liquid vehicles that may be used in liquid pharmaceutical dosage forms, however, the liquid vehicle that is used in a particular dosage form must be compatible with the suspending agent(s). For example, nonpolar liquid vehicles such as fatty

esters and oils liquid vehicles are best used with suspending agents such as low HLB (Hydrophile-Lipophile Balance) surfactants, stearalkonium hectorite, water insoluble resins, water insoluble film forming polymers and the like. Conversely, polar liquids such as water, alcohols, polyols and glycols are best used with suspending agents such as higher HLB surfactants, clays silicates, gums, water soluble cellulosics, water soluble polymers and the like. For parenteral administration, sterile suspensions and solutions are desired. Liquid forms useful for parenteral administration include sterile solutions, emulsions and suspensions. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Furthermore, compounds of the present invention can be administered in an intranasal dosage form via topical use of suitable intranasal vehicles or via transdermal skin patches, the composition of which are well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the administration of a therapeutic dose will, of course, be continuous rather than intermittent throughout the dosage regimen.

Compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, multilamellar vesicles and the like. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, phosphatidylcholines and the like.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include, but are not limited to polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyl eneoxidepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of

biodegradable polymers useful in achieving controlled release of a drug, for example, to homopolymers and copolymers (which means polymers containing two or more chemically distinguishable repeating units) of lactide (which includes lactic acid d-, l- and meso lactide), glycolide (including glycolic acid), ε-caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene carbonate, δ-valerolactone, β-butyrolactone, γ-butyrolactone, ε-decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels and blends thereof.

Compounds of this invention may be administered in any of the foregoing compositions and dosage regimens or by means of those compositions and dosage regimens established in the art whenever treating or ameliorating a kinase or dual-kinase mediated disorder is required for a subject in need thereof; in particular, whenever treating or ameliorating a kinase disorder mediated by selective inhibition of a kinase selected from protein kinase C or glycogen synthase kinase-3 is required; and, whenever treating or ameliorating a kinase disorder mediated by dual inhibition of at least two kinases selected from protein kinase C and glycogen synthase kinase-3 is required; and, more particularly, whenever treating or ameliorating a kinase disorder mediated by selective inhibition of a kinase selected from protein kinase C α, protein kinase C β-I, protein kinase C β-II, protein kinase C γ or glycogen synthase kinase-3β is required; and, whenever treating or ameliorating a kinase disorder mediated by dual inhibition of at least two kinases selected from protein kinase C α, protein kinase C β-I, protein kinase C β-II, protein kinase C γ or glycogen synthase kinase-3β is required.

The daily dose of a pharmaceutical composition of the present invention may be varied over a wide range from about 0.7 mg to about 21,000 mg per 70

kilogram (kg) adult human per day; preferably in the range of from about 7 mg to about 7,000 mg per adult human per day; and, more preferably, in the range of from about 7 mg to about 2,100 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. A therapeutically effective amount of the drug is ordinarily supplied at a dosage level of from about 0.001 mg/kg to about 300 mg/kg of body weight per day. Preferably, the range is from about 0.1 mg/kg to about 100 mg/kg of body weight per day; and, most preferably, from about 0.1 mg/kg to about 30 mg/kg of body weight per day. Advantageously, compounds of the present invention may be administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily.

Optimal dosages to be administered may be readily determined by those skilled in the art and will vary with the particular compound used, the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

ATP	=	adenosinetriphosphate
BSA	=	bovine serum albumin
DCM	=	dichloromethane
DMF	=	N, N-dimethylformamide
DMSO	=	dimethylsulfoxide
EGTA	=	ethylenebis(oxyethylenenitrilo)tetraacetic acid
h	=	hour
HEPES	=	4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid

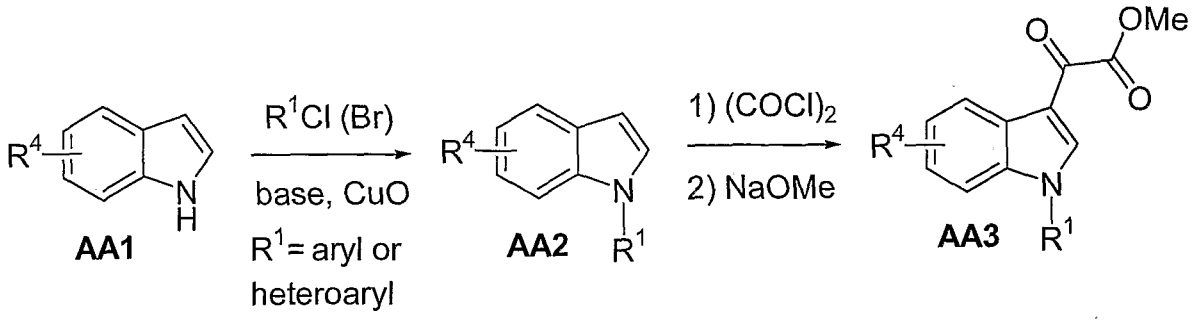
min	=	minute
rt	=	room temperature
TCA	=	trichloroacetic acid
THF	=	tetrahydrofuran
TFA	=	trifluoroacetic acid
$TMSCHN_2$	=	trimethylsilyldiazomethane

General Synthetic Methods

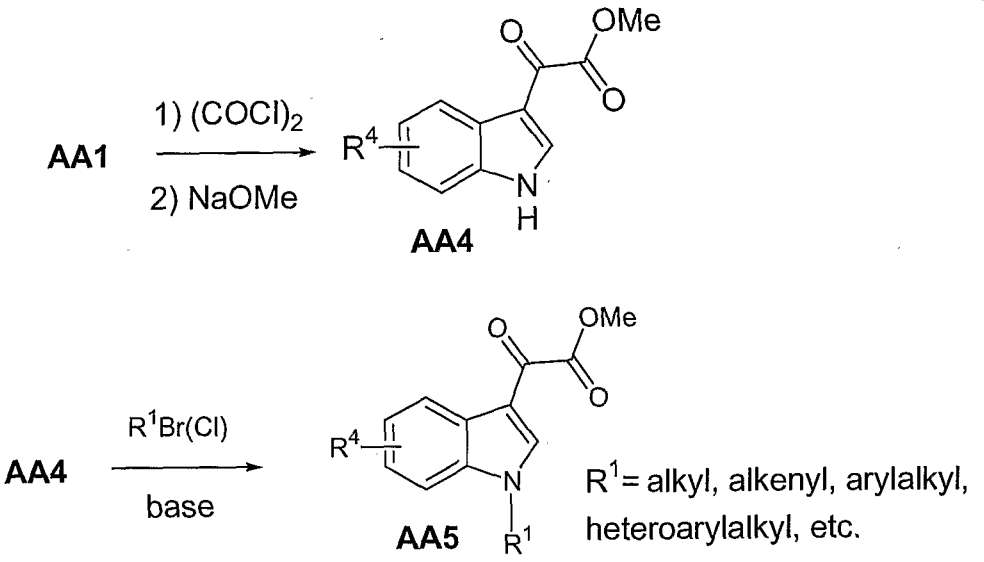
Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated more particularly in the schemes that follow. Since the schemes are an illustration, the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

The following schemes describe general synthetic methods whereby intermediate and target compounds of the present invention may be prepared. Additional representative compounds of the present invention can be synthesized using the intermediates prepared in accordance with the schemes and other materials, compounds and reagents known to those skilled in the art.

In Scheme AA, the substituted indole Compound **AA1** was arylated with an appropriately substituted aryl or heteroaryl halide and a base such as cesium or potassium carbonate and copper oxide in a dipolar aprotic solvent such as DMF to give Compound **AA2**. Compound **AA2** was acylated with oxalyl chloride in an aprotic solvent such as diethyl ether or DCM and quenched with sodium methoxide to afford an intermediate glyoxylic ester Compound **AA3**.

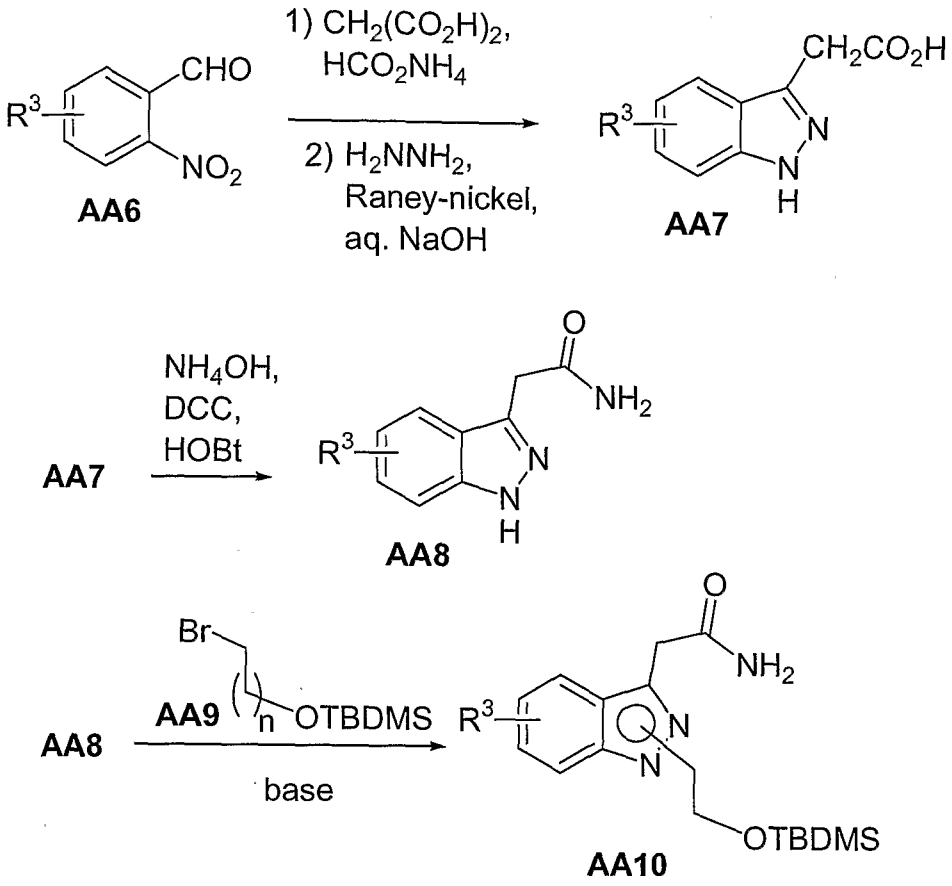


Another intermediate Compound **AA5** was prepared from Compound **AA1** via acylation with oxalyl chloride followed by treatment with sodium methoxide to afford glyoxylic ester Compound **AA4** which was then alkylated with an appropriate alkylating agent under basic conditions.

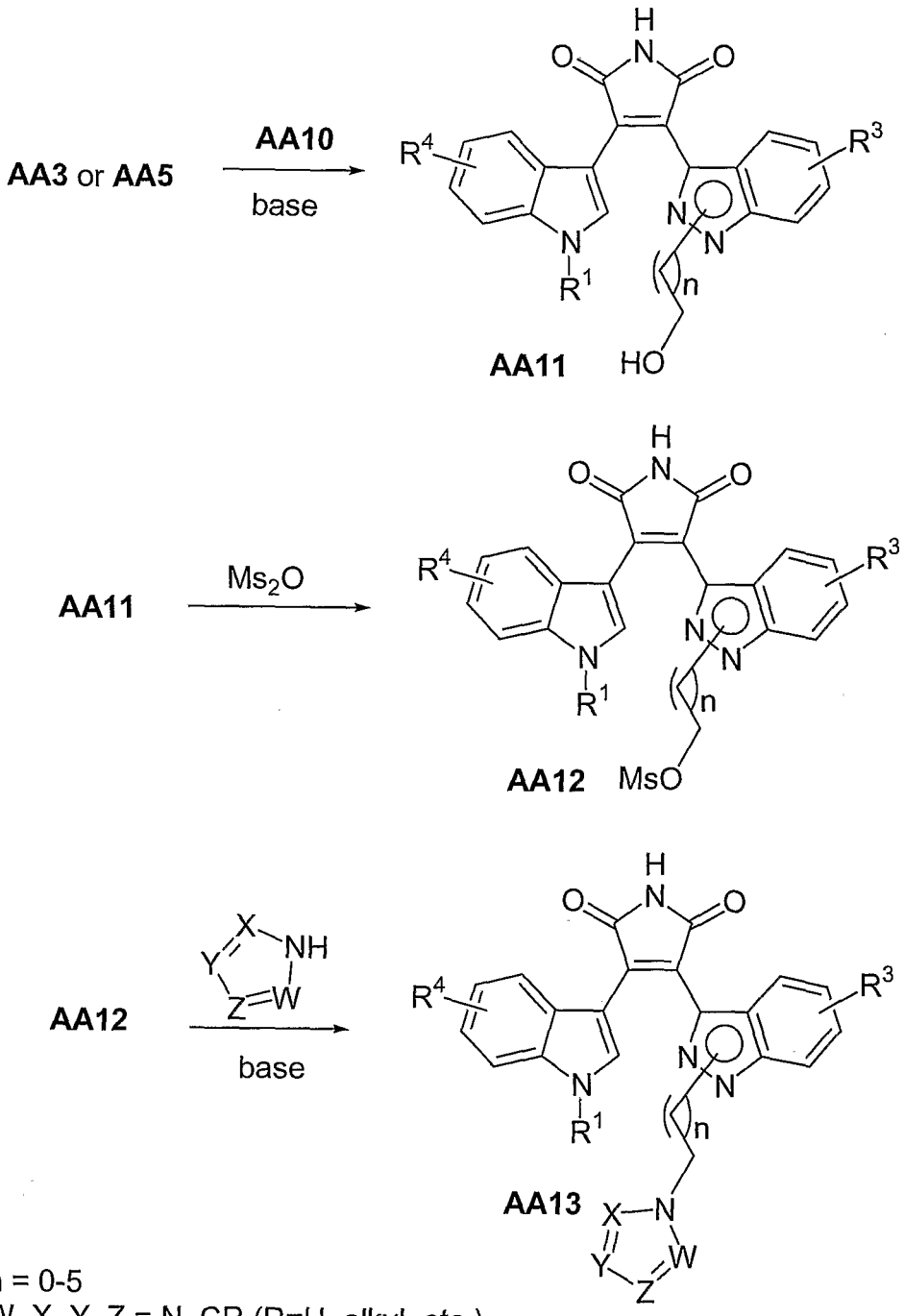


The substituted 3-indazoleacetic acid Compound **AA7** was prepared from aldehyde Compound **AA6** by reaction with malonic acid and ammonium formate followed by reductive cyclization under basic conditions (B. Mylari, et al., *J. Med. Chem.*, **1992**, *35*, 2155). The acid Compound **AA7** was coupled with ammonium hydroxide in an aprotic solvent such as DCM or acetonitrile using a dehydrating agent like dicyclohexyl carbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) to give amide Compound **AA8**, which was treated with an appropriate alkylating agent **AA9** in the presence of a base such as sodium hydride to afford indazole Compound **AA10** as a mixture of

*N*1-alkylated (major) and *N*2-alkylated (minor) products.

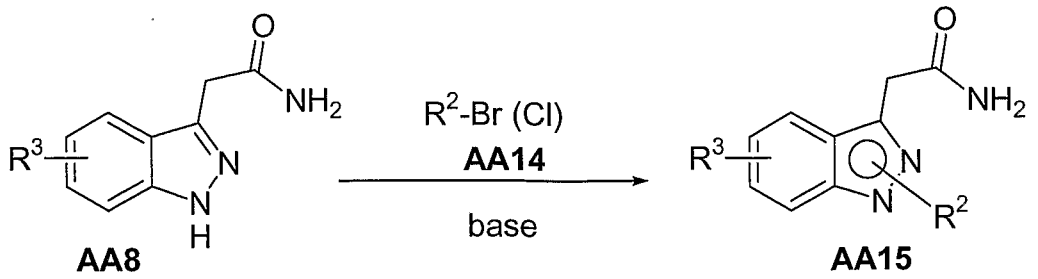


The ester Compound **AA3** or **AA5** may be reacted with the amide Compound **AA10** stirred in an aprotic solvent such as THF with ice bath cooling and a base, such as potassium *tert*-butoxide or sodium hydride, to give Compound **AA11**. Compound **AA11** was converted its mesylate **AA12** by treating with methanesulfonic anhydride. Treatment of **AA12** with an NH-containing heteroaryl in the presence of a base afforded the target Compound **AA13**. *N*1-alkylated (major) and *N*2-alkylated (minor) products can be separated by chromatography.



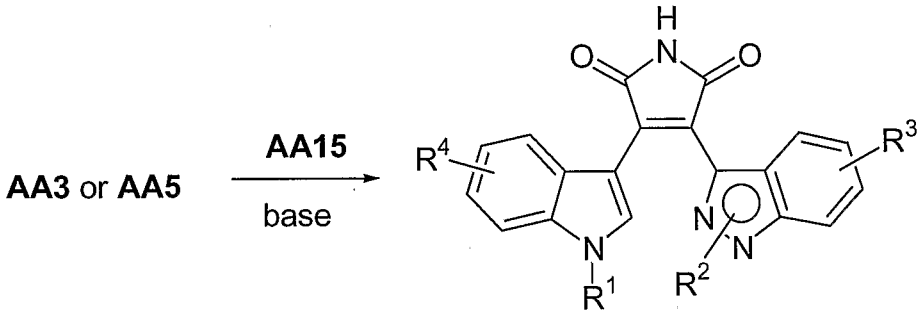
Indazole amide Compound **AA15** was prepared via alkylation of **AA8** with a heteroaryl-containing alkylating agent **AA14** in the presence of a base, such as potassium carbonate or sodium hydride. The amide **AA15** may be reacted with the ester Compound **AA3** or **AA5** in an aprotic solvent such as THF with ice bath cooling and a base, such as potassium *tert*-butoxide or

sodium hydride, to give product **AA16**.



AA8 **AA15**

R^2 = heteroarylalkyl, etc.



AA16

Specific Synthetic Methods

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The depicted intermediates may also be used in subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

All chemicals were obtained from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300B (300 MHz proton) or a Bruker AM-400 (400 MHz proton) spectrometer

with Me_4Si as an internal standard (s = singlet, d = doublet, t = triplet, br = broad). APCI-MS and ES-MS were recorded on a VG Platform II mass spectrometer; methane was used for chemical ionization, unless noted otherwise. Accurate mass measurements were obtained by using a VG ZAB 2-SE spectrometer in the FAB mode. TLC was performed with Whatman 250-μm silica gel plates. Preparative TLC was performed with Analtech 1000-μm silica gel GF plates. Flash column chromatography was conducted with flash column silica gel (40-63 μm) and column chromatography was conducted with standard silica gel. HPLC separations were carried out on three Waters PrepPak® Cartridges (25 x 100 mm, Bondapak® C18, 15-20 μm, 125 Å) connected in series; detection was at 254 nm on a Waters 486 UV detector. Analytical HPLC was carried out on a Supelcosil ABZ+PLUS column (5 cm x 2.1 mm), with detection at 254 nm on a Hewlett Packard 1100 UV detector. Microanalysis was performed by Robertson Microlit Laboratories, Inc.

Representative Chemical Abstracts Service (CAS) Index-like names for the compounds of the present invention were derived using the ACD/LABS SOFTWARE™ Index Name Pro Version 4.5 nomenclature software program provided by Advanced Chemistry Development, Inc., Toronto, Ontario, Canada.

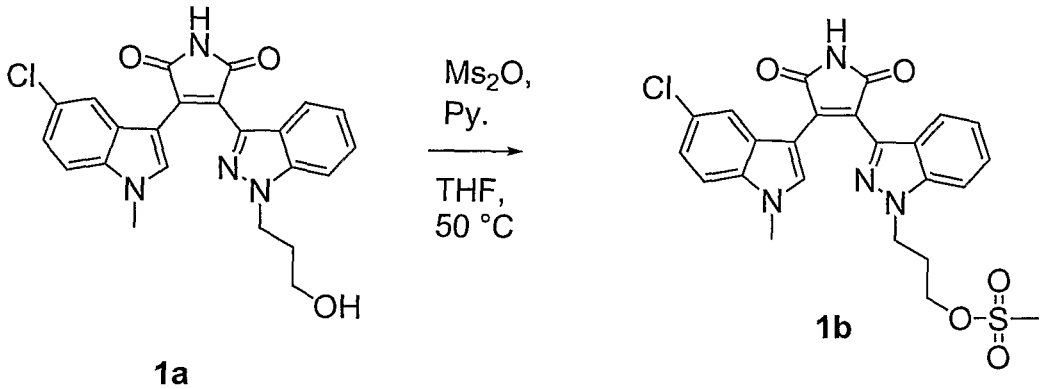
Example 1

3-(5-Chloro-1-methyl-1*H*-indol-3-yl)-4-[1-(3-imidazol-1-yl-propyl)-1*H*-indazol-3-yl]-pyrrole-2,5-dione (Compound **1**)

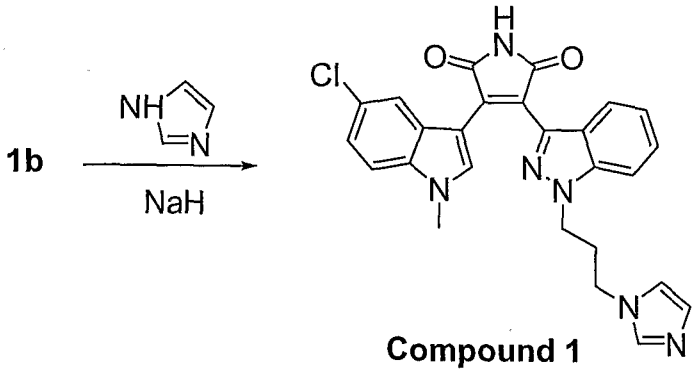
Pyridine (1.024 g, 12.95 mmol) and methanesulfonic anhydride (1.3 g, 7.45 mmol) were added to compound **1a** (1.62 g, 3.7 mmol, preparation described in WO 02/46183) in THF (50 mL). The mixture was heated at 50 °C for 3h, and then cooled to room temperature. Another portion of THF (10 mL) was added, followed by 1N HCl (10 mL). The mixture was stirred for another 15 min, then extracted with EtOAc several times. The combined EtOAc layers were washed once with 1 N HCl (10 mL), water (2 x 20 mL) and saturated

NaCl (20 mL), then dried (Na_2SO_4) and evaporated *in vacuo* to obtain Compound **1b** (1.6 g, 84%) as a reddish solid. ES-MS m/z 513 (MH^+).

75 % NaH (3.74 mg, 0.117 mmol) was added to the mixture of Imidazole (7.96 mg, 0.117 mmol) in DMF (5 mL) at 0 °C. The mixture was heated to reflux for 30 min. Then the solution was cooled down to room temperature. Compound **1b** (50 mg, 0.0975 mmol) in DMF (1 mL) was added dropwise. The mixture was heated to 80 °C for 1 h, and then stirred at room temperature overnight. The solvent was evaporated *in vacuo* to a dark oil. The oil was purified by Gilson to afford Compound **1** (5.3 mg) as TFA salt. ^1H NMR (CD_3OD) δ 8.93 (s, 1H), 8.15 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 7.36 (m, 3 H), 6.96 (m, 2H), 6.06 (d, *J* = 1.9 Hz, 1H), 4.52 (t, *J* = 6.2 Hz, 2H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.88 (s, 3H), 2.45 (t, *J* = 6.3 Hz, 2H). ES-MS m/z 485(MH^+).



1a



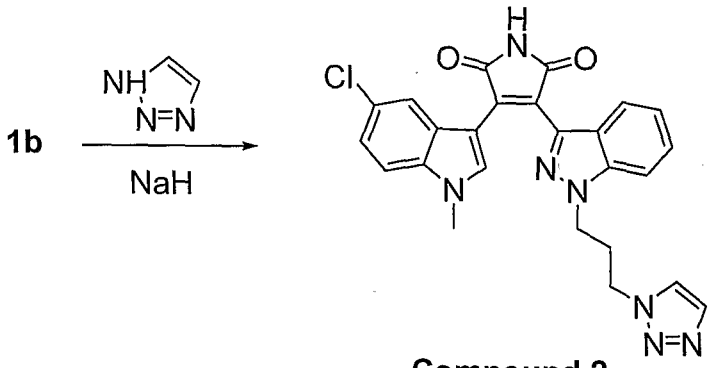
Compound 1

Example 2

3-(5-Chloro-1-methyl-1*H*-indole-3-yl)-4-[1-(3-[1,2,3]triazole-1-yl-propyl)-1*H*-indzol-3-yl]-pyrrole-2,5-dione

(Compound **2**)

75 % NaH (3 mg, 0.093 mmol) was added to the mixture of trizole (5 mg, 0.072 mmol) in DMF (4 mL) at 0 °C. The mixture was heated to reflux for 30 min. Then the solution was cooled down to room temperature. Compound **1b** (20 mg, 0.03 mmol) in DMF (1 mL) was added dropwise. The mixture was heated to 80 °C for 1 h, and then stirred at room temperature overnight. TLC shown still contained some starting material. The mixture was heated to 90 °C overnight. The solvent was evaporated *in vacuo* to a dark oil. The oil was purified by prep. TLC to afford Compound **2** (3 mg) as an orange solid. . ^{1}H NMR (CDCl3) δ 8.08 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.64 (s, 1H), 7.43 (m, 3H), 7.17 (m, 2H), 7.01 (dd, *J* = 1.9, 8.7 Hz, 1H), 6.12 (d, *J* = 1.8 Hz, 1H), 4.31 (t, *J* = 6.2 Hz, 2H), 4.12 (t, *J* = 6.5 Hz, 2H), 3.86 (s, 3H), 2.40 (m, 2H). ES-MS m/z 486 (MH^+).



Compound 2

Example 3

3-(5-Chloro-1-methyl-1*H*-indol-3-yl)-4-[1-(3-tetrazol-2-yl-propyl)-1*H*-indazol-3-yl]pyrrole-2,5-dione

and

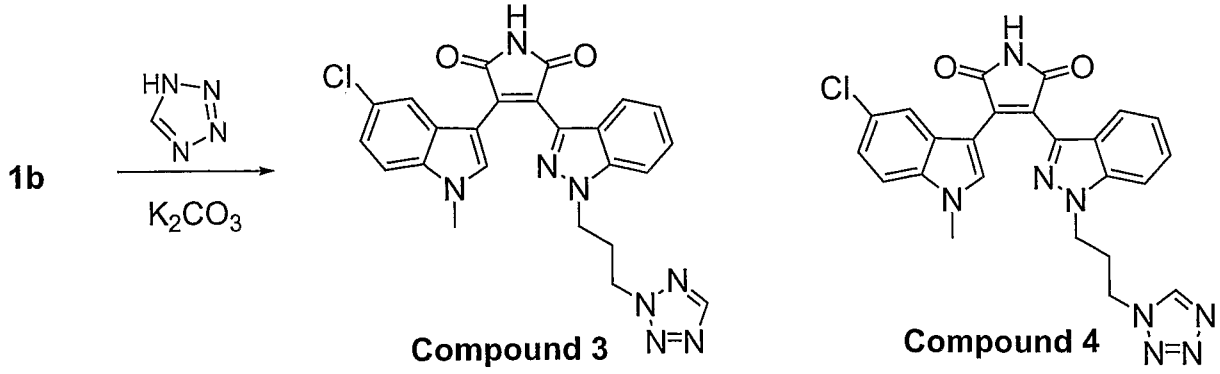
3-(5-Chloro-1-methyl-1*H*-indol-3-yl)-4-[1-(3-tetrazol-1-yl-

propyl)-1*H*-indazol-3-yl]-pyrrole-2,5-dione

(Compound **3** and Compound **4**)

A solution of 3% tetrazole in CH_3CN (10.15 mL, 3.4 mmol) was diluted with DMF (10 mL), potassium carbonate (0.47g, 3.4 mmol) was added and the mixture was heated to 90 °C for 2h. The mixture was cooled down to room temperature. Compound **1b** (350 mg, 0.68 mmol) in DMF (5 mL) was added dropwise. The mixture was heated to 80 °C overnight. The solvent was evaporated. Water (10 mL) was added, and then the mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with H_2O and brine, then dried (Na_2SO_4) and evaporated *in vacuo* to a dark oil. The oil was purified by flash column chromatography (96:4:0.4; DCM: MeOH: NH_4OH) to afford Compound **3** (50 mg) and compound **4** (34 mg). Compound **3**: ^1H NMR ($CDCl_3$) δ 8.53 (s, 1H), 8.09 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.44 (m, 2H), 7.19 (m, 2H), 7.01 (dd, *J* =2.0, 8.7 Hz, 1H), 6.06 (d, *J* =1.9 Hz, 1H), 4.49 (t, *J* = 6.5 Hz, 2H), 4.42 (t, *J* = 6.5 Hz, 2H), 3.87 (s, 3H), 2.43 (m, 2H). ES-MS m/z 487 (MH^+).

Compound **4**: ^1H NMR ($CDCl_3$) δ 8.36 (s, 1H), 8.07 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.44 (m, 2H), 7.20 (m, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.99 (dd, *J* =2.0, 8.7 Hz, 1H), 6.12 (d, *J* =1.9 Hz, 1H), 4.25 (t, *J* = 5.9 Hz, 2H), 4.07 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 2.38 (m, 2H). ES-MS m/z 487 (MH^+).



Using the procedure of Example 1 and the appropriate reagents and starting

materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	ES-MS m/z (MH^+)
9		501
10		501

Example 4

3-(1-Naphthalen-2-yl-1*H*-indole-3-yl)-4-[1-(3-tetrazol-2-yl-propyl)-1*H*-indazol-3-yl]-pyrrole-2,5-dione

and

3-(1-Naphthalen-2-yl-1H-indol-3-yl)-4-[1-(3-tetrazol-1-yl-propyl)-1*H*-indazol-3-yl] pyrrole-2,5-dione

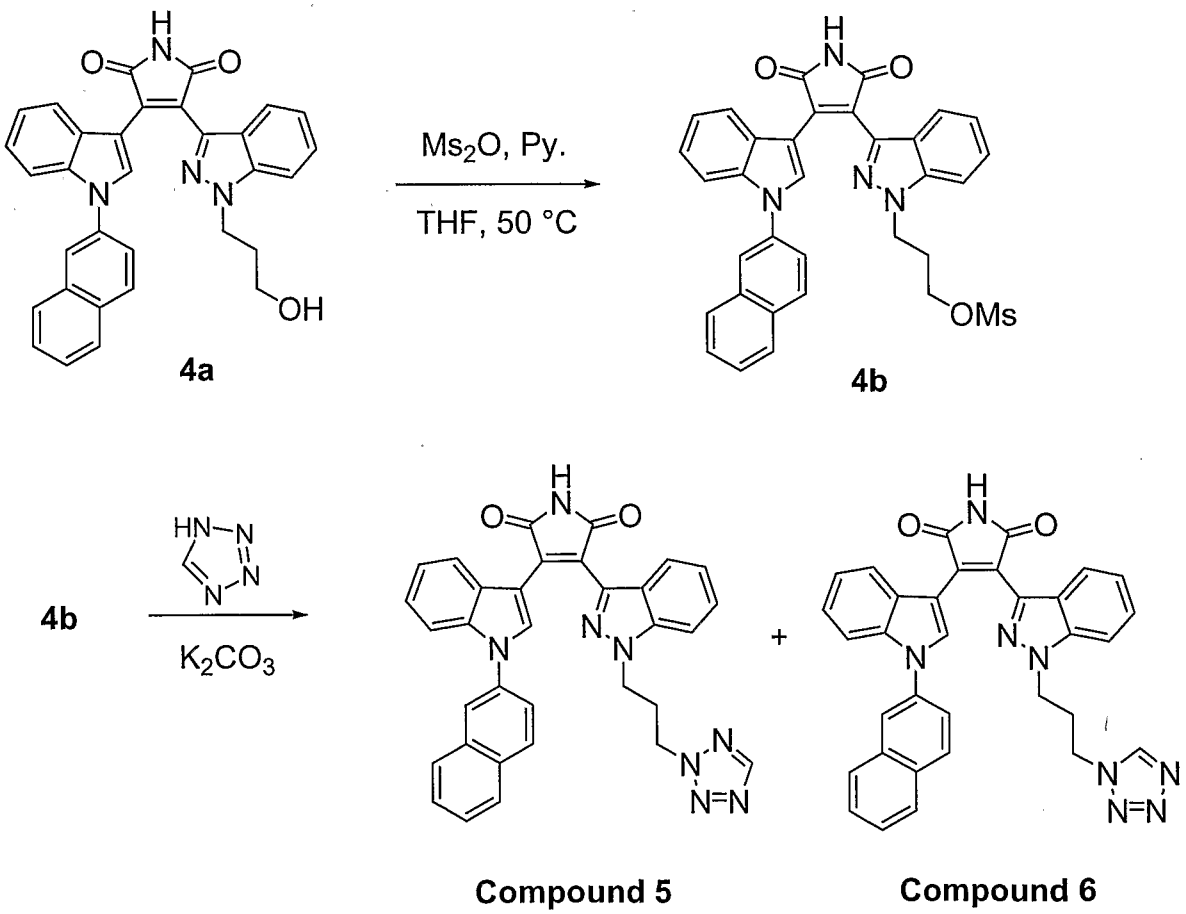
(Compound **5** and Compound **6**)

Into a solution of **4a** (95 mg, 0.185 mmol) in THF (10 mL) was added methanesulfonic anhydride (48.4 mg, 0.278 mmol) and pyridine (44 mg, 0.555 mmol). The mixture was heated to 50 °C for 3 h. Then cooled to rt. Another portion of THF (5 mL) was added, followed by 1N HCl (2 mL). The mixture was stirred for another 15 min, and then extracted with EtOAc several times. The combined EtOAc layers were washed once with 1 N HCl (10 mL), water (2 x 20 mL) and saturated NaCl (20 mL), then dried (Na_2SO_4) and concentrated to give a red solid (0.11 g) as **4b**.

A solution of 3% tetrazole in CH_3CN (7 mL, 2.4 mmol) was diluted with DMF (10 mL), potassium carbonate (0.5 g, 3.6 mmol) was added and the mixture was heated to 90 °C for 2h. The mixture was cooled down to room temperature. Compound **4b** (110 mg, 0.19 mmol) in DMF (10 mL) was added dropwise. The mixture was heated to 80 °C overnight. The solvent was evaporated. Water (10 mL) was added, and then the mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with H_2O and brine, then dried (Na_2SO_4) and evaporated *in vacuo* to a dark oil. The oil

was purified by prep. TLC to afford Compound **5** (10 mg) and compound **6** (10 mg). Compound **5** ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H), 8.37 (s, 1H), 8.02 (m, 2H), 7.94 (m, 3H), 7.68 (dd, *J* =2.1, 8.7 Hz, 1H), 7.60 (m, 2H), 7.54 (m, 2H), 7.46 (d, *J* =8.7 Hz, 2H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.77 (t, *J* =7.2 Hz, 1H), 6.42 (d, *J* =8.1 Hz, 1H), 4.38 (t, *J* = 6.3 Hz, 2H), 4.32 (t, *J* = 6.6 Hz, 2H), 2.34 (t, *J* = 6.5 Hz, 2H). ES-MS m/z 565 (MH^+).

Compound **6** ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 8.32 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.91 (m, 4H), 7.89 (m, 3H), 7.47 (m, 3H), 7.26 (t, *J* = 7.0 Hz, 1H), 7.07(t, *J* = 7.2 Hz, 1H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.54 (d, *J* =8.0 Hz, 1H), 4.19 (t, *J* = 5.8 Hz, 2H), 3.90 (t, *J* = 6.3 Hz, 2H), 2.31(m, 2H). ES-MS m/z 565 (MH^+).



Example 5

3-(1-Pyridin-3-yl-1*H*-indol-3-yl)-4-[1-(3-tetrazol-2-yl-

propyl)-1*H*-indazole-3-yl]-pyrrole-2,5-dione

and

3-(1-Pyridin-3-yl-1*H*-indol-3-yl)-4-[1-(3-tetrazol-1-yl-propyl)-1*H*-indazol-3-yl]-pyrrole-2,5-dione

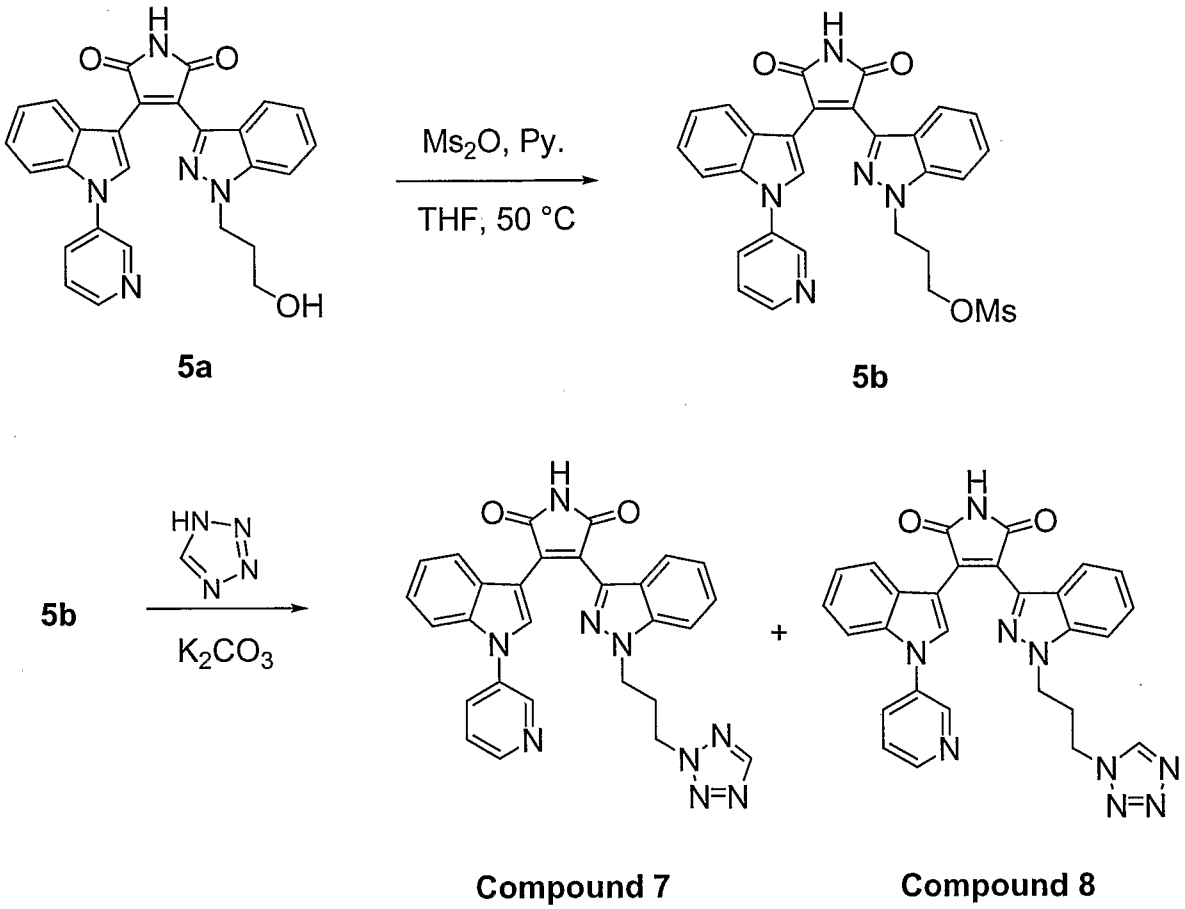
(Compound **7** and Compound **8**)

Into a solution of **5a** (100 mg, 0.22 mmol) in THF (5 mL) was added methanesulfonic anhydride (77 mg, 0.44 mmol) and pyridine (52.2 mg, 0.66 mmol). The mixture was heated to 50 °C for 3h. Then cooled to room temperature. Another portion of THF (5 mL) was added, followed by 1N HCl (2 mL). The mixture was stirred for another 15 min, and then extracted with EtOAc several times. The combined EtOAc layers were washed once with 1 N HCl (10 mL), water (2 x 20 mL) and saturated NaCl (20 mL), then dried (Na_2SO_4) and concentrated to give a red solid (0.11 g) as **5b**.

A solution of 3% tetrazole in CH_3CN (7 mL, 2.4 mmol) was diluted with DMF (10 mL), potassium carbonate (0.5 g, 3.6 mmol) was added and the mixture was heated to 90 °C for 2h. The mixture was cooled down to room temperature. Compound **5b** (110 mg, 0.2 mmol) in DMF (10 mL) was added dropwise. The mixture was heated to 80 °C overnight. The solvent was evaporated. Water (10 mL) was added, and then the mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with H_2O and brine, then dried (Na_2SO_4) and evaporated *in vacuo* to a dark oil. The oil was purified by flash column chromatography (from 100 % DCM to DCM: MeOH: NH4OH; 97:3:0.3) to afford Compound **7** (32 mg) and Compound **8** (27 mg). Compound **7** ^{1}H NMR ($CDCl_3$) δ 8.92 (s, 1H), 8.70 (s, 1H), 8.50 (s, 1H), 8.26 (s, 1H), 7.92 (dd, *J* = 3.2, 8.2 Hz, 2H), 7.52 (m, 1H), 7.42 (m, 3H), 7.25 (m, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.78 (t, *J* = 7.6 Hz, 1H), 6.43 (d, *J* = 8.1 Hz, 1H), 4.37 (t, *J* = 6.3 Hz, 2H), 4.30 (t, *J* = 6.6 Hz, 2H), 2.32 (m, 2H). ES-MS m/z 516 (MH^+).

Compound **8** ^{1}H NMR ($CDCl_3$) δ 8.85 (d, *J* = 2.4 Hz, 1H), 8.70 (dd, *J* =1.4, 4.7

Hz, 1H), 8.41 (s, 1H), 8.20 (s, 1H), 7.91 (m, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.53 (dd, *J* = 4.8, 8.0 Hz, 1H), 7.45 (m, 2H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.23 (dd, *J* = 6.8, 8.3 Hz, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 4.19 (t, *J* = 5.8 Hz, 2H), 3.96 (t, *J* = 6.2 Hz, 2H), 2.31 (m, 2H). ES-MS m/z 516 (MH^+).



Example 6

3-(5-Chloro-1-methyl-1*H*-indol-3-yl)-4-{1-[2-(1*H*-tetrazol-5-yl)-ethyl]-1*H*-indazol-3-yl)-pyrrole-2,5-dione

(Compound **11**)

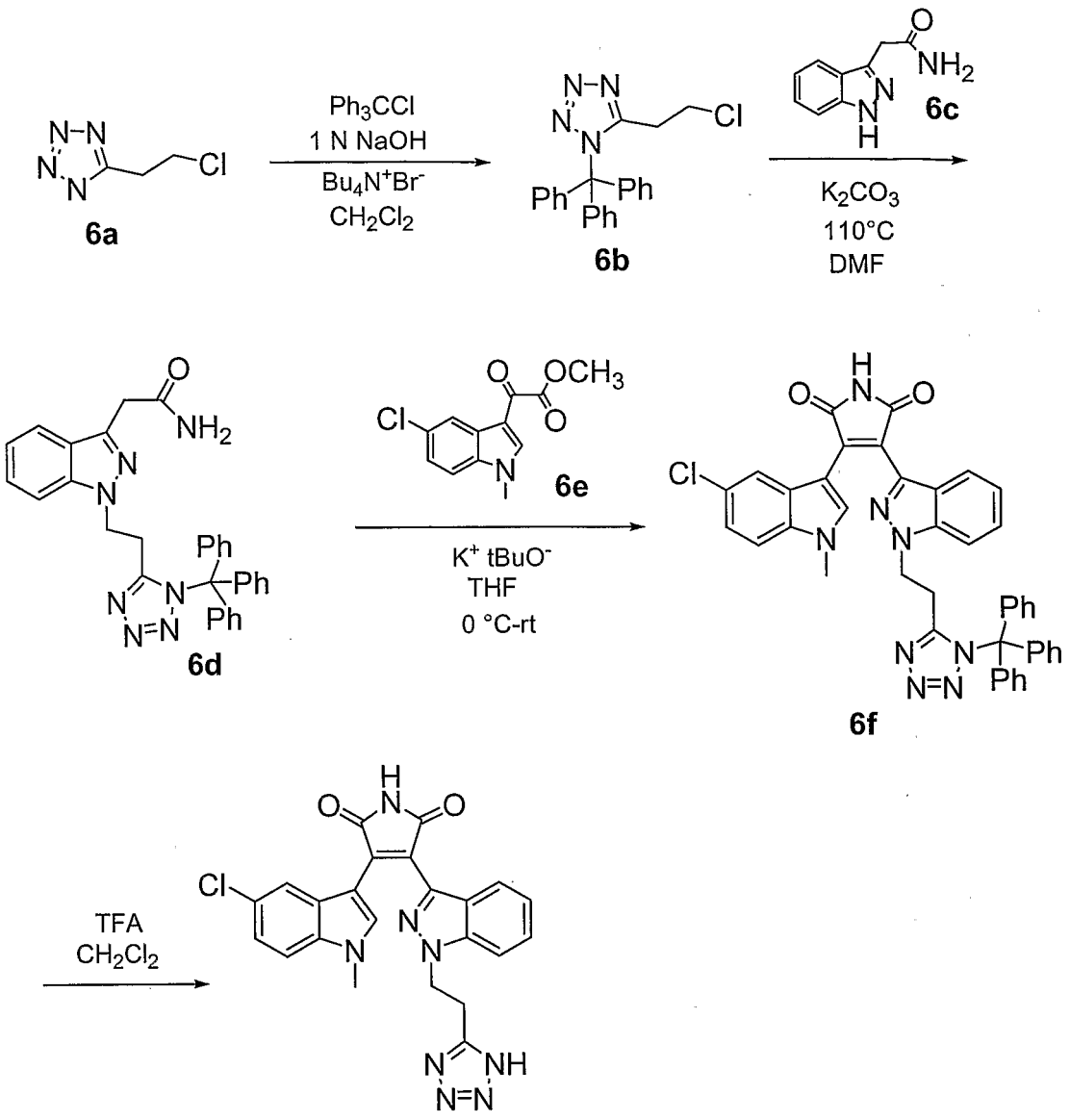
To a solution of **6a** (880 mg, 6.6 mmol) in anhydrous CH_2Cl_2 (50 mL) was added trityl chloride (1.84 g, 6.6 mmol), 1N NaOH (6.9 mL, 6.9 mmol) and catalytic tetrabutyl ammonia bromide. The reaction mixture was stirred vigorously at room temperature overnight. Then water was added followed by CH_2Cl_2 extraction. The organic layers were combined, washed with H_2O (2x20 mL), sat'd $NaHCO_3$ (25 mL) and brine (25 mL). Dried (Na_2SO_4) and concentrated to give **6b** as a white solid (2.27 g, 92%). ^1H NMR ($CDCl_3$) δ 7.31 (m, 9H), 7.09 (m, 6H), 3.91 (t, *J* = 7.1 Hz, 2H), 3.40 (t, *J* = 7.0 Hz, 2H); MS (ES) m/z: 375 (MH^+).

To a solution of **6c** (957 mg, 5.47 mmol) in anhydrous DMF (50 mL) was added K_2CO_3 (3.78 g, 27.35 mmol) and **6b** under N_2. The reaction mixture was heated at 110 °C for 4 hours. TLC shown still contained lots of starting material **6c**, but no more **6b**. Then more **6b** (1 g, 2.67 mmol) was added and the mixture heated at 110 °C for overnight. Water was added and the solution was extracted with EtOAc (3 times). The organic layers were combined, washed with water, brine, dried ((Na_2SO_4) and concentrated to a brown oil. The oil was purified by flash column chromatography (from 100 % DCM to DCM: MeOH: NH_4OH; 97:3:0.3) to afford Compound **6d** (0.6 g, 21%). as a light yellow solid. ^1H NMR (DMSO-d_6) δ 7.75 (d, *J* = 8.1, 1H), 7.51 (s, 1H), 7.33 (m, 9H), 7.20 (m, 1H), 7.02 (m, 2H), 6.81 (m, 5H), 4.74 (t, *J* = 6.3 Hz, 2H), 3.68 (s, 2H), 3.45 (m, 2H); MS (ES) m/z: 536 (MH^+).

A mixture of Compound **6d** (100 mg, 0.195 mmol) and Compound **6e** (94.7 mg, 0.27 mmol) in 4 mL of anhydrous THF was stirred under nitrogen and cooled in an ice bath while treating dropwise with 1.0 mL of 1N potassium *t*-butoxide in THF. The mixture was stirred for 30 minutes in an ice bath then at room temperature for another 30 min. Then ethyl acetate (150 mL) and H_2O (10 mL) were added. The organic layer was separated and washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a crude product which was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH, 97:3:0.3) to give 22.3 mg of Compound **6f** as a red

solid. ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.30 (m, 12 H), 7.10 (m, 2H), 7.04 (dd, *J* = 1.9, 8.7 Hz, 1H), 6.98 (m, 5H), 6.32 (d, *J* = 1.8 Hz, 1H), 4.75 (t, *J* = 7.4 Hz, 2H), 3.75 (s, 3H), 3.40 (t, *J* = 7.4 Hz, 2H). ES-MS m/z 715 (MH^+).

Compound **6f** (22.3 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) was cooled in an ice bath. TFA (0.5 mL) was added dropwise. The mixture was then stirred at room temperature for 2 h. The solvent was evaporated and the residue was purified by flash chromatography (from 100 % DCM to DCM: MeOH; 94:6) to afford Compound **11** (13 mg, 92%). ^{1}H NMR (DMSO-d_6) δ 8.24 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.11 (m, 2H), 6.22 (d, *J* = 2.0 Hz, 1H), 4.77 (t, *J* = 7.5 Hz, 2H), 3.90 (s, 3H), 3.34 (m, 2H). ES-MS m/z 473 (MH^+).



Compound 11

Example 7

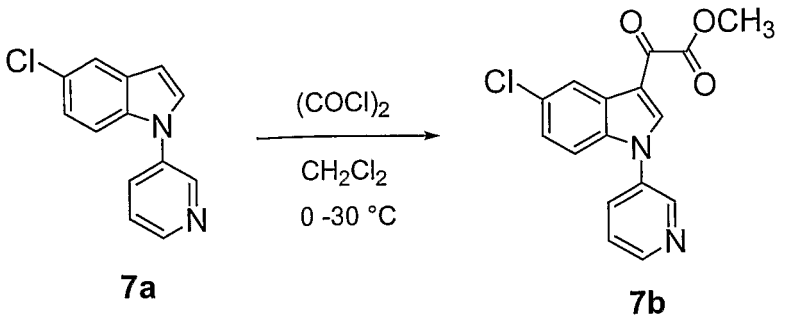
3-(5-Chloro-1-pyridin-3-yl-1H-indol-3-yl)-4-{1-[2-(1H-tetrazol-5-yl)-ethyl]-1H-indazol-3-yl(Compound **12**)

A 5-chloroindole Compound **7a** (6.0 g, 0.026 mole) in CH_2Cl_2 (40 mL) was cooled in an ice bath and treated dropwise with oxalyl chloride (6.66 g, 0.052 mole) while stirring under argon. The resulting yellow slurry was stirred at room temperature for 1h, then 30 °C overnight. Some yellow solid was formed, filtered and washed with CH_2Cl_2. The solid was dried over vacuum and

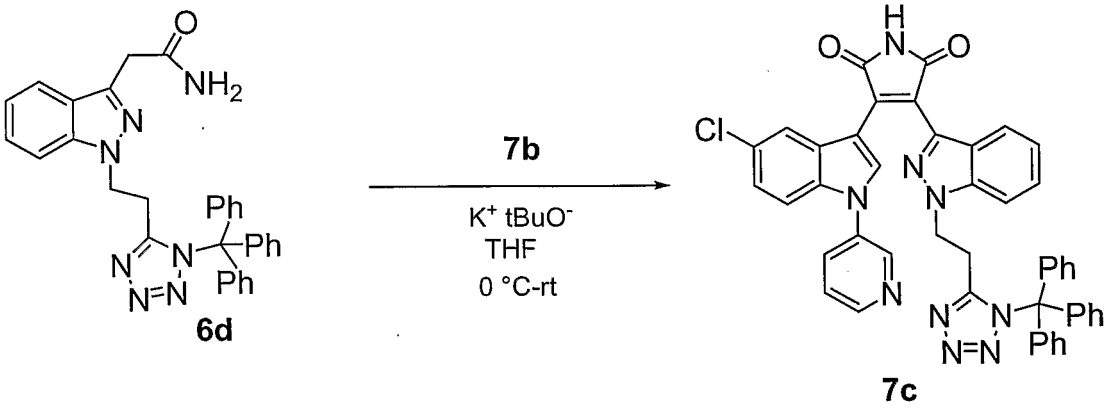
resubmitted in anhydrous methanol (100 mL) and heated to 45 °C for 3h. The solid was filtered and dried to give compound **7b** (7.94 g, 86%) as HCl salt. The solid was neutralized by treated with sat $NaHCO_3$, ethyl acetate extraction, dried (Na_2SO_4) and concentrated *in vacuo* to give compound **7b** as a free base. ^1H NMR ($CDCl_3$) δ 8.86 (s, 1H), 8.79 (m, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.57 (m, 1H), 7.34 (m, 2H), 3.98 (s, 3H). ES-MS m/z 315 (MH^+).

A mixture of Compound **6d** (150 mg, 0.292 mmol) and Compound **7f** (142 mg, 0.41 mmol) in 5 mL of anhydrous THF was stirred under nitrogen and cooled in an ice bath while treating dropwise with 1.5 mL of 1N potassium *t*-butoxide in THF. The mixture was stirred for 1 h in an ice bath then at room temperature for another 2 h. Then ethyl acetate (150 mL) and H_2O (10 mL) were added. The organic layer was separated and washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a crude product which was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH, 97:3:0.3) to give 20 mg (6%) of compound **7c** as a red solid.

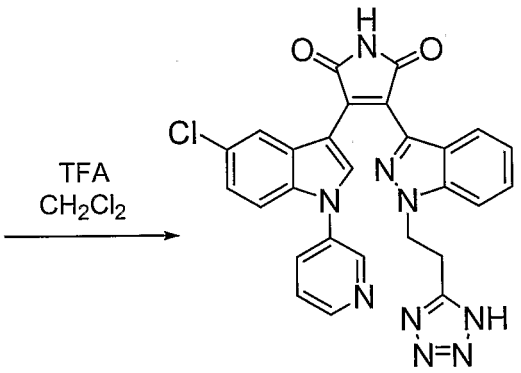
Compound **7c** (18 mg, 0.023 mmol) in CH_2Cl_2 (5 mL) was cooled in an ice bath. TFA (0.5 mL) was added dropwise. The mixture was then stirred at room temperature for 2h. The solvent was evaporated and the residue was purified by flash chromatography (from 100 % DCM to DCM: MeOH; 94:6) to afford Compound **12** (5.2 mg, 42%). ^1H NMR (CD_3OD) δ 8.85 (s, 1H), 8.66 (s, 1H), 8.31 (s, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.65 (m, 3H), 7.42 (m, 2H), 7.11 (m, 2H), 6.30 (s, 1H), 4.73 (m, 2H), 3.30 (m, 2H). ES-MS m/z 536 (MH^+).



7a 7b



6d 7c



Compound 12

Example 8

As a specific embodiment of an oral composition, 100 mg of Compound **14** is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

Biological Experimental Examples

The utility of the compounds to treat kinase or dual-kinase mediated disorders (in particular, kinases selected from protein kinase C and glycogen synthase

kinase-3; and, more particularly, kinases selected from protein kinase C α, protein kinase C β-II, protein kinase C γ or glycogen synthase kinase-3β) was determined using the following procedures.

Example 9

Protein Kinase C Histone-Based Assay

Compounds were evaluated for PKC selectivity using histone III as the substrate. The PKC isoforms α, β-II or γ were added to a reaction mixture that contained 20 mM HEPES, (pH 7.4), 940 μM $CaCl_2$, 10 mM $MgCl_2$, 1 mM EGTA. 100 μg/mL phosphatidylserine, 20 μg/mL diacylglycerol, 30 μM ATP, 1 μCi (^{33}P)ATP and 200 μg/mL histone III. The reaction was incubated for 10 min at 30°C. Reactions were terminated by TCA precipitation and spotting on Whatman P81 filters. Filters were washed in 75 mM phosphoric acid and the radioactivity quantified by liquid scintillation counting.

Table 1 shows the biological activity in the histone based assay as IC_{50} values (μM) for representative compounds of the present invention.

Table 1
PKC Activity (IC_{50} μM, Histone Based Assay)

Cpd	Alpha	Beta II	Gamma
1	0.567	0.015	0.476
2	1.212	0.046	0.395
3	2.349	0.045	1.010
4	0.505	0.035	0.544
5	0.542	0.025	1.698
6	0.326	0.022	1.106
7	0.451	0.044	1.447
8	1.039	0.052	4.301
9	2.976	0.041	1.421
10	0.424	0.009	0.602
11	1.359	0.123	1.934
12	0.554	0.069	0.226

Example 10

Glycogen Synthase Kinase-3 Assay

Compounds were tested for the ability to inhibit recombinant rabbit GSK-3β protein using the following protocol. The test compound was added to a reaction mixture containing Protein phosphatase inhibitor-2 (PPI-2) (Calbiochem) (45 ng), rabbit GSK-3β protein (New England Biolabs) (0.75 units) and ^{33}P-ATP (1 μCi) in 50 mM Tris-HCl (pH 8.0), 10 mM $MgCl_2$, 0.1% BSA, 1 mM DTT and 100 μM Sodium Vanadate. The mixture was reacted for 90 minutes at 30°C to allow phosphorylation of the PPI-2 protein and then the protein in the reaction was precipitated using 10 % TCA. The precipitated protein was collected on filter plates (MultiScreen-DV/Millipore), which were subsequently washed. Finally, the radioactivity was quantified using a TopCount Scintillation Counter (Packard). GSK-3 inhibitory compounds resulted in less phosphorylated PPI-2 and thus a lower radioactive signal in the precipitated protein. Staurosporine or Valproate, known inhibitors of GSK-3β, were used as a positive control for screening.

Table 2 shows the biological activity in the GSK-3β assay as IC_{50} values (μM) for representative compounds of the present invention.

Table 2
GSK-3β Assay Activity (IC_{50} μM)

Cpd	GSK-3β
1	0.004
2	0.003
3	0.004
4	0.004
5	0.776
6	29%@1μM
7	0.027

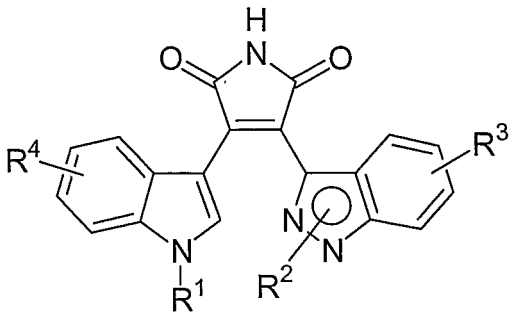
8	0.034
9	0.005
10	0.005
11	0.005
12	0.107

The results from the foregoing indicate that a compound of the present invention would be expected to be useful in treating or ameliorating a kinase or dual-kinase mediated disorder.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. The compounds of Formula (I)



Formula (I)

wherein

R^1 is selected from the group consisting of:

hydrogen,

C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{3-8} cycloalkyl {wherein alkyl, alkenyl, alkynyl and C_{3-8} cycloalkyl are optionally substituted with one to two substituents independently selected from the group consisting of -O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-OH, -O-(C_{1-8})alkyl-O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-NH_2, -O-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -O-(C_{1-8})alkyl-S-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-NH_2, -O-(C_{1-8})alkyl-SO_2-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-N[(C_{1-8})alkyl]$_2$, -O-C(O)H, -O-C(O)-(C_{1-8})alkyl, -O-C(O)-NH_2, -O-C(O)-NH-(C_{1-8})alkyl, -O-C(O)-N[(C_{1-8})alkyl]$_2$, -O-(C_{1-8})alkyl-C(O)H, -O-(C_{1-8})alkyl-C(O)-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-CO_2H, -O-(C_{1-8})alkyl-C(O)-O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-C(O)-NH_2, -O-(C_{1-8})alkyl-C(O)-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-C(O)-N[(C_{1-8})alkyl]$_2$, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2,

-C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-S-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-OH, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-NH_2, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -S-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-OH, -(C_{1-8})alkyl-O-(C_{1-8})alkyl, -(C_{1-8})alkyl-NH_2, -(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -(C_{1-8})alkyl-S-(C_{1-8})alkyl, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, -C(N)-NH_2, aryl and aryl(C_{1-8})alkyl (wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-8}alkyl, C_{1-8}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-8}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl, (halo)$_{1-3}$(C_{1-8})alkoxy, hydroxy, hydroxy(C_{1-8})alkyl and nitro)), cyano, (halo)$_{1-3}$, hydroxy, nitro, oxo, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-8}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl, (halo)$_{1-3}$(C_{1-8})alkoxy, hydroxy, hydroxy(C_{1-8})alkyl and nitro)},

-C(O)-(C_{1-8})alkyl, -C(O)-aryl, -C(O)-O-(C_{1-8})alkyl, -C(O)-O-aryl, -C(O)-NH-(C_{1-8})alkyl, -C(O)-NH-aryl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-aryl,

heterocyclyl, aryl and heteroaryl {wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy,

-C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-8})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl-, (halo)$_{1-3}$(C_{1-8})alkoxy-, hydroxy, hydroxy(C_{1-8})alkyl, nitro, aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl};

R^2 is selected from the group consisting of -C_{1-8}alkyl-Z, -C_{2-8}alkenyl-Z and -C_{2-8}alkynyl-Z; wherein the -C_{1-8}alkyl, -C_{2-8}alkenyl and -C_{2-8}alkynyl is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4})alkylamino, C_{1-4}alkyl, C_{1-4}alkoxy, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy and hydroxy(C_{1-4})alkyl;

Z is a 5 to 6 member monocyclic heteroaryl ring having from 2 to 4 heteroatoms containing at least one carbon atom and at least one nitrogen atom; wherein Z optionally is substituted with R^5;

R^5 is 1 to 2 substituents attached to a carbon or nitrogen atom of Z and each substitute is independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH(C_{1-8}alkyl),

-C(O)-N(C_{1-8})alkyl)$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-8}alkyl), -SO_2-N(C_{1-8}alkyl)$_2$, -(C_{1-8})alkyl-NH_2, -(C_{1-8})alkyl-NH(C_{1-8}alkyl), -(C_{1-8})alkyl-N(C_{1-8}alkyl)$_2$, -(C_{1-8})alkyl-(halo)$_{1-3}$, -(C_{1-8})alkyl-OH, -aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl;

with the proviso that, when R^5 is attached to a carbon atom, R^5 is further selected from the group consisting of -C_{1-8}alkoxy, -(C_{1-8})alkoxy-(halo)$_{1-3}$, -SH, -S-(C_{1-8})alkyl, -N-R^6, cyano, halo, hydroxy, and nitro;

R^6 is 2 substituents independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, - C_{3-8}cycloalkyl, -C(O)H, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-8}alkyl), -C(O)-N(C_{1-8}alkyl)$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-8}alkyl), -SO_2-N(C_{1-8}alkyl)$_2$, -C(N)-NH_2, -C(N)-NH(C_{1-8}alkyl) and -C(N)-N(C_{1-8}alkyl)$_2$;

R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-8})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl-, (halo)$_{1-3}$(C_{1-8})alkoxy-, hydroxy, hydroxy(C_{1-8})alkyl-, nitro, aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl;

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein R^1 is independently selected from the group consisting of:

hydrogen,

C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl and C_{3-8} cycloalkyl {wherein alkyl, alkenyl, alkynyl and C_{3-8} cycloalkyl are optionally substituted with one to two substituents independently selected from the group consisting of -O-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-OH, -O-(C_{1-4})alkyl-O-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-NH_2, -O-(C_{1-4})alkyl-NH-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-N[(C_{1-4})alkyl]$_2$, -O-(C_{1-4})alkyl-S-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-SO_2-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-SO_2-NH_2, -O-(C_{1-4})alkyl-SO_2-NH-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-SO_2-N[(C_{1-4})alkyl]$_2$, -O-C(O)H, -O-C(O)-(C_{1-4})alkyl, -O-C(O)-NH_2, -O-C(O)-NH-(C_{1-4})alkyl, -O-C(O)-N[(C_{1-4})alkyl]$_2$, -O-(C_{1-4})alkyl-C(O)H, -O-(C_{1-4})alkyl-C(O)-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-CO_2H, -O-(C_{1-4})alkyl-C(O)-O-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-C(O)-NH_2, -O-(C_{1-4})alkyl-C(O)-NH-(C_{1-4})alkyl, -O-(C_{1-4})alkyl-C(O)-N[(C_{1-4})alkyl]$_2$, -C(O)H, -C(O)-(C_{1-4})alkyl, -CO_2H, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SH, -S-(C_{1-4})alkyl, -S-(C_{1-4})alkyl-S-(C_{1-4})alkyl, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl-OH, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl-NH_2, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl-NH-(C_{1-4})alkyl, -S-(C_{1-4})alkyl-O-(C_{1-4})alkyl-N[(C_{1-4})alkyl]$_2$, -S-(C_{1-4})alkyl-NH-(C_{1-4})alkyl, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$, amino {substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, -(C_{1-4})alkyl-OH, -(C_{1-4})alkyl-O-(C_{1-4})alkyl, -(C_{1-4})alkyl-NH_2, -(C_{1-4})alkyl-NH-(C_{1-4})alkyl, -(C_{1-4})alkyl-N[(C_{1-4})alkyl]$_2$, -(C_{1-4})alkyl-S-(C_{1-4})alkyl, -C(O)-(C_{1-4})alkyl, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$,

-C(N)-NH_2, aryl and aryl(C_{1-4})alkyl (wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-4}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy, hydroxy, hydroxy(C_{1-4})alkyl and nitro)), cyano, (halo)$_{1-3}$, hydroxy, nitro, oxo, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-4}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy, hydroxy, hydroxy(C_{1-4})alkyl and nitro)},

-C(O)-(C_{1-4})alkyl, -C(O)-aryl, -C(O)-O-(C_{1-4})alkyl, -C(O)-O-aryl, -C(O)-NH-(C_{1-4})alkyl, -C(O)-NH-aryl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-aryl,

heterocyclyl, aryl and heteroaryl {wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, -C(O)H, -C(O)-(C_{1-4})alkyl, -CO_2H, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SH, -S-(C_{1-4})alkyl, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, -(C_{1-4})alkyl-NH_2, -C(O)-(C_{1-4})alkyl, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-4})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, -(C_{1-4})alkyl-NH_2, -C(O)-(C_{1-4})alkyl, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl,

$-SO_2-N[(C_{1-4})alkyl]_2$ and $-C(NH)-NH_2$), cyano, halo, $(halo)_{1-3}(C_{1-4})alkyl$, $(halo)_{1-3}(C_{1-4})alkoxy$, hydroxy, $hydroxy(C_{1-4})alkyl$, nitro, aryl, $-(C_{1-4})alkyl$-aryl, heteroaryl and $-(C_{1-4})alkyl$-heteroaryl}.

3. The compound of claim 1 wherein R^1 is selected from the group consisting of:

hydrogen,

$C_{1-4}alkyl$, $C_{2-4}alkenyl$ {wherein alkyl is substituted with one to two substituents independently selected from the group consisting of $-O-(C_{1-4})alkyl$, $-O-(C_{1-4})alkyl-OH$, $-O-(C_{1-4})alkyl-NH-(C_{1-4})alkyl$, $-O-C(O)-(C_{1-4})alkyl$, $-C(O)H$, $-CO_2H$, $-C(O)-O-(C_{1-4})alkyl$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, $C_{1-4}alkyl$, $-(C_{1-4})alkyl-OH$, $-C(O)-O-(C_{1-4})alkyl$ and $aryl(C_{1-4})alkyl$), hydroxy, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of $C_{1-4}alkyl$ and halo)},

aryl and heteroaryl {wherein aryl and heteroaryl are optionally substituted with one to two substituents independently selected from the group consisting of $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $-CO_2H$, $-C(O)-O-(C_{1-4})alkyl$, $-C(O)-NH_2$, $-C(NH)-NH_2$, $-C(O)-NH-(C_{1-4})alkyl$, $-C(O)-N[(C_{1-4})alkyl]_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-4}alkyl$), cyano, halo, $(halo)_{1-3}(C_{1-4})alkyl$, $(halo)_{1-3}(C_{1-4})alkoxy$, hydroxy, $hydroxy(C_{1-4})alkyl$, aryl and heteroaryl}.

4. The compound of claim 1 wherein R^1 is selected from the group consisting of:

hydrogen,

$C_{1-4}alkyl$, $C_{2-4}alkenyl$ {wherein alkyl is substituted with one to two substituents independently selected from the group consisting of $-O-(C_{1-4})alkyl-NH-(C_{1-4})alkyl$, amino (substituted with two substituents

independently selected from the group consisting of hydrogen and C_{1-4}alkyl), hydroxy, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkyl and halo)},

aryl and heteroaryl {wherein aryl and heteroaryl are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, $-CO_2H$, $-C(O)-O-(C_{1-4})$alkyl, $-C(O)-NH_2$, $-C(NH)-NH_2$, $-C(O)-NH-(C_{1-4})$alkyl, $-C(O)-N[(C_{1-4})alkyl]_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4}alkyl), cyano, halo, $(halo)_{1-3}(C_{1-4})$alkyl, $(halo)_{1-3}(C_{1-4})$alkoxy, hydroxy, hydroxy(C_{1-4})alkyl, aryl and heteroaryl}.

5. The compound of claim 1 wherein R^1 is selected from the group consisting of:

hydrogen,

C_{1-4}alkyl, C_{2-3}alkenyl {wherein alkyl is substituted with one to two substituents independently selected from the group consisting of $-O-(C_{1-4})$alkyl-NH-(C_{1-4})alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4}alkyl), hydroxy, pyrrolidinyl, morpholinyl, piperazinyl (wherein piperazinyl is optionally substituted with methyl), phenyl, naphthalenyl, benzo[b]thienyl and quinolinyl (wherein phenyl and benzo[b]thienyl are optionally substituted with one to two chloro substituents)},

phenyl, naphthalenyl, furyl, thienyl, pyridinyl, pyrimidinyl, benzo[b]thienyl, quinolinyl and isoquinolinyl (wherein phenyl, naphthalenyl and pyridinyl are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halo and hydroxy; and, wherein phenyl is optionally substituted with one substituent selected from the group consisting of phenyl and thienyl).

6. The compound of claim 1 wherein R^2 is selected from the group consisting of -C_{1-4}alkyl-Z, -C_{2-4}alkenyl-Z and -C_{2-4}alkynyl-Z; wherein the -C_{1-4}alkyl, -C_{2-4}alkenyl and -C_{2-4}alkynyl is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4})alkylamino, C_{1-4}alkyl, C_{1-4}alkoxy, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy and hydroxy(C_{1-4})alkyl.

7. The compound of claim 1 wherein R^2 is selected from the group consisting of -C_{1-4}alkyl-Z; wherein the -C_{1-4}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4})alkylamino, C_{1-4}alkyl, C_{1-4}alkoxy, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy and hydroxy(C_{1-4})alkyl.

8. The compound of claim 1 wherein Z is selected from the group consisting of pyrazine, pyrimidine, imidazol, pyridazine, triazine, furazan, isoxazole, isothiazole, thiazole, isothiazole, triazole, oxatriazole and tetrazole.

9. The compound of claim 1 wherein Z is selected from the group consisting of imidazol, triazole, oxatriazole and tetrazole.

10. The compound of claim 1 wherein Z is selected from the group consisting of oxatriazole and tetrazole.

11. The compound of claim 1 wherein R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, -C(O)H, -C(O)-(C_{1-4})alkyl, -CO_2H, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SH, -S-(C_{1-4})alkyl, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, -(C_{1-4})alkyl-NH_2, -C(O)-(C_{1-4})alkyl, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-4})alkyl,

-C(O)-N[(C_{1-4})alkyl]$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-4})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, -(C_{1-4})alkyl-NH_2, -C(O)-(C_{1-4})alkyl, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-4})alkyl, -C(O)-N[(C_{1-4})alkyl]$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-4})alkyl, -SO_2-N[(C_{1-4})alkyl]$_2$ and -C(NH)-NH_2), cyano, halo, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy, hydroxy, hydroxy(C_{1-4})alkyl, nitro, aryl, -(C_{1-4})alkyl-aryl, heteroaryl and -(C_{1-4})alkyl-heteroaryl.

12. The compound of claim 1 wherein R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, cyano and halogen.

13. The compound of claim 1 wherein R^3 and R^4 are independently selected from the group consisting of hydrogen, methyl, methoxy, cyano and chloro.

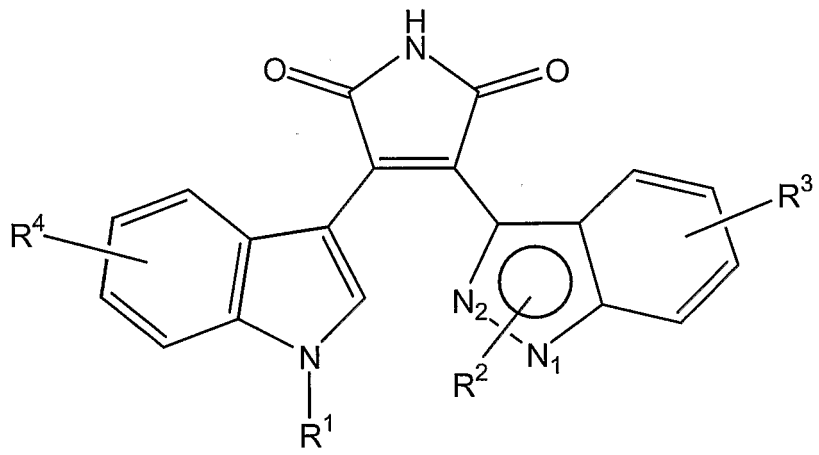
14. The compound of claim 1 wherein R^5 is 1 to 2 substituents attached to a carbon or nitrogen atom of Z and each substitute is independently selected from the group consisting of hydrogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -C(O)H, -C(O)-(C_{1-4})alkyl, -CO_2H, -C(O)-O-(C_{1-4})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH(C_{1-4}alkyl), -C(O)-N(C_{1-4})alkyl)$_2$, -SO_2-(C_{1-4})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-4}alkyl), -SO_2-N(C_{1-4}alkyl)$_2$, -(C_{1-4})alkyl-NH_2, -(C_{1-4})alkyl-NH(C_{1-4}alkyl), -(C_{1-4})alkyl- N(C_{1-4}alkyl)$_2$, -(C_{1-4})alkyl-(halo)$_{1-3}$, -(C_{1-4})alkyl-OH, -aryl, -(C_{1-4})alkyl-aryl, heteroaryl and -(C_{1-4})alkyl-heteroaryl; with the proviso that, when R^5 is attached to a carbon atom, R^5 is further selected from the group consisting of -C_{1-4}alkoxy, -(C_{1-4})alkoxy-(halo)$_{1-3}$, -SH, -S-(C_{1-4})alkyl, -N-R^6, cyano, halo, hydroxy, and nitro.

15. The compound of claim 1 wherein R^5 is 1 to 2 substituents attached to a carbon or nitrogen atom of Z and each substitute is independently selected from the group consisting of -C_{1-4}alkyl, -C_{2-4}alkenyl, -(C_{1-4})alkyl-NH_2,

-(C_{1-4})alkyl-NH(C_{1-4}alkyl), -(C_{1-4})alkyl- N(C_{1-4}alkyl)$_2$, -(C_{1-4})alkyl-(halo)$_{1-3}$, -(C_{1-4})alkyl-OH, -(C_{1-4})alkyl-aryl, heteroaryl and -(C_{1-4})alkyl-heteroaryl; with the proviso that, when R^5 is attached to a carbon atom, R^5 is further selected from the group consisting of -C_{1-4}alkoxy, -(C_{1-4})alkoxy-(halo)$_{1-3}$, -S-(C_{1-4})alkyl, -N-R^6, halo, and hydroxy.

16. The compound of claim 1 wherein R^5 is selected from the group consisting of -C_{1-4}alkyl

17. The compound of claim 1 wherein the compound of Formula (I) is a compound selected from Formula (Ia):



Formula (Ia)

wherein R^1, R^2, R^3 and R^4 are dependently selected from the group consisting of:

Formula (Ia)

R^1	R^2	R^3	R^4
Me	N1-[imidazol-1-yl(CH_2)$_3$]	H	5-Cl;
Me	N1-[triazol-1-yl(CH_2)$_3$]	H	5-Cl;
Me	N1-[tetrazol-2-yl(CH_2)$_3$]	H	5-Cl;
Me	N1-[tetrazol-1-yl(CH_2)$_3$]	H	5-Cl;
2-naphthyl	N1-[tetrazol-	H	H;

	2-yl(CH_2)$_3$]		
2-naphthyl	N1-[tetrazol-1-yl(CH_2)$_3$]	H	H;
3-pyridinyl	N1-[tetrazol-2-yl(CH_2)$_3$]	H	H;
3-pyridinyl	N1-[tetrazol-1-yl(CH_2)$_3$]	H	H;
Me	N1-[5-Me-tetrazol-2-yl(CH_2)$_3$]	H	5-Cl;
Me	N1-[5-Me-tetrazol-1-yl(CH_2)$_3$]	H	5-Cl;
Me	N1-[tetrazol-5-yl(CH_2)$_2$]	H	5-Cl;
3-pyridinyl	N1-[tetrazol-5-yl(CH_2)$_2$]	H	5-Cl;

18. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

19. A method for preparing a pharmaceutical composition comprising mixing a compound of claim 1 and a pharmaceutically acceptable carrier.

20. A method for treating or ameliorating a kinase mediated disorder comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

21. The method of claim 20 wherein the disorder is mediated by selective inhibition of a kinase selected from the group consisting of protein kinase C and glycogen synthase kinase-3.

22. The method of claim 21 wherein the kinase is selected from the group

consisting of protein kinase C α, protein kinase C , protein kinase C γ and glycogen synthase kinase-3β.

23. The method of claim 22 wherein the disorder is mediated by dual inhibition of at least two kinases selected from the group consisting of protein kinase C and glycogen synthase kinase-3.

24. The method of claim 23 wherein at least two kinases are selected from the group consisting of protein kinase C α, protein kinase C β-I, protein kinase C β-II, protein kinase C γ and glycogen synthase kinase-3β.

25. The method of claim 20 wherein the therapeutically effective amount of the compound of claim 1 is from about 0.001 mg/kg/day to about 300 mg/kg/day.

26. The method of claim 20 wherein the kinase mediated disorder is selected from the group consisting of cardiovascular diseases, diabetes, diabetes-associated disorders, inflammatory diseases, immunological disorders, dermatological disorders, oncological disorders and CNS disorders.

27. The method of claim 26 wherein cardiovascular diseases are selected from the group consisting of acute stroke, heart failure, cardiovascular ischemia, thrombosis, atherosclerosis, hypertension, restenosis, retinopathy of prematurity and age-related macular degeneration.

28. The method of claim 26 wherein diabetes is selected from the group consisting of insulin dependent diabetes and Type II non-insulin dependent diabetes mellitus.

29. The method of claim 26 wherein diabetes-associated disorders are selected from the group consisting of impaired glucose tolerance, diabetic retinopathy, proliferative retinopathy, retinal vein occlusion, macular edema,

cardiomyopathy, nephropathy and neuropathy.

30. The method of claim 26 wherein inflammatory diseases are selected from the group consisting of vascular permeability, inflammation, asthma, rheumatoid arthritis and osteoarthritis.

31. The method of claim 26 wherein immunological disorders are selected from the group consisting of transplant tissue rejection, HIV-1 and PKC modulated immunological disorders.

32. The method of claim 26 wherein dermatological disorders are selected from the group consisting of psoriasis, hair loss and baldness.

33. The method of claim 26 wherein oncological disorders are selected from the group consisting of cancer or tumor growth, proliferative angiopathy, and angiogenesis.

34. The method of claim 26 wherein central nervous system disorders are selected from the group consisting of chronic pain, neuropathic pain, epilepsy, chronic neurodegenerative conditions, dementia, Alzheimer's disease, mood disorders, schizophrenia, manic depression and neurotraumatic, cognitive decline and ischemia-related diseases (as a result of head trauma or transient ischemic stroke).

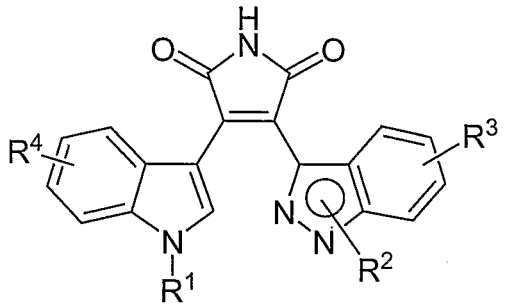
35. The method of claim 20 further comprising a method for use for a compound of claim 1 as an adjunct to chemotherapy and radiation therapy.

36. The method of claim 20 further comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 20.

37. The method of claim 36 wherein the therapeutically effective amount of

a pharmaceutical composition of claim 20 is from about 0.001 mg/kg/day to about 300 mg/kg/day.

38. A method of treating or ameliorating a disorder selected from the group consisting of diabetes-associated disorders, dermatological disorders, oncological disorders and central nervous system disorders comprising administering to a subject in need of treatment a therapeutically effective amount of a compound of Formula (I):



Formula (I)

wherein

R^1 is selected from the group consisting of:

hydrogen,

C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{3-8} cycloalkyl {wherein alkyl, alkenyl, alkynyl and C_{3-8} cycloalkyl are optionally substituted with one to two substituents independently selected from the group consisting of -O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-OH, -O-(C_{1-8})alkyl-O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-NH_2, -O-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -O-(C_{1-8})alkyl-S-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-NH_2, -O-(C_{1-8})alkyl-SO_2-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-SO_2-N[(C_{1-8})alkyl]$_2$, -O-C(O)H, -O-C(O)-(C_{1-8})alkyl, -O-C(O)-NH_2, -O-C(O)-NH-(C_{1-8})alkyl, -O-C(O)-N[(C_{1-8})alkyl]$_2$, -O-(C_{1-8})alkyl-C(O)H, -O-(C_{1-8})alkyl-C(O)-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-CO_2H,

-O-(C_{1-8})alkyl-C(O)-O-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-C(O)-NH_2, -O-(C_{1-8})alkyl-C(O)-NH-(C_{1-8})alkyl, -O-(C_{1-8})alkyl-C(O)-N[(C_{1-8})alkyl]$_2$, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-S-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-OH, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-NH_2, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -S-(C_{1-8})alkyl-O-(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -S-(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-OH, -(C_{1-8})alkyl-O-(C_{1-8})alkyl, -(C_{1-8})alkyl-NH_2, -(C_{1-8})alkyl-NH-(C_{1-8})alkyl, -(C_{1-8})alkyl-N[(C_{1-8})alkyl]$_2$, -(C_{1-8})alkyl-S-(C_{1-8})alkyl, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, -C(N)-NH_2, aryl and aryl(C_{1-8})alkyl (wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, C_{1-8}alkyl, C_{1-8}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-8}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl, (halo)$_{1-3}$(C_{1-8})alkoxy, hydroxy, hydroxy(C_{1-8})alkyl and nitro)), cyano, (halo)$_{1-3}$, hydroxy, nitro, oxo, heterocyclyl, aryl and heteroaryl (wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkoxy, amino (substituted with two substituents selected from the group consisting of hydrogen and C_{1-8}alkyl), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl, (halo)$_{1-3}$(C_{1-8})alkoxy, hydroxy, hydroxy(C_{1-8})alkyl and nitro)},

-C(O)-(C_{1-8})alkyl, -C(O)-aryl, -C(O)-O-(C_{1-8})alkyl, -C(O)-O-aryl, -C(O)-NH-(C_{1-8})alkyl, -C(O)-NH-aryl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-aryl,

heterocyclyl, aryl and heteroaryl {wherein heterocyclyl, aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-8})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl-, (halo)$_{1-3}$(C_{1-8})alkoxy-, hydroxy, hydroxy(C_{1-8})alkyl, nitro, aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl};

R^2 is selected from the group consisting of -C_{1-8}alkyl-Z, -C_{2-8}alkenyl-Z and -C_{2-8}alkynyl-Z; wherein the -C_{1-8}alkyl, -C_{2-8}alkenyl and -C_{2-8}alkynyl is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, amino, C_{1-4}alkylamino, di(C_{1-4})alkylamino, C_{1-4}alkyl, C_{1-4}alkoxy, (halo)$_{1-3}$(C_{1-4})alkyl, (halo)$_{1-3}$(C_{1-4})alkoxy and hydroxy(C_{1-4})alkyl;

Z is a 5 to 6 member monocyclic heteroaryl ring having from 2 to 4 heteroatoms containing at least one carbon atom and at least one nitrogen atom; wherein Z optionally is substituted with R^5;

R^5 is 1 to 2 substituents attached to a carbon or nitrogen atom of Z and each

substitute is independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH(C_{1-8}alkyl), -C(O)-N(C_{1-8})alkyl)$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-8}alkyl), -SO_2-N(C_{1-8}alkyl)$_2$, -(C_{1-8})alkyl-NH_2, -(C_{1-8})alkyl-NH(C_{1-8}alkyl), -(C_{1-8})alkyl-N(C_{1-8}alkyl)$_2$, -(C_{1-8})alkyl-(halo)$_{1-3}$, -(C_{1-8})alkyl-OH, -aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl;

with the proviso that, when R^5 is attached to a carbon atom, R^5 is further selected from the group consisting of -C_{1-8}alkoxy, -(C_{1-8})alkoxy-(halo)$_{1-3}$, -SH, -S-(C_{1-8})alkyl, -N-R^6, cyano, halo, hydroxy, and nitro;

R^6 is 1 to 2 substituents independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, - C_{3-8}cycloalkyl, -C(O)H, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-8}alkyl), -C(O)-N(C_{1-8}alkyl)$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH(C_{1-8}alkyl), -SO_2-N(C_{1-8}alkyl)$_2$, -C(N)-NH_2, -C(N)-NH(C_{1-8}alkyl) and -C(N)-N(C_{1-8}alkyl)$_2$;

R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, -C(O)H, -C(O)-(C_{1-8})alkyl, -CO_2H, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(NH)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SH, -S-(C_{1-8})alkyl, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$, amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and -C(NH)-NH_2), amino-(C_{1-8})alkyl- (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, -(C_{1-8})alkyl-NH_2, -C(O)-(C_{1-8})alkyl, -C(O)-O-(C_{1-8})alkyl, -C(O)-NH_2, -C(O)-NH-(C_{1-8})alkyl, -C(O)-N[(C_{1-8})alkyl]$_2$, -SO_2-(C_{1-8})alkyl, -SO_2-NH_2, -SO_2-NH-(C_{1-8})alkyl, -SO_2-N[(C_{1-8})alkyl]$_2$ and

-C(NH)-NH_2), cyano, halo, (halo)$_{1-3}$(C_{1-8})alkyl-, (halo)$_{1-3}$(C_{1-8})alkoxy-, hydroxy, hydroxy(C_{1-8})alkyl-, nitro, aryl, -(C_{1-8})alkyl-aryl, heteroaryl and -(C_{1-8})alkyl-heteroaryl;

and pharmaceutically acceptable salts thereof.

39. The method of claim 38 wherein diabetes-associated disorders are selected from the group consisting of impaired glucose tolerance, diabetic retinopathy, proliferative retinopathy, retinal vein occlusion, macular edema, cardiomyopathy, nephropathy and neuropathy.

40. The method of claim 38 wherein dermatological disorders are selected from the group consisting of psoriasis, hair loss and baldness.

41. The method of claim 38 wherein oncological disorders are selected from the group consisting of cancer or tumor growth, proliferative angiopathy, and angiogenesis.

42. The method of claim 38 wherein central nervous system disorders are selected from the group consisting of chronic pain, neuropathic pain, epilepsy, chronic neurodegenerative conditions, dementia, Alzheimer's disease, mood disorders, schizophrenia, manic depression and neurotraumatic, cognitive decline and ischemia-related diseases (as a result of head trauma or transient ischemic stroke).