N-LINKED HETEROCYCLIC ANTAGONISTS OF $P2Y_1$ RECEPTOR USEFUL IN THE TREATMENT OF THROMBOTIC CONDITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the priority benefit of U.S. Provisional Application Serial No. 60/694,596, filed June 27, 2005 and U.S. Provisional Application Serial No. 60/797,064, filed May 2, 2006. The entire disclosure of each of the foregoing applications is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention provides novel *N*-aryl or *N*-heteroaryl substituted heterocycles and analogues thereof, which are selective inhibitors of the human $P2Y_1$ receptor. The invention also provides for various pharmaceutical compositions of the same and methods for treating diseases responsive to modulation of $P2Y_1$ receptor activity.

BACKGROUND OF THE INVENTION

[0003] Purinoreceptors bind to and are activated by a variety of both ribosylated (nucleotide) and non-ribosylated (nucleoside) purines. This distinction has been used to classify these receptors into two broad groups: the P1 receptors (A1, A2a, A2b, and A3), which bind to and are activated by the nucleoside adenosine, and the P2 receptors, which comprise a second, more diverse class of receptors which are activated by a wide variety of nucleotides including ATP, ADP, UTP, and UDP. The P2 receptors can be further subdivided into two distinct types of receptors; the ionotropic P2X receptors that mediate cation flux across cellular membranes in response to ATP and the metabotropic P2Y family of receptors which are G-protein coupled receptors. In humans, the P2Y family of receptors is generally considered to consist of seven distantly related members; $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, and $P2Y_{13}$ (Boeynaems, J. M. et al. *Drug Development Research* **2001**, *52*, 187-9). In addition, an eighth receptor, $P2Y_{14}$, has been considered by some to be a member of this class although it does not respond to ribosylated nucleotides and is activated by UDP-glucose (Abbracchio, M. P. et al. *Trends Pharmacol. Sci.* **2003**, *24*, 52-5).

[0004] Several studies have suggested that modulators of specific members of the P2Y family of receptors could have therapeutic potential for the treatment of a variety of disorders (for review see Burnstock, G. and Williams, M. *J.Pharm. Exp Ther.* **2000**, *295*, 862-9), including diabetes, cancer, cystic fibrosis, and the treatment of ischemia-reperfusion injury (Abbracchio M.P. and Burnstock G. *Pharmacol. Ther.* ***1994,*** 64, 445-475). $P2Y_1$ receptors, almost ubiquitous among human organs (Janssens, R. et al. *Biochem. Biophys. Res. Comm.* **1996**, 221, 588-593) have been identified on microglia (Norenberg, W. et al. *Br. J. Pharmacol.* **1994**, *111,* 942-950) and on astrocytes (Salter M.W. and Hicks J.L. *J.Neurosc.* **1995**, *15*, 2961-2971). Extracellular ATP activates microglial and/or astrocytes via P2Y receptors and leads directly to the release of inflammatory mediators. Microglia and astrocytes are believed to play a role in the progression of Alzheimer's disease and other CNS inflammatory disorders such as stroke and multiple sclerosis.

[0005] Two members of the P2Y family, $P2Y_1$ and $P2Y_{12}$, are of particular interest as they have now both been shown to act as important receptors for ADP in platelets (Jin, J. et al. *Proc. Natl. Acad. Sci.* **1998**, *95*, 8070-4). ADP is a key activator of platelets and platelet activation is known to play a pivotal role in thrombus formation under conditions of high shear stress such as those found in the arterial circulation. In addition, more recent data has suggested that platelet activation may also play a role in mediating thrombus formation under lower shear stress such as that found in the venous circulation. ADP activates platelets by simultaneously interacting with both $P2Y_1$ and $P2Y_{12}$ to produce two separate intracellular signals which synergize together to produce complete platelet activation (Jin, J. et al. *J. Biol. Chem.* **1998**, *273*, 2030-4). The first signal arises from ADP driven activation of the $P2Y_1$ receptor and can most easily be tracked by measuring the transitory increase in intracellular free Ca^{+2}. This signal appears to mediate the initial shape change reaction and to initiate the process of platelet activation. The second signal appears to be derived from ADP activation of the $P2Y_{12}$ receptor and serves to consolidate the process and produce an irreversible platelet aggregate. Using three structurally related but distinct inhibitors of $P2Y_1$ (A3P5P, A3P5PS, and A2P5P), Daniel, J. L. et al. (*J. Biol. Chem.* **1998**, *273*, 2024-9), Savi, P. et al. (*FEBS Letters* **1998**, *422*, 291-5), and Hechler, B. et al. (*Br. J. Haematol.* **1998**, *103*, 858-66) were the first to publish

the observation that the inhibition of $P2Y_1$ activity alone could block ADP-driven aggregation independently of the $P2Y_{12}$ receptor. Although inhibition of platelet reactivity is often thought of as firm evidence of an anti-thrombotic activity, these antagonists lacked the necessary pharmacological properties for *in vivo* study. The first direct demonstration that inhibition of $P2Y_1$ activity could lead to an anti-thrombotic effect *in vivo* was reported by Leon, C. et al. *Circulation* **2001**, *103*, 718-23, in a model of thromboplastin induced thromboembolism using both a $P2Y_1$ knock-out mouse and the $P2Y_1$ antagonist MRS-2179 (Baurand, A. and Gachet, C. *Cardiovascular Drug Reviews* **2003**, *21*, 67-76). These results were subsequently extended to include the inhibition of both venous and arterial thrombosis in the rat (Lenain, N. et al. *J. Thromb. Haemost.* **2003**, *1*, 1144-9) and the confirmation of the phenotype of the $P2Y_1$ knock-out mouse in a second laboratory using an independently derived animal (Fabre, J-E. et al. *Nature Medicine* **1999**, *5*, 1199-1202). These studies highlighted the need for more potent and selective $P2Y_1$ antagonists and recently, using the $P2Y_1$ antagonist MRS-2500 (Hechler, B. et al. *J. Pharmacol Exp. Ther.* **2006**, *316*, 556-563) succeeded in demonstrating strong antithrombotic activity for a selective $P2Y_1$ antagonist in the mouse. Taken together, these data suggest that the discovery of novel $P2Y_1$ antagonists with improved pharmaceutical characteristics could have significant utility in the treatment of a variety of thrombotic or thromboembolic disorders (see Gachet, C. et al. *Blood Cell, Molecules and Disease* **2006**, *36*, 223-227 for a recent review).

SUMMARY OF THE INVENTION

[0006] Accordingly, the present invention provides novel *N*-aryl or *N*-heteroaryl substituted heterocycles, which are useful as selective inhibitors of the $P2Y_1$ receptor, including stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

[0007] The present invention also provides processes and intermediates for making the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0008] The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0009] The present invention also provides a method for modulation of platelet reactivity comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0010] The present invention also provides a method for treating thrombotic or thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof.

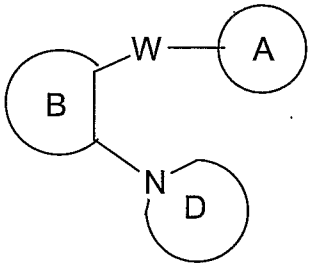
[0011] The present invention also provides the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for use in therapy.

[0012] The present invention also provides the use of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for the manufacture of a medicament for the treatment of thrombotic or thromboembolic or other disorders.

[0013] These and other features of the invention will be set forth in the expanded form as the disclosure continues.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0014] In a first aspect, the present invention provides, *inter alia*, a compound of Formula (I):



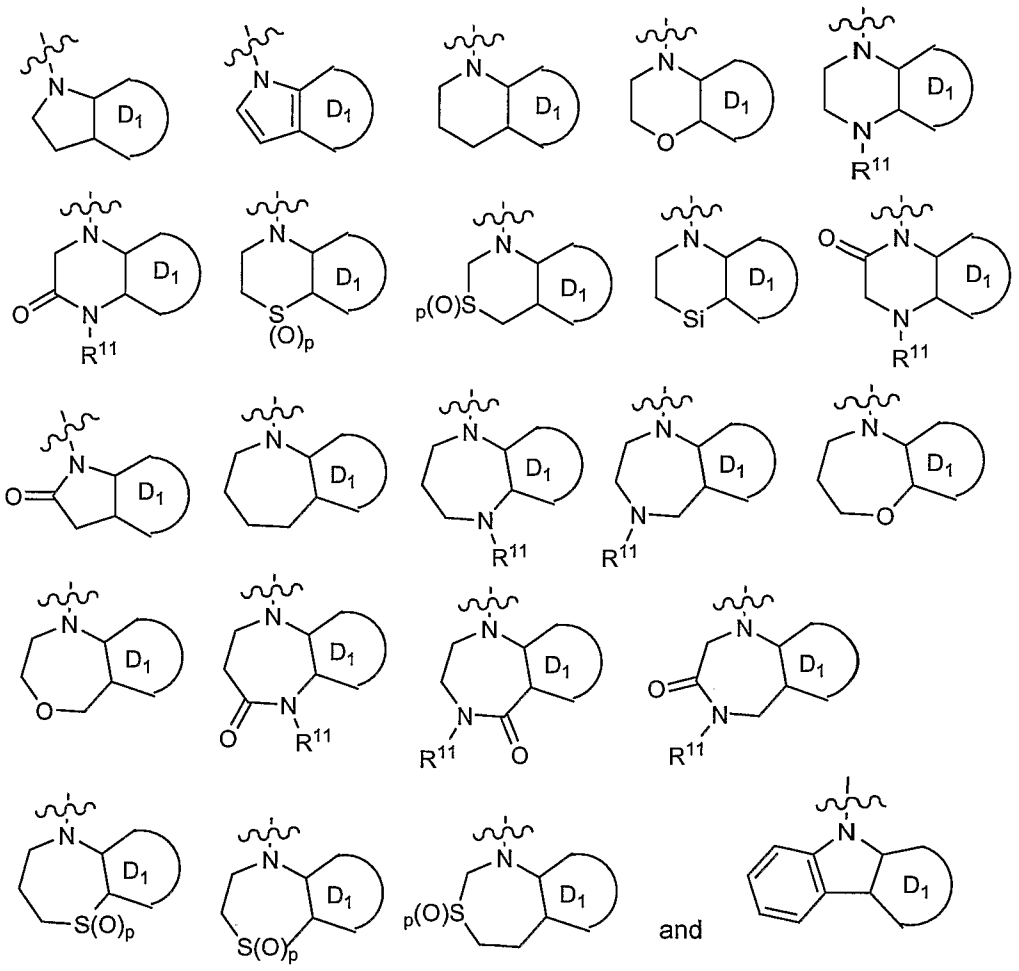
(I)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

ring A is C_{6-10} aryl substituted with 0-5 R^1, or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-5 R^1;

ring B is C_{6-10} aryl substituted with 0-4 R^7, or a 5- to 10-membered heteroaryl comprising: carbon atoms and 1-4 ring heteroatoms selected from N, NR^{11}, N→O, $S(O)_p$, and O, wherein said heteroaryl is substituted with 0-4 R^7;

ring D is substituted with 0-5 R^{6a} and selected from:

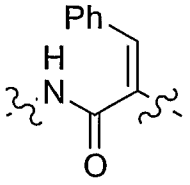


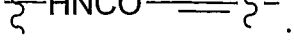
;

wherein D_1 is a 5- to 7-membered carbocycle or a 5-6-membered heterocycle comprising: carbon atoms and 0-3 ring heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-2 carbonyl groups, and 0-3 double bonds;

W is NR^{18}, O, S, -NHCOCH=CH-, -NHCO-, $-NHCO_2-$, $-NHCO_2CH_2-$,

-NHCON(Me)-, -NHCOCH$_2$NH-, -NHCOCH(Me)-, -NHCOCH$_2$CH$_2$-, -NHCOCH$_2$CONH-, -NHCH$_2$-, -NHCH$_2$CH$_2$CH$_2$-, -NHSO$_2$-, -NHSO$_2$NH-, -NHSO$_2$CH$_2$-, -NHSO$_2$CH=CH-, -NHCONHNHCO-, -CH$_2$CONH-,



or 

;

R^1 is, independently at each occurrence, =O, F, Cl, Br, I, CF$_3$, -CF$_2$CF$_3$, OCF$_3$, -OCF$_2$CF$_2$H, -OCF$_2$CF$_3$, SiMe$_3$, -(CR^{f}R^f)$_r$OR^c, SR^c, CN, NO$_2$, -(CR^{f}R^f)$_r$NR^{12}R^{13}, -(CR^{f}R^f)$_r$C(O)R^c, -(CR^{f}R^f)$_r$CO$_2$R^c, -(CR^{f}R^f)$_r$C(O)NR^{12}R^{13}, -C(O)NR^{14}(CR^{f}R^f)$_t$N^{12}R^{13}, -(CR^{f}R^f)$_r$OC(O)NR^{12}R^{13}, -(CR^{f}R^f)$_r$NR^{14}C(O)NR^{12}R^{13}, -(CR^{f}R^f)$_r$NR^{14}C(O)R^d, -(CR^{f}R^f)$_r$NR^{14}C(O)OR^h, -NR^{14}(CR^{f}R^f)$_n$C(O)R^d, -NR^{14}CO(CR^{f}R^f)$_n$OR^c, -(CH$_2$)$_r$CR^{13}(=NOR^c), -(CH$_2$)$_r$-C(NH$_2$)(=NOR^c), -S(O)$_p$NR^{12}R^{13}, -(CR^{f}R^f)$_r$NR^{14}S(O)$_p$NR^{12}R^{13}, -NR^{14}SO$_2$CF$_3$, -NR^{14}S(O)$_p$R^d, -S(O)$_2$CF$_3$, -S(O)R^d, -S(O)$_2$R^d, -OP(O)(OEt)$_2$, -O(CH$_2$)$_2$OP(O)(OEt)$_2$, -N(C$_{1-4}$ alkyl)$_3$$^+Cl^-$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl, C$_{1-8}$ alkyl substituted with 0-2 R^a, C$_{2-8}$ alkenyl substituted with 0-2 R^a, C$_{2-8}$ alkynyl substituted with 0-2 R^a, -(CR^{f}R^f)$_r$-C$_{3-13}$ carbocycle substituted with 0-5 R^b, or -(CR^{f}R^f)$_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and S(O)$_p$, wherein said heterocycle is substituted with 0-5 R^b;

alternatively, two R^{1}s on two adjacent carbon atoms are combined with the carbon atoms to which they are attached, form a 5- to 10-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and S(O)$_p$, and 0-2 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-4 R^b;

R^{6a} is, independently at each occurrence, =O, F, Cl, Br, I, -(CR^{i}R^i)$_r$-OR^c, SR^c, CN, NO$_2$, CF$_3$, OCF$_3$, -CF$_2$CF$_3$, -OCF$_2$CF$_2$H, -OCF$_2$CF$_3$, -(CR^{f}R^f)$_r$-NR^{12}R^{13}, -C(O)R^c, -(CR^{f}R^f)$_r$-C(O)OR^c, -(CR^{f}R^f)$_r$-C(O)NR^{12}R^{13}, -(CR^{f}R^f)$_r$-NR^{14}C(O)R^d, -S(O)$_p$NR^{12}R^{13}, -S(O)R^d, -S(O)$_2$R^d, Si(Me)$_3$, Si(C$_{1-4}$ alkyl)$_3$, C$_{1-4}$ haloalkyl, C$_{1-4}$ haloalkyloxy-, C$_{1-4}$ alkyloxy-, C$_{1-4}$ alkylthio-, C$_1$-C$_4$ alkyl-C(O)-,

C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-8} alkyl substituted with 0-1 R^a, C_{2-8} alkenyl substituted with 0-1 R^a, C_{2-8} alkynyl substituted with 0-1 R^a, $-(CR^fR^f)_r-C_{3-10}$ carbocycle substituted with 0-2 R^e, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^e;

alternatively, when two R^{6a} groups are attached to the same carbon atom or silicon atom, together with the carbon atom or silicon atom to which they are attached, they form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

alternatively, when two R^{6a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

R^7 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^c, SR^c, CN, NO_2, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CR^fR^f)_r-C_{3-10}$ carbocycle substituted with 0-3 R^b, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{7b}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^b;

alternatively, two R^7s on two adjacent carbon atoms form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 ring heteroatoms selected from O, N, NR^{7b}, and $S(O)_p$, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^{7c};

R^{7b} is H, C_{1-4} alkyl, $-C(O)(C_{1-4}$ alkyl), -C(O)phenyl, -C(O)benzyl, or benzyl;

R^{7c} is, independently at each occurrence, H, F, Cl, Br, I, OCF_3, CF_3, OR^c, SR^c, CN, NO_2, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$,

$-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-4} alkyl, phenyl substituted with 0-3 R^b, or benzyl substituted with 0-3 R^b;

R^{11} is, independently at each occurrence, H, C_{1-4} alkoxy, C_{1-6} alkyl substituted with 1-5 fluorine, $-(CR^fR^f)_rC(O)NR^{12}R^{13}$, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-4} alkenyl substituted with 0-1 R^a, C_{2-4} alkynyl substituted with 0-1 R^a, $-C(O)(C_{1-6}$ alkyl), $-C(O)(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)(CH_2)_n(C_{6-10}$ aryl), $-C(O)(CH_2)_n$(5- to 10-membered heteroaryl), $-C(O)O(C_{1-8}$ alkyl), $-C(O)O(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)O(CH_2)_n(C_{6-10}$ aryl), $-C(O)O(CH_2)_n$(5- to 10-membered heteroaryl), $-C(O)O(CH_2)_{2-4}(C_{1-4}$ alkyl), $-C(O)NH(C_{1-8}$ alkyl), $-C(O)NH(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)NH(CH_2)_n(C_{6-10}$ aryl), $-C(O)NH(CH_2)_n$(5- to 10-membered heteroaryl), $-S(O)_2(C_{1-8}$ alkyl), $-S(O)_2(CH_2)_n(C_{3-6}$ cycloalkyl), $-S(O)_2(CH_2)_n(C_{6-10}$ aryl), $-S(O)_2(CH_2)_n$(5- to 10-membered heteroaryl), $-(CR^fR^f)_r-C_{3-10}$ carbocycle, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle; wherein said alkyl, cycloalkyl, aryl, and carbocycle are substituted with 0-2 R^b, and said heteroaryl and heterocycle are substituted with 0-2 R^b and comprise: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$;

R^{12} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 1-5 fluorine, $-(CR^fR^f)_rC(O)NR^fR^f$, C_{1-6} alkyl, $-C(O)(C_{1-6}$ alkyl), $-C(O)(CH_2)_n(C_{6-10}$ aryl), $-C(O)(CH_2)_n$(5- to 10-membered heteroaryl), $-C(O)O(C_{1-4}$ alkyl), $-C(O)OCH_2(C_{6-10}$ aryl), $-(CH_2)_nC(O)OCH_2$(5- to 10-membered heteroaryl), $-(CH_2)_nOC(O)(C_{1-4}$ alkyl), $-(CH_2)_nOC(O)(C_{6-10}$ aryl), $-(CH_2)_nOC(O)$(5- to 10-membered heteroaryl), $-(CH_2)_nC(O)O(C_{1-4}$ alkyl), $-(CH_2)_nC(O)O(C_{6-10}$ aryl), $-(CH_2)_nC(O)O$(5- to 10-membered heteroaryl), $-(CH_2)_nC(O)NH(C_{1-6}$ alkyl), $-(CH_2)_nC(O)NH(C_{6-10}$ aryl), $-(CH_2)_nC(O)NH$(5- to 10-membered heteroaryl), $-(CH_2)_tOC(O)NH(C_{1-6}$ alkyl), $-(CH_2)_tOC(O)NH(C_{6-10}$ aryl), $-(CH_2)_tOC(O)NH$(5- to 10-membered heteroaryl), $-S(O)_2(C_{1-6}$ alkyl), $-S(O)_2(CH_2)_n(C_{6-10}$ aryl), $-S(O)_2(CH_2)_n$(5- to 10-membered heteroaryl),

$-(CR^fR^f)_n-(C_{6-10}$ aryl), or $-(CR^fR^f)_n-$ 5- to 10-membered heteroaryl; wherein said alkyl and aryl are substituted with 0-2 R^g; and said heteroaryl is substituted with 0-2 R^g and comprises: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

alternatively, R^{12} and R^{13}, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising: carbon atoms and 1-2 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{14} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{14a}, C_{2-6} alkenyl substituted with 0-2 R^{14a}, C_{2-6} alkynyl substituted with 0-2 R^{14a}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^g, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^g;

R^{14a} is, independently at each occurrence, H, C_{1-4} alkyl, OR^f, Cl, F, Br, I, =O, CF_3, CN, NO_2, $NR^{12}R^{13}$, $-C(O)R^f$, $-C(O)OR^f$, $-C(O)NR^{12}R^{13}$, or $-S(O)_pR^f$;

R^{16} is, independently at each occurrence, H, F, C_{1-6} alkyl substituted with 0-2 R^a, C_{2-6} alkenyl substituted with 0-2 R^a, C_{2-6} alkynyl substituted with 0-2 R^a, or $-(CH_2)_r$-phenyl substituted with 0-2 R^b;

R^{17} is, independently at each occurrence, H, OH, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

alternatively, R^{16} and R^{17} on the same carbon atom combine to form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl, and 0-3 double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

alternatively, two R^{16} groups on adjacent atoms combine to form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl, and 0-3 double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

R^{18} is H, C_{1-6} alkyl substituted with 0-2 R^a, C_{2-6} alkenyl substituted with 0-2 R^a, C_{2-6} alkynyl substituted with 0-2 R^a, -C(O)R^c, -C(O)OR^c, -C(O)N$R^{12}R^{13}$, -S(O)$_2R^h$, -S(O)$_2$N$R^{12}R^{13}$, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^b, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and S(O)$_p$, and substituted with 0-3 R^b;

R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, -$(CR^fR^f)_r$OR^c, -$(CR^fR^f)_r$SR^c, CN, -$(CR^fR^f)_r$N$R^{12}R^{13}$, -$(CR^fR^f)_r$C(O)R^c, -$(CR^fR^f)_r$C(O)OR^c, -$(CR^fR^f)_r$C(O)N$R^{12}R^{13}$, -$(CR^fR^f)_r$NR^{14}C(O)R^d, -$(CR^fR^f)_r$S(O)$_p$N$R^{12}R^{13}$, -$(CR^fR^f)_r$S(O)R^d, -$(CR^fR^f)_r$S(O)$_2R^d$, C_{1-4} alkyl substituted with 1-5 fluorine, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^e, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and S(O)$_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^b is, independently at each occurrence, H, =O, F, Cl, Br, I, -$(CH_2)_r$-OR^c, SR^c, CN, NO_2, CF_3, OCF_3, -$(CR^fR^f)_r$N$R^{12}R^{13}$, -C(O)R^c, -$(CH_2)_r$-C(O)OR^c, -$(CH_2)_r$-C(O)N$R^{12}R^{13}$, -NR^{14}C(O)R^d, -S(O)$_p$N$R^{12}R^{13}$, -S(O)R^d, -S(O)$_2R^d$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_{1-4} alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, -$(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^e, or -$(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and S(O)$_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^c is, independently at each occurrence, H, -OP(O)(OEt)$_2$, C_{1-8} alkyl substituted with 0-3 R^e, C_{2-8} alkenyl substituted with 0-3 R^e, C_{2-8} alkynyl substituted with 0-3 R^e, -$(CR^fR^f)_r$-C_{3-8} cycloalkyl substituted with 0-3 R^e, -$(CR^fR^f)_r$-C_{6-10} aryl substituted with 0-3 R^e, or -$(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and S(O)$_p$, wherein said heterocycle is substitutd with 0-3 R^e;

R^d is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl,

$-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^e, or $-(CH_2)_r$-5- to 10- membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^e is, independently at each occurrence, H, =O, $-(CH_2)_r-OR^f$, F, Cl, Br, I, CN, NO_2, $-(CH_2)_r-NR^{12}R^{13}$, $-C(O)R^f$, $-(CH_2)_r-C(O)OR^f$, $-NR^{14}C(O)R^f$, $-(CH_2)_r-C(O)NR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$, $-NR^{14}SO_2NR^{12}R^{13}$, $-NR^{14}SO_2-C_{1-4}$ alkyl, $-NR^{14}SO_2CF_3$, $-NR^{14}SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p-OR^h$, $-(CF_2)_rCF_3$, $Si(Me)_3$, $Si(Me)_2(t\text{-Bu})$, $Si(C_{1-4}\text{ alkyl})_3$, C_{1-8} alkyl substituted with 0-2 R^g, C_{2-8} alkenyl substituted with 0-2 R^g, C_{2-8} alkynyl substituted with 0-2 R^g, $-(CH_2)_r-C_{3-8}$ cycloalkyl substituted with 0-2 R^g, $-(CH_2)_r-C_{6-10}$ aryl substituted with 0-2 R^g, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

alternatively, two R^e groups, together with the atoms to which they are attached, form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^f, O, and $S(O)_p$, 0-1 carbonyl and 0-3 double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^g;

R^f is, independently at each occurrence, H, F, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

R^g is, independently at each occurrence, H, =O, OR^f, F, Cl, Br, I, CN, NO_2, $-NR^fR^f$, $-C(O)R^f$, $-C(O)OR^f$, $-NR^fC(O)R^f$, $-C(O)NR^fR^f$, $-SO_2NR^fR^f$, $-NR^fSO_2NR^fR^f$, $-NR^fSO_2-C_{1-4}$ alkyl, $-NR^fSO_2CF_3$, $-NR^fSO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p-C_{1-4}$ alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

R^h is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^g, $-(CH_2)_n$-phenyl substituted with 0-2 R^g, or $-(CH_2)_n$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

R^i is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^g, $-(CH_2)_n$-phenyl substituted with 0-2 R^g, or $-(CH_2)_n$-5- to 10-membered heterocycle

comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

s, at each occurrence, is selected from 0, 1, 2, and 3; and

t, at each occurrence, is selected from 1, 2, 3, and 4;

provided that:

(i) when W is -NHCO-, $-NHCO_2-$, or $-NHCOCH_2CH_2-$, ring B is substituted or unsubstituted phenylene and ring D is substituted or unsubstituted 2,3-dihydro-1H-indol-1-yl or substituted or unsubstituted 3,4-dihydro-1(2H)-quinolinyl, then ring A is other than unsubstituted or substituted phenyl, furanyl, pyridyl, or 4-methyl-piperazin-1-yl;

(ii) when W is $-NHSO_2-$, ring B is quinoxalinylene and ring D is 3,4-dihydro-1(2H)-quinolinyl, then ring A is other than phenyl or substituted phenyl; or

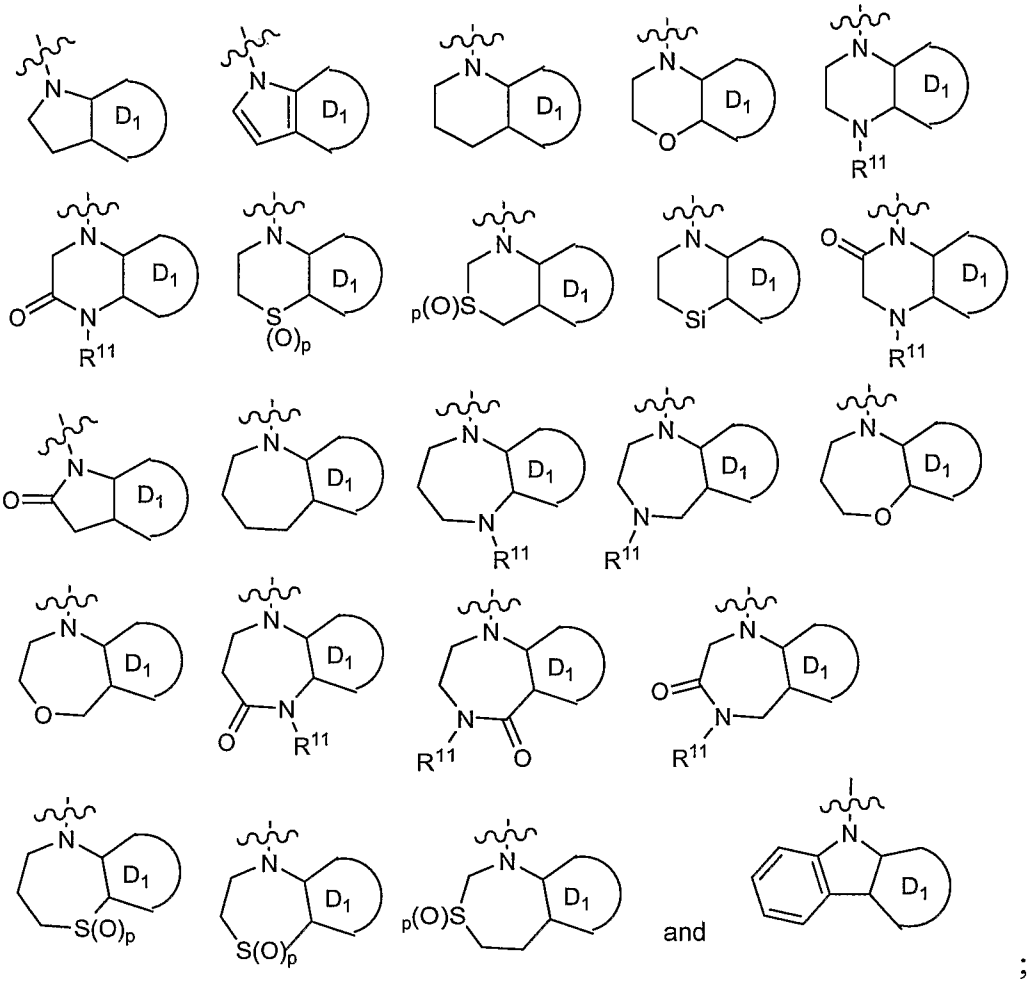
(iii) the compound is other than 2-(2,3-dinydro-7-methylcyclopent[b]indol-4(1H)-yl)-N,N-diphenylbenzenamide.

[0015] In a second aspect, the present invention provides a compound of Formula (I), within the scope of the first aspect wherein:

ring B is C_{6-10} aryl substituted with 0-4 R^7, or a 5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 ring heteroatoms selected from N, NR^{11}, $S(O)_p$, and O, wherein said heteroaryl is substituted with 0-4 R^7;

W is NR^{18}, O, S, -NHCOCH=CH-, $-NHSO_2-$, $-NHSO_2CH_2-$, or $-NHSO_2CH=CH-$; and

ring D is substituted with 0-5 R^{6a} and selected from:

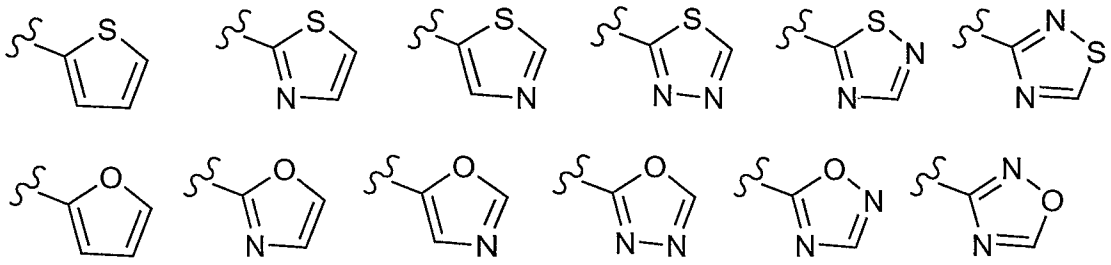


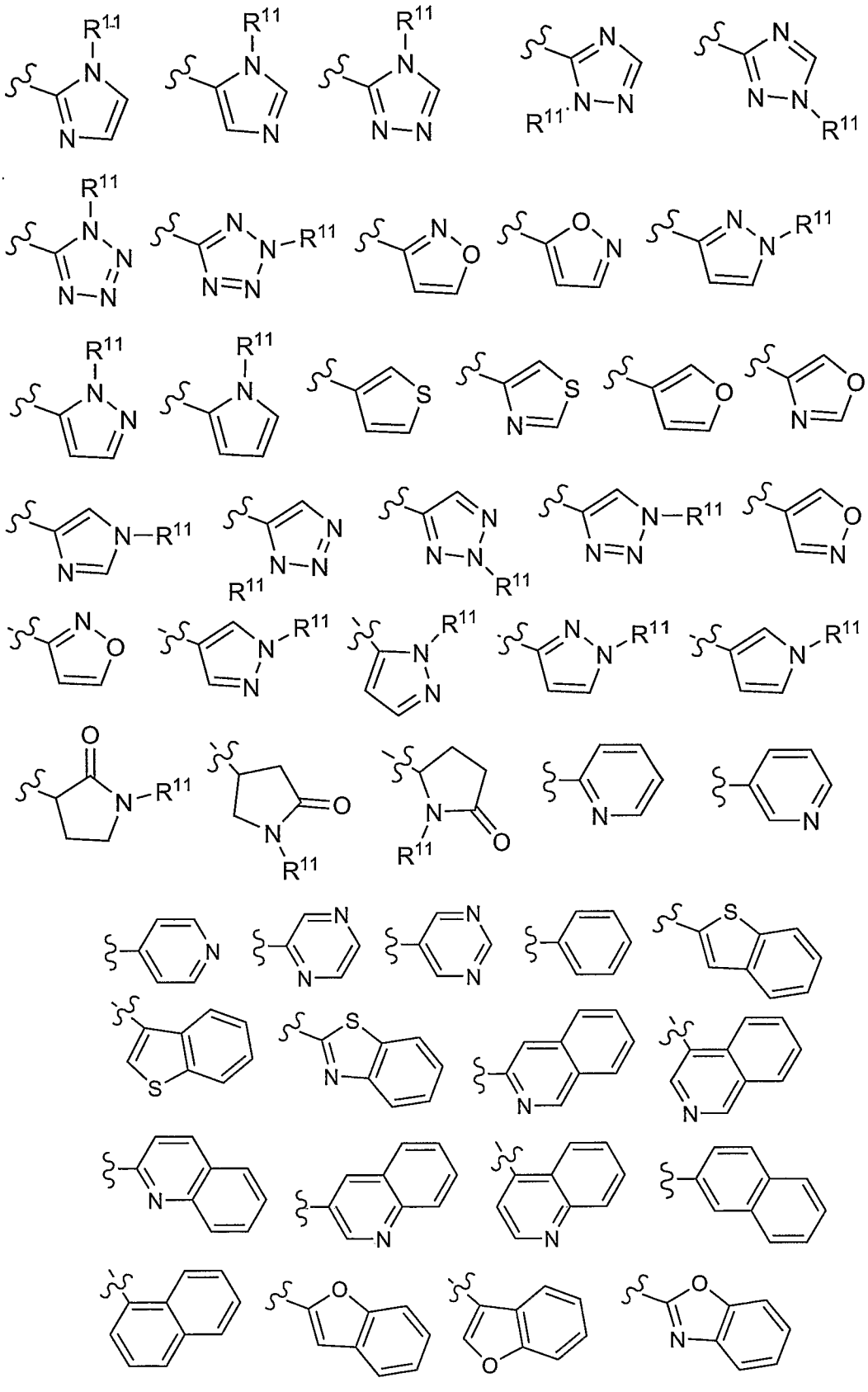
;

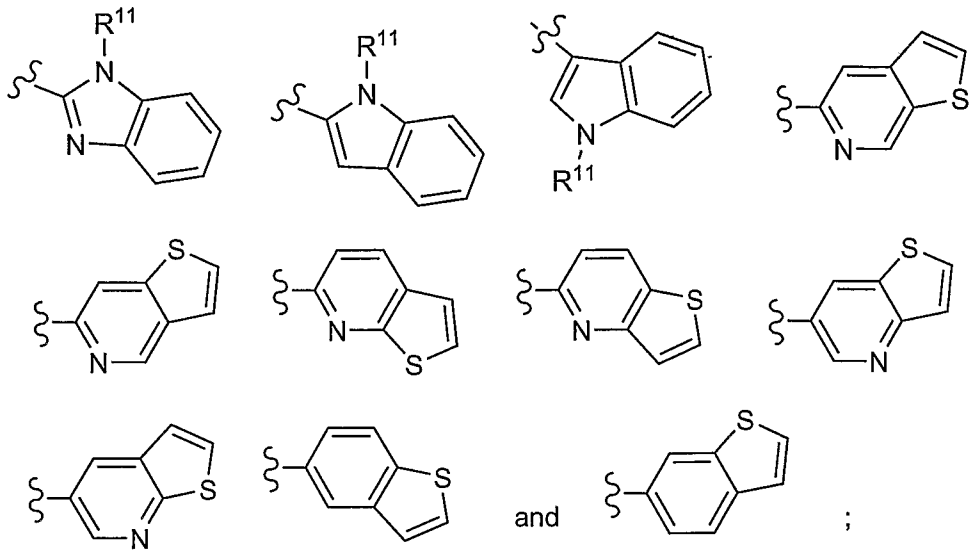
wherein D_1 is selected from: cyclopentyl, cylohexyl, piperidinyl, tetrahydropyranyl, phenyl, pyridinyl, pyrimidinyl, thiophenyl, pyrrolyl, furanyl, thiazolyl, imidazolyl, and oxazolyl.

[0016] In another embodiment, the present invention provides a compound of Formula (I), within the scope of the first aspect wherein:

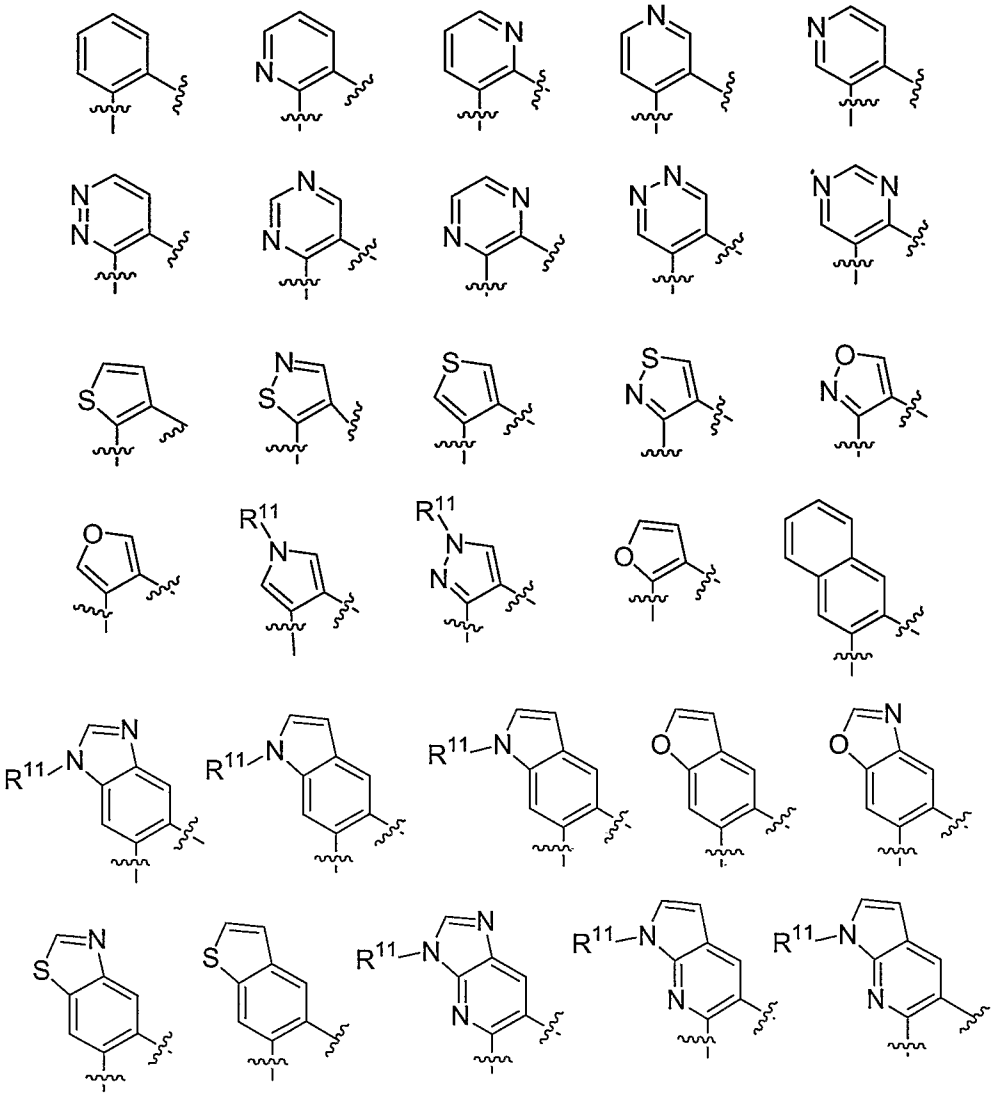
ring A is substituted with 0-5 R^1 and selected from:

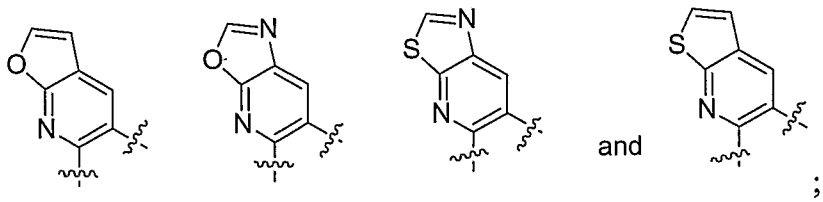





and ;

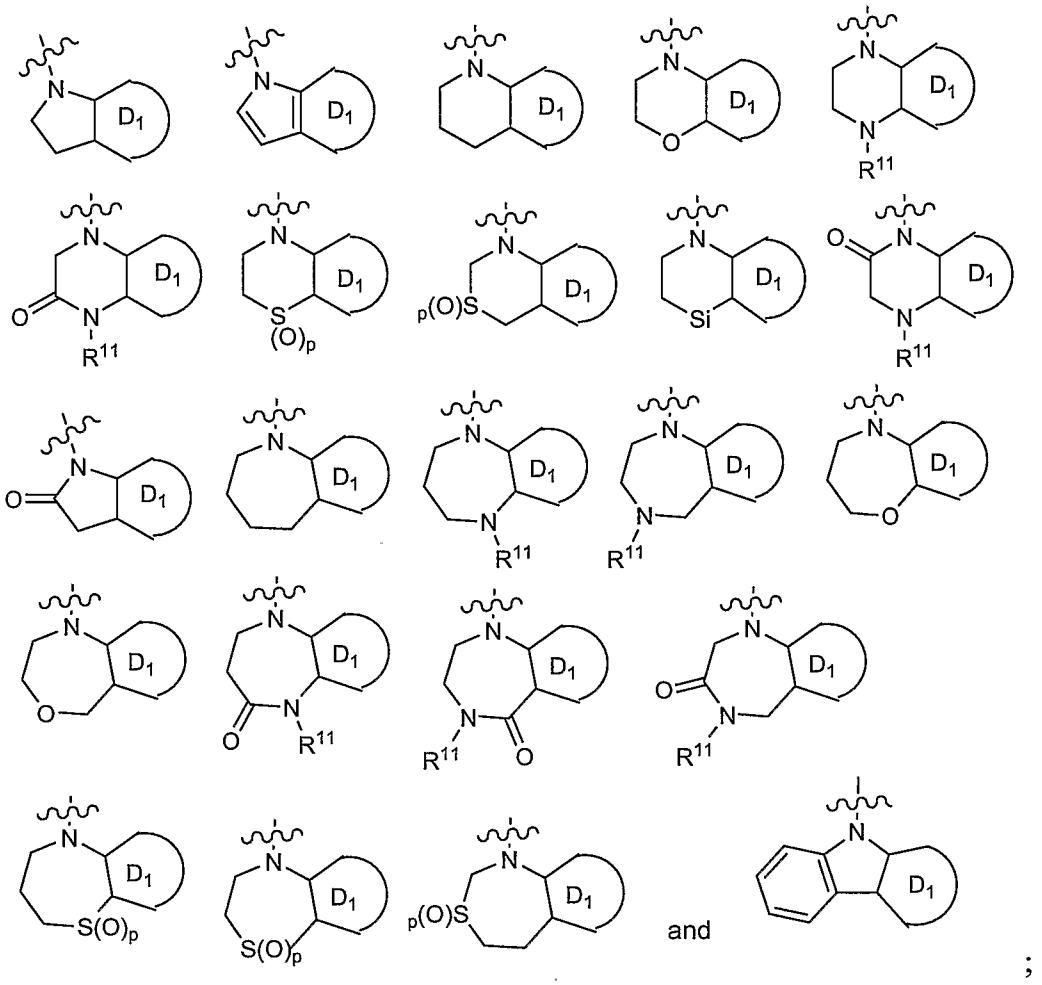
ring B is substituted with 0-3 R^7 and selected from:





; and

ring D is substituted with 0-5 R^{6a} and selected from:

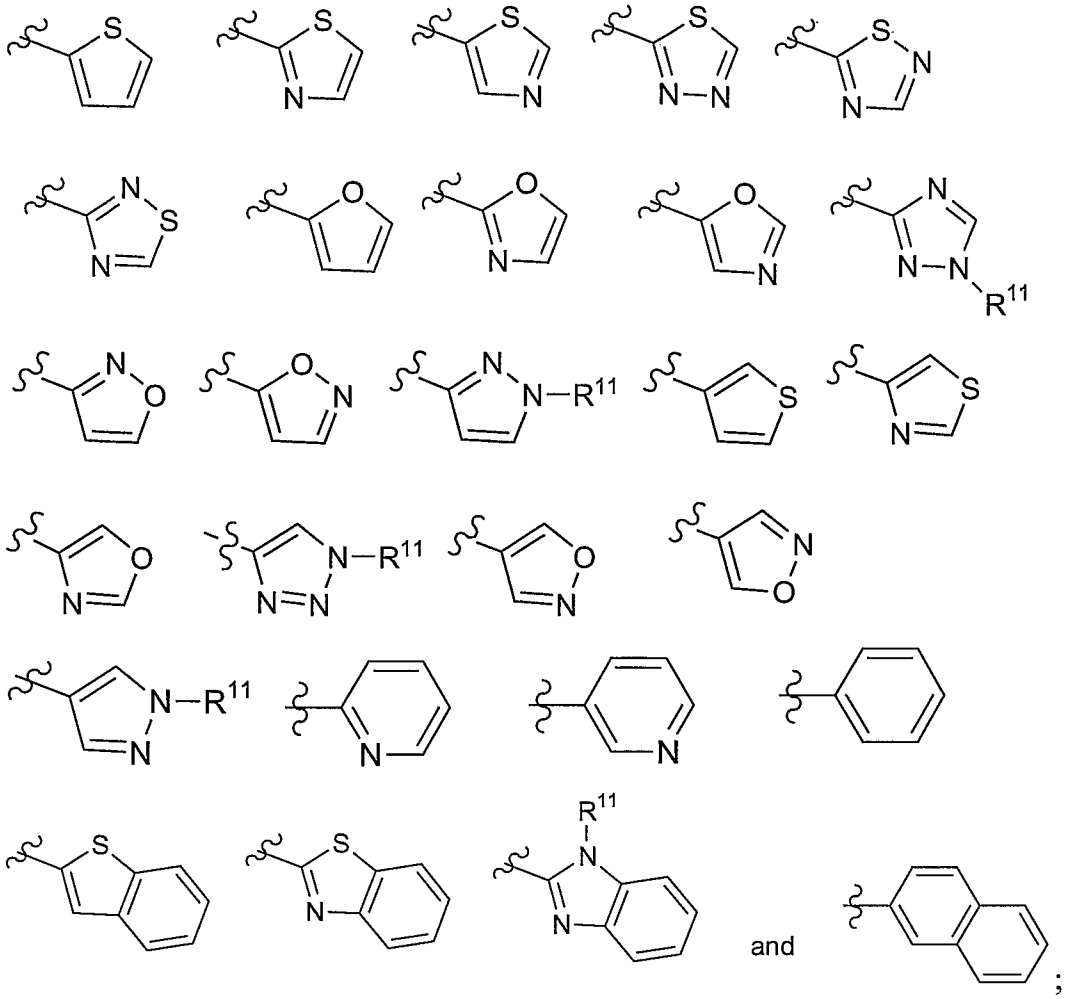


;

wherein D_1 is selected from: cyclopentyl, cylohexyl, piperidinyl, tetrahydropyranyl, phenyl, pyridinyl, pyrimidinyl, thiophenyl, pyrrolyl, furanyl, thiazolyl, imidazolyl, and oxazolyl.

[0017] In another embodiment, the present invention provides a compound of Formula (I), within the scope of the first aspect wherein:

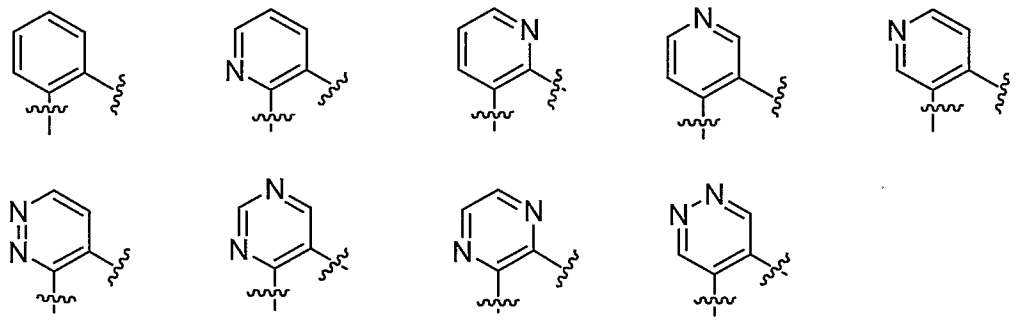
ring A is substituted with 0-4 R^1 and selected from:

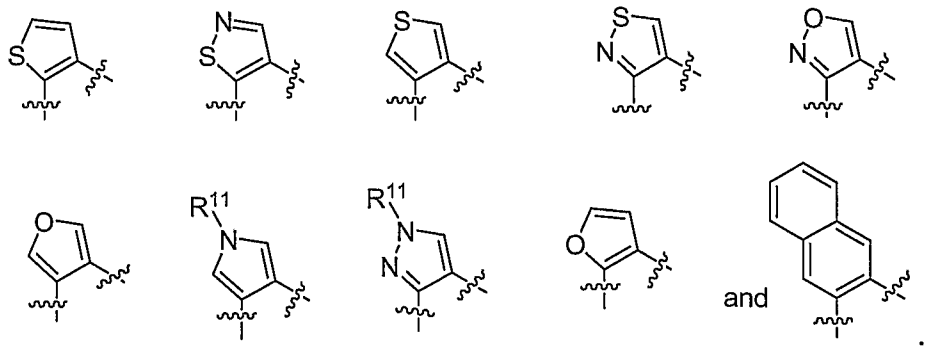


;

and

ring B is substituted with 0-3 R^7 and selected from:





[0018] In another embodiment, the present invention provides a compound of Formula (I), within the scope of the first aspect wherein:

R^1 is, independently at each occurrence, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $SiMe_3$, $-(CR^fR^f)_r-OR^c$, SR^c, CN, NO_2, $-(CR^fR^f)_r-NR^{12}R^{13}$, $-(CR^fR^f)_r-C(O)R^c$, $-(CR^fR^f)_r-CO_2R^c$, $-(CR^fR^f)_r-C(O)NR^{12}R^{13}$, $-OP(O)(OEt)_2$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CR^fR^f)_r-C_{3-13}$ carbocycle substituted with 0-5 R^b, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-5 R^b;

alternatively, two R^1s on two adjacent carbon atoms are combined with the carbon atoms to which they attached, form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-2 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-4 R^b.

[0019] In another embodiment, the present invention provides a compound of Formula (I), within the scope of the first aspect wherein:

R^{6a} is, independently at each occurrence, F, Cl, Br, I, $-(CR^iR^i)_r-OR^c$, SR^c, CN, CF_3, OCF_3, $-CF_2CF_3$, $-OCF_2CF_2H$, $-OCF_2CF_3$, $-NR^{12}R^{13}$, $-C(O)R^c$, $-(CR^fR^f)_r-C(O)OR^c$, $-Si(Me)_3$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_1-C_4 alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-,

C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CR^fR^f)_r-C_{3-10}$ carbocycle substituted with 0-2 R^e, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^e; and

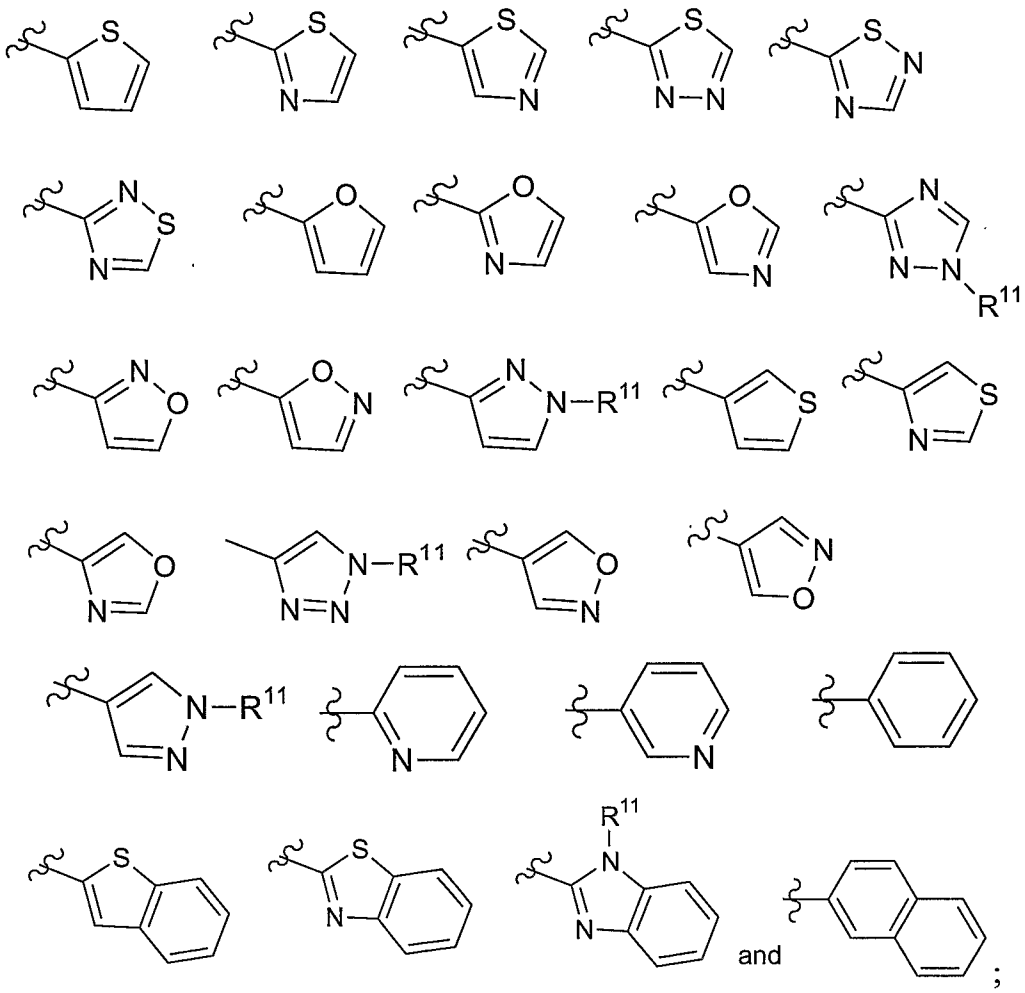
alternatively, when two R^{6a} groups are attached to the same carbon atom or silicon atom, together with the carbon atom or silicon atom to which they are attached, they form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

alternatively, when two R^{6a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b.

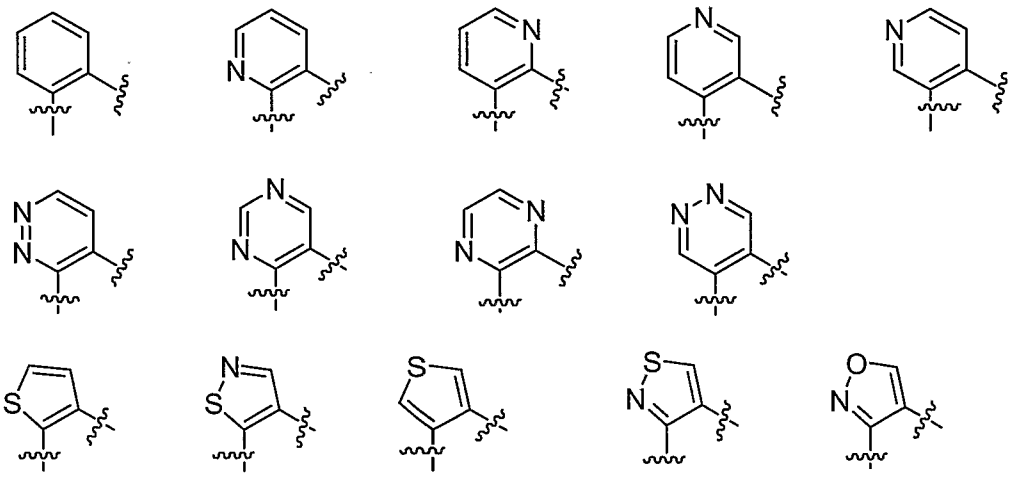
[0020] In another embodiment, the present invention provides a compound of Formula (I), within the scope of the first aspect wherein: R^{11} is, independently at each occurrence, H, C_{1-8} alkyl substituted with 0-2 R^a, $-C(O)(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)(CH_2)_n$phenyl, $-C(O)O(C_{1-8}$ alkyl), $-C(O)O(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)O(CH_2)_n$phenyl, $-C(O)O(CH_2)_{2-4}(C_{1-4}$ alkyl), $-C(O)NH(C_{1-6}$ alkyl), $-S(O)_2(C_{1-6}$ alkyl), $-S(O)_2(CH_2)_n$phenyl, $-(CR^fR^f)_r-C_{3-7}$ cycloalkyl, $-(CR^fR^f)_r$-phenyl, or $-(CR^fR^f)_r$-5- to 6-membered heterocycle; wherein said alkyl, cycloalkyl, phenyl, and aryl are substituted with 0-2 R^b, and said heteroaryl and heterocycle are substituted with 0-2 R^b and comprise: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$.

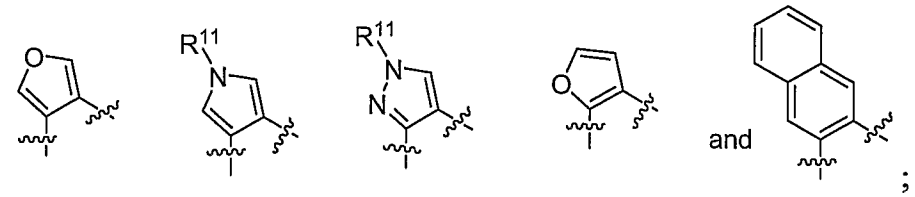
[0021] In another embodiment, the present invention provides a compound of Formula (I), within the scope of the first aspect wherein: ring A is substituted with

0-4 R^1 and selected from:



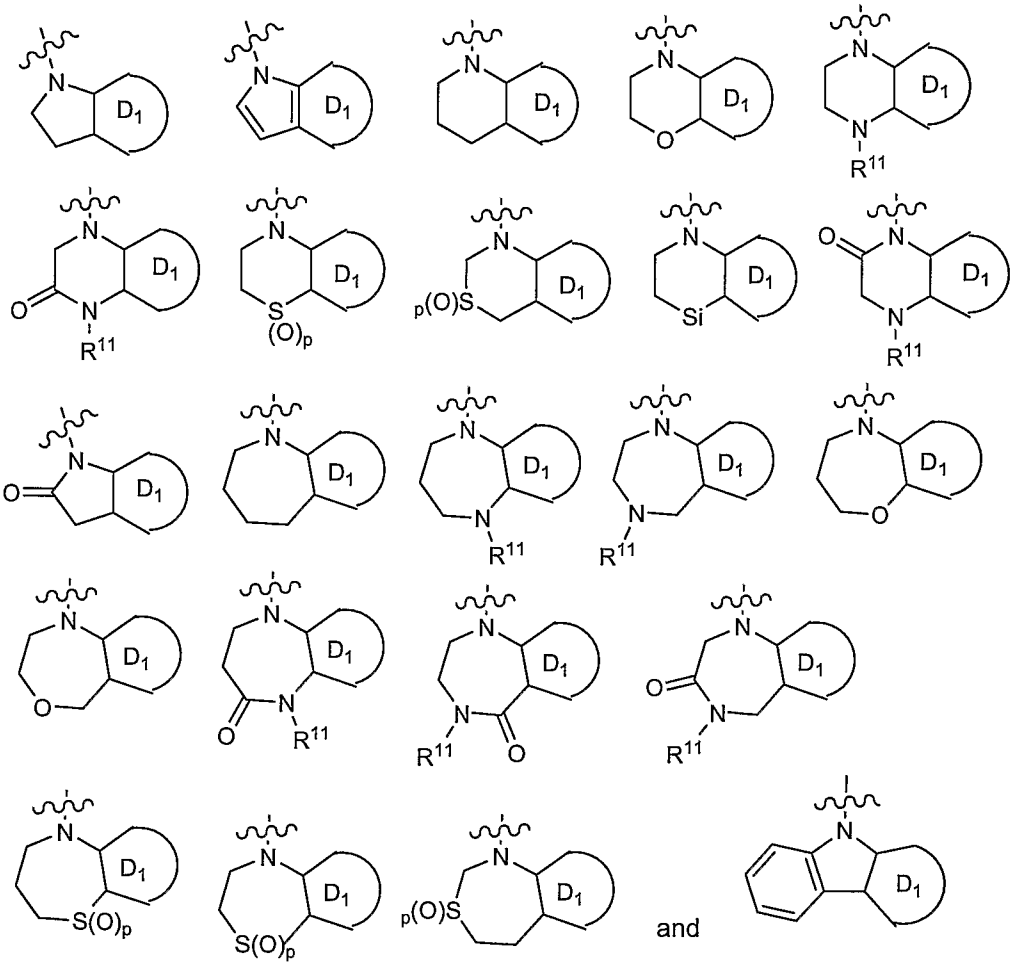
ring B is substited with 0-3 R^7 and selected from:





;

ring D is substituted with 0-5 R^{6a} and selected from:



;

wherein D_1 is selected from: cyclopentyl, cylohexyl, piperidinyl, tetrahydropyranyl, phenyl, pyridinyl, pyrimidinyl, thiophenyl, pyrrolyl, furanyl, thiazolyl, imidazolyl, and oxazolyl;

R^1 is, independently at each occurrence, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $SiMe_3$, $-(CR^fR^f)_r-OR^c$, SR^c, CN, NO_2, $-(CR^fR^f)_r-NR^{12}R^{13}$, $-(CR^fR^f)_r-C(O)R^c$, $-(CR^fR^f)_r-CO_2R^c$, $-(CR^fR^f)_r-C(O)NR^{12}R^{13}$, $-OP(O)(OEt)_2$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a,

-$(CR^fR^f)_r$-C_{3-13} carbocycle substituted with 0-5 R^b, or -$(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-5 R^b;

alternatively, two R^1s on two adjacent carbon atoms are combined with the carbon atoms to which they attached, form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-2 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-4 R^b;

R^{6a} is, independently at each occurrence, F, Cl, Br, I, -$(CR^iR^i)_r$-OR^c, SR^c, CN, CF_3, OCF_3, -CF_2CF_3, -OCF_2CF_2H, -OCF_2CF_3, -$NR^{12}R^{13}$, -$C(O)R^c$, -$(CR^fR^f)_r$-$C(O)OR^c$, -$Si(Me)_3$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_1-C_4 alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, -$(CR^fR^f)_r$-C_{3-10} carbocycle substituted with 0-2 R^e, or -$(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^e;

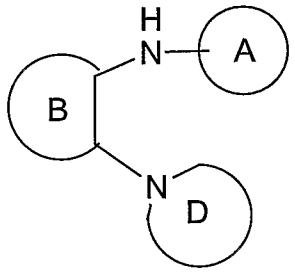
alternatively, when two R^{6a} groups are attached to the same carbon atom or silicon atom, together with the carbon atom or silicon atom to which they are attached, they form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

alternatively, when two R^{6a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b; and

R^{11} is, independently at each occurrence, H, C_{1-8} alkyl substituted with 0-2 R^a, -$C(O)(CH_2)_n$(C_{3-6} cycloalkyl), -$C(O)(CH_2)_n$phenyl, -$C(O)O(C_{1-8}$ alkyl),

-C(O)O(CH_2)$_n$(C_{3-6} cycloalkyl), -C(O)O(CH_2)$_n$phenyl, -C(O)O(CH_2)$_{2-4}$(C_{1-4} alkyl), -C(O)NH(C_{1-6} alkyl), -S(O)$_2$(C_{1-6} alkyl), -S(O)$_2$(CH_2)$_n$phenyl, -(CR^fR^f)$_r$-C_{3-7} cycloalkyl, -(CR^fR^f)$_r$-phenyl, or -(CR^fR^f)$_r$-5- to 6-membered heterocycle; wherein said alkyl, cycloalkyl, phenyl, and aryl are substituted with 0-2 R^b, and said heteroaryl and heterocycle are substituted with 0-2 R^b and comprise: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and S(O)$_p$.

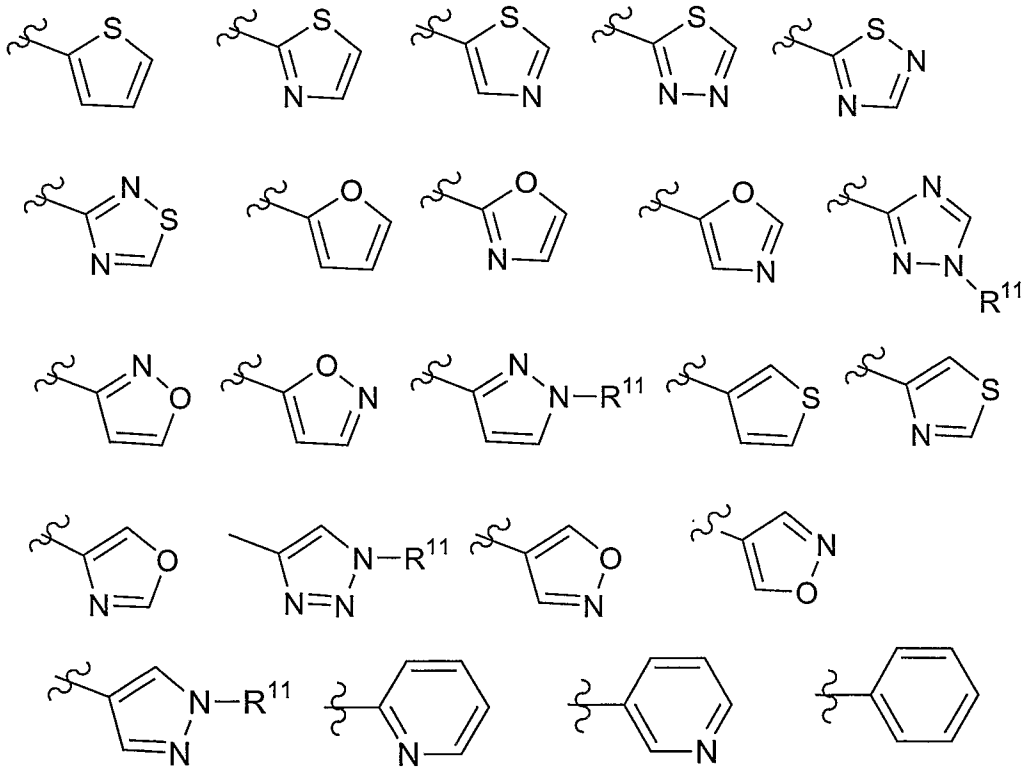
[0022] In a third aspect, the present invention provides a compound of Formula (II):

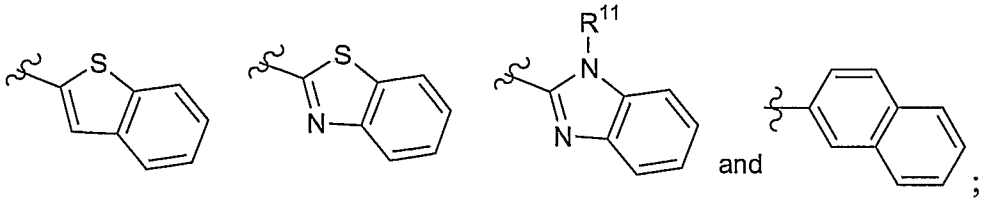


(II)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

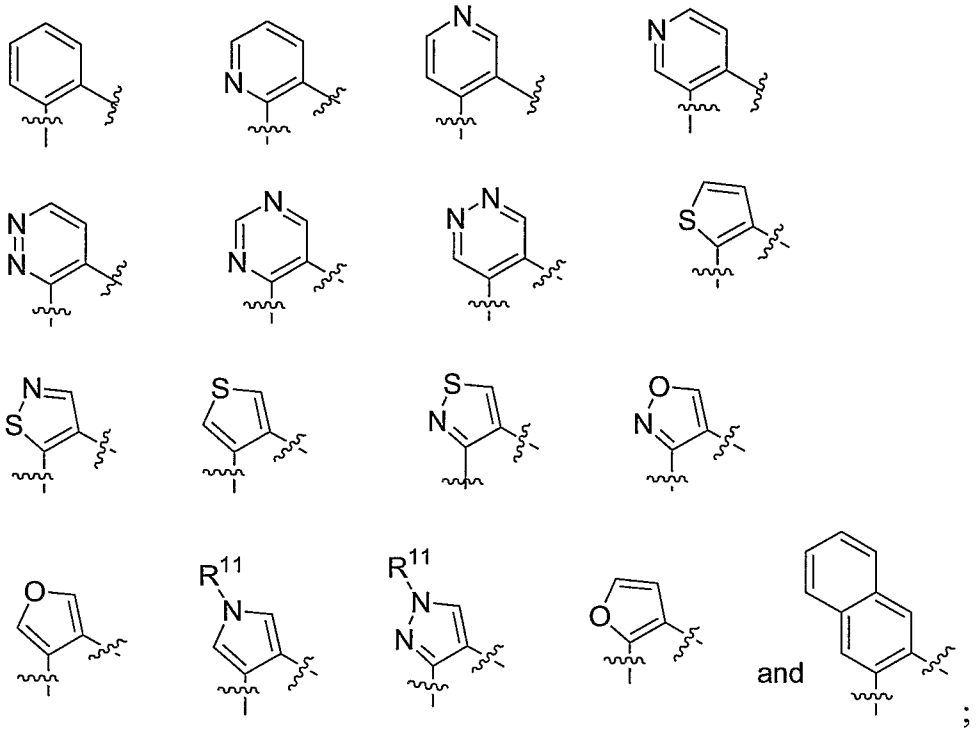
ring A is substituted with 0-4 R^1 and selected from:





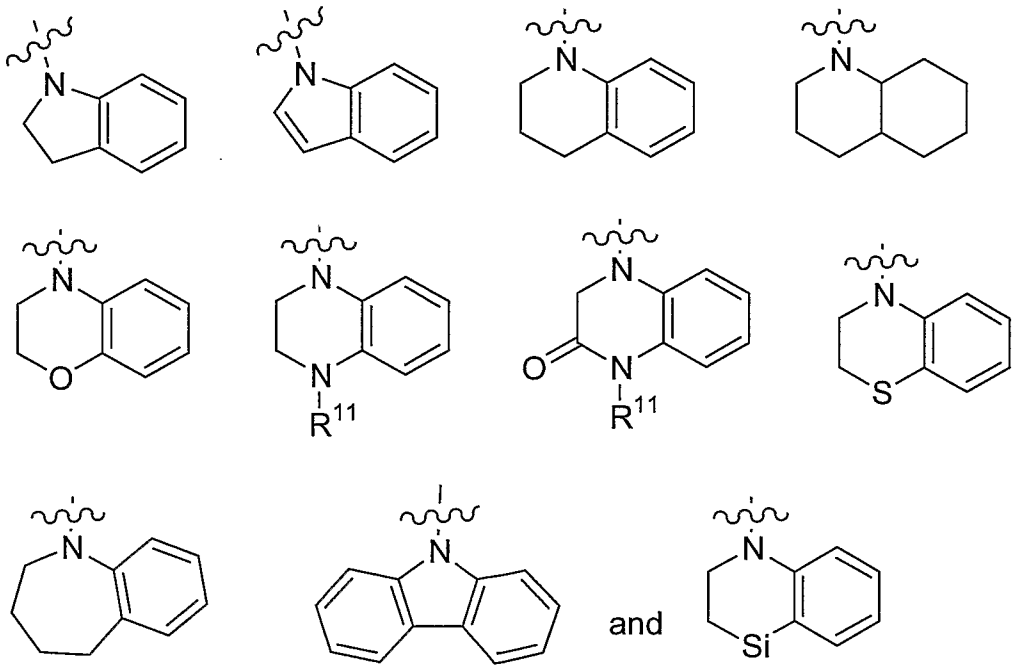
;

ring B is substituted with 0-3 R^7 and selected from:



;

ring D is substituted with 0-5 R^{6a} and selected from:



;

R^1 is, independently at each occurrence, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $SiMe_3$, $-(CR^fR^f)_r-OR^c$, SR^c, CN, NO_2, $-(CR^fR^f)_r-NR^{12}R^{13}$, $-(CR^fR^f)_u-C(O)R^c$, $-(CR^fR^f)_r-CO_2R^c$, $-(CR^fR^f)_u-C(O)NR^{12}R^{13}$, $-OP(O)(OEt)_2$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl, C_{1-8} alkyl substituted with 0-2 R^a, $-(CR^fR^f)_u-C_{3-6}$ carbocycle substituted with 0-2 R^b, or $-(CR^fR^f)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^b;

alternatively, two R^1s on two adjacent carbon atoms are combined with the carbon atoms to which they attached, form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-1 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-2 R^b;

R^{6a} is, independently at each occurrence, F, Cl, Br, I, $-(CR^fR^f)_r-OR^c$, SR^c, CN, CF_3, OCF_3, $-CF_2CF_3$, $-OCF_2CF_2H$, $-OCF_2CF_3$, $-NR^{12}R^{13}$, $-C(O)R^c$, $-(CR^fR^f)_r-C(O)OR^c$, $-Si(Me)_3$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_1-C_4 alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CR^fR^f)_r-C_{3-10}$ carbocycle substituted with 0-2 R^e, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^e;

alternatively, when two R^{6a} groups are attached to the same carbon atom or silicon atom, together with the carbon atom or silicon atom to which they are attached, they form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

alternatively, when two R^{6a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N,

NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

R^7 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^c, SR^c, CN, NO_2, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-6} alkyl substituted with 0-2 R^a, $-(CH_2)_u$-C_{3-10} carbocycle substituted with 0-3 R^b, or $-(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{7b}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^b;

R^{7b} is H, C_{1-4} alkyl, $-C(O)(C_{1-4}$ alkyl), -C(O)phenyl, -C(O)benzyl, or benzyl;

R^{11} is, independently at each occurrence, H, C_{1-8} alkyl substituted with 0-2 R^a, $-C(O)(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)(CH_2)_n$phenyl, $-C(O)O(C_{1-8}$ alkyl), $-C(O)O(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)O(CH_2)_n$phenyl, $-C(O)O(CH_2)_{2-4}(C_{1-4}$ alkyl), $-C(O)NH(C_{1-6}$ alkyl), $-S(O)_2(C_{1-6}$ alkyl), $-S(O)_2(CH_2)_n$phenyl, $-(CR^fR^f)_r$-C_{3-7} cycloalkyl, $-(CR^fR^f)_r$-phenyl, or $-(CR^fR^f)_r$-5- to 6-membered heterocycle; wherein said alkyl, cycloalkyl, phenyl, and aryl are substituted with 0-2 R^b, and said heteroaryl and heterocycle are substituted with 0-2 R^b and comprise: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$;

R^{12} is, independently at each occurrence, H, C_{1-6} alkyl, $-C(O)(C_{1-6}$ alkyl), $-C(O)(CH_2)_n$phenyl, $-C(O)(CH_2)_n$(5- to 6-membered heteroaryl), $-C(O)O(C_{1-4}$ alkyl), $-C(O)OCH_2$phenyl, $-(CH_2)_nC(O)OCH_2$(5- to 6-membered heteroaryl), $-(CH_2)_nOC(O)(C_{1-4}$ alkyl), $-(CH_2)_n$OC(O)phenyl, $-(CH_2)_n$OC(O)(5- to 6-membered heteroaryl), $-(CH_2)_nC(O)O(C_{1-4}$ alkyl), $-(CH_2)_n$C(O)Ophenyl, $-(CH_2)_n$C(O)O(5- to 6-membered heteroaryl), $-(CH_2)_nC(O)NH(C_{1-6}$ alkyl), $-(CH_2)_n$C(O)NHphenyl, $-(CH_2)_n$C(O)NH(5- to 6-membered heteroaryl), $-(CH_2)_tOC(O)NH(C_{1-6}$ alkyl), $-(CH_2)_t$OC(O)NHphenyl, $-(CH_2)_t$OC(O)NH(5- to 6-membered heteroaryl), $-S(O)_2(C_{1-6}$ alkyl), $-S(O)_2(CH_2)_n$phenyl, $-S(O)_2(CH_2)_n$(5- to 6-membered heteroaryl), $-(CR^fR^f)_n$-phenyl, or $-(CR^fR^f)_n$-5- to 6-membered heteroaryl; wherein said alkyl, and aryl are substituted with 0-2 R^g; and

said heteroaryl is substituted with 0-2 R^g and comprises: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

alternatively, R^{12} and R^{13}, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising: carbon atoms and 1-2 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{14} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{14a}, C_{2-6} alkenyl substituted with 0-2 R^{14a}, C_{2-6} alkynyl substituted with 0-2 R^{14a}, $-(CH_2)_u$-C_{3-6} cycloalkyl substituted with 0-3 R^g, $-(CH_2)_u$-phenyl substituted with 0-3 R^g, or $-(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^g;

R^{14a} is, independently at each occurrence, H, C_{1-4} alkyl, OR^f, Cl, F, Br, I, =O, CF_3, CN, NO_2, $-C(O)R^f$, $-C(O)OR^f$, $-C(O)NR^{12}R^{13}$, or $-S(O)_pR^f$;

R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, OR^c, SR^c, CN, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, $-(CH_2)_u$-C_{3-10} carbocycle substituted with 0-3 R^e, or $-(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^b is, independently at each occurrence, H, =O, F, Cl, Br, I, $-(CH_2)_r$-OR^c, SR^c, CN, NO_2, CF_3, OCF_3, $-(CH_2)_r$-$NR^{12}R^{13}$, $-C(O)R^c$, $-(CH_2)_r$-$C(O)OR^c$, $-(CH_2)_r$-$C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_{1-4} alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-6} alkyl substituted with 0-2 R^a, C_{2-4} alkenyl substituted with 0-2 R^a, C_{2-4} alkynyl substituted with 0-2 R^a, $-(CH_2)_u$-C_{3-10} carbocycle substituted with 0-3 R^e, or $-(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^c is, independently at each occurrence, H, $-OP(O)(OEt)_2$, C_{1-8} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl substituted with 0-3 R^e, C_{2-4} alkynyl substituted with 0-3 R^e, $-(CH_2)_u-C_{3-8}$ cycloalkyl substituted with 0-3 R^e, $-(CH_2)_u-C_{6-10}$ aryl substituted with 0-3 R^e, or $-(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^d is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_u-C_{3-10}$ carbocycle substituted with 0-3 R^e, or $-(CH_2)_u$-5- to 10- membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^e is, independently at each occurrence, H, =O, $-(CH_2)_r-OR^f$, F, Cl, Br, I, CN, NO_2, $-(CH_2)_u-NR^{12}R^{13}$, $-C(O)R^f$, $-(CH_2)_r-C(O)OR^f$, $-NR^{14}C(O)R^f$, $-(CH_2)_r-C(O)NR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$, $-NR^{14}SO_2NR^{12}R^{13}$, $-NR^{14}SO_2-C_{1-4}$ alkyl, $-NR^{14}SO_2CF_3$, $-NR^{14}SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p-C_{1-4}$ alkyl, $-S(O)_p$-phenyl, $-(CF_2)_uCF_3$, C_{1-6} alkyl substituted with 0-2 R^g, C_{2-4} alkenyl substituted with 0-2 R^g, C_{2-4} alkynyl substituted with 0-2 R^g, $-(CH_2)_u-C_{3-8}$ cycloalkyl substituted with 0-2 R^g, $-(CH_2)_u-C_{6-10}$ aryl substituted with 0-2 R^g, or $-(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

R^f is, independently at each occurrence, H, or C_{1-4} alkyl;

R^g is, independently at each occurrence, H, =O, OR^f, F, Cl, Br, I, CN, NO_2, $-NR^fR^f$, $-C(O)R^f$, $-C(O)OR^f$, $-NR^fC(O)R^f$, $-C(O)NR^fR^f$, $-SO_2NR^fR^f$, $-NR^fSO_2NR^fR^f$, $-NR^fSO_2-C_{1-4}$ alkyl, $-NR^fSO_2CF_3$, $-NR^fSO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p-C_{1-4}$ alkyl, $-S(O)_p$-phenyl, $-(CF_2)_uCF_3$, C_{1-6} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl;

R^h is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^g, or $-(CH_2)_n$-phenyl substituted with 0-2 R^g;

n, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

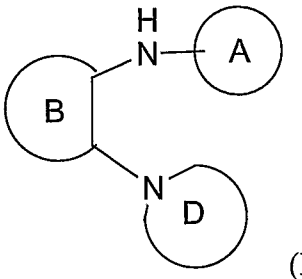
r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

s, at each occurrence, is selected from 0, 1, 2, and 3;

t, at each occurrence, is selected from 1 and 2; and

u, at each occurrence, is selected from 0, 1, and 2.

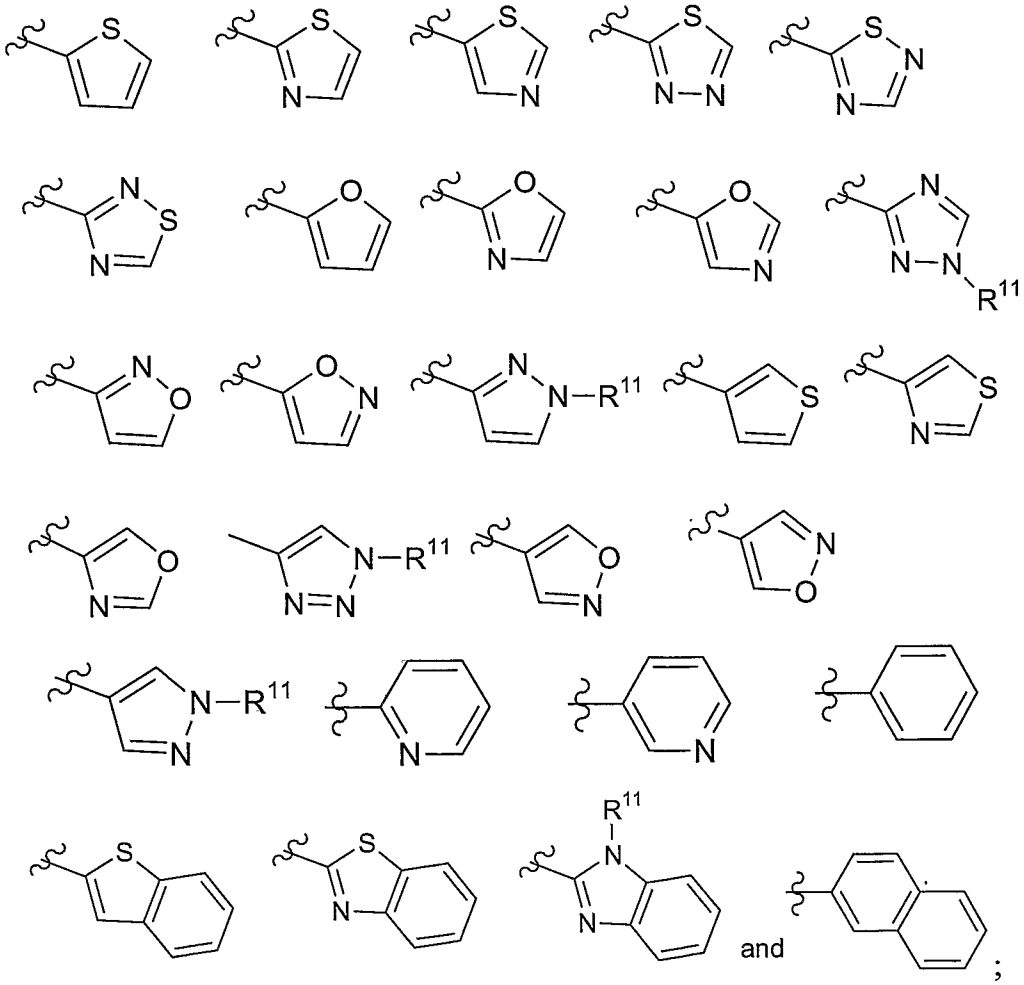
[0023] In a fourth aspect, the present invention provides a compound of Formula (II):



(II)

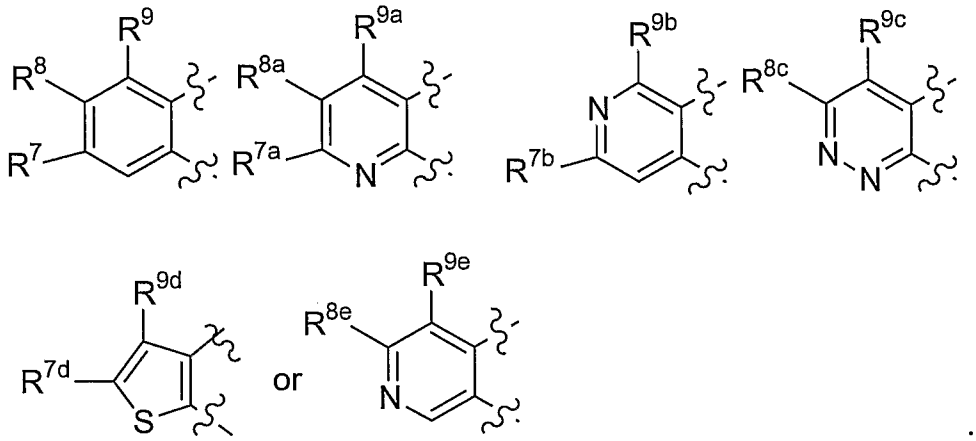
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

ring A is substituted with 0-4 R^1 and selected from:



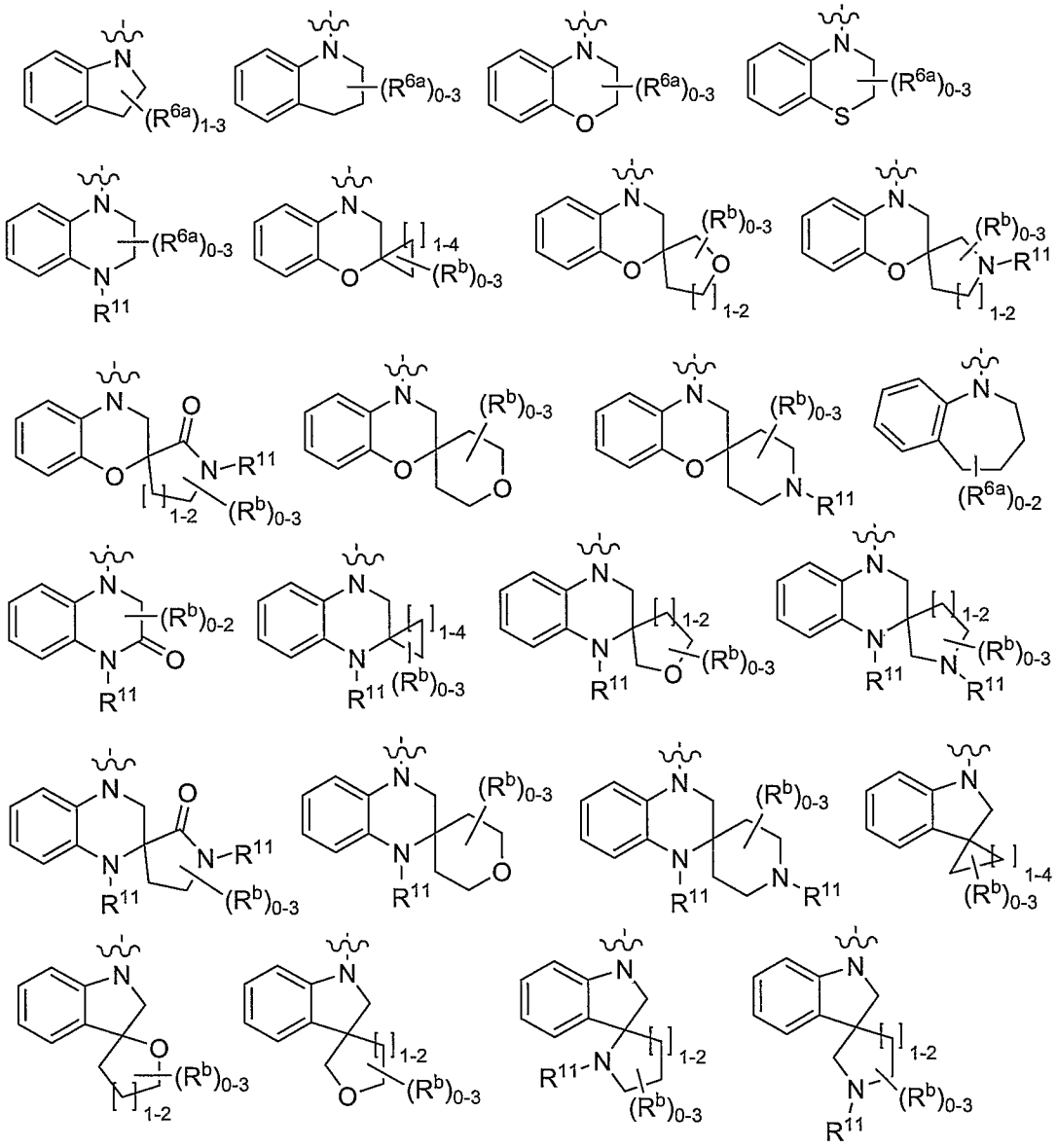
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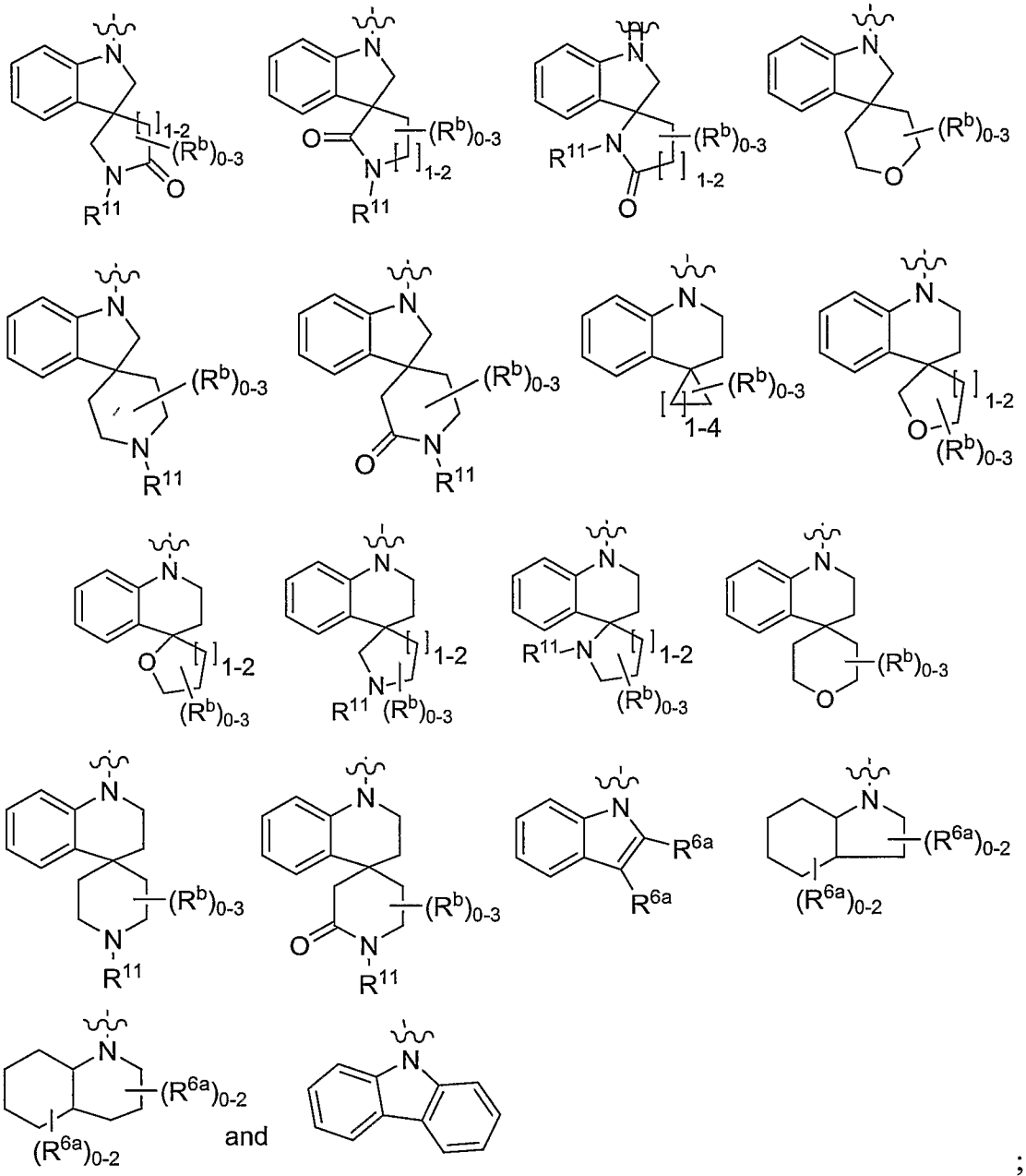
ring B is



;

ring D is selected from:





;

wherein the phenyl ring in each of the structures is substituted with 0-2 R^{6a};

R^1 is, independently at each occurrence, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $SiMe_3$, $-(CH_2)_r-OR^c$, SR^c, CN, NO_2, $-(CH_2)_r-NR^{12}R^{13}$, $-(CH_2)_u-C(O)R^c$, $-(CH_2)_r-CO_2R^c$, $-(CH_2)_u-C(O)NR^{12}R^{13}$, $-OP(O)(OEt)_2$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl, C_{1-8} alkyl substituted with 0-2 R^a, $-(CH_2)_u-C_{3-6}$ cycloalkyl substituted with 0-2 R^b, $-(CH_2)_u$-phenyl substituted with 0-2 R^b, or $-(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4

heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^b;

alternatively, two R^1s on two adjacent carbon atoms are combined with the carbon atoms to which they attached, form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-1 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-2 R^b;

R^{6a} is, independently at each occurrence, H, F, Cl, Br, I, CN, $-C(Me)_2CN$, C_{1-8} alkyl, C_{2-8} alkenyl, OH, SMe, S(*i*-Pr), $-C(Me)_2OMe$, $-C(Me)_2OEt$, $-C(Me)_2OPr$, $-CHMeO(CH_2)_2OMe$, $-C(Me)_2O(CH_2)_2OMe$, $-C(Et)_2OMe$, $-C(Et)_2OEt$, COPh, $-CH{=}CHCO_2(t\text{-Bu})$, CF_3, OCF_3, C_{1-4} alkyloxy, CO_2Me, $-CH_2CO_2Me$, C_{3-7} cycloalkyl, Ph, Bn, 1-pyrrolidinyl, 5-isoxazolyl, N-morpholinyl, 4-Bn-piperazinyl, 1-piperidinyl, 1-Bn-piperidin-4-yl, or $-Si(Me)_3$;

alternatively, when two R^{6a} groups are attached to the same carbon atom, together with the carbon atom to which they are attached, they form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

alternatively, when two R^{6a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

R^7, R^{7a}, R^{7b}, and R^{7d}, independently at each occurrence, H, Me, Cl, Br, CN, OMe, SMe, or NHMe;

R^8, R^{8a} , R^{8b}, and R^{8e} are, independently at each occurrence, H, Me, Cl, or CN;

R^{11} is, independently at each occurrence, C_{1-6} alkyl, $-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-C(O)(C_{1-6}$ alkyl), -C(O)phenyl, -C(O)benzyl, $-C(O)O(C_{1-6}$ alkyl), -C(O)Obenzyl, $-CH_2CO_2H$, $-CH_2CO_2(C_{1-6}$ alkyl), $-C(O)NH(C_{1-6}$ alkyl), -C(O)NHbenzyl, $-S(O)_2(C_{1-6}$ alkyl), $-S(O)_2$phenyl, $-S(O)_2$benzyl, phenyl, or benzyl;

R^{12} is, independently at each occurrence, H, C_{1-6} alkyl, -C(O)(C_{1-6} alkyl), -C(O)$(CH_2)_n$phenyl, -C(O)$(CH_2)_n$(5- to 6-membered heteroaryl), -$(CH_2)_n$C(O)NH(C_{1-6} alkyl), -$(CH_2)_n$C(O)NHphenyl, -$(CH_2)_n$C(O)NH(5- to 6-membered heteroaryl), -$(CH_2)_t$OC(O)NH(C_{1-6} alkyl), -$S(O)_2$(C_{1-6} alkyl), -$S(O)_2(CH_2)_n$phenyl, -$S(O)_2(CH_2)_n$(5- to 6-membered heteroaryl), -$(CH_2)_n$-phenyl, or -$(CH_2)_n$-5- to 6-membered heteroaryl; and said heteroaryl comprises: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$-phenyl;

alternatively, R^{12} and R^{13}, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising: carbon atoms and 1-2 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, OR^c, SR^c, CN, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, -$(CH_2)_u$-C_{3-6} cycloalkyl substituted with 0-2 R^e, -$(CH_2)_u$-phenyl substituted with 0-2 R^e, or -$(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^e;

R^b is, independently at each occurrence, H, F, Cl, Br, C_{1-4} alkyl, OH, CO_2H, NH_2, CF_3, OCF_3, C_{1-4} alkyloxy, C_{3-7} cycloalkyl, phenyl, or benzyl;

R^c is, independently at each occurrence, H, -OP(O)$(OEt)_2$, C_{1-8} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl substituted with 0-3 R^e, C_{2-4} alkynyl substituted with 0-3 R^e, -$(CH_2)_u$-C_{3-6} cycloalkyl substituted with 0-3 R^e, -$(CH_2)_u$-phenyl substituted with 0-3 R^e, or -$(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^d is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, -$(CH_2)_u$-C_{3-6} cycloalkyl substituted with 0-3 R^e, -$(CH_2)_u$-phenyl substituted with 0-3 R^e, or -$(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4

heteroatoms selected from N, NH^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^e is, independently at each occurrence, H, F, Cl, C_{1-4} alkyl, OH, CO_2H, NH_2, CF_3, OCF_3, or C_{1-4} alkyloxy;

R^f is, independently at each occurrence, H, or C_{1-4} alkyl; and

n, at each occurrence, is selected from 0, 1, and 2;

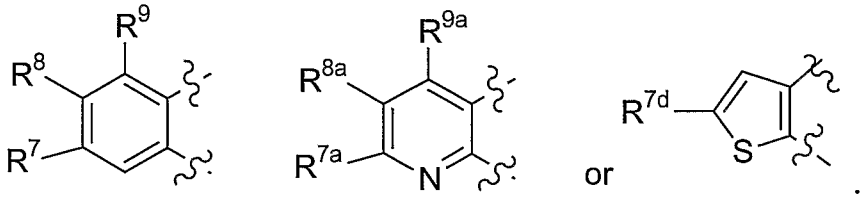
p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and

u, at each occurrence, is selected from 0, 1, and 2.

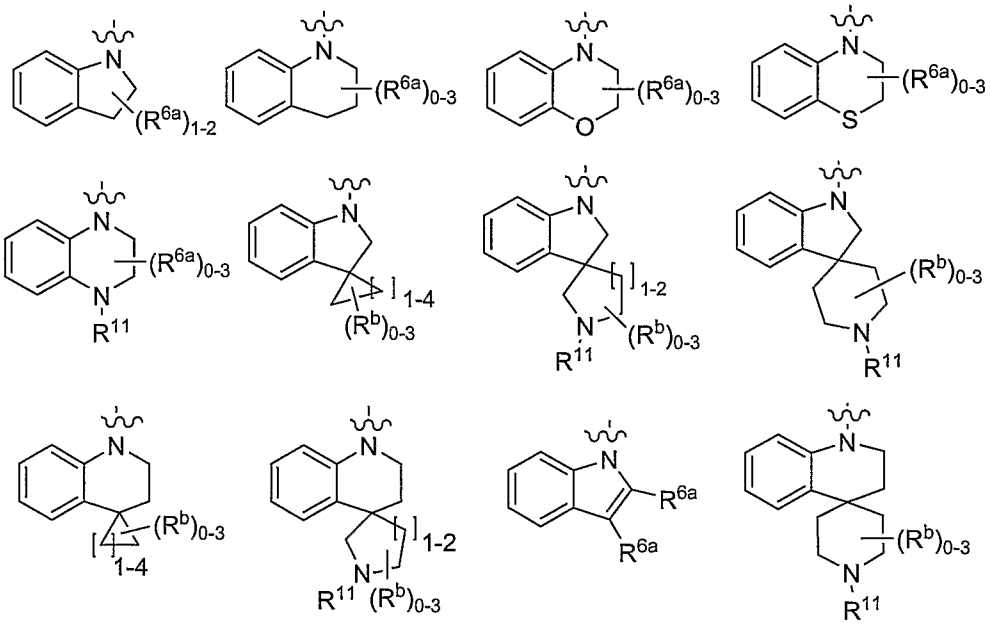
[0024] In a fifth aspect, the present invention includes compounds of Formula (II), within the scope of the fourth apsect wherein:

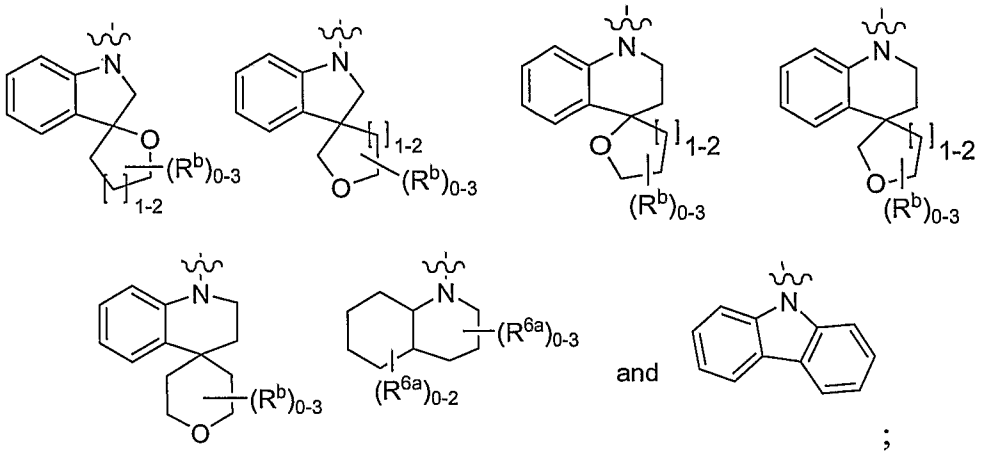
ring B is



;

ring D is selected from:





;

wherein the phenyl ring in each of the structures is substituted with 0-1 R^{6a};

R^7, R^{7a}, and R^{7d} are, independently at each occurrence, H, Me, Cl, Br, CN, OMe, SMe, or NHMe;

R^8 and R^{8a} are, independently at each occurrence, H, Me, F, Cl, or CN;

R^9 and R^{9a} are, independently at each occurrence, H, Me, F, Cl, or CN;

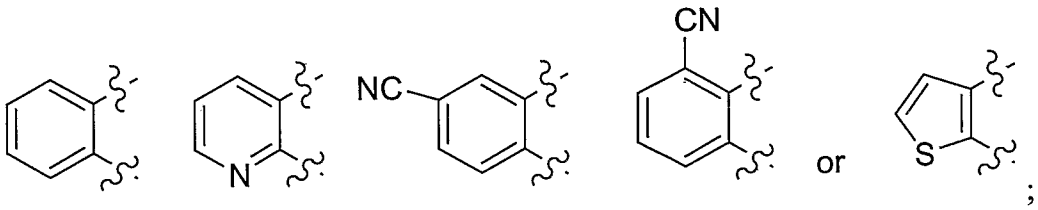
R^{11} is, independently at each occurrence, C_{1-6} alkyl, Bn, $-CH_2CH_2OH$, $-CH_2CH_2OMe$, -CO(i-Pr), CO_2Me, CO_2Et, CO_2Bn, $-CH_2CO_2H$, $-CH_2CO_2Me$, $-CONH(i\text{-}Pr)$, or $SO_2(i\text{-}Pr)$;

R^b is, independently at each occurrence, H, F, Cl, C_{1-4} alkyl, OH, CO_2H, NH_2, CF_3, OCF_3, or C_{1-4} alkyloxy; and

R^e is, independently at each occurrence, H, F, Cl, C_{1-4} alkyl, OH, CO_2H, NH_2, CF_3, OCF_3, or C_{1-4} alkyloxy.

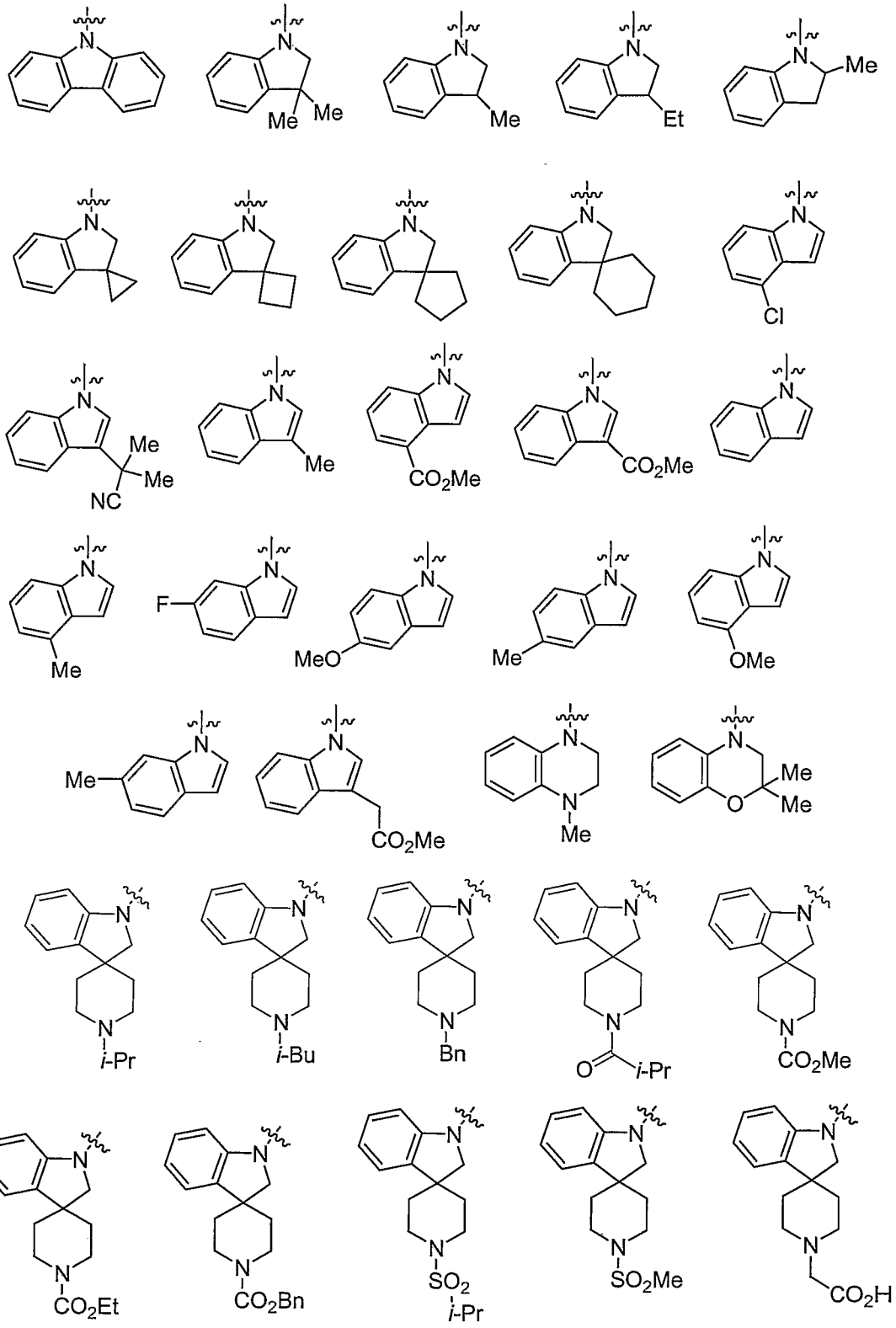
[0025] In a sixth aspect, the present invention includes compounds of Formula (II), within the scope of the fifth aspect wherein:

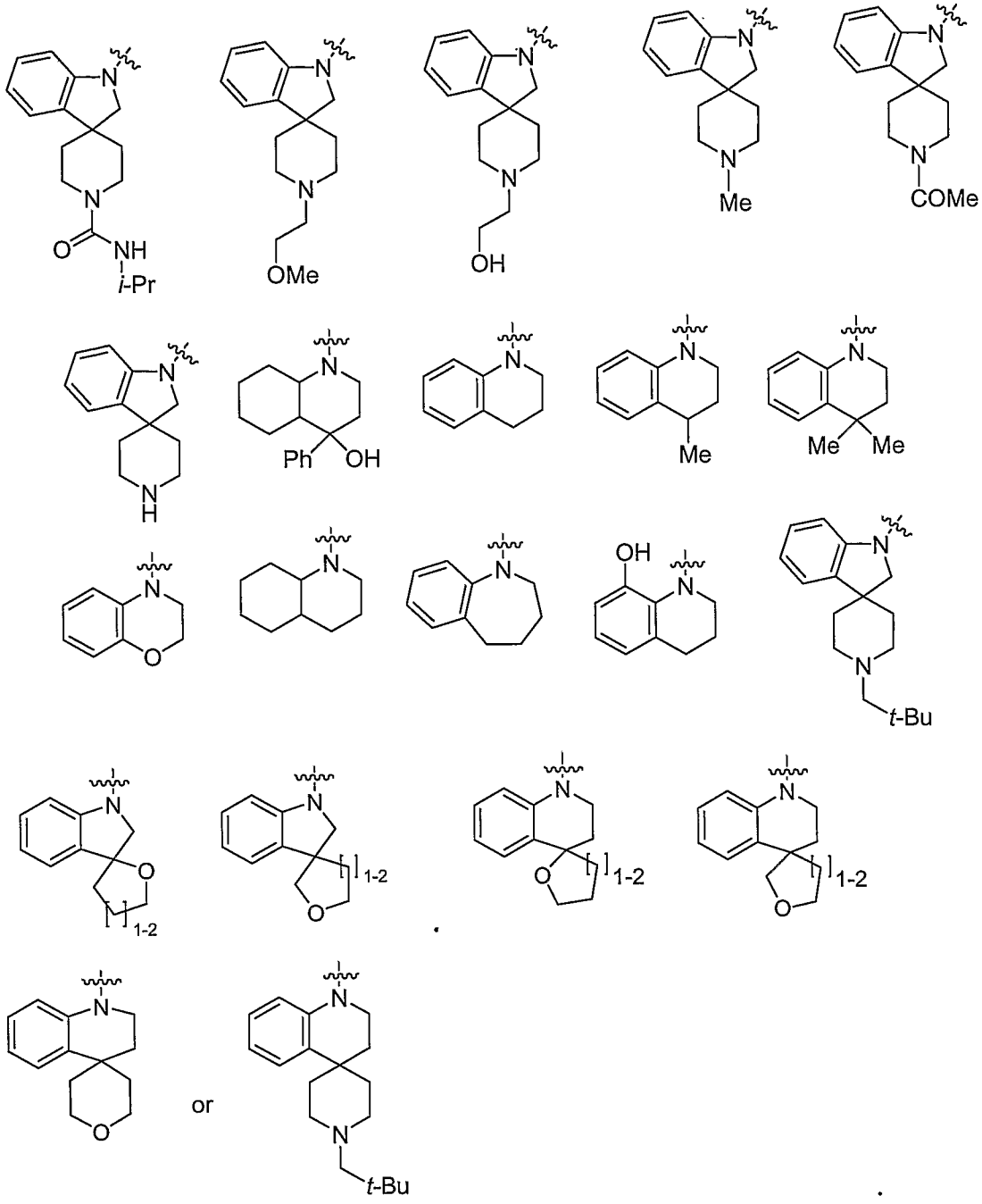
ring B is



; and

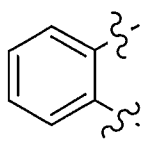
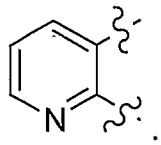
ring D is selected from:


Me
Me
Me
Et
Me
Cl
Me
Me
NC
Me
CO2Me
CO2Me
Me
F
MeO
Me
OMe
Me
CO2Me
Me
O
Me
Me
i-Pr
i-Bu
Bn
O
i-Pr
CO2Me
CO2Et
CO2Bn
SO2
i-Pr
SO2Me
CO2H

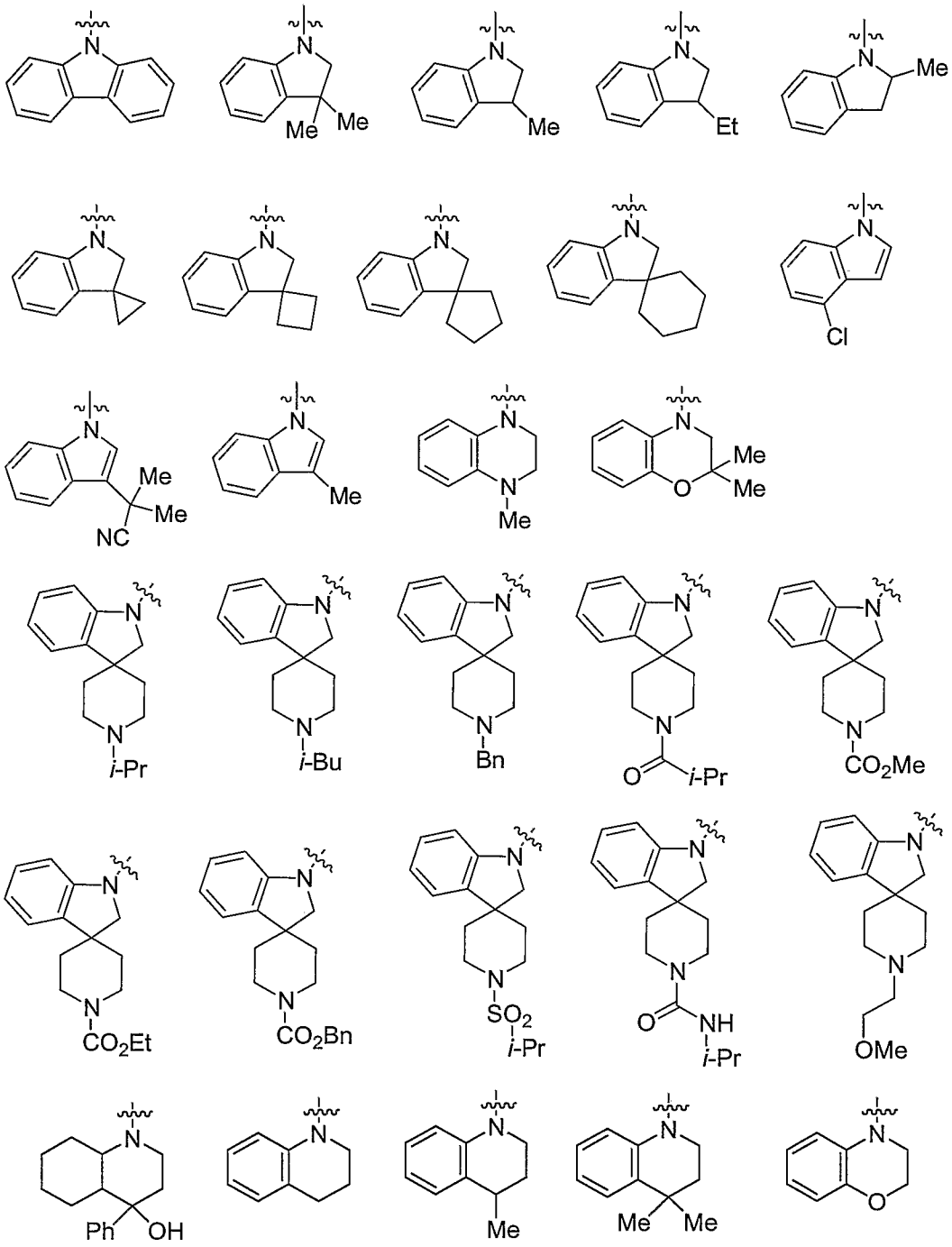


[0026] In a seventh aspect, the present invention includes compounds of Formula (II), within the scope of the sixth aspect wherein:

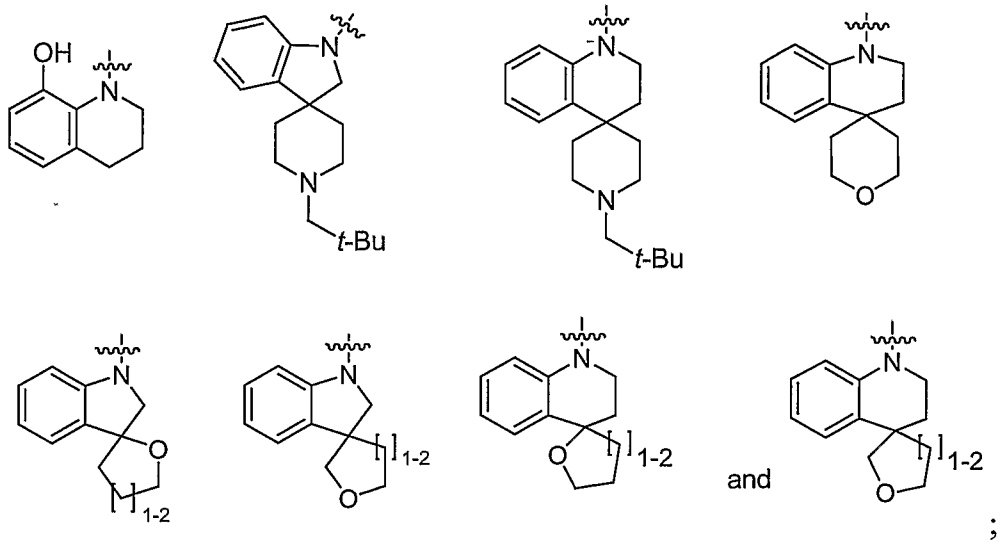
ring A is substituted with 0-2 R^1 and selected from: thiazolyl, benzothizolyl, and benzimidazolyl;

ring B is  or ;

ring D is selected from:



5



;

R^1 is, independently at each occurrence, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $-(CH_2)_r-OR^c$, SR^c, CN, NO_2, $-(CH_2)_r-NR^{12}R^{13}$, $-(CH_2)_u-C(O)R^c$, $-(CH_2)_r-CO_2R^c$, $-(CH_2)_u-C(O)NR^{12}R^{13}$, or C_{1-4} alkyl substituted with 0-2 R^a;

R^{12} is, independently at each occurrence, H, C_{1-4} alkyl, phenyl, or benzyl;

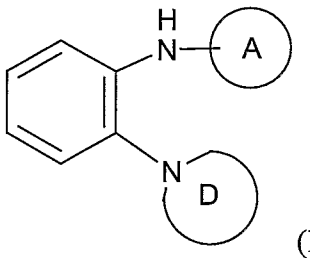
R^{13} is, independently at each occurrence, H, C_{1-4} alkyl, phenyl, or benzyl;

alternatively, R^{12} and R^{13}, when attached to the same nitrogen, combine to form a 5- to 6-membered heterocyclic ring comprising: carbon atoms and 1-2 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, OR^c, SR^c, CN, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, or $-S(O)_pNR^{12}R^{13}$; and

R^c is, independently at each occurrence, H, C_{1-4} alkyl, phenyl, or benzyl.

[0027] In an eighth aspect, the present invention includes compounds of Formula (III):

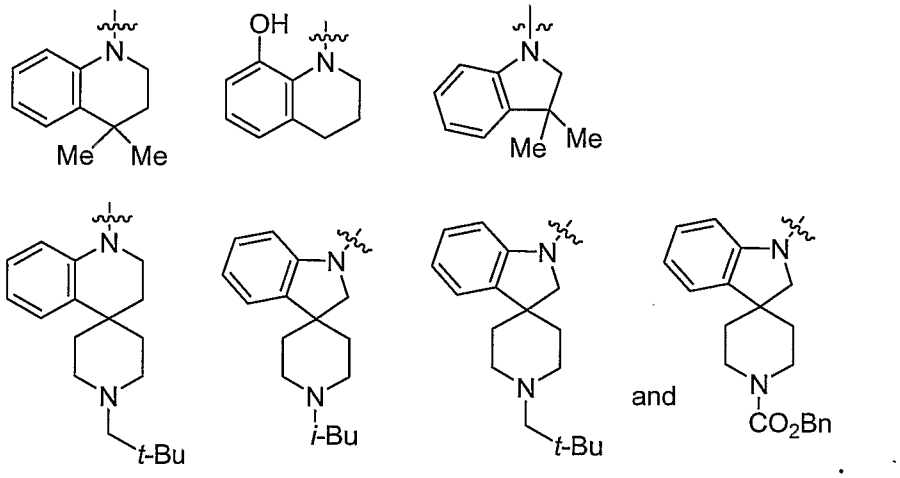


(III)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

ring A is 4-CF_3-thiazol-2-yl, 4-CF_3-5-Me-thiazol-2-yl, 4-Me-5-CO_2Me-thiazol-2-yl, 4-CF_3-5-CO_2Et-thiazol-2-yl, 4-CF_3-5-Ph-thiazol-2-yl, 3-(*t*-Bu)-1,2,4-thiadiazol-5-yl, benzothizol-2-yl, 5-Cl-benzothizol-2-yl, 5-CF_3-benzothizol-2-yl, 6-(*t*-Bu)-benzimidazol-2-yl, or 7-CO_2Et-benzimidazol-2-yl; and

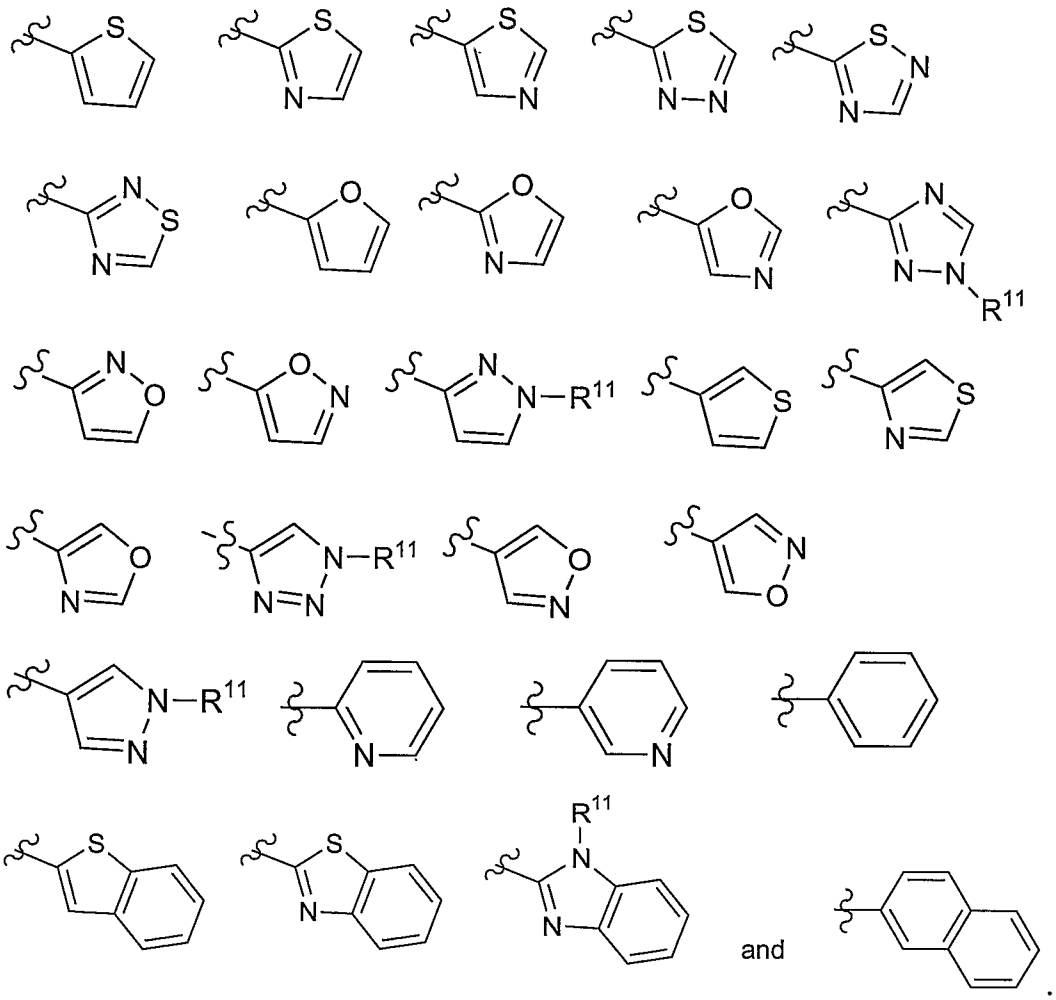
ring D is selected from:



[0028] In a ninth aspect, the present invention provides a compound selected from the exemplified examples of the present invention or a stereoisomer or pharmaceutically acceptable salt, solvate, or prodrug form thereof.

[0029] In another embodiment, ring A is C_{6-10} aryl substituted with 0-5 R^1, or a 5- to 10-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-5 R^1.

[0030] In another embodiment, ring A is substituted with 0-4 R^1 and selected from:



and

.

[0031] In another embodiment, ring A is substituted with 0-2 R^1 and selected from: thiazolyl, benzothizolyl and benzimidazolyl.

[0032] In another embodiment, ring A is 4-CF_3-thiazol-2-yl, 4-CF_3-5-Me-thiazol-2-yl, 4-Me-5-CO_2Me-thiazol-2-yl, 4-CF_3-5-CO_2Et-thiazol-2-yl, 4-CF_3-5-Ph-thiazol-2-yl, 3-(*t*-Bu)-1,2,4-thiadiazol-5-yl, benzothizol-2-yl, 5-Cl-benzothizol-2-yl, 5-CF_3-benzothizol-2-yl, 6-(*t*-Bu)-benzimidazol-2-yl, or 7-CO_2Et-benzimidazol-2-yl.

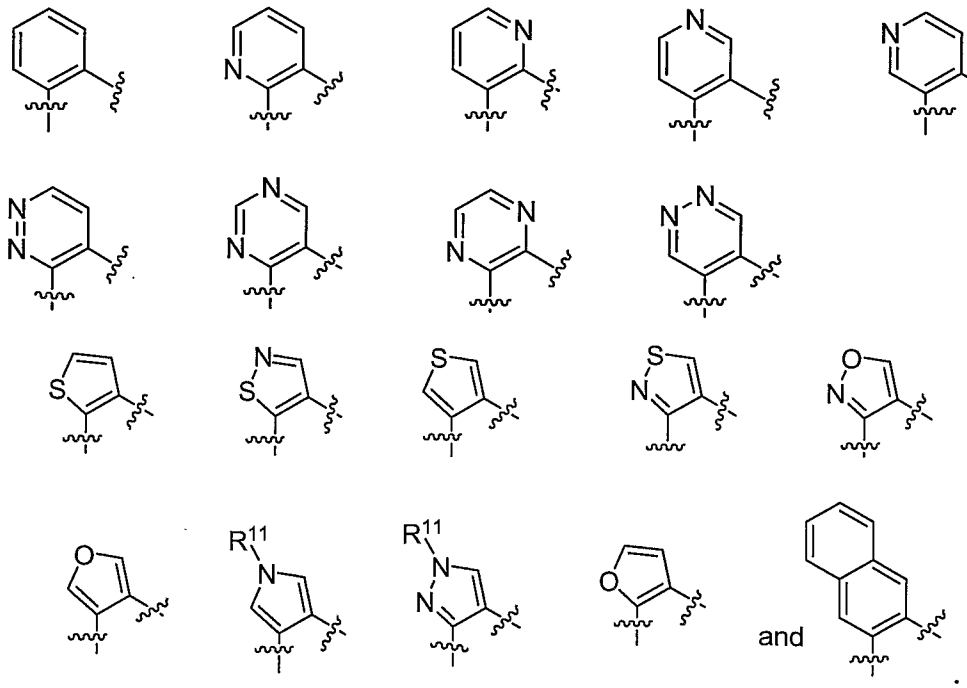
[0033] In another embodiment, ring B is phenyl or naphthyl substituted with 0-4 R^7, or a 5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 ring

heteroatoms selected from N, NR^{11}, $S(O)_p$, and O, wherein said heteroaryl is substituted with 0-4 R^7.

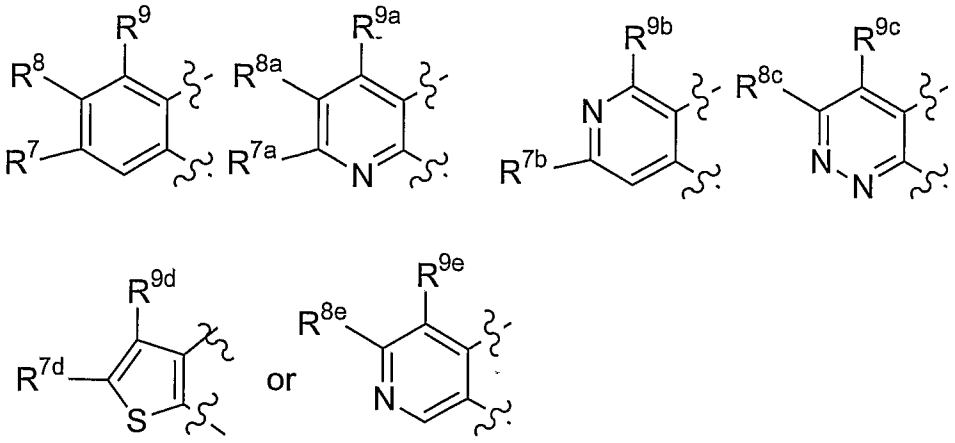
[0034] In another embodiment, ring B is phenyl or naphthyl substituted with 0-4 R^7, or a 5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 ring heteroatoms selected from N, NR^{11}, $S(O)_p$, and O, wherein said heteroaryl is substituted with 0-4 R^7.

[0035] In another embodiment, ring B is substituted with 0-4 R^7 and selected from phenyl, nathphyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, pyrrolyl, furanyl, thiazolyl, isothiazolyl, isoxazolyl, pyrazolyl, and imidazolyl.

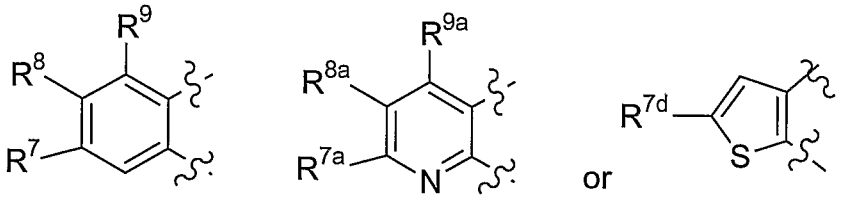
[0036] In another embodiment, ring B is substituted with 0-3 R^7 and selected from:



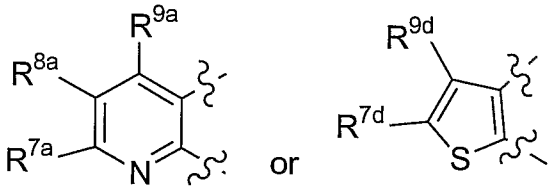
[0037] In another embodiment, ring B is

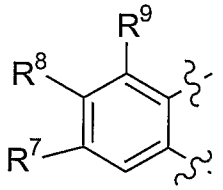


[0038] In another embodiment, ring B is



[0039] In another embodiment, ring B is



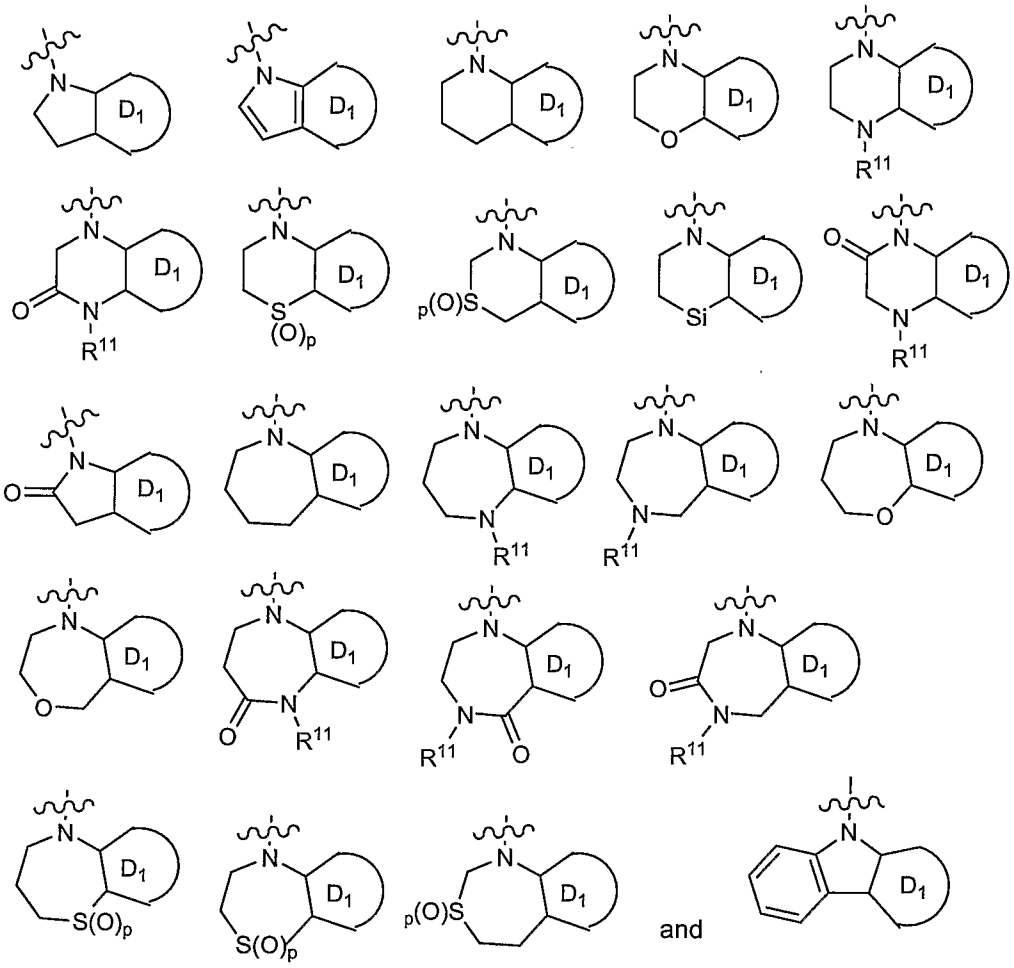
[0040] In another embodiment, ring B is .

[0041] In another embodiment, W is NR^{18}, O, S, -NHCOCH=CH-, $-NHSO_2-$, $-NHSO_2CH_2-$, or $-NHSO_2CH=CH-$.

[0042] In another embodiment, W is NH, -NHCOCH=CH-, or $-NHSO_2-$.

[0043] In another embodiment, W is NH.

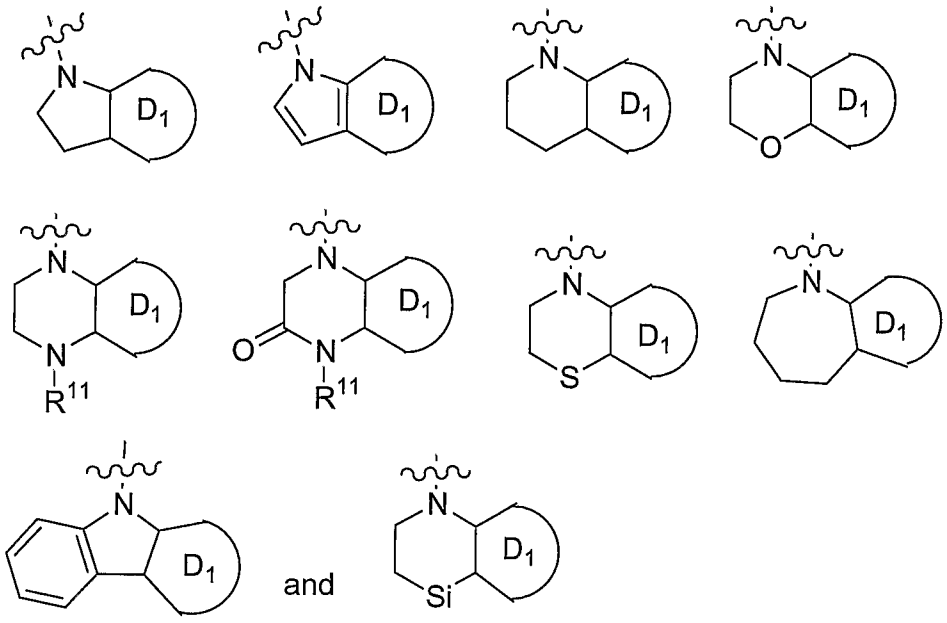
[0044] In another embodiment, ring D is substituted with 0-5 R^{6a} and selected from:



;

wherein D_1 is selected from: cyclopentyl, cylohexyl, piperidinyl, tetrahydropyranyl, phenyl, pyridinyl, pyrimidinyl, thiophenyl, pyrrolyl, furanyl, thiazolyl, imidazolyl, and oxazolyl.

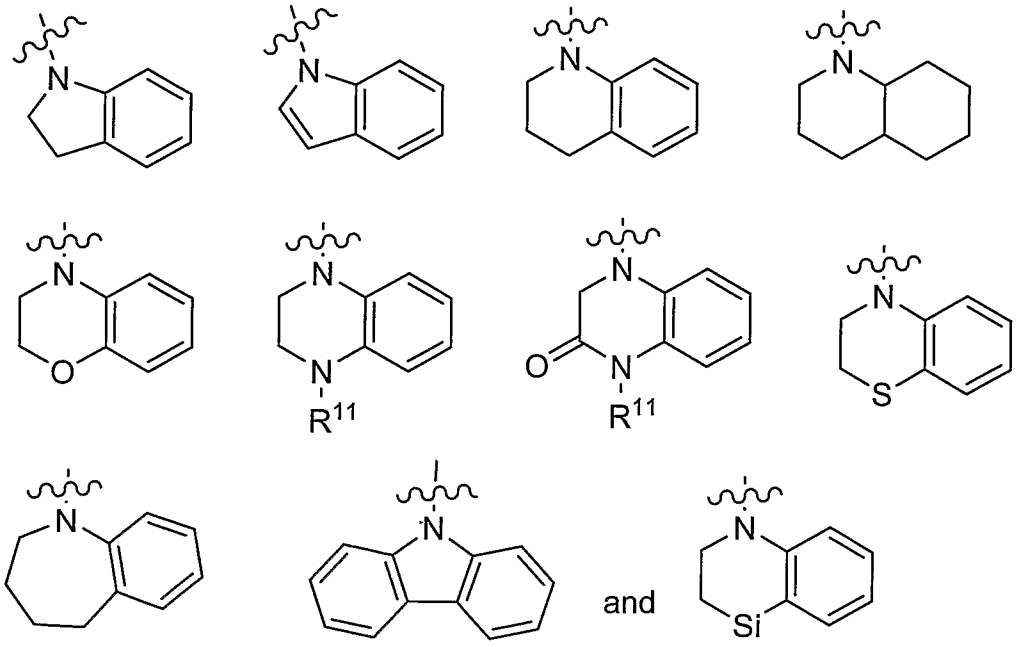
[0045] In another embodiment, ring D is substituted with 0-5 R^{6a} and selected from:



;

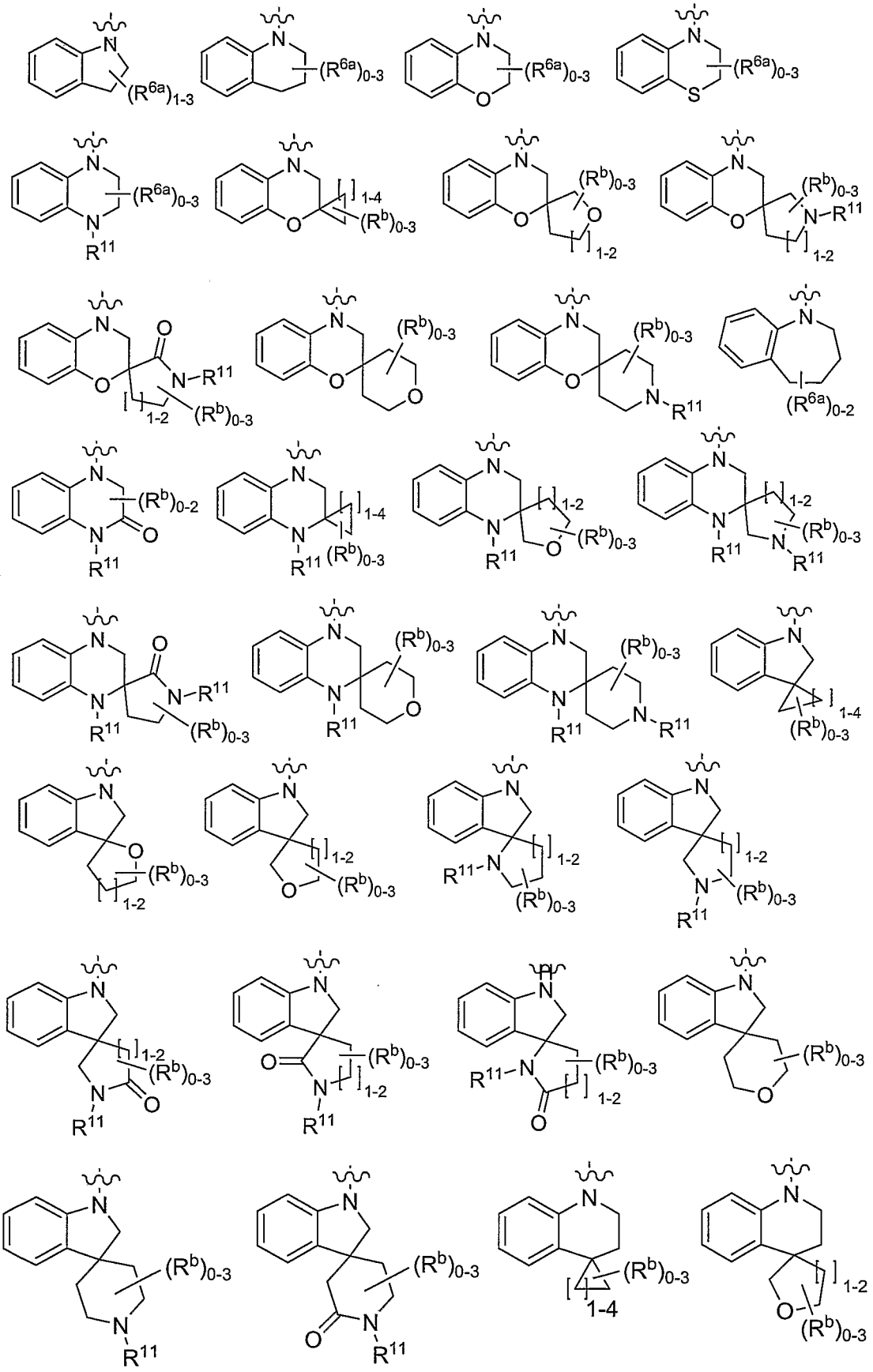
wherein D_1 is selected from: cyclopentyl, cylohexyl, piperidinyl, tetrahydropyranyl, phenyl, pyridinyl, pyrimidinyl, thiophenyl, pyrrolyl, furanyl, thiazolyl, imidazolyl, and oxazolyl.

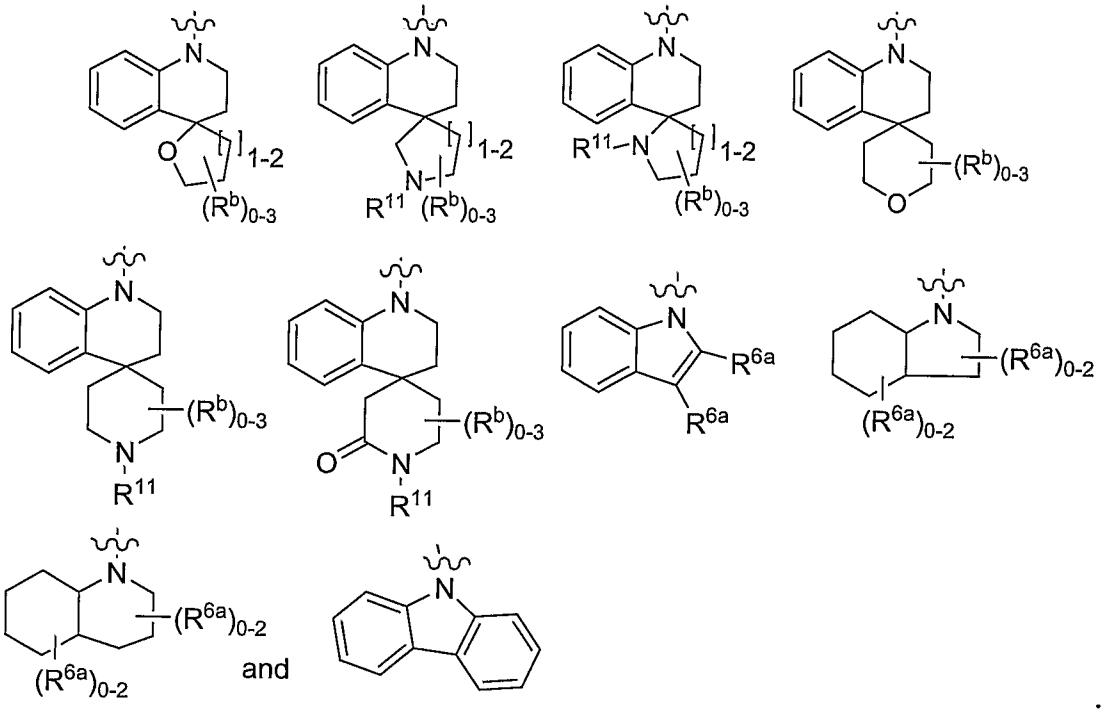
[0046] In another embodiment, ring D is substituted with 0-5 R^{6a} and selected from:



.

[0047] In another embodiment, ring D is selected from:



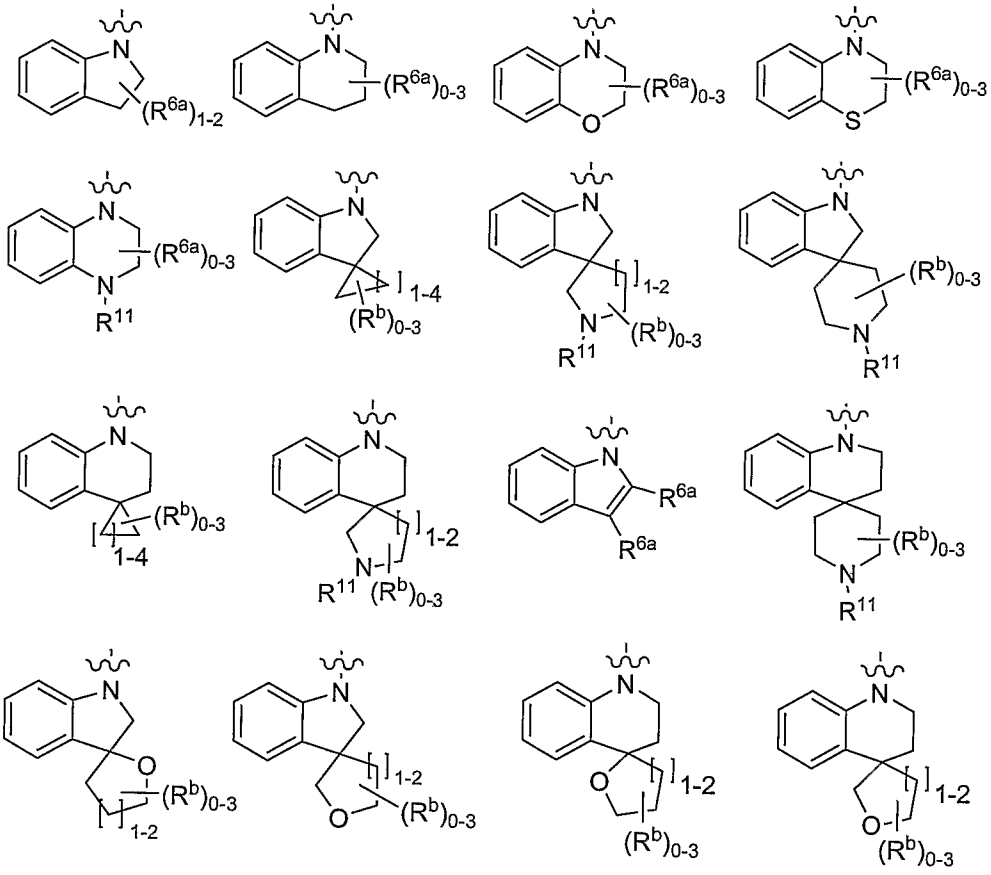


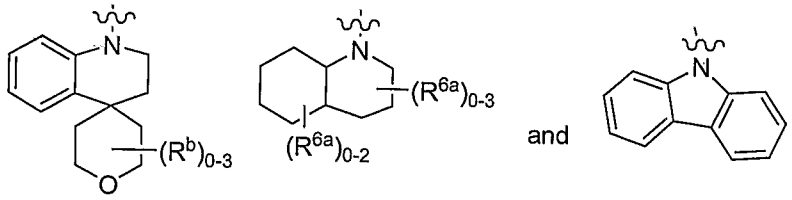
and

;

wherein the phenyl ring in each of the structures is substituted with 0-2 R^{6a}.

[0048] In another embodiment, ring D is selected from:

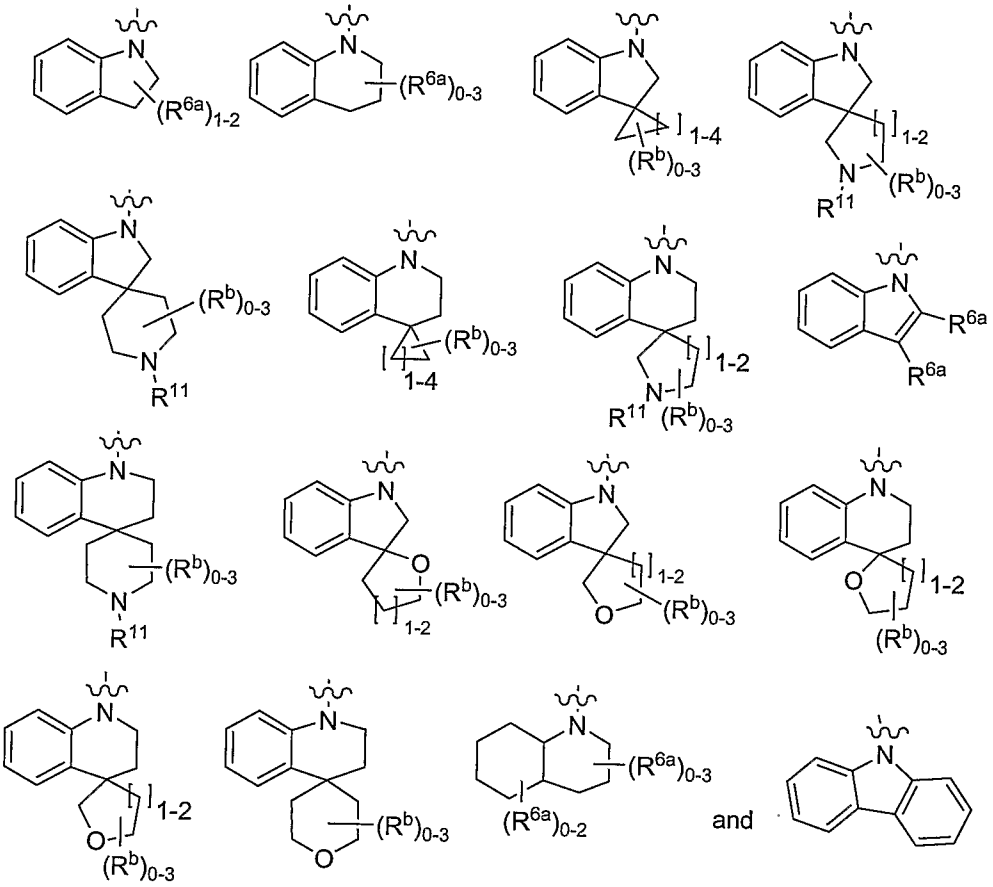




;

wherein the phenyl ring in each of the structures is substituted with 0-1 R^{6a}.

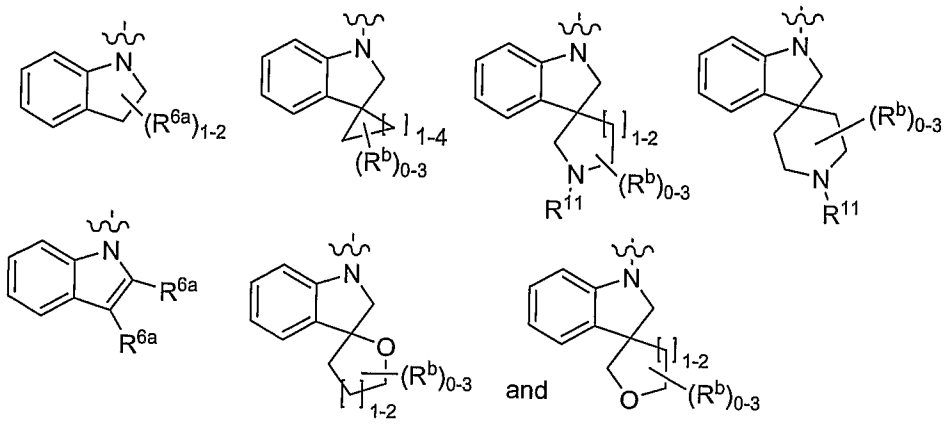
[0049] In another embodiment, ring D is selected from:



;

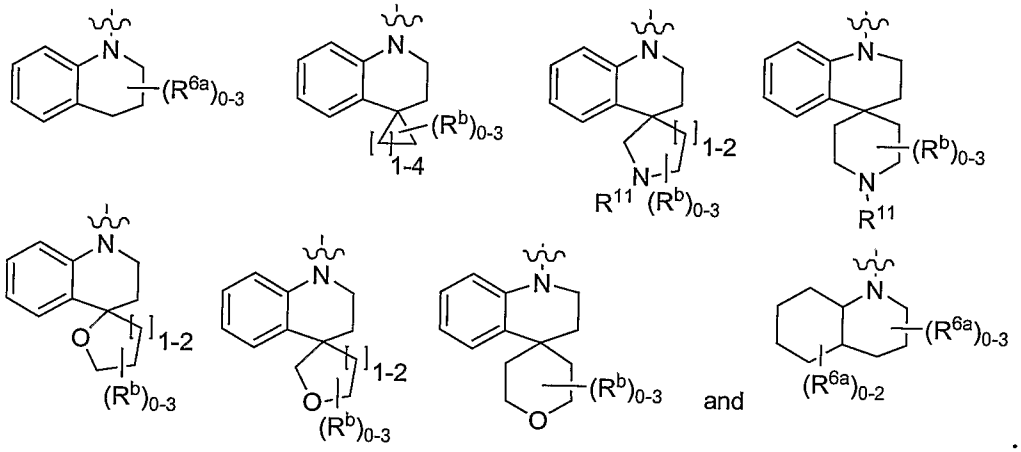
wherein the phenyl ring in each of the structures is substituted with 0-1 R^{6a}.

[0050] In another embodiment, ring D is selected from:



wherein the phenyl ring in each of the structures is substituted with 0-1 R^{6a}.

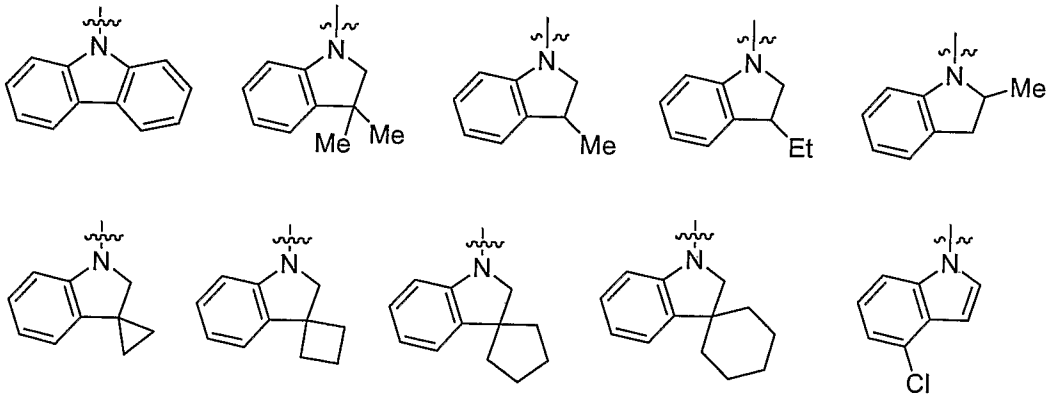
[0051] In another embodiment, ring D is selected from:

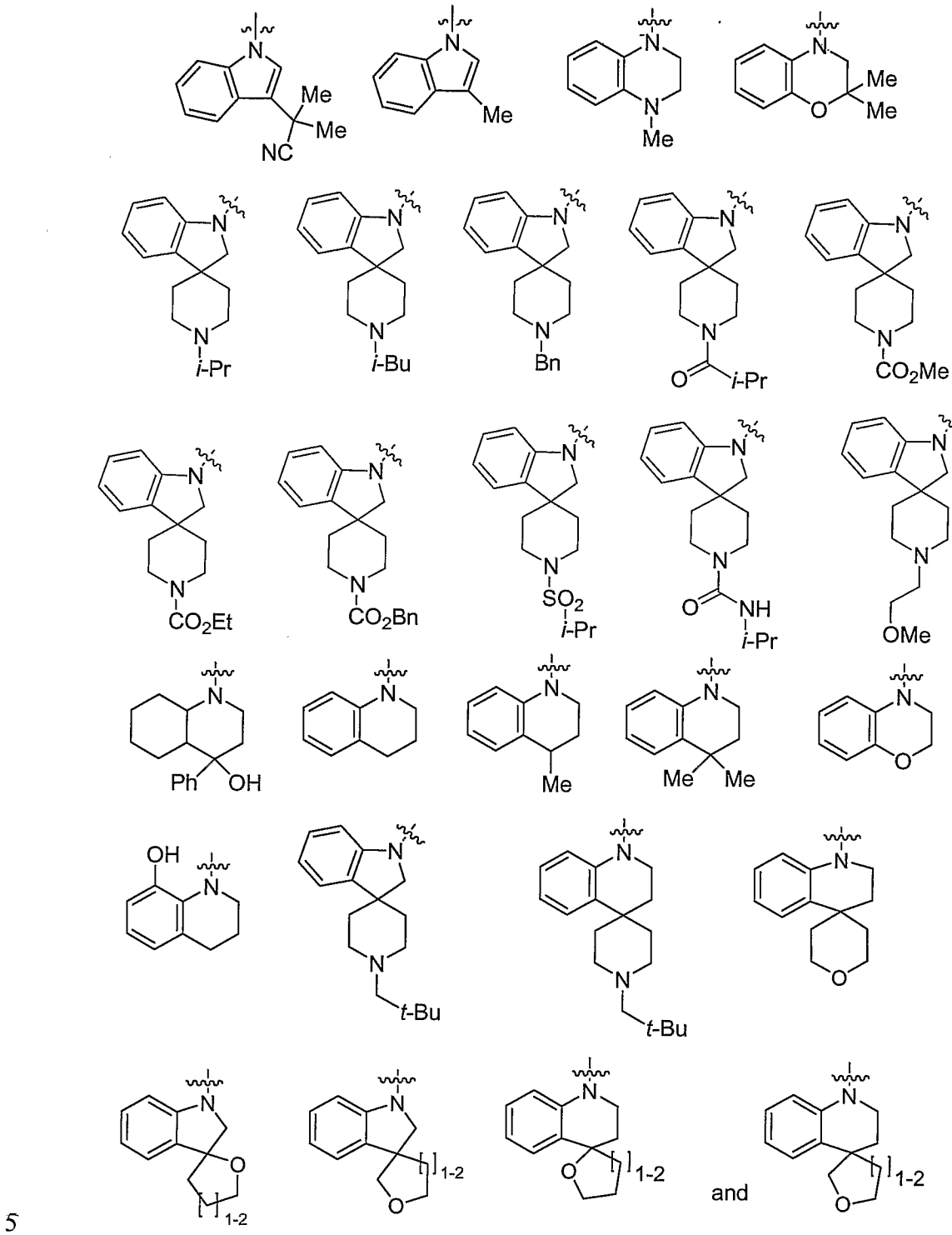


;

wherein the phenyl ring in each of the structures is substituted with 0-1 R^{6a}.

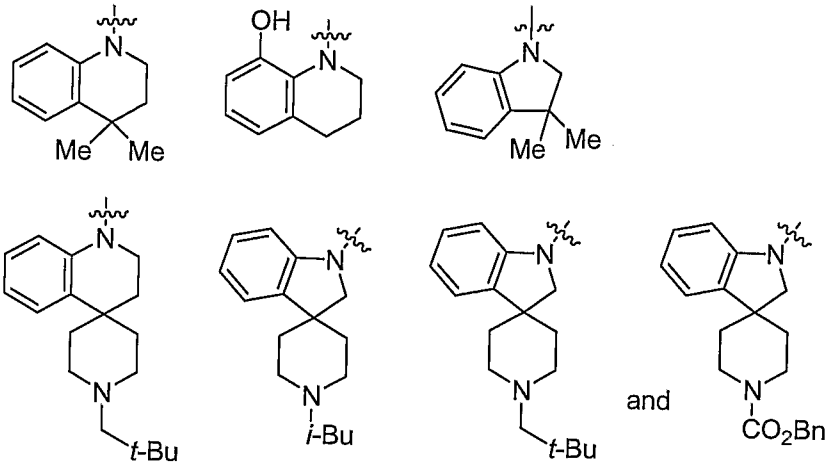
[0052] In another embodiment, ring D is selected from:





5

[0053] In another embodiment, ring D is selected from:



[0054] In another embodiment, R^1 is, independently at each occurrence, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $-(CH_2)_r-OR^c$, SR^c, CN, NO_2, $-(CH_2)_r-NR^{12}R^{13}$, $-(CH_2)_u-C(O)R^c$, $-(CH_2)_r-CO_2R^c$, $-(CH_2)_u-C(O)NR^{12}R^{13}$, or C_{1-4} alkyl substituted with 0-2 R^a.

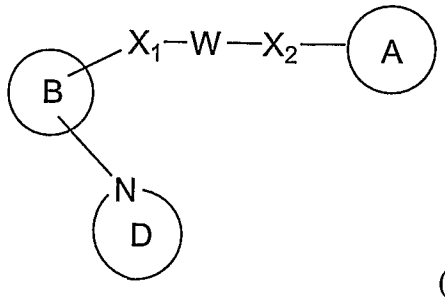
[0055] In another embodiment, R^{12} is, independently at each occurrence, H, C_{1-4} alkyl, phenyl, or benzyl.

[0056] In another embodiment, R^{13} is, independently at each occurrence, H, C_{1-4} alkyl, phenyl, or benzyl.

[0057] In another embodiment, R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, OR^c, SR^c, CN, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, or $-S(O)_pNR^{12}R^{13}$.

[0058] In another embodiment, R^c is, independently at each occurrence, H, C_{1-4} alkyl, phenyl, or benzyl.

[0059] In another embodiment, the present invention provides, *inter alia*, a compound of Formula (IV):



(IV)

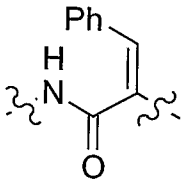
or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

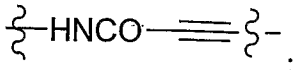
ring A is C_{3-13} carbocycle substituted with 0-5 R^1, or a 4- to 14-membered heterocycle comprising: carbon atoms and 1-5 ring heteroatoms selected from O, N, NR^{11}, and $S(O)_p$, wherein said heterocycle is substituted with 0-5 R^1;

ring B is phenyl substituted with 0-4 R^7, naphthyl substituted with 0-5 R^7, or a 5- to 10-membered heteroaryl comprising: carbon atoms and 1-4 ring heteroatoms selected from N, NR^{11}, N→O, $S(O)_p$, and O, wherein said heteroaryl is substituted with 0-5 R^7;

ring D is a 5- to 10-membered heterocycle comprising: in addition to the N atom shown, carbon atoms and 0-4 ring heteroatoms selected from N, NR^{11}, $S(O)_p$, Si, and O, wherein said heterocycle is substituted with 0-5 R^{6a};

W is NR^{18}, O, S, $-NR^{18}COCH=CH-$, $-NR^{18}CO-$, $-NR^{18}CO_2-$, $-NR^{18}CO_2CH_2-$, $-NR^{18}CONR^{18}-$, $-NR^{18}COCH(Me)-$, $-NR^{18}COCH_2CH_2-$, $-NR^{18}COCH_2NR^{18}-$, $-NR^{18}COCH_2CONR^{18}-$, $-NR^{18}SO_2-$, $-NR^{18}SO_2NR^{18}-$, $-NR^{18}SO_2CH_2-$, $-NR^{18}SO_2CH=CH-$, $-NR^{18}CONHNHCO-$, $-CH_2CONR^{18}-$,



or 

;

X_1 and X_2 are, independently at each occurrence, X is $-(CR^{16}R^{17})_s-$, $-(CR^{16}R^{17})_rCR^{16}=CR^{16}(CR^{16}R^{17})_r-$, $-(CR^{16}R^{17})_rC\equiv C(CR^{16}R^{17})_r-$, $-(CR^{16}R^{17})_tO(CR^{16}R^{17})_r-$, $-(CR^{16}R^{17})_tNR^{14}(CR^{16}R^{17})_r-$, $-(CR^{16}R^{17})_tC(O)(CR^{16}R^{17})_r-$, $-(CR^{16}R^{17})_tC(O)O(CR^{16}R^{17})_r-$,

$-(CR^{16}R^{17})_tOC(O)(CR^{16}R^{17})_r-$, $-(CR^{16}R^{17})_tC(O)NR^{14}(CR^{16}R^{17})_r-$, $-(CR^{16}R^{17})_tS(CR^{16}R^{17})_r-$, $-(CR^{16}R^{17})_tS(O)(CR^{16}R^{17})_s-$, $-(CR^{16}R^{17})_tS(O)_2(CR^{16}R^{17})_r-$, $-(CR^{16}R^{17})_tSO_2NR^{14}(CR^{16}R^{17})_r-$, or $-(CR^{16}R^{17})_tNR^{14}SO_2(CR^{16}R^{17})_r-$;

R^1 is, independently at each occurrence, H, =O, F, Cl, Br, I, CF_3, $-CF_2CF_3$, $-OCF_3$, $-OCF_2CF_2H$, $-OCF_2CF_3$, $SiMe_3$, $-(CR^fR^f)_rOR^c$, SR^c, CN, NO_2, $-(CR^fR^f)_rNR^{12}R^{13}$, $-(CR^fR^f)_rC(O)R^c$, $-(CR^fR^f)_rCO_2R^c$, $-(CR^fR^f)_rC(O)NR^{12}R^{13}$, $-C(O)NR^{14}(CR^fR^f)_tN^{12}R^{13}$, $-(CR^fR^f)_rOC(O)NR^{12}R^{13}$, $-(CR^fR^f)_rNR^{14}C(O)NR^{12}R^{13}$, $-(CR^fR^f)_rNR^{14}C(O)R^d$, $-(CR^fR^f)_rNR^{14}C(O)OR^h$, $-NR^{14}(CR^fR^f)_nC(O)R^d$, $-NR^{14}CO(CR^fR^f)_nOR^c$, $-(CH_2)_rCR^{13}(=NOR^c)$, $-(CH_2)_r-C(NH_2)(=NOR^c)$, $-S(O)_pNR^{12}R^{13}$, $-(CR^fR^f)_rNR^{14}S(O)_pNR^{12}R^{13}$, $-NR^{14}SO_2CF_3$, $-NR^{14}S(O)_pR^d$, $-S(O)_2CF_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-OP(O)(OEt)_2$, $-O(CH_2)_2OP(O)(OEt)_2$, $-N(C_{1-4}\text{ alkyl})_3{}^+Cl^-$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CR^fR^f)_r-C_{3-13}$ carbocycle substituted with 0-5 R^b, or $-(CR^fR^f)_r-$5- to 12-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-5 R^b;

alternatively, two R^1s on two adjacent carbon atoms are combined with the carbon atoms to which they attached, form a 5- to 10-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-2 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-4 R^b;

alternatively, two R^1s on the same carbon atom are combined with the carbon atom to which they attached, form a 3- to 10-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-2 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-4 R^b;

R^{6a} is, independently at each occurrence, =O, F, Cl, Br, I, $-(CR^fR^f)_r-OR^c$, SR^c, CN, NO_2, CF_3, OCF_3, $-CF_2CF_3$, $-OCF_2CF_2H$, $-OCF_2CF_3$, $-(CR^fR^f)_r-NR^{12}R^{13}$,

$-C(O)R^c$, $-(CR^fR^f)_r-C(O)OR^c$, $-(CR^fR^f)_r-C(O)NR^{12}R^{13}$, $-(CR^fR^f)_r-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, $-Si(Me)_3$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_1-C_4 alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CR^fR^f)_r-C_{3-10}$ carbocycle substituted with 0-3 R^e, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

alternatively, when two R^{6a} groups are attached to the same carbon atom or silicon atom, together with the carbon atom or silicon atom to which they are attached, they form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

alternatively, when two R^{6a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

R^7 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^c, SR^c, CN, NO_2, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^b, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{7b}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^b;

alternatively, two R^7s on two adjacent carbon atoms form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 ring heteroatoms selected from O, N, NR^{7b}, and $S(O)_p$, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^{7c};

R^{7b} is, independently at each occurrence, H, C_{1-4} alkyl, (C_{1-4} alkyl)C(O)-, phenyl-C(O)-, benzyl-C(O)-, benzyl-$S(O)_2$-, (C_{1-4} alkyl)NHC(O)-, (C_{1-4} alkyl)$_2$NC(O)-, phenyl-NHC(O)-, benzyl-NHC(O)-, (C_{1-4} alkyl)-$S(O)_2$-, phenyl-$S(O)_2$-, phenyl substituted with 0-3 R^b, or benzyl substituted with 0-3 R^b;

R^{7c} is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^c, SR^c, CN, NO_2, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-4} alkyl, phenyl substituted with 0-3 R^b, or benzyl substituted with 0-3 R^b;

R^{11} is, independently at each occurrence, H, C_{1-4} alkoxy, C_{1-6} alkyl substituted with 1-5 fluorine, $-(CR^fR^f)_rC(O)NR^{12}R^{13}$, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-4} alkenyl substituted with 0-1 R^a, C_{2-4} alkynyl substituted with 0-1 R^a, $-C(O)(C_{1-6}$ alkyl), $-C(O)(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)(CH_2)_n(C_{6-10}$ aryl), $-C(O)(CH_2)_n$(5- to 10-membered heteroaryl), $-C(O)O(C_{1-8}$ alkyl), $-C(O)O(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)O(CH_2)_n(C_{6-10}$ aryl), $-C(O)O(CH_2)_n$(5- to 10-membered heteroaryl), $-C(O)O(CH_2)_{2-4}(C_{1-4}$ alkyl), $-C(O)NH(C_{1-8}$ alkyl), $-C(O)NH(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)NH(CH_2)_n(C_{6-10}$ aryl), $-C(O)NH(CH_2)_n$(5- to 10-membered heteroaryl), $-S(O)_2(C_{1-8}$ alkyl), $-S(O)_2(CH_2)_n(C_{3-6}$ cycloalkyl), $-S(O)_2(CH_2)_n(C_{6-10}$ aryl), $-S(O)_2(CH_2)_n$(5- to 10-membered heteroaryl), $-(CR^fR^f)_r-C_{3-10}$ carbocycle, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle; wherein said alkyl, cycloalkyl, aryl and carbocycle are substituted with 0-2 R^b, and said heteroaryl and heterocycle are substituted with 0-2 R^b and comprise: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$;

R^{12} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 1-5 fluorine, $-(CR^fR^f)_rC(O)NR^fR^f$, C_{1-6} alkyl, $-C(O)(C_{1-6}$ alkyl), $-C(O)(CH_2)_n(C_{6-10}$ aryl), $-C(O)(CH_2)_n$(5- to 10-membered heteroaryl), $-C(O)O(C_{1-4}$ alkyl), $-C(O)OCH_2(C_{6-10}$ aryl), $-(CH_2)_nC(O)OCH_2$(5- to 10-membered heteroaryl), $-(CH_2)_nOC(O)(C_{1-4}$ alkyl), $-(CH_2)_nOC(O)(C_{6-10}$ aryl), $-(CH_2)_nOC(O)$(5- to 10-membered heteroaryl),

$-(CH_2)_nC(O)O(C_{1-4}$ alkyl), $-(CH_2)_nC(O)O(C_{6-10}$ aryl), $-(CH_2)_nC(O)O(5-$ to 10-membered heteroaryl), $-(CH_2)_nC(O)NH(C_{1-6}$ alkyl), $-(CH_2)_nC(O)NH(C_{6-10}$ aryl), $-(CH_2)_nC(O)NH(5-$ to 10-membered heteroaryl), $-(CH_2)_tOC(O)NH(C_{1-6}$ alkyl), $-(CH_2)_tOC(O)NH(C_{6-10}$ aryl), $-(CH_2)_tOC(O)NH(5-$ to 10-membered heteroaryl), $-S(O)_2(C_{1-6}$ alkyl), $-S(O)_2(CH_2)_n(C_{6-10}$ aryl), $-S(O)_2(CH_2)_n(5-$ to 10-membered heteroaryl), $-(CH_2)_n-(C_{6-10}$ aryl), or $-(CH_2)_n-$ 5- to 10-membered heteroaryl; wherein said alkyl, and aryl are substituted with 0-2 R^g; and said heteroaryl is substituted with 0-2 R^g and comprises: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl; alternatively, R^{12} and R^{13}, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising: carbon atoms and 1-2 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{14} is, independently at each occurrence, H, C_{1-8} alkyl substituted with 0-2 R^{14a}, C_{2-8} alkenyl substituted with 0-2 R^{14a}, C_{2-8} alkynyl substituted with 0-2 R^{14a}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^g, or $-(CH_2)_r-5-$ to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^g;

R^{14a} is, independently at each occurrence, H, C_{1-4} alkyl, OR^f, Cl, F, Br, I, =O, CF_3, CN, NO_2, $NR^{12}R^{13}$, $-C(O)R^f$, $-C(O)OR^f$, $-C(O)NR^{12}R^{13}$, or $-S(O)_pR^f$;

R^{16} is, independently at each occurrence, H, F, Cl, Br, I, OCF_3, CF_3, $-(CH_2)_r-OR^c$, SR^c, CN, NO_2, $-(CH_2)_r-NR^{12}R^{13}$, $-(CH_2)_r-C(O)R^c$, $-(CH_2)_r-CO_2R^c$, $-(CH_2)_r-C(O)NR^{12}R^{13}$, $-(CH_2)_r-OC(O)NR^{12}R^{13}$, $-(CH_2)_r-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-NR^{14}S(O)_pNR^{12}R^{13}$, $-NR^{14}SO_2CF_3$, $-NR^{14}SO_2R^d$, $-S(O)_2CF_3$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-5 R^b, or $-(CH_2)_r-5-$ to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-5 R^b;

R^{17} is, independently at each occurrence, H, OH, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

alternatively, R^{16} and R^{17} combine to form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl, and 0-3 double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

alternatively, two R^{16} groups on adjacent atoms combine to form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl, and 0-3 double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

R^{18} is H, C_{1-6} alkyl substituted with 0-2 R^a, C_{2-6} alkenyl substituted with 0-2 R^a, C_{2-6} alkynyl substituted with 0-2 R^a, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-S(O)_2R^h$, $-S(O)_2NR^{12}R^{13}$, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^b, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^b;

R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, $-(CR^fR^f)_rOR^c$, $-(CR^fR^f)_rSR^c$, CN, $-(CR^fR^f)_rNR^{12}R^{13}$, $-(CR^fR^f)_rC(O)R^c$, $-(CR^fR^f)_rC(O)OR^c$, $-(CR^fR^f)_rC(O)NR^{12}R^{13}$, $-(CR^fR^f)_rNR^{14}C(O)R^d$, $-(CR^fR^f)_rS(O)_pNR^{12}R^{13}$, $-(CR^fR^f)_rS(O)R^d$, $-(CR^fR^f)_rS(O)_2R^d$, C_{1-4} alkyl substituted with 1-5 fluorine, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^e, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^b is, independently at each occurrence, H, =O, F, Cl, Br, I, $-(CH_2)_r$-OR^c, SR^c, CN, NO_2, CF_3, OCF_3, $-(CR^fR^f)_rNR^{12}R^{13}$, $-C(O)R^c$, $-(CH_2)_r$-$C(O)OR^c$, $-(CH_2)_r$-$C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_{1-4} alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CH_2)_r$-C_{3-10} carbocycle substituted with 0-3 R^e, or $-(CH_2)_r$-5- to 10-membered heterocycle

comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^c is, independently at each occurrence, H, $-OP(O)(OEt)_2$, C_{1-8} alkyl substituted with 0-3 R^e, C_{2-8} alkenyl substituted with 0-3 R^e, C_{2-8} alkynyl substituted with 0-3 R^e, $-(CR^fR^f)_r-C_{3-8}$ cycloalkyl substituted with 0-3 R^e, $-(CR^fR^f)_r-C_{6-10}$ aryl substituted with 0-3 R^e, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^d is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^e, or $-(CH_2)_r$-5- to 10- membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^e is, independently at each occurrence, H, =O, $-(CH_2)_r-OR^f$, F, Cl, Br, I, CN, NO_2, $-(CH_2)_r-NR^{12}R^{13}$, $-C(O)R^f$, $-(CH_2)_r-C(O)OR^f$, $-NR^{14}C(O)R^f$, $-(CH_2)_r-C(O)NR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$, $-NR^{14}SO_2NR^{12}R^{13}$, $-NR^{14}SO_2-C_{1-4}$ alkyl, $-NR^{14}SO_2CF_3$, $-NR^{14}SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p-OR^h$, $-(CF_2)_rCF_3$, $Si(Me)_3$, $Si(Me)_2(t\text{-Bu})$, $Si(C_{1-4}\text{ alkyl})_3$, C_{1-8} alkyl substituted with 0-2 R^g, C_{2-8} alkenyl substituted with 0-2 R^g, C_{2-8} alkynyl substituted with 0-2 R^g, $-(CH_2)_r-C_{3-8}$ cycloalkyl substituted with 0-2 R^g, $-(CH_2)_r-C_{6-10}$ aryl substituted with 0-2 R^g, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

alternatively, two R^e groups, together with the atoms to which they are attached, form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^f, O, and $S(O)_p$, 0-1 carbonyl and 0-3 double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^g;

R^f is, independently at each occurrence, H, F, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

R^g is, independently at each occurrence, H, =O, OR^f, F, Cl, Br, I, CN, NO_2,

$-NR^fR^f$, $-C(O)R^f$, $-C(O)OR^f$, $-NR^fC(O)R^f$, $-C(O)NR^fR^f$, $-SO_2NR^fR^f$, $-NR^fSO_2NR^fR^f$, $-NR^fSO_2$-C_{1-4} alkyl, $-NR^fSO_2CF_3$, $-NR^fSO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

R^h is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^g, $-(CH_2)_n$-phenyl substituted with 0-2 R^g, or $-(CH_2)_n$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

R^i is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^g, $-(CH_2)_n$-phenyl substituted with 0-2 R^g, or $-(CH_2)_n$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

s, at each occurrence, is selected from 0, 1, 2, 3, 4, 5, and 6; and

t, at each occurrence, is selected from 1, 2, 3, and 4;

provided that:

(i) when W is -NHCO-, $-NHCO_2$-, or $-NHCOCH_2CH_2$-, ring B is substituted or unsubstituted phenylene and ring D is substituted or unsubstituted 2,3-dihydro-1H-indol-1-yl or substituted or unsubstituted 3,4-dihydro-1(2H)-quinolinyl, then ring A is other than unsubstituted or substituted phenyl, furanyl, pyridyl, or 4-methyl-piperazin-1-yl;

(ii) when W is $-NHSO_2$-, ring B is quinoxalinylene and ring D is 3,4-dihydro-1(2H)-quinolinyl, then ring A is other than phenyl or substituted phenyl; or

(iii) the compound is other than 2-(2,3-dinydro-7-methylcyclopent[b]indol-4(1H)-yl)-N,N-diphenylbenzenamide.

[0060] In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at

least one of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0061] In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0062] In another embodiment, the present invention provides a novel process for making a compound of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof.

[0063] In another embodiment, the present invention provides a novel intermediate for making a compound of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate or prodrug thereof.

[0064] In another embodiment, the present invention provides a pharmaceutical composition further comprising at least one additional therapeutic agent selected from potassium channel openers, potassium channel blockers, calcium channel blockers, sodium hydrogen exchanger inhibitors, antiarrhythmic agents, antiatherosclerotic agents, anticoagulants, antithrombotic agents, prothrombolytic agents, fibrinogen antagonists, diuretics, antihypertensive agents, ATPase inhibitors, mineralocorticoid receptor antagonists, phospodiesterase inhibitors, antidiabetic agents, anti-inflammatory agents, antioxidants, angiogenesis modulators, antiosteoporosis agents, hormone replacement therapies, hormone receptor modulators, oral contraceptives, antiobesity agents, antidepressants, antianxiety agents, antipsychotic agents, antiproliferative agents, antitumor agents, antiulcer and gastroesophageal reflux disease agents, growth hormone agents and/or growth hormone secretagogues, thyroid mimetics, anti-infective agents, antiviral agents, antibacterial agents, antifungal agents, cholesterol/lipid lowering agents and lipid profile therapies, and agents that mimic ischemic preconditioning and/or myocardial stunning, or a combination thereof.

[0065] In another embodiment, the present invention provides a pharmaceutical composition wherein the additional therapeutic agent(s) is an antihypertensive agent selected from ACE inhibitors, AT-1 receptor antagonists, beta-

adrenergic receptor antagonists, ETA receptor antagonists, dual ETA/AT-1 receptor antagonists, and vasopeptidase inhibitors, an antiarrythmic agent selected from IKur inhibitors, an anticoagulants selected from thrombin inhibitors, antithrombin-III activators, heparin co-factor II activators, factor VIIa inhibitors, factor Xa inhibitors, factor XIa inhibitors and kallikrein inhibitors, or antiplatelet agents selected from GPIIb/IIIa blockers, protease activated receptor (PAR-1) antagonists, phosphodiesterase-III inhibitors, other $P2Y_1$ antagonists, $P2Y_{12}$ antagonists, thromboxane receptor antagonists, cyclooxygense-1 inhibitors, and aspirin, or a combination thereof.

[0066] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from an anti-arrhythmic agent, an anti-hypertensive agent, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, a fibrinolytic agent, a calcium channel blocker, a potassium channel blocker, a cholesterol/lipid lowering agent, or a combination thereof.

[0067] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from warfarin, unfractionated heparin, low molecular weight heparin, synthetic pentasaccharide, hirudin, argatroban, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, dipyridamol, droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, melagatran, ximelagatran, disulfatohirudin, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, and streptokinase, or a combination thereof.

[0068] In a preferred embodiment, the present invention provides pharmaceutical composition, wherein the additional therapeutic agent(s) are an anti-platelet agent or a combination thereof.

[0069] In a preferred embodiment, the present invention provides a pharmaceutical composition, wherein the additional therapeutic agent is the anti-platelet agent selected from clopidogrel and aspirin, or a combination thereof.

[0070] In a preferred embodiment, the present invention provides a pharmaceutical composition, wherein the additional therapeutic agent is the anti-platelet agent clopidogrel.

[0071] In another embodiment, the present invention provides a method for modulation of platelet reactivity comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0072] In another embodiment, the present invention provides a method for treating thrombotic or thromboembolic disorders comprising: administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0073] In another embodiment, the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, venous cerebrovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart.

[0074] In another embodiment, the thromboembolic disorder is selected from the group consisting of unstable angina, an acute coronary syndrome, atrial fibrillation, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface that promotes thrombosis.

[0075] In another embodiment, the present invention provides a method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug form thereof in an amount effective to treat a thromboembolic disorder.

[0076] In another embodiment, the present invention provides a method, comprising: administering a compound of the present invention or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof in an amount effective to treat a thrombotic or thromboembolic disorder.

[0077] In another embodiment, the present invention provides a compound of the present invention for use in therapy.

[0078] In another embodiment, the present invention provides a compound of the present invention for use in therapy for treating a thrombotic and thromboembolic disorder.

[0079] In another embodiment, the present invention also provides the use of a compound of the present invention for the manufacture of a medicament for the treatment of a thrombotic or thromboembolic disorder.

[0080] In another embodiment, the present invention provides a novel article of manufacture, comprising: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention; and (c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thrombotic or thromboembolic disorder.

[0081] In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising: (d) a second container; wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

[0082] In another embodiment, the present invention provides a novel article of manufacture, comprising: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention; and (c) a package insert stating that the pharmaceutical composition can be used in combination with a second therapeutic agent to treat a thrombotic or thromboembolic disorder.

[0083] In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising: (d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

[0084] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is its own independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

DEFINITIONS

[0085] The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials or optically active catalysts. Geometric isomers of double bonds such as olefins and C=N double bonds can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. When no specific mention is made of the configuration (*cis, trans* or R or S) of a compound (or of an asymmetric carbon), then any one of the isomers or a mixture of more than one isomer is intended. The processes for preparation can use racemates, enantiomers, or diastereomers as starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they can be separated by conventional methods, for example, by chromatography or fractional crystallization.

Compounds of the present invention, and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention. The inventive compounds may be in the free or hydrate form.

[0086] Preferably, the molecular weight of compounds of the present invention is less than about 500, 550, 600, 650, 700, 750, or 800 grams per mole. Preferably, the molecular weight is less than about 800 grams per mole. More preferably, the molecular weight is less than about 750 grams per mole. Even more preferably, the molecular weight is less than about 700 grams per mole.

[0087] The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbon atom of the carbonyl group or one carbon atom of the double bond be part of (i.e., within) the ring. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N).

[0088] In cases wherein there are nitrogen atoms (e.g., amines) on compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative. In cases wherein there are quarternary carbon atoms on compounds of the present invention, these can be replaced by silicone atoms, provided they do not form Si-N or Si-O bond.

[0089] When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R^1, then said group may optionally be substituted with up to three R^1 groups and R^1 at each occurrence is selected independently from the definition of

R^1. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0090] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0091] As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_1-C_{10} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

[0092] "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration having the specified number of carbon atoms and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain. For example, "C_2-C_6 alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

[0093] "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more carbon-carbon triple bonds which may occur in any stable point along the chain. For example, "C_2-C_6 alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

[0094] The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and

C_7 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like.

[0095] "Alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_1-C_6 alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S-, ethyl-S-, and the like.

[0096] "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

[0097] "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" which is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

[0098] "Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_1-C_6 haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, and the like. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, pentafluoroethyl-S-, and the like.

[0099] As used herein, "carbocycle" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic

or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, and indanyl. When the term "carbocycle" is used, it is intended to include "aryl".

[00100] As used herein, the term "bicyclic carbocycle" or "bicyclic carbocyclic group" is intended to mean a stable 9- or 10-membered carbocyclic ring system which contains two fused rings and consists of carbon atoms. Of the two fused rings, one ring is a benzo ring fused to a second ring; and the second ring is a 5 or 6 membered carbon ring which is saturated, partially unsaturated, or unsaturated. The bicyclic carbocyclic group may be attached to its pendant group at any carbon atom which results in a stable structure. The bicyclic carbocyclic group described herein may be substituted on any carbon if the resulting compound is stable. Examples of a bicyclic carbocyclic group are, but not limited to, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl.

[00101] As used herein, the term "aryl", "C_6-C_{10} aryl" or "aromatic residue", is intended to mean an aromatic moiety containing, if specified, the specified number of carbon atoms; for example phenyl or naphthyl. Unless otherwise specified, "aryl", "C_6-C_{10} aryl" or "aromatic residue" may be unsubstituted or substituted with 0 to 3 groups selected from H, OH, OCH_3, Cl, F, Br, I, CN, NO_2, NH_2, $N(CH_3)H$, $N(CH_3)_2$, CF_3, OCF_3, $C(=O)CH_3$, SCH_3, $S(=O)CH_3$, $S(=O)_2CH_3$, CH_3, CH_2CH_3, CO_2H, and CO_2CH_3.

[00102] As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 3, 4, 5, 6, or 7- membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, 13, or 14-membered bicyclic or tricyclic heterocyclic ring which is saturated, partially unsaturated or fully unsaturated, and which consists of carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms

may optionally be oxidized to -NO-, -SO-, or -SO_2-. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen atom in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

[00103] Examples of heterocycles include, but are not limited to, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4a*H*-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, imidazolopyridinyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thiazolopyridinyl, thienyl, thienothiazolyl,

thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[00104] Preferred 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

[00105] Preferred 5- to 6- membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl.

[00106] As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. Of the two fused rings, one ring is a 5 or 6-membered monocyclic aromatic ring comprising a 5 membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5 or 6 membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5 membered heterocycle, a 6 membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

[00107] The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent

to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

[00108] Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1H-indazolyl, benzimidazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinoline, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxaline, and 1,2,3,4-tetrahydro-quinazoline.

[00109] Also included are fused ring and spiro compounds containing, for example, the above carbocycles or heterocycles.

[00110] Bridged rings are also included in the definition of carbocycle or heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00111] As used herein, the term "amine protecting group" means any group known in the art of organic synthesis for the protection of amine groups which is stable to an ester reducing agent, a disubstituted hydrazine, R4-M and R7-M, a nucleophile, a hydrazine reducing agent, an activator, a strong base, a hindered amine base and a cyclizing agent. Such amine protecting groups fitting these criteria include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Examples of amine protecting groups include, but are not limited to, the following: (Fmoc); (1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; (2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); (3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; (4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; (5) alkyl types such as

triphenylmethyl and benzyl; (6) trialkylsilane such as trimethylsilane; (7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl; and (8) alkyl types such as triphenylmethyl, methyl, and benzyl; and substituted alkyl types such as 2,2,2-trichloroethyl, 2-phenylethyl, and t-butyl; and trialkylsilane types such as trimethylsilane.

[00112] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00113] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

[00114] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's*

Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA, **1990**, the disclosure of which is hereby incorporated by reference.

[00115] Isotopically labeled compounds of the present invention, i.e., wherein one or more of the atoms described are replaced by an isotope of that atom (e.g., C replaced by ^{13}C or by ^{14}C; and isotopes of hydrogen include tritium and deuterium), are also provided herein. Such compounds have a variety of potential uses, e.g., as standards and reagents in determining the ability of a potential pharmaceutical to bind to target proteins or receptors, or for imaging compounds of this invention bound to biological receptors in vivo or in vitro.

[00116] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% compound of the present invention ("substantially pure"), which is then used or formulated as described herein. Such "substantially pure" compounds are also contemplated herein as part of the present invention.

[00117] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that compounds of the present invention do not contain a N-halo, $S(O)_2H$, or S(O)H group.

[00118] In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula I) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, **1985**), and *Methods in Enzymology*, Vol. 112, at pp. 309-396, edited by K. Widder, *et. al.* (Academic Press, **1985**);

b) *A Textbook of Drug Design and Development*, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "*Design and Application of Prodrugs*," by H. Bundgaard, at pp. 113-191 (**1991**);

c) H. Bundgaard, *Advanced Drug Delivery Reviews*, Vol. 8, p. 1-38 (**1992**);

d) H. Bundgaard, *et al.*, *Journal of Pharmaceutical Sciences*, Vol. 77, p. 285 (**1988**); and

e) N. Kakeya, *et. al.*, *Chem Phar Bull.*, Vol. 32, p. 692 (**1984**).

[00119] Compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield compounds of the present invention *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6} alkanoyloxy-C_{1-6}alkyl, *e.g.* acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl, *e.g.* methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl, and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

[00120] The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanolates, methanolates, isopropanolates and the like. Methods of solvation are generally known in the art.

[00121] As used herein, the term "patient" encompasses all mammalian species.

[00122] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b)

inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

[00123] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination with other active ingredients to inhibit $P2Y_1$ or to treat the conditions or disorders listed herein. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*:27-55, occurs when the effect (in this case, inhibition of $P2Y_1$) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antithrombotic effect, or some other beneficial effect of the combination compared with the individual components.

[00124] The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutical carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, i.e., adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and, the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such

carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Remington's Pharmaceutical Sciences*, 18th ed., **1990**, which is incorporated herein by reference in its entirety.

[00125] Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "rt" for room temperature, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "sat" or "sat'd " for saturated, "MW" for molecular weight, "mp" for melting point, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "LC-MS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, "tlc" for thin layer chromatography, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Me	methyl
Et	ethyl
MeOH	methanol
EtOH	ethanol
i-PrOH	isopropanol
Ph	phenyl
Bn	benzyl
Bu	butyl
iBu or *i*-Bu	isobutyl

Pr	propyl
iPr or *i*-Pr	isopropyl
t-Bu	tertiary butyl
AcOH	acetic acid
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
EtOAc	ethyl acetate
ADP	adenosine diphosphate
2MeS-ADP	2 methylthio adenosine diphosphate
cDNA	complimentary DNA
DCC	dicyclohexylcarbodiimide
DCE	1,2 dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIC or DIPCDI	diisopropylcarbodiimide
DIEA	diethylpropyl amine
DMAP	4-dimethylaminopyridine
DMEM	Dulbecco's modified Eagle media
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC	3-ethyl-3'-(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)
EDTA	ethylenediaminetetraacetic acid
FBS	Fetal Bovine Serum
HEPES	4-(2-hydroxyethyl)piperaxine-1-ethanesulfonic acid
LDA	lithium diisopropylamide
mCPBA or MCPBA	*meta*-chloroperbenzoic acid
OMs	mesylate, methanesulfoate
OTf	triflate, trifluoromethanesulfonate
OTs	tosylate, para-toluenesulfonate
D-PBS	Dulbecco's Phosphate Buffered Saline
Pd/C	palladium on carbon

SCX	Strong Cation Exchanger
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TRIS	tris (hydroxymethyl) aminomethane

[00126] Solution ratios express a volume relationship, unless stated otherwise. NMR chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel according to Still's method (Still, W. C. *et al. J. Org. Chem.* **1978**, *43*, 2923). Alternatively, flash chromatography was carried out on an ISCO CombiFlash™ System Sq16x using prepacked SiO_2 cartridges eluted with gradients of hexanes and ethyl acetate.

SYNTHESIS

[00127] The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

[00128] A particularly useful compendium of synthetic methods which may be applicable to the preparation of compounds of the present invention may be found in Larock, R. C. *Comprehensive Organic Transformations*, VCH: New York, **1989**. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference.

[00129] The novel compounds of this invention may be prepared using the reactions and techniques described in this section. Also, in the description of the

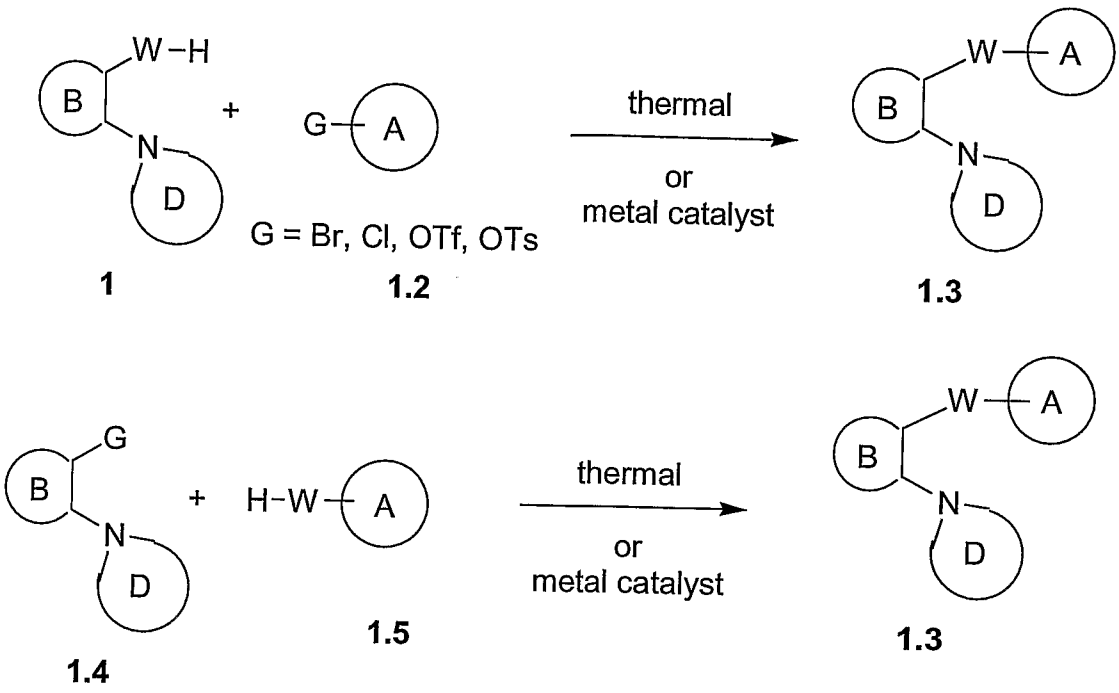
synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

[00130] It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety by reference.

[00131] U.S. Patent Application No. 11/126,567 (Publication No. US20050261244A1), filed May 10, 2005 and U.S. Patent Application No. 11/038,862 (Publication No. US20050203146A1), filed January 19, 2005, which are incorporated herein by reference, disclose preparations of starting materials and intermediates which can be utilized in making compounds of the present invention.

[00132] Scheme 1 describes the preparation of compounds of the invention from functionalized intermediates of formula **1.1** wherein X, for example, is a nucleophilic nitrogen or oxygen species. Coupling of intermediates of formula **1.1** with intermediates of formula **1.2** wherein G, for example, is a halide or tosylate can be accomplished thermally by methods known to one skilled in the art of organic synthesis at temperatures between -78 °C and 250 °C in a variety of solvents such as tetrahydrofuran, ethanol, dichloroethane, dichloromethane, toluene, dimethylformamide or dioxane provides compounds of formula **1.3**.

Scheme 1



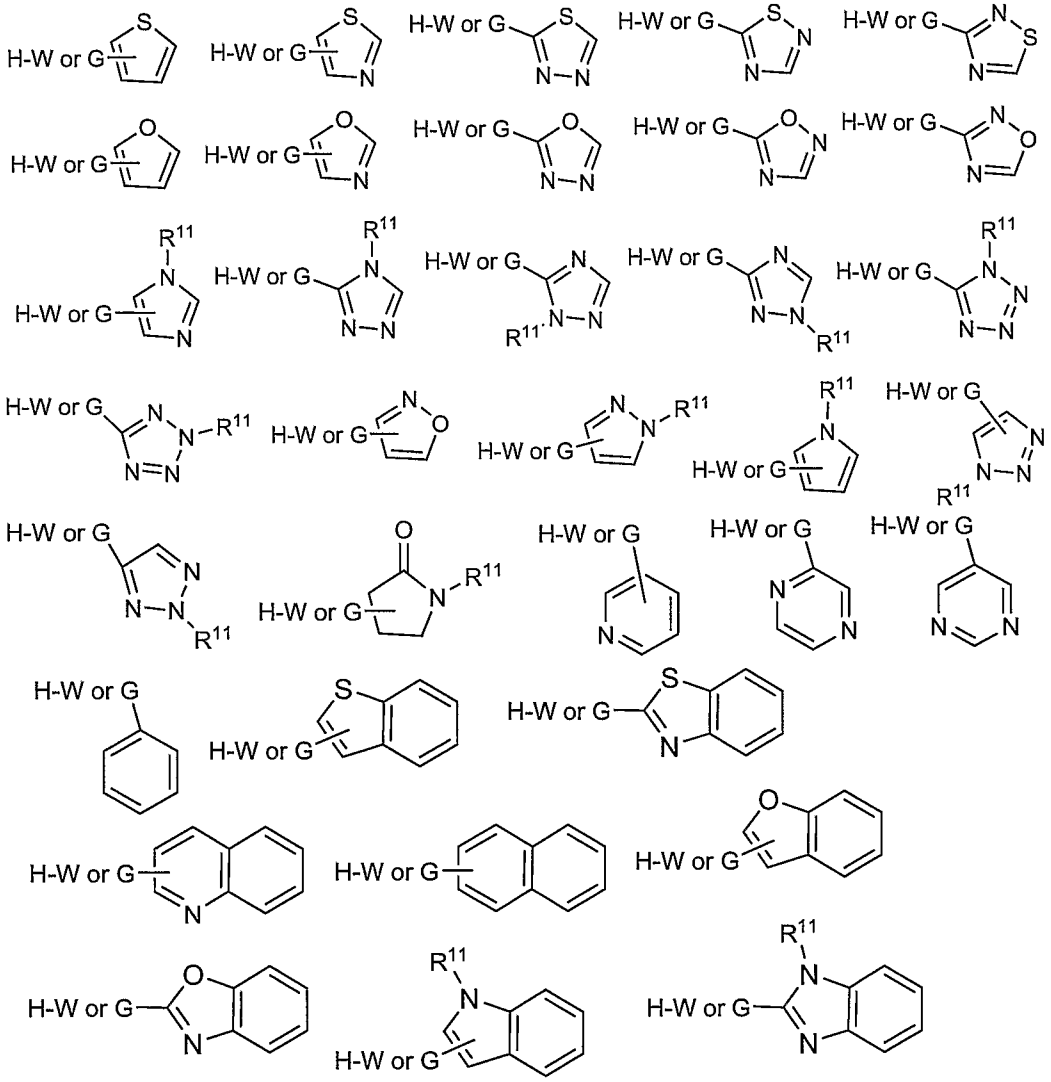
for example G = halide, OTf, $B(OH)_2$, $B(O\text{-alkyl})_2$, $Sn(alkyl)_3$

[00133] Alternately, coupling of intermediates of formula **1.1** with intermediates of formula **1.2** wherein G, for example, is halide, tosylate, boronic acid, boronate ester, or trialkylstanane can be accomplished using metal catalyzed couplings known to one skilled in the art of organic synthesis or described herein at temperatures between -78 °C and 250 °C in a variety of solvents such as tetrahydrofuran, ethanol, dichloroethane, dichloromethane, toluene, dimethylformamide, or dioxane provides compounds of formula **1.3**. A variety of examples of such metal catalyzed couplings are provided in the following literature: Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131 and Hartwig, J. F. In Modern Amination Methods; Ricci, A., Ed., Wiley-VCH: Weinheim, Germany, **2000**. The metal catalyst is usually palladium or nickel complexed with ligands such as a diphosphine or a ferrocene. Structures of formula **1.2** or structures of formula **1.5** are exemplified in Scheme 1.

[00134] In similar fashion as described above, intermediates of formula **1.4** and formula **1.5** can be coupled to provide compounds of formula **1.3**. Intermediates of

formula **1.1, 1.2, 1.4** and **1.5** are commercially available or can readily be prepared from commercially available materials by methods known to one skilled in the art of organic synthesis or can be prepared from commercially available materials through schemes and examples provided herein.

Figure 1



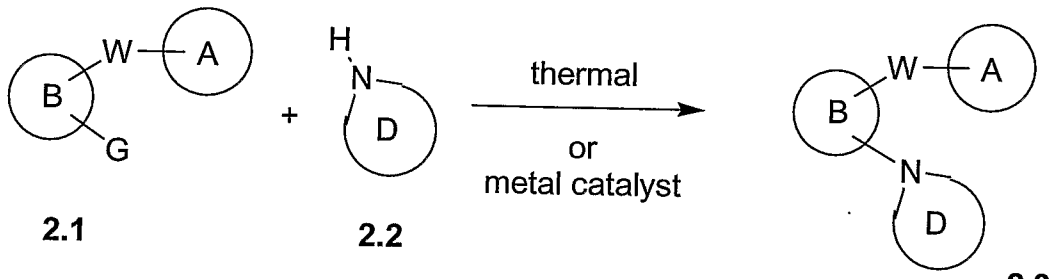
G= Br, Cl, OTf etc.W-H = NH_2 or OH;
all the heteroaryls are optionally further substituted.

[00135] Scheme 2 describes the preparation of compounds of the invention from functionalized intermediates of formula **2.1** wherein G, for example, is a halide or tosylate. Coupling of intermediates of formula **2.1** with cyclic amines of formula **2.2** can be accomplished thermally by methods known to one skilled in the art of

organic synthesis at temperatures between -78 °C and 250 °C in a variety of solvents such as tetrahydrofuran, ethanol, dichloroethane, dichloromethane, toluene, dimethylformamide, or dioxane, provides compounds of the invention of formula **2.3**. Alternately, coupling of intermediates of formula **2.1**, wherein G, for example, is a halide, tosylate, boronic acid, boronate ester, or trialkylstanane with cyclic amine intermediates of formula **2.2** can be accomplished using metal catalyzed couplings known to one skilled in the art of organic synthesis or described herein at temperatures between -78 °C and 250 °C in a variety of solvents such as tetrahydrofuran, ethanol, dichloroethane, dichloromethane, toluene, dimethylformamide, or dioxane, provides compounds of the invention of formula **2.3**. A variety of examples of such metal catalyzed couplings are provided in the following literature: Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. and Hartwig, J. F. In Modern Amination Methods; Ricci, A., Ed., Wiley-VCH: Weinheim, Germany, **2000**. The metal catalyst is usually palladium or nickel complexed with ligands such as a diphosphine or a ferrocene.

[00136] Intermediates of formula **2.1, 2.2,** and **2.3** are commercially available or can readily be prepared from commercially available materials by methods known to one skilled in the art of organic synthesis or can be prepared from commercially available materials through schemes and examples provided herein.

Scheme 2



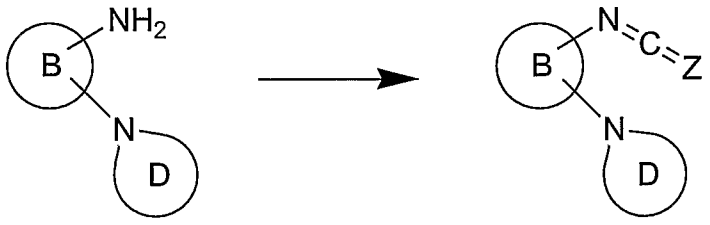
2.1 **2.2** **2.3**

for example G = halide, OTf, $B(OH)_2$, $B(O\text{-alkyl})_2$, $Sn(alkyl)_3$

[00137] Scheme 3 outlines a preparation of the key isocyanate or isothiocyanate intermediate **3.2**. Anilines **3.1**, prepared according to Schemes 4 and 5, can be treated with a phosgene or a thiophosgene equivalent in an organic solvent such as dichloromethane, dichloroethane, or toluene, to produce the corresponding isocyanate or isothiocyanate. Phosgene or thiophosgene equivalents include

diphosgene, triphosgene, carbonyl diimidazole, trichloromethyl chloroformate, and disuccinimidyl carbonate, or thiocarbonic acid *O,O*-dipyridin-2-yl ester1,1'-thiocarbonyldi-2,2'-pyridone, carbon disulfide, thiocarbonyl-diimidazole, and thiophosgene.

Scheme 3

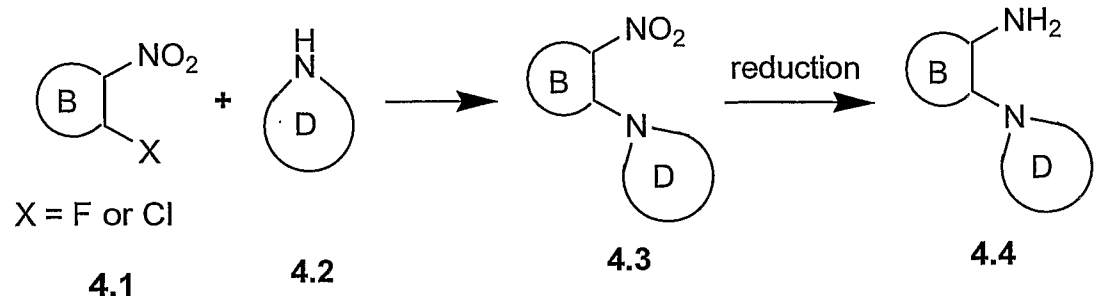


3.1 **3.2**

Z = O or S

[00138] Scheme 4 outlines one possible preparation of amino derivatives **4.4**, which proceeds by aromatic nucleophilic substitution followed by reduction. Nitro aryl derivatives or nitro heteroaryl derivatives **4.1**, substituted in the *ortho* position with a halogen (such as chlorine, fluorine or bromine), are commercially available or can readily be prepared by one skilled in the art of organic synthesis. They can be reacted with NH-containing cyclics **4.2** as nucleophiles to provide the corresponding compounds **4.3**. Typical reaction conditions involve the reaction of a nucleophile and a halonitroaryl/heteroaryl derivative either in an organic solvent such as THF, DMF, toluene, dioxane, or n-butanol, or under neat condition, in the presence of a base such as potassium carbonate, cesium carbonate, triethylamine, tert-butoxide, or DIEA, etc. The reaction temperature is usually between room temperature and reflux condition. Reaction conditions can be chosen based on the nucleophilicity of **4.2** and/or halogen difference. Microwave irradiation and/or heating at higher temperature can also be used to accelerate the rate of reaction. For example, when **4.2** is tetrahydroquinoline derivative, the SN_{Ar} reaction can be performed with neat **4.1** and **4.2** in the presence of 2,4,6-collidine at 250 °C under microwave irradiation.

Scheme 4



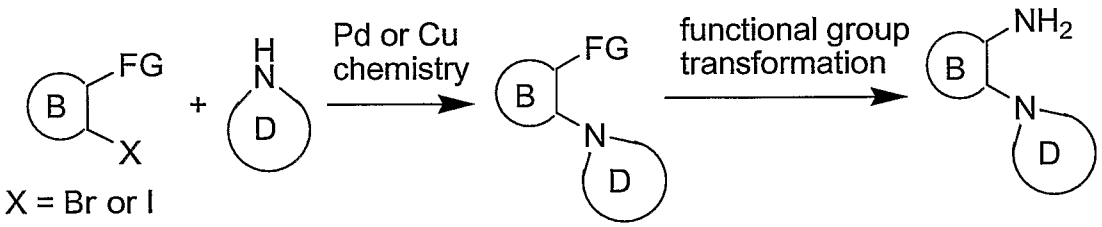
X = F or Cl

4.1 **4.2** **4.3** **4.4**

[00139] Following aromatic nucleophilic substitution, the resulting nitro derivative **4.3** can be reduced to the corresponding aniline. Typical conditions include hydrogenation in the presence of a metal catalyst such as palladium or platinum. Other conditions include treatment with reducing agents such as $SnCl_2$ or Zinc powder with ammonium chloride.

[00140] Intermediates **5.4** can be synthesized via Cu or Pd chemistry (for a review paper, see, *Angew. Chem. Int. Ed.* 42, 5400-5449) between 1,2-substituted aryl/heteroaryl halides and NH-containing cyclics **5.3** followed by deprotection or functional transformation as exemplified in Scheme 5. Microwave irradiation can also be used to accelerate the rate of reaction in the coupling step when using the Pd or Cu chemistry.

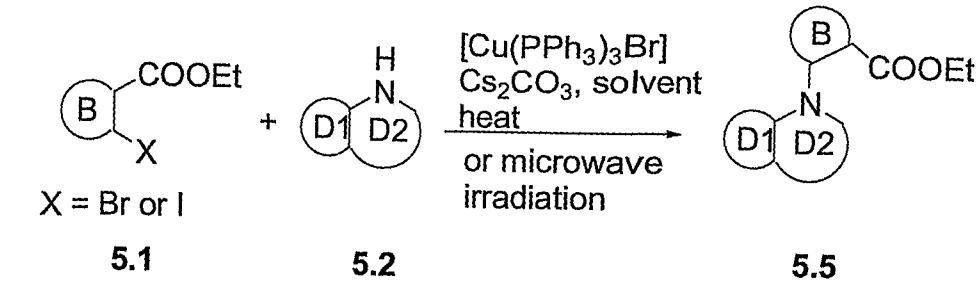
Scheme 5



X = Br or I

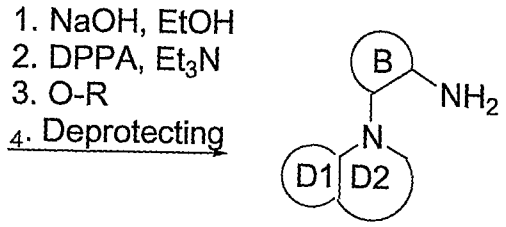
5.1 **5.2** **5.3** **5.4**

FG: functional group

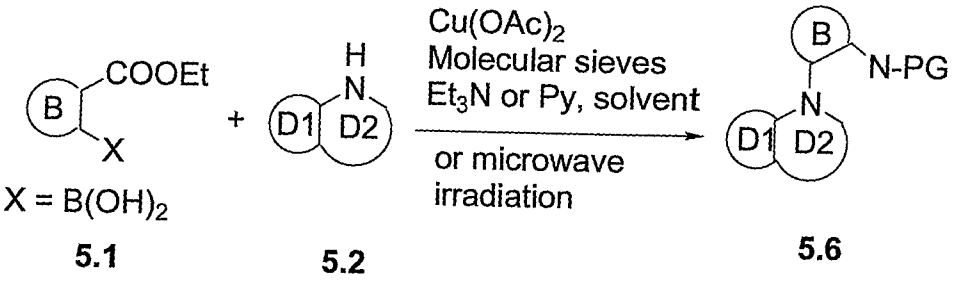


X = Br or I

5.1 **5.2** **5.5**



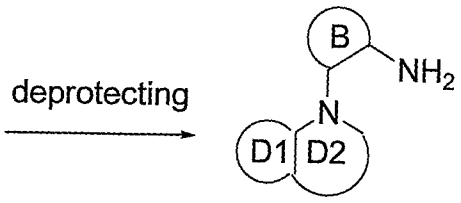
5.4



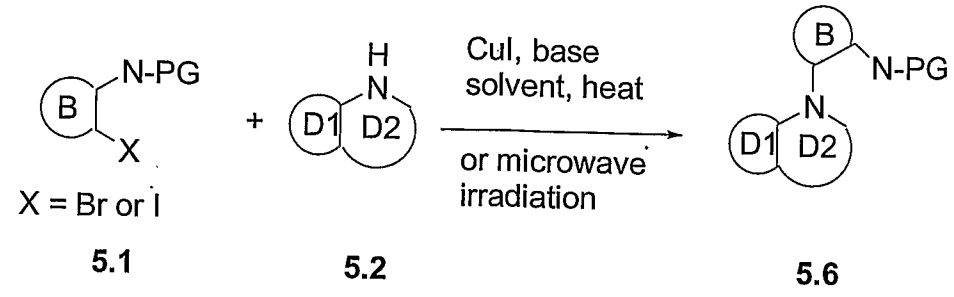
X = $B(OH)_2$

5.1 **5.2** **5.6**

PG: protecting group

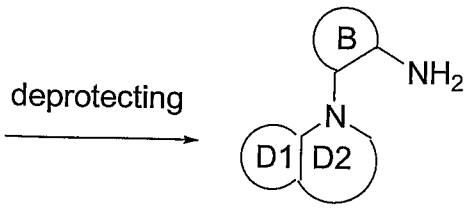


5.4

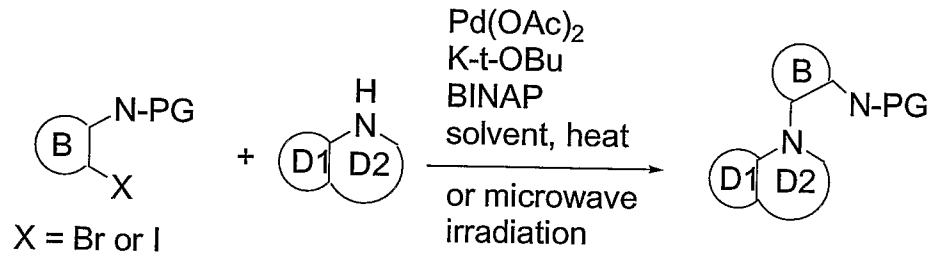


5.1 5.2 5.6

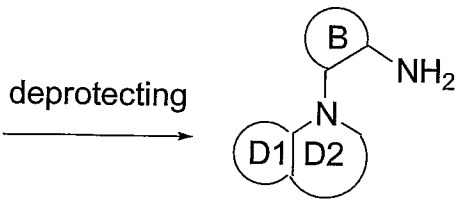
PG: protecting group



5.4



5.1 5.2 5.6

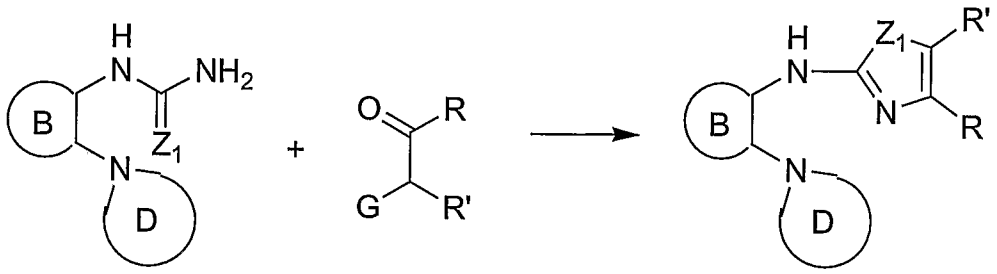


5.4

[00141] Scheme 6 describes the preparation of compounds of the present invention wherein A ring is either from functionalized intermediates of formula **6.1** wherein Z is a nitrogen or sulfur. Treatment of intermediate **6.1** with reagents such as α-haloketones or α-haloaldehydes, or equivalent reagents, in a solvent such as ethanol with or without a base such as 2,6-lutidine or NaOAc, at temperatures between 0 °C to 110 °C provides compounds of formula **6.3**. (Similar chemistry for Z = sulfur described in: Udapudi, V. T. et al. Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry **1986**, *25B(12)*, 1269-72. Singh, S. P.; *et.*

al. Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry **1985**, *24B(1)*, 119-23.)

Scheme 6

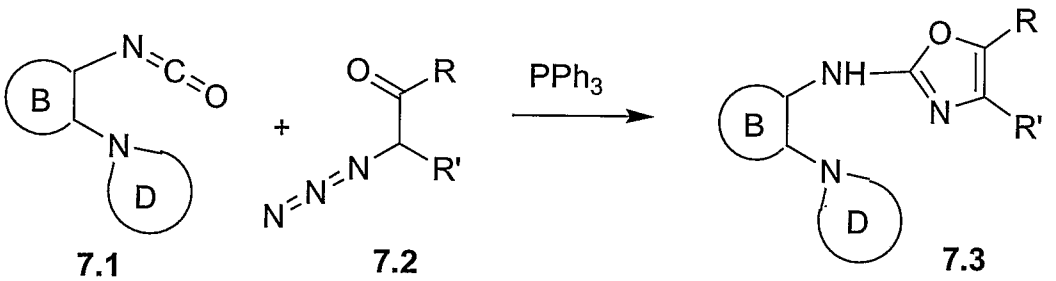


6.1 **6.2** **6.3**

for example Z_1 = S or NH, and G = halide, OTf, OMs

[00142] Scheme 7 describes the preparation of compounds of the present invention wherein A ring is a substituted oxazole from functionalized intermediates of formula **7.1**. Treatment of intermediate **7.1** with reagents such as α-azidoketones or α-azidoaldehydes, or equivalent reagent, and triphenylphosphine, or equivalent reagent, in a solvents such as toluene or DMF at temperatures between 0 °C to 150 °C provides compounds of formula **7.3**. α-Azidoketones and α-azidoaldehydes can be prepared by methods known to one skilled in the art of synthetic chemistry from the corresponding commercially available α-haloketones or α-haloaldehydes, or equivalent reagents.

Scheme 7

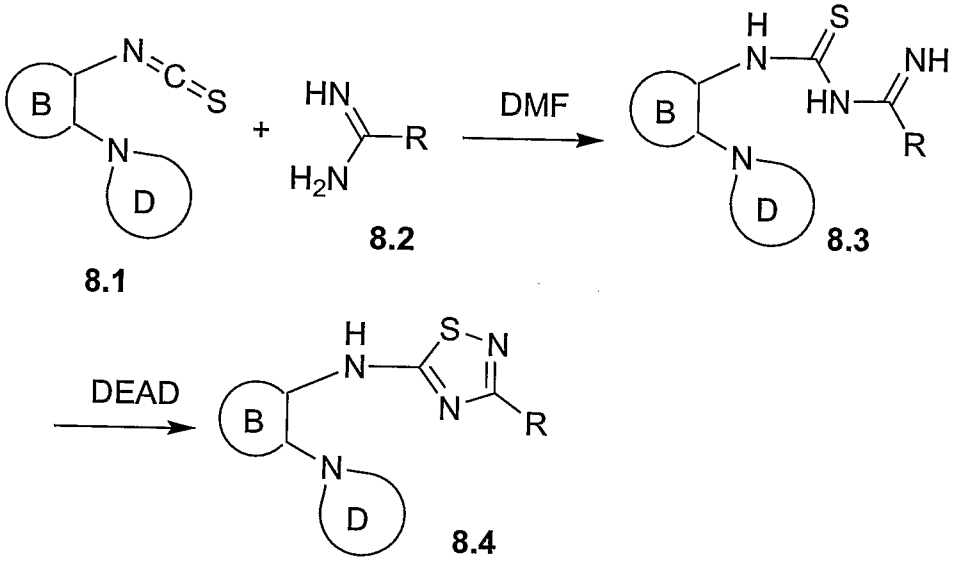


7.1 **7.2** **7.3**

[00143] Scheme 8 describes the preparation of compounds of the present invention wherein A ring is a substituted 1,2,4-thiadiazole from functionalized intermediates of formula **8.1**. Treatment of intermediate **8.1** with amidines of formula **8.2** in a solvent, such as dimethylformamide at temperatures between 70 °C to 120 °C

provide intermediates formula **8.3**. Treatment of intermediates of formula **8.3** with DEAD (M. Furukawa et al., *Synthesis*, **1990**, 1020-1023), or an equivalent reagent, in a solvent such as ethanol or acetonitrile, at temperatures between 0 °C to 70 °C provide compounds of formula **8.4**. Amidines **8.2** are commercially available or can be prepared by methods known to one skilled in the art of synthetic chemistry (such as described in M. Anbazhagan, D.W. Boykin, C. E. Stephens, *Synthesis*, **2003**, 2467-2469.)

Scheme 8

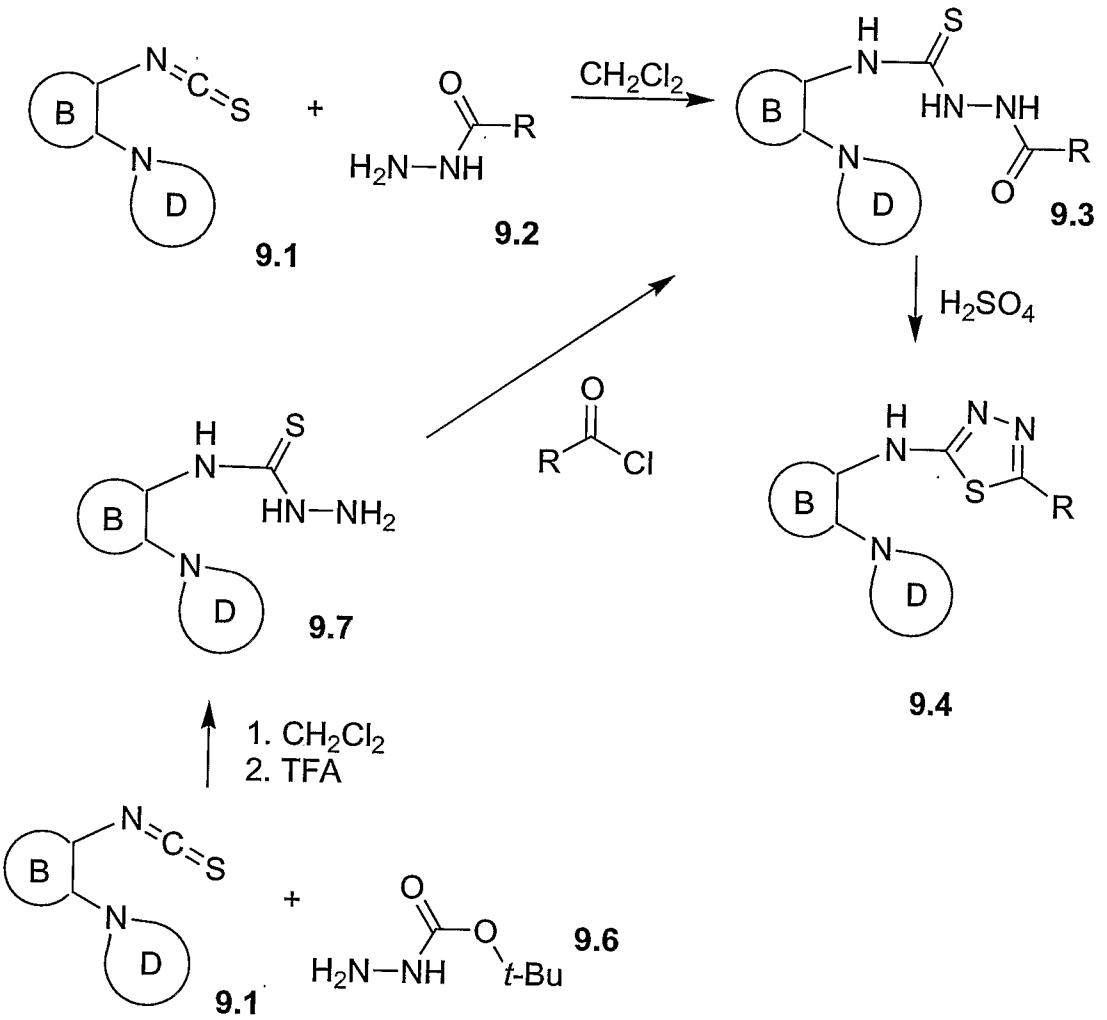


[00144] Scheme 9 describes the preparation of compounds of the present invention wherein A ring is a substituted 1,3,4-thiadiazole from functionalized intermediates of formula **9.1**. Treatment of thioisocyanate intermediate **9.1** with acylhydrazides of formula **9.2** in a solvent such as dichloromethane, at temperatures between 0 °C to 50 °C provide intermediates formula **9.3**. Treatment of intermediates of formula **9.3** with an acid, such as neat sulfuric acid or an equivalent reagent, at temperatures between 0 °C to 20 °C provide compounds of formula **9.4**. Acylhydrazides of formula **9.2** are commercially available or can be prepared from carboxylic acids, acyl chlorides or equivalent reagents by methods known to one skilled in the art of synthetic chemistry.

[00145] Alternately, compounds of formula **9.4** can be prepared by treatment of intermediate **9.1** with *tert*-butyl carbazate **9.6**, or an equivalent reagent, in a solvent, such as dichloromethane at temperature between 0 °C to 50 °C. Subsequent removal

of the tert-butoxycarbonyl with an acid such as TFA, in a solvent such as dichloromethane, provides intermediates of formula **9.7**. Treatment of intermediates of formula **9.7** with an acyl chloride, or similar suitably activated acylating reagent, in a solvent, such as tetrahydrofuran at temperatures between 0 °C to 50 °C provides intermediates of the formula **9.3**. Treatment of intermediates of formula **9.3** with an acid such as neat sulfuric acid, or an equivalent reagent such as trifluoroacetic acid, at temperatures between 0 °C to 20 °C provide compounds of formula **9.4**.

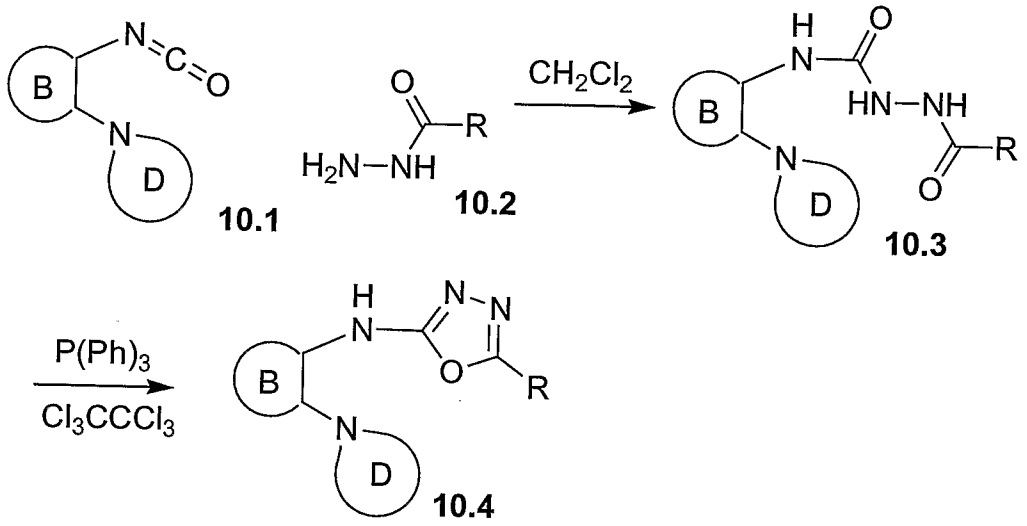
Scheme 9



[00146] Scheme 10 describes the preparation of compounds of the present invention wherein A ring is a substituted 1,3,4-oxadiazole from functionalized intermediates of formula **10.1**. Treatment of isocyanate intermediate **10.1** with acylhydrazides of formula **10.2** in a solvent, such as tetrahydrofuran at temperatures

between 20 °C to 65 °C provide intermediates formula **10.3**. Treatment of intermediates of formula **10.3** with triphenylphosphine, or an equivalent reagent, in a solvent, such as hexachloroethane, with a base, such as triethylamine, at temperatures between 0 °C to 50 °C provide compounds of formula **10.4**. Acyl hydrazides of formula **10.2** are commercially available or can be prepared from carboxylic acids, acyl chlorides or equivalent reagents by methods known to one skilled in the art of synthetic chemistry.

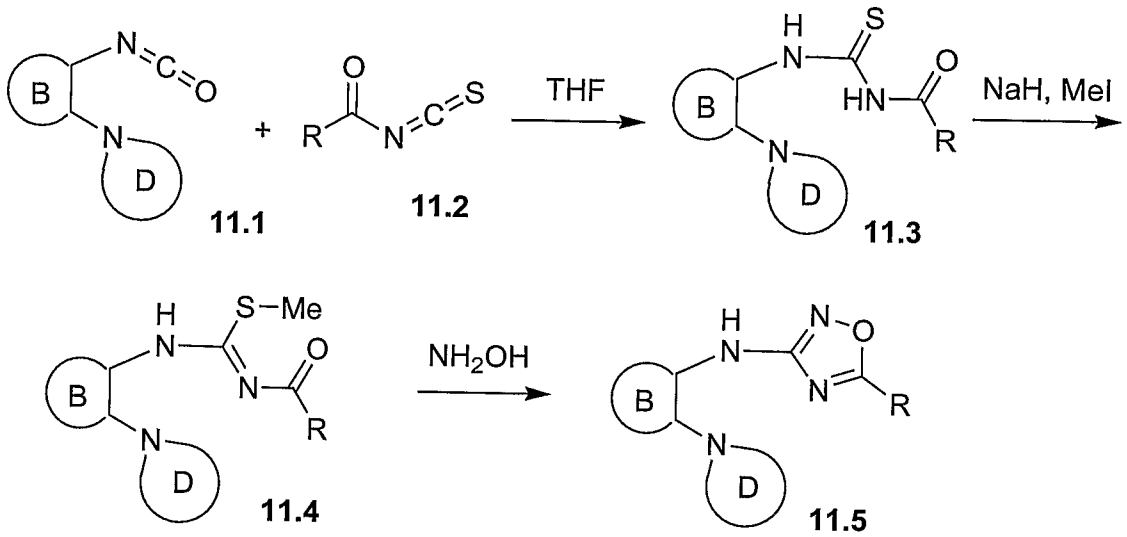
Scheme 10



[00147] Scheme 11 describes the preparation of compounds of the present invention wherein A ring is a substituted 1,2,4-oxadiazole from functionalized intermediates of formula **11.1**. Treatment of intermediates of formula **11.1** with acyl isothiocyanates of formula **11.2** in a solvent, such as tetrahydrofuran, at temperatures between -78 °C to 70 °C provides intermediates of formula **11.3**. Treatment of intermediates of formula **11.4** with a base, such as sodium hydride, followed by treatment with an alkylating agent, such as methyliodide, in a solvent, such as THF, at temperatures between -78 °C to 70 °C provides intermediates of formula **11.4**. Treatment of intermediates of formula **11.4** with hydroxylamine in a solvent such as, for example, THF at temperatures between -78 °C to 20 °C provides compounds of formula **11.5** (T.G.M. Dhar et al. Bioorg. Med. Chem. Lett. 2002, 12, 3125). Acyl isothiocyanates of formula **11.2** are commercially available or can be prepared from

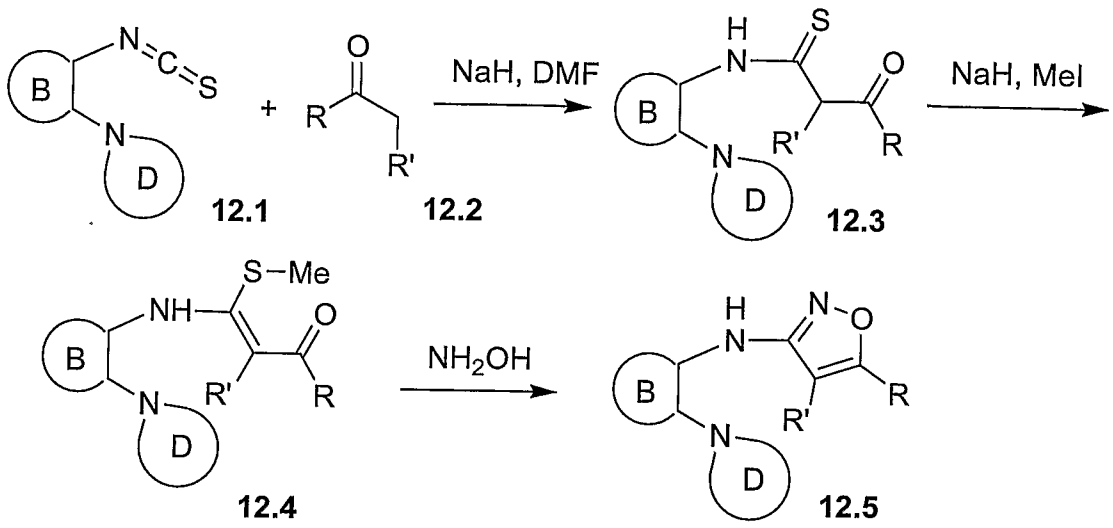
carboxylic acids, acyl chlorides or equivalent reagents by methods known to one skilled in the art of synthetic chemistry.

Scheme 11



[00148] Scheme 12 describes the preparation of compounds of the present invention wherein A ring is a substituted isoxazole, from functionalized intermediates of formula **12.1**. Treatment ketones or aldehydes of formula **12.2** with a base such as sodium hydride, in a solvent such as dimethylformamide, at temperatures between -78 °C to 20 °C with subsequent addition of isothiocyanate intermediates of formula **12.1** provide intermediates of formula **12.3**. Treatment of intermediates of formula **12.3** with a base such as sodium hydride, followed by treatment with an alkylating agent such as methyl iodide, in a solvent such as THF, at temperatures between -78 °C to 70 °C provides intermediates of formula **12.4**. Treatment of intermediates of formula **12.4** with hydroxylamine in a solvent, such as dimethylformamide, at temperatures between -78 °C to 70 °C provides compounds of formula **12.5**. Ketones and aldehydes of formula **12.2** are commercially available or can be prepared from carboxylic acids, acyl chlorides, alcohols or equivalent reagents by methods known to one skilled in the art of synthetic chemistry.

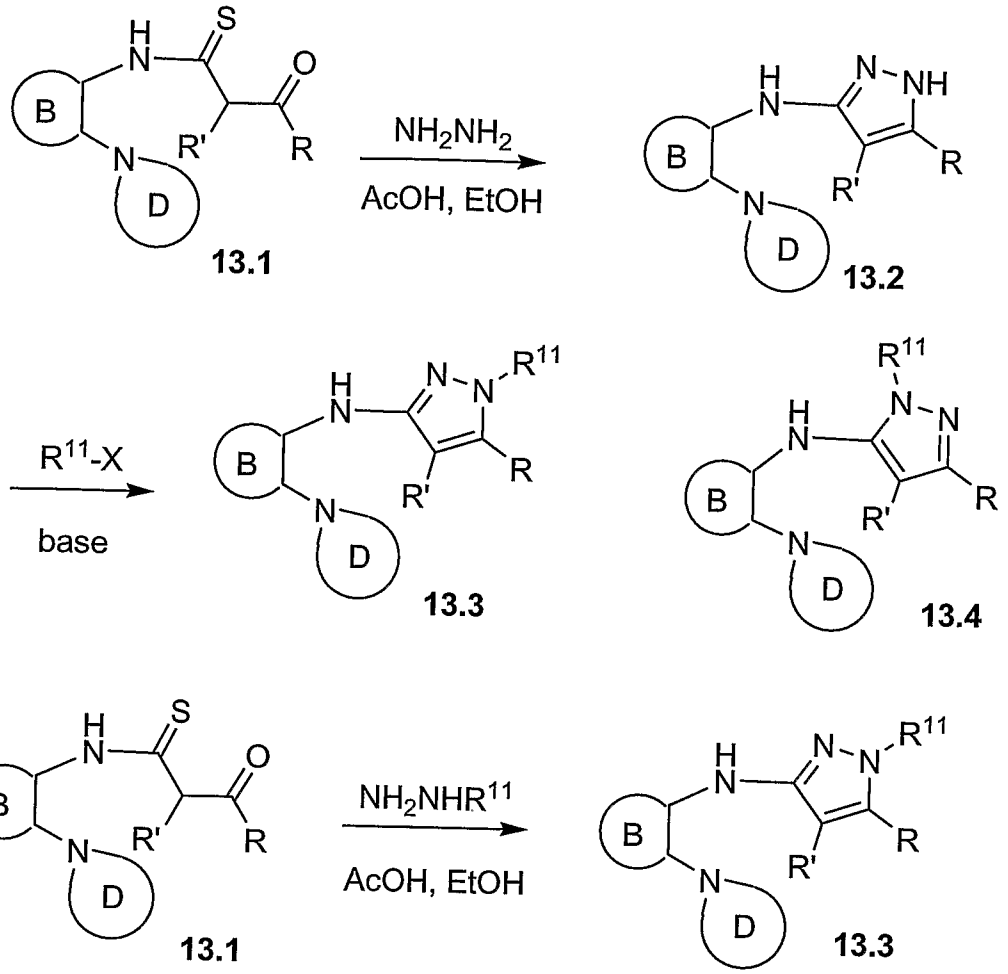
Scheme 12



[00149] Scheme 13 describes the preparation of compounds of the present invention wherein A ring is a substituted pyrazole, from functionalized intermediates of formula **13.1** (intermediate **12.3** as described previously). Treatment of intermediates of formula **13.1** with hydrazine, or an equivalent reagent, in the presence of an acid such as acetic acid, in a solvent such as ethanol, at temperatures between 20 °C to 70 °C provides compounds of formula **13.2**. Treatment of **13.2** with a base such as LDA or NaH followed by addition of an alkylating reagent in a solvent such as tetrahydrofuran, dioxane or dimethyformamide provide compounds of formula **13.3** and **13.4**.

[00150] Alternately, treatment of intermediate **13.1** with reagents such as alkyl-, aryl- or heteroaryl-substituted hydrazines in the presence of an acid such as acetic acid, in a solvent such as ethanol, provides compounds of formula **13.3**.

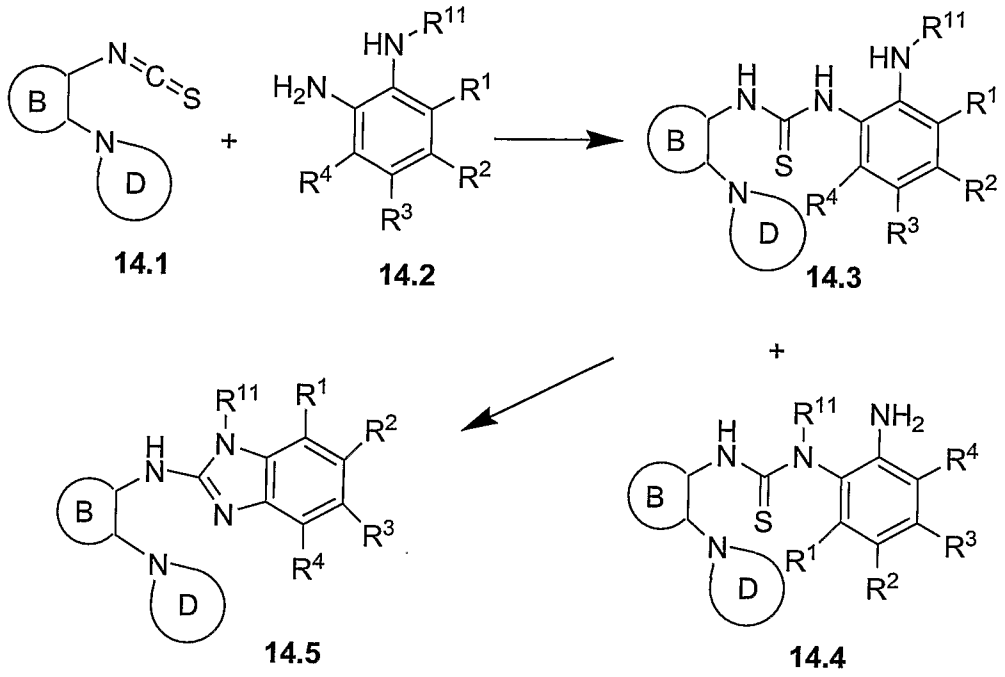
Scheme 13



[00151] Scheme 14 describes the preparation of compounds of the present invention wherein A ring is a substituted benzimidazole, from the key isothiocyanate intermediate **14.1**. 2-Amino substituted anilines are commercially available or can readily be prepared from commercially available materials by methods known to one skilled in the art of organic synthesis. Reaction of the thioisocyanate **14.1** with 1-amino substituted aniline **14.2** typically occurs at temperatures between 20 °C and 60 °C in a variety of solvents such as tetrahydrofuran, ethanol, dichloroethane or dioxane. The reaction leads to two isomeric thioureas **14.3** and **14.4**, which can both be reacted subsequently to produce a single isomer of a benzimidazole **14.5**. Transformation of the thiourea to an imidazole can be achieved with carbodiimide reagents at rt in an organic solvent such as dichloromethane, dichloroethane or dimethylformamide. Suitable carbodiimide reagents include EDC, DCC, or DIC. Alternative methods to convert **14.4** to **14.5** include treating **14.4** with yellow

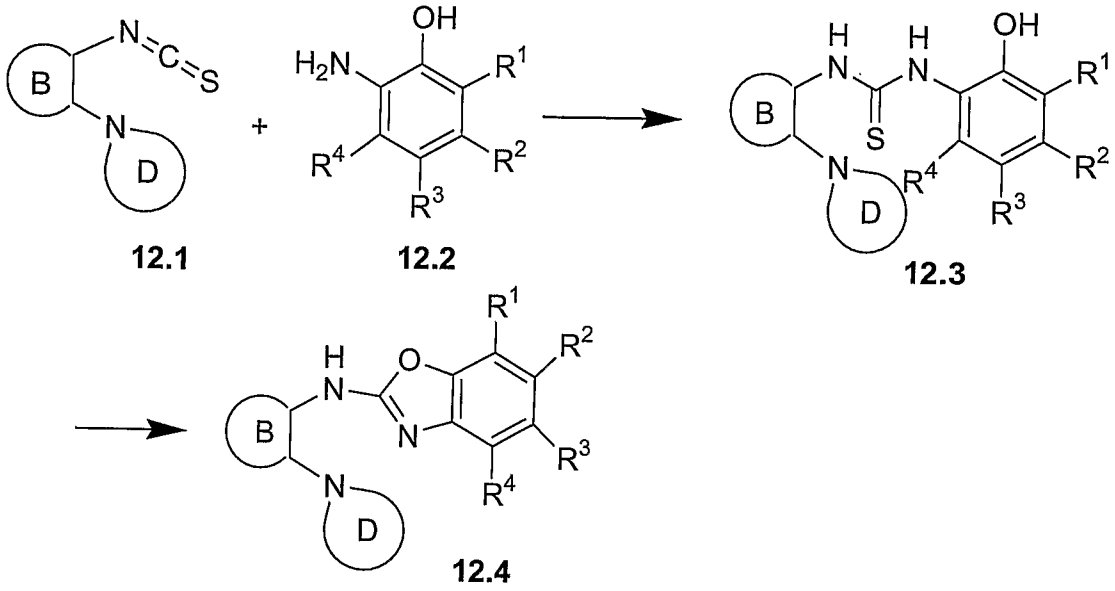
mercuric oxide and sulfur in boiling ethanol or treating **14.4** with methyl iodide in ethanol.

Scheme 14



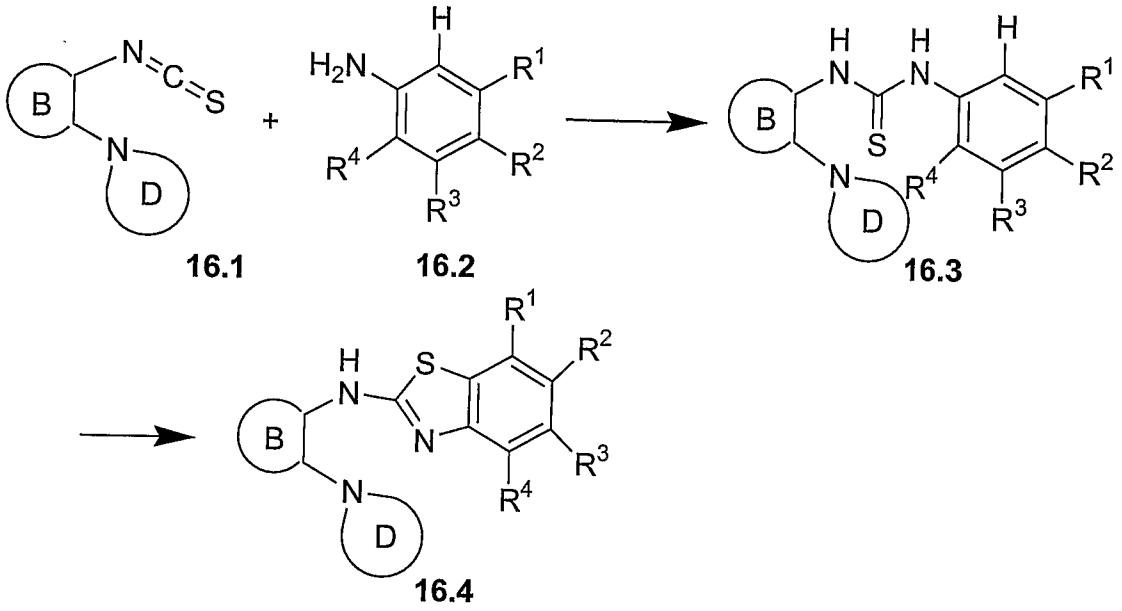
[00152] Scheme 15 describes preparation of compounds of the present invention wherein A ring is a substituted benzoxazole from the key isothiocyanate intermediate **15.1**. 2-Amino substituted phenols are commercially available or can readily be prepared from commercially available materials by methods known to one skilled in the art of organic synthesis. Reaction of the thioisocyanate **15.1** with 1-amino substituted aniline **15.2** typically occurs at temperatures between 20 °C and 60 °C in a variety of solvents such as tetrahydrofuran, ethanol, dichloroethane, or dioxane. The reaction leads to a thiourea **15.3**, which can be reacted subsequently to produce a benzoxazole **15.4**. Transformation of the thiourea to the benzoxazole can be achieved with carbodiimide reagents at rt in an organic solvent such as dichloromethane, dichloroethane, or dimethylformamide. Suitable carbodiimide reagents include EDC, DCC, or DIC. Alternative methods to convert **15.3** to **15.4** include treating **15.3** with mercuric oxide in methanol or treating **15.3** with methyl iodide in ethanol.

Scheme 15



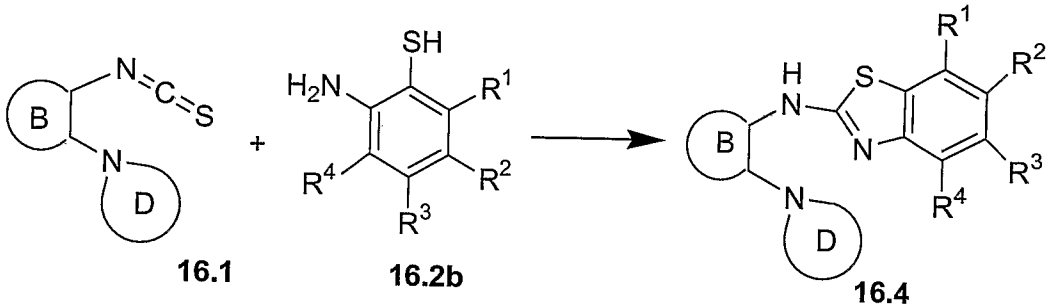
[00153] Scheme 16-a describes preparation of compounds of the present invention wherein A ring is a substituted benzothiazole from the key isothiocyanate intermediate **16.1**. Substituted anilines such as **16.2** are commercially available or can readily be prepared by methods known to one skilled in the art of organic synthesis from commercially available materials. Reaction of the thioisocyanate **16.1** with the substituted aniline **16.2** typically occurs at temperatures between 20 °C and 60 °C in a variety of solvents such as tetrahydrofuran, ethanol, dichloroethane or dioxane. The reaction leads to a thiourea **16.3**, which can be reacted subsequently to produce a benzothiaole **16.4**. Transformation of the thiourea to the benzothiazole can be achieved by treatment with neat thionyl chloride, or by treatment with bromine in a solvent such as acetic acid or chloroform.

Scheme 16-a



[00154] An alternative method for the preparation of compounds of the present invention wherein A ring is a substituted benzothiazole is outlined in Scheme 16-b. The key isothiocyanate intermediate **16.1** can be reacted with 2-amino substituted thiophenols **16.2b** which are commercially available or can readily be prepared from commercially available materials by methods known to one skilled in the art of organic synthesis. Reaction of the thioisocyanate **16.1** with 2-amino substituted thiophenols **16.2b** typically occurs at temperatures between 20 °C and 160 °C in different reaction-inert solvents such as tetrahydrofuran, pyridine, 1-methyl-2-pyrrolidinone.

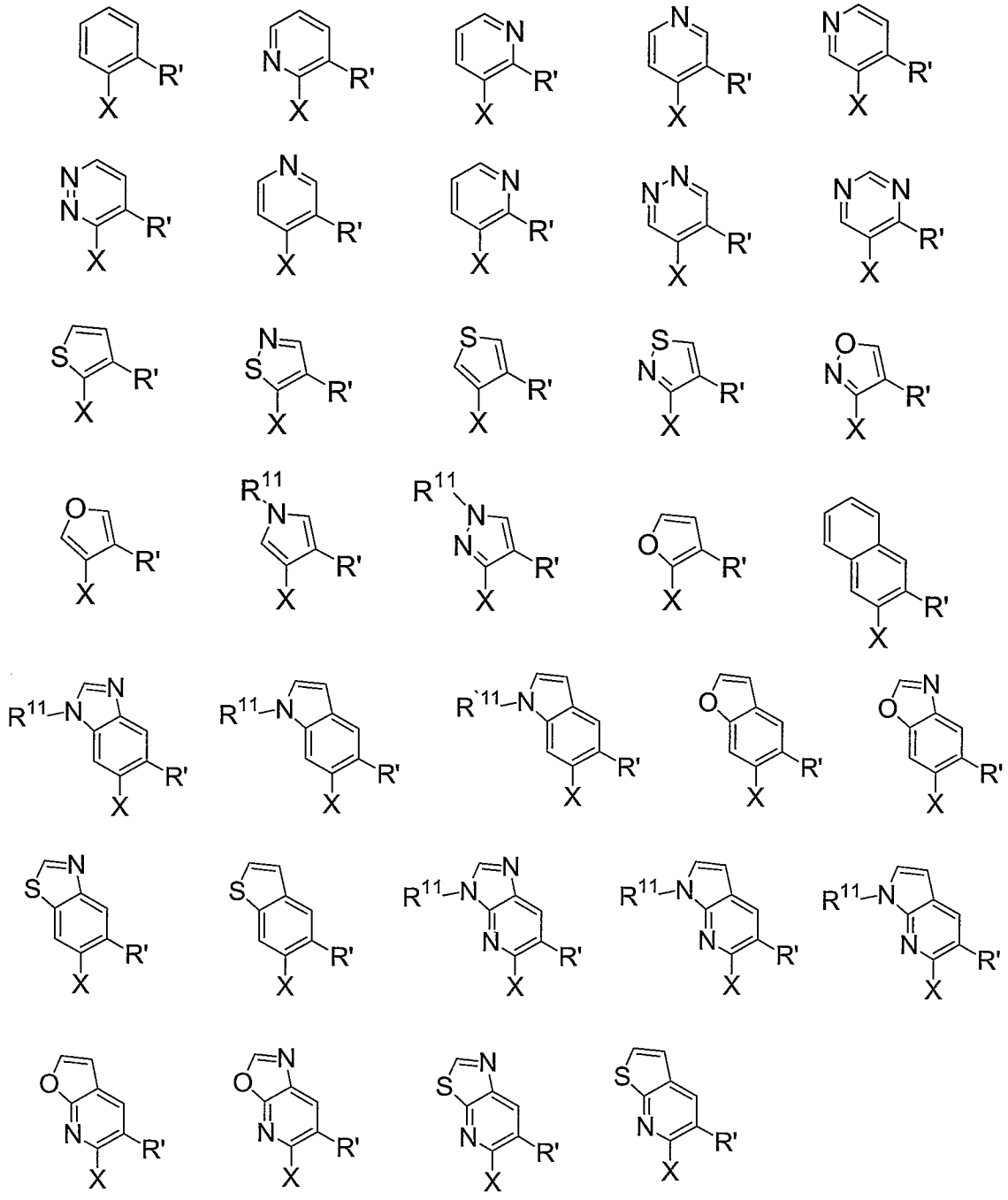
Scheme 16-b



[00155] Scheme 17 illustrates some of the monocyclic/heterocyclic B halo-aryl, halo-heteroaryl intermediates that can be used to prepare compounds of the present

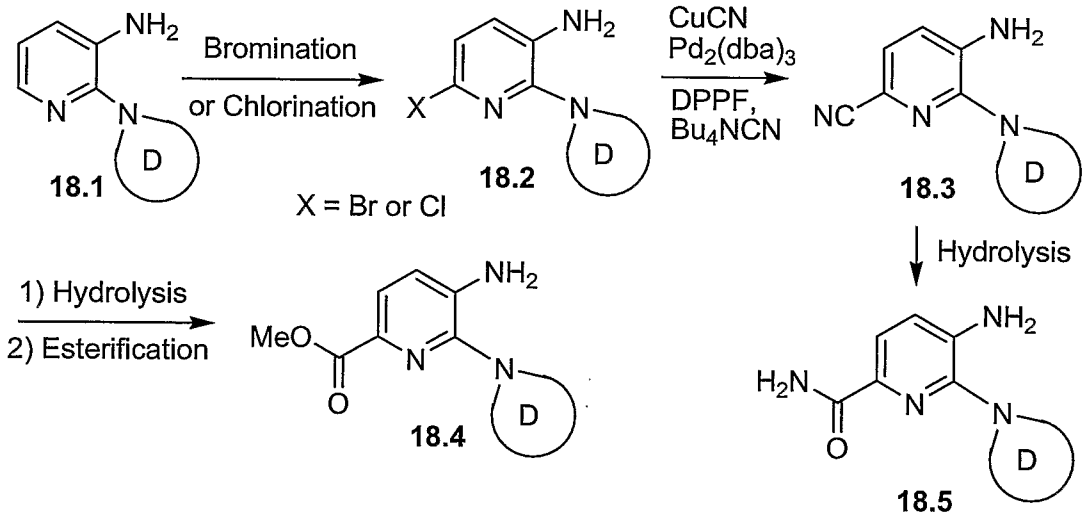
invention. Ring B is optionally substituted. These intermediates are either commercially available or can be prepared using methods known to those skilled in the art of organic synthesis. R' is NO_2 or N-PG, PG is protecting group, and X is halogen.

Scheme 17



[00156] Preparation of substituted pyridine amines such as **18.2**, **18.3**, **18.4**, or **18.5** is shown in Scheme 18. The pyridine aniline **18.1** prepared as described in Scheme 4 can be brominated or chlorinated using agents such as N-bromosuccinimide or N-chlorosuccinimide in an organic solvent such as DMF. The resulting aromatic bromide can be converted to the corresponding nitrile by metal catalyzed cyanation. For example, reaction of the bromide **18.2** (X=Br) with copper (I) cyanide, tris-(dibenzylideneaceteone)-bispalladium, diphenylphosphine ferrocene, and tetrabutylammonium cyanide affords the corresponding nitrile **18.3**. The resulting nitrile can be hydrolyzed to the corresponding carboxylic acid using methods known in the art of organic synthesis such as treatment with aqueous sodium hydroxide. Conversion of the corresponding carboxylic acid to the methyl ester can be accomplished by treatment with trimethylsilyl diazomethane or with hydrochloric acid in methanol. Alternatively, the nitrile **18.3** can be converted to the corresponding ester **18.4** and amide **18.5** by acidic or basic hydrolysis.

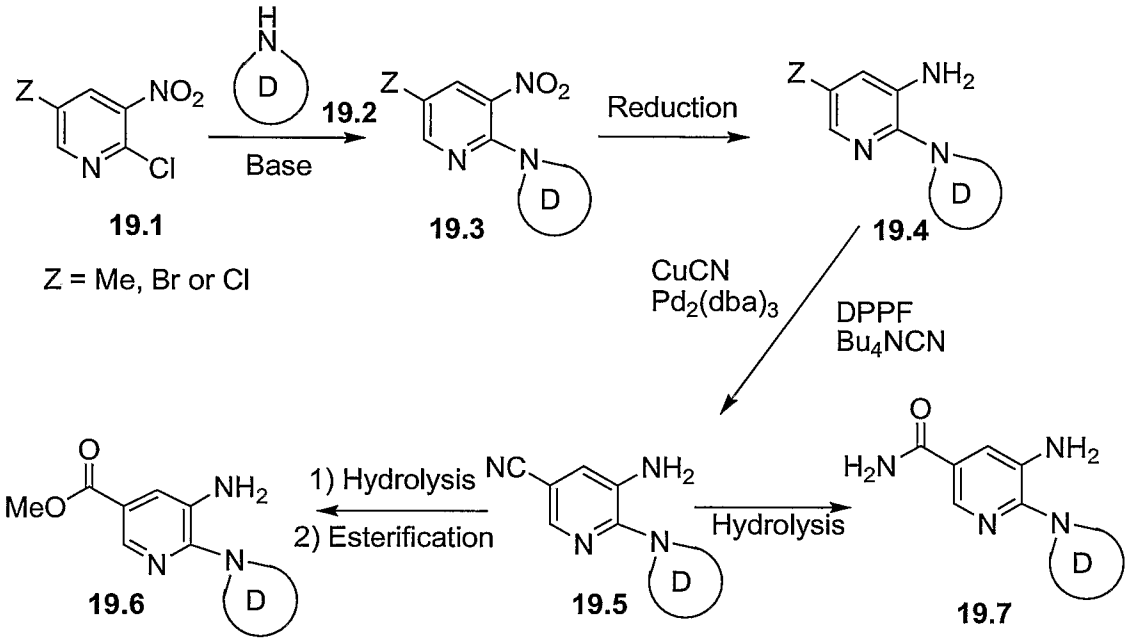
Scheme 18



[00157] Preparation of substituted pyridine amines such as **19.4**, **19.5**, **19.5** or **19.7** is shown in Scheme 19. The nitrochloro pyridine **19.1** can be prepared as described above for Scheme 4. The resulting aromatic bromide can be converted to the corresponding nitrile by metal catalyzed cyanation. For example, reaction of the bromide **19.4** (X = Br) with copper (I) cyanide, tris-(dibenzylideneaceteone)-bispalladium, diphenylphosphine ferrocene, and tetrabutylammonium cyanide affords the corresponding nitrile **19.5**. The resulting nitrile can be hydrolyzed to the

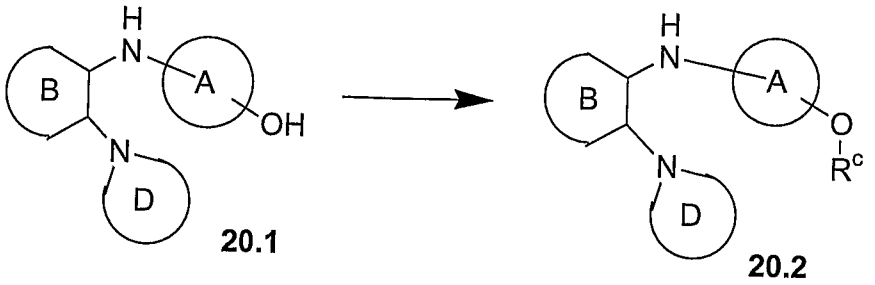
corresponding carboxylic acid using methods known in the art of organic synthesis such as treatment with aqueous sodium hydroxide. Conversion of the corresponding carboxylic acid to the methyl ester **19.6** can be accomplished by treatment with trimethylsilyl diazomethane or with hydrochloric acid in methanol. Alternatively, the nitrile **19.5** can be converted to the corresponding amide **19.7** by acidic or basic hydrolysis.

Scheme 19



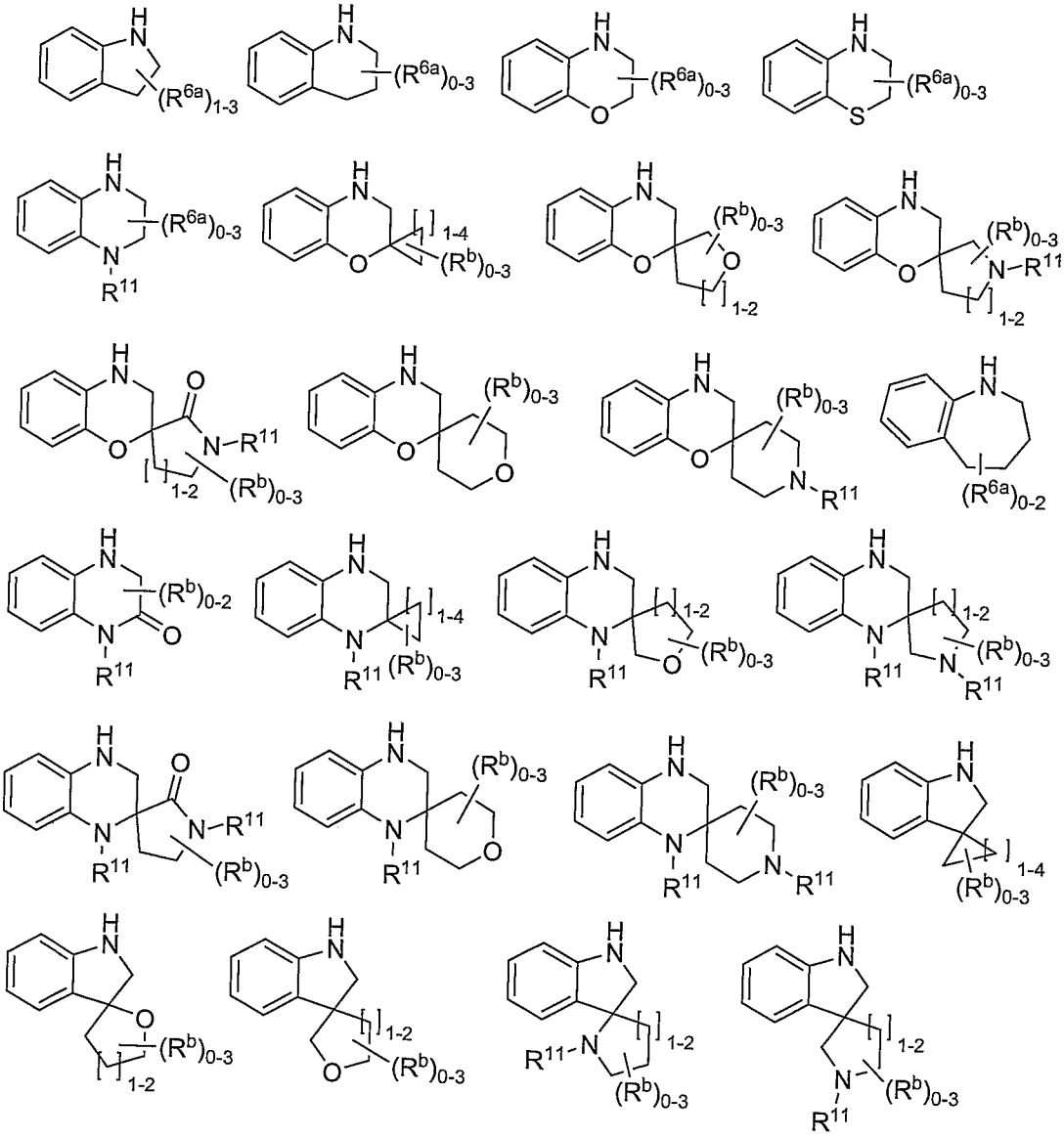
[00158] Scheme 20 describes further functionalization of urea **20.1** to form **20.2** by alkylation with alcohols via Mitsunobu chemistry or by direct reaction with alkyl halides. Ring B and ring D are optionally substituted. The preferred conditions for the alkylation of such phenols involve treatment with an excess of a primary or secondary alcohol in the presence of an azodicarboxylate equivalent such as diethyl, diisopropyl, or di-*tert*-butyl azodicarboxylate and in the presence of triphenylphosphine or polystyrene bound triphenylphosphine. The reactions can be run in solvents such as tetrahydrofuran, toluene, or dichloromethane and from 0 °C to 50 °C.

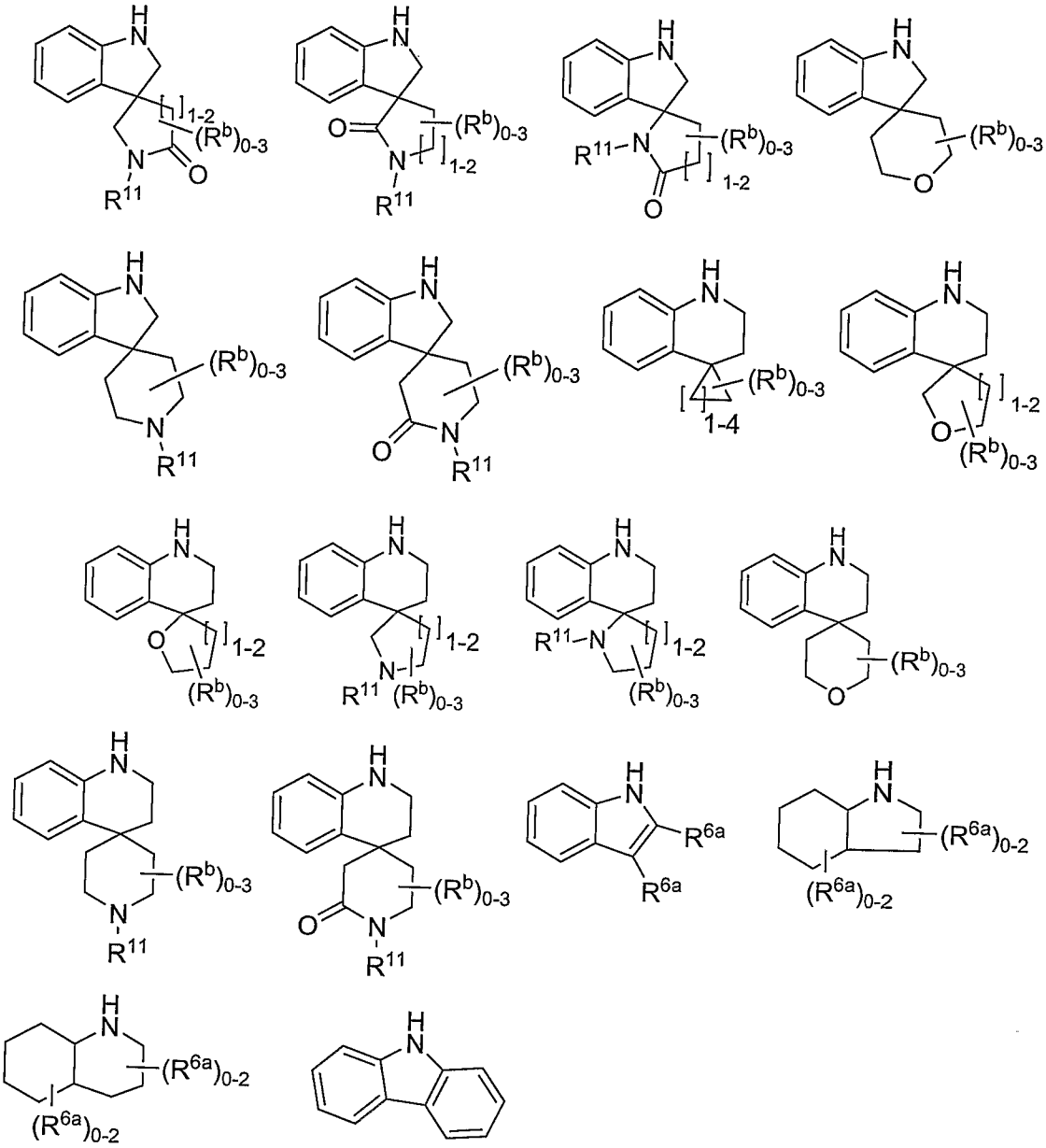
Scheme 20



[00159] Scheme 21 illustrates various NH-containing bicyclic **D** intermediates that can be used to prepare compounds of the present invention. The phenyl ring in each of the structures listed below is optionally substituted.

Scheme 21

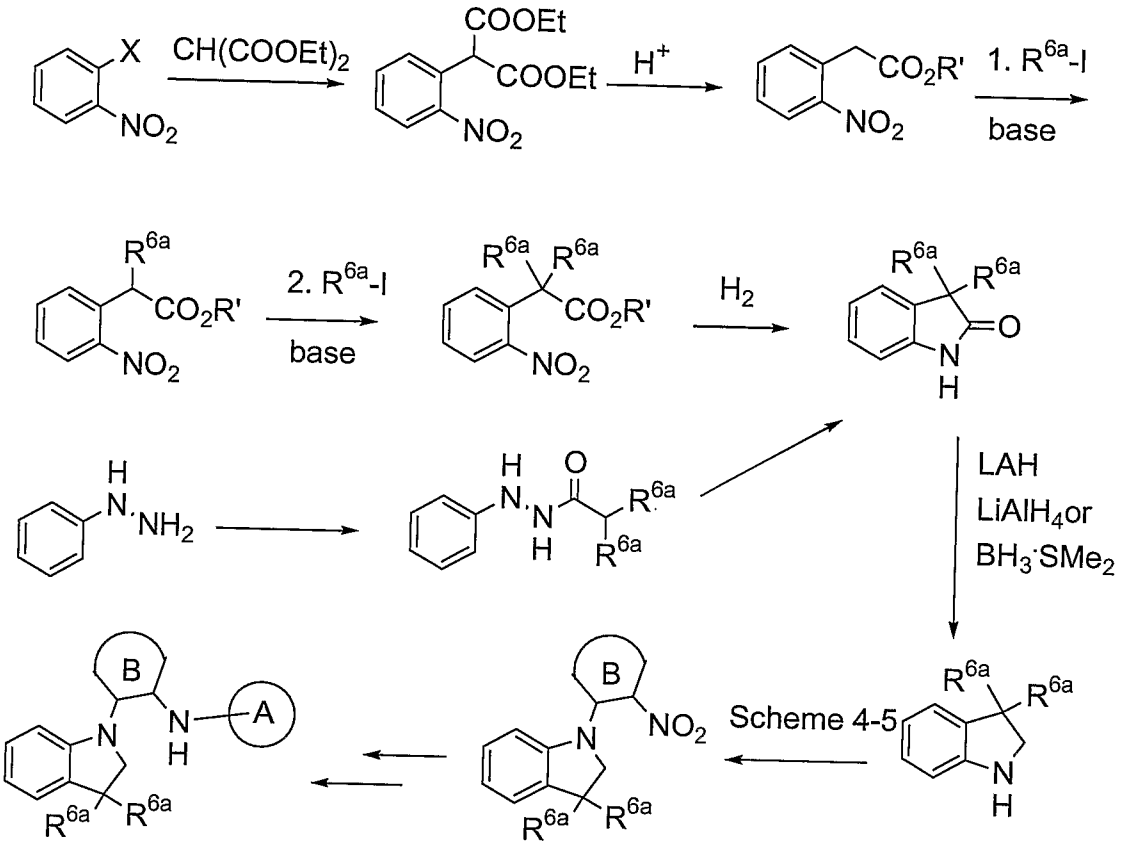




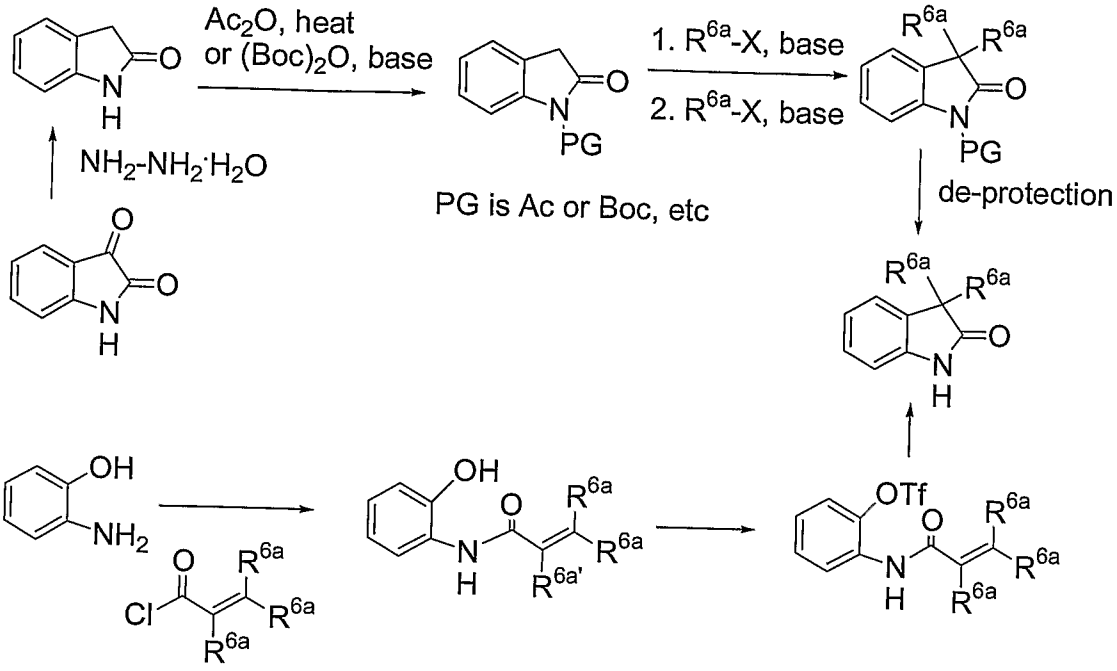
[00160] Compounds of the present invention wherein ring D is a NH-containing bicycle can be prepared by using the following methods described in Schemes 22-29 and by using methods known to those skilled in the art of organic synthesis. When D is a substituted indoline derivative, it can be prepared by using the methods shown in Schemes 22-24 and by using methods known to those skilled in the art of organic synthesis. When D is a substituted tetrahydroquinoline derivative, it can be prepared by using the methods shown in Scheme 25 and by using methods known to those skilled in the art of organic synthesis. When D is a substituted 3,4-dihydro-2H-benzo[b][1,4]oxazine derivative or a substituted 3,4-dihydro-2H-benzo[b][1,4]thiazine derivative, it can be prepared by using the methods shown in

Scheme 26 and by using methods known to those skilled in the art of organic synthesis. When D is a substituted 1,2,3,4-tetrahydroquinoxaline derivative, it can be prepared by using the methods shown in Scheme 27 and by using methods known to those skilled in the art of organic synthesis. The phenyl ring in each of the structures shown below is optionally substituted.

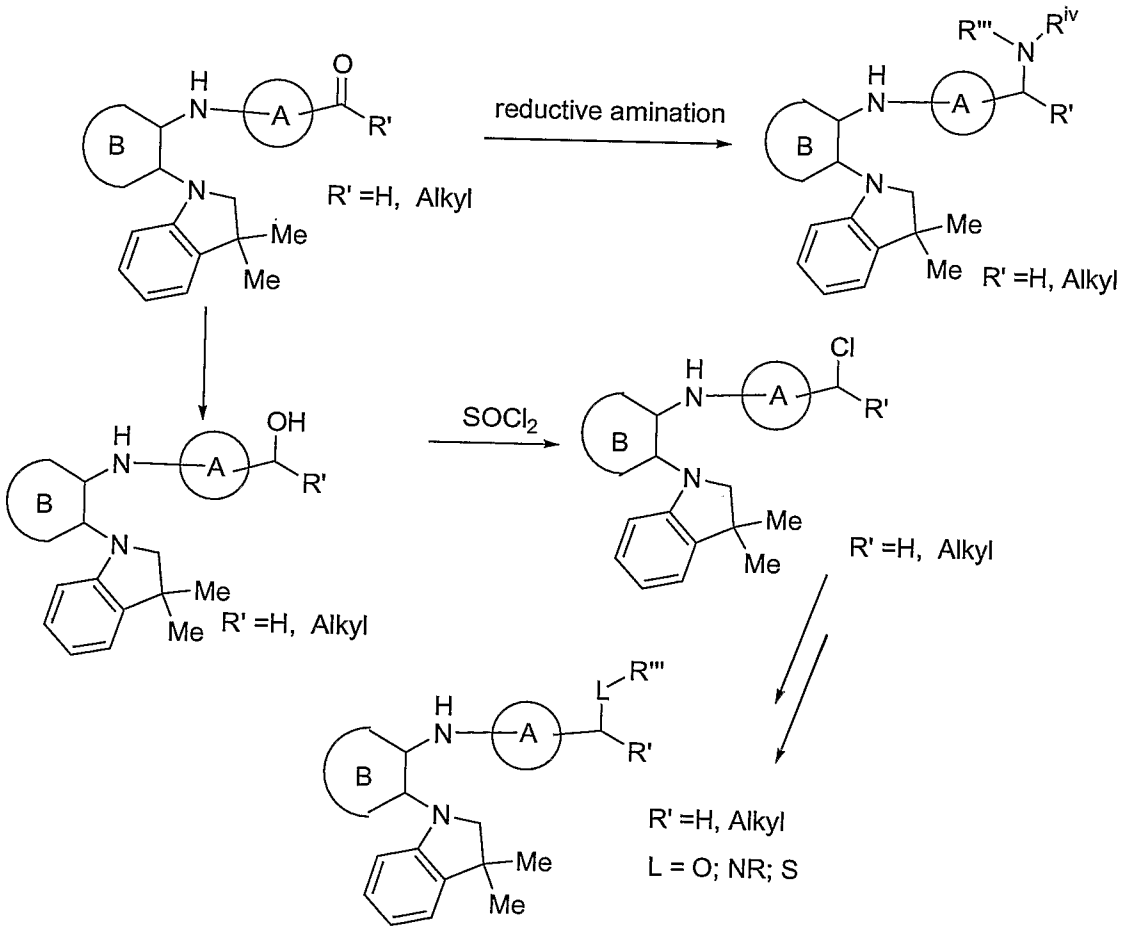
Scheme 22



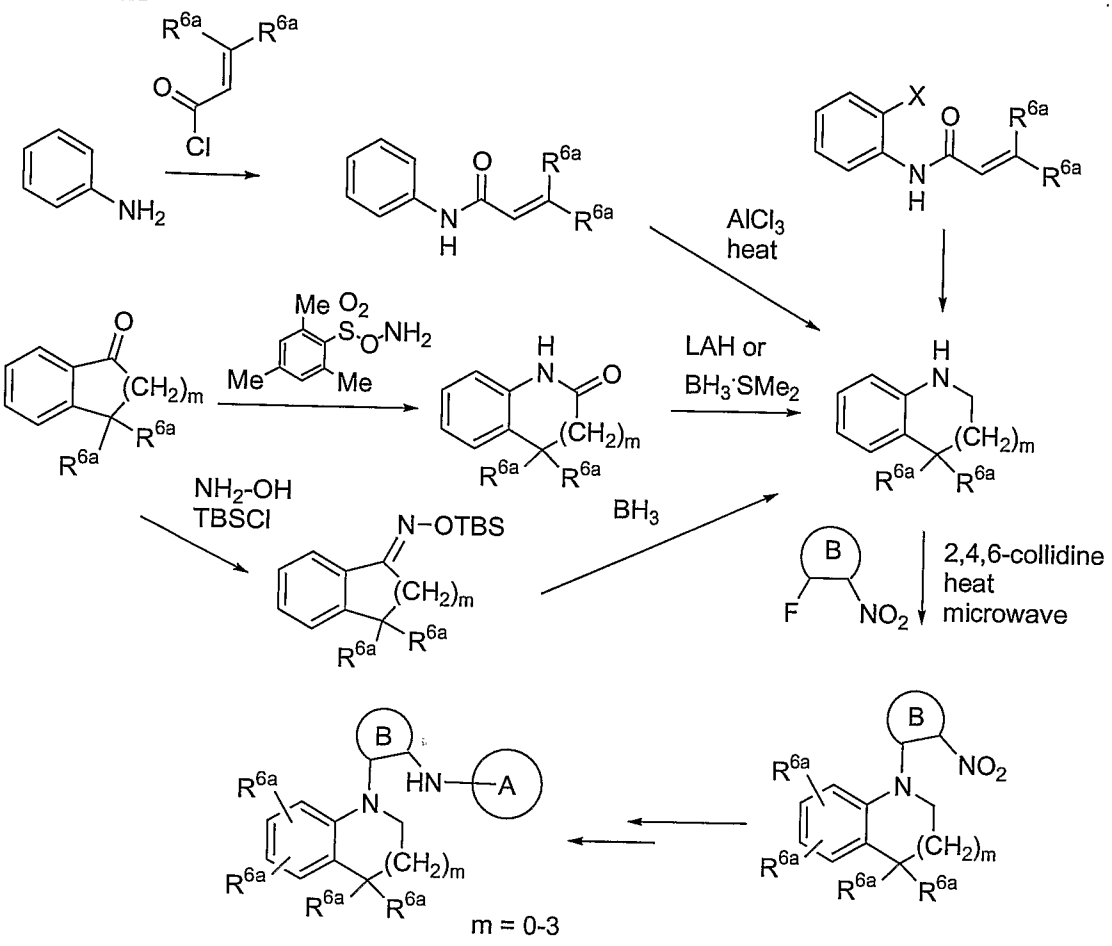
Scheme 23



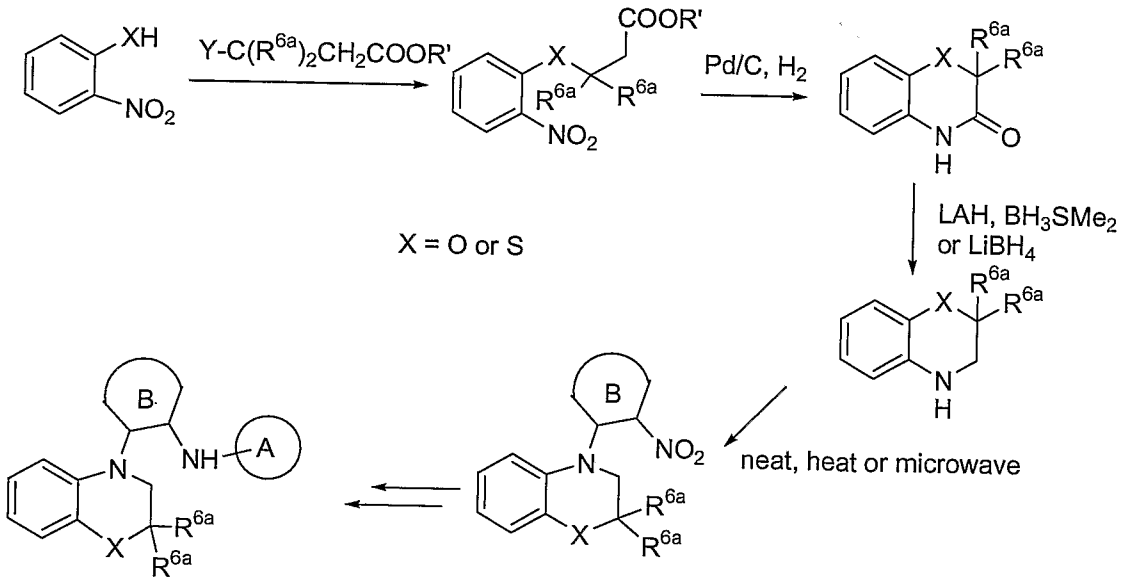
Scheme 24



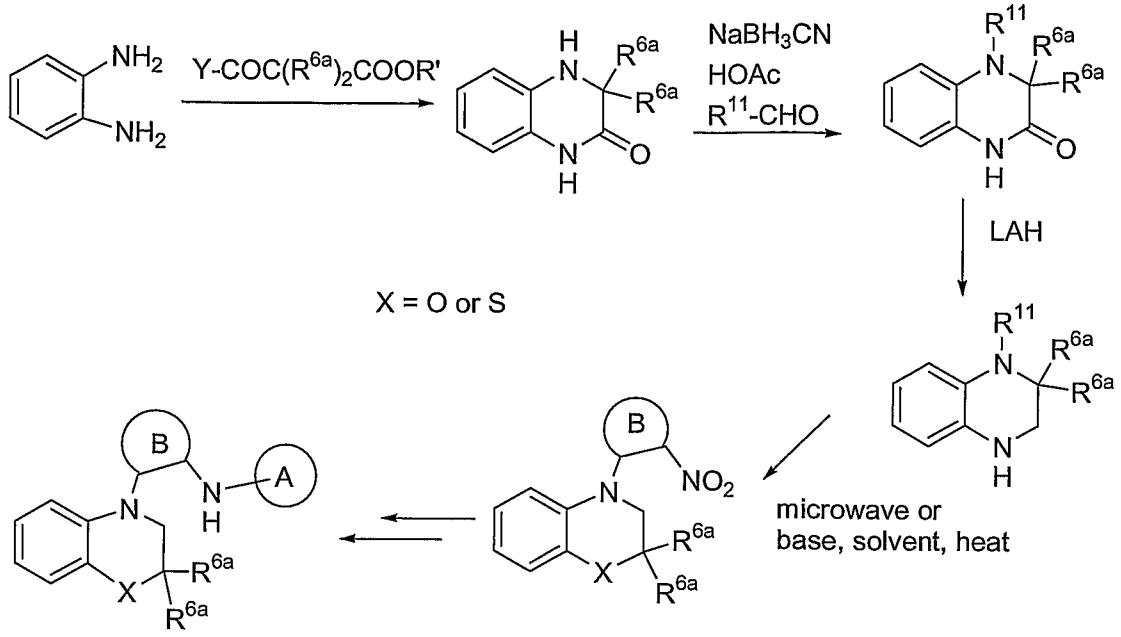
Scheme 25



Scheme 26

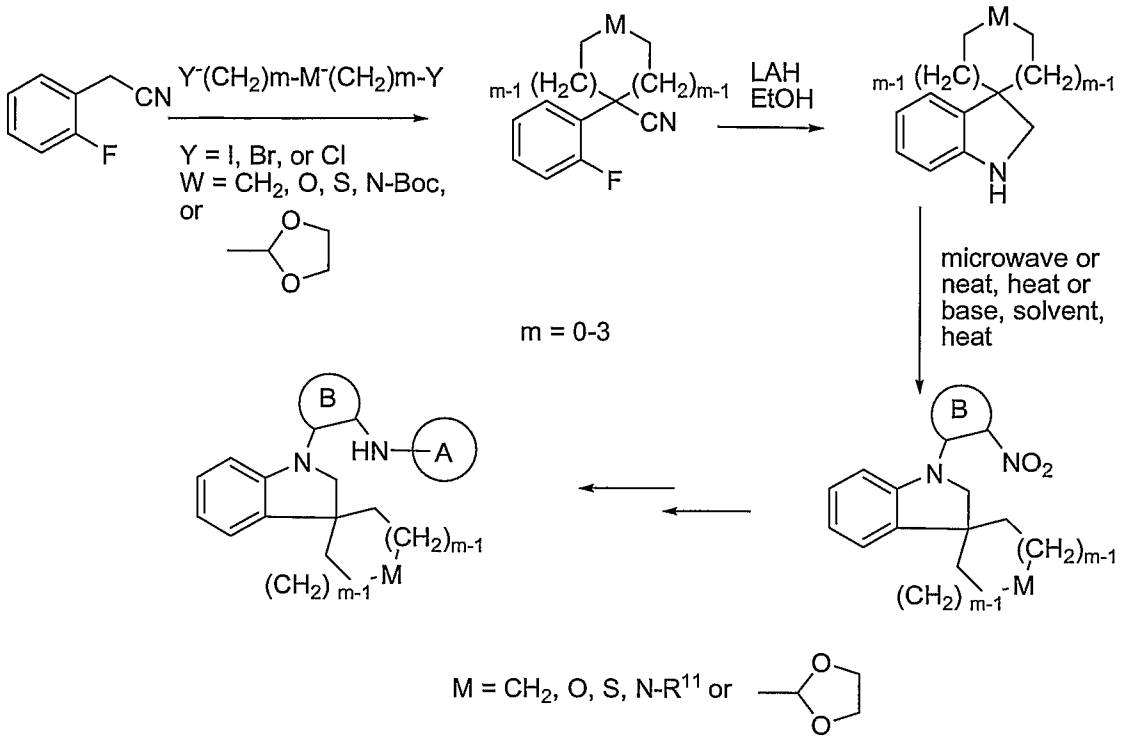


Scheme 27

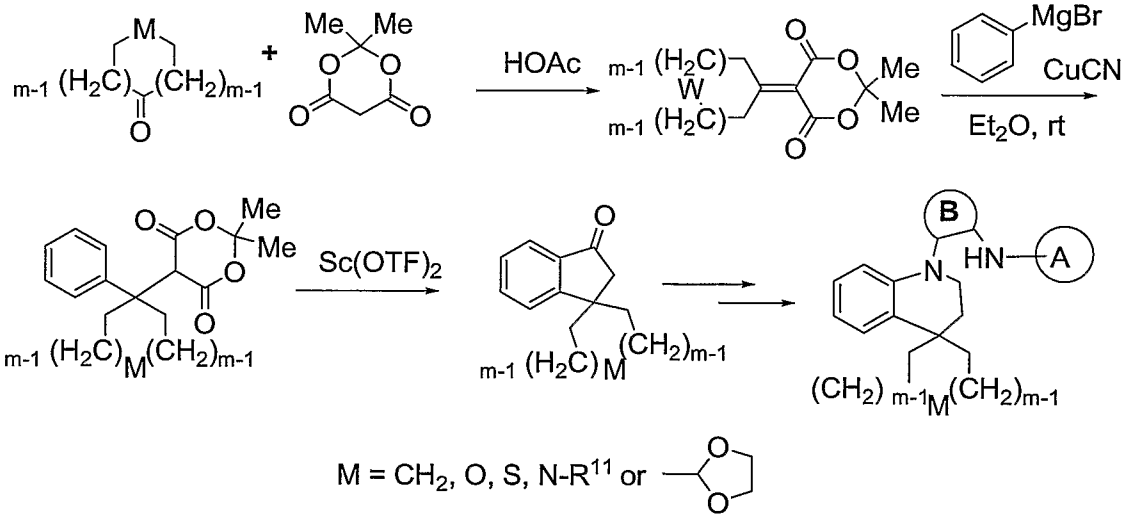


[00161] Compounds of the present invention when two R^{6a} groups are attached to the same carbon atom together with the carbon atom to which they are attached, they form a 3-7 membered carbocycle/heterocycle resulting in spiro NH-containing cyclic D. These spiro systems can be prepared by using methods known to those skilled in the art of organic synthesis and by using methods represented in Schemes 28 and 29.

Scheme 28



Scheme 29



[00162] An alternative synthesis of the compounds of the invention involves the metal catalyzed coupling of the aniline **4.4** with an aryl or heteroaryl halide or triflate (Scheme 30). A variety of examples of such couplings are provided the following articles and book: Muci, A. R. and Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131 and Hartwig, J. F. in *Modern Amination Methods*; Ricci, A., Ed., Wiley-VCH: Weinheim, Germany, **2000**. The metal catalyst is usually palladium or nickel

complexed with ligands such as a diphosphine or a ferrocene. Figure 2 provides a non exhaustive list of possible heteroaryl halide or triflate that can be used in the reaction.

Scheme 30

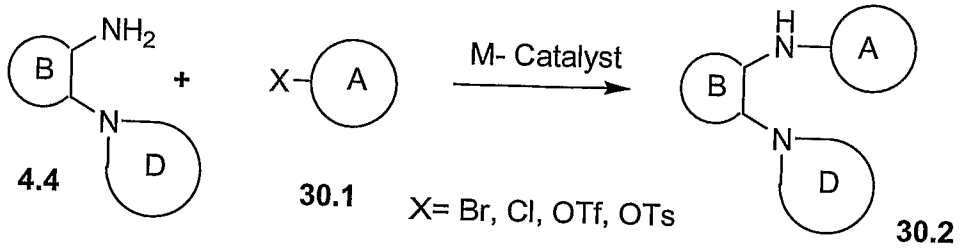
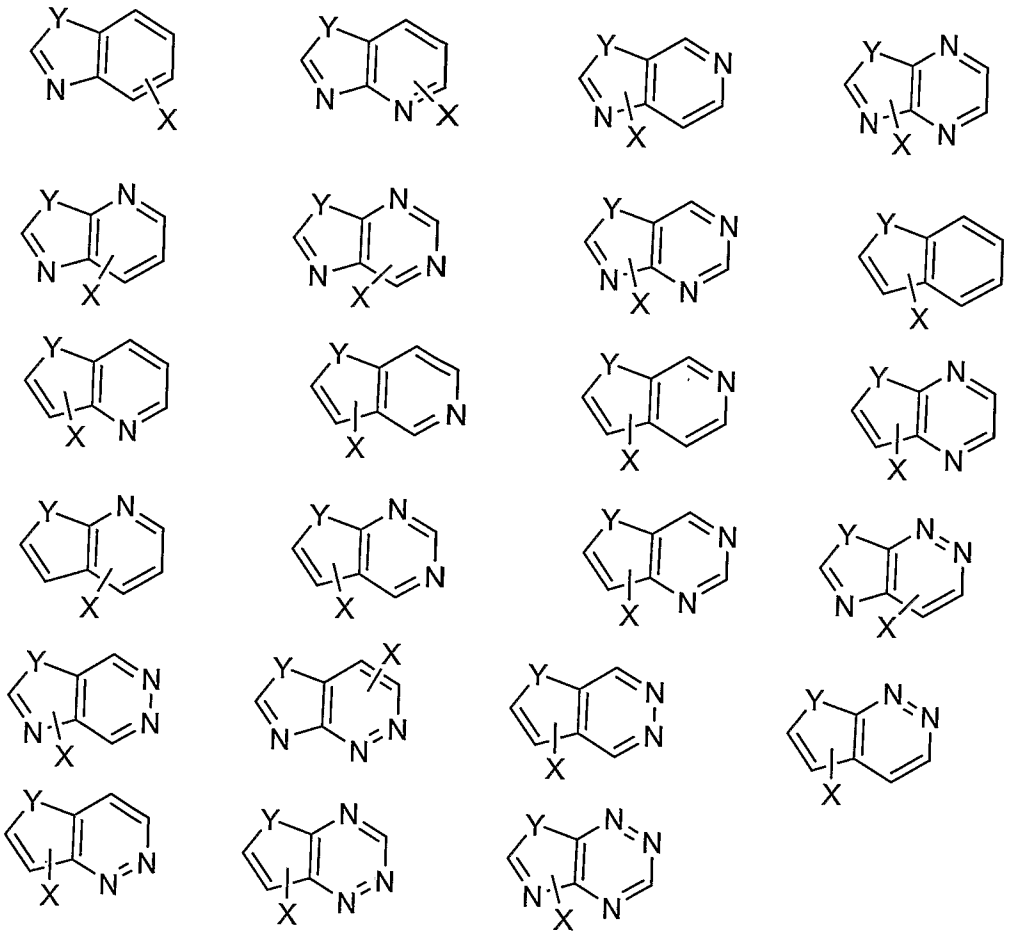


Figure 2



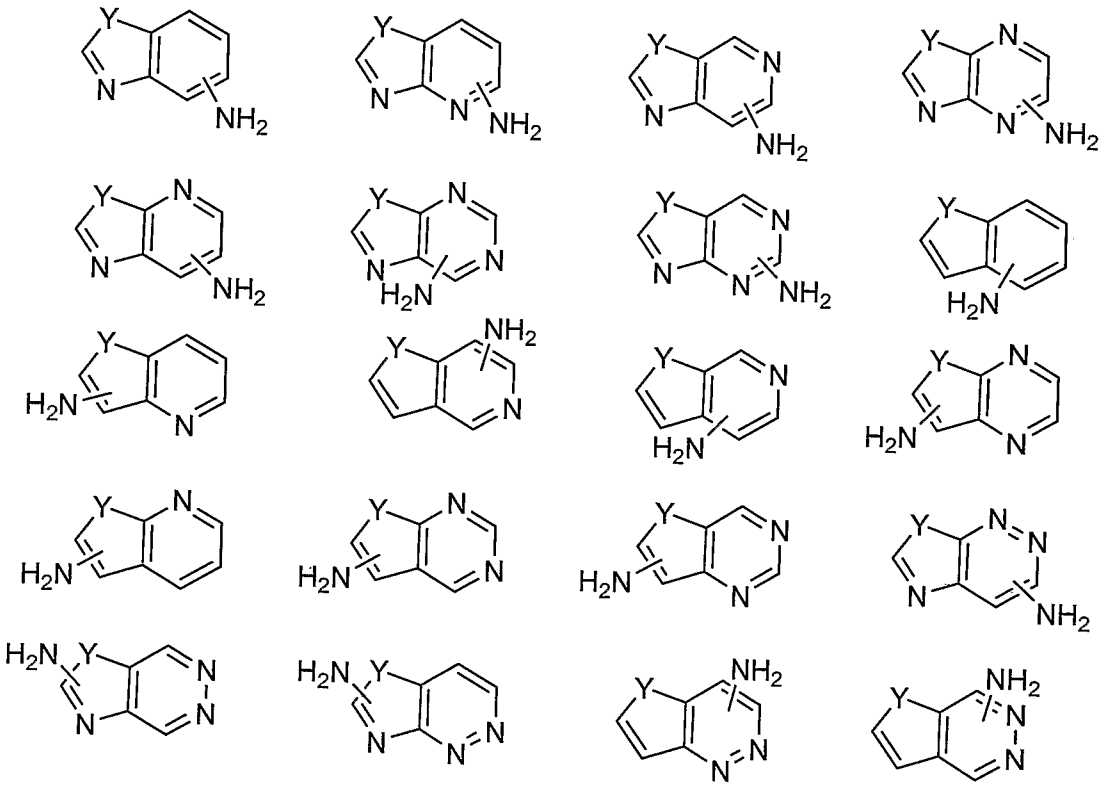
X= Br, Cl, OTf; Y= N, O, S; all the heteroaryls are optionally further substituted.

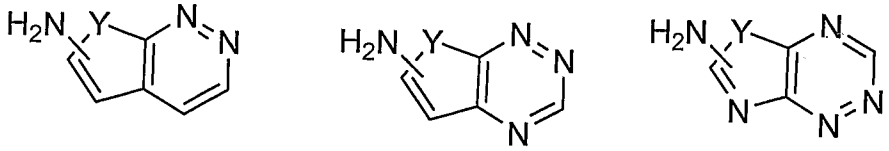
[00163] An alternative synthesis of the compounds of the invention involves the coupling of the boronic acid derivatives **31.3** (or boronate, borate) with,

commercially available or readily prepared by one skilled in the art, amino compounds **31.4** according to Scheme 31. Depending on the structure and substituents involved, the reaction is carried out with or without micro waves and molecular sieves, at temperatures between 0 °C and 200 °C in an appropriated organic solvent such as CH_2Cl_2, in the presence of a base such as pyridine or TEA. Figure 3 provides a non exhaustive list of possible aryl or heteroaryl amines that can be used in the reaction.

[00164] The title compounds can also be prepared by one of the methods described in articles for cooper-mediated C(aryl)-O; C(aryl)-N and C(aryl)-S bond formation by Lay, S. V. and Thomas, A. W. in *Angew. Chem. Int. Ed.* **2003**, *42*, 5400-5449 or Chan, D. M. and Lam, P. Y. S. in *Boronic Acids*, Ed Hall, D. G. p 205-240, Wiley-VCH **2005**. Alternatively other organometalloides such as siloxanes, stannanes or organobismuth reagents can be employed in place of boronic acid derivatives.

Figure 3

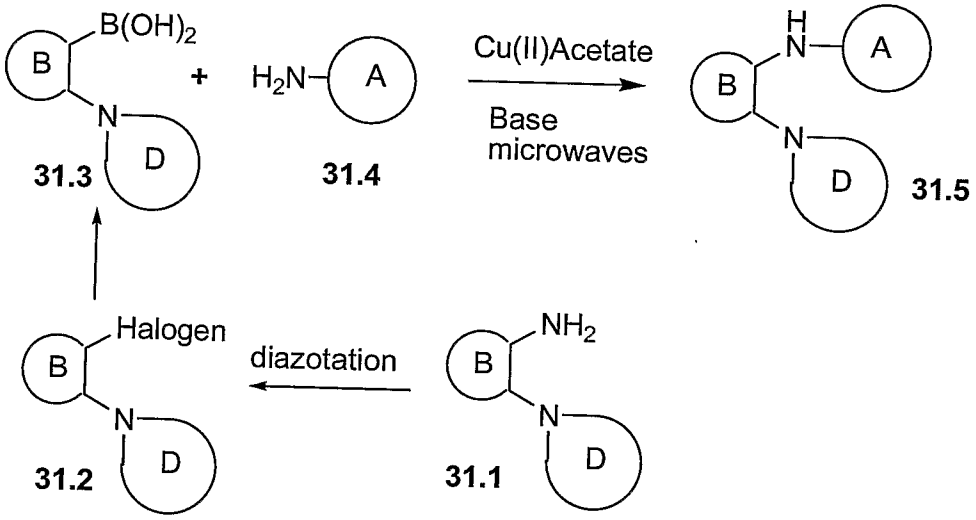




Y= N, O, S; all the heteroaryls are optionally further substituted.

[00165] The amino derivative **31.1,** is transformed to the corresponding halogeno intermediate **31.2** by well known diazotation reaction. In turn, **31.2** is transformed to the boronic acid compound **31.3** by the classical boronic acid derivatives preparation methods known in the literature (Pd-catalyzed borylation of aryl halides. Marshall, J. A. *Chemtracts* **2000**, *13(4)*, 219-222; new methods for the synthesis of proximally functionalized arylboranes and silanes. Katz, H. E. *Organometallics* **1986**, *5(11)*, 2308-11; Murata, M. *et al. Journal of Organic Chemistry* **2000**, *65(1)*, 164-168).

Scheme 31



[00166] In the following experimental procedures, solution ratios express a volume relationship, unless stated otherwise. NMR chemical shifts (δ) are reported in parts per million.

[00167] Products were analyzed by reverse phase analytical HPLC carried out on a Shimadzu Analytical HPLC system running DiscoveryVP software using Method A: Phenomenex Luna C18 column (4.6 x 50 mm) eluted at 4 mL/min with a 4 min gradient from 100% A to 100% B (A: 10% methanol, 89.9% water, 0.1% TFA;

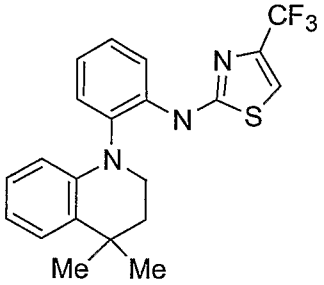
B: 10% water, 89.9% methanol, 0.1% TFA, UV 220 nm), Method B: Phenomenex Luna C18 column (4.6 x 50 mm) eluted at 4 mL/min with a 4 min gradient from 100% A to 100% B (A: 10% acetonitrile, 89.9% water, 0.1% TFA; B: 10% water, 89.9% acetonitrile, 0.1% TFA, UV 220 nm), or Method C: Zorbax SB C18 column (4.6 x 75 mm) eluted at 2.5 mL/min with methanol/water with 0.2% H_3PO_4 as a gradient of 10% to 90% methanol over 8 min followed by holding at 90% methanol for 3 min (UV 220 nm). Purification of intermediates and final products was carried out via either normal or reverse phase chromatography. Normal phase chromatography was carried out on an ISCO CombiFlash™ System Sq16x using prepacked SiO_2 cartridges eluted with gradients of hexanes and ethyl acetate. Reverse phase preparative HPLC was carried out using a Shimadzu Preparative HPLC system running DiscoveryVP software on a Shim-PackVP-ODS column (50L X 20 mm) at 20 mL/min, 6 min gradient 100% A to 100% B with the solvent system used for the analytical. LCMS were obtained on a Shimadzu HPLC system running DiscoveryVP software, coupled with a Waters Model PlatformLC mass spectrometer running MassLynx version 3.5 software using the same column and conditions as utilized for analytical described above.

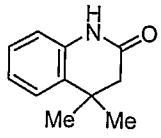
EXAMPLES

[00168] The following Examples have been prepared, isolated and characterized using the methods disclosed herein. The following Examples demonstrate a partial scope of the present invention and are not meant to be limiting of the scope of the invention.

Example 1

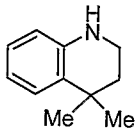
N-(2-(4,4-dimethyl-3,4-dihydroquinolin-1(2H)-yl)phenyl)-4-(trifluoromethyl)thiazol-2-amine





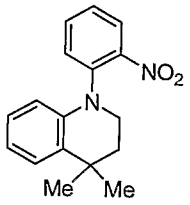
1a. 4,4-Dimethyl-3,4-dihydro-1*H*-quinolin-2-one:

[00169] Aniline (7.26 g, 45.2 mmol) and 3-methylbut-2-enoyl chloride (53.2g, 45.2 mmol) were heated in chloroform at reflux for 2 h. After cooling, the mixture was filtered. The filtrate was concentrated to dryness and dried under vacuum. The crude 3-methyl-but-2-enoic acid phenylamide (ca. 10 g) was dissolved in toluene (50 mL). This toluene solution was added to the stirred $AlCl_3$ powder (27 g) portion-wise. After addition, the resulting dark brown solution was heated at 80 °C for 2.5 h. The warm slurry was poured carefully to stirred crashed ice. The resulting mixture was extracted with EtOAc (3x), washed with sat'd $NaHCO_3$, H_2O, brine, and dried over $MgSO_4$. The residue was purified by silica gel flash chromatography (CH_2Cl_2, then EtOAc) to give 2.2 g of pure **1a** and about 4-5 g of less pure portion **1a**. LC-MS ESI 176 (M+H).



1b. 4,4-dimethyl-1,2,3,4-tetrahydroquinoline:

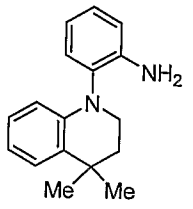
[00170] To a stirred solution of $LiAlH_4$ (1.0 M in THF, 35 mL, 35 mmol), was added a solution of **1a**. (2.17 g, 12.4 mmol) in THF (10 mL) for 5 min at 0 °C under nitrogen. The resulting mixture was warmed gradually to reflux, and heated at reflux for 5.5 h. To the cooled mixture with stirring, was added sat'd Na_2SO_4 dropwise till the complete decomposition of $LiAlH_4$. The mixture was filtered, and rinsed with EtOAc. The organic was washed with H_2O, brine, dried ($MgSO_4$), and concentrated to dryness. It was purified by flash chromatography (silica gel, 0-20% EtOAc in hexanes) to give pure **1b** (1.86 g, yield: 93%). LC-MS ESI 162 (M+H).



1c. 4,4-dimethyl-1-(2-nitro-phenyl)-1,2,3,4-tetrahydro-quinoline:

[00171] **1b** (0.762 g, 4.73 mmol), *ortho*-fluoronitrobenzene (0.88 g, 5.67 mmol, 1.19 eq), and 2,4,6-collidine (0.66 mL, 1.05 eq) were pre-stirred 40s in a conical

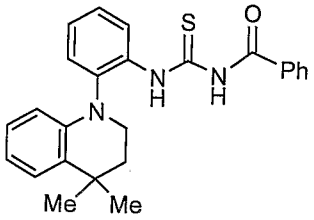
microwave container. It was then heated with stirring at a Personal Chemistry Microwave reactor with normal absorption at 250 °C for 1 h. The crude mixture was dissolved in $CHCl_3$, and was purified by flash chromatography (hexanes/EtOAc) to give 0.66 g of crude **1c**. LC-MS ESI 283 (M+H).



1d. 2-(4,4-Dimethyl-3,4-dihydro-2*H*-quinolin-1-yl)-phenylamine:

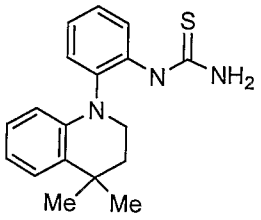
[00172] The crude **1c** (0.66 g) was stirred in MeOH (20 mL) at rt. Solid NH_4Cl (0.62 g) was added, followed by addition of Zn dust (3.0 g) portionwise. The resulting mixture was stirred at rt for 2 h. It was filtered through Celite®, rinsed with CH_2Cl_2, and concentrated to dryness. The residue was purified by flash chromatography (hexanes/EtOAc) to give pure amine **1d** (0.43 g, 73% for two steps). LC-MS ESI 253 (M+H).

1e. 1-benzoyl-3-(2-(4,4-dimethyl-3,4-dihydroquinolin-1(2H)-yl)phenyl)thiourea:



[00173] **1d** (65.4 mg, mmol) and benzoyl isothiocyanate (60 mg) were heated at refluxing CH_2Cl_2 for 2 h. After cooling, the solvent was evaporated. The resulting crude **1e** was dried over vacuum and used directly in the next step: LC-MS ESI, 416.3 (M+H) (10-90% MeOH in H_2O with 0.1% TFA in a 4 min run, t_R = 4.49 min).

1f. 1-(2-(4,4-dimethyl-3,4-dihydroquinolin-1(2H)-yl)phenyl)thioure:



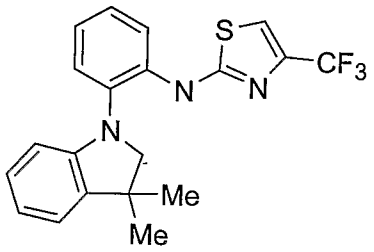
[00174] **1e** was heated at 80°C in the presence of MeOH (2.5 mL and 1N NaOH 0.5 mL) for 40 min. LC-MS showed completion of the reaction. The solvent was concentrated, and 1N HCl was added followed by the addition of Et_2O. The Et_2O layer was separated and was washed with H_2O (2x), brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The resulting crude **1f** was used directly in the next step: LC-MS (ESI) 312.1 (M+H) (10-90% MeOH in H_2O with 0.1% TFA in a 4 min run, t_R = 3.51 min).

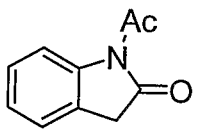
Example 1

[00175] A mixture of **1f** (22 mg) and 3-bromo-1,1,1-trifluoropropan-2-one (0.01 mL) were heated in EtOH (0.7 mL) for 2 h. LC-MS showed completion of the reaction. The mixture was concentrated. The residue was dissolved in a small amount of CH_2Cl_2, and purified by silica gel chromatography (hexanes: EtOAc = 100:0 to 80:20) to give pure **Example 1** as colorless amorphous solids (16 mg, yield: 56%): LC-MS ESI 404.3 (M+H) (10-90% MeOH in H_2O with 0.1% TFA in a 4 min run, t_R = 4.43 min). ^1H NMR ($CDCl_3$) δ 8.03 (m, 1H), 7.29 (td, J = 8, 4 Hz, 1H), 7.23 (dd, J = 8, 3 Hz, 1H), 7.16 (dd, J = 8, 2.5 Hz, 1H), 7.05 (dd, J = 8, 2 Hz, 1H), 7.02 (s, br, 1H), 6.81 (td, J = 8, 4 Hz, 1H), 6.70 (td, J = 8, 3 Hz, 1H), 6.09 (dd, J = 8, 2 Hz, 1H), 3.48 (td, J = 12, 4 Hz, 1H), 3.24 (dt, J = 12, 4 Hz, 1H), 1.99 (td, J = 12, 4 Hz, 1H), 1.78 (dt, J = 12, 4 Hz, 1H), 1.34 (s, 3H), 1.31 (s, 3H) ppm.

Example 2

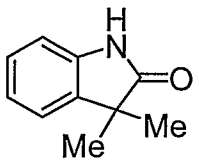
N-(2-(3,3-dimethylindolin-1-yl)phenyl)-4-(trifluoromethyl)thiazol-2-amine



2a: 1-Acetyl-1,3-dihydro-indol-2-one: 

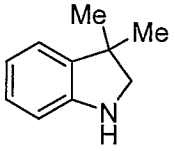
[00176] Indoline-2-one (6.65 g, 50 mmol) and acetic anhydride (9 mL) were heated at reflux for 15 h. After cooling, the product was filtered and rinsed with Et_2O to give **2a** as solids after vacuum drying (8.2 g, yield: 93.7 %).

2b. 3,3-dimethylindolin-2-one:

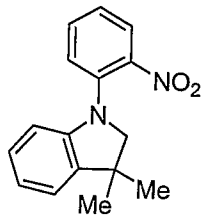


[00177] To a stirred solution of **2a** (3.2 g, 18.29 mmol) in dry THF (100 mL) was added MeI (2.6 mL, 41.75 mmol, 2.3 eq), followed by the addition of 18-crown-6 (0.51 g, 4.57 mmol, 0.25 eq) at -78 °C under nitrogen. Potassium tert-butoxide (5.12 g, 45.73 mmol, 2.5 eq) was added portionwise. The resulting slurry was stirred at -78 °C for 1 h. The mixture was stirred at -78 °C to rt for 3 h. Cooled in an ice bath, sat'd NH_4Cl was added. It was extracted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc) to give pure 1-acetyl-3,3-dimethylindolin-2-one (1.3 g) (LC-MS ESI 204 (M+H)) and pure 3,3-dimethylindolin-2-one (1.0 g) (LC-MS ESI 162 (M+H)) respectively. 1-Acetyl-3,3-dimethylindolin-2-one (1.3 g) was heated in 6N HCl at reflux for 1 h. After cooling, it was poured into crushed ice. It was extracted with Et_2O, washed with sat'd $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, filtered, and concentrated to dryness to give almost pure **2b** (1.0 g).

2c. 3,3-dimethylindoline:

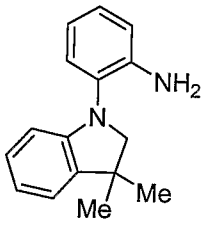


[00178] To a 1M of LAH (30 mL) in THF was added **2b** (630 mg, 3.88 mmol) in portion. The reaction mixture was stirred at rt for 2 h, then refluxed for 1 h. The reaction mixture was quench with 1 part of H_2O (10 mL), one part of 15% NaOH (5 mL) and another part of H_2O (5 mL). The aqueous layer was extracted with EtOAc. The EtOAc layer was dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to afford **2c** (320 mg, 56%) as an oil. MS (ES) *m/z* 150 $[M+H]^+$.



2d. 3,3-dimethyl-1-(2-nitrophenyl)indoline:

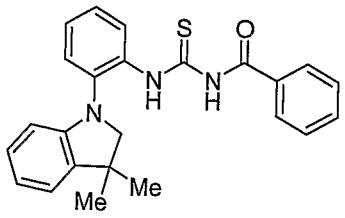
[00179] To **2c** (317 mg, 2.12 mmol) was added 1-fluoro-2-nitrobenzene (200 mg, 1.42 mmol). The reaction mixture was stirred at 175 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1N HCl and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and purified by column chromatography using 0 to 10% EtOAc in hexane over 30 min as eluting solvent to afford **2d** (360 mg, 95%) as an oil. MS (ES) *m/z* 269 $[M+H]^+$.



2e. 2-(3,3-dimethylindolin-1-yl)benzenamine:

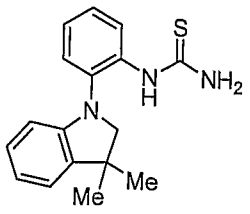
[00180] To a solution of **2d** (123 mg, 0.458 mmol) in MeOH was added 10% Pd/C (20 mg). The reaction mixture was stirred at rt under H_2 for 2 h. The catalyst was filtered through a cake of Celite® and the filtrate was evaporated under reduced pressure to afford **2e** (80 mg, 75%) as a yellowish powder. MS (ES) *m/z* 239 $[M+H]^+$.

2f. 1-benzoyl-3-(2-(3,3-dimethylindolin-1-yl)phenyl)thiourea:



[00181] To a solution of **2e** (40 mg, 0.168 mmol) in CH_2Cl_2 was added benzoyl isothiocyanate (30 mg, 0.189 mmol). The reaction mixture was kept at reflux for 2.5 h. The reaction mixture was filtered through a cake of Celite® and washed the cake with CH_2Cl_2. The solvent was evaporated under reduced pressure. The desired product was purified by column chromatography using 0 to 80% EtOAc in hexane

over 60 min as eluting gradient to afford **2f** (76 mg, 99%) as a powder. MS (ES) *m/z* 402 $[M+H]^+$.



2g. 1-(2-(3,3-dimethylindolin-1-yl)phenyl)thiourea:

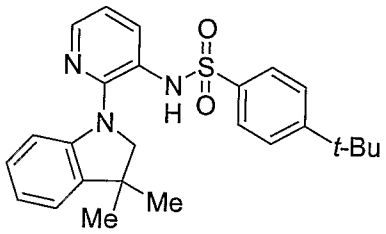
[00182] To a solution of **2f** (60 mg, 0.149 mmol) in MeOH was added 1N NaOH (0.2 mL, 0.2 mmol). The reaction mixture was stirred at 50 °C for 2 h. The solvent was evaporated under reduced pressure and co-evaporated with toluene to afford **2g** (35 mg, 80%). MS (ES) *m/z* 298 $[M+H]^+$.

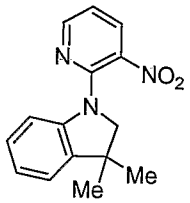
Example 2

[00183] To a solution of 1-(2-(3,3-dimethylindolin-1-yl)phenyl)thiourea (30 mg, 0.101 mmol) in EtOH was added 3-bromo-1,1,1-trifluoropropan-2-one (0.05 mL, 0.149 mmol). The reaction mixture was stirred at 80 °C for 2 h. The solvent was evaporated under reduced pressure and purified by column chromatography using 0 to 30% EtOAc in hexane as diluting gradient to afford **Example 2** (32 mg, 81%) as an off-white powder. MS (ES) *m/z* 298 $[M+H]^+$.

Example 4

4-tert-butyl-N-(2-(3,3-dimethylindolin-1-yl)pyridine-3-yl)benzenesulfonamide



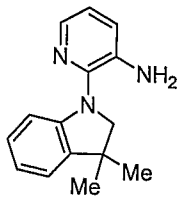


4a. 3,3-dimethyl-1-(3-nitropyridin-2-yl)indoline:

[00184] To **2a** (90 mg, 0.61 mmol) was added 2-nitro-3-chloropyridine (200 mg, 1.26 mmol). The reaction mixture was heated at 220 °C microwave for 15 min.

The desired compound was isolated via preparative HPLC to afford **4a** (30 mg, 18%) as white lyophilizes. Column: Luna 25 X100 mm; Eluted from 35 % CH_3CN to 100% CH_3CN in H_2O with 0.1 % TFA MS (ES) *m/z* 269 $[M+H]^+$.

4b. 2-(3,3-dimethylindolin-yl)pyridin-3-amine:



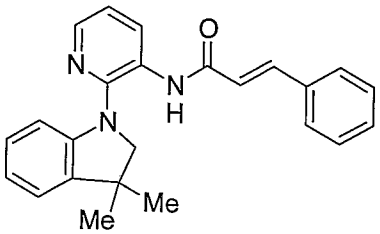
[00185] To a solution of **4a** (30 mg, 0.111 mmol) in MeOH was added 10% Pd/C (10 mg). The reaction mixture was stirred at rt under H_2 for 2 h. The catalyst was filtered through a cake of Celite® and the filtrate was evaporated under reduced pressure to afford **4b** (20 mg, 76 %) as a yellowish powder. MS (ES) *m/z* 240 $[M+H]^+$.

Example 4

[00186] To a solution of **4b** (20 mg, 0.083 mmol) in DMF was added Et_3N (0.026 ml, 0.186 mmol) followed by the tert-butyl-benzyl sulfonyl chloride (29 mg, 0.124 mmol). The reaction mixture was stirred at rt for 16 h. The desired product was purified by column chromatography using 0 to 50% EtOAc in hexane as eluting gradient and tried with 1 eq. TFA to afford **Example 4** (18 mg, 50%) as a white lyophilizes. MS (ES) *m/z* 436 $[M+H]^+$.

Example 5

N-(2-(4,4-dimethyl-3,4-dihydroquinolin-1(2H)-yl)pyridine-3-yl)cinnamamide

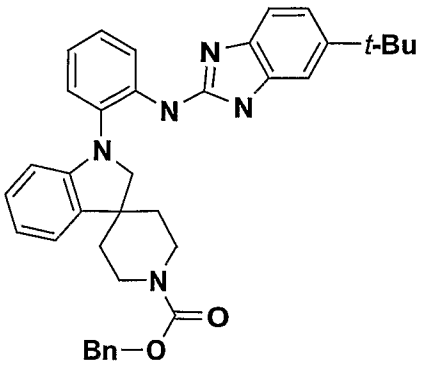


[00187] To a solution of **4b** (15 mg, 0.062 mmol) in DMF was added pyridine (0.015 mL, 0.094 mmol) followed by cinnamoylchloride (15 mg, 0.064 mmol). The reaction mixture was stirred at rt for 3 h. The desired compound was purified by column chromatography using 0 to 50% EtOAc in hexane as eluting gradient then via

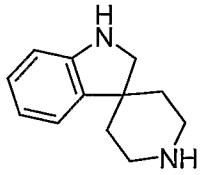
preparative HPLC to afford **Example 5** (13 mg, 56%) as white lyophilizes. MS (ES) *m/z* 370 $[M+H]^+$.

Example 6

spiro[3*H*-indole-3,4'-piperidine]-1'-carboxylic acid, 1-[2-[[5-(1,1-dimethylethyl)-1*H*-benzimidazol-2-yl]amino]phenyl]-1,2-dihydro-, phenylmethyl ester

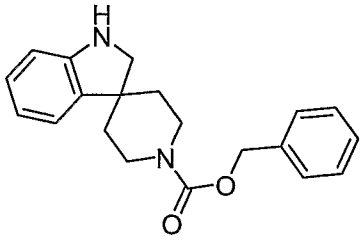


6a. Spiro[3*H*-indole-3,4'-piperidine], 1,2-dihydro-:



[00188] **6a** was obtained accroding to literature procedure (Journal of Medicinal Chemistry, **1983**, *26*, 981-6) from 2-fluorophenylacetonitrile and 2,2'-dichloro-*N*-methyl-diethylamine hydrochoride. LC-MS, ESI 189 $(M+H)^+$.

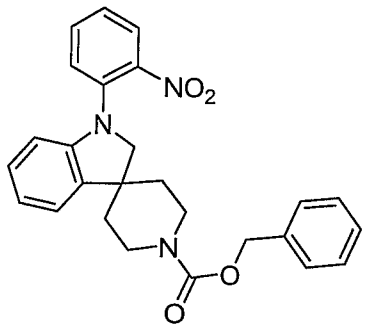
6b. Spiro[3*H*-indole-3,4'-piperidine]-1'-carboxylic acid, 1,2-dihydro-, phenylmethyl ester:



[00189] To a stirred solution of **6a** (0.90 g, 4.78 mmol) in dry THF (25 mL) was added (*N*-benzyloxycarbonyloxy)-succinimide (1.2 g, 4.8 mmol) in THF (5 mL) over a 2-min period of time at rt under N_2. The resulting mixture was stirred at rt for 1 h. EtOAc was added. It was washed with saturated $NaHCO_3$, H_2O, brine, dried over $MgSO_4$, filtered , and concentrated to dryness. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc) to give pure **6b** as colorless crystals

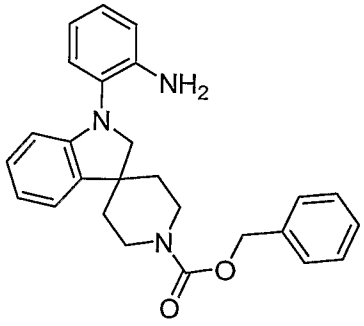
(0.96 g, yield: 69%). LC-MS ESI 323.15 $(M+H)^+$ (t_R = 2.62 min, 10%-90% MeOH in H_2O in a 4-min run).

6c. Spiro[3*H*-indole-3,4'-piperidine]-1'-carboxylic acid, 1,2-dihydro-1-(2-nitrophenyl)-, phenylmethyl ester:



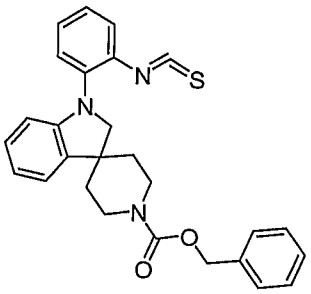
[00190] To **6b** (200 mg, 0.62 mmol, 10025-B) was added 2-fluoro-nitrobenzene (400 mg, 2.8 mmol). The reaction was stirred at 175 °C for 8 h. The desired compound was purified by column chromatography using 0% to 40% EtOAc in hexanex as eluting gradient to afford **6c** (250 mg, 91%). MS (ES) *m/z* 444 $[M+H]^+$.

6d. Spiro[3*H*-indole-3,4'-piperidine]-1'-carboxylic acid, 1-(2-aminophenyl)-1,2-dihydro-, phenylmethyl ester:



[00191] To a solution of **6c** (250 mg, 0.564 mmol) in MeOH was added ammonium chloride (632 mg, 11.2 mmol), followed by the zinc (733 mg, 11.3 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was filtered through a cake of Celite®. The solvent was evaporated under reduced pressure to afford **6d** (230 mg, 99%). LC-MS ESI 414.06 $(M+H)^+$ (t_R = 3.55 min, 10%-90% MeOH in H_2O in a 4 min run).

6e. spiro[3*H*-indole-3,4'-piperidine]-1'-carboxylic acid, 1,2-dihydro-1-(2-isothiocyanatophenyl)-, phenylmethyl ester:



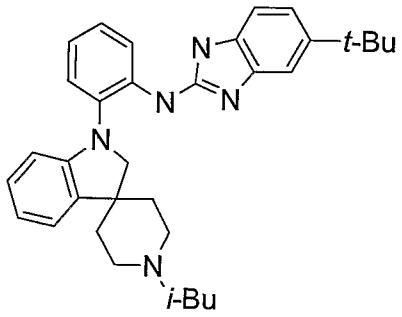
[00192] To a solution of **6d** (500 mg, 1.21 mmol) in CH_2Cl_2 was added pyridine (0.030 ml, 0.160 mmol) followed by the 3-(4-bromo-2-fluoro)phenyl-acryloyl chloride (30 mg, 0.160 mmol). The reaction mixture was stirred at rt for 16 h. The desired product was purified by column chromatography using 100% hexane as eluting gradient to afford the title compound (30 mg, 55%). MS (ES) *m/z* 506 $[M+H]^+$.

Example 6

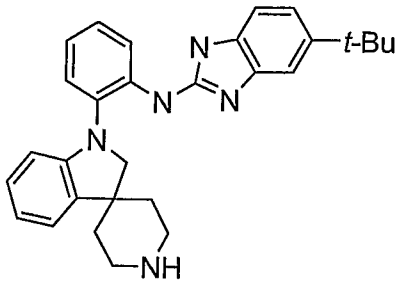
[00193] To a solution of benzene-1,2-diamine (44 mg, 0.26 mmol) in 2 mL of CH_2Cl_2 was added **6e** (50 mg, 0.109 mmol) in DCM. The reaction mixture was stirred at rt for 3 h. Then EDC (57 mg, 0.26 mmol) was added to the reaction mixture and stirred at rt for 16 h. The crude residue was subjected to column chromatography using 0 to 5% MeOH in CH_2Cl_2 as eluting solvent to afford **Example 6** (63 mg, 98%) as off-white powder. MS (ES) *m/z* 586 $[M+H]^+$.

Example 7

1*H*-benzimidazol-2-amine, 5-(1,1-dimethylethyl)-*N*-[2-[1'-(2-methylpropyl)spiro[3*H*-indole-3,4'-piperidin]-1(2*H*)-yl]phenyl]-



7a. 1*H*-benzimidazol-2-amine, 5-(1,1-dimethylethyl)-*N*-(2-spiro[3*H*-indole-3,4'-piperidin]-1(2*H*)-ylphenyl)-:



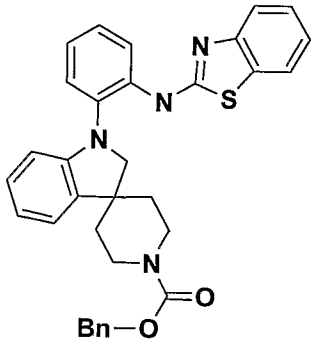
[00194] To a solution of the product of **Example 6** (63 mg, 0.107 mmol) in 2 mL of MeOH was added 10% Pd/C (20 mg). The reaction mixture was stirred under H_2, at rt for 2 h. The catalyst was removed by filtration. The solvent was then evaporated under reduced pressure to afford **7a** (30 mg, 62%) as an off-white powder. MS (ES) *m/z* 452 $[M+H]^+$.

Example 7

[00195] To a solution of **7a** (25 mg, 0.055 mmol) in 1 mL of MeOH was added $NaBH_3CN$ (10 mg, 0.159 mmol), isobutyl aldehyde (0.01 mL, 0.109 mmol), followed by HOAc (0.01 mL). The reaction mixture was stirred under at rt for 4 h. The crude residue was isolated by Preparative HPLC using 0 to 100% ACN in H_2O with 0.1% TFA as eluting solvent to afford **Example 7** (15 mg, 55%) as off-white powder. MS (ES) *m/z* 508 $[M+H]^+$.

Example 8

spiro[3*H*-indole-3,4'-piperidine]-1'-carboxylic acid, 1-[2-(2-benzothiazolylamino)phenyl]-1,2-dihydro-, phenylmethyl ester

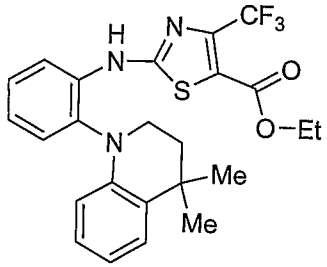


[00196] To a solution of 2-amino thiophenol (44 mg, 0.35 mmol) in 2 mL of CH_2Cl_2 was added **6e** (50 mg, 0.17 mmol). The reaction mixture was stirred at rt for

16 h. The crude residue was subjected to column chromatography using 0 to 10% MeOH in CH_2Cl_2 as eluting solvent to afford **Example 8** (51 mg, 55%) as an off-white powder. MS (ES) *m/z* 547 $[M+H]^+$.

Example 9

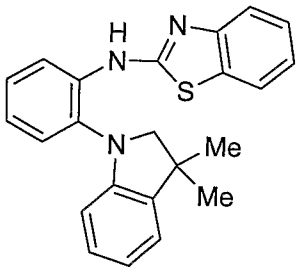
Ethyl 2-(2-(4,4-dimethyl-3,4-dihydroquinolin-1(2H)-yl)phenylamino)-4-(trifluoromethyl)thiazole-5-carboxylate



[00197] Following similar procedures as those for **Example 1**, **Example 9** was obtained. LC-MS m/z 476 $[M+H]^+$.

Example 10

N-(2-(3,3-dimethylindolin-1-yl)phenyl)benzo[d]thiazol-2-amine



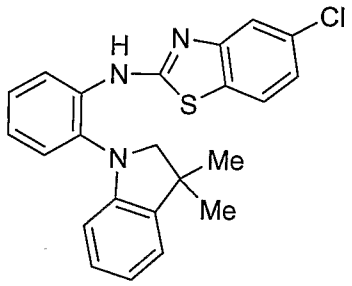
[00198] 51.2 mg (0.183 mmol) of 1-(2-isothiocyanatophenyl)-3,3-dimethylindoline were mixed with 22.9 mg (0.183 mmol) of 2-aminobenzenethiol and 4 mL of dry pyridine. The mixture was stirred at rt overnight under N_2 atmosphere, then heated to 110 °C for 6 h. After cooling, ice/water was added and the mixture was extracted with DCM, dried over $MgSO_4$, and concentrated to yield 102.4 mg of crude oil which was purified by preparative HPLC (A = 90:10:0.1 H2O:MeOH:TFA; B = 90:10:0.1 MeOH:H2O:TFA) to afford **Example 10** as a grey powder. $[M+H]^+$ = 372; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.24 (s, 6H); 3.57 (s, 2H); 6.62 (d, J=9.1 Hz, 1H); 6.79 (t, J= 7.25 Hz, 1H), 7.04 (t, J=7.5 Hz, 1 H), 7.07 (d, J=7.03 Hz, 1H),

7.23-7.28 (m, 2 H), 7.38-7.45 (m, 2 H), 7.49 (d, J=9.1 Hz , 2H); 7.54-7.59 (m, 2H); HRMS (ESI) *m/z* calcd for $C_{23}H_{22}N_3S$ $[M + H]^+$ 372.1534, found 372.1539.

[00199] According to the procedure of **Example 10** and using the appropriated reagents, **Examples 11-12** were prepared.

Example 11

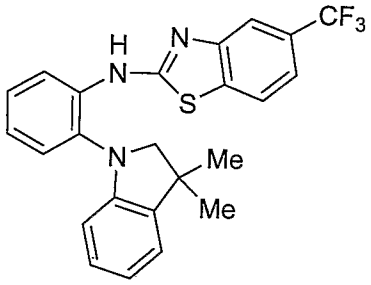
5-chloro-N-(2-(3,3-dimethylindolin-1-yl)phenyl)benzo[d]thiazol-2-amine



[00200] From 52.2 mg (0.186 mmol) of 1-(2-isothiocyanatophenyl)-3,3-dimethylindoline and 29.7 mg (0.186 mmol) of 2-amino-4-chlorobenzenethiol to give **Example 11** as a grey powder. HRMS (ESI) *m/z* calcd for $C_{23}H_{21}N_3SCl$ $[M + H]^+$ 406.1145, found 406.1133.

Example 12

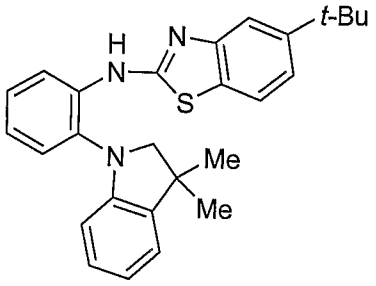
N-(2-(3,3-dimethylindolin-1-yl)phenyl)-5-(trifluoromethyl)benzo[d]thiazol-2-amine



[00201] From 68 mg (0.243 mmol) of 1-(2-isothiocyanatophenyl)-3,3-dimethylindoline and 64.5 mg (0.243 mmol) of 2-amino-4-trifluoromethyl benzenethiol to give **Example 12** as a grey powder. HRMS (ESI) *m/z* calcd for $C_{24}H_{21}N_3SF_3$ $[M + H]^+$ 440.1408, found 440.1407.

Example 13

5-tert-butyl-N-(2-(3,3-dimethylindolin-1-yl)phenyl)-1H-benzo[d]imidazol-2-amine

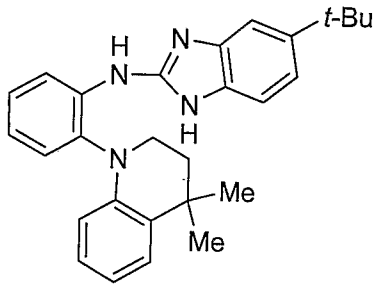


[00202] 4-tert-butyl-1,2-diamine benzene (94 mg, 0.517 mmol, 2 eq) was dissolved in DCE (4 mL). At 0 °C, 1-(2-isothiocyanatophenyl)-3,3-dimethylindoline (80 mg, 0.285 mmol) in DCE (2 mL) was slowly added. The whole mixture was stirred overnight, EDC (78 mg, 0.41 mmol) was added and the mixture was stirred again overnight at rt. The mixture was concentrated and purified by preparative HPLC (A = 90:10:0.1 H_2O:MeOH:TFA; B = 90:10:0.1 MeOH:H_2O:TFA) to afford **Example 13** as an off-white solid. LC-MS ESI m/z 411 $[M+H]^+$.

[00203] According to the procedure of **Example 13** and by reacting 2-(4,4-dimethyl-3,4-dihydroquinolin-1(2H)-yl)benzenamine, prepared as above, with the appropriated reagents, **Examples 14-15** were prepared.

Example 14

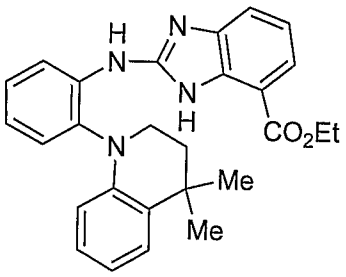
5-tert-butyl-N-(2-(4,4-dimethyl-3,4-dihydroquinolin-1(2H)-yl)phenyl)-1H-benzo[d]imidazol-2-amine



[00204] LC-MS m/z 425 $[M+H]^+$.

Example 15

Ethyl 2-(2-(4,4-dimethyl-3,4-dihydroquinolin-1(2H)-yl)phenylamino)-3H-benzo[d]imidazole-4-carboxylate

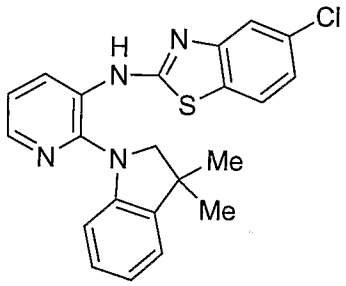


[00205] LC-MS m/z 441 $[M+H]^+$.

[00206] According to the procedure of **Example 10** and by reacting 1-(3-isothiocyanatopyridin-2-yl)-3,3-dimethylindoline with the appropriated reagents, **Examples 16-18** were prepared.

Example 16

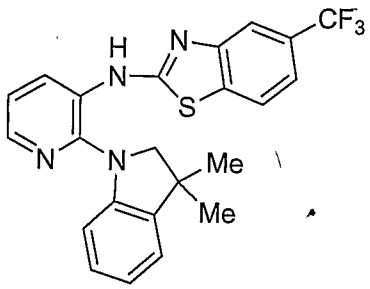
5-chloro-N-(2-(3,3-dimethylindolin-1-yl)pyridin-3-yl)benzo[d]thiazol-2-amine



[00207] From 58 mg (0.206 mmol) of 1-(3-isothiocyanatopyridin-2-yl)-3,3-dimethylindoline and 40.4 mg (0.420 mmol) of 2-amino-4-chlorobenzenethiol HCl salt to give **Example 16** as a yellow powder. HRMS (ESI) *m/z* calcd for $C_{22}H_{20}N_4ClS$ $[M + H]^+$ 407.1097, found 407.1093.

Example 17

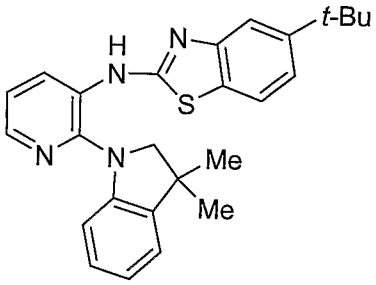
N-(2-(3,3-dimethylindolin-1-yl)pyridin-3-yl)-5-(trifluoromethyl)benzo[d]thiazol-2-amine



[00208] From 64.8 mg (0.230 mmol) of 1-(3-isothiocyanatopyridin-2-yl)-3,3-dimethylindoline and 52.8 mg (0.230 mmol) of 2-amino-4-trifluoromethyl benzenethiol to give **Example 17** as a yellow powder. HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_4SF_3$ $[M + H]^+$ 441.1361, found 441.1358.

Example 18

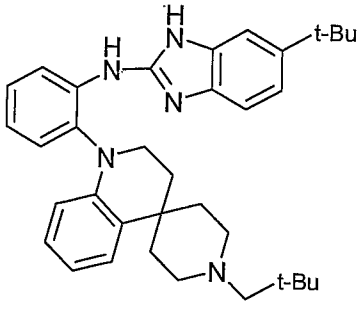
5-tert-butyl-N-(2-(3,3-dimethylindolin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-2-amine



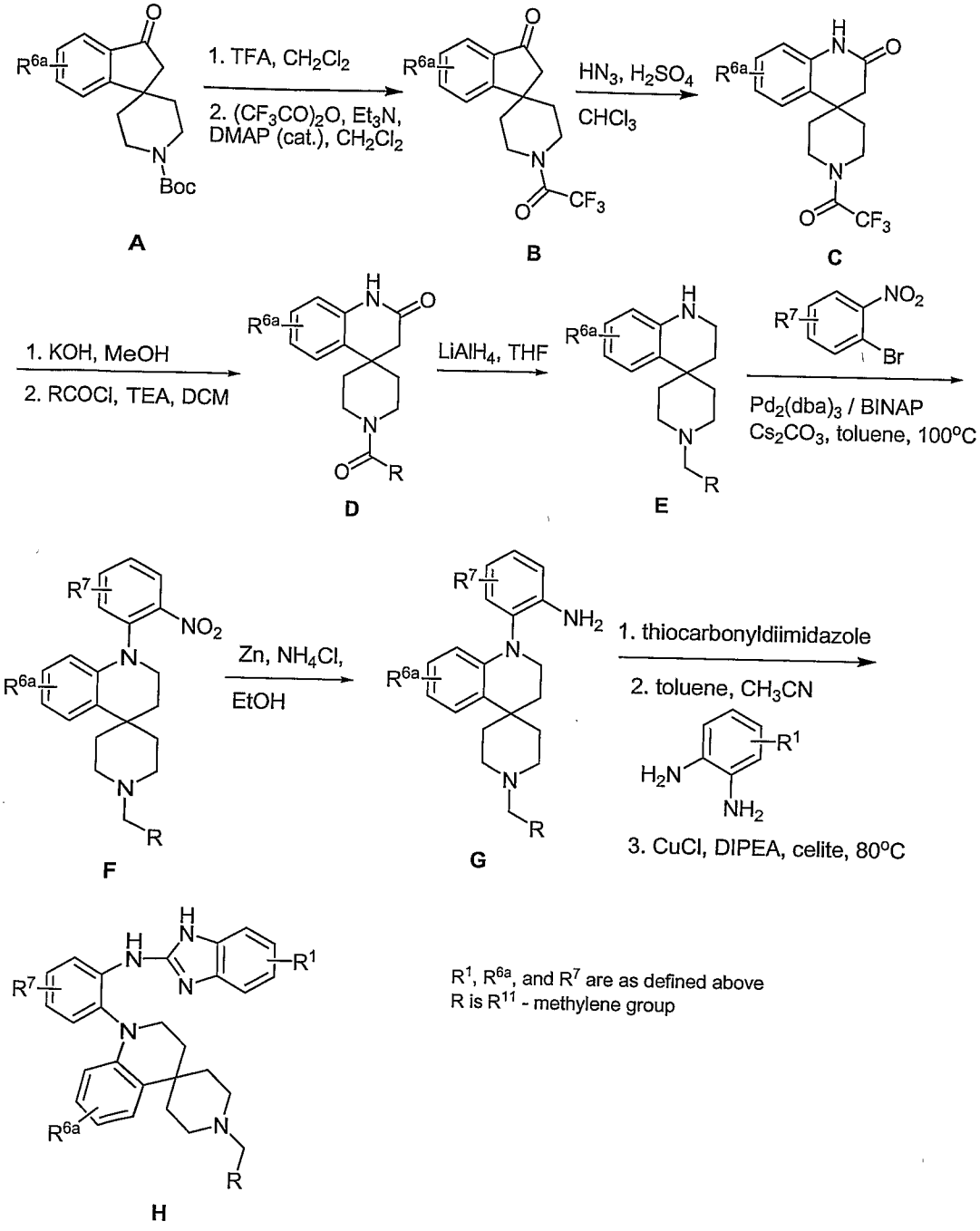
[00209] 97 mg (0.59 mmol) 1, 2-diamino benzene and (144 mg, 0.51 mmol, 0.87 eq) isothiocyanate to give **Example 18** as a yellow powder. HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_5$ $[M + H]^+$ 412.2501, found 412.2510.

Example 19

6-tert-butyl-N-(2-(1-neopentyl-2',3'-dihydro-1'H-spiro[piperidine-4,4'-quinoline]-1'-yl)phenyl)-1H-benzo[d]imidazol-2-amine

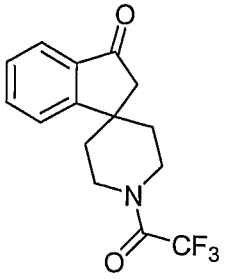


General reaction scheme for the preparation of Example 19



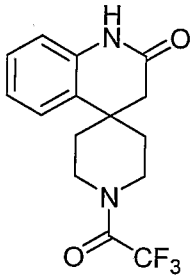
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19a. 1'-(2,2,2-trifluoroacetyl)spiro[indene-1,4'-piperidin]-3(2H)-one:



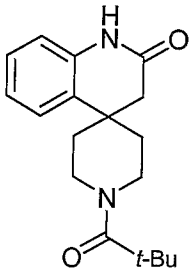
[00210] TFA (25 mL) was added to a solution of commercially available tert-butyl 3-oxo-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate (5.0 g, 16.6 mmol) in dichloromethane (25 mL) at 0 °C. The reaction was then allowed to warm to rt for 30 min. The reaction was evaporated and dried under high vacuum for 30 min. The crude amine was dissolved in dichloromethane (25 mL) and triethylamine (6.9 mL, 49.8 mmol), trifluroacetic anhydride (2.6 mL, 18.3 mmol) and DMAP (20 mg, 0.17 mmol) were added in that order. The reaction was stirred at rt for 2 h and then diluted in dichloromethane and washed with water, sat. NH_4Cl solution and brine. The organics were then dried ($MgSO_4$), filtered and evaporated to give **19a** as a light yellow solid (4.55 g, 92%). $(M+H)^+ = 298$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, $J = 7.6$ Hz, 1H); 7.66 (t, $J = 7.0$ Hz, 1H); 7.48 (d, $J = 7.9$ Hz, 1H); 7.44 (t, $J = 7.5$ Hz, 1H); 4.69 (d, $J = 15.9$ Hz, 1H); 4.13 (d, $J = 14.1$ Hz, 1H); 3.30 (t, $J = 11.8$ Hz, 1H); 2.90 (t, $J = 13.4$ Hz, 1H); 2.68 (m, 2H); 2.05 (dt, $J = 13.6$, 3.8 Hz, 2H); 1.66 (d, $J = 13.9$ Hz, 2H).

19b. 1-(2,2,2-trifluoroacetyl)-1'H-spiro[piperidine-4,4'-quinolin]-2'(3'H)-one:



[00211] Concentrated H_2SO_4 (1.1 mL) was added slowly to sodium azide (2.49 g, 38.3 mmol) in water (2.7 mL) and chloroform (15 mL) keeping the temperature between 0-5 °C. After 10 min the cold bath was removed and the reaction was stirred for 3 h at rt. Na_2SO_4 was added to the solution to dry it and the resulting chloroform

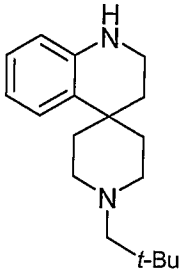
solution (containing HN_3) was then decanted into a solution of **19a** (4.55 g, 15.3 mmol) in chloroform (16 mL). Concentrated H_2SO_4 (4.1 mL) was added and the reaction was stirred for 30 min. at rt. The mixture was heated to 50 °C for 45 min. and then stirred at rt for 2 h. The reaction was poured into sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x) and with EtOAc (2 x). The combined organics were dried ($MgSO_4$), filtered and evaporated to give the crude product. The crude product was purified by flash chromatography on Biotage using EtOAc/CH_2Cl_2 (50-80%) to give **19b** as lightly colored foam (2.6 g, 54%). $(M+H)^+ = 313$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.29 (s, 1H); 7.29 (d, J = 7.8 Hz, 1H); 7.24 (t, J = 7.8 Hz, 1H); 7.10 (t, J = 7.6 Hz, 1H); 6.83 (d, J = 7.8 Hz, 1H); 4.44 (d, J = 13.9 Hz, 1H); 3.92 (d, J = 14.1 Hz, 1H); 3.48 (t, J = 13.2 Hz, 1H); 3.18 (t, J = 11.9 Hz, 1H); 2.77 (m, 2H); 2.00 (m, 2H); 1.85 (m, 2H).



19c. 1-pivaloyl-1'H-spiro[piperidine-4,4'-quinolin]-2'(3'H)-one:

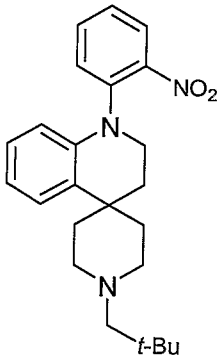
[00212] KOH (0.65 g, 11.5 mmol) in water (3.0 mL) was added to **19b** (1.20 g, 3.8 mmol) in methanol (15 mL) and stirred at rt overnight. The reaction was neutralized with conc. HCl (1 mL) and then concentrated. The crude reaction mixture was evaporated from toluene to remove water. The crude amine was taken up in dichloromethane (30 mL) and triethylamine (2.5 mL, 19.2 mmol) and pivaloyl chloride (0.9 mL, 7.7 mmol) were added. This was stirred at rt for 4 h and then water was added to quench the reaction. The aqueous layer was extracted with dichloromethane (3 x) and the combined organics were dried ($MgSO_4$), filtered and evaporated to give the crude product. The crude product was purified by flash chromatography on Biotage using EtOAc/Hexanes (50-100%) to give **19c** as a white solid (0.91 g, 79%). $(M+H)^+ = 301$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (s, 1H); 7.30 (d, J = 7.3 Hz, 1H); 7.22 (t, J = 7.7 Hz, 1H); 7.08 (t, J = 7.6 Hz, 1H); 6.78 (d, J = 7.8 Hz, 1H); 4.30 (m, 2H); 3.18 (m, 2H); 2.75 (s, 2H); 1.91 (m, 2H); 1.71 (m, 2H); 1.28 (s, 9H).

19d. 1-neopentyl-2',3'-dihydro-1'H-spiro[piperidine-4,4'-quinoline]:



[00213] Lithium aluminum hydride (0.57 g, 15.2 mmol) was added to **19c** in THF (30.0 mL) at rt and stirred overnight. The reaction was diluted with dichloromethane (30 mL) and quenched by dropwise addition of several drops of sat. Na_2SO_4 solution. After precipitation of the aluminum salts the resulting mixture was filtered through Celite® and evaporated to give **19d** (670 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.35 (d, J = 7.8 Hz, 1H); 6.96 (t, J = 7.6 Hz, 1H); 6.69 (t, J = 7.6 Hz, 1H); 6.48 (d, J = 7.8 Hz, 1H); 3.70 (br s, 1H); 3.23 (m, 2H); 2.64 (m, 2H); 2.49 (t, J = 12.0 Hz, 2H); 2.13 (m, 2H); 2.08 (s, 2H); 1.93 (m, 2H); 1.53 (d, J = 13.1 Hz, 2H); 0.89 (s, 9H).

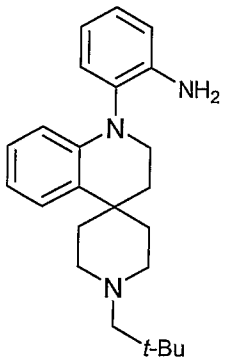
19e. 1-neopentyl-1'-(2-nitrophenyl)-2',3'-dihydro-1'H-spiro[piperidine-4,4'-quinoline]:



[00214] Toluene (2.0 mL, sparged with argon for 30 min.) was added to a sealable flask containing **19d** (100 mg, 0.37 mmol), 1-bromo-2-nitrobenzene (148 mg, 0.73 mmol), $Pd_2(dba)_3$ (3 mg, 0.004 mmol), *rac*-BINAP (7 mg, 0.011 mmol), and cesium carbonate (167 mg, 0.51 mmol) under argon. The reaction was then sealed and heated to 100 °C overnight. The reaction was cooled and purified directly by flash chromatography on Biotage using EtOAc/Hexanes (10-20%) to give **19e** as a red

solid (130 mg, 90%). $(M+H)^+ = 394$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.86 (dd, J = 8.3, 1.5 Hz, 1H); 7.54 (td, J = 7.7, 1.5 Hz, 1H); 7.43 (dd, J = 7.8, 1.5 Hz, 1H); 7.38 (dd, J = 8.1, 1.3 Hz, 1H); 7.24 (td, J = 7.7, 1.5 Hz, 1H); 6.90 (td, J = 7.7, 1.5 Hz, 1H); 6.81 (td, J = 7.4, 1.3 Hz, 1H); 6.42 (dd, J = 8.2, 1.2 Hz, 1H); 3.70 (br s, 1H); 3.30 (br s, 1H); 2.68 (d, J = 11.6 Hz, 2H); 2.50 (t, J = 11.8 Hz, 2H); 2.50-1.90 (br m, 4H); 2.09 (s, 2H); 1.70 (br s, 2H); 0.89 (s, 9H).

19f. 1-neopentyl-1'-(2-aminophenyl)-2',3'-dihydro-1'H-spiro[piperidine-4,4'-quinoline]:



[00215] Zinc (216 mg, 3.30 mmol) was added to **19e** (130 mg, 0.33 mmol) and ammonium chloride (177 mg, 3.30 mmol) in ethanol (5.0 mL) at rt and stirred overnight. The reaction was diluted with EtOAc, filtered through Celite® and then concentrated to give the crude product. The crude product was purified by preperative HPLC to give **19f** as a tan solid (76 mg, 63%). $(M+H)^+ = 364$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 (d, J = 7.6 Hz, 1H); 7.15-7.07 (m, 2H); 6.91(m, 1H); 6.87-6.74 (m, 3H); 6.22 (dd, J = 8.1, 1.3 Hz, 1H); 3.70 (br s, 2H); 3.50 (m, 1H); 3.37 (m, 1H); 2.70 (br m, 2H); 2.55 (br m, 2H); 2.37 (m, 1H); 2.28 (m, 1H); 2.10 (m, 3H); 1.89 (m, 1H); 1.75 (d, J = 13.1 Hz, 1H); 1.55 (d, J = 12.4 Hz, 1H); 0.92 (s, 9H).

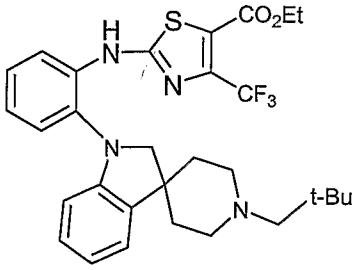
Example 19

[00216] 1,1'-Thiocarbonyldiimidazole (12 mg, 0.07 mmol) was added to **19f** (20 mg, 0.06 mmol) in THF (0.5 mL) at rt and stirred overnight. The reaction was diluted with EtOAc and washed with water. The organics were dried ($MgSO_4$), filtered and concentrated to give crude isothiocyanate. 4-*tert*-Butylbenzene-1,2-diamine (9 mg, 0.06 mmol) was added to the isothiocyanate in toluene (1.0 mL) and

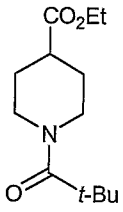
acetonitrile (0.5 mL) and stirred at rt overnight. Celite® (10 mg), copper (I) chloride (11 mg, 0.12 mmol) and diisopropylethylamine (16 mg, 0.12 mmol) were added and the reaction was heated to 80 °C for 1 h. The reaction was cooled to rt and sat. NH_4Cl solution (1 mL) was added and stirred for 1 h. The mixture was filtered through a Celite® plug and then the organics were separated and evaporated to give the crude product. The crude product was taken up in DMF and purified by preperative HPLC to give **Example 19** as a tan colored solid (4 mg, 14%). $(M+H)^+ = 536$.

Example 20

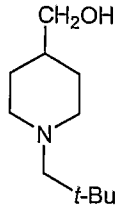
ethyl 2-(2-(1'-neopentylspiro[indoline-3,4'-piperidine]-1-yl)phenylamino)-4-(trifluoromethyl)thiazole-5-carboxylate



20a. ethyl 1-pivaloylpiperidine-4-carboxylate:

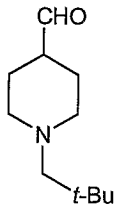


[00217] Ethyl isonipecotate (20 mL, 130 mmol) was dissolved in 130 mL of dichloromethane and cooled to 0 °C and triethyl amine (19.9 mL, 143 mmol) was added. Trimethylacetyl chloride (16.8 mL, 136 mmol) was added dropwise and the reaction was allowed to warm to rt and stirred for 16 h. The reaction mixture was washed with hydrochloric acid solution (1.0 M, aq), sodium bicarbonate (sat., aq.) and sodium chloride (sat., aq.). The organic layer dried over magnesium sulfate, filtered and the solvent removed to provide 29.5 g (94%) of **20a** as a pale orange liquid. LC-MS m/z 242 $[M+H]^+$.



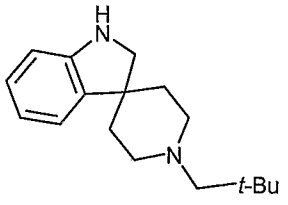
20b. (1-neopentylpiperidin-4-yl)methanol:

[00218] **20a** (29.5 g, 122 mmol) was dissolved in 200 mL of tetrahydrofuran and cooled to 0 °C. Lithium aluminum hydride (s) (10.6 g, 279 mmol) was added slowly and the reaction was allowed to warm to rt and stirred for 24 h. The reaction was quenched by slow addition of sodium sulfate hydrated crystals ($Na_2SO_4.10H_2O$) until there was no bubbling on addition followed by 20 mL of water. The mixture was filtered through Celite®, and the Celite® washed with diethyl ether. The solvent was removed from the filtrate to provide 20 g (97%) of the desired product as a white solid. ^1H NMR (400 MHz, $CDCl_3$).



20c. 1-Neopentylpiperidine-4-carbaldehyde:

[00219] To a solution of oxalyl chloride (490 µL, 5.6 mmol) in DCM (10 mL) at -78 °C was added DMSO (796 µL, 11.2 mmol) dropwise followed by the addition of a solution of **20b** (943 mg, 5.6 mmol) in DCM (2 mL). The mixture was stirred at -78 °C for 30 min and TEA (3.6 mL, 25.5 mmol) was added. The reaction was stirred at -78 °C for 5 min, warmed to rt and stirred at rt for 30 min. The reaction was quenched with water and extracted with DCM. The organic layers were combined and washed with water, dried over magnesium sulfate to give **20c** as a yellow semi-solid (880 mg).

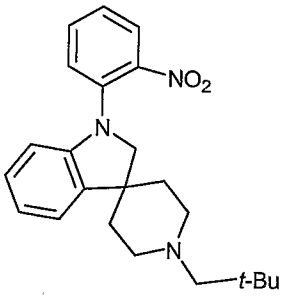


20d. 1'-Neopentylspiro[indoline-3,4'-piperidine]:

[00220] To a solution of **20c** (2.6 g, 14.2 mmol) in AcOH (40 mL) was added phenyl hydrazine (14. 6 mL, 14.9 mmol). The mixture was stirred at rt for 2 h and boron trifluoride diethyl etherate (4.9 mL, 38.3 mmol) was added. The reaction was

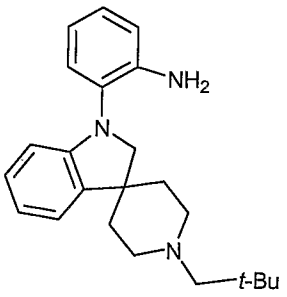
immediately heated at 80 °C (preheated oil bath) for 1.5 h. The mixture was then cooled to -20 °C and $NaBH_4$ was cautiously added in portion. The reaction was stirred at rt overnight, quenched with water and concentrated. The residue was basified with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate to give the crude product as an orange solid. Purification of the crude product by flash chromatography (silica gel, 0-20% MeOH/DCM) provided **20d** as a yellow solid (1.91 g). LC-MS m/z 259.1 $[M+H]^+$.

20e. 1'-neopentyl-1-(2-nitrophenyl)spiro[indoline-3,4'-piperidine]:



[00221] To a solution of **20d** (1.61 g, 8 mmol) in toluene (30 mL) was added $CsCO_3$ (5.2 g, 16 mmol), rac-BINAP (224 mg, 0.36 mmol) and $Pd_2(dba)_3$ (110 mg, 0.12 mmol) while bubbling Argon through the mixture. The mixture was heated at 100 °C for 6 h. The mixture was diluted with hexane and loaded on a 40 g silica gel column and eluted with 0-50% EtOAc/hexane to give **20e** as an orange thick oil (1.44 g). LC-MS m/z 380.1 $[M+H]^+$.

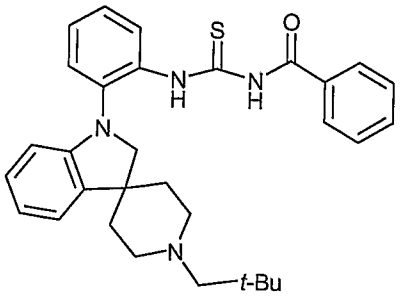
20f. 2-(1'-neopentylspiro[indoline-3,4'-piperidine]-1-yl)aniline:



[00222] To a solution of **20e** (1.44 g, 3.79 mmol) in MeOH/THF (2:1, 75 mL) was added 10% Pd/C (387 mg). The mixture was stirred under hydrogen atmosphere

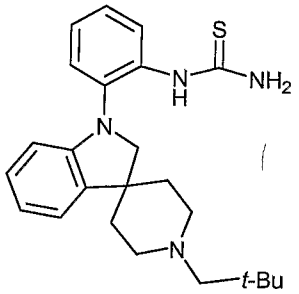
overnight. The reaction was filtered and the filtrate was concentrated to give **20f** as a white solid (1.3 g). LC-MS m/z 350.1 $[M+H]^+$.

20g. N-(2-(1'-neopentylspiro[indoline-3,4'-piperidine]-1-yl)phenylcarbamothioyl)benzamide:



[00223] A mixture of **20f** (118 mg, 0.33 mmol) and benzoylisothiocyanate (63 μL, 0.47 mmol) in DCM (3 mL) was stirred at rt for 3 h. The reaction was concentrated and the residue was purified by flash chromatography (silica gel, 0-10% MeOH/DCM) to give **20g**, as yellow solid (156 mg). LC-MS m/z 513.06 $[M+H]^+$.

20h. 1-(2-(1'-neopentylspiro[indoline-3,4'-piperidine]-1-yl)phenyl)thiourea:



[00224] A mixture of **20g** (138 mg, 0.27 mmol) and 1 N LiOH (0.5 mL) in THF/MeOH (2:1, 3 mL) was stirred at 50 °C for 2 h. The reaction was concentrated and the residue was extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, concentrated and purified by flash chromatography (silica gel, 0-10% MeOH/DCM) to give **20h** as yellow solid (83 mg). LC-MS m/z 409.0 $[M+H]^+$.

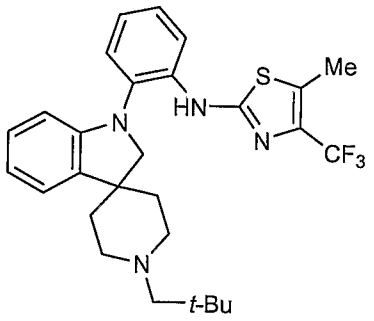
Example 20

[00225] A mixture of **20h** (20 mg, 0.05 mmol), ethyl 2-chloro-4,4,4-trifluoro-3-oxobutanoate (15 μL) and 2,6-lutidine (9 μL, 0.07 mmol) in ethanol (2 mL) was

heated at 95 °C overnight. The reaction was concentrated and the residue was purified by reverse preparative HPLC to give **Example 20** (TFA salt, 12 mg) as a yellow film. LC-MS m/z 573.1 $[M+H]^+$.

Example 21

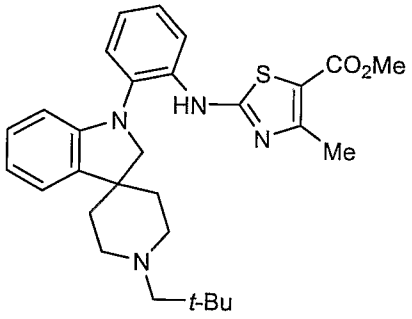
5-methyl-N-(2-(1'-neopentylspiro[indoline-3,4'-piperidine]-1-yl)phenyl)-4-(trifluoromethyl)thiazol-2-amine



[00226] **Example 21** was prepared from **20h** using the procedure described for **Example 20** to give the TFA salt as a yellow film. LC-MS m/z 515.1 $[M+H]^+$.

Example 22

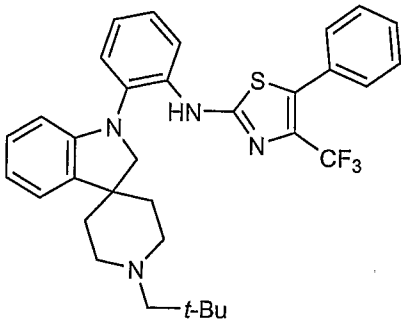
methyl 4-methyl-2-(2-(1'-neopentylspiro[indoline-3,4'-piperidine]-1-yl)phenylamino)thiazole-5-carboxylate



[00227] **Example 22** was prepared from **20h** using the procedure described for **Example 1** to give the TFA salt as a yellow film. LC-MS m/z 505.1 $[M+H]^+$.

Example 23

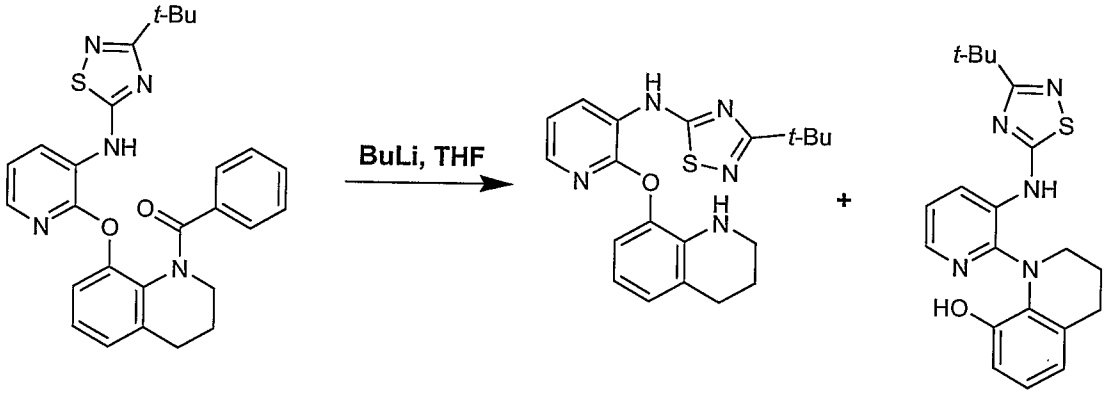
N-(2-(1'-neopentylspiro[indoline-3,4'-piperidine]-1-yl)phenyl)-5-phenyl-4-(trifluoromethyl)thiazol-2-amine



[00228] **Example 23** was prepared from **20h** using the procedure described for **Example 20** to give the TFA salt as a yellow film. LC-MS m/z 577.2 $[M+H]^+$.

Example 24

1-(3-(3-tert-butyl-1,2,4-thiadiazol-5-ylamino)pyridin-2-yl)-1,2,3,4-tetrahydroquinolin-8-ol



24a **Example 24**

24a. 3-amino-phenoxypyridyl intermediate ((8-(3-aminopyridin-2-yloxy)-3,4-dihydroquinolin-1(2H)-yl)(phenyl)methanone):

[00229] **24a** was prepared according to the sequence described in Scheme 13 in U.S. Patent Application 11/126,915, which is hereby incorporated by reference.

[00230] **24a** (12 mg, 0.025 mmol) in THF (3 mL) was cooled to -78 °C. Butyllithium (120 µL, 0.19 mmol) was added and mixture was stirred for 1 h. A saturated solution of ammonium chloride was added, the reaction mixture was extracted using ethylacetate twice. The organic phases were combined, dried using magnesium sulfate, and concentrated *in* vacuo. The crude material was purified by

preparative HPLC to give **Example 24** (1.3 mg) as a yellow oil. ^{1}H NMR (400 MHz, Acetone) δ ppm 1.38 (s, 9 H) 1.83 - 1.94 (m, 2 H) 2.83 (t, *J*=6.44 Hz, 2 H) 3.41 (ddd, *J*=5.12, 3.03, 2.72 Hz, 2 H) 6.51 (dd, *J*=7.83, 1.26 Hz, 1 H) 6.63 (dd, *J*=7.45, 1.14 Hz, 1 H) 6.72 (t, *J*=7.71 Hz, 1 H) 7.16 (dd, *J*=8.08, 4.80 Hz, 1 H) 7.86 (dd, *J*=4.80, 1.77 Hz, 1 H) 8.84 (dd, *J*=8.08, 1.52 Hz, 1 H) 9.73 (s, 1 H). M+H = 382.

UTILITY

[00231] The compounds of the present invention are anti-platelet agents and thus are useful to maintain the fluidity of blood. Additionally, compounds of the present invention are useful for the treatment or prophylaxis of platelet-associated disorders. As used herein, the term "platelet-associated disorder" refers to any disorder which may be prevented, partially alleviated, or cured by the administration of an anti-platelet agent.

[00232] The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function, for example, by inhibiting the aggregation, adhesion or granule content secretion of platelets.

[00233] The term "thrombosis", as used herein, refers to formation or presence of a thrombus (pl. thrombi); clotting within a blood vessel which may cause ischemia or infarction of tissues supplied by the vessel. The term "embolism", as used herein, refers to sudden blocking of an artery by a clot or foreign material which has been brought to its site of lodgment by the blood current. The term "thromboembolism", as used herein, refers to obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to plug another vessel.

[00234] In general, a thromboembolic disorder is a circulatory disease caused by blood clots (i.e., diseases involving fibrin formation, platelet activation, and/or platelet aggregation). The term "thromboembolic disorders (or conditions)" as used herein also includes arterial or venous cardiovascular or cerebovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart or in the peripheral circulation.

[00235] Thus, the compounds of the present invention are useful in the treatment or prevention of various platelet associated disorders including: thrombotic or thromboembolic conditions; acute coronary syndromes (such as coronary artery disease, myocardial infarction (MI), unstable angina, and non-Q Wave MI);

thromboembolic stroke (such as that resulting from atrial fibrillation or from ventricular mural thrombus (low ejection fraction)); venous thrombosis (including deep vein thrombosis); arterial thrombosis; cerebral thrombosis; pulmonary embolism; cerebral embolism; kidney embolisms; peripheral occlusive arterial disease (e.g., peripheral arterial disease, intermittent claudication, critical leg ischemia, prevention of amputation, prevention of cardiovascular morbidity such as MI, transient ischemic attack, stroke, or ischemic sudden death); thromboembolic consequenses of surgery, interventional cardiology or immobility; thromboembolic consequenses of medication (such as oral contraceptives, hormome replacement, and heparin); thrombotic consequenses of atherosclerotic vascular disease and atherosclerotic plaque rupture leading to tissue ischemia; prevention of atherosclerotic plaque formation; transplant atherosclerosis; thromboembolic complications of pregancy including fetal loss; thromboembolic consequences of thrombophilia (e.g., Factor V Leiden, and homocystinenimia); prothrombotic consequences and/or complications of cancer; coagulopathies (e.g., disseminated intravascular coagulation (DIC)); coagulation syndromes; vascular remodeling atherosclerosis, restenosis and systemic infection; prevention of metastesis and tumor implantation; diabetic complications including retinopathy, nephropathy and neuropathy; inflammation (e.g., thrombophlebitis); ischemia (such as that resulting from vascular occlusion, cerebral infarction, transient ischemic attack, stroke and related cerebral vascular diseases); Kasabach-Merritt syndrome; atrial fibrillation; ventricular enlargement (including dilated cardiac myopathy and heart failure); restenosis (e.g., following arterial injury-induced either endogenously or exogenously); thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface that promotes thrombosis. The medical implants or devices include, but are not limited to: prosthetic valves, artificial valves, indwelling catheters, stents, blood oxygenators, shunts, vascular access ports, and vessel grafts. The procedures include, but are not limited to: cardiopulmonary bypass, percutaneous coronary intervention, and hemodialysis.

[00236] In addition to acting as anti-platelet agents, the compounds of the present invention may also find utility in a variety of other settings including as inhibitors of bone resorption such as encountered in various osteoporotic conditions,

as inhibitors of insulin secretion in conditions of hyperinsulinemia, as vasoconstrictive agents such as those used in cases of septic or hypovolemic shock, as inhibitors of smooth muscle relaxation such for the treatment of incontinence or in other cases where inhibition of sympathetic nerve transmission would be of therapeutic benefit such as nociception or neuronal tissue regeneration. These and many other potential utilities for $P2Y_1$ antagonists have been recently reviewed (Burnstock, G. and Williams, M. *J.Pharm. Exp Ther.* **2000**, *295*, 862-9) and are suggested therein.

[00237] Compounds of the present invention may additionally be useful as diagnostic agents and adjuncts. For example, the present compounds may be useful in maintaining the reactivity of fractionated whole blood containing platelets such as required for analytical and biological testing or transfusions. In addition, the compounds of the present invention may be useful for maintaining blood vessel patency in conjunction with vascular surgery including bypass grafting, arterial reconstruction, atherectomy, vascular graft and stent patency, organ, tissue and cell implantation and transplantation. In addition, the compounds of the present invention may be useful for maintaining blood vessel patency in conjunction with interventional cardiology or vascular surgery including bypass grafting, arterial reconstruction, atherectomy, vascular graft and stent patency, organ, tissue and cell implantation and transplantation.

$P2Y_1$ ASSAYS

A. Binding Assay

[00238] A membrane binding assay was used to identify inhibitors of [^{33}P] 2MeS-ADP binding to cloned human $P2Y_1$ receptors. The cDNA clone for human $P2Y_1$ was obtained from Incyte Pharmaceuticals and its sequence confirmed by established techniques (for a compendium of techniques used see Ausubel, F. et al. *Current Protocols in Molecular Biology* **1995** John Wiley and Sons, NY, NY). The essential coding sequences were subcloned into pCDNA 3.1 (Invitrogen) to produce a $P2Y_1$ expression construct. This construct was then transfected into the human embryonic kidney cell line HEK-293 and stable transfectants selected in Genetcin® (G418 sulfate; Life Technologies). Several lines were screened for binding activity

and one (HEK293 #49) selected for further characterization. Membranes were prepared by growing HEK293 #49 in 150 mm dishes in DMEM/10% FBS in the presence of 1mg/ml G418 until cells were 80-90% confluent. Plates were then washed with cold (4°C) D-PBS twice and cells harvested by scraping into 10mL D-PBS. Cells were pelleted by centrifugation (1,000g, 10min, 4°C) and the resulting pellet resuspended in Lysis Buffer (10 mM Tris (7.4), 5mM $MgCl_2$ containing Complete® protease inhibitor cocktail (Roche Cat #1873580) as recommended by the manufacturer). The suspension was then homogenized in a Dounce homogenizer (10-15 strokes; B pestle, on ice) and the homogenate spun at 1,000g, 4°C, 5 min to pellet large debris. The supernatant was centrifuged at 150,000g, 4°C, for 1 hour and the resulting membrane pellet resuspended in 0.5-1mL of Buffer B (15mM HEPES (7.4), 145mM NaCl, 0.1 mM $MgCl_2$, 5mM EDTA, 5 mM KCl) and stored at -70°C until used.

[00239] Binding reactions were performed in WGA FlashPlates (PerkinElmer Life Sciences, Cat # SMP105A) in a volume of 200µL containing ~45 fmol of $P2Y_1$ receptor (5 µg of total protein), 0.5 nM [^{33}P] 2MeS-ADP (PerkinElmer; 2,000 Ci/mmol), and various concentrations of the test compound (usually between 50µM and 10pM) in Buffer B containing 1% DMSO. Reactions were allowed to proceed to completion at room temperature for 1 hour and then the aqueous solution aspirated. Plates were sealed and the residual [^{33}P] bound to the plate determined by scintillation counting. Dose-response curves (IC_{50}) were fit by non-linear regression (XLFit, ID Business Solutions Ltd.) and binding constants (K_i) calculated using the Cheng- Prusoff relationship ($K_i = IC_{50}/(1+L/K_d)$ in which a K_d for 2MeS-ADP to the $P2Y_1$ receptor was determined to be 1.4 nM.

[00240] In general, preferred compounds of the present invention, such as the particular compounds disclosed in the above examples, have been identified to exhibit K_i's of equal to or less than 10 µM in the $P2Y_1$ binding assay, thereby demonstrating these preferred compounds of the present invention as especially effective modulators of $P2Y_1$ activity. More preferred compounds have K_i's of equal to or less than 5 µM, preferably equal to or less than 1 µM, more preferably equal to or less than 0.5 µM.

[00241] The effectiveness of compounds of the present invention as antithrombotic agents can be determined using relevant *in vivo* thrombosis models, including *In Vivo* Electrically-induced Carotid Artery Thrombosis Models and *In Vivo* Rabbit Arterio-venous Shunt Thrombosis Models.

***In Vivo* Electrically-induced Carotid Artery Thrombosis (ECAT) Model:**

[00242] The rabbit ECAT model, described by Wong et al. (*J Pharmacol Exp Ther* **2000**, *295*, 212-218), can be used in this study. Male New Zealand White rabbits are anesthetized with ketamine (50 mg/kg + 50 mg/kg/h IM) and xylazine (10 mg/kg + 10 mg/kg/h IM). These anesthetics are supplemented as needed. An electromagnetic flow probe is placed on a segment of an isolated carotid artery to monitor blood flow. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the initiation of thrombosis. Thrombus formation is induced by electrical stimulation of the carotid artery for 3 min at 4 mA using an external stainless-steel bipolar electrode. Carotid blood flow is measured continuously over a 90-min period to monitor thrombus-induced occlusion. Total carotid blood flow over 90 min is calculated by trapezoidal rule. Average carotid flow over 90 min is then determined by converting total carotid blood flow over 90 min to percent of total control carotid blood flow, which would result if control blood flow had been maintained continuously for 90 min. The ED_{50} (dose that increased average carotid blood flow over 90 min to 50% of the control) of compounds are estimated by a nonlinear least square regression program using the Hill sigmoid E_{max} equation (DeltaGraph; SPSS Inc., Chicago, IL).

***In Vivo* Rabbit Arterio-venous (AV) Shunt Thrombosis Model:**

[00243] The rabbit AV shunt model, described by Wong et al. (Wong, P. C. et al. *J Pharmacol Exp Ther* **2000**, *292*, 351-357), can be used in this study. Male New Zealand White rabbits are anesthetized with ketamine (50 mg/kg + 50 mg/kg/h IM) and xylazine (10 mg/kg + 10 mg/kg/h IM). These anesthetics are supplemented as needed. The femoral artery, jugular vein and femoral vein are isolated and catheterized. A saline-filled AV shunt device is connected between the femoral

arterial and the femoral venous cannulae. The AV shunt device consists of an outer piece of tygon tubing (length = 8 cm; internal diameter = 7.9 mm) and an inner piece of tubing (length = 2.5 cm; internal diameter = 4.8 mm). The AV shunt also contains an 8-cm-long 2-0 silk thread (Ethicon, Somerville, NJ). Blood flows from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread induces the formation of a significant thrombus. Forty minutes later, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID_{50} values (dose which produces 50% inhibition of thrombus formation) are estimated by a nonlinear least square regression program using the Hill sigmoid E_{max} equation (DeltaGraph; SPSS Inc., Chicago, IL).

[00244] The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These other agents include, but are not limited to, anticoagulant or coagulation inhibitory agents, other antiplatelet or platelet inhibitory agents, or thrombolytic or fibrinolytic agents.

[00245] By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

[00246] Examples of suitable anti-arrhythmic agents for use in combination with the present compounds include: Class I agents (such as propafenone); Class II agents (such as carvadiol and propranolol); Class III agents (such as sotalol, dofetilide, amiodarone, azimilide, and ibutilide); Class IV agents (such as ditiazem and verapamil); K^+ channel openers such as I_{Ach} inhibitors, and I_{Kur} inhibitors (e.g., compounds such as those disclosed in WO01/40231).

[00247] Examples of suitable antihypertensive agents for use in combination with the compounds of the present invention include: alpha adrenergic blockers; beta

adrenergic blockers; calcium channel blockers (e.g. diltiazem, verapamil, nifedipine, amlodipine, and mybefradil); diruetics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone); renin inhibitors; angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril); angiotensin AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan); ET-A receptor antagonists (e.g., sitaxsentan, atrsentan, and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265); Dual ET-A/AT-1 antagonist (e.g., compounds disclosed in WO 00/01389); neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat, gemopatrilat, and nitrates); and β-blockers (e.g., propanolol, nadolo, or carvedilol).

[00248] Examples of other suitable anti-platelet agents for use in combination with the compounds of the present invention, include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as acetaminophen, aspirin, codeine, diclofenac, droxicam, fentaynl, ibuprofen, indomethacin, ketorolac, mefenamate, morphine, naproxen, phenacetin, piroxicam, sufentanyl, sulfinpyrazone, sulindac, and pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA) and piroxicam are preferred. Other suitable platelet inhibitory agents include glycoprotein IIb/IIIa blockers (e.g., abciximab, eptifibatide, tirofiban, integrelin), thromboxane-A2-receptor antagonists (e.g., ifetroban), thromboxane-A2-synthetase inhibitors, phosphodiesterase-III (PDE-III) inhibitors (e.g., dipyridamole, cilostazol), and PDE V inhibitors (such as sildenafil), protease-activated receptor 1 (PAR-1) antagonists (e.g., SCH-530348, SCH-203099, SCH-529153, and SCH-205831), and pharmaceutically acceptable salts or prodrugs thereof.

[00249] Other examples of suitable anti-platelet agents for use in combination with the compounds of the present invention, with or without aspirin, include: ADP (adenosine diphosphate) receptor antagonists including P_2Y_{12} antagonists and other P_2Y_1 antagonists. Preferred P_2Y_{12} receptor antagonists , but are not limited to,

clopidogrel, ticlopidine, prasugrel, and AZD-6140, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine and clopidogrel are also preferred compounds since they are known to be more gentle than aspirin on the gastro-intestinal tract in use. Clopidogrel is an even more preferred agent.

[00250] Examples of suitable anticoagulants for use in combination with the compounds of the present invention include warfarin and heparin (either unfractionated heparin such as enoxaparin and dalteparin or any commercially available low molecular weight heparin, for example LOVENOX™), synthetic pentasaccharide, direct acting thrombin inhibitors including hirudin and argatroban, factor VIIa inhibitors, factor IXa inhibitors, factor Xa inhibitors (e.g., Arixtra™, apixaban, rivaroxaban, LY-517717, DU-176b, DX-9065a, and those disclosed in WO 98/57951, WO 03/026652, WO 01/047919, and WO 00/076970), factor XIa inhibitors, and inhibitors of activated TAFI and PAI-1 known in the art.

[00251] The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the secretion of platelet granule contents including serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boropeptides, heparins, hirudin, argatroban, dabigatran, AZD-0837, and those disclosed in WO 98/37075 and WO 02/044145, and pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal a-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin.

[00252] The term thrombolytic (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator (TPA, natural or recombinant) and modified forms thereof, anistreplase, urokinase, streptokinase, tenecteplase (TNK),

lanoteplase (nPA), factor VIIa inhibitors, thrombin inhibitors, inhibitors of factors IXa, Xa, and XIa, PAI-1 inhibitors (i.e., inactivators of tissue plasminogen activator inhibitors), inhibitors of activated TAFI, alpha-2-antiplasmin inhibitors, and anisoylated plasminogen streptokinase activator complex, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

[00253] Examples of suitable calcium channel blockers (L-type or T-type) for use in combination with the compounds of the present invention include diltiazem, verapamil, nifedipine, amlodipine and mybefradil.

[00254] Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

[00255] Examples of suitable diruetics for use in combination with the compounds of the present invention include: chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, and spironolactone.

[00256] Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include sprionolactone and eplirinone.

[00257] Examples of suitable cholesterol/lipid lowering agents and lipid profile therapies for use in combination with the compounds of the present invention include: HMG-CoA reductase inhibitors (e.g., pravastatin lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin)); squalene synthetase inhibitors; fibrates; bile acid sequestrants (such as questran); ACAT inhibitors; MTP inhibitors; lipooxygenase inhibitors; nicotonic acid; fenofibric acid derivatives (e.g., gemfibrozil, clofibrat,

fenofibrate and benzafibrate); probucol; choesterol absorption inhibitors; and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

[00258] Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include: biguanides (e.g. metformin); glucosidase inhibitors (e.g. acarbose); insulins (including insulin secretagogues or insulin sensitizers); meglitinides (e.g. repaglinide); sulfonylureas (e.g., glimepiride, glyburide and glipizide); biguanide/glyburide combinations (e.g., glucovance), thiozolidinediones (e.g. troglitazone, rosiglitazone, and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in WO00/59506, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DPP4) inhibitors.

[00259] Examples of suitable anti-depressant agents for use in combination with the compounds of the present invention include nefazodone and sertraline.

[00260] Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include: prednisone; dexamethasone; enbrel; protein tyrosine kinase (PTK) inhibitors; cyclooxygenase inhibitors (including NSAIDs, and COX-1 and/or COX-2 inhibitors); aspirin; indomethacin; ibuprofen; prioxicam; naproxen; celecoxib; and/or rofecoxib.

[00261] Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate and raloxifene.

[00262] Examples of suitable hormone replacement therapies for use in combination with the compounds of the present invention include estrogen (e.g., congugated estrogens) and estradiol.

[00263] Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include orlistat, aP2 inhibitors (such as those disclosed in WO00/59506), and cannabinoid receptor CB1 antagonists (e.g., rimonabant, AVE-1625, SR-147778, and CP-945598).

[00264] Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, and hydroxyzine pamoate.

[00265] Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, paclitaxel, adriamycin; epithilones, cisplatin, and carboplatin.

[00266] Examples of suitable anti-ulcer and gastroesophageal reflux disease agents for use in combination with the compounds of the present invention include famotidine, ranitidine, and omeprazole.

[00267] Administration of the compounds of the present invention (i.e., a first therapeutic agent) in combination with at least one additional therapeutic agent (i.e., a second therapeutic agent), preferably affords an efficacy advantage over the compounds and agents alone, preferably while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety. It is preferred that at least one of the therapeutic agents is administered in a sub-therapeutic dose. It is even more preferred that all of the therapeutic agents be administered in sub-therapeutic doses. Sub-therapeutic is intended to mean an amount of a therapeutic agent that by itself does not give the desired therapeutic effect for the condition or disease being treated. Synergistic combination is intended to mean that the observed effect of the combination is greater than the sum of the individual agents administered alone.

[00268] The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of platelet ADP receptor. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving platelet ADP receptor. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

[00269] The compounds of the present invention may also be used in diagnostic assays involving platelet ADP receptor. For example, the presence of $P2Y_1$ in an unknown sample could be determined by addition of the relevant

radiolabled compound to the sample and measuring the extend of binding to the $P2Y_1$ receptor.

[00270] The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic disorder (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat a thromboembolic disorder. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

[00271] The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (e.g., for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

[00272] The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (e.g., cardboard or plastic), crates, cartons, bags (e.g., paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or

another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

[00273] The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (e.g., the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (e.g., paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (e.g., printed or applied).

DOSAGE AND FORMULATION

[00274] The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[00275] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

[00276] By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 0.1 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 0.001 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this 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.

[00277] Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[00278] The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

[00279] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate,

sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

[00280] The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[00281] Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. 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, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

[00282] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.1-95% by weight based on the total weight of the composition.

[00283] Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[00284] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[00285] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

[00286] Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, a standard reference text in this field.

[00287] Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of the present invention and about 0.1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 100 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 50 milligrams per dosage unit.

[00288] Where the compounds of the present invention are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of the present invention and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of the present invention and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

[00289] Where the compounds of the present invention are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of the present invention, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 50-80% when administered with a compound of the present invention.

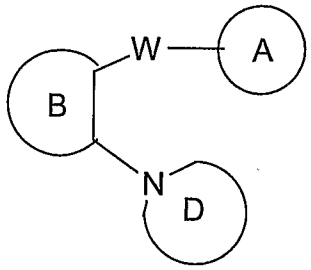
[00290] Where two or more of the foregoing second therapeutic agents are administered with the compound of the present invention, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

[00291] Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the present invention and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

[00292] These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

What is claimed is:

1. A compound of Formula (I):



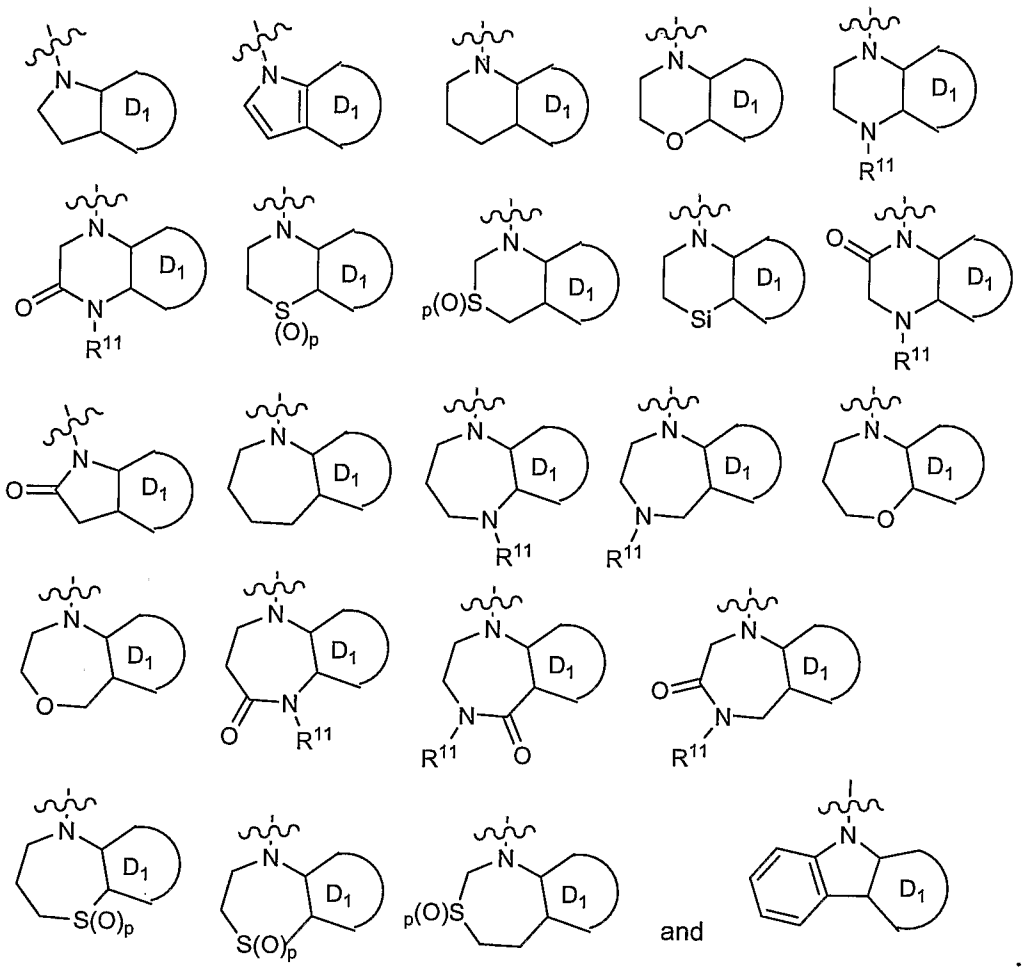
(I)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

ring A is C_{6-10} aryl substituted with 0-5 R^1, or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-5 R^1;

ring B is C_{6-10} aryl substituted with 0-4 R^7, or a 5- to 10-membered heteroaryl comprising: carbon atoms and 1-4 ring heteroatoms selected from N, NR^{11}, N→O, $S(O)_p$, and O, wherein said heteroaryl is substituted with 0-4 R^7;

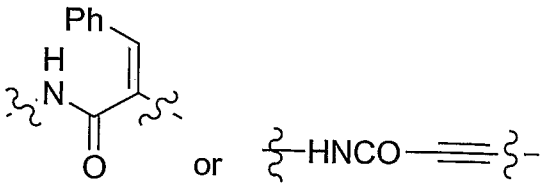
ring D is substituted with 0-5 R^{6a} and selected from:



;

wherein D_1 is a 5- to 7-membered carbocycle or a 5-6-membered heterocycle comprising: carbon atoms and 0-3 ring heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-2 carbonyl groups, and 0-3 double bonds;

W is NR^{18}, O, S, -NHCOCH=CH-, -NHCO-, $-NHCO_2$-, $-NHCO_2CH_2$-, -NHCON(Me)-, $-NHCOCH_2NH$-, -NHCOCH(Me)-, $-NHCOCH_2CH_2$-, $-NHCOCH_2CONH$-, $-NHCH_2$-, $-NHCH_2CH_2CH_2$-, $-NHSO_2$-, $-NHSO_2NH$-, $-NHSO_2CH_2$-, $-NHSO_2CH$=CH-, -NHCONHNHCO-, $-CH_2CONH$-,



;

R^1 is, independently at each occurrence, =O, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $SiMe_3$, $-(CR^fR^f)_rOR^c$, SR^c, CN, NO_2, $-(CR^fR^f)_rNR^{12}R^{13}$, $-(CR^fR^f)_rC(O)R^c$, $-(CR^fR^f)_rCO_2R^c$, $-(CR^fR^f)_rC(O)NR^{12}R^{13}$,

$-C(O)NR^{14}(CR^fR^f)_tN^{12}R^{13}$, $-(CR^fR^f)_rOC(O)NR^{12}R^{13}$, $-(CR^fR^f)_rNR^{14}C(O)NR^{12}R^{13}$, $-(CR^fR^f)_rNR^{14}C(O)R^d$, $-(CR^fR^f)_rNR^{14}C(O)OR^h$, $-NR^{14}(CR^fR^f)_nC(O)R^d$, $-NR^{14}CO(CR^fR^f)_nOR^c$, $-(CH_2)_rCR^{13}(=NOR^c)$, $-(CH_2)_r-C(NH_2)(=NOR^c)$, $-S(O)_pNR^{12}R^{13}$, $-(CR^fR^f)_rNR^{14}S(O)_pNR^{12}R^{13}$, $-NR^{14}SO_2CF_3$, $-NR^{14}S(O)_pR^d$, $-S(O)_2CF_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-OP(O)(OEt)_2$, $-O(CH_2)_2OP(O)(OEt)_2$, $-N(C_{1-4}$ alkyl$)_3{}^+Cl^-$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CR^fR^f)_r-C_{3-13}$ carbocycle substituted with 0-5 R^b, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-5 R^b;

alternatively, two R^1s on two adjacent carbon atoms are combined with the carbon atoms to which they are attached, form a 5- to 10-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-2 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-4 R^b;

R^{6a} is, independently at each occurrence, =O, F, Cl, Br, I, $-(CR^iR^i)_r-OR^c$, SR^c, CN, NO_2, CF_3, OCF_3, $-CF_2CF_3$, $-OCF_2CF_2H$, $-OCF_2CF_3$, $-(CR^fR^f)_r-NR^{12}R^{13}$, $-C(O)R^c$, $-(CR^fR^f)_r-C(O)OR^c$, $-(CR^fR^f)_r-C(O)NR^{12}R^{13}$, $-(CR^fR^f)_r-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, $Si(Me)_3$, $Si(C_{1-4}$ alkyl$)_3$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_1-C_4 alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-8} alkyl substituted with 0-1 R^a, C_{2-8} alkenyl substituted with 0-1 R^a, C_{2-8} alkynyl substituted with 0-1 R^a, $-(CR^fR^f)_r-C_{3-10}$ carbocycle substituted with 0-2 R^e, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^e;

alternatively, when two R^{6a} groups are attached to the same carbon atom or silicon atom, together with the carbon atom or silicon atom to which they are attached, they form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1

carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

alternatively, when two R^{6a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

R^7 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^c, SR^c, CN, NO_2, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CR^fR^f)_r-C_{3-10}$ carbocycle substituted with 0-3 R^b, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{7b}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^b;

alternatively, two R^7s on two adjacent carbon atoms form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 ring heteroatoms selected from O, N, NR^{7b}, and $S(O)_p$, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^{7c};

R^{7b} is H, C_{1-4} alkyl, $-C(O)(C_{1-4}$ alkyl), -C(O)phenyl, -C(O)benzyl, or benzyl;

R^{7c} is, independently at each occurrence, H, F, Cl, Br, I, OCF_3, CF_3, OR^c, SR^c, CN, NO_2, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-4} alkyl, phenyl substituted with 0-3 R^b, or benzyl substituted with 0-3 R^b;

R^{11} is, independently at each occurrence, H, C_{1-4} alkoxy, C_{1-6} alkyl substituted with 1-5 fluorine, $-(CR^fR^f)_rC(O)NR^{12}R^{13}$, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-4} alkenyl substituted with 0-1 R^a, C_{2-4} alkynyl substituted with 0-1 R^a, $-C(O)(C_{1-6}$ alkyl), $-C(O)(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)(CH_2)_n(C_{6-10}$ aryl), $-C(O)(CH_2)_n$(5- to 10-membered heteroaryl), $-C(O)O(C_{1-8}$ alkyl), $-C(O)O(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)O(CH_2)_n(C_{6-10}$ aryl), $-C(O)O(CH_2)_n$(5- to 10-membered heteroaryl), $-C(O)O(CH_2)_{2-4}(C_{1-4}$ alkyl),

-C(O)NH(C_{1-8} alkyl), -C(O)NH(CH_2)$_n$(C_{3-6} cycloalkyl), -C(O)NH(CH_2)$_n$(C_{6-10} aryl), -C(O)NH(CH_2)$_n$(5- to 10-membered heteroaryl), -S(O)$_2$(C_{1-8} alkyl), -S(O)$_2$(CH_2)$_n$(C_{3-6} cycloalkyl), -S(O)$_2$(CH_2)$_n$(C_{6-10} aryl), -S(O)$_2$(CH_2)$_n$(5- to 10-membered heteroaryl), -(CR^fR^f)$_r$-C_{3-10} carbocycle, or -(CR^fR^f)$_r$-5- to 10-membered heterocycle; wherein said alkyl, cycloalkyl, aryl, and carbocycle are substituted with 0-2 R^b, and said heteroaryl and heterocycle are substituted with 0-2 R^b and comprise: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and S(O)$_p$;

R^{12} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 1-5 fluorine, -(CR^fR^f)$_r$C(O)NR^fR^f, C_{1-6} alkyl, -C(O)(C_{1-6} alkyl), -C(O)(CH_2)$_n$(C_{6-10} aryl), -C(O)(CH_2)$_n$(5- to 10-membered heteroaryl), -C(O)O(C_{1-4} alkyl), -C(O)OCH_2(C_{6-10} aryl), -(CH_2)$_n$C(O)OCH_2(5- to 10-membered heteroaryl), -(CH_2)$_n$OC(O)(C_{1-4} alkyl), -(CH_2)$_n$OC(O)(C_{6-10} aryl), -(CH_2)$_n$OC(O)(5- to 10-membered heteroaryl), -(CH_2)$_n$C(O)O(C_{1-4} alkyl), -(CH_2)$_n$C(O)O(C_{6-10} aryl), -(CH_2)$_n$C(O)O(5- to 10-membered heteroaryl), -(CH_2)$_n$C(O)NH(C_{1-6} alkyl), -(CH_2)$_n$C(O)NH(C_{6-10} aryl), -(CH_2)$_n$C(O)NH(5- to 10-membered heteroaryl), -(CH_2)$_t$OC(O)NH(C_{1-6} alkyl), -(CH_2)$_t$OC(O)NH(C_{6-10} aryl), -(CH_2)$_t$OC(O)NH(5- to 10-membered heteroaryl), -S(O)$_2$(C_{1-6} alkyl), -S(O)$_2$(CH_2)$_n$(C_{6-10} aryl), -S(O)$_2$(CH_2)$_n$(5- to 10-membered heteroaryl), -(CR^fR^f)$_n$-(C_{6-10} aryl), or -(CR^fR^f)$_n$- 5- to 10-membered heteroaryl; wherein said alkyl and aryl are substituted with 0-2 R^g; and said heteroaryl is substituted with 0-2 R^g and comprises: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and S(O)$_p$;

R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, or -(CH_2)$_n$-phenyl;

alternatively, R^{12} and R^{13}, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising: carbon atoms and 1-2 additional heteroatoms selected from N, NR^{11}, O, and S(O)$_p$;

R^{14} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{14a}, C_{2-6} alkenyl substituted with 0-2 R^{14a}, C_{2-6} alkynyl substituted with 0-2 R^{14a},

$-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^g, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^g;

R^{14a} is, independently at each occurrence, H, C_{1-4} alkyl, OR^f, Cl, F, Br, I, =O, CF_3, CN, NO_2, $NR^{12}R^{13}$, $-C(O)R^f$, $-C(O)OR^f$, $-C(O)NR^{12}R^{13}$, or $-S(O)_pR^f$;

R^{16} is, independently at each occurrence, H, F, C_{1-6} alkyl substituted with 0-2 R^a, C_{2-6} alkenyl substituted with 0-2 R^a, C_{2-6} alkynyl substituted with 0-2 R^a, or $-(CH_2)_r$-phenyl substituted with 0-2 R^b;

R^{17} is, independently at each occurrence, H, OH, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

alternatively, R^{16} and R^{17} on the same carbon atom combine to form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl, and 0-3 double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

alternatively, two R^{16} groups on adjacent atoms combine to form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl, and 0-3 double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

R^{18} is H, C_{1-6} alkyl substituted with 0-2 R^a, C_{2-6} alkenyl substituted with 0-2 R^a, C_{2-6} alkynyl substituted with 0-2 R^a, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-S(O)_2R^h$, $-S(O)_2NR^{12}R^{13}$, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^b, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, and substituted with 0-3 R^b;

R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, $-(CR^fR^f)_rOR^c$, $-(CR^fR^f)_rSR^c$, CN, $-(CR^fR^f)_rNR^{12}R^{13}$, $-(CR^fR^f)_rC(O)R^c$, $-(CR^fR^f)_rC(O)OR^c$, $-(CR^fR^f)_rC(O)NR^{12}R^{13}$, $-(CR^fR^f)_rNR^{14}C(O)R^d$, $-(CR^fR^f)_rS(O)_pNR^{12}R^{13}$, $-(CR^fR^f)_rS(O)R^d$, $-(CR^fR^f)_rS(O)_2R^d$, C_{1-4} alkyl substituted with 1-5 fluorine,

$-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^e, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^b is, independently at each occurrence, H, =O, F, Cl, Br, I, $-(CH_2)_r-OR^c$, SR^c, CN, NO_2, CF_3, OCF_3, $-(CR^fR^f)_rNR^{12}R^{13}$, $-C(O)R^c$, $-(CH_2)_r-C(O)OR^c$, $-(CH_2)_r-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_{1-4} alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^e, or $-(CH_2)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^c is, independently at each occurrence, H, $-OP(O)(OEt)_2$, C_{1-8} alkyl substituted with 0-3 R^e, C_{2-8} alkenyl substituted with 0-3 R^e, C_{2-8} alkynyl substituted with 0-3 R^e, $-(CR^fR^f)_r-C_{3-8}$ cycloalkyl substituted with 0-3 R^e, $-(CR^fR^f)_r-C_{6-10}$ aryl substituted with 0-3 R^e, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substitutd with 0-3 R^e;

R^d is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-3 R^e, or $-(CH_2)_r$-5- to 10- membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^e is, independently at each occurrence, H, =O, $-(CH_2)_r-OR^f$, F, Cl, Br, I, CN, NO_2, $-(CH_2)_r-NR^{12}R^{13}$, $-C(O)R^f$, $-(CH_2)_r-C(O)OR^f$, $-NR^{14}C(O)R^f$, $-(CH_2)_r-C(O)NR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$, $-NR^{14}SO_2NR^{12}R^{13}$, $-NR^{14}SO_2-C_{1-4}$ alkyl, $-NR^{14}SO_2CF_3$, $-NR^{14}SO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p-OR^h$, $-(CF_2)_rCF_3$, $Si(Me)_3$, $Si(Me)_2(t\text{-Bu})$, $Si(C_{1-4}\text{ alkyl})_3$, C_{1-8} alkyl substituted with 0-2 R^g, C_{2-8} alkenyl substituted with 0-2 R^g, C_{2-8} alkynyl substituted with 0-2 R^g, $-(CH_2)_r-C_{3-8}$ cycloalkyl substituted with 0-2 R^g, $-(CH_2)_r-C_{6-10}$ aryl substituted with 0-2 R^g, or $-(CH_2)_r$-5- to

10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

alternatively, two R^e groups, together with the atoms to which they are attached, form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^f, O, and $S(O)_p$, 0-1 carbonyl and 0-3 double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^g;

R^f is, independently at each occurrence, H, F, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

R^g is, independently at each occurrence, H, =O, OR^f, F, Cl, Br, I, CN, NO_2, $-NR^fR^f$, $-C(O)R^f$, $-C(O)OR^f$, $-NR^fC(O)R^f$, $-C(O)NR^fR^f$, $-SO_2NR^fR^f$, $-NR^fSO_2NR^fR^f$, $-NR^fSO_2$-C_{1-4} alkyl, $-NR^fSO_2CF_3$, $-NR^fSO_2$-phenyl, $-S(O)_2CF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-(CF_2)_rCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

R^h is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^g, $-(CH_2)_n$-phenyl substituted with 0-2 R^g, or $-(CH_2)_n$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

R^i is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^g, $-(CH_2)_n$-phenyl substituted with 0-2 R^g, or $-(CH_2)_n$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

s, at each occurrence, is selected from 0, 1, 2, and 3; and

t, at each occurrence, is selected from 1, 2, 3, and 4;

provided that:

(i) when W is -NHCO-, $-NHCO_2$-, or $-NHCOCH_2CH_2$-, ring B is substituted or unsubstituted phenylene and ring D is substituted or unsubstituted 2,3-dihydro-1H-indol-1-yl or substituted or unsubstituted 3,4-

dihydro-1(2H)-quinolinyl, then ring A is other than unsubstituted or substituted phenyl, furanyl, pyridyl, or 4-methyl-piperazin-1-yl;

(ii) when W is -$NHSO_2$-, ring B is quinoxalinylene and ring D is 3,4-dihydro-1(2H)-quinolinyl, then ring A is other than phenyl or substituted phenyl; or

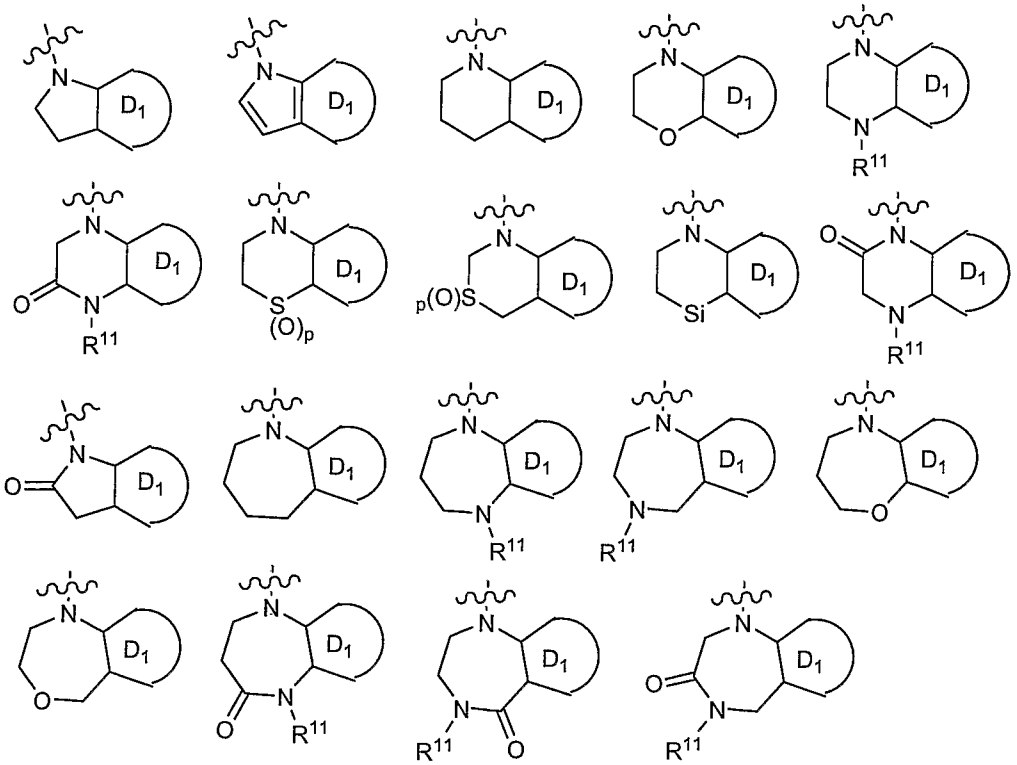
(iii) the compound is other than 2-(2,3-dinydro-7-methylcyclopent[b]indol-4(1H)-yl)-N,N-diphenylbenzenamide.

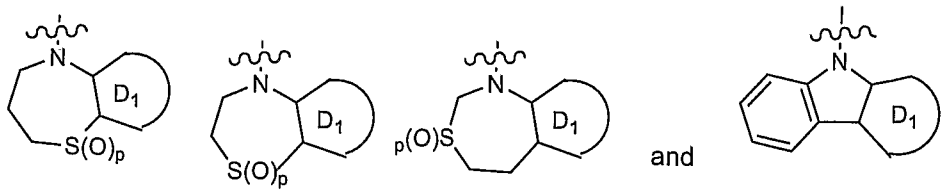
2. A compound according to Claim 1, wherein:

ring B is C_{6-10} aryl substituted with 0-4 R^7, or a 5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 ring heteroatoms selected from N, NR^{11}, $S(O)_p$, and O, wherein said heteroaryl is substituted with 0-4 R^7;

W is NR^{18}, O, S, -NHCOCH=CH-, -$NHSO_2$-, -$NHSO_2CH_2$-, or -$NHSO_2CH$=CH-; and

ring D is substituted with 0-5 R^{6a} and selected from:

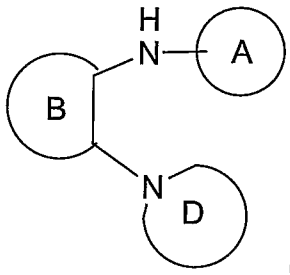




;

wherein D_1 is selected from: cyclopentyl, cylohexyl, piperidinyl, tetrahydropyranyl, phenyl, pyridinyl, pyrimidinyl, thiophenyl, pyrrolyl, furanyl, thiazolyl, imidazolyl, and oxazolyl.

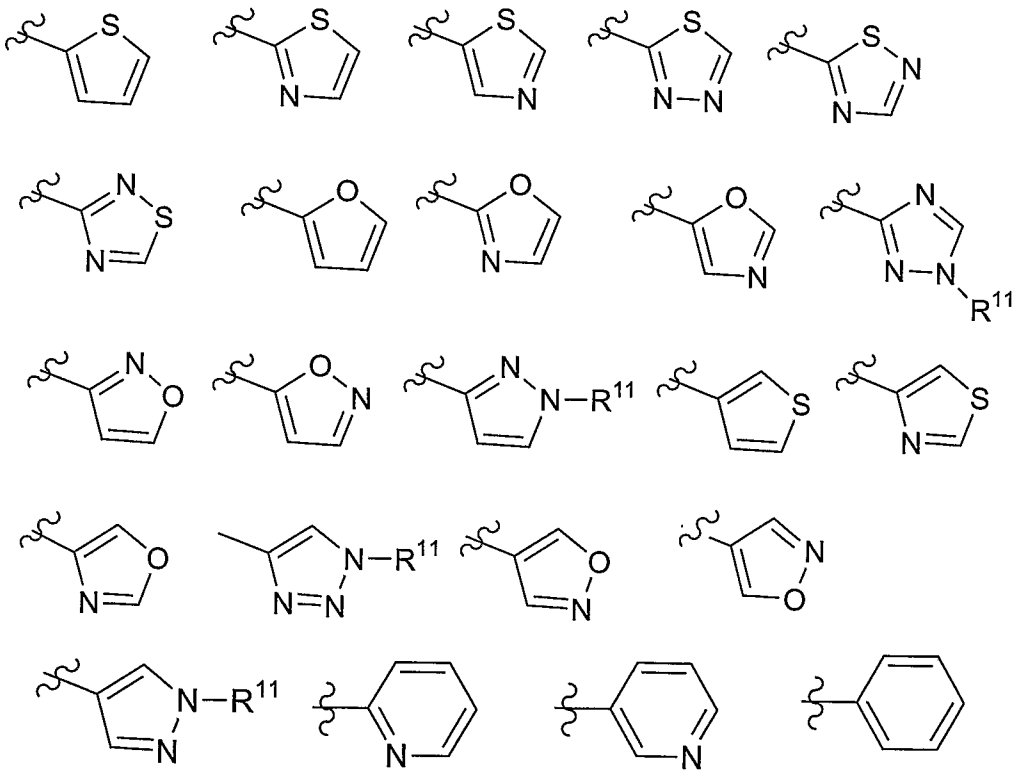
3. A compound according to Claim 1, wherein the compound is of Formula (II):

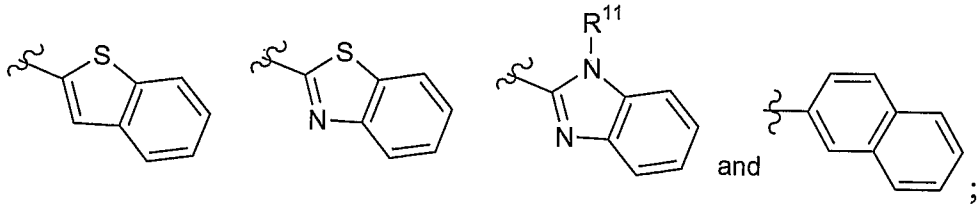


(II)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

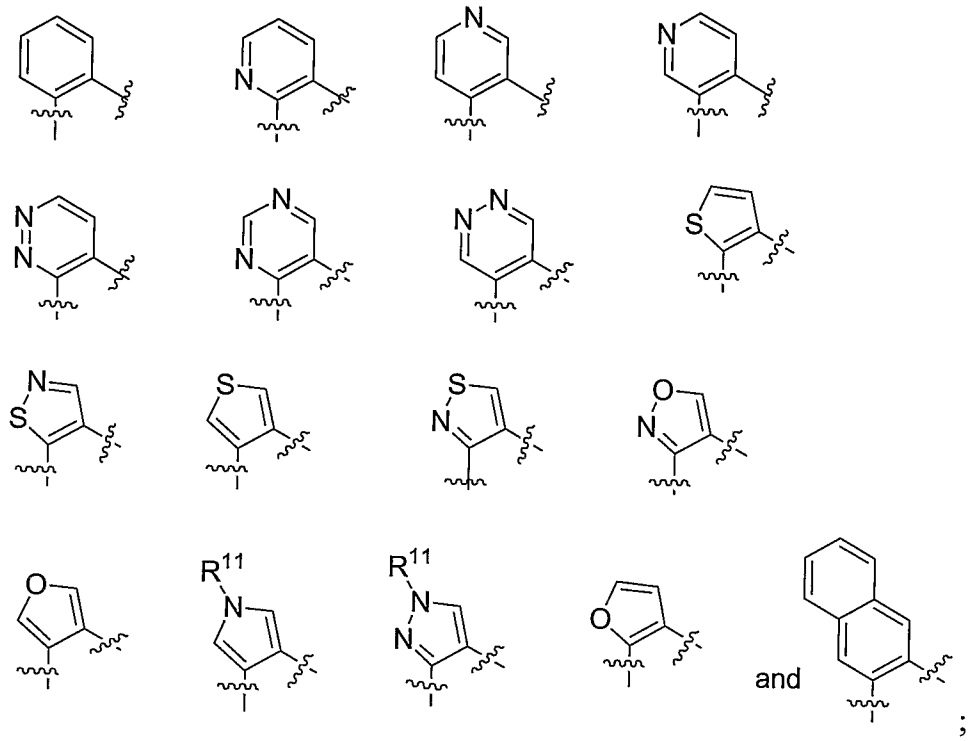
ring A is substituted with 0-4 R^1 and selected from:





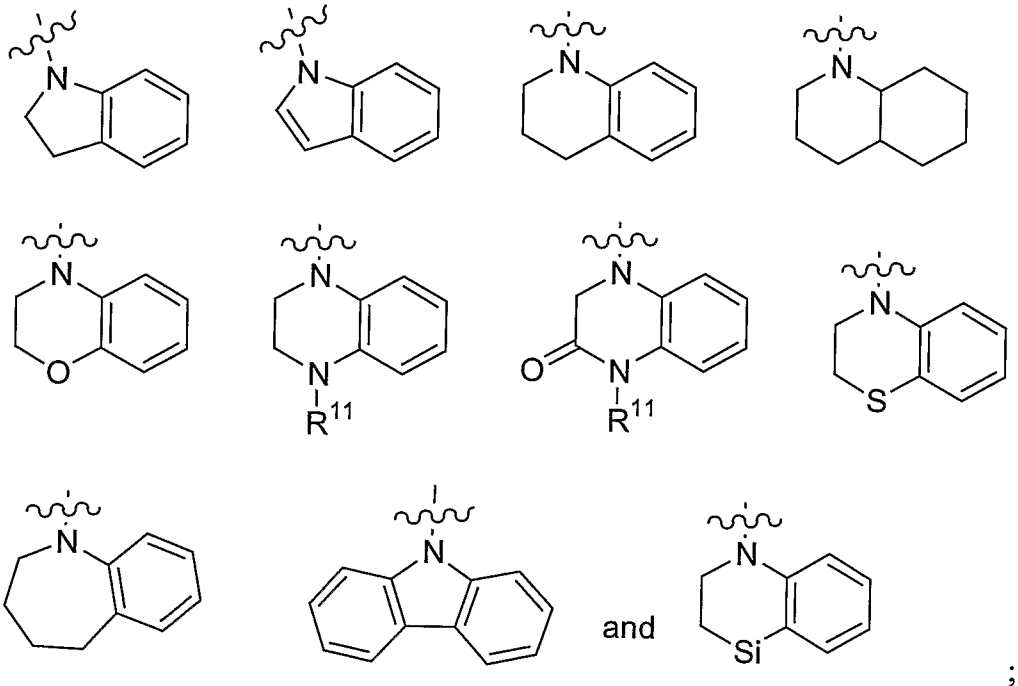
;

ring B is substituted with 0-3 R^7 and selected from:



;

ring D is substituted with 0-5 R^{6a} and selected from:



;

R^I is, independently at each occurrence, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $SiMe_3$, $-(CR^fR^f)_r-OR^c$, SR^c, CN, NO_2, $-(CR^fR^f)_r-NR^{12}R^{13}$, $-(CR^fR^f)_u-C(O)R^c$, $-(CR^fR^f)_r-CO_2R^c$, $-(CR^fR^f)_u-C(O)NR^{12}R^{13}$, $-OP(O)(OEt)_2$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl, C_{1-8} alkyl substituted with 0-2 R^a, $-(CR^fR^f)_u-C_{3-6}$ carbocycle substituted with 0-2 R^b, or $-(CR^fR^f)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^b;

alternatively, two R^1s on two adjacent carbon atoms are combined with the carbon atoms to which they attached, form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-1 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-2 R^b;

R^{6a} is, independently at each occurrence, F, Cl, Br, I, $-(CR^fR^f)_r-OR^c$, SR^c, CN, CF_3, OCF_3, $-CF_2CF_3$, $-OCF_2CF_2H$, $-OCF_2CF_3$, $-NR^{12}R^{13}$, $-C(O)R^c$, $-(CR^fR^f)_r-C(O)OR^c$, $-Si(Me)_3$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_1-C_4 alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-8} alkyl substituted with 0-2 R^a, C_{2-8} alkenyl substituted with 0-2 R^a, C_{2-8} alkynyl substituted with 0-2 R^a, $-(CR^fR^f)_r-C_{3-10}$ carbocycle substituted with 0-2 R^e, or $-(CR^fR^f)_r$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^e;

alternatively, when two R^{6a} groups are attached to the same carbon atom or silicon atom, together with the carbon atom or silicon atom to which they are attached, they form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-3 heteroatoms selected from N, NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

alternatively, when two R^{6a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N,

NR^{11}, O, Si, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-3 R^b;

R^7 is, independently at each occurrence, H, =O, F, Cl, Br, I, OCF_3, CF_3, OR^c, SR^c, CN, NO_2, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-6} alkyl substituted with 0-2 R^a, $-(CH_2)_u$-C_{3-10} carbocycle substituted with 0-3 R^b, or $-(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{7b}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^b;

R^{7b} is H, C_{1-4} alkyl, $-C(O)(C_{1-4}$ alkyl), -C(O)phenyl, -C(O)benzyl, or benzyl;

R^{11} is, independently at each occurrence, H, C_{1-8} alkyl substituted with 0-2 R^a, $-C(O)(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)(CH_2)_n$phenyl, $-C(O)O(C_{1-8}$ alkyl), $-C(O)O(CH_2)_n(C_{3-6}$ cycloalkyl), $-C(O)O(CH_2)_n$phenyl, $-C(O)O(CH_2)_{2-4}(C_{1-4}$ alkyl), $-C(O)NH(C_{1-6}$ alkyl), $-S(O)_2(C_{1-6}$ alkyl), $-S(O)_2(CH_2)_n$phenyl, $-(CR^fR^f)_r$-C_{3-7} cycloalkyl, $-(CR^fR^f)_r$-phenyl, or $-(CR^fR^f)_r$-5- to 6-membered heterocycle; wherein said alkyl, cycloalkyl, phenyl, and aryl are substituted with 0-2 R^b, and said heteroaryl and heterocycle are substituted with 0-2 R^b and comprise: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$;

R^{12} is, independently at each occurrence, H, C_{1-6} alkyl, $-C(O)(C_{1-6}$ alkyl), $-C(O)(CH_2)_n$phenyl, $-C(O)(CH_2)_n$(5- to 6-membered heteroaryl), $-C(O)O(C_{1-4}$ alkyl), $-C(O)OCH_2$phenyl, $-(CH_2)_nC(O)OCH_2$(5- to 6-membered heteroaryl), $-(CH_2)_nOC(O)(C_{1-4}$ alkyl), $-(CH_2)_nOC(O)$phenyl, $-(CH_2)_nOC(O)$(5- to 6-membered heteroaryl), $-(CH_2)_nC(O)O(C_{1-4}$ alkyl), $-(CH_2)_nC(O)O$phenyl, $-(CH_2)_nC(O)O$(5- to 6-membered heteroaryl), $-(CH_2)_nC(O)NH(C_{1-6}$ alkyl), $-(CH_2)_nC(O)NH$phenyl, $-(CH_2)_nC(O)NH$(5- to 6-membered heteroaryl), $-(CH_2)_tOC(O)NH(C_{1-6}$ alkyl), $-(CH_2)_tOC(O)NH$phenyl, $-(CH_2)_tOC(O)NH$(5- to 6-membered heteroaryl), $-S(O)_2(C_{1-6}$ alkyl), $-S(O)_2(CH_2)_n$phenyl, $-S(O)_2(CH_2)_n$(5- to 6-membered heteroaryl), $-(CR^fR^f)_n$-phenyl, or $-(CR^fR^f)_n$-5- to 6-membered heteroaryl; wherein said alkyl, and aryl are substituted with 0-2 R^g; and

said heteroaryl is substituted with 0-2 R^g and comprises: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, or $-(CH_2)_n$-phenyl;

alternatively, R^{12} and R^{13}, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising: carbon atoms and 1-2 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{14} is, independently at each occurrence, H, C_{1-6} alkyl substituted with 0-2 R^{14a}, C_{2-6} alkenyl substituted with 0-2 R^{14a}, C_{2-6} alkynyl substituted with 0-2 R^{14a}, $-(CH_2)_u$-C_{3-6} cycloalkyl substituted with 0-3 R^g, $-(CH_2)_u$-phenyl substituted with 0-3 R^g, or $-(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^g;

R^{14a} is, independently at each occurrence, H, C_{1-4} alkyl, OR^f, Cl, F, Br, I, =O, CF_3, CN, NO_2, $-C(O)R^f$, $-C(O)OR^f$, $-C(O)NR^{12}R^{13}$, or $-S(O)_pR^f$;

R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, OR^c, SR^c, CN, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, $-(CH_2)_u$-C_{3-10} carbocycle substituted with 0-3 R^e, or $-(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^b is, independently at each occurrence, H, =O, F, Cl, Br, I, $-(CH_2)_r$-OR^c, SR^c, CN, NO_2, CF_3, OCF_3, $-(CH_2)_r$-$NR^{12}R^{13}$, $-C(O)R^c$, $-(CH_2)_r$-$C(O)OR^c$, $-(CH_2)_r$-$C(O)NR^{12}R^{13}$, $-NR^{14}C(O)R^d$, $-S(O)_pNR^{12}R^{13}$, $-S(O)R^d$, $-S(O)_2R^d$, C_{1-4} haloalkyl, C_{1-4} haloalkyloxy-, C_{1-4} alkyloxy-, C_{1-4} alkylthio-, C_{1-4} alkyl-C(O)-, C_{1-4} alkyl-O-C(O)-, C_{1-4} alkyl-C(O)NH-, C_{1-6} alkyl substituted with 0-2 R^a, C_{2-4} alkenyl substituted with 0-2 R^a, C_{2-4} alkynyl substituted with 0-2 R^a, $-(CH_2)_u$-C_{3-10} carbocycle substituted with 0-3 R^e, or $-(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^c is, independently at each occurrence, H, -OP(O)(OEt)$_2$, C_{1-8} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl substituted with 0-3 R^e, C_{2-4} alkynyl substituted with 0-3 R^e, -$(CH_2)_u$-C_{3-8} cycloalkyl substituted with 0-3 R^e, -$(CH_2)_u$-C_{6-10} aryl substituted with 0-3 R^e, or -$(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^d is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, -$(CH_2)_u$-C_{3-10} carbocycle substituted with 0-3 R^e, or -$(CH_2)_u$-5- to 10- membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^e is, independently at each occurrence, H, =O, -$(CH_2)_r$-OR^f, F, Cl, Br, I, CN, NO_2, -$(CH_2)_u$-$NR^{12}R^{13}$, -$C(O)R^f$, -$(CH_2)_r$-$C(O)OR^f$, -$NR^{14}C(O)R^f$, -$(CH_2)_r$-$C(O)NR^{12}R^{13}$, -$SO_2NR^{12}R^{13}$, -$NR^{14}SO_2NR^{12}R^{13}$, -$NR^{14}SO_2$-C_{1-4} alkyl, -$NR^{14}SO_2CF_3$, -$NR^{14}SO_2$-phenyl, -$S(O)_2CF_3$, -$S(O)_p$-C_{1-4} alkyl, -$S(O)_p$-phenyl, -$(CF_2)_uCF_3$, C_{1-6} alkyl substituted with 0-2 R^g, C_{2-4} alkenyl substituted with 0-2 R^g, C_{2-4} alkynyl substituted with 0-2 R^g, -$(CH_2)_u$-C_{3-8} cycloalkyl substituted with 0-2 R^g, -$(CH_2)_u$-C_{6-10} aryl substituted with 0-2 R^g, or -$(CH_2)_u$-5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^g;

R^f is, independently at each occurrence, H, or C_{1-4} alkyl;

R^g is, independently at each occurrence, H, =O, OR^f, F, Cl, Br, I, CN, NO_2, -NR^fR^f, -$C(O)R^f$, -$C(O)OR^f$, -$NR^fC(O)R^f$, -$C(O)NR^fR^f$, -$SO_2NR^fR^f$, -$NR^fSO_2NR^fR^f$, -NR^fSO_2-C_{1-4} alkyl, -$NR^fSO_2CF_3$, -NR^fSO_2-phenyl, -$S(O)_2CF_3$, -$S(O)_p$-C_{1-4} alkyl, -$S(O)_p$-phenyl, -$(CF_2)_uCF_3$, C_{1-6} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl;

R^h is, independently at each occurrence, C_{1-6} alkyl substituted with 0-2 R^g, or -$(CH_2)_n$-phenyl substituted with 0-2 R^g;

n, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

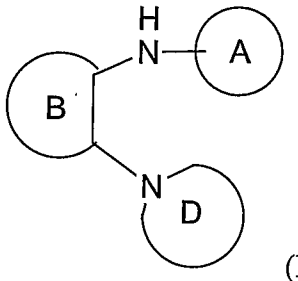
r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

s, at each occurrence, is selected from 0, 1, 2, and 3;

t, at each occurrence, is selected from 1 and 2; and

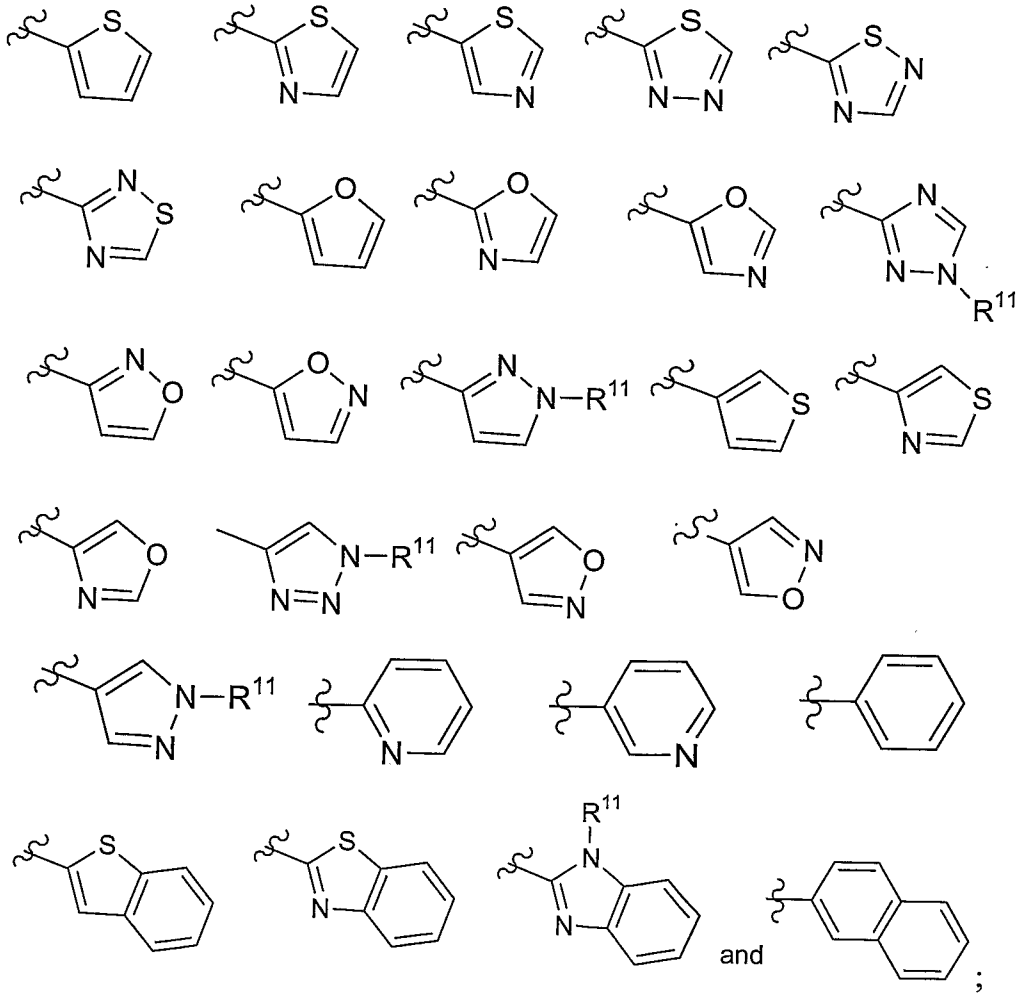
u, at each occurrence, is selected from 0, 1, and 2.

4. A compound according to Claim 1, wherein the compound is of Formula (II):

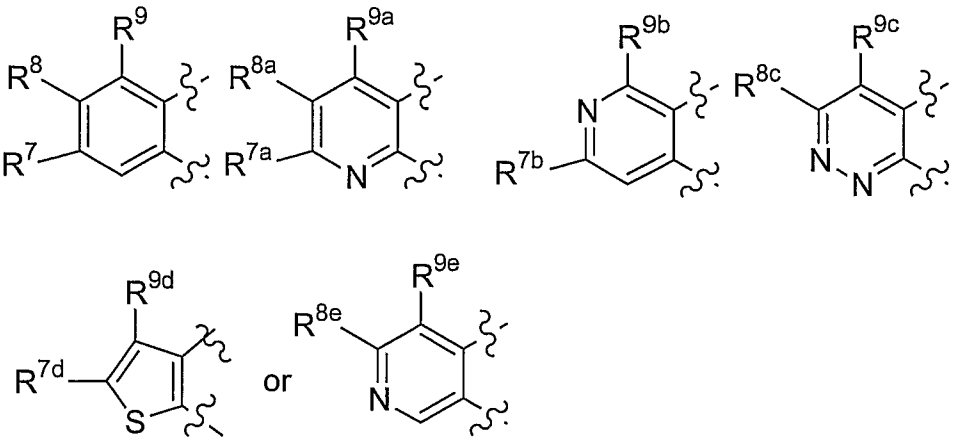


(II)

ring A is substituted with 0-4 R^1 and selected from:

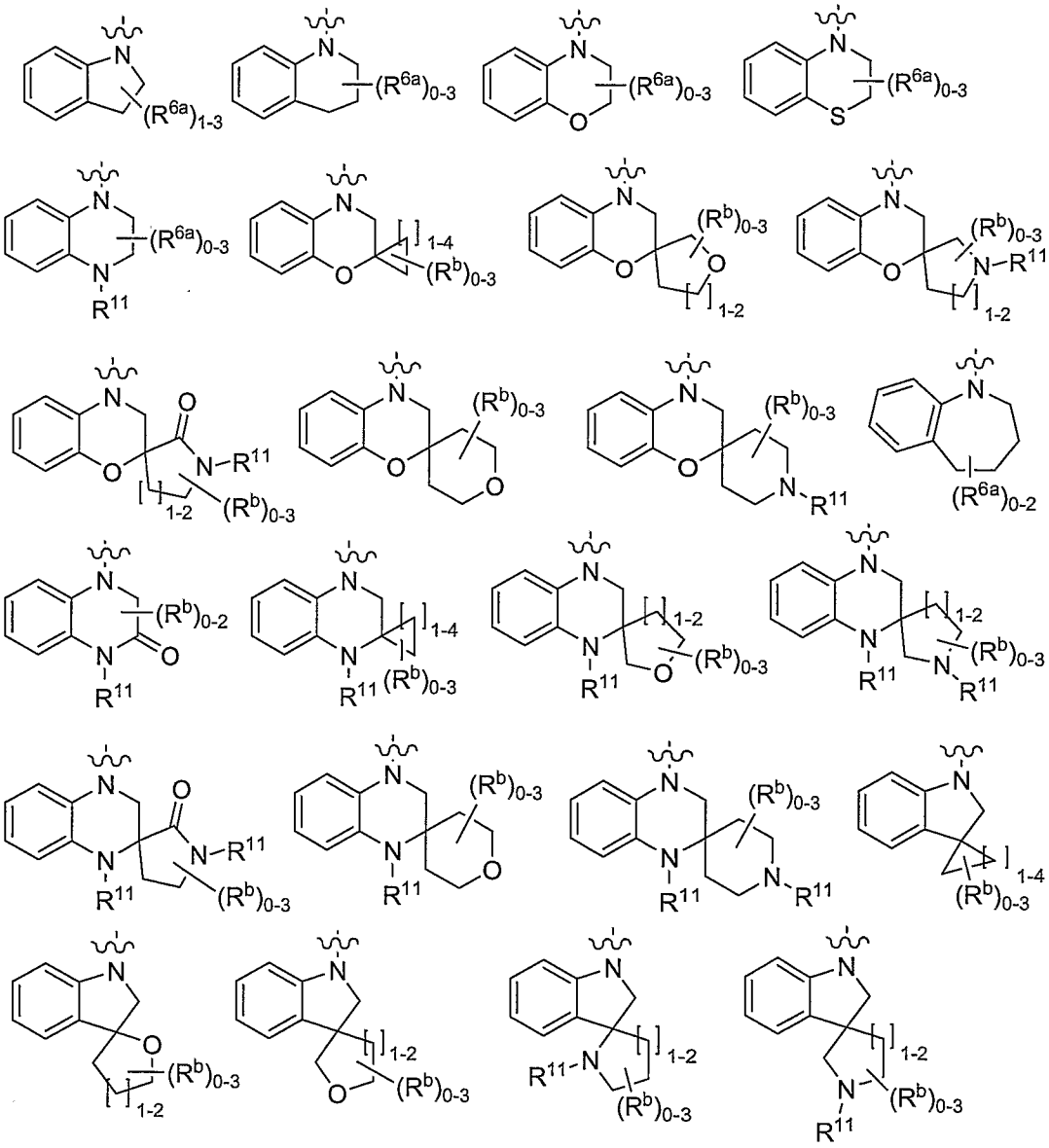


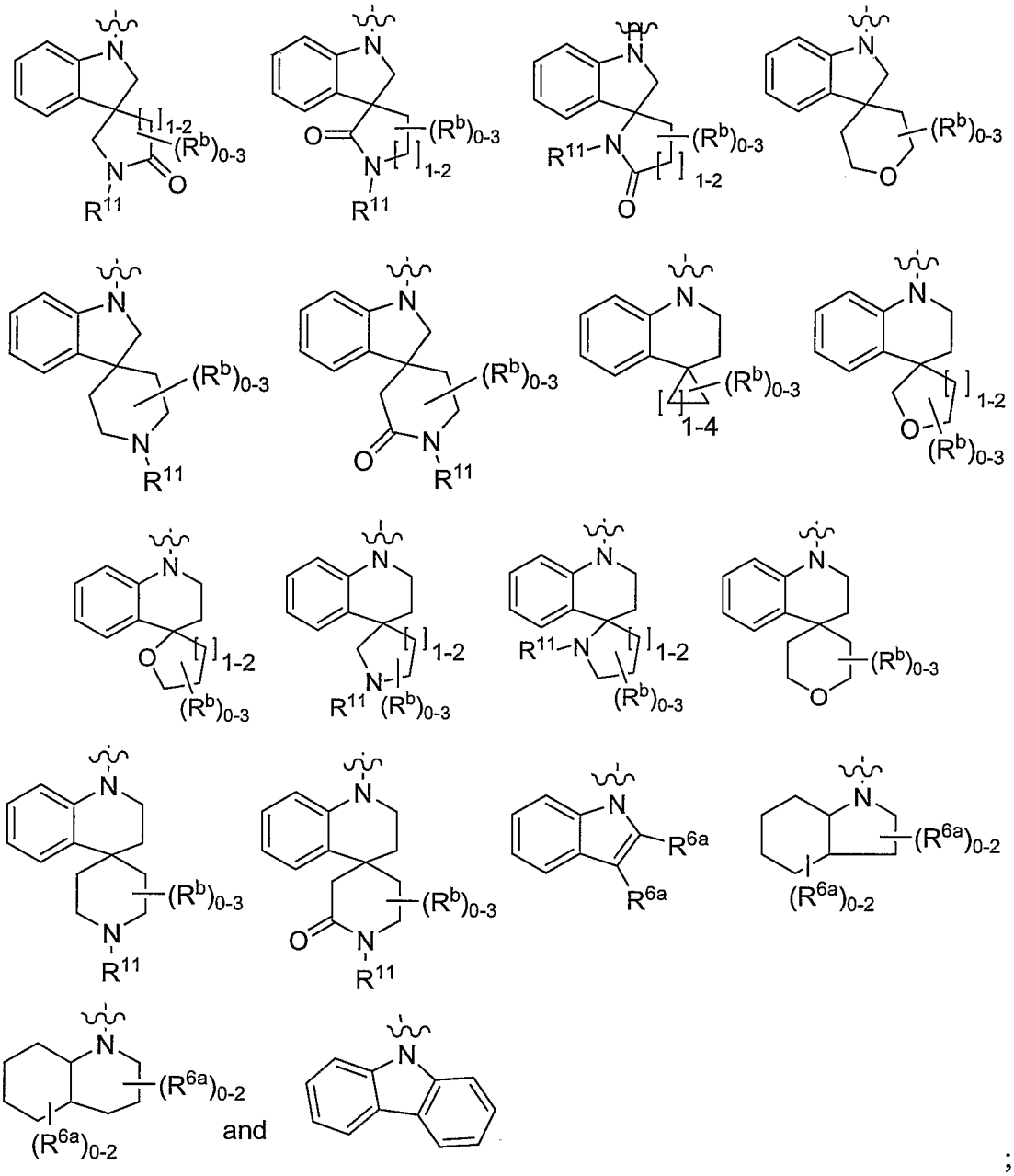
ring B is



;

ring D is selected from:





;

wherein the phenyl ring in each of the structures is substituted with 0-2 R^{6a};

R^1 is, independently at each occurrence, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $SiMe_3$, $-(CH_2)_r-OR^c$, SR^c, CN, NO_2, $-(CH_2)_r-NR^{12}R^{13}$, $-(CH_2)_u-C(O)R^c$, $-(CH_2)_r-CO_2R^c$, $-(CH_2)_u-C(O)NR^{12}R^{13}$, $-OP(O)(OEt)_2$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl, C_{1-8} alkyl substituted with 0-2 R^a, $-(CH_2)_u-C_{3-6}$ cycloalkyl substituted with 0-2 R^b, $-(CH_2)_u$-phenyl substituted with 0-2 R^b, or $-(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4

heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^b;

alternatively, two R^1s on two adjacent carbon atoms are combined with the carbon atoms to which they attached, form a 5- to 7-membered carbocycle or heterocycle comprising: carbon atoms and 0-3 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, and 0-1 carbonyl groups, wherein said carbocycle or heterocycle is substituted with 0-2 R^b;

R^{6a} is, independently at each occurrence, H, F, Cl, Br, I, CN, $-C(Me)_2CN$, C_{1-8} alkyl, C_{2-8} alkenyl, OH, SMe, S(*i*-Pr), $-C(Me)_2OMe$, $-C(Me)_2OEt$, $-C(Me)_2OPr$, $-CHMeO(CH_2)_2OMe$, $-C(Me)_2O(CH_2)_2OMe$, $-C(Et)_2OMe$, $-C(Et)_2OEt$, COPh, $-CH{=}CHCO_2$(*t*-Bu), CF_3, OCF_3, C_{1-4} alkyloxy, CO_2Me, $-CH_2CO_2Me$, C_{3-7} cycloalkyl, Ph, Bn, 1-pyrrolidinyl, 5-isoxazolyl, N-morpholinyl, 4-Bn-piperazinyl, 1-piperidinyl, 1-Bn-piperidin-4-yl, or $-Si(Me)_3$;

alternatively, when two R^{6a} groups are attached to the same carbon atom, together with the carbon atom to which they are attached, they form a 3- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

alternatively, when two R^{6a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5- to 7-membered carbocyclic or heterocyclic ring comprising: carbon atoms and 0-2 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$, 0-1 carbonyl and 0-3 ring double bonds, wherein said carbocyclic or heterocyclic ring is substituted with 0-2 R^b;

R^7, R^{7a}, R^{7b}, and R^{7d}, independently at each occurrence, H, Me, Cl, Br, CN, OMe, SMe, or NHMe;

R^8, R^{8a} , R^{8b}, and R^{8e} are, independently at each occurrence, H, Me, Cl, or CN;

R^{11} is, independently at each occurrence, C_{1-6} alkyl, $-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-C(O)(C_{1-6}$ alkyl), -C(O)phenyl, -C(O)benzyl, $-C(O)O(C_{1-6}$ alkyl), -C(O)Obenzyl, $-CH_2CO_2H$, $-CH_2CO_2(C_{1-6}$ alkyl), $-C(O)NH(C_{1-6}$ alkyl), -C(O)NHbenzyl, $-S(O)_2(C_{1-6}$ alkyl), $-S(O)_2$phenyl, $-S(O)_2$benzyl, phenyl, or benzyl;

R^{12} is, independently at each occurrence, H, C_{1-6} alkyl, -C(O)(C_{1-6} alkyl), -C(O)$(CH_2)_n$phenyl, -C(O)$(CH_2)_n$(5- to 6-membered heteroaryl), -$(CH_2)_n$C(O)NH(C_{1-6} alkyl), -$(CH_2)_n$C(O)NHphenyl, -$(CH_2)_n$C(O)NH(5- to 6-membered heteroaryl), -$(CH_2)_t$OC(O)NH(C_{1-6} alkyl), -$S(O)_2$(C_{1-6} alkyl), -$S(O)_2(CH_2)_n$phenyl, -$S(O)_2(CH_2)_n$(5- to 6-membered heteroaryl), -$(CH_2)_n$-phenyl, or -$(CH_2)_n$-5- to 6-membered heteroaryl; and said heteroaryl comprises: carbon atoms and 1-4 heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^{13} is, independently at each occurrence, H, C_{1-6} alkyl, or -$(CH_2)_n$-phenyl;

alternatively, R^{12} and R^{13}, when attached to the same nitrogen, combine to form a 5- to 10-membered heterocyclic ring comprising: carbon atoms and 1-2 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, OR^c, SR^c, CN, -$NR^{12}R^{13}$, -C(O)R^c, -C(O)OR^c, -C(O)$NR^{12}R^{13}$, -NR^{14}C(O)R^d, -$S(O)_pNR^{12}R^{13}$, -S(O)R^d, -$S(O)_2R^d$, -$(CH_2)_u$-C_{3-6} cycloalkyl substituted with 0-2 R^e, -$(CH_2)_u$-phenyl substituted with 0-2 R^e, or -$(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^e;

R^b is, independently at each occurrence, H, F, Cl, Br, C_{1-4} alkyl, OH, CO_2H, NH_2, CF_3, OCF_3, C_{1-4} alkyloxy, C_{3-7} cycloalkyl, phenyl, or benzyl;

R^c is, independently at each occurrence, H, -$OP(O)(OEt)_2$, C_{1-8} alkyl substituted with 0-3 R^e, C_{2-4} alkenyl substituted with 0-3 R^e, C_{2-4} alkynyl substituted with 0-3 R^e, -$(CH_2)_u$-C_{3-6} cycloalkyl substituted with 0-3 R^e, -$(CH_2)_u$-phenyl substituted with 0-3 R^e, or -$(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^d is, independently at each occurrence, CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, -$(CH_2)_u$-C_{3-6} cycloalkyl substituted with 0-3 R^e, -$(CH_2)_u$-phenyl substituted with 0-3 R^e, or -$(CH_2)_u$-5- to 6-membered heterocycle comprising: carbon atoms and 1-4

heteroatoms selected from N, NH^f, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-3 R^e;

R^e is, independently at each occurrence, H, F, Cl, C_{1-4} alkyl, OH, CO_2H, NH_2, CF_3, OCF_3, or C_{1-4} alkyloxy;

R^f is, independently at each occurrence, H, or C_{1-4} alkyl; and

n, at each occurrence, is selected from 0, 1, and 2;

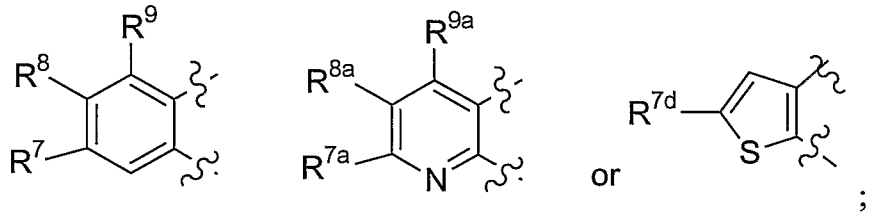
p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and

u, at each occurrence, is selected from 0, 1, and 2.

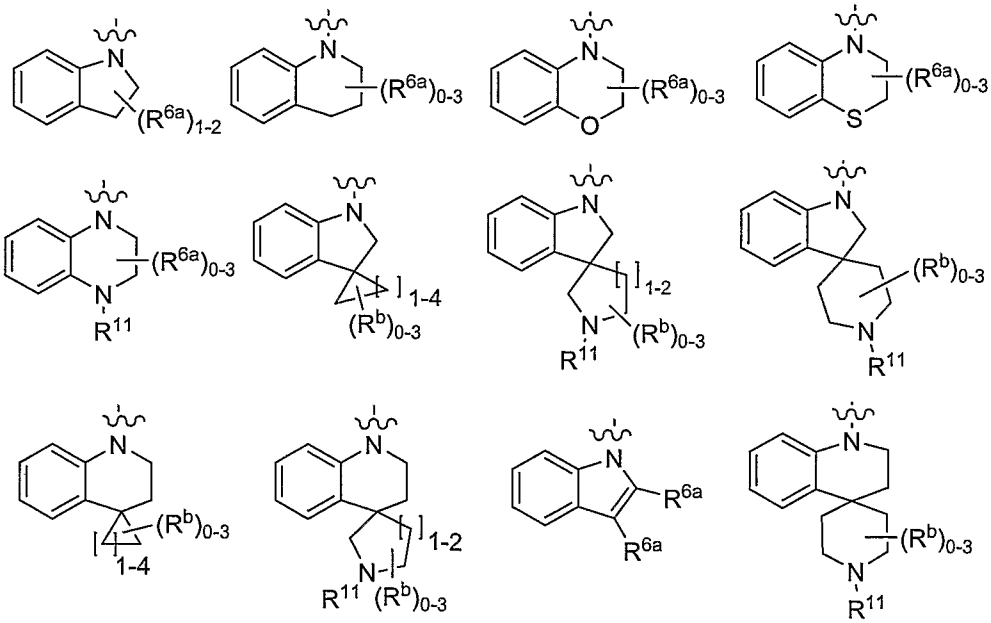
5. A compound according to Claim 4, wherein:

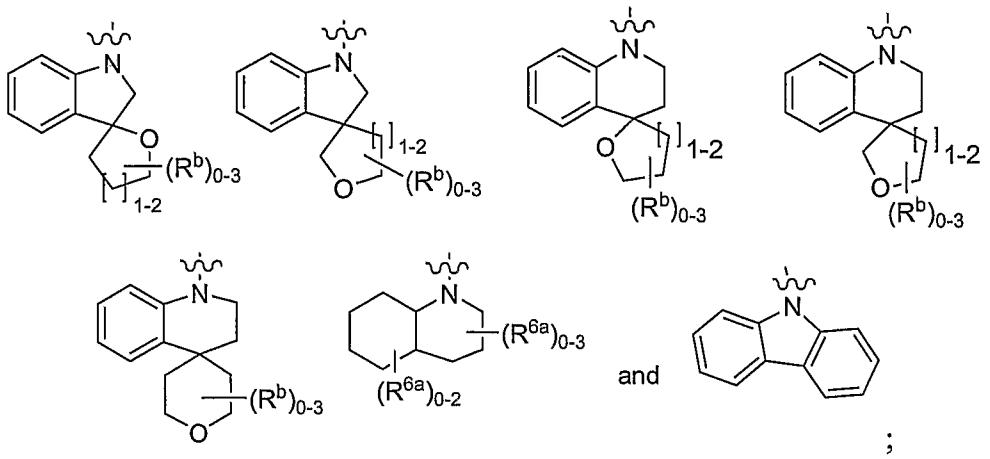
ring B is



;

ring D is selected from:





;

wherein the phenyl ring in each of the structures is substituted with 0-1 R^{6a};

R^7, R^{7a}, and R^{7d} are, independently at each occurrence, H, Me, Cl, Br, CN, OMe, SMe, or NHMe;

R^8 and R^{8a} are, independently at each occurrence, H, Me, F, Cl, or CN;

R^9 and R^{9a} are, independently at each occurrence, H, Me, F, Cl, or CN;

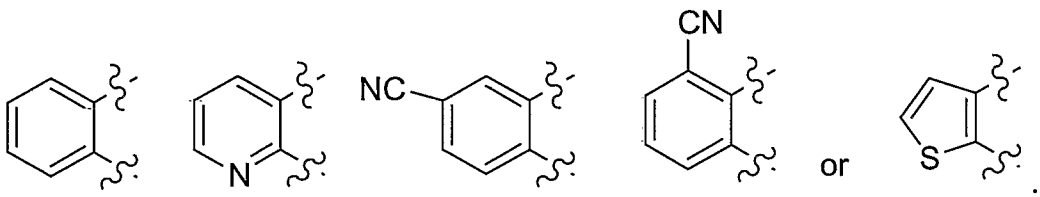
R^{11} is, independently at each occurrence, C_{1-6} alkyl, Bn, $-CH_2CH_2OH$, $-CH_2CH_2OMe$, -CO(i-Pr), CO_2Me, CO_2Et, CO_2Bn, $-CH_2CO_2H$, $-CH_2CO_2Me$, -CONH(*i*-Pr), or SO_2(*i*-Pr);

R^b is, independently at each occurrence, H, F, Cl, C_{1-4} alkyl, OH, CO_2H, NH_2, CF_3, OCF_3, or C_{1-4} alkyloxy; and

R^e is, independently at each occurrence, H, F, Cl, C_{1-4} alkyl, OH, CO_2H, NH_2, CF_3, OCF_3, or C_{1-4} alkyloxy.

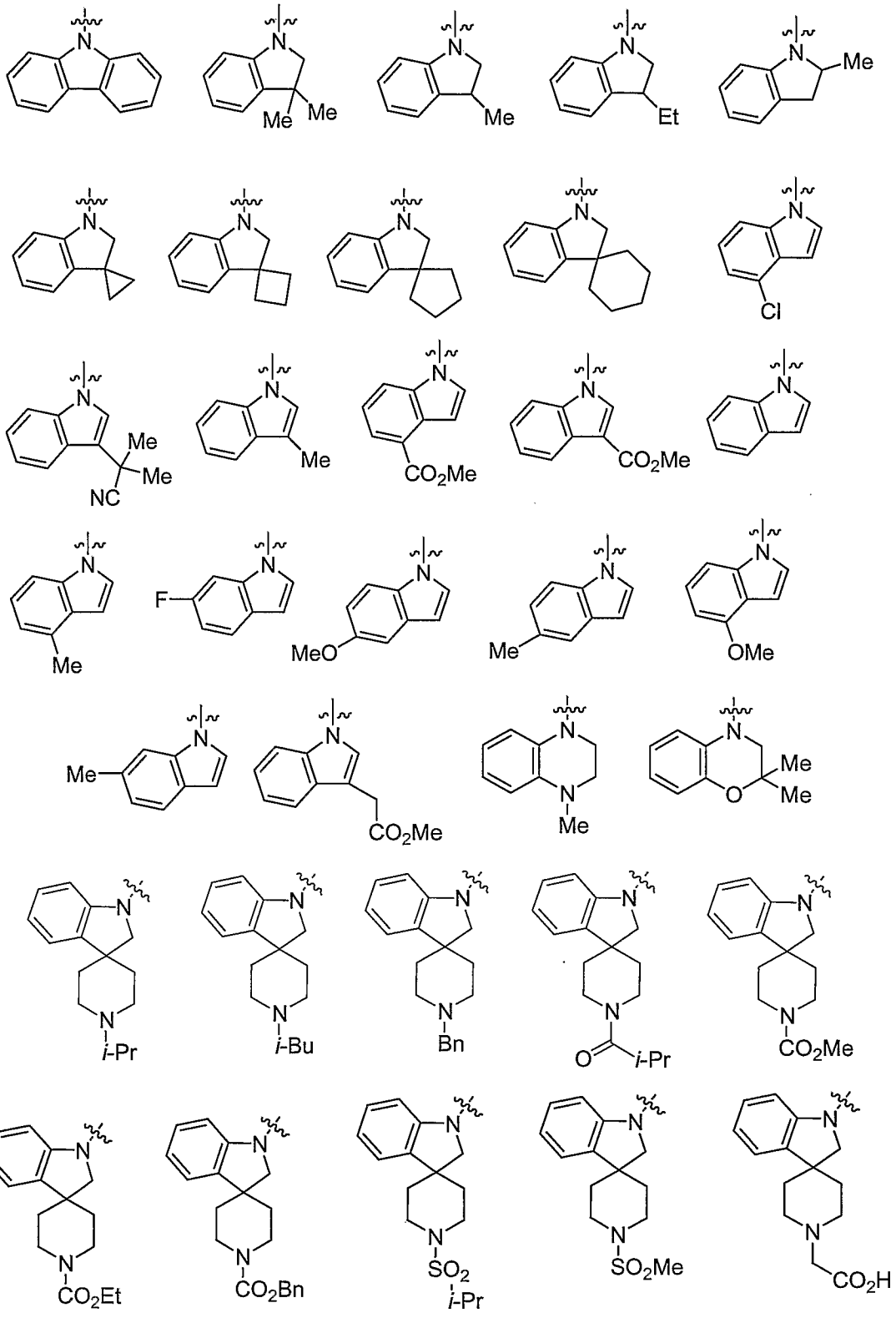
6. A compound according to Claim 5, wherein:

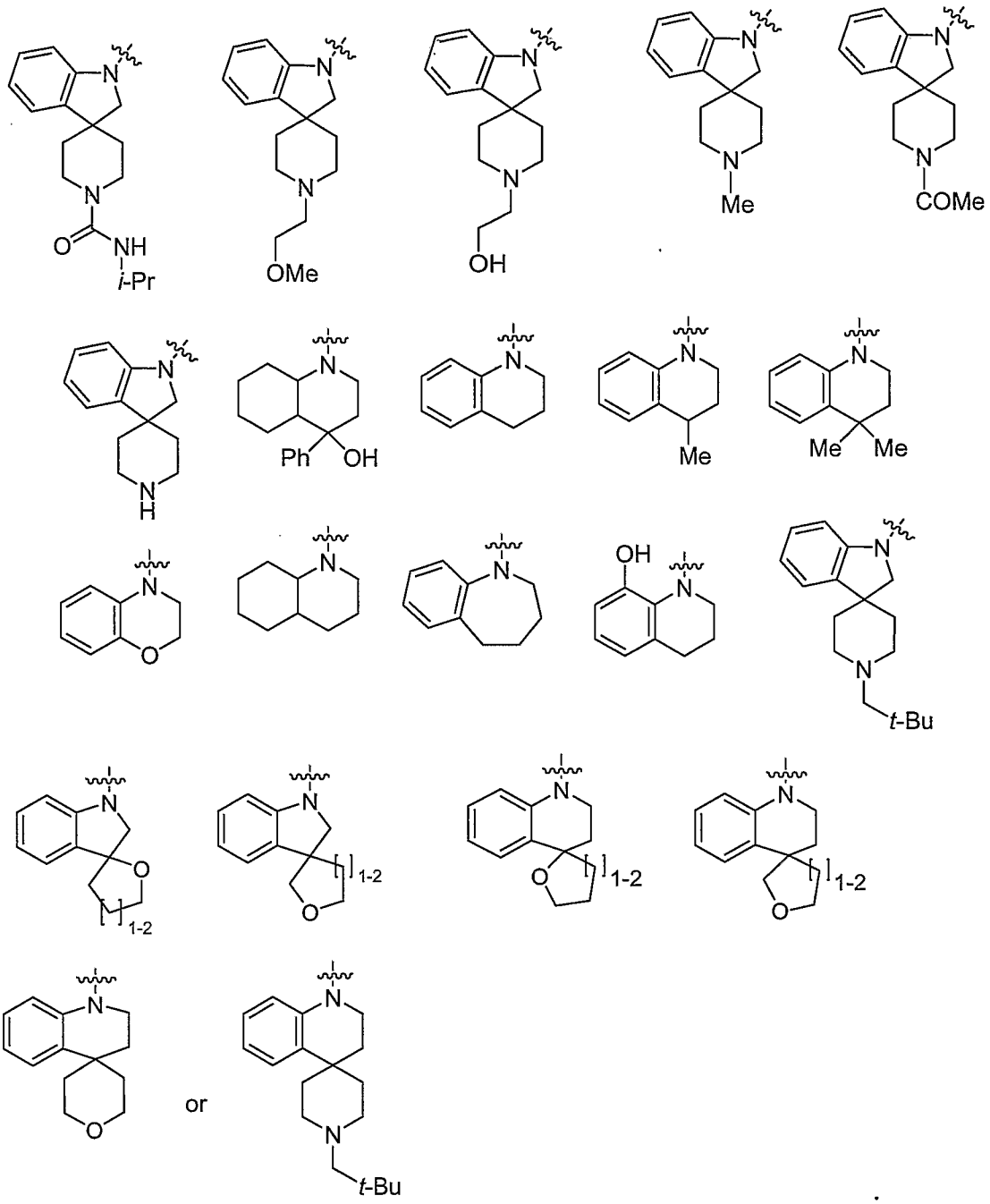
ring B is



; and

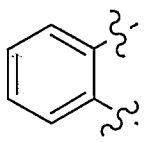
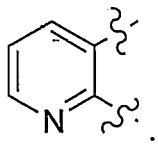
ring D is selected from:


Me
Me
Me
Me
Et
Me
Cl
Me
Me
NC
Me
CO2Me
CO2Me
Me
F
MeO
Me
OMe
Me
CO2Me
Me
Me
Me
O
i-Pr
i-Bu
Bn
i-Pr
CO2Me
CO2Et
CO2Bn
SO2
i-Pr
SO2Me
CO2H

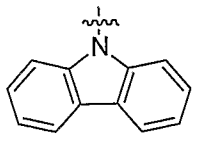
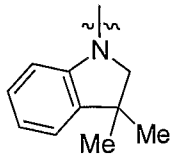
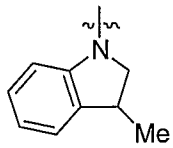
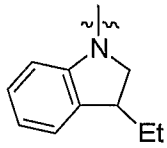
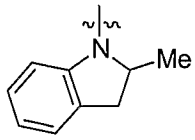
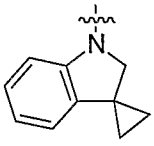
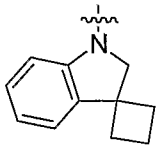
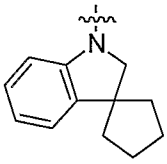
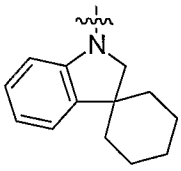
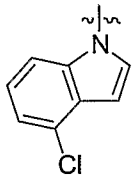
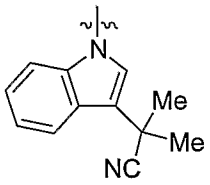
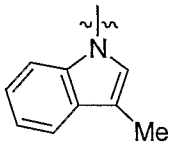
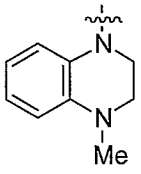
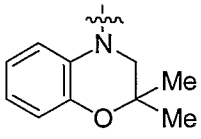
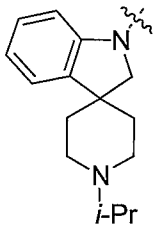
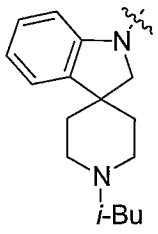
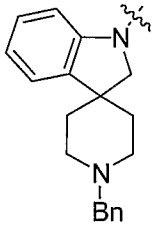
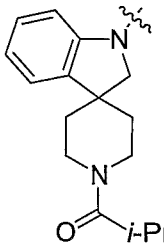
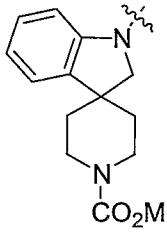
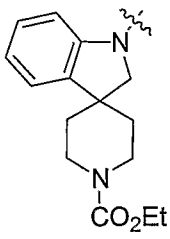
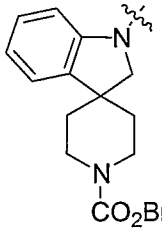
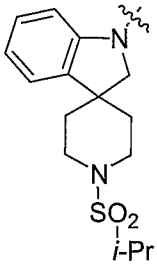
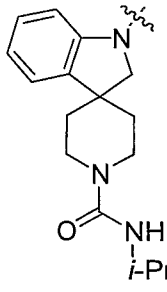
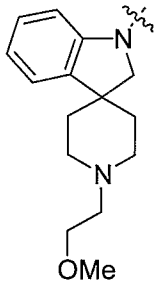
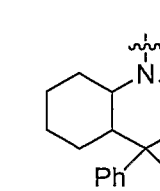
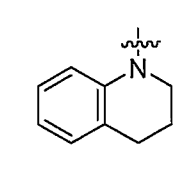
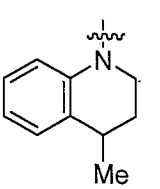
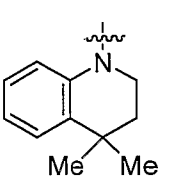
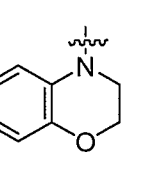


7. A compound according to Claim 6, wherein:

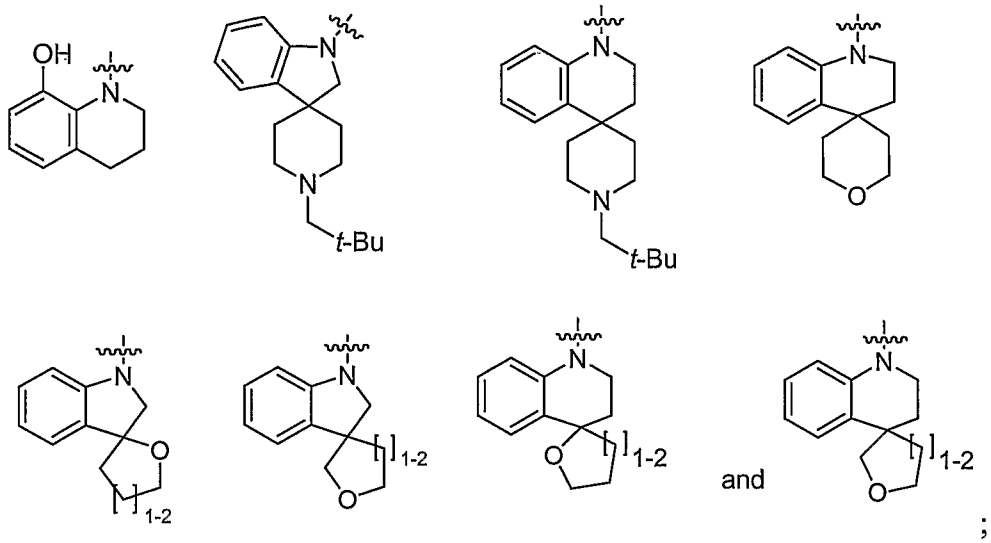
ring A is substituted with 0-2 R^1 and selected from: thiazolyl, benzothizolyl, and benzimidazolyl;

ring B is  or ;

ring D is selected from:

5



;

R^1 is, independently at each occurrence, F, Cl, Br, I, CF_3, $-CF_2CF_3$, OCF_3, $-OCF_2CF_2H$, $-OCF_2CF_3$, $-(CH_2)_r-OR^c$, SR^c, CN, NO_2, $-(CH_2)_r-NR^{12}R^{13}$, $-(CH_2)_u-C(O)R^c$, $-(CH_2)_r-CO_2R^c$, $-(CH_2)_u-C(O)NR^{12}R^{13}$, or C_{1-4} alkyl substituted with 0-2 R^a;

R^{12} is, independently at each occurrence, H, C_{1-4} alkyl, phenyl, or benzyl;

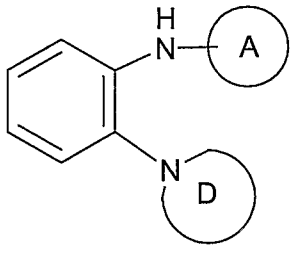
R^{13} is, independently at each occurrence, H, C_{1-4} alkyl, phenyl, or benzyl;

alternatively, R^{12} and R^{13}, when attached to the same nitrogen, combine to form a 5- to 6-membered heterocyclic ring comprising: carbon atoms and 1-2 additional heteroatoms selected from N, NR^{11}, O, and $S(O)_p$;

R^a is, independently at each occurrence, H, =O, F, OCF_3, CF_3, OR^c, SR^c, CN, $-NR^{12}R^{13}$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^{12}R^{13}$, or $-S(O)_pNR^{12}R^{13}$; and

R^c is, independently at each occurrence, H, C_{1-4} alkyl, phenyl, or benzyl.

8. A compound according to Claim 1, wherein the compound is of Formula (III):

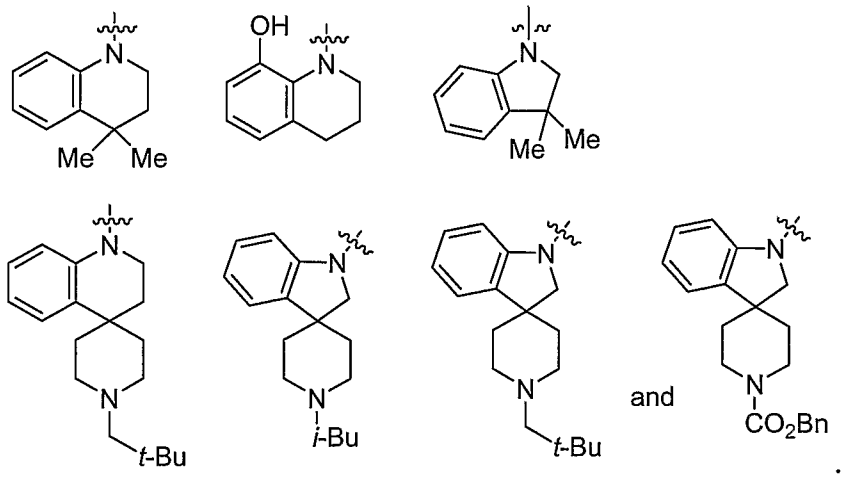


(III)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

ring A is 4-CF_3-thiazol-2-yl, 4-CF_3-5-Me-thiazol-2-yl, 4-Me-5-CO_2Me-thiazol-2-yl, 4-CF_3-5-CO_2Et-thiazol-2-yl, 4-CF_3-5-Ph-thiazol-2-yl, 3-(*t*-Bu)-1,2,4-thiadiazol-5-yl, benzothizol-2-yl, 5-Cl-benzothizol-2-yl, 5-CF_3-benzothizol-2-yl, 6-(*t*-Bu)-benzimidazol-2-yl, or 7-CO_2Et-benzimidazol-2-yl; and

ring D is selected from:



9. A compound according to Claim 1, wherein the compound is selected from the exemplified examples of the present invention or a stereoisomer or pharmaceutically acceptable salt, or solvate thereof.

10. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a compound of any one of Claims 1-9.

11. A compound of any one of Claims 1-9 for use in therapy.

12. Use of a compound of any one of Claims 1-9 for the manufacture of a medicament for the treatment of a thromboembolic disorder.

13. Use of a compound according to Claim 12, wherein the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart or in the peripheral circulation.

14. Use of a compound according to Claim 12, wherein the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, atrial fibrillation, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface that promotes thrombosis.